Palladium-Catalyzed Asymmetric Conjugate Addition of Arylboronic Acids to 5- 6- and 7-Membered β-substituted Cyclic Enones: Enantioselective Construction of All-Carbon Quaternary Stereocenters

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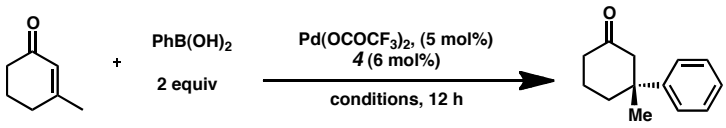
Materials and Methods

Unless otherwise stated, reactions were performed with no extra precautions taken to exclude air or moisture. Commercially available reagents were used as received from Sigma Aldrich unless otherwise stated. Enone substrates (Table 3) were prepared according to literature procedure.[1] Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (250 nm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 40-63 nm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralcel OJ column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm and flow rate of 1 mL/min, unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 125 MHz, respectively) and a Varian Mercury 300 spectrometer (300 MHz and 75 MHz, respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{1}H NMR spectra are referenced to the centerline of $CDCl_3$ (δ 7.26) as the internal standard and are reported in terms of chemical shift relative to Me_4Si (δ 0.00). Data for ^{13}C NMR spectra are referenced to the centerline of $CDCl_3$ (δ 77.0) and are reported in terms of chemical shift relative to Me_4Si (δ 0.00). Infrared spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained on an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MultiMode ESI/APCI) ionization mode. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm.

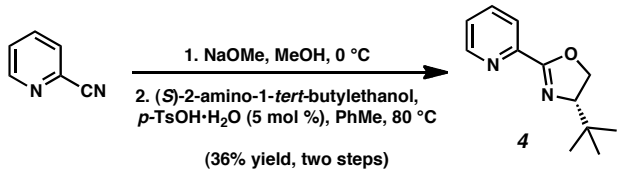
Solvent Screen

Table S1. *Solvent Optimization.*



Entry	solvent	temp.	yield	*ee*
1	*t*-amylalcohol	40 °C	14% (NMR)	--
2	dioxane	40 °C	17% (NMR)	--
3	THF	40 °C	31% (NMR)	--
4	toluene	40 °C	65% (NMR)	82%
5	CH_2Cl_2	40 °C	87% (isolated)	91%
6	toluene	60 °C	63% (isolated)	77%
7	hexane	60 °C	68% (isolated)	62%

Experimental Procedures



(*S*)-4-(*tert*-butyl)-2-(pyridin-2-yl)-4,5-dihydrooxazole (4)

The ligand was prepared according to literature procedures.[2] A round bottom flask was charged with a stir bar, 2-cyanopyridine (13.00 g, 124.9 mmol, 1.0 equiv) and methanol (110 mL). The mixture was cooled to 0 °C, at which time sodium methoxide (0.68 g, 12.5 mmol, 0.1 eq) was added and the reaction mixture was stirred overnight at room temperature. Glacial acetic acid (1 mL) was then slowly added to quench the reaction and the solvent was evaporated under reduced pressure. Dichloromethane (100 mL) was added and the organic phase was washed with brine (2 x 50 mL). Upon evaporation of the solvent, crude methyl pyridine-2-carboxyimidate was obtained as a clear yellow oil (14.50 g, 85% yield) and used without further purification. A round bottom flask was charged with a stir bar, the crude methyl pyridine-2-carboxyimidate (2.32 g, 17.1 mmol,

1.0 equiv), (*S*)-2-amino-1-*tert*-butylethanol (2.00 g, 17.1 mmol, 1.0 equiv) and dry toluene (100 mL). To the obtained solution was added *p*-TsOH•H_2O (162 mg, 0.86 mmol, 5 mol%) and the mixture was refluxed under an argon atmosphere until all the starting material was consumed (as monitored by TLC, 1:2 hexanes/EtOAc). When the reaction was complete (3 h), the mixture was diluted with a saturated aqueous solution of $NaHCO_3$ (60 mL) and extracted with EtOAc (3 x 50 mL). After evaporation of the solvent under reduced pressure, the residue was purified by silica gel chromatography (1:1 hexanes/EtOAc) to afford a white solid (1.46 g, 42% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (dd, *J* = 0.9, 4.8 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.77 (dt, *J* = 1.7, 7.7 Hz, 1H), 7.37 (dd, *J* = 4.5, 7.0, 1H), 4.45 (dd, *J* = 9.0, 10.0 Hz, 1H), 4.31 (t, *J* = 8.54 Hz, 1H), 4.12 (dd, *J* = 8.4, 10.1 Hz, 1H), 0.98 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 149.6, 147.0, 136.5, 125.4, 124.0, 76.5, 69.3, 34.0, 26.0; IR (Neat Film, NaCl): 2981, 2961, 2904, 2863, 1640, 1589, 1566, 1475, 1439, 1356, 1341, 1315, 1271, 1243, 1093, 1041, 1021, 966 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calc'd for $C_{12}H_{17}ON_2$ $[M+H]^+$: 205.1335, found 205.1327; $[\alpha]^{25}_D$ –72.7° (*c* 1.04, CH_2Cl_2).

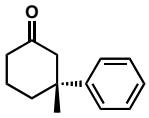
Representative General Procedure for the Enantioselective 1,4-Addition of Arylboronic Acids to β-Substituted Cyclic Enones

A screw-top 1 dram vial was charged with a stir bar, $Pd(OCOCF_3)_2$ (4.2 mg, 0.0125 mmol, 5 mol%), (*S*)-*t*-BuPyOx (3.1 mg, 0.015 mmol, 6 mol%), and $PhB(OH)_2$ (61 mg, 0.50 mmol, 2.0 equiv). The solids were dissolved in dichloroethane (0.5 mL) and 3-methyl-2-cyclohexenone (29 μL, 0.25 mmol) was added. The walls of the vial were rinsed with an additional portion of dichloroethane (0.5 mL). The vial was capped with a Teflon/silicone septum and stirred at 60 °C in an oil bath for 12 h. Upon complete consumption of the starting material (monitored by TLC, 4:1 hexanes/EtOAc, *p*-anisaldehyde stain) the reaction was purified directly by column chromatography (CH_2Cl_2) to afford a clear colorless oil (47 mg, 99% yield).

General Procedure for the Synthesis of Racemic Products

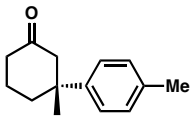
Racemic products were synthesized in a manner analogous to the general procedure using bipyridine (2.1 mg, 0.015 mmol, 6 mol%) as an achiral ligand.

Spectroscopic Data for Enantioenriched β,β-Disubstituted Cyclic Ketones



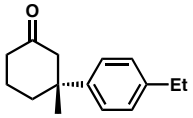
(*R*)-3-phenyl-3-methylcyclohexanone 3 (Table 1, Entry 6)

Synthesized according to the general procedure and purified by flash chromatography (CH_2Cl_2) to afford a colorless oil (93% yield). $[\alpha]^{25}_D$ –56.1° (*c* 1.36, $CHCl_3$, 92% ee). All characterization data matches previously reported data.[3, 4, 5, 6, 7, 8, 9]



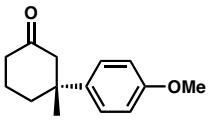
(*R*)-3-(4-methylphenyl)-3-methylcyclohexanone (Table 2, Entry 1)

Synthesized according to the general procedure and purified by flash chromatography (CH_2Cl_2) to afford a colorless oil (99% yield). $[\alpha]^{25}_D$ –60.9° (*c* 1.11, CH_2Cl_2, 87% ee). All characterization data matches previously reported data.[3, 5, 7]



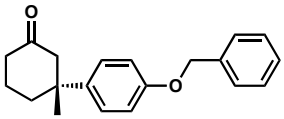
(*R*)-3-(4-ethylphenyl)-3-methylcyclohexanone (Table 2, Entry 2)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 95:5) to afford a colorless oil (90% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (ddd, *J* = 2.0, 8.5 Hz, 2H), 7.16 (ddd, *J* = 2.0, 8.5 Hz, 2H), 2.87 (d, *J* = 14.0 Hz, 1H), 2.62 (q, *J* = 7.5, 2H), 2.42 (d, *J* = 14.0 Hz, 1H), 2.35–2.26 (m, 2H), 2.20–2.15 (m, 1H), 1.93–1.83 (m, 2H), 1.73–1.64 (m, 1H), 1.31 (s, 3H), 1.23 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.6, 144.7, 142.0, 127.9, 125.5, 53.2, 42.5, 40.8, 38.0, 29.8, 28.2, 22.0, 15.4; IR (Neat Film, NaCl): 2957, 2933, 2863, 1710, 1513, 1453, 1416, 1315, 1288, 1226, 1078 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calc'd for $C_{15}H_{21}O$ $[M+H]^+$: 217.1587, found 217.1592; $[\alpha]^{25}_D$ –56.8° (*c* 1.61, $CHCl_3$, 85% ee).



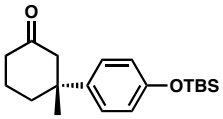
(*R*)-3-(4-methoxyphenyl)-3-methylcyclohexanone (Table 2, Entry 3)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 90:10) as colorless oil (58% yield). $[\alpha]^{25}_{D}$ –47.9° (*c* 1.05, $CHCl_3$, 69% ee). All characterization data matches previously reported data.[4, 5, 6, 7, 8]



(*R*)-3-(4-benzyloxylphenyl)-3-methylcyclohexanone (Table 2, Entry 4)

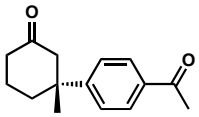
Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 95:5) to afford a colorless oil (96% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (ddd, *J* = 1.5, 2.0, 7.5 Hz, 2H), 7.39 (ddd, *J* = 1.0, 7.0, 7.5, 2H), 7.33 (tt, *J* = 1.5, 7.0 Hz, 1H), 7.22 (ddd, *J* = 2.0, 3.5, 10.0 Hz, 2H), 6.93 (ddd, *J* = 2.0, 3.5, 10.0 Hz, 2H), 5.04 (s, 2H), 2.85 (d, *J* = 14.0 Hz, 1H), 2.42 (d, *J* = 14.0 Hz, 1H), 2.30 (t, *J* = 7.0 Hz, 2H), 2.18–2.13 (m, 1H), 1.92–1.83 (m, 2H), 1.71–1.62 (m, 1H), 1.30 (s, 3H), 0.97 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.6, 157.0, 139.7, 137.0, 128.6, 127.9, 127.5, 126.7, 114.7, 70.0, 53.3, 42.3, 40.8, 38.0, 30.0, 22.0; IR (Neat Film, NaCl) 3066, 3027, 2947, 2873, 1710, 1609, 1579, 1510, 1453, 1426, 1379, 1312, 1290, 1246, 1181, 1021 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calc'd for $C_{20}H_{23}O_2$ $[M+H]^+$: 295.1693, found 295.1673; $[\alpha]^{25}_{D}$ –26.8° (*c* 4.90, $CHCl_3$, 74% ee).



(*R*)-3-(4-*tert*-butyldimethylsiloxylphenyl)-3-methylcyclohexanone (Table 2, Entry 4)

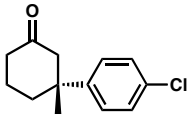
Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 95:5) to afford a colorless oil (52% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (ddd, *J* = 2.0, 3.0, 9.0 Hz, 2H), 6.71 (ddd, *J* = 2.0, 3.0, 9.0 Hz, 2H),

2.83 (d, *J* = 14.0 Hz, 1H), 2.40 (d, *J* = 14.0 Hz, 1H), 2.30 (t, *J* = 7.0 Hz, 2H), 2.16–2.10 (m, 1H), 1.90–1.81 (m, 2H), 1.70–1.61 (m, 1H), 1.29 (s, 3H), 0.97 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7, 153.8, 140.1, 126.5, 119.8, 53.3, 42.3, 40.8, 38.1, 29.9, 25.6, 22.0, 18.1, –4.4; IR (Neat Film, NaCl) 2952, 2933, 2858, 1713, 1607, 1510, 1473, 1458, 1263, 1181 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calc'd for $C_{19}H_{31}O_2Si$ $[M+H]^+$: 319.2088, found 319.2090; $[\alpha]^{25}_D$ –36.4° (*c* 1.11, $CHCl_3$, 82% ee).



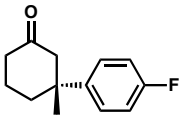
(*R*)-3-(4-acetylphenyl)-3-methylcyclohexanone (Table 2, Entry 6)

Synthesized according to the general procedure and purified by flash chromatography (CH_2Cl_2/EtOAc = 100:0 to 98:2) to afford colorless oil (99% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (ddd, *J* = 2.0, 9.0 Hz, 2H), 7.42 (ddd, *J* = 2.0, 9.0 Hz, 2H), 2.90 (d, *J* = 14.0 Hz, 1H), 2.58 (s, 1H), 2.47 (d, *J* = 14.0 Hz, 1H), 2.38–2.26 (m, 2H), 2.25–2.20 (m, 1H), 1.98–1.88 (m, 2H), 1.68–1.59 (m, 1H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.8, 197.6, 152.9, 135.2, 128.6, 125.9, 52.8, 43.2, 40.7, 37.8, 29.7, 26.5, 22.0; IR (Neat Film, NaCl) 2957, 2868, 1708, 1683, 1607, 1569, 1456, 1421, 1404, 1359, 1312, 1268, 1228, 1194 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calc'd for $C_{15}H_{19}O$ $[M+H]^+$: 231.1379, found 231.1380; $[\alpha]^{25}_D$ –58.9° (*c* 1.39, $CHCl_3$, 96% ee).



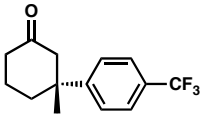
(*R*)-3-(4-chlorophenyl)-3-methylcyclohexanone (Table 2, Entry 7)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 95:5) to afford a white solid (94% yield). $[\alpha]^{25}_D$ –69.4° (*c* 0.56, $CHCl_3$). All characterization data matches previously reported data.[4]



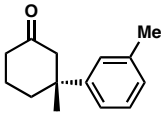
(*R*)-3-(4-fluorophenyl)-3-methylcyclohexanone (Table 2, Entry 8)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 95:5) to afford a colorless oil (84% yield). $[\alpha]^{25}_{D}$ –59.5° (*c* 1.00, $CHCl_3$). All characterization data matches previously reported data.[3, 4]



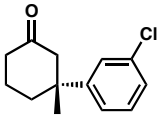
(*R*)-3-(4-trifluoromethylphenyl)-3-methylcyclohexanone (Table 2, Entry 9)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 95:5) to afford a colorless oil (99% yield). $[\alpha]^{25}_{D}$ –58.5° (*c* 0.92, $CHCl_3$). All characterization data matches previously reported data.[5, 6, 7]



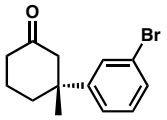
(*R*)-3-methyl-3-(*m*-tolyl)cyclohexanone (Table 2, Entry 10)

Synthesized according to the general procedure and purified by flash chromatography (CH_2Cl_2) to afford a colorless oil (99% yield). $[\alpha]^{25}_{D}$ –59.8° (*c* 2.95, CH_2Cl_2). All characterization data matches previously reported data.[3, 5, 7]



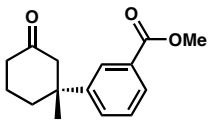
(*R*)-3-(3-chlorophenyl)-3-methylcyclohexanone (Table 2, Entry 11)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 95:5) to afford a colorless oil (55% yield). $[\alpha]^{25}_{D}$ –56.7° (*c* 1.48, $CHCl_3$). All characterization data matches previously reported data.[3, 4]



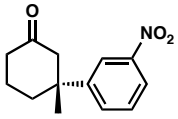
(*R*)-3-(3-bromophenyl)-3-methylcyclohexanone (Table 2, Entry 12)

Synthesized according to the general procedure and purified by flash chromatography (CH_2Cl_2) to afford a colorless oil (44% yield). $[\alpha]^{25}_D$ –56.7° (*c* 0.68, $CHCl_3$). All characterization data matches previously reported data.[7]



(*R*)-3-(3-methoxycarbonylphenyl)-3-methylcyclohexanone (Table 2, Entry 13)

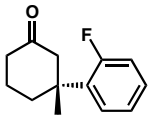
Synthesized according to the general procedure and purified by flash chromatography (CH_2Cl_2/EtOAc 100:0 to 98:2) to afford a white solid (91% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 1.5, 2.0 Hz, 1H), 7.88 (dd, *J* = 1.5, 9.0 Hz, 1H), 7.51 (dd, *J* = 2.0, 9.0 Hz, 1H), 7.39 (dd, *J* = 9.0 Hz, 1H), 3.91 (s, 3H), 2.88 (d, *J* = 14.0 Hz, 1H), 2.47 (d, *J* = 14.0 Hz, 1H), 2.37–2.28 (m, 2H), 2.24-2.19 (m, 1H), 1.98–1.86 (m, 2H), 1.73–1.65 (m, 1H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.9, 167.1, 147.9, 130.4, 130.2, 128.6, 127.5, 126.7, 53.0, 52.1, 42.8, 40.7, 37.7, 29.3, 22.0; IR (Neat Film, NaCl) 2952, 2878, 1720, 1604, 1582, 1438, 1350, 1310, 1273, 1243, 1209, 1194, 1120, 1085 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calc'd for $C_{15}H_{19}O_3$ $[M+H]^+$: 247.1329, found 247.1334; $[\alpha]^{25}_D$ –58.9° (*c* 1.39, $CHCl_3$).



(*R*)-3-(3-nitrophenyl)-3-methylcyclohexanone (Table 2, Entry 14)

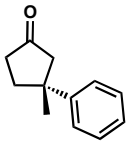
Synthesized according to the general procedure and purified by flash chromatography (CH_2Cl_2) to afford a colorless oil (40% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (t, *J* = 2.0 Hz, 1H), 8.08 (ddd, *J* = 1.0, 2.0, 8.0 Hz, 1H), 7.66 (ddd, *J* = 1.0, 2.0, 8.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 2.88 (d, *J* = 14.0 Hz, 1H), 2.53 (ddd, *J* = 1.0, 1.5, 14.0 Hz, 1H), 2.41–2.31 (m, 2H), 2.26–2.20 (m, 1H), 2.03–1.90 (m, 2H), 1.74–1.66 (m, 1H), 1.37 (s,

3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 149.7, 148.6, 131.9, 129.5, 121.4, 120.7, 52.8, 43.1, 40.6, 37.6, 29.4, 22.0; IR (Neat Film, NaCl) 2957, 2873, 1713, 1525, 1480, 1453, 1426, 1347, 1298, 1226, 1107, 1075 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calc'd for $C_{13}H_{15}O_3N$ [M]: 233.1052, found 233.1055; $[\alpha]^{25}_D$ –61.5° (*c* 0.96, $CHCl_3$)



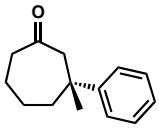
(*R*)-3-(2-fluorophenyl)-3-methylcyclohexanone (Table 2, Entry 15)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 95:5) to afford a colorless oil (32% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.19 (m, 2H), 7.07 (ddd, *J* = 1.5, 2.0, 7.5 Hz, 2H), 7.39 (ddd, *J* = 1.0, 7.0, 7.5, 2H), 7.33 (tt, *J* = 1.5, 7.0 Hz, 1H), 7.22 (ddd, *J* = 1.5, 7.5 Hz, 1H), 7.02 (ddd, *J* = 1.5, 8.0, 13.0 Hz, 1H), 2.94 (d, *J* = 14.5 Hz, 1H), 2.44 (d, *J* = 14.5 Hz, 1H), 2.48–2.44 (m, 1H), 2.37–2.28 (m, 2H), 1.96–1.87 (m, 2H), 1.67-1.60 (m, 1H), 1.41 (s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.3, 128.3, 128.0, 127.9, 124.1, 116.7, 53.2, 42.4, 40.9, 35.7, 27.1; IR (Neat Film, NaCl) 2957, 2933, 2873, 1710, 1611, 1577, 1488, 1443, 1315, 1290, 1214, 1117, 1083 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calc'd for $C_{13}H_{16}OF$ $[M+H]^+$: 207.1180, found 207.1188; $[\alpha]^{25}_D$ –41.0° (*c* 0.64, $CHCl_3$).



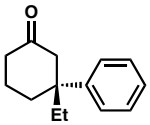
(*R*)-3-phenyl-3-methylcyclopentanone (5)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 95:5) to afford a colorless oil (84% yield). $[\alpha]^{25}_D$ +21.3° (*c* 1.51, $CHCl_3$). All characterization data matches previously reported data.[5, 6, 7]



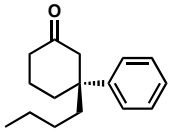
(*R*)-3-phenyl-3-methylcycloheptanone (6)

This product was synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 95:5) to afford a colorless oil (85% yield). $[\alpha]^{25}_{D}$ –75.1° (*c* 1.34, $CHCl_3$). All characterization data matches previously reported data.[3, 5, 7]



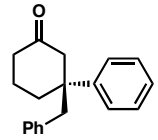
(*R*)-3-phenyl-3-ethylcyclohexanone (7)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 95:5) to afford a colorless oil (96% yield). $[\alpha]^{25}_{D}$ –74.5° (*c* 3.39, $CHCl_3$). All characterization data matches previously reported data.[3, 5, 7, 8]



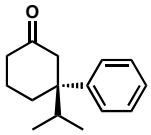
(*R*)-3-phenyl-3-*n*-butylcyclohexanone (8)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 95:5) to afford colorless oil (95% yield). $[\alpha]^{25}_{D}$ –56.7° (*c* 1.48, $CHCl_3$). All characterization data matches previously reported data.[8]



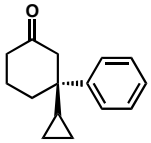
(*R*)-3-benzyl-3-phenylcyclohexanone (9)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 95:5) to afford a colorless oil (74% yield). $[\alpha]^{25}_{D}$ +01.0°(*c* 3.83, $CHCl_3$). All characterization data matches previously reported data.[9]



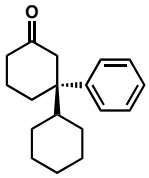
(*R*)-3-phenyl-3-*iso*-propylcyclohexanone (10)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 95:5) to afford a colorless oil (86% yield). $[\alpha]^{25}_{D}$ –79.4° (*c* 3.24, $CHCl_3$). All characterization data matches previously reported data.[9]



(*R*)-3-phenyl-3-methylcyclohexanone (11)

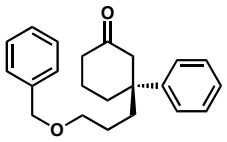
Synthesized according to the general procedure and purified by flash chromatography (CH_2Cl_2) to afford a colorless oil (68% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.28 (m, 4H), 7.21–7.17 (m, 1H), 2.90 (dt, *J* = 2.0, 14.5 Hz, 1H), 2.48 (d, *J* = 14.5 Hz, 1H), 2.31–2.19 (m, 3H), 1.94–1.86 (m, 2H), 1.60–1.51 (m, 1H), 0.99 (tt, *J* = 5.5, 8.5, 1H), 0.45–0.39 (m, 1H), 0.35–0.29 (m, 1H), 0.24–0.19 (m, 1H), 0.17–0.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.8, 143.2, 127.6, 126.5, 125.7, 50.0, 44.9, 40.3, 34.1, 23.1, 20.8, 1.1, 0.0; IR (Neat Film, NaCl) 3081, 3057, 3007, 2947, 2873, 1708, 1498, 1443, 1421, 1315, 1285, 1226, 1046, 1023 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calc'd for $C_{15}H_{19}O$ $[M+H]^+$: 215.1430, found 215.1425; $[\alpha]^{25}_{D}$ –83.1° (*c* 1.39, $CHCl_3$).



(*R*)-3-phenyl-3-cyclohexylcyclohexanone (12)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 95:5) to afford a colorless oil (86% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (ddd, *J* = 2.0, 7.0, 8.0 Hz, 2H), 7.23 (ddd, *J* = 1.0, 2.0, 8.0 Hz, 2H), 7.18 (tt, *J* = 1.0, 7.0 Hz, 1H), 2.97 (dd, *J* = 2.0, 15.0 Hz, 1H), 2.46 (d, *J* = 15.0 Hz, 1H),

2.26–2.17 (m, 3H), 2.07 (ddd, *J* = 3.5, 12.5, 13.5 Hz, 1H), 1.94–1.88 (m, 1H), 1.84–1.75 (m, 2H), 1.68–1.56 (m, 2H), 1.52–1.45 (m, 1H), 1.44–1.38 (m, 1H), 1.37–1.31 (m, 1H), 1.26–1.17 (m, 1H), 1.11–0.95 (m, 2H), 0.88–0.75 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0, 143.8, 128.1, 127.4, 125.9, 49.5, 49.0, 47.2, 41.0, 33.6, 27.5, 27.4, 26.9, 26.5, 21.4; IR (Neat Film, NaCl) 2928, 2853, 1713, 1495, 1443, 1315, 1285, 1228 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calc'd for $C_{18}H_{24}O$ $[M+H]^+$: 257.1900, found 257.1888; $[\alpha]^{25}_D$ –52.4° (*c* 3.87, $CHCl_3$).



(*S*)-3-(3-(benzyloxy)propyl)-3-phenylcyclohexanone (13)

Synthesized according to the general procedure and purified by flash chromatography (hexanes/EtOAc = 100:0 to 95:5) to afford a colorless oil (65% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.28 (m, 4H), 7.27–7.24 (m, 5H), 7.18 (tt, *J* = 1.5, 7.0 Hz, 1H), 4.37 (s, 2H), 3.30 (dt, *J* = 1.5, 6.5 Hz, 2H), 2.93 (d, *J* = 14.5 Hz, 1H), 2.43 (d, *J* = 14.5 Hz, 1H), 2.33–2.26 (m, 2H), 2.22–2.16 (m, 1H), 1.98 (ddd, *J* = 3.0, 10.0, 13.5 Hz, 1H), 1.86–1.77 (m, 2H), 1.68 (ddd, *J* = 4.5, 12.0 Hz, 1H), 1.61–1.53 (m, 1H), 1.43–1.32 (m, 1H), 1.23–1.14 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.2, 144.8, 138.4, 128.5, 128.3, 127.6, 127.5, 126.4, 126.2, 72.7, 70.4, 51.0, 45.9, 41.0, 39.7, 36.6, 23.9, 21.4; IR (Neat Film, NaCl) 3057, 3027, 2947, 2858, 1710, 1602, 1495, 1451, 1359, 1312, 1280, 1228, 1100, 1075, 1026 cm^{-1}; HRMS (MultiMode ESI/APCI) *m/z* calc'd for $C_{22}H_{26}O_2$ $[M+H]^+$: 323.2006, found 323.1993; $[\alpha]^{25}_D$ –42.9° (*c* 4.25, $CHCl_3$).

References

(1) (a) 3-ethylcyclohex-2-enone: Kehrli, S.; Alexakis, A.; Martin, D.; Rix, D.; Mauduit, M. *Chem.–Eur. J.* **2010**, *16*, 9890. (b) 3-isopropylcyclohex-2-enone: Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368. (c) 3-butylcyclohex-2-enone: Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797. (d) 3-cyclopropylcyclohex-2-enone: Piers, E.; Banville, J.; Lau, C. K.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 2965. (e) 3-benzylcyclohex-2-enone: Wang, X.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070. (f) [1,1'-bi(cyclohexan)]-1-en-3-one: Yeh, M. C.; Knochel, P.; Butler, W. M.; Berk, S. C. *Tetrahedron Lett.* **1988**, *29*, 6693. (g) 3-(3-(benzyloxy)propyl)cyclohex-2-enone: Kim, S.; Koh, J. S. *J. Chem. Soc., Chem. Commun.* **1992**, *18*, 1377. (h) 3-methylcyclohept-2-enone: Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368.

(2) (a) Brunner, H.; Obermann, U. *Chem. Ber.* **1989**, *122*, 499. (b) Malkov, A. V.; Stewart Liddon, A. J.; Ramirez-Lopez, P.; Bendova, L.; Haigh, D.; Kocovsky, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 1432.

(3) Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588.

(4) Shintani, R.; Takeda, M.; Nishimura, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3969.

(5) Hawner, C.; Muller, D.; Gremaud, L.; Fellouat, A.; Woodward, S.; Alexakis, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 7769.

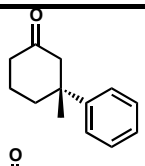
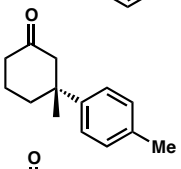
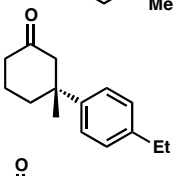
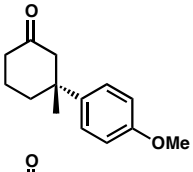
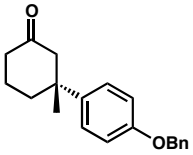
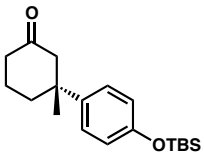
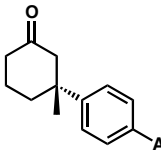
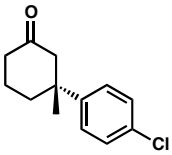
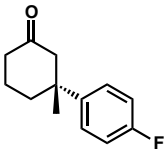
(6) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358.

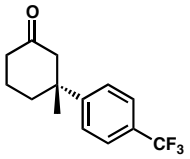
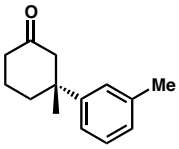
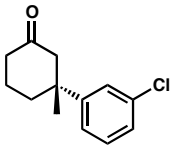
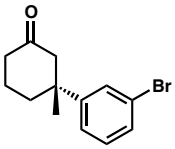
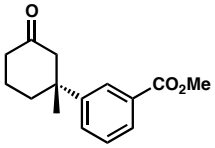
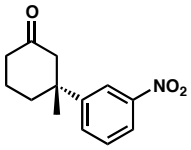
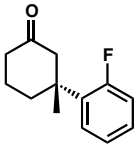
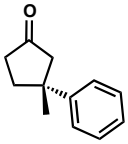
(**7**) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8211.

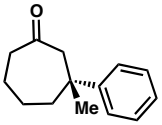
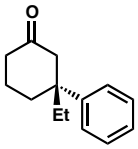
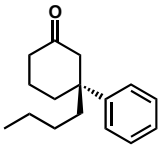
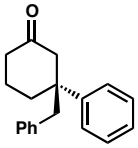
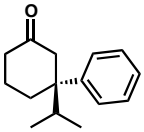
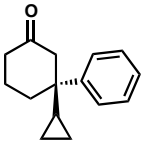
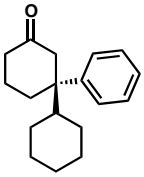
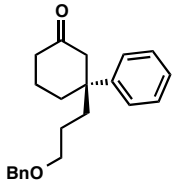
(**8**) Palais, L.; Alexakis, A. *Chem.–Eur. J.* **2009**, *15*, 10473.

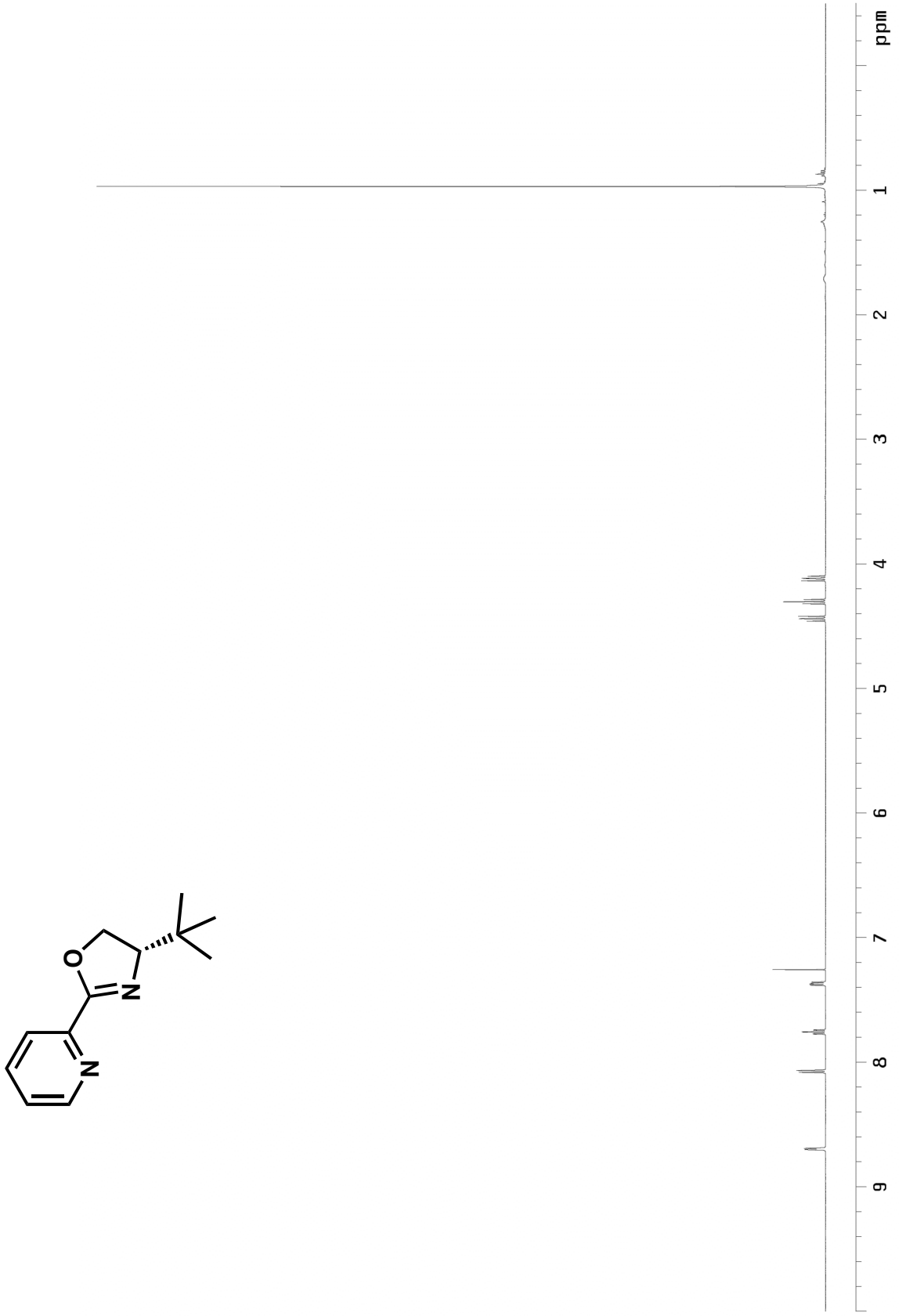
(9) Lin, S.; Lu, X. *Org. Lett.* **2010**, *12*, 2536.

Table S2. *Chiral Assays*

entry	product	HPLC conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% *ee*
1		Chiralcel OJ-H 1% IPA/Hexanes isocratic 1 mL/min	15.3	19.6	92
2		Chiralcel OJ-H 1% IPA/Hexanes isocratic 1 mL/min	15.2	17.1	87
3		Chiralcel OJ-H 0.5% IPA/Hexanes isocratic 1 mL/min	25.9	34.4	85
4		Chiralcel OJ-H 1% IPA/Hexanes isocratic 1 mL/min	29.5	37.1	69
5		Chiralpak AD-H 5% IPA/Hexanes isocratic 1 mL/min	37.9	35.3	74
6		Chiralcel OJ-H 0.5% IPA/Hexanes isocratic 1 mL/min	16.6	24.9	82
7		Chiralpak AD-H 5% IPA/Hexanes isocratic 1 mL/min	30.4	29.5	96
8		Chiralpak AD-H 1% IPA/Hexanes isocratic 1 mL/min	12.8	11.7	95
9		Chiralcel OJ-H 1% IPA/Hexanes isocratic 1 mL/min	13.9	16.9	92

entry	product	HPLC conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% *ee*
10		Chiralcel OJ-H 0.5% IPA/Hexanes isocratic 1 mL/min	35.0	41.1	96
11		Chiralcel OJ-H 1% IPA/Hexanes isocratic 1 mL/min	11.0	13.0	91
12		Chiralcel OJ-H 1% IPA/Hexanes isocratic 1 mL/min	17.2	20.4	96
13		Chiralcel OJ-H 1% IPA/Hexanes isocratic 1 mL/min	14.7	16.9	85
14		Chiralpak AD-H 5% IPA/Hexanes Isocratic 1mL/min	11.1	10.4	95
15		Chiralpak AD-H 1% IPA/Hexanes Isocratic 1mL/min	29.0	30.6	92
16		Chiralcel OJ-H 1% IPA/Hexanes isocratic 1 mL/min	9.3	10.9	77
17		Chiralpak AD-H 1% IPA/Hexanes Isocratic 1mL/min	12.6	10.2	91

entry	product	HPLC conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% *ee*
18		Chiralcel OJ-H 1% IPA/Hexanes isocratic 1 mL/min	14.5	19.8	93
19		Chiralcel OJ-H 1% IPA/Hexanes isocratic 1 mL/min	15.5	18.0	92
20		Chiralcel OJ-H 1% IPA/Hexanes isocratic 1 mL/min	8.2	9.2	91
21		Chiralpak AD-H 5% IPA/Hexanes isocratic 1 mL/min	7.3	9.4	91
22		Chiralcel OJ-H 1% IPA/Hexanes isocratic 1 mL/min	13.1	14.7	79
23		Chiralcel OJ-H 1% IPA/Hexanes isocratic 1 mL/min	18.7	20.6	88
24		Chiralpak AD-H 1% IPA/Hexanes isocratic 1 mL/min	8.9	8.2	85
25		Chiralpak AD-H 1% IPA/Hexanes isocratic 1 mL/min	28.3	26.8	91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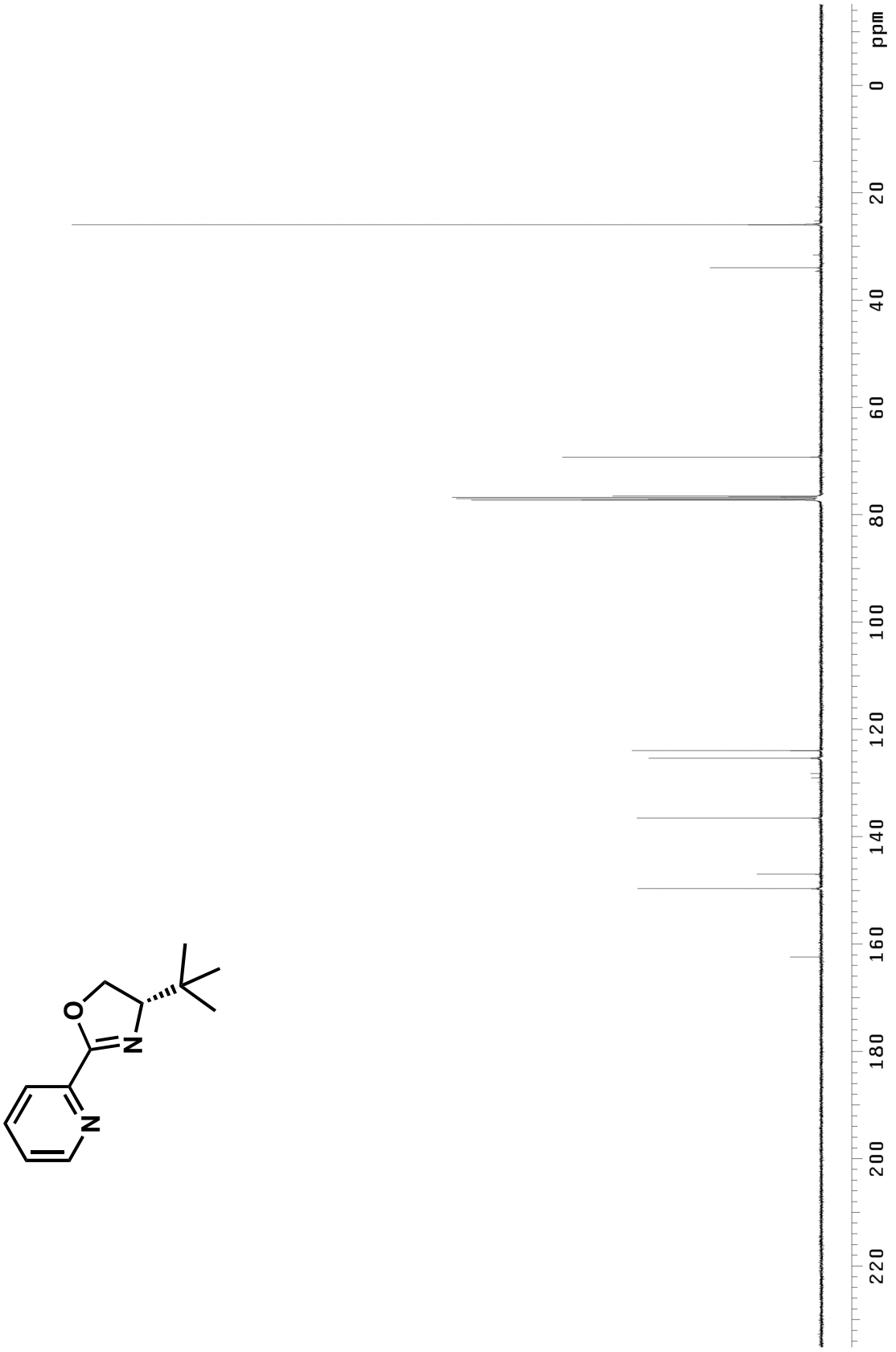
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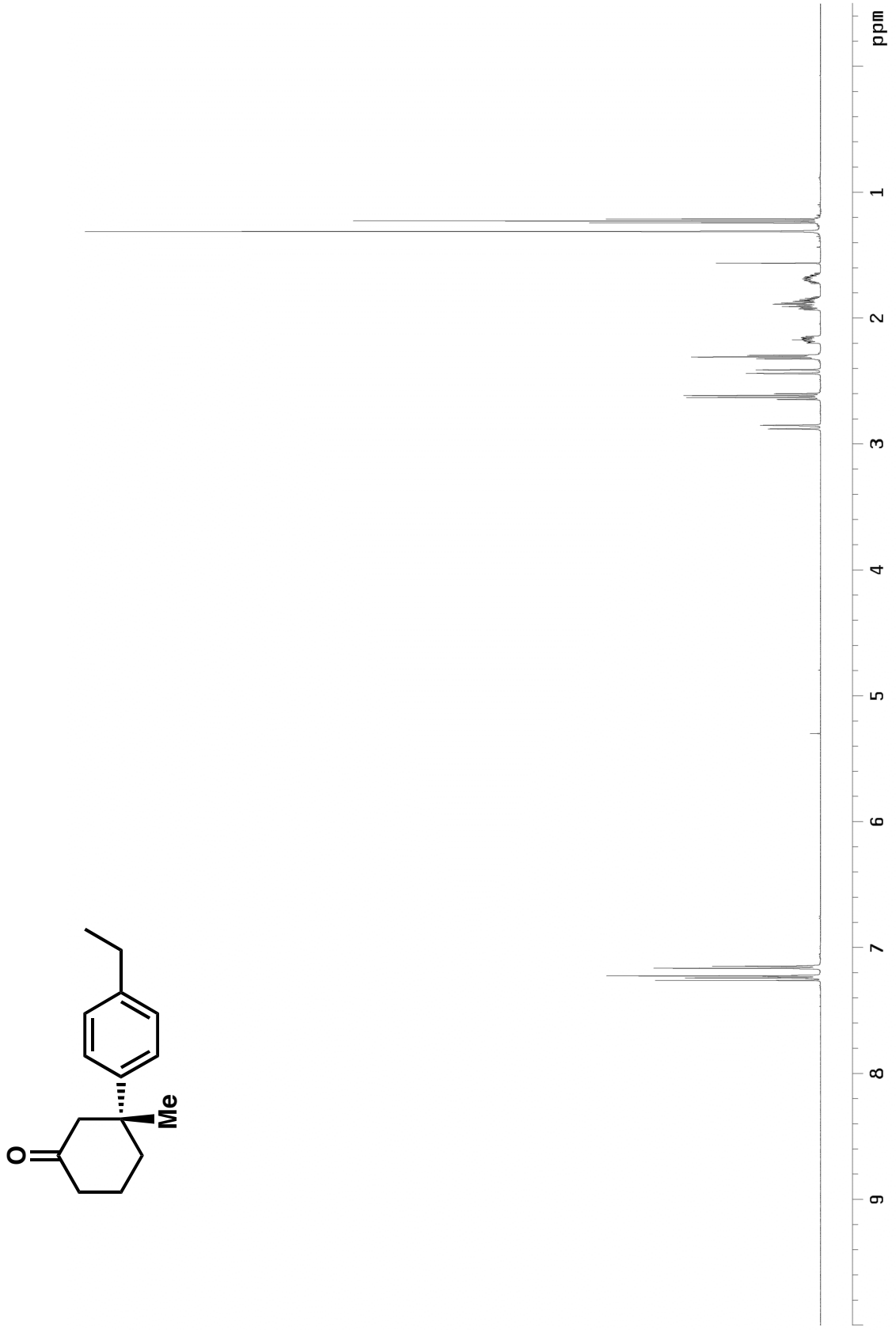
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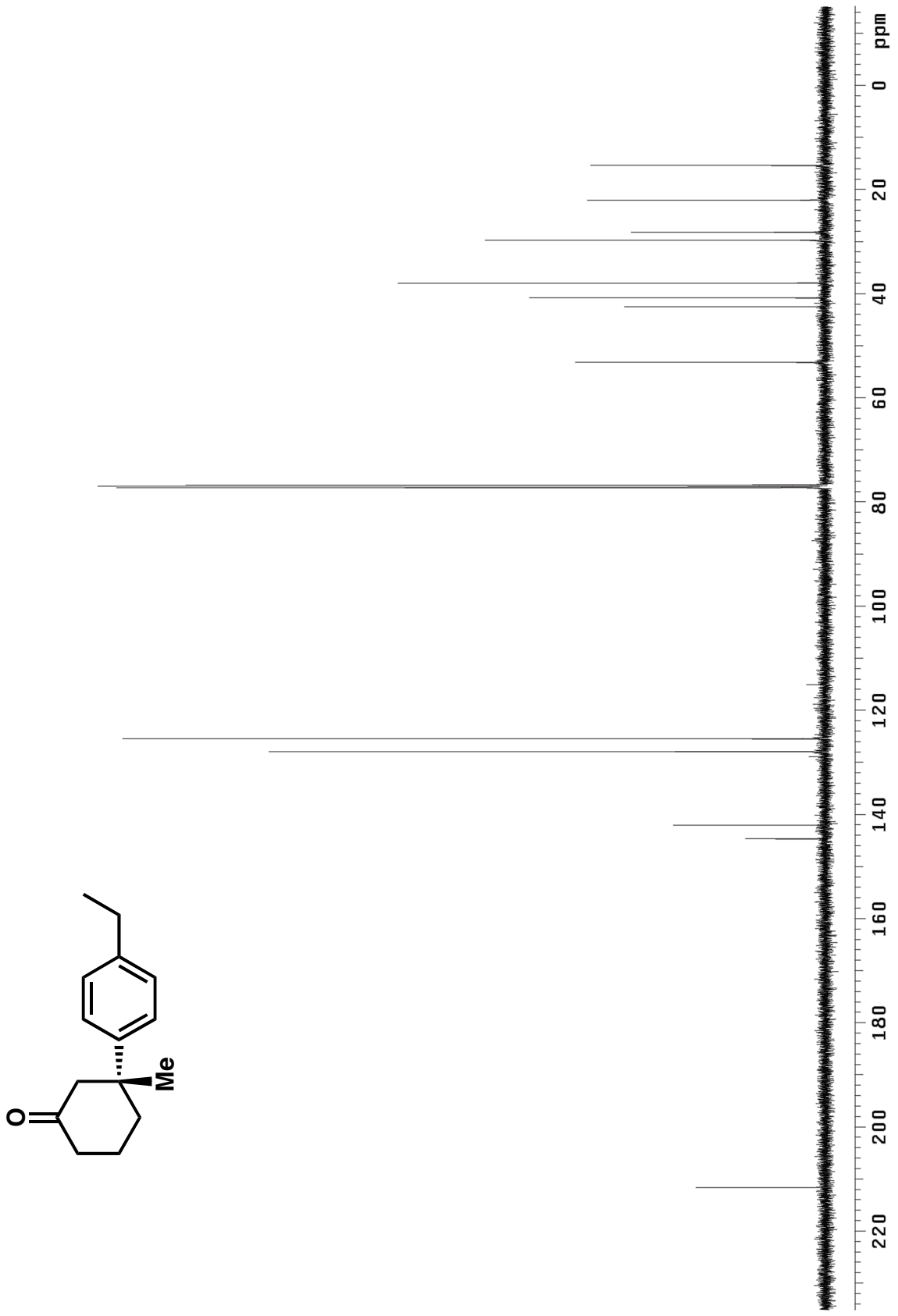
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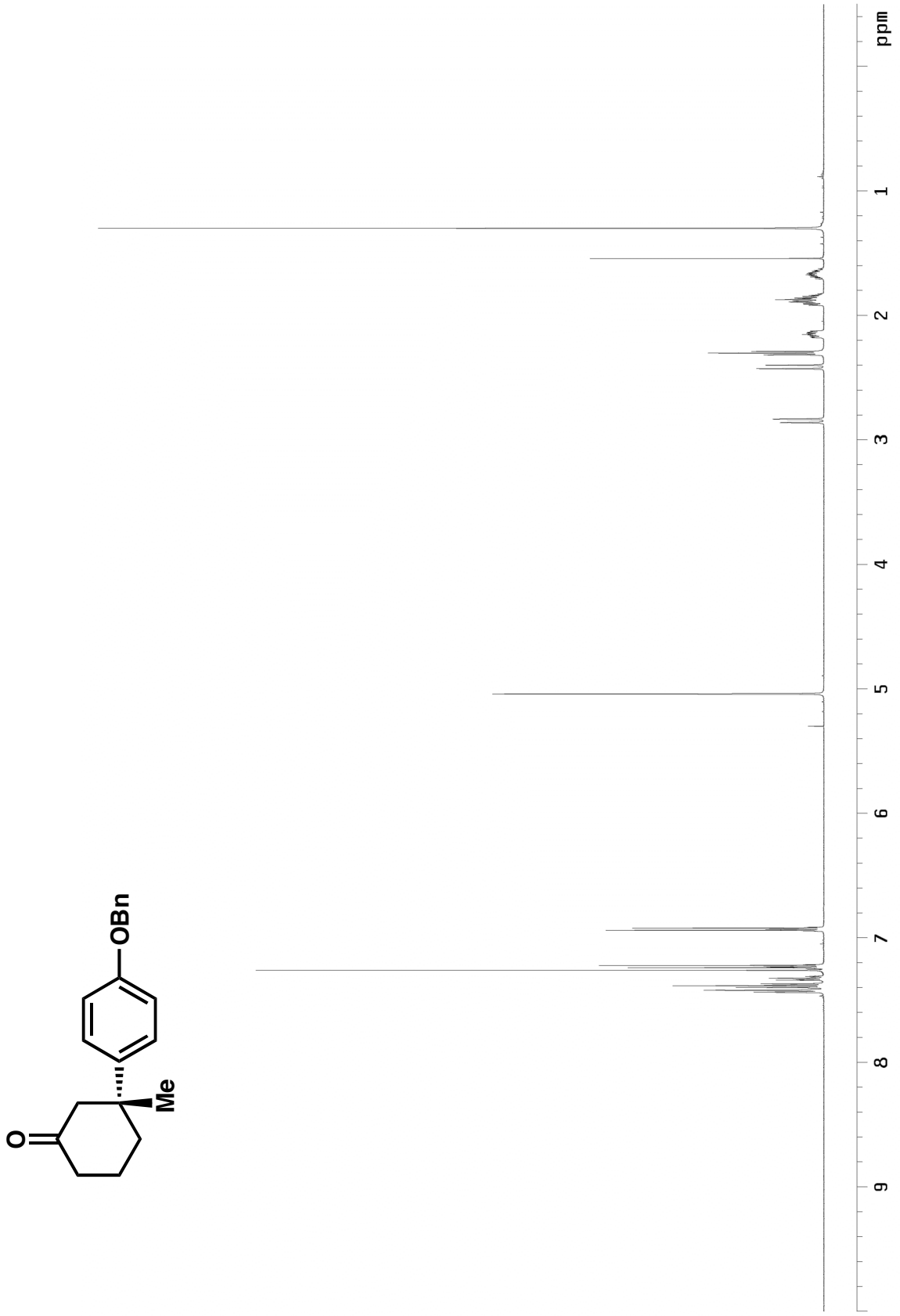
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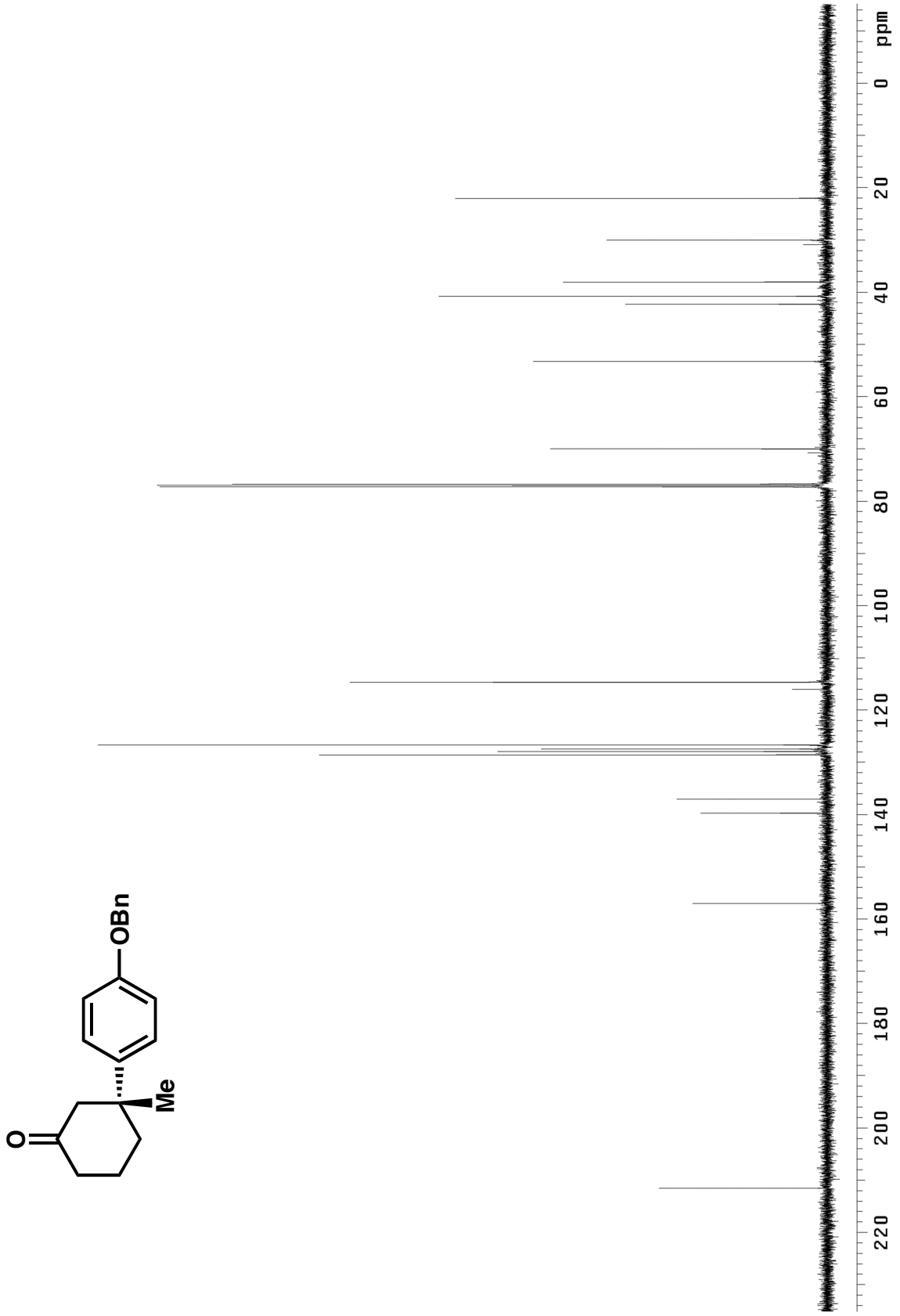
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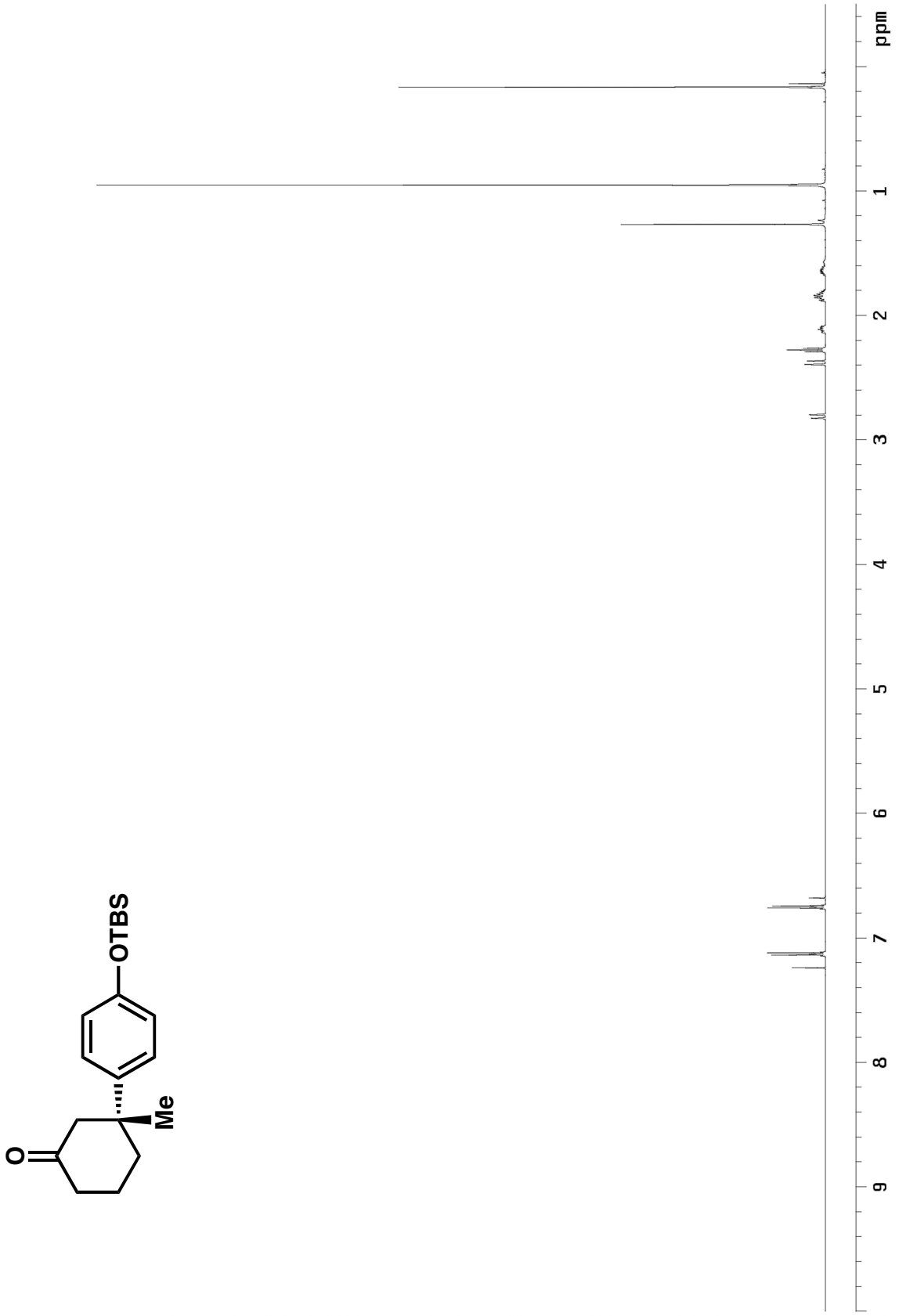
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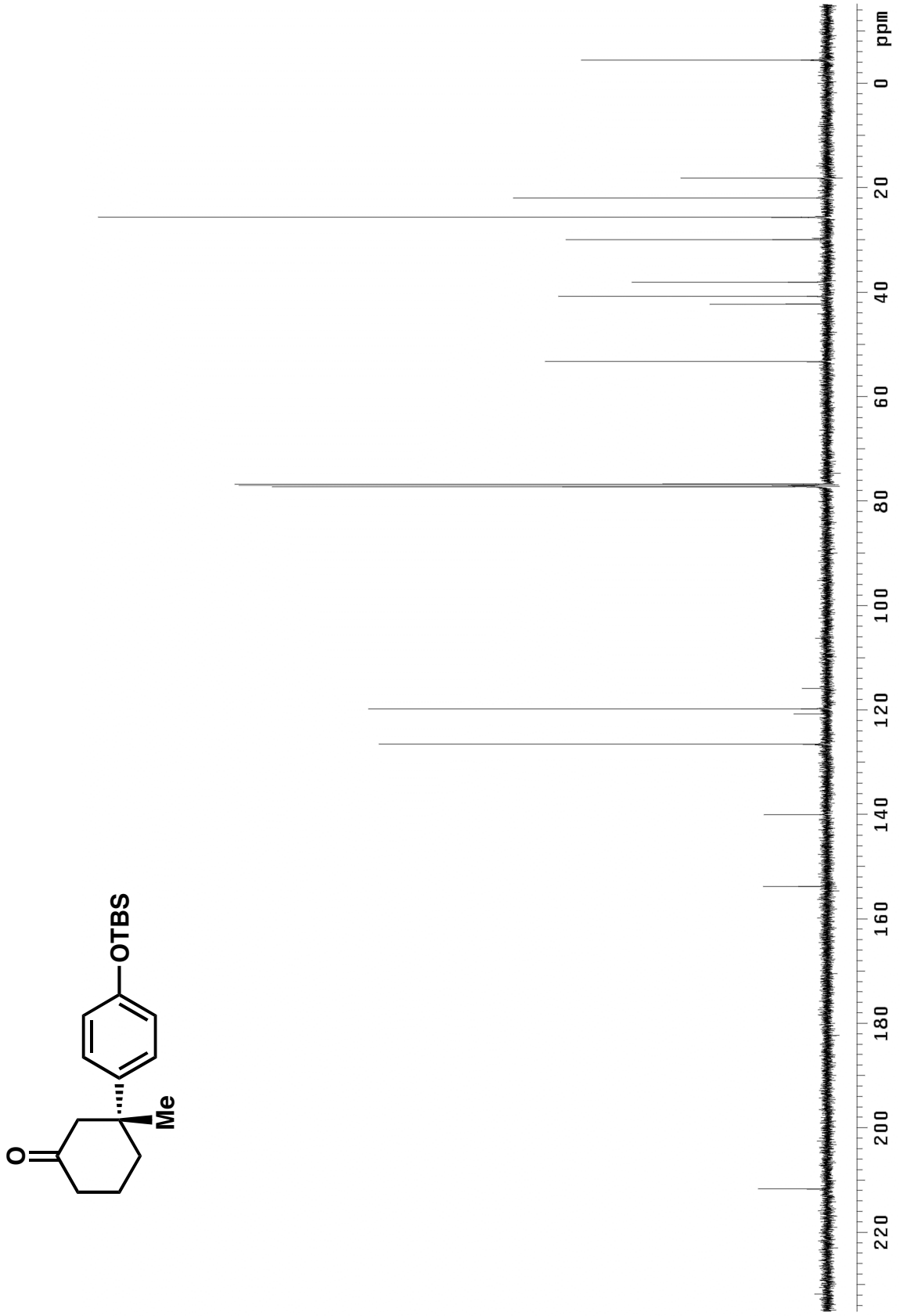
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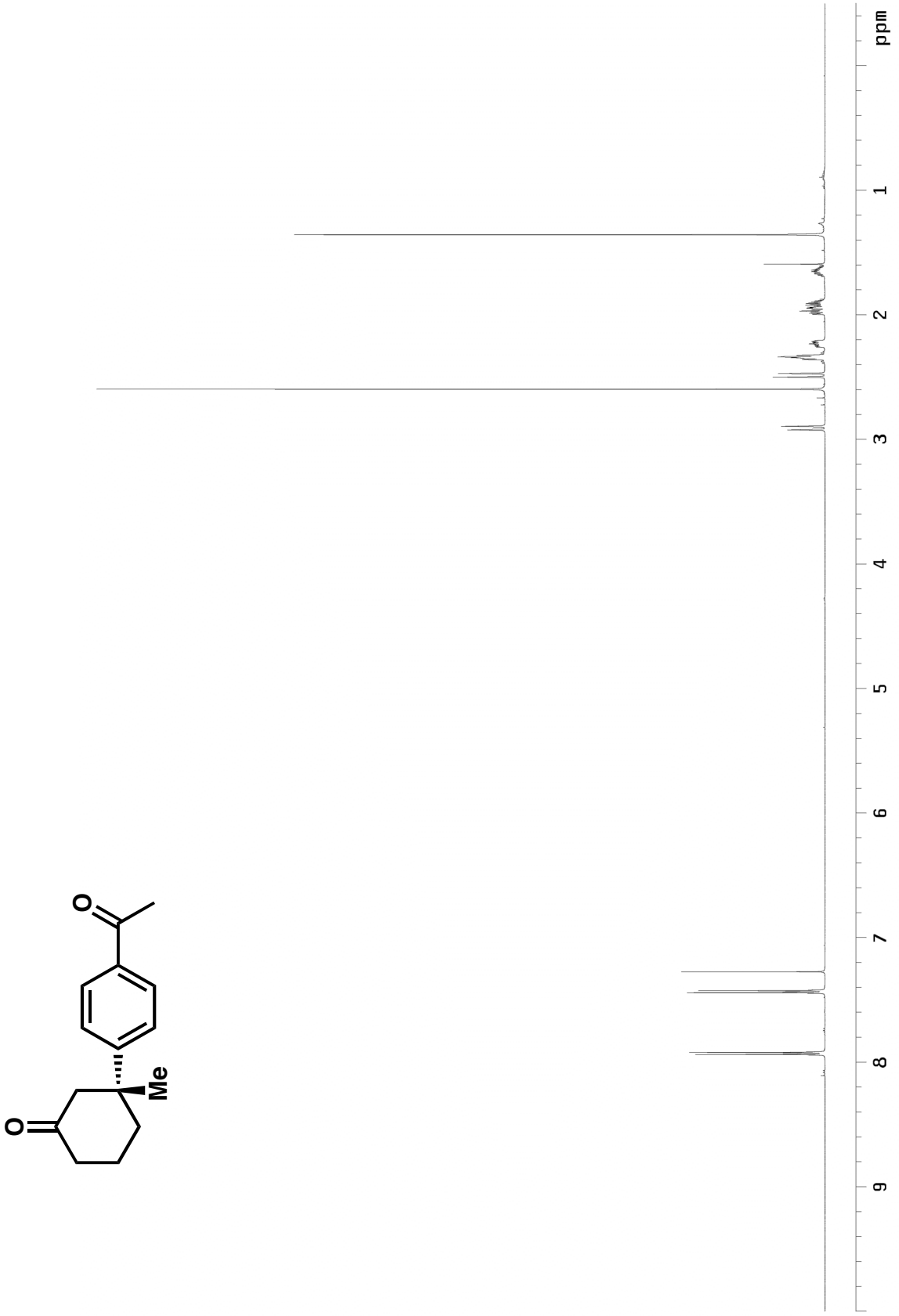
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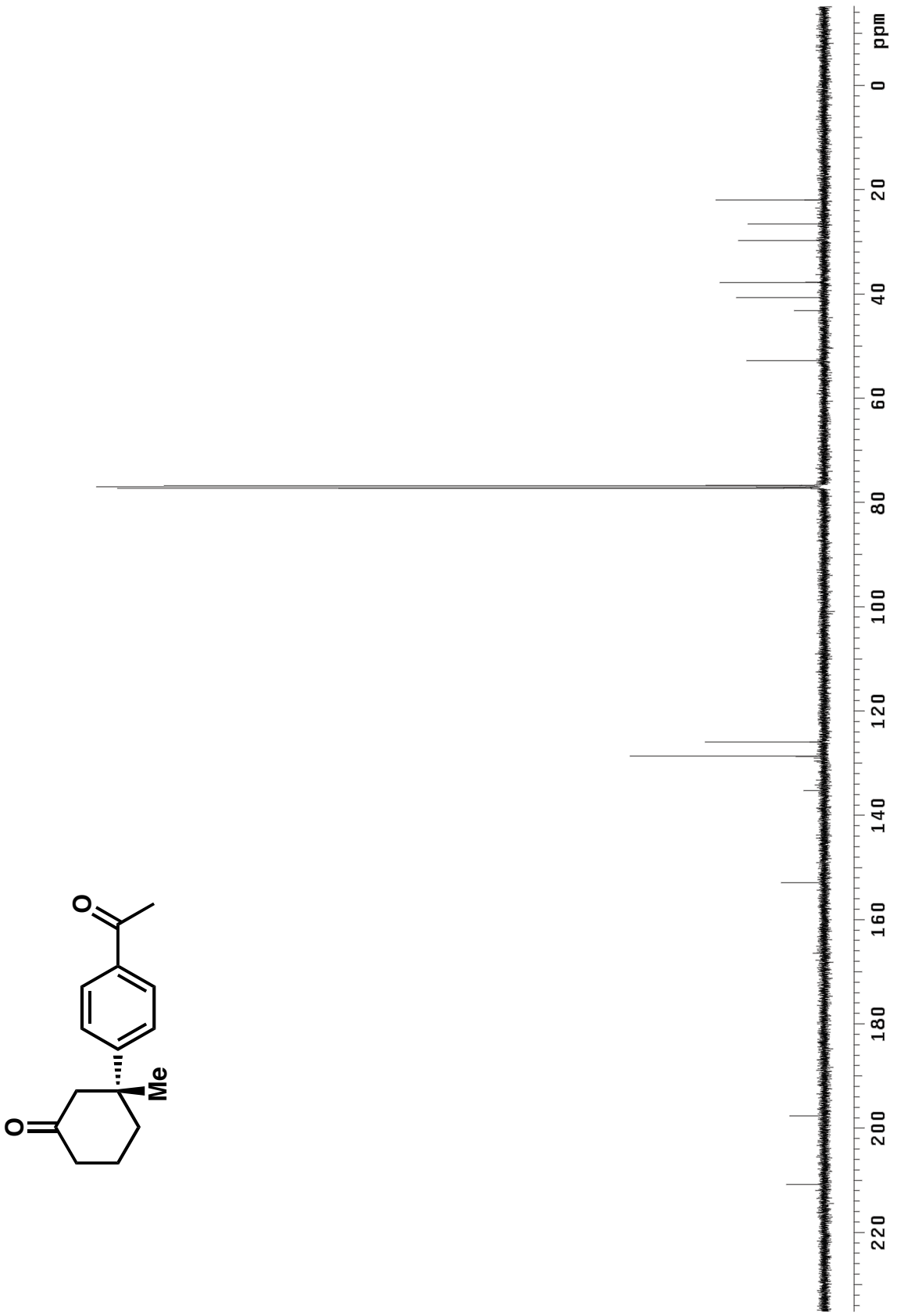
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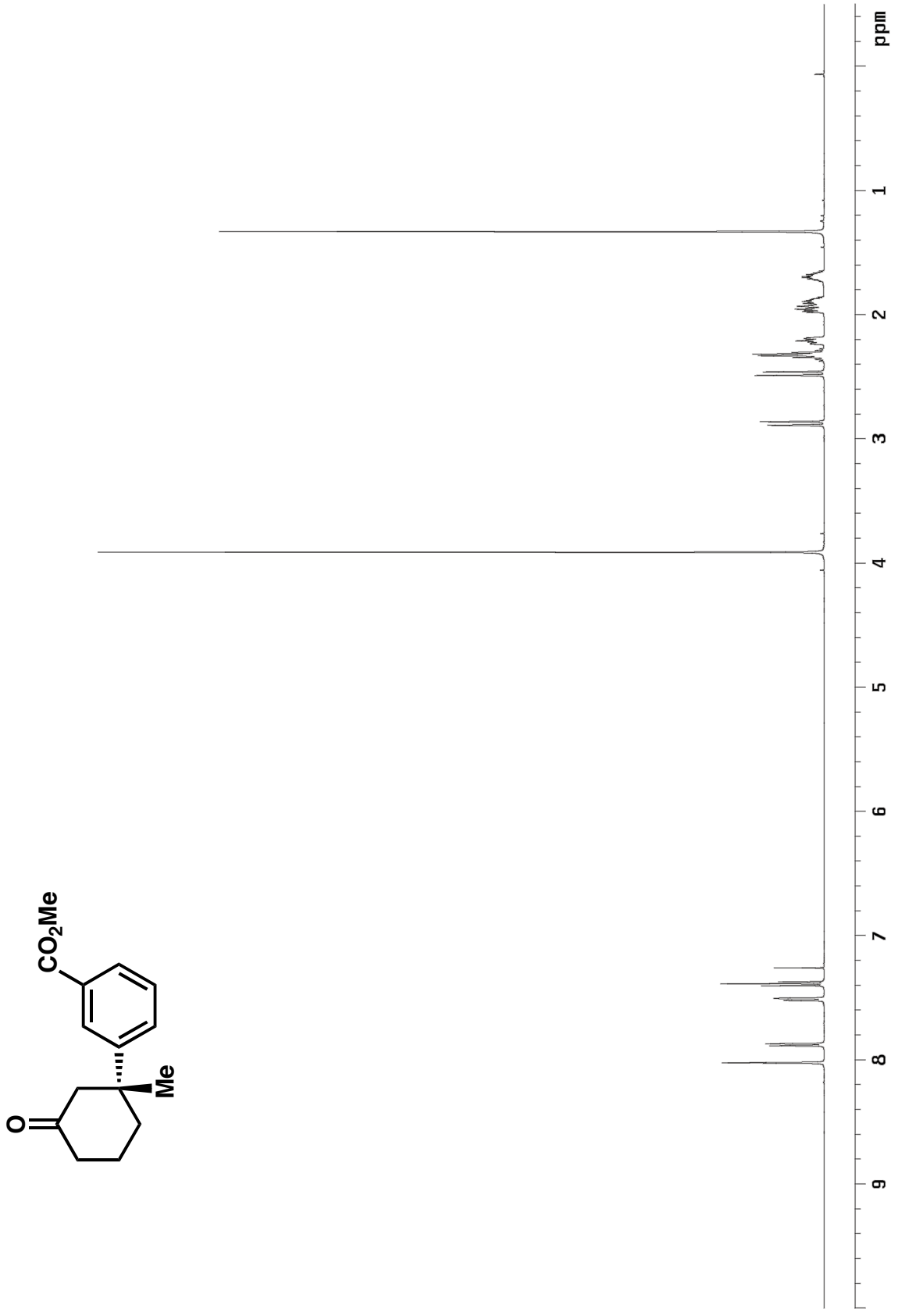
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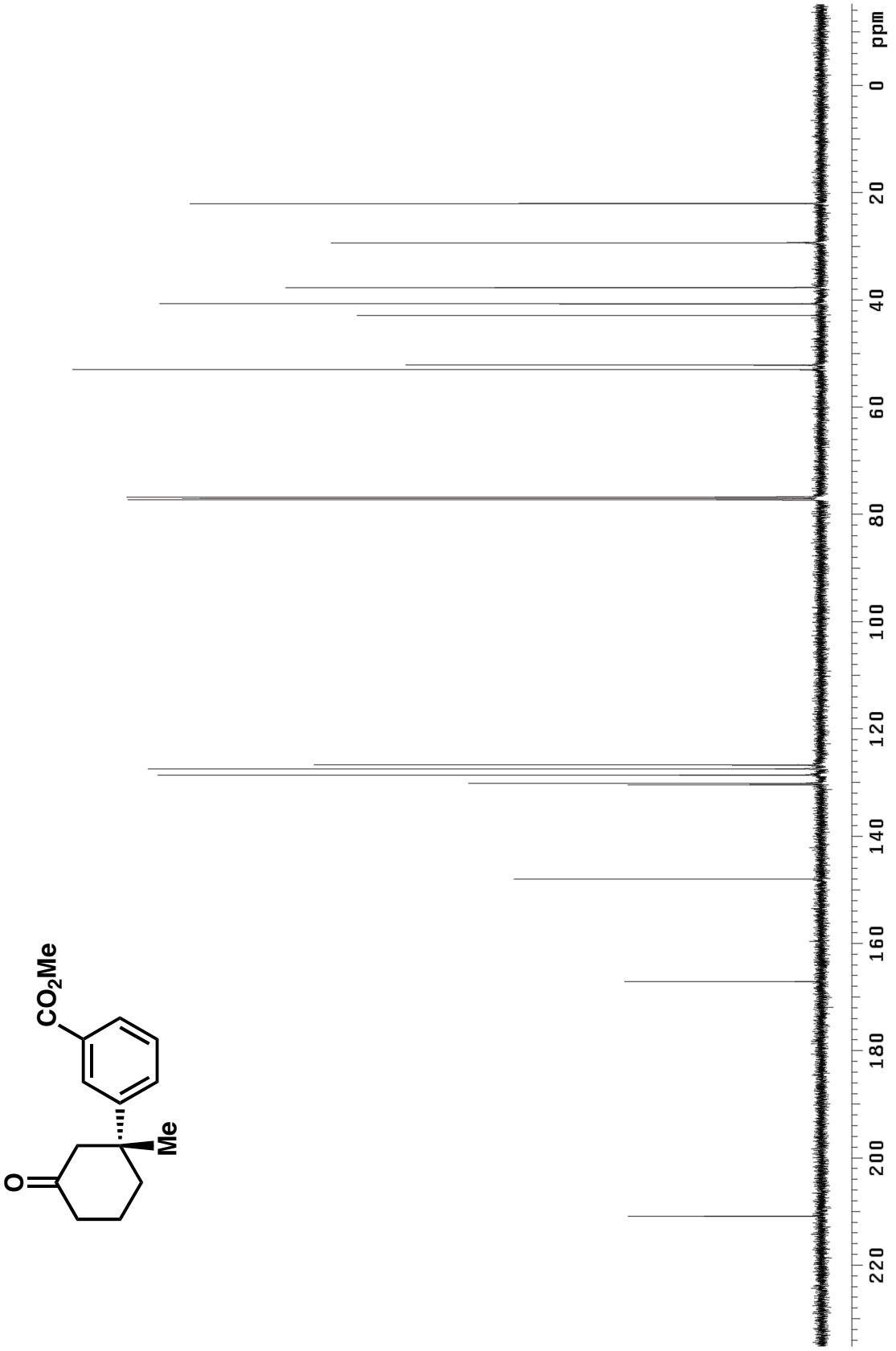
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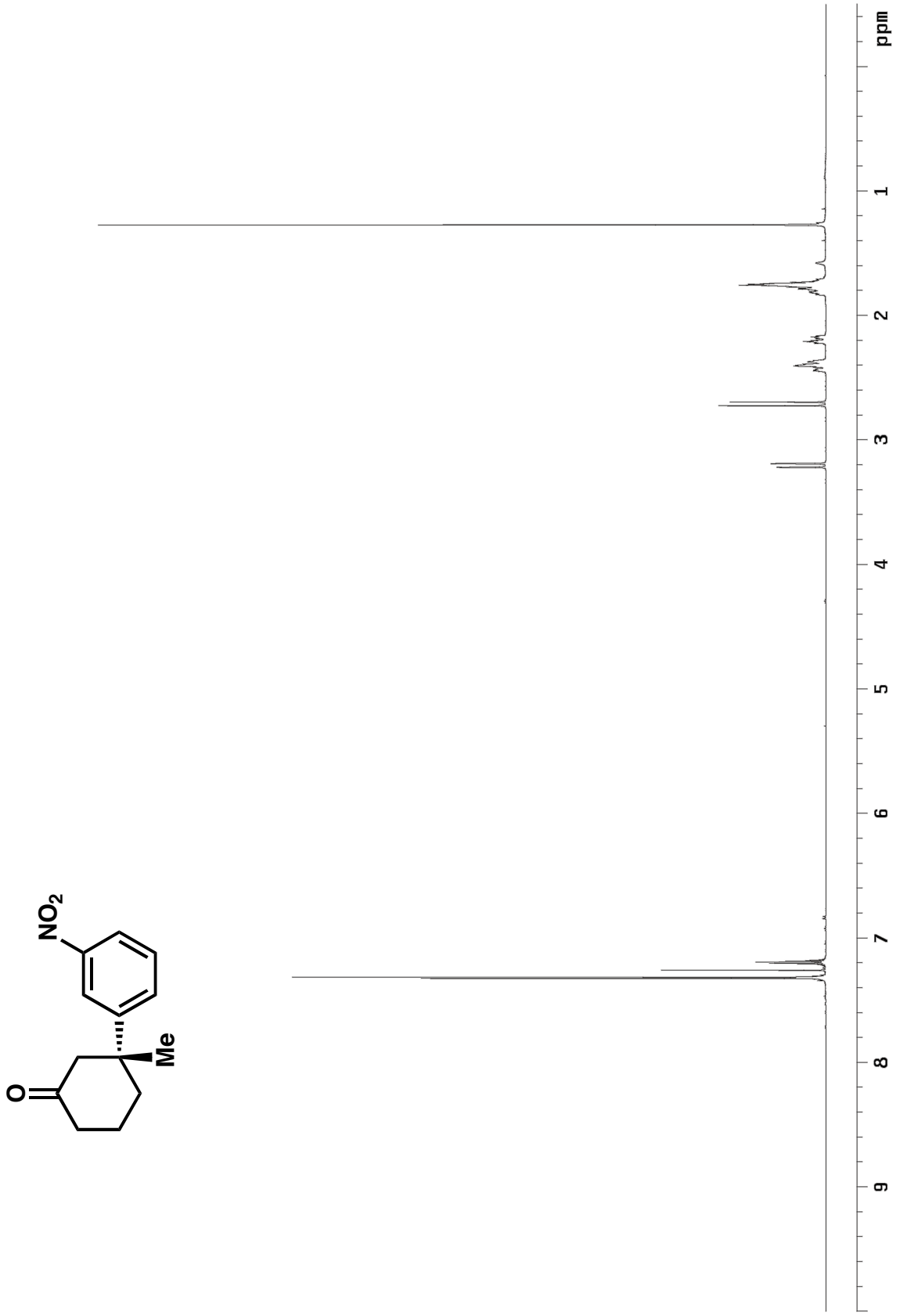
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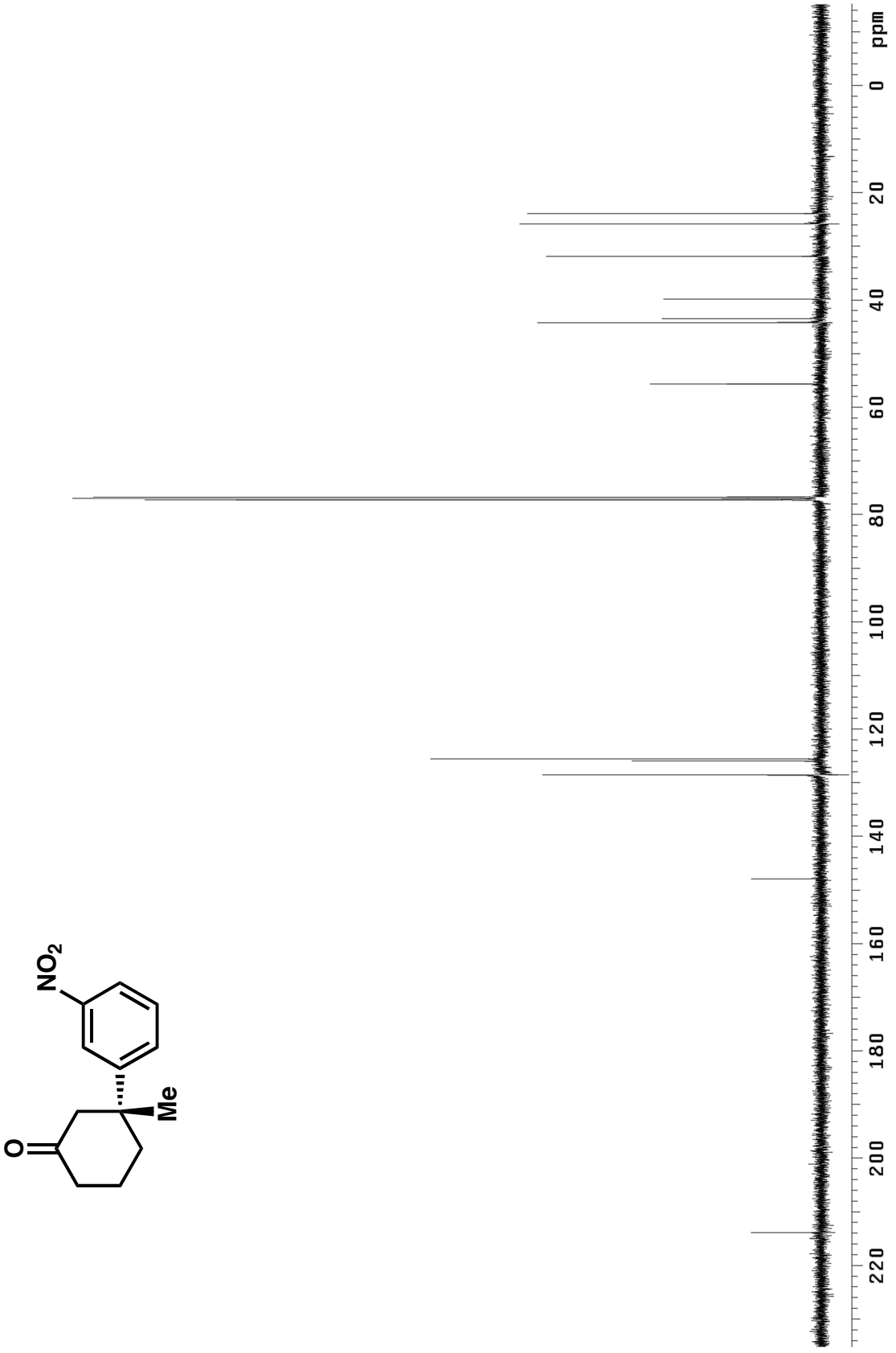
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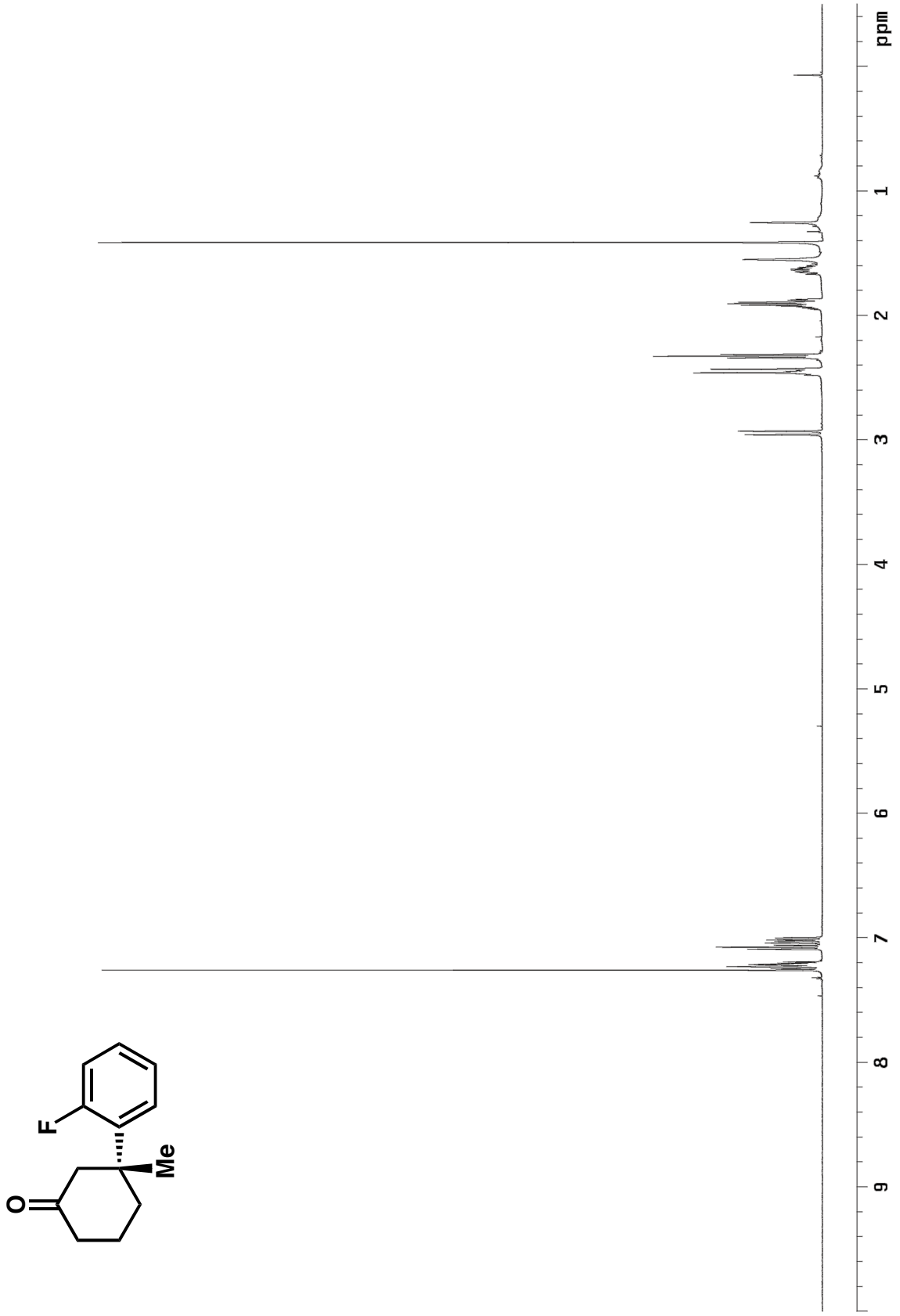
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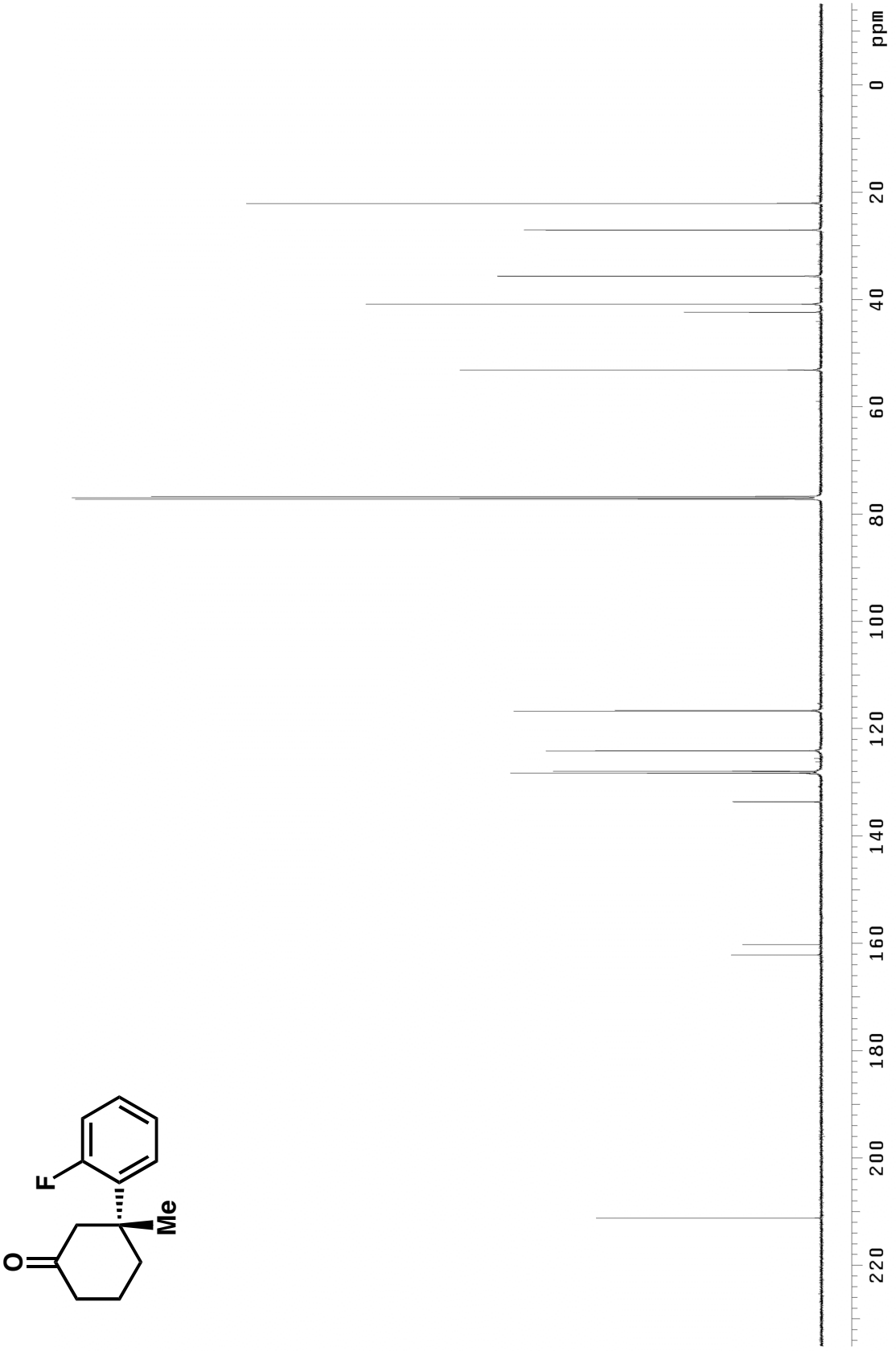
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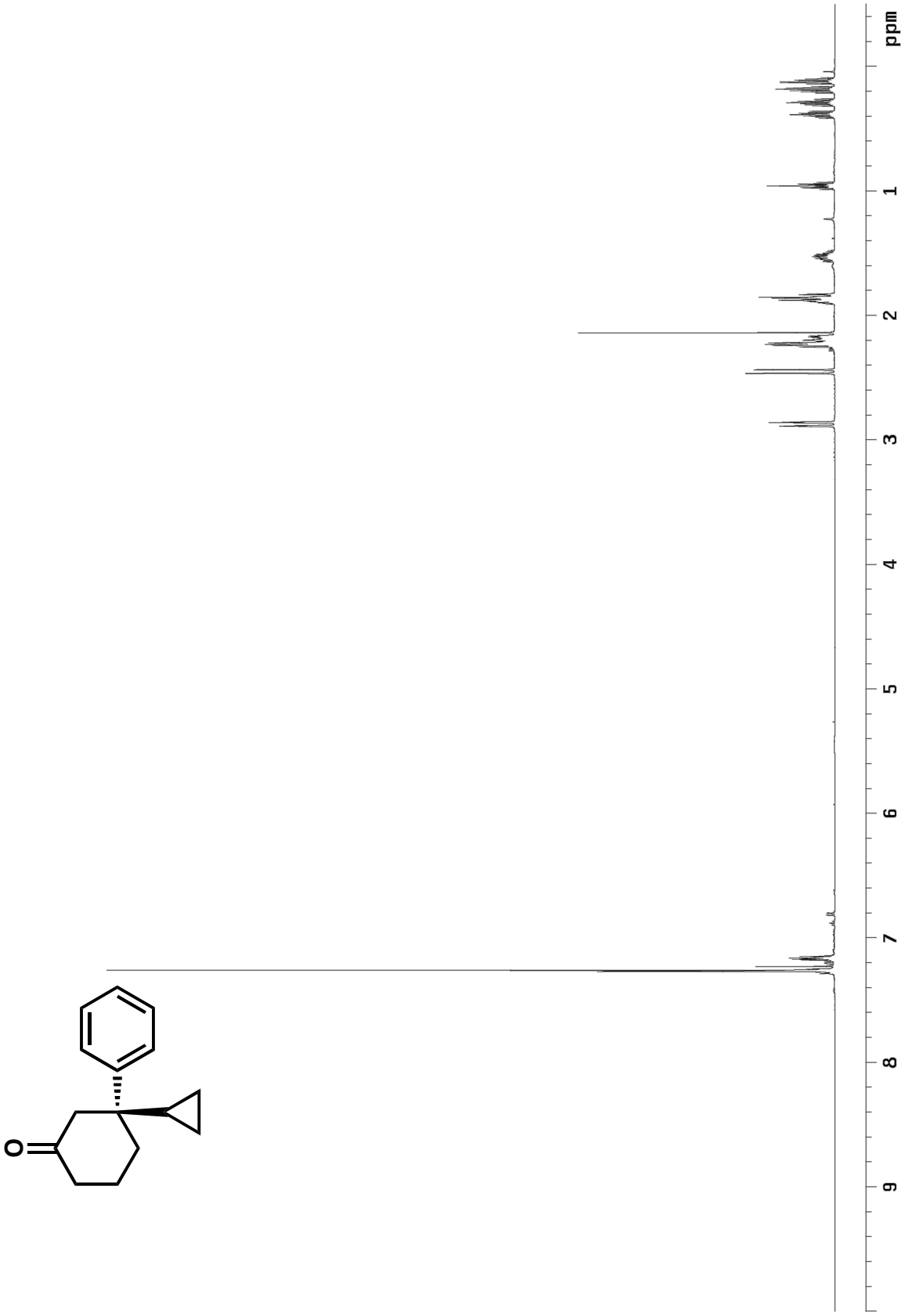
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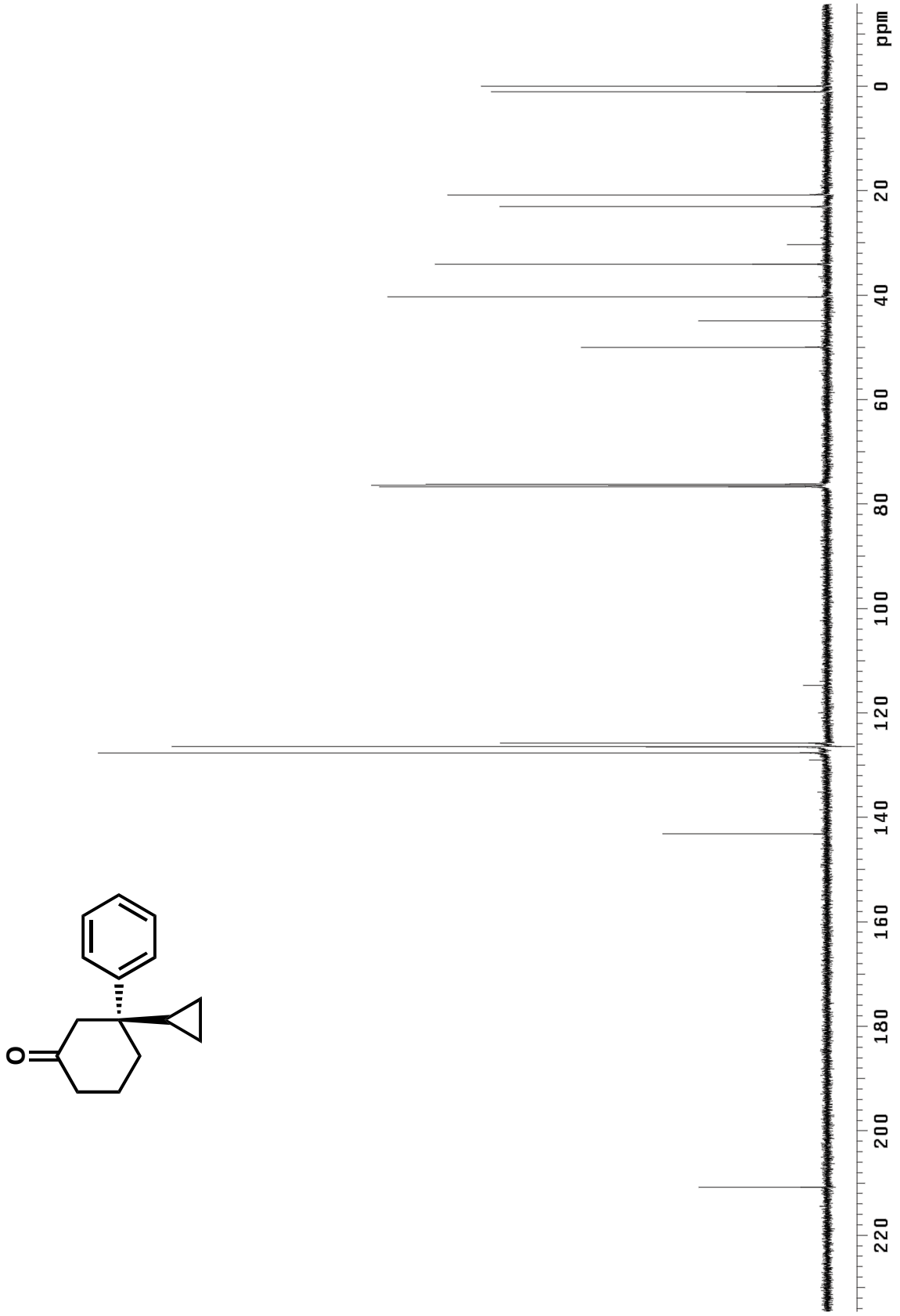
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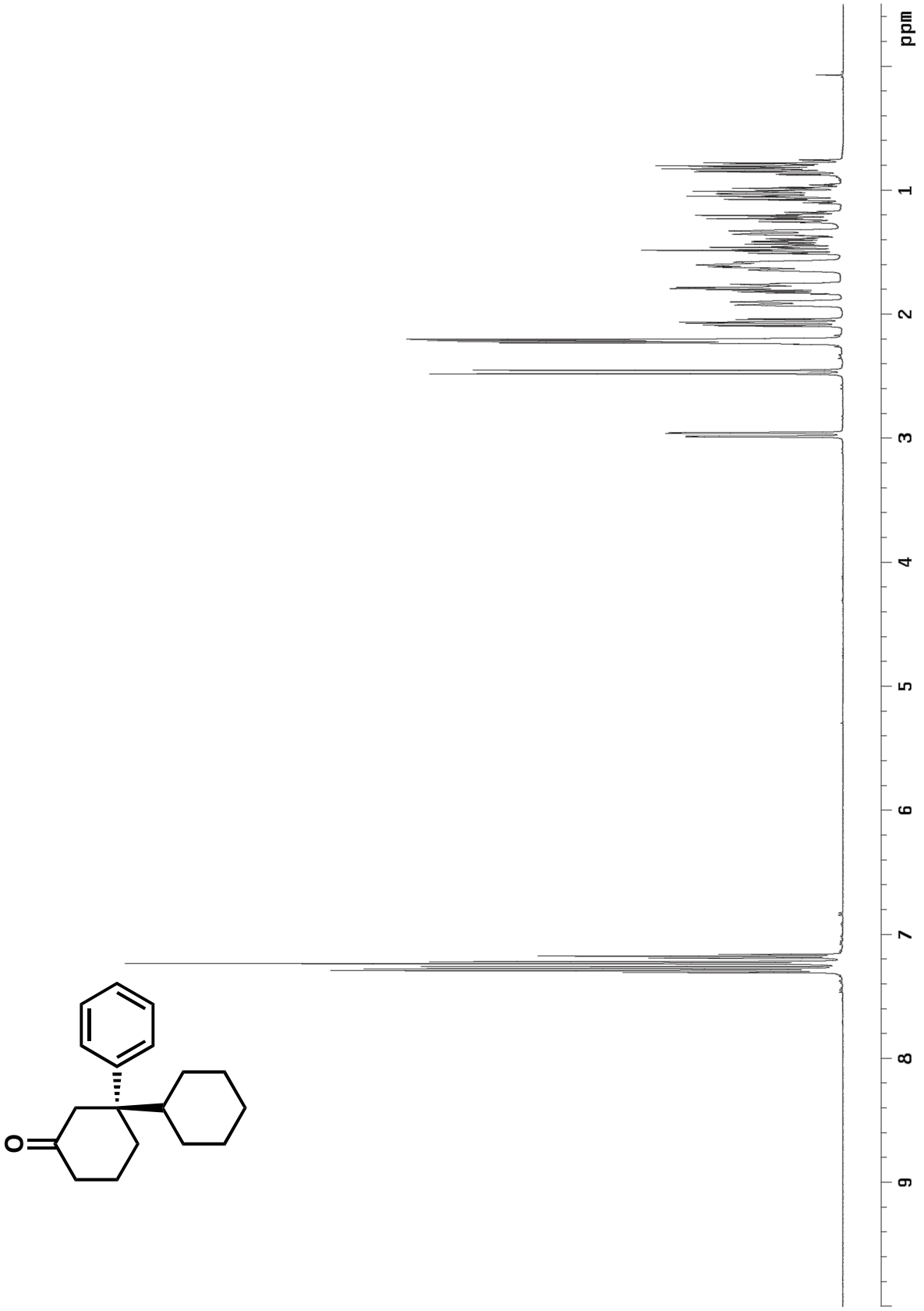
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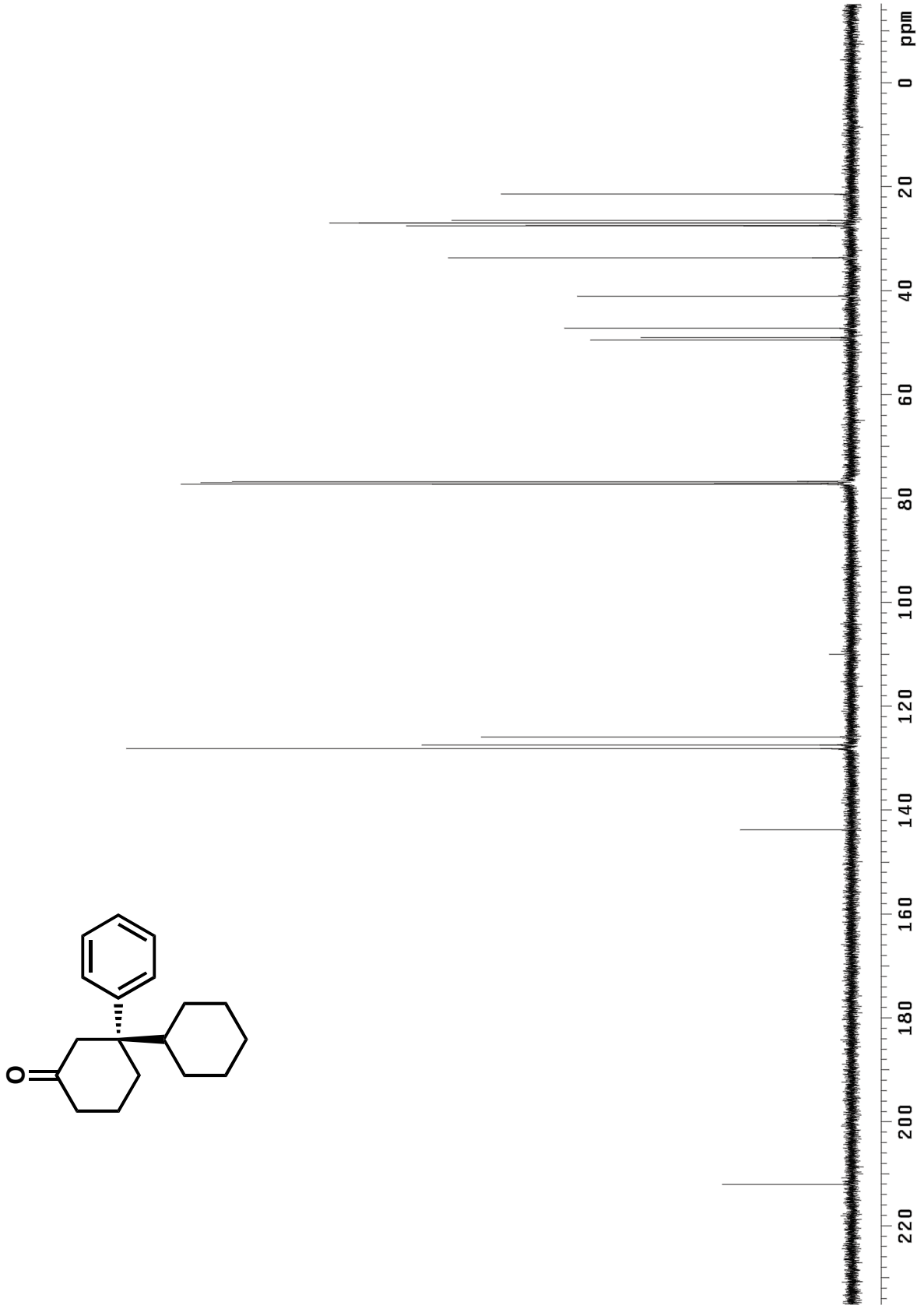
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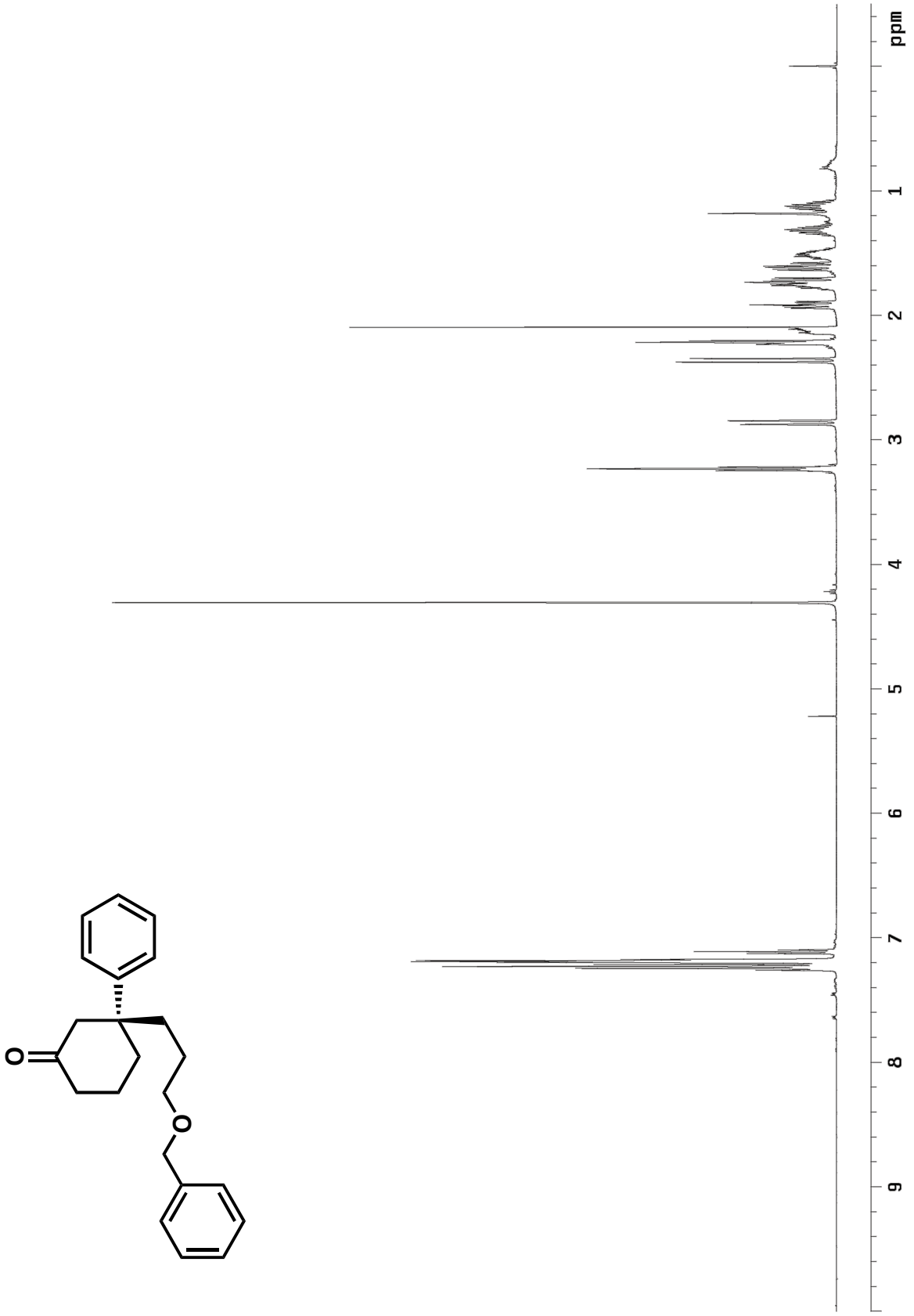
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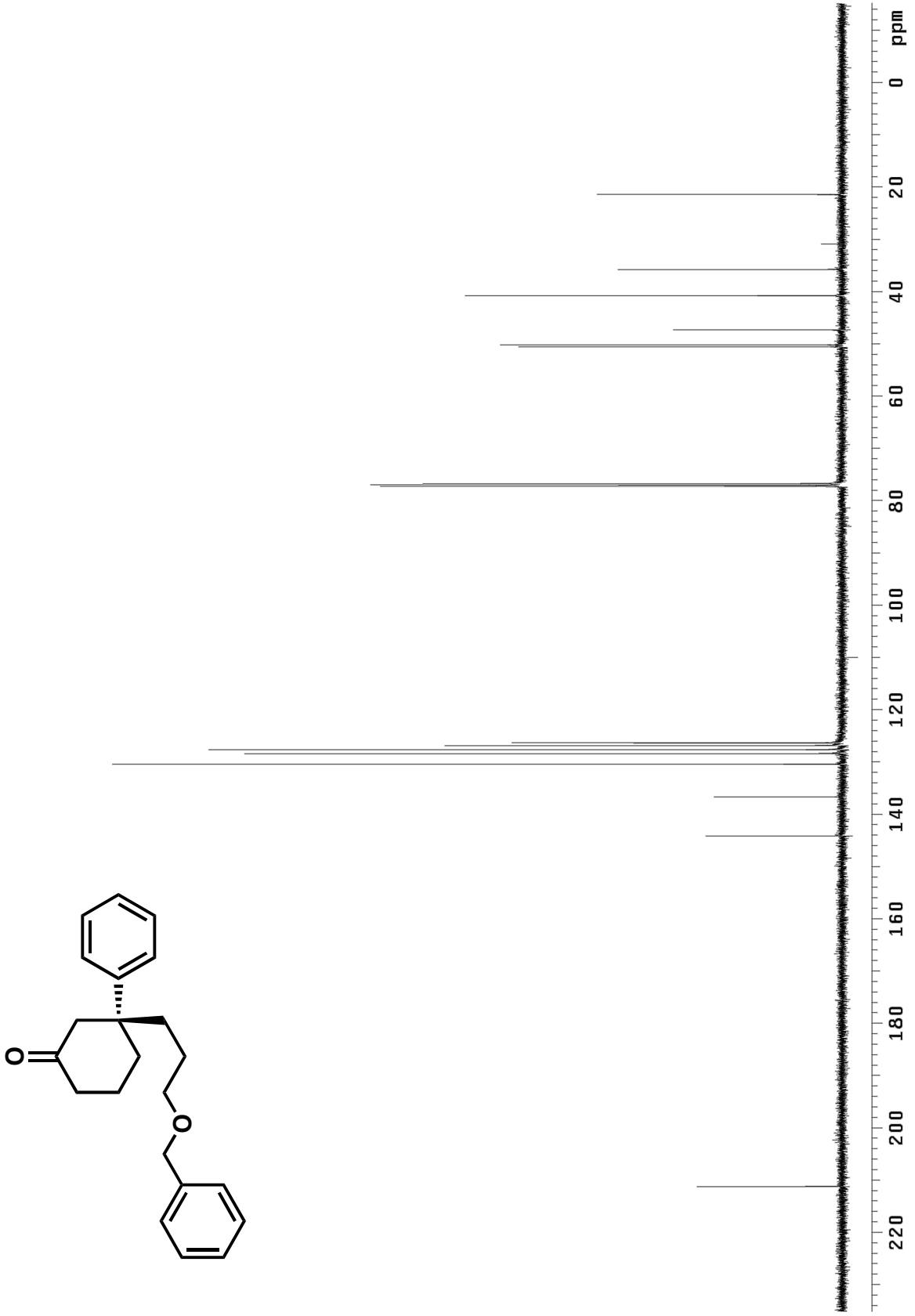
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