Organocatalytic Transfer Hydrogenation of Cyclic Enones

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Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] Non-aqueous reagents were transferred under nitrogen via syringe or cannula and purified according to the method of Grubbs.[2] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel and Iatrobeads® according to the method of Still.[3] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Chromatograms were visualized by fluorescence quenching or by staining using either potassium permanganate or *p*-anisaldehyde stain.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 Spectrometer, and are internally referenced to residual solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the Caltech Mass Spectrometry facility by electron ionization, chemical ionization, or fast atom/ion bombardment techniques. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex β-DM (30 m × 0.25 mm), a Bodman Chiraldex Γ-TA (30 m × 0.25 mm) or a Hydrodex-B-TBDAc (50

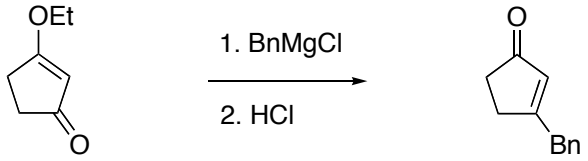
[1] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pergamon Press, Oxford, 1988.
[2] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
[3] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

m × 0.25 mm) column as noted. Optical rotations were measured on a Jasco P-1010 polarimeter, and $[\alpha]_D$ values are reported in 10^{-1} dg cm^2 g^{-1}; concentration (c) is in g/100 ml.

Preparation of the starting materials

These α,β-unsaturated cyclic enones are commercially available from Aldrich: 3-methyl-2-cyclopenten-1-one and isophorone (3,5,5-trimethylcyclohex-2-enone). The following α,β-unsaturated cyclic enones have already been described in the literature: 3-hexylcyclopent-2-enone, 3-cyclohexylcyclopent-2-enone,[4] 3-*tert*-butylcyclopent-2-enone,[5] 3-phenylcyclopent-2-enone,[6] 3-benzylcyclopent-2-enone,[7] 3-(benzyloxymethyl)cyclopent-2-enone,[8] methyl 3-oxocyclopent-1-enecarboxylate[16], 3-acetylcyclopent-2-enone,[9] 3-butylcyclohex-2-enone[10], 3-cyclohexylcyclohex-2-one[11]

General procedure for the preparation of starting materials:



3-benzylcyclopent-2-enone: To a –78 °C solution of benzyl magnesium chloride (14.3 mL, 28.5 mmol, 1.2 eq., 2 M solution in THF) in ether (50 mL) was slowly added 3-ethoxycyclopent-2-enone (2.84 mL, 23.8 mmol, 1 eq.). The reaction mixture was warmed up to –30 °C over 1 hour followed by addition of a 1 M solution of HCl until the pH was adjusted to 1 as indicated by litmus paper. The solution was warmed up to room temperature and the layers were separated. The aqueous phase was extracted with 40 mL of Et_2O (3×) and the combined organic layers were washed with 100 mL of brine (1×), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residual oil was purified by flash chromatography (25% EtOAc/hexanes) to afford the title compound as a colorless oil (3.1 g, 76% yield).

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[4] Collins, S.; Hong, Y.; Mataoka, M.; Nguyen, T. *J. Org. Chem.* **1990**, *55*, 3395.
[5] Ponaras, A. A.; Zaim, O.; Pazo, Y.; Ohannesian, L. *J. Org. Chem.* **1988**, *53*, 1110. and Garbisch, E. W., Jr.; Sprecher, R. F. *J. Am. Chem. Soc.* **1969**, *91*, 6785.
[6] Jurkauskas, V.; Sadigni, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417.
[7] Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797.
[8] Dauben, W. G.; Warshawsky, A. M. *J. Org. Chem.* **1990**, *55*, 3075.
[9] Yu, J.-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232. And Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622.
[10] Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1993**, *115*, 3854.

(*Z*)-1-butylcyclohept-2-enol: To a clear solution of 2-cyclohepten-1-one (5 g, 45.5 mmol) in ether (50 mL), cooled to 0 °C, was added *n*-BuLi (2.0 M in hexanes, 25 mL, 50.0 mmol) dropwise to produce an opaque yellow solution. The reaction stirred for 2 h at 0 °C and then warmed to room temperature. After 1h, the reaction was complete as determined by TLC, and quenched in 50 mL NH_4Cl. The organic layer was separated and the aqueous layer was extracted with 50 mL of Et_2O (3×). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (10% Et_2O/pentane) to afford the title compound as a light yellow oil (2 g, 26% yield). IR (film) 3377, 3015, 2930, 2860, 1456, 1378, 1335, 1223, 1121, 1103, 1043, 997 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (dt, 1H, J = 11.9, 5.6 Hz, CCH=C**H**), 5.59 (d, 1H, J = 11.9 Hz, CC**H**=CH), 2.17 – 2.09 (m, 2H), 1.84 – 1.45 (m, 9H), 1.38 – 1.27 (m, 4H), 0.93 – 0.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 130.0, 76.1, 41.1, 38.5, 27.6, 27.5, 25.6, 24.1, 23.2, 14.1; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_{11}H_{20}O$) requires *m/z* 168.1514, found *m/z* 168.1516.

(*Z*)-3-butylcyclohept-2-enone: To a solution of (*Z*)-1-butylcyclohept-2-enol (2 g, 11.9 mmol) dissolved in dichloromethane (60 mL) was added pyridine chlorochromate on basic alumina (20 wt.%, 25.7 g, 23.8 mmol). The resulting reddish solution was stirred at room temperature for 2 h until determined to be complete by TLC. The mixture was diluted in 100 mL Et_2O and stirred for 1 h after which it was poured over filter paper that was subsequently washed with the Et_2O. The filtrate was partially concentrated (30 mL) and passed through a Florisil column with Et_2O (100 mL). The resulting colorless solution was concentrated and purified by flash chromatography (5% Et_2O/Pentane) to provide a colorless oil (920 mg, 47% yield). IR (film) 2933, 2864, 1662, 1458, 1421, 1375, 1344, 1322, 1267, 1201, 1124, 1103, 1048, 937, 875, 855 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (s, 1H, COC**H**), 2.58 – 2.53 (m, 2H, COC$\mathbf{H_2}$), 2.41 – 2.38 (m, 2H, HC=CC$\mathbf{H_2}$), 2.18 (t, 2H, J = 6.91 Hz, HC=CC$\mathbf{H_2}(CH_2)_2CH_3$), 1.80 – 1.74 (m, 2H, $COCH_2C\mathbf{H_2}$), 1.50 – 1.40 (m, 2H, $HC{=}CCH_2C\mathbf{H_2}$), 1.38 – 1.25 (m, 2H, $HC{=}C(CH_2)_2C\mathbf{H_2}CH_3$), 0.90 (t, 3H, J = 7.18 Hz, $CH_2C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 162.4, 128.2, 42.1, 40.8, 32.5, 29.7, 25.1, 22.4, 21.2, 13.9; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_{11}H_{18}O$) requires *m/z* 166.1358, found *m/z* 166.1359.

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[11] Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872.

General Procedure for the enantioselective hydrogenation of cyclic enones:
To a solution of 3-substituted-cyclopent-2-enone (1 mmol) dissolved in 0.5 mL of Et_2O (0.5 M), cooled to 4 °C using an ice bath, was added (2*S*,5*S*)-5-benzyl-3-methyl-2-(5-methylfuran-2-yl)imidazolidin-4-one (54 mg, 0.2 mmol, 0.2 eq.), followed by *t*-Butyl Hantzsch ester (340 mg, 1.1 mmol, 1.1 eq.), then trichloroacetic acid (33 mg, 0.2 mmol, 0.2 eq.). The resulting yellow suspension was stirred at 4 °C until the reaction was judged to be complete by TLC. The reaction mixture was passed through a short pad of silica gel and eluted with Et_2O. The resulting solution was concentrated *in vacuo* and purified by flash chromatography (solvent noted) to provide the title compound. Where noted, the pyridine by-product was removed by washing the final compound with 5 mL 6 M HCl (3×), 5 ml H_2O (1×) and 5 ml sat. $NaHCO_3$ (1×) to provide the title compound. These conditions were used as an alternative to repeating the column chromatography.

(*R*)-3-methylcyclopentanone: Prepared according to the general procedure from 3-methylcyclopent-2-enone (100 mg, 1.04 mmol) for 8.5 h to provide the title compound (72% conversion, 95% ee). Conversion was determined via GLC analysis by comparison with an internal standard (BnOMe). The physical data were identical in all respects to those of the commercially available (*R*)-3-methylcyclopentanone. The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m × 0.25 mm) column (100 °C isotherm, 1 mL/min.); (*S*) isomer t_r = 25.1 min. and (*R*) isomer t_r = 25.8 min.

(*R*)-3-cyclohexylcyclopentanone: Prepared according to the general procedure from 3-cyclohexylcyclopent-2-enone (200 mg, 1.31 mmol) for 11 h to provide the title compound as a yellow oil (165 mg, 82% yield, 93% ee) after purification by flash chromatography on Iatrobeads® (15 – 20% Et_2O/pentane) and a final acid wash. The physical data were identical in all respects to those previously reported.[12] The enantiomeric ratio was determined by GLC using a Hydrodex-B-TBDAc (50 m × 0.25 mm) column (105 °C isotherm, 1 mL/min.); (*S*) isomer t_r = 127.7 min. and (*R*) isomer t_r = 127.9 min. $[\alpha]_D^{22}$ = +8.6 ° (c = 1.00, $CHCl_3$).

[12] Jones, P.; Reddy, C. K.; Knochel, P. *Tetrahedron* **1998**, *54*, 1471. (racemic product, no optical rotation)

(*R*)-3-*tert*-butylcyclopentanone: Prepared according to the general procedure from 3-*tert*-butylcyclopent-2-enone (100 mg, 0.723 mmol) for 5.5 h to provide the title compound as a colorless oil (81% conversion, 96% ee). Conversion was determined via GLC analysis by comparison with an internal standard (BnOMe). The physical data were identical in all respects to those previously reported.[13] The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m × 0.25 mm) column (90 °C isotherm, 1 mL/min.); (*S*) isomer t_r = 14.4 min. and (*R*) isomer t_r = 15.0 min. $[\alpha]_D^{22}$ = +150.3 ° (c = 1.00, $CHCl_3$).
General procedure B provided the title compound (81% conversion, 96% ee) after 5.5 hours.

(*R*)-3-benzylcyclopentanone: Prepared according to the general procedure from 3-benzylcyclopent-2-enone (200 mg, 1.16 mmol) for 11 h. After the reaction mixture was passed though a short pad of silica gel, the resulting mixture was poured into 5 mL of a 10% HCl solution and diluted with 5 mL of Et_2O. The layers were separated, then the organic layer was washed with 5 mL of a 10% HCl solution (4×) and with 5 mL of water (1×). The resulting solution was dried over $MgSO_4$ and concentrated *in vacuo* to provide the title compound as a colorless oil (157 mg, 78% yield, 90% ee) after purification by flash chromatography on Iatrobeads® (2% Et_2O/benzene) and a final acid wash. The physical data were identical in all respects to those previously reported.[14] The enantiomeric ratio was determined by GLC using a Hydrodex-B-TBDAc (50 m × 0.25 mm) column (145 °C isotherm, 1 mL/min.); (*S*) isomer t_r = 91.5 min. and (*R*) isomer t_r = 90.1 min. $[\alpha]_D^{22}$ = +83.9 ° (c = 1.00, $CHCl_3$).

(*R*)-3-(benzyloxymethyl)cyclopentanone: Prepared according to the general procedure from 3-(benzyloxymethyl)cyclopent-2-enone (200 mg, 1.06 mmol) for 13 h. After the reaction mixture was passed though a short pad of silica gel, the resulting solution was poured into 5 mL of a 10% HCl solution and diluted with 5 mL of Et_2O. The layers were separated, then the organic layer was washed with 5 mL of a 10% HCl solution (4×) and with 5 mL of water (1×). The resulting solution was dried over $MgSO_4$ and concentrated *in vacuo* to provide the title compound as a colorless oil (180 mg, 89% yield, 91% ee) after purification by flash chromatography on silica

[13] Ahlbrecht, H.; Weber, P. *Synthesis* ***1992***, 1019. (racemic product, no optical rotation)

gel (10% Et_2O/pentane). The enantiomeric ratio was determined by GLC using a Hydrodex-B-TBDAc (50 m × 0.25 mm) column (150 °C isotherm, 1 mL/min.); (*S*) isomer t_r = 151.2 min. and (*R*) isomer t_r = 153.2 min. IR (film) 3030, 2860, 1740, 1404, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H, Ar**H$_5$**), 4.55 (s, 2H, C**H$_2$**Ph), 3.51 (d, 2H, *J* = 6.3 Hz, CHC**H$_2$**O), 2.61 – 2.49 (m, 1H), 2.44 – 2.25 (m, 2H), 2.23 – 2.01 (m, 3H), 1.84 – 1.71 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.2, 138.1, 128.3, 127.4, 126.8, 73.2, 73.0, 41.9, 37.8, 36.7, 26.0; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_{13}H_{16}O_2$) requires *m/z* 204.1150, found *m/z* 204.1144; $[\alpha]_D^{22}$ = +31.2 ° (c = 1.0, $CHCl_3$).

***R*)-3-phenylcyclopentanone**: Prepared according to the general procedure from 3-phenylcyclopent-2-enone (200 mg, 1.26 mmol) for 8.5 h to provide the title compound as a light yellow oil (147 mg, 73% yield, 91% ee) after purification by flash chromatography on Iatrobeads® (10% Et_2O/benzene) and a final acid wash. The physical data were identical in all respects to those previously reported.[15] The enantiomeric ratio was determined by GLC using a Hydrodex-B-TBDAc (50 m × 0.25 mm) column (145 °C isotherm, 1 mL/min.); (*S*) isomer t_r = 56.3 min. and (*R*) isomer t_r = 61.3 min. $[\alpha]_D^{22}$ = +83.5 ° (c = 1.00, $CHCl_3$).

(*R*)-methyl 3-oxocyclopentanecarboxylate: Prepared according to the general procedure from methyl 3-oxocyclopent-1-enecarboxylate (200 mg, 1.43 mmol) for 1 h at –10 °C to provide the title compound as a colorless oil (168 mg, 83% yield, 90% ee) after purification by flash chromatography on silica gel (30% EtOAc/hexane). The physical data were identical in all respects to those previously reported.[16] The enantiomeric ratio was determined by GLC using a Hydrodex-B-TBDAc (50 m × 0.25 mm) column (130 °C isotherm, 1 mL/min.); (*S*) isomer t_r = 41.9 min. and (*R*) isomer t_r = 43.5 min. $[\alpha]_D^{22}$ = +28.0 ° (c = 1.00, $CHCl_3$).

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[14] Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 6130. and Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797. (reported an optical rotation of –96 ° for the (*S*) isomer that is 96% ee)

[15] Gadwood, R. C.; Mallick, I. M.; DeWinter, A. J. *J. Org. Chem.* **1987**, *52*, 774. Gomez-Bengoa, E.; Heron, N. M.; Didiuk, M. T.; Luchaco, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 7649. and Hashimoto, S.-I.; Watanabe, N.; Ikegami, S. *Synlett.* **1994**, 353.

[16] Ranu, B. C.; Dutta, J. Guchhait, S. K. *Org. Lett.* **2001**, *3*, 2603. The absolute stereochemistry was assigned by analogy.

(*R*)-3-acetylcyclopentanone: Prepared according to the general procedure from 3-acetylcyclopent-2-enone (200 mg, 1.61 mmol) for 1 h at –10 °C to provide the title compound as a colorless oil (158 mg, 78% yield, 91% ee) after purification by flash chromatography on silica gel (50% EtOAc/hexane). The physical data were identical in all respects to those previously reported.[17] The enantiomeric ratio was determined by GLC using a Hydrodex-B-TBDAc (50 m × 0.25 mm) column (145 °C isotherm, 1 mL/min.); (*S*) isomer t_r = 52.0 min. and (*R*) isomer t_r = 53.3 min. $[\alpha]_D^{22}$ = +56.3 ° (c = 1.0, $CHCl_3$).

(*R*)-3-butylcyclohexanone: Prepared according to the general procedure from 3-butylcyclohexen-2-one (200 mg, 1.31 mmol) for 25 h to provide the title compound as a colorless oil (165 mg, 82% yield, 90% ee) after purification by flash chromatography on silica gel (5% Et_2O/pentane). The physical data were identical in all respects to those previously reported.[18] The enantiomeric ratio was determined by GLC using a Hydrodex-B-TBDAc (50 m × 0.25 mm) column (150 °C isotherm, 1 mL/min.); (*S*) isomer t_r = 37.0 min. and (*R*) isomer t_r = 36.0 min. $[\alpha]_D^{22}$ = +12.2 ° (c = 1.00, $CHCl_3$).

(*R*)-3-cyclohexylcyclohexanone: Prepared according to the general procedure from 3-cyclohexylcyclohexen-2-one (85 mg, 0.478 mmol) for 24 h to provide the title compound as a colorless oil (61 mg, 71% yield, 88% ee) after purification by flash chromatography on silica gel (5% Et_2O/pentane). The enantiomeric ratio was determined by GLC using a Hydrodex-B-TBDAc (50 m × 0.25 mm) column (110 °C isotherm, 1 mL/min.); (*S*) isomer t_r = 73.5 min. and (*R*) isomer t_r = 65.2 min. IR (film) 2924, 2853, 1715, 1449, 14223, 1346, 1317, 1263, 1225, 1101, 1056, 982, 892, 866 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.44 – 2.21 (m, 3H), 2.16 – 2.04 (m, 2H), 1.93 – 1.85 (m, 1H), 1.80 – 1.54 (m, 8H), 1.47 – 1.33 (m, 1H), 1.32 – 1.11 (m, 3H), 1.08 – 0.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) _ 212.9, 45.6, 44.7, 42.7, 41.6, 30.0, 29.9, 28.4, 26.6, 26.59, 25.54, 25.6; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_{12}H_{20}O$) requires *m/z* 180.1514, found *m/z* 180.1508; $[\alpha]_D^{22}$ = +11.9 ° (c = 1.05, $CHCl_3$).

[17] Monte, W. T.; Baizer, M. M.; Little, R. D. *J. Org. Chem.* **1983**, *48*, 803. (racemic product, no optical rotation)

(*R*)-3,3,5-trimethylcyclohexanone: Prepared according to the general procedure from isophorone (200 mg, 1.45 mmol) for 48 h to provide the title compound as a colorless oil (134 mg, 66% yield, 98% ee) after purification by flash chromatography on silica gel (5% Et_2O/pentane). The physical data were identical in all respects to those previously reported.[19] The enantiomeric ratio was determined by GLC using a Hydrodex-B-TBDAc (50 m × 0.25 mm) column (110 °C isotherm, 1 mL/min.); (*S*) isomer t_r = 11.8 min. and (*R*) isomer t_r = 12.4 min. $[\alpha]_D^{22}$ = –18.7 °(c = 1.03, $CHCl_3$).

(*R*)-3-butylcycloheptanone: Prepared according to the general procedure from 3-butylcyclohept-2-enone (200 mg, 1.20 mmol) for 9h to provide the title compound as a light yellow oil (141 mg, 70% yield, 92% ee) after purification by flash chromatography on silica gel (10% Et_2O/pentane) and a final acid wash. The physical data were identical in all respects to those previously reported.[20] The enantiomeric ratio was determined by GLC using a Hydrodex-B-TBDAc (50 m × 0.25 mm) column (105 °C isotherm, 1 mL/min.); (*S*) isomer t_r = 100.6 min. and (*R*) isomer t_r = 102.7 min. $[\alpha]_D^{22}$ = +38.5 ° (c = 1.05, $CHCl_3$).

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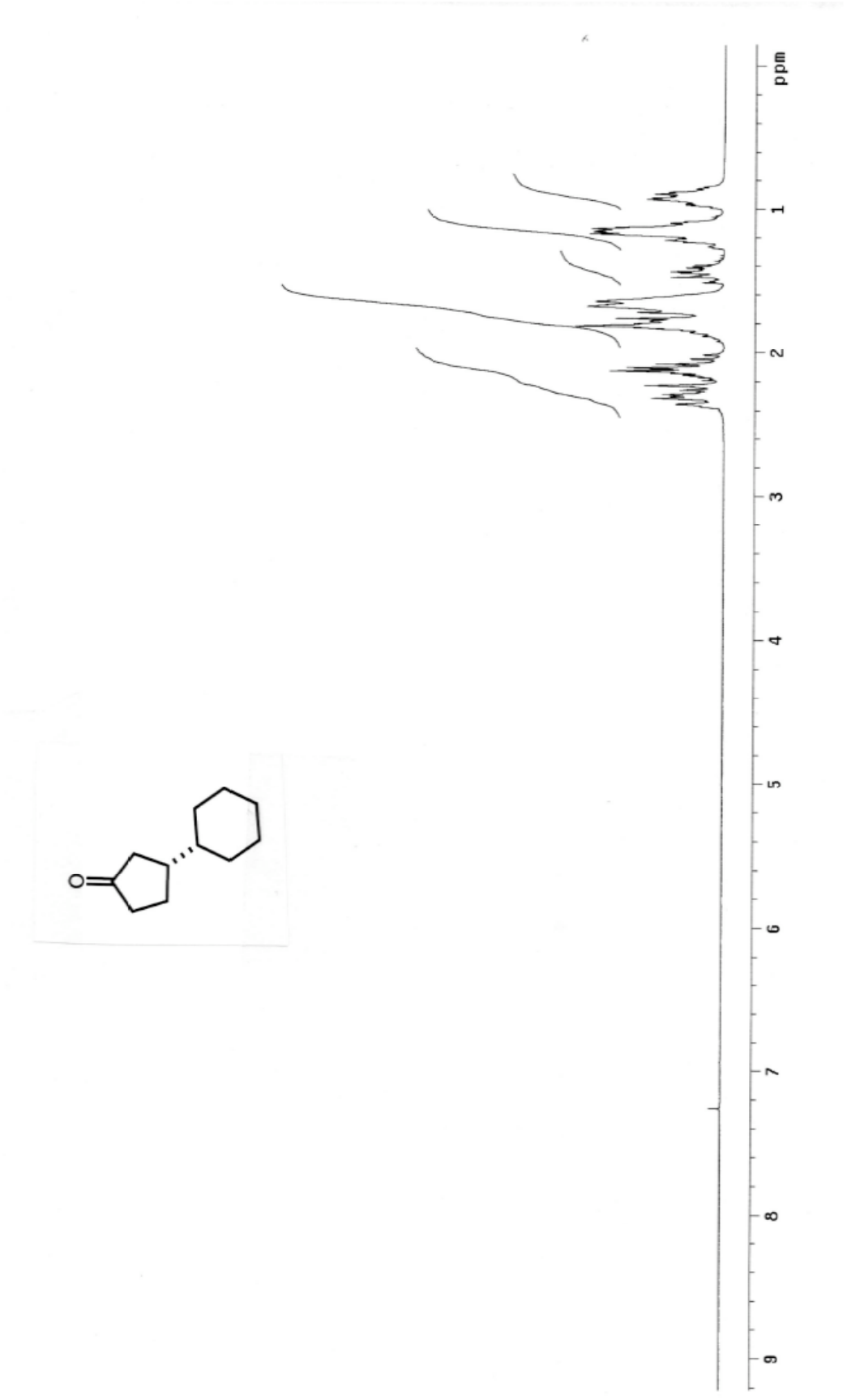
[18] Jones, P.; Reddy, C. K.; Knowche, P. *Tetrahedron* **1998**, *54*, 1471. and Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797. (reported a rotation of –17 ° for the (*S*)-enantiomer that is 87% ee)

[19] Allinger, N. L.; Riew, C. K. *J. Org. Chem.* **1975**, *40*, 1316. (reported a rotation of +20.3 ° for the (*S*)-enantiomer that is 75% ee)

[20] Strangeland, E. L.; Sammakia, T. *Tetrahedron* **1997**, *53*, 16503. (reported a rotation of +31.4 ° for a product that is 92% ee)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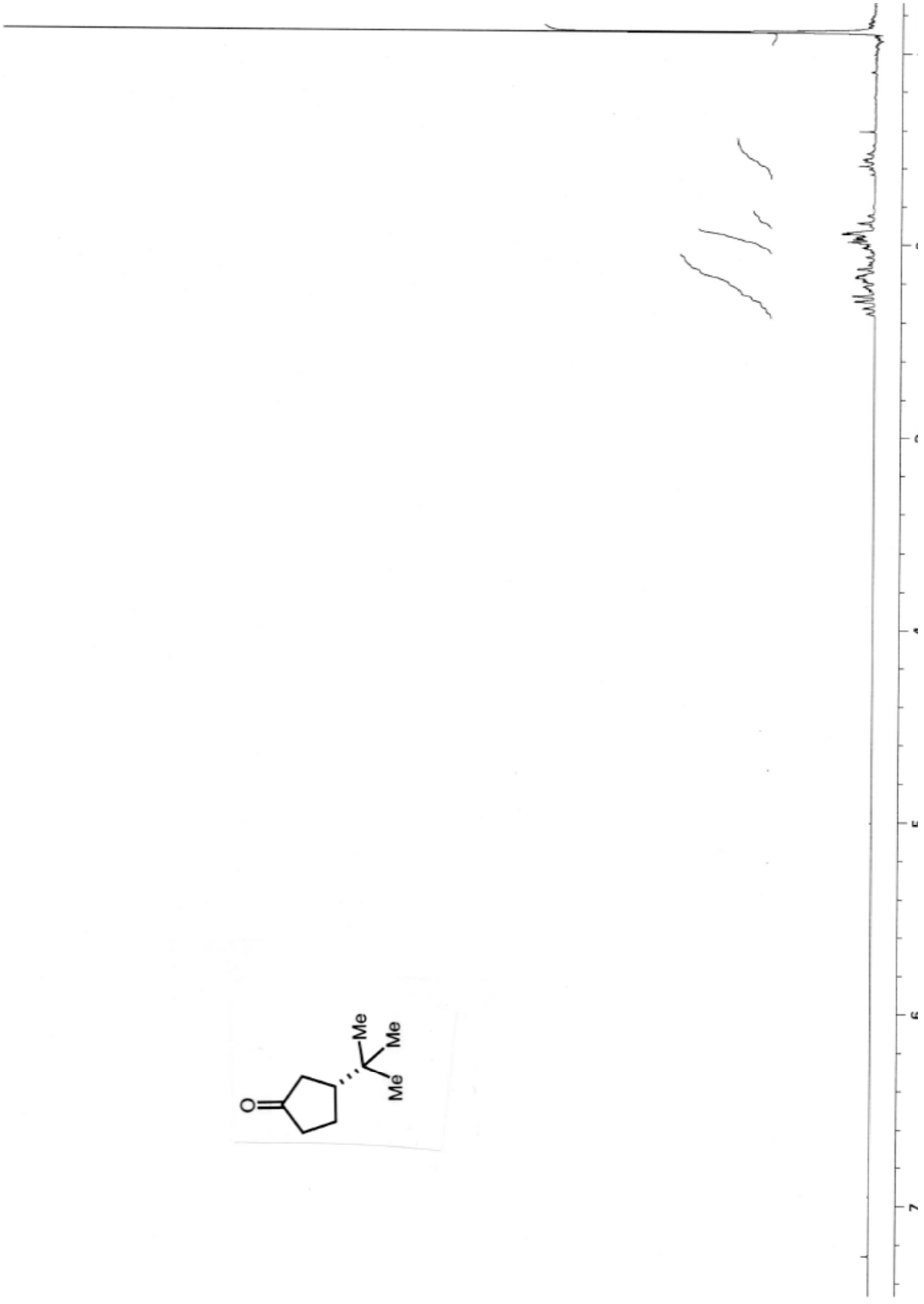
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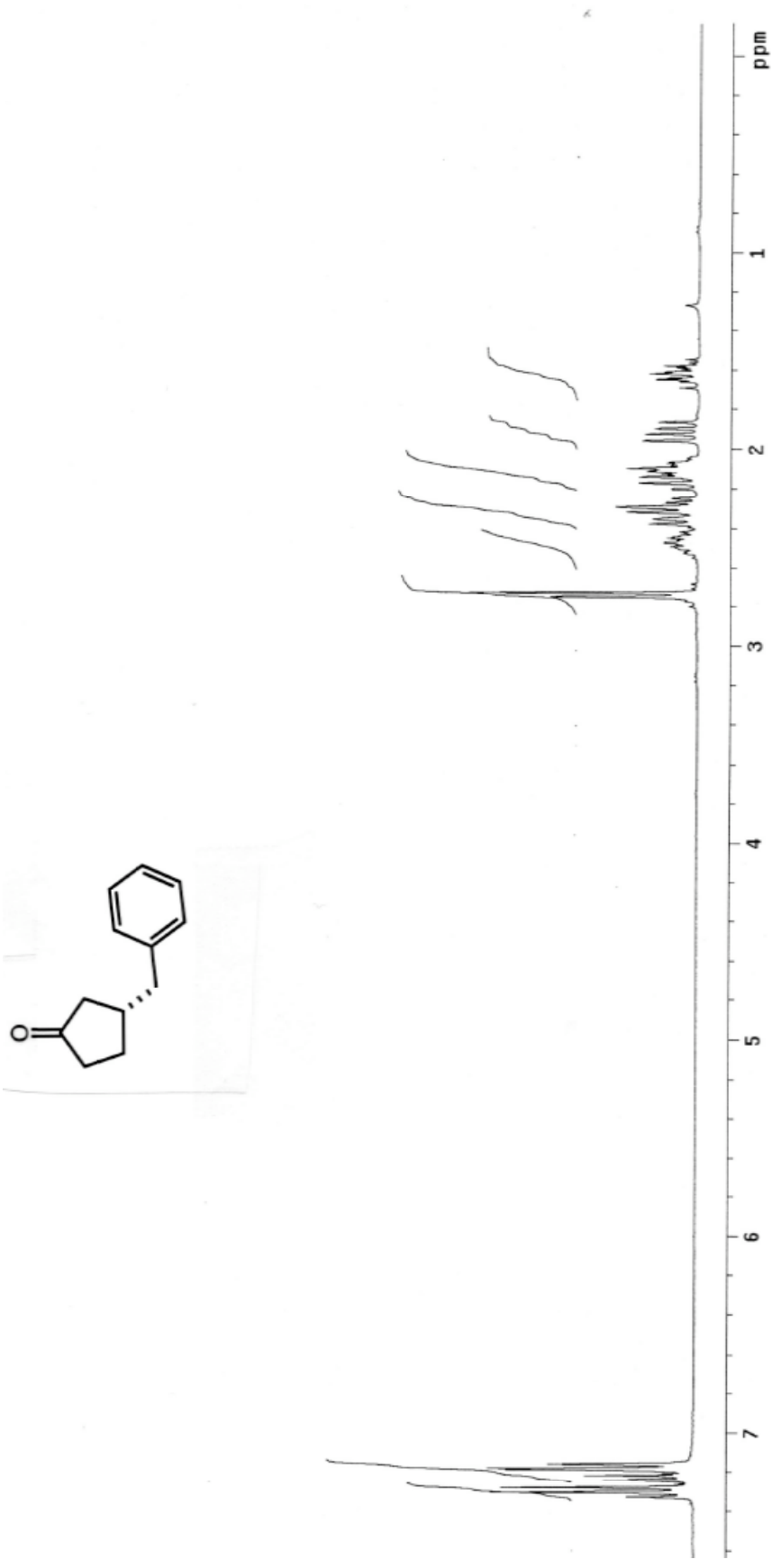
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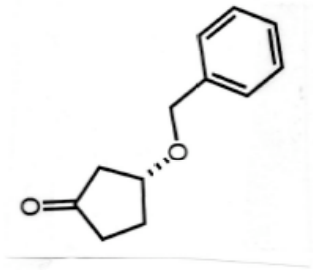

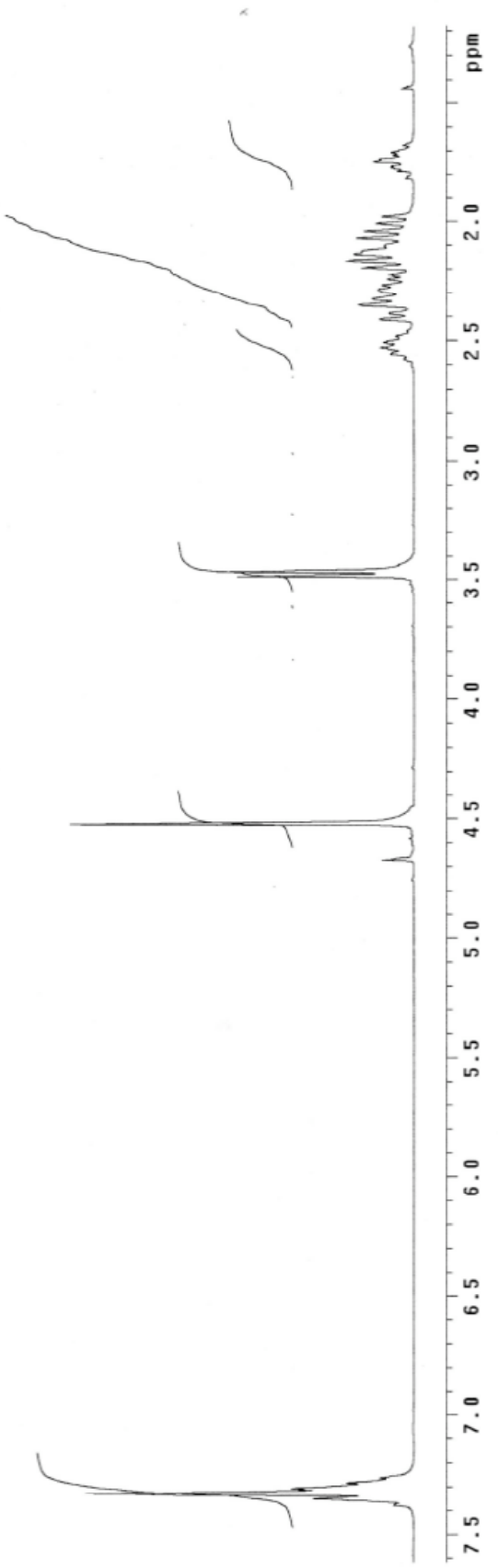
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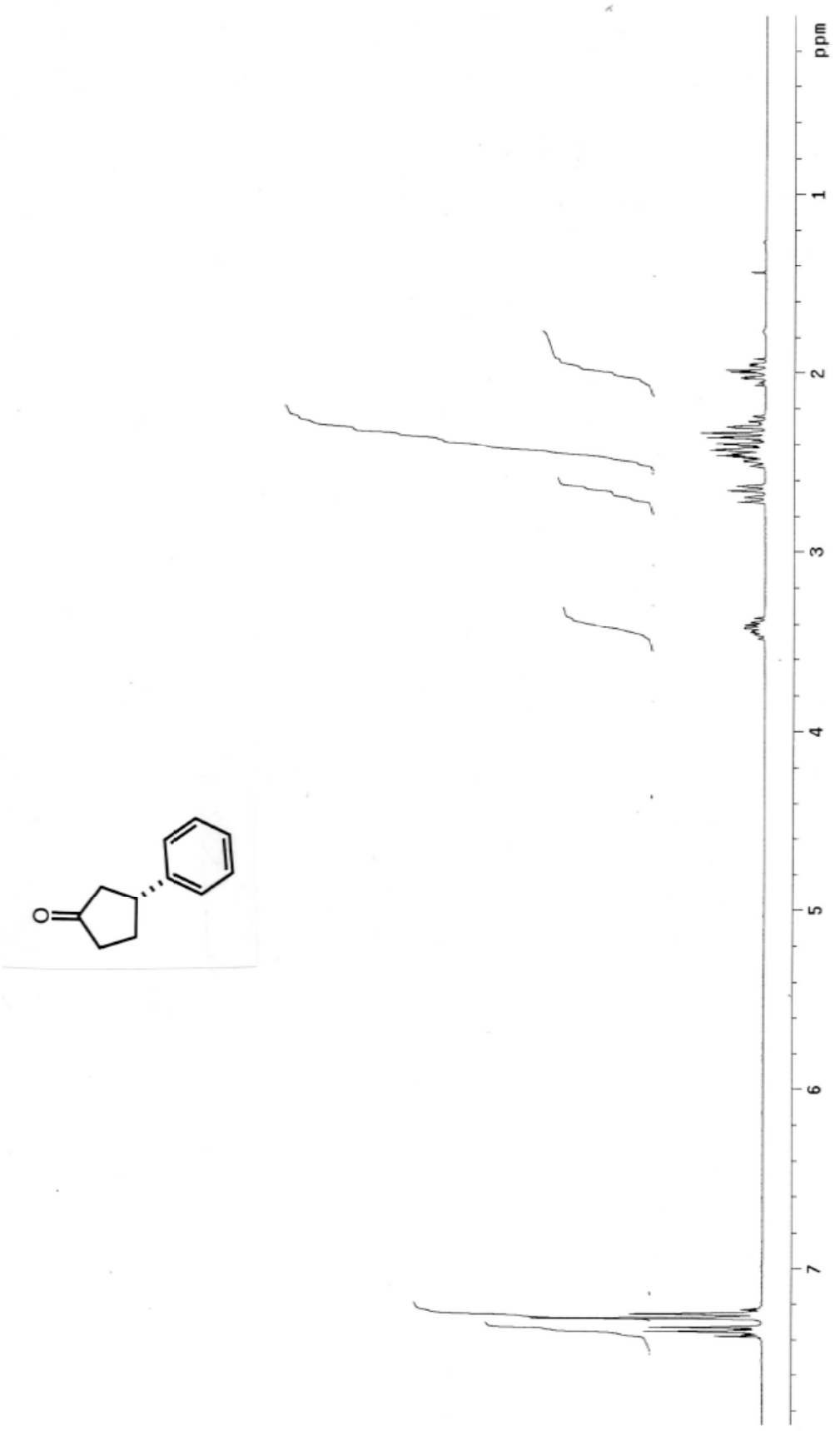
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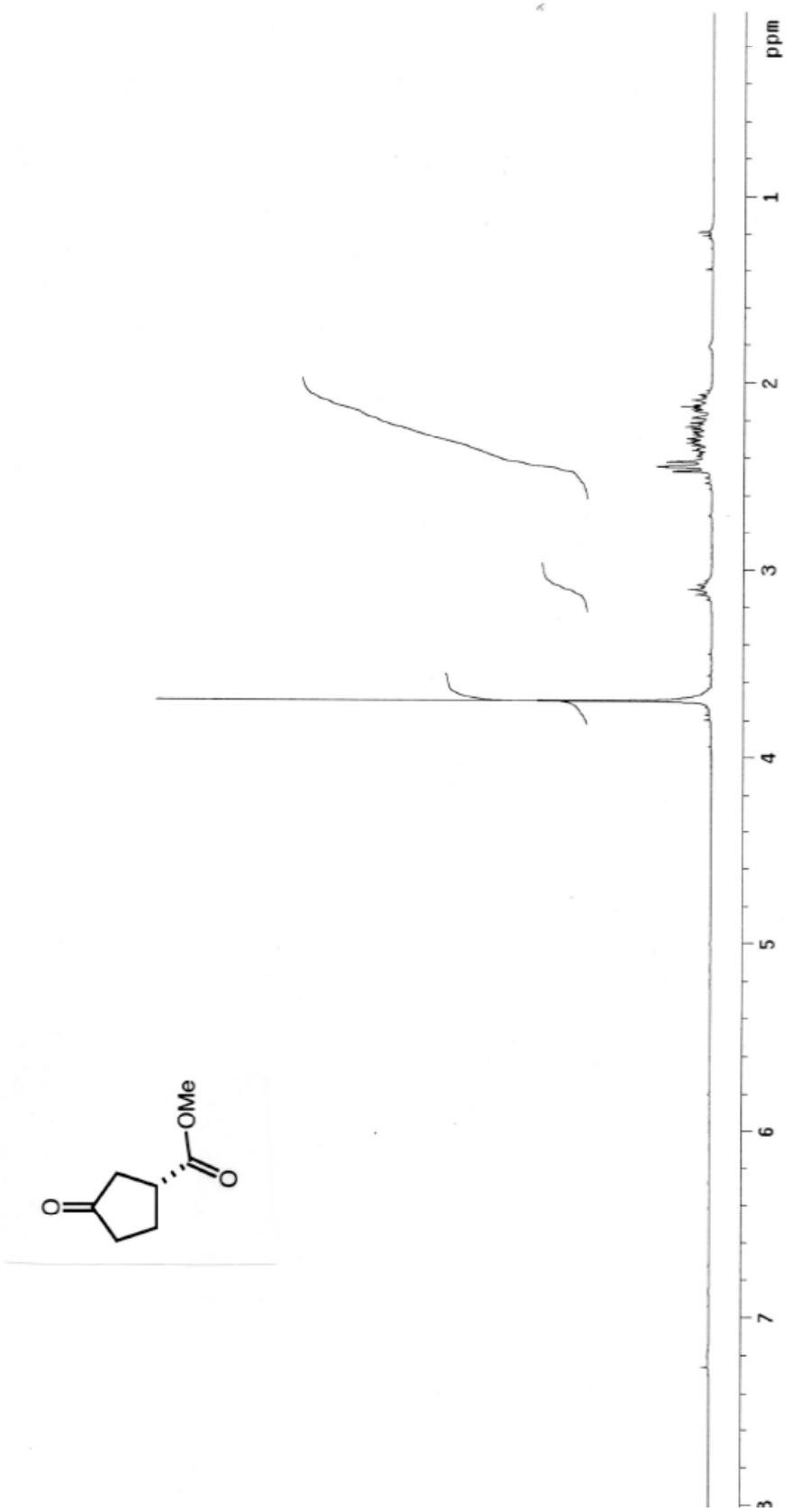
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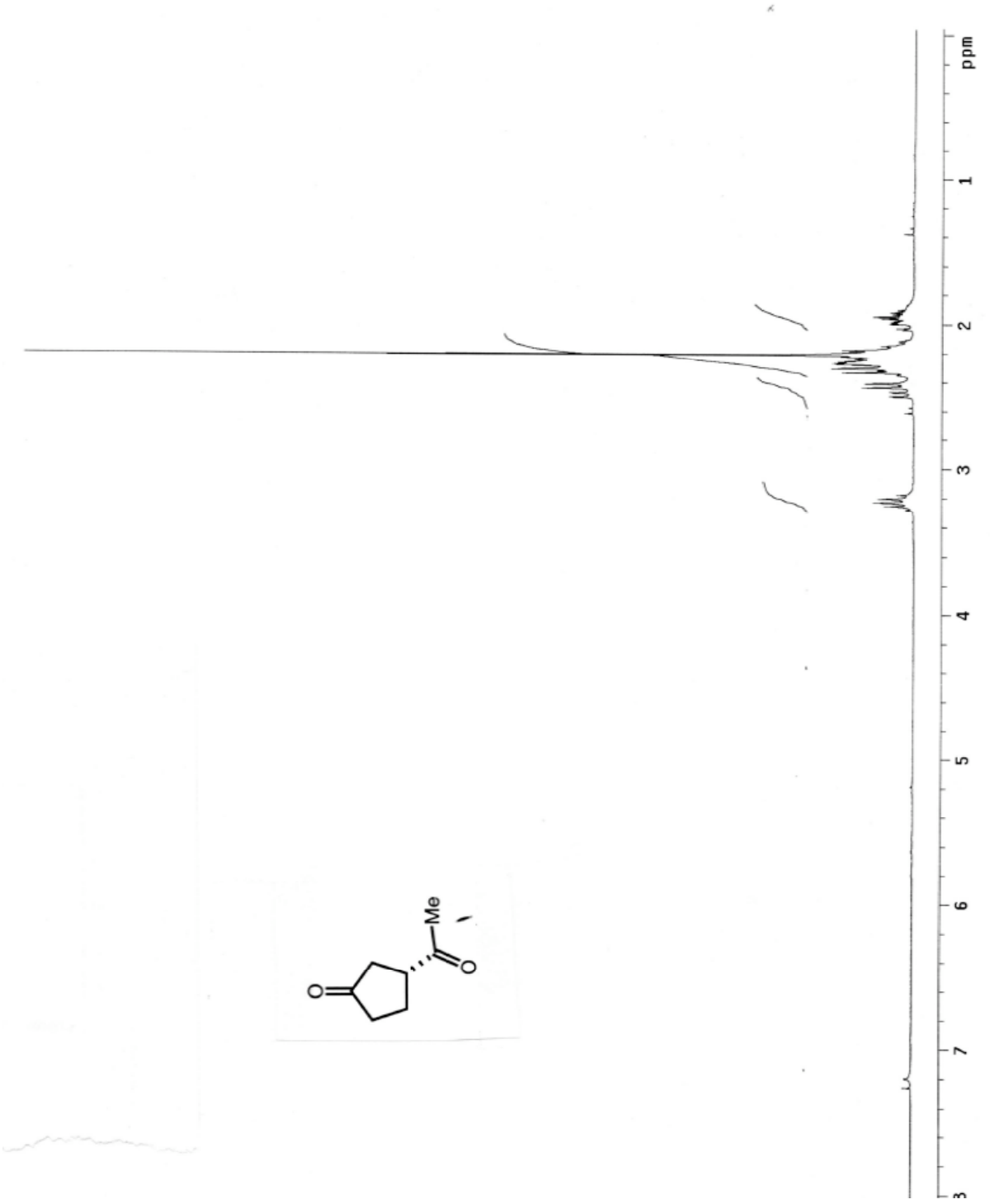
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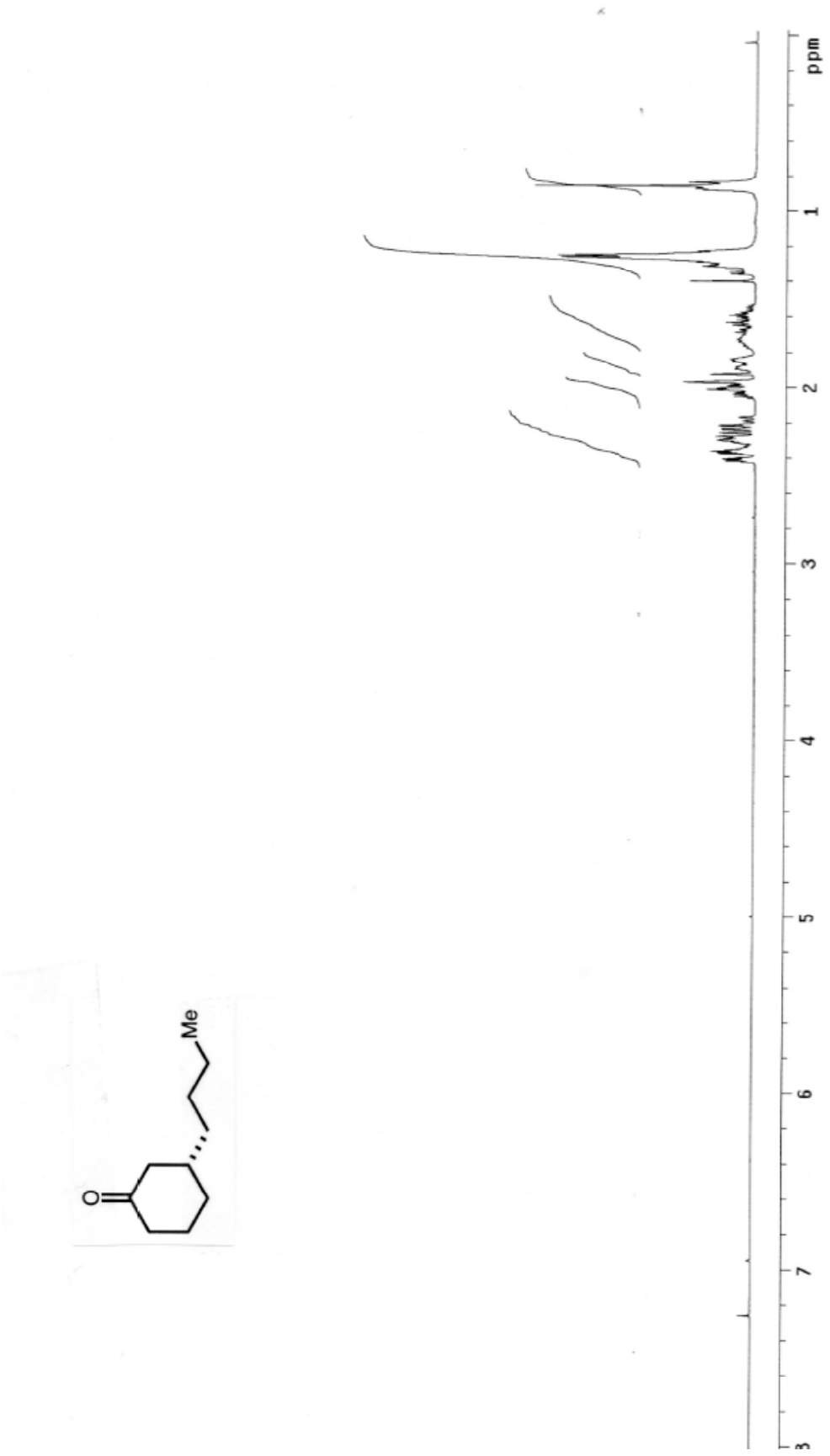
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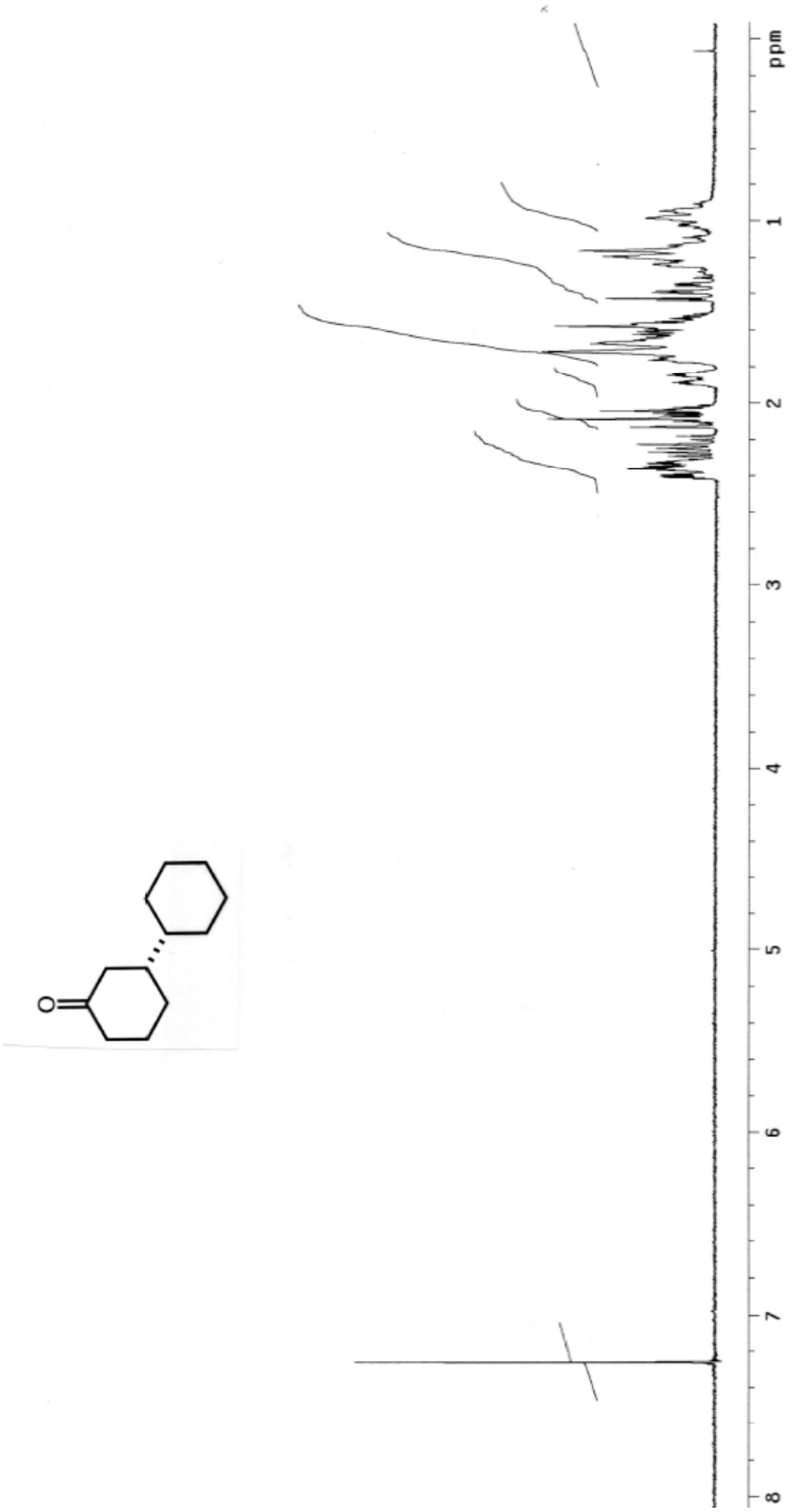
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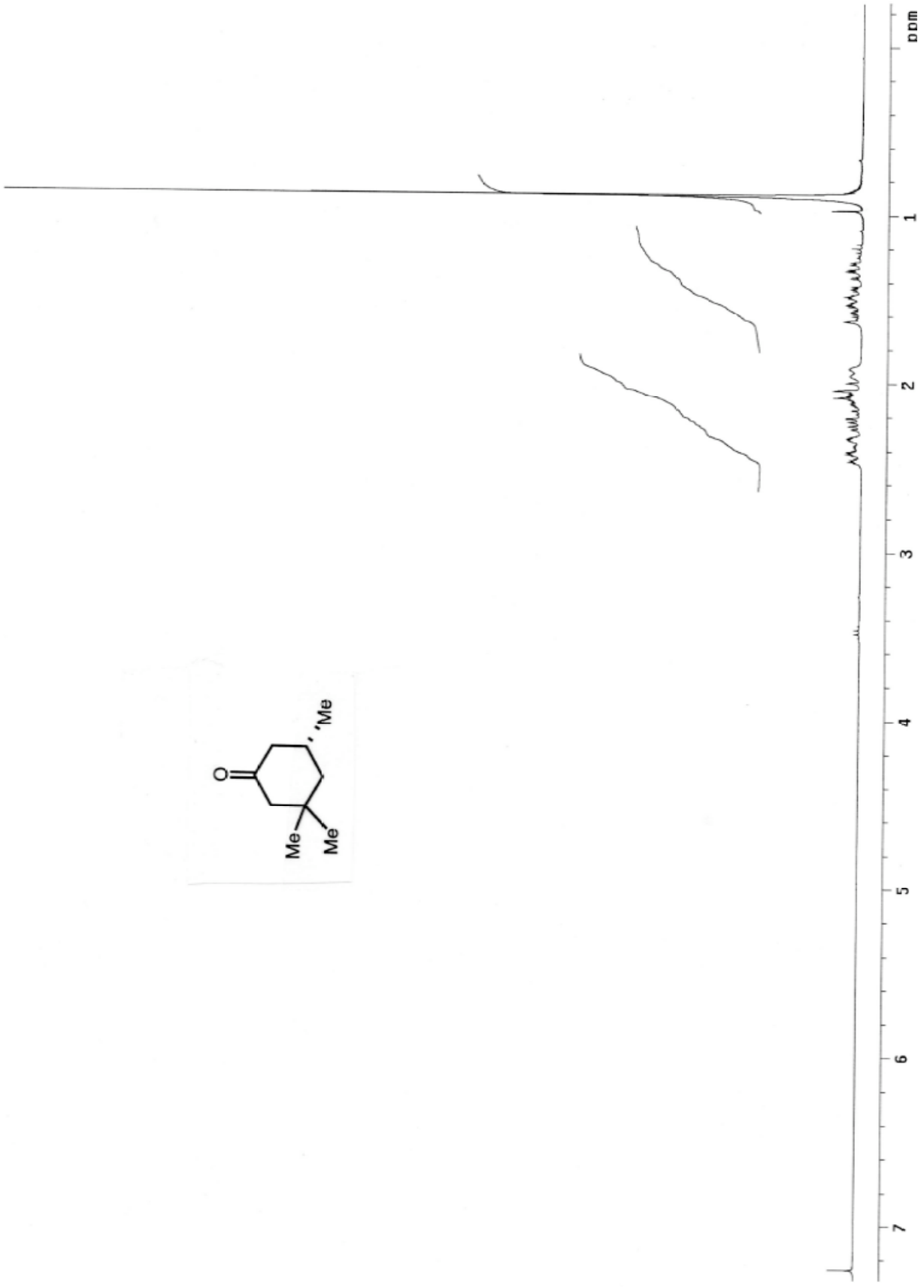
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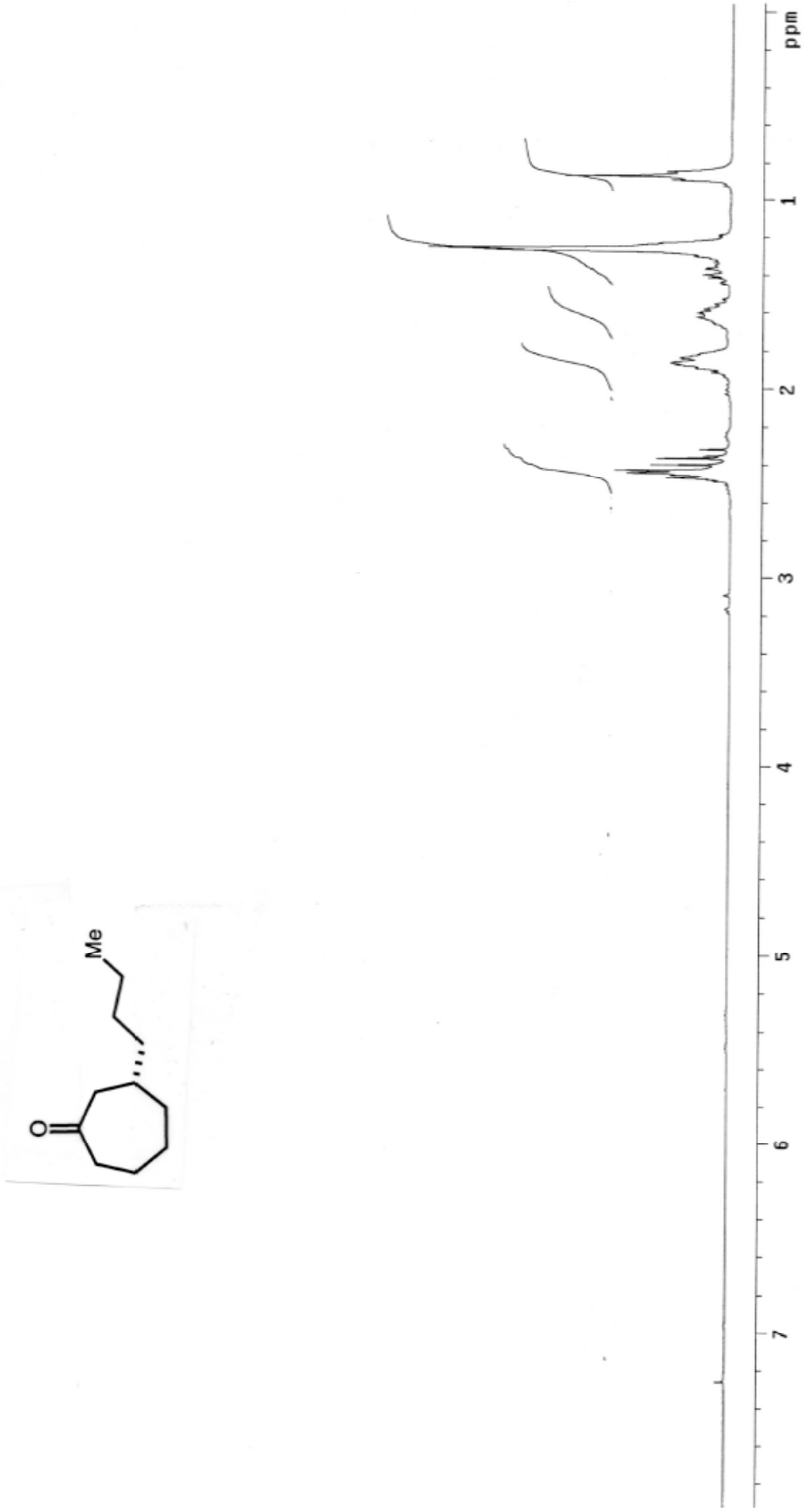
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