# Examination of the Role of Taft-Type Steric Parameters in Asymmetric Catalysis

Matthew S. Sigman* and Jeremie J. Miller
Department of Chemistry, University of Utah, 315 S. 1400 East, Salt Lake City, Utah 84112-8500

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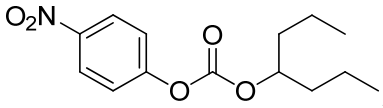
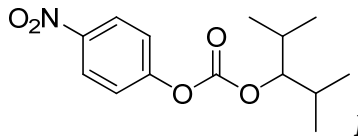
**General Information:**

Unless otherwise noted all reactions were performed under a nitrogen atmosphere with stirring. Tetrahydrofuran was distilled from benzophenone and sodium ketyl prior to use. Triethylamine and dichloromethane were distilled from $CaH_2$ prior to use. All other reagents were purchased from commercial sources and used without further purification. Yields were calculated for material judged homogeneous by thin-layer chromatography and NMR. Thin-layer chromatography was performed with EMD silica gel 60 $F_{254}$ plates eluting with the solvents indicated, visualized by a 254 nm UV lamp, and stained with potassium permanganate or either an ethanolic solution of *p*-anisaldehyde, phosphomolybdic acid, or Ninhydrin. Flash column chromatography was performed with EcoChrom MP Silitech 32-63D 60Å silica gel, slurry packed with solvents indicated in glass columns. Nuclear magnetic resonance spectra were acquired at 300, 400, and 500 MHz for $^1$H, and 75, 100 and 125 MHz for $^{13}$C. Chemical shifts for proton nuclear magnetic resonance ($^1$H NMR) spectra are reported in parts per million downfield relative to the line of $CDCl_3$ singlet at 7.26 ppm. Chemical shifts for carbon nuclear magnetic resonance ($^{13}$C NMR) spectra are reported in parts per million downfield relative to the center line of the $CDCl_3$ triplet at 77.00 ppm. The abbreviations s, d, t, q, quin, tdd and m stand for the resonance multiplicities singlet, doublet, triplet, quartet, quintet, triplet of doublet of doublet and multiplet, respectively. Optical rotations were obtained (Na D line) using a Perkin Elmer Model 343 Polarimeter fitted with a micro cell with a 1 dm path length. Concentrations are reported in g/100 mL. IR spectra were recorded using a Mattson Satellite FTIR instrument. LRMS were recorded using a Micromass Quattro II spectrometer. GC analysis was performed using a Hewlett Packard HP 6890 Series GC system fitted with a HP-Chiral permethylated β-cyclodextrin column. HPLC analysis was performed using a Hewlett Packard Series 1100 instrument fitted with a chiral stationary phase (as indicated). Melting points were obtained on an electrothermal melting point apparatus and are uncorrected. Glassware for all reactions was oven-dried at 115 °C and cooled while purging with nitrogen prior to use. **Ligands 1a,[1] 1b-1e,[2] 2,** and **3d**[1] were prepared according to previous reports.

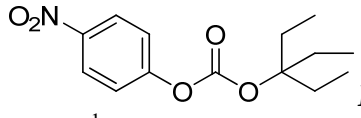
**Ligand Synthesis:**



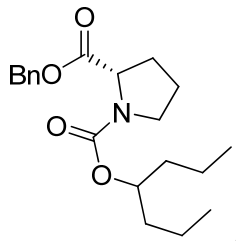
***Preparation of heptan-4-yl 4-nitrophenyl carbonate (SI-1)***.[1] To a stirring solution of 4-heptanol (495 μL, 4.26 mmol, 1 equiv.), $CH_2Cl_2$ (10 mL), and pyridine (520 μL, 6.39 mmol, 1.5 equiv.) at -5 °C, was added *p*-nitrophenyl chloroformate (1.03 g, 5.11 mmol, 1.2 equiv.) in four equal portions. The reaction flask was removed from the cooling bath and allowed to warm to room temperature while stirring. After reaction mixture was stirred for 3 h, the precipitated pyridine hydrochloride salt was removed by filtration; $H_2O$ (15 mL) was added to the filtrate and the solution was extracted with $Et_2O$ (3 x 30 mL). The organics were washed with 1 M HCl (3 x 30 mL), saturated aqueous $NaHCO_3$ (2 x 30 mL), and saturated aqueous NaCl (30 mL). The organics were dried over $Na_2SO_4$, filtered, and then concentrated under reduced pressure. The crude mixture was taken on without further purification. $R_f$ = 0.68 (33% EtOAc/hexanes, stained with $KMnO_4$).



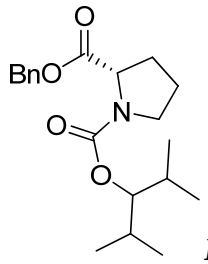
***Preparation of 2,4-dimethylpentan-3-yl 4-nitrophenyl carbonate (SI-2)***.[1] This compound was synthesized using the method for **SI-1**, to yield ***SI*-2** (845 mg, 84% yield): $R_f$ = 0.64 (33% EtOAc/hexanes, stained with $KMnO_4$) and used immediately.



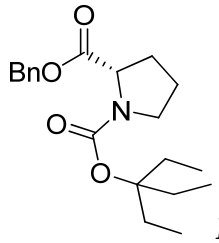
***Preparation of 3-ethylpentan-3-yl 4-nitrophenyl carbonate (SI-3)***.[1] This compound was synthesized using the method for **SI-1**, to yield **SI-3** (950 mg, 95% yield): $R_f$ = 0.69 (33% EtOAc/hexanes, stained with $KMnO_4$) and used immediately..



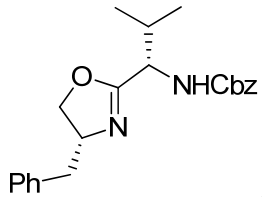
***Preparation of (S)-2-benzyl 1-heptan-4-yl pyrrolidine-1,2-dicarboxylate (SI-4)***. To a stirring solution of **SI-1** (1.11 g, 3.96 mmol, 1.1 equiv.), THF (6 mL), and saturated aqueous $NaHCO_3$ (6 mL) was slowly added Bn-Pro-OH (870 mg, 3.6 mmol, 1 equiv.) in three equal portions. The reaction mixture was then heated to 50 ºC. After stirring for 12 h, the mixture was concentrated under reduced pressure to remove THF. The resulting mixture was then extracted with $CH_2Cl_2$ (3 x 40 mL). In order to remove the residual *p*-nitro phenol, the organics were washed repeatedly with 10% aqueous $NaHCO_3$ until the yellow color did not persist. The organic layer was dried over $Na_2SO_4$, filtered, and then concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3.5 x 13 cm column, eluting with 8% EtOAc/hexanes, collecting 9 mL fractions. The product containing fractions were combined and concentrated under reduced pressure to give the desired product **SI-4** (950 mg, 76% yield) as clear viscous oil: $R_f$ = 0.47 (33% EtOAc/hexanes, stained with $KMnO_4$); $[\alpha]^{23}_D$ -38.2 (c = 0.55, $CHCl_3$); 300 MHz $^1$H NMR ($CDCl_3$) at 50 $^o$C δ 7.36-7.29 (m, 5H), 5.26-5.00 (m, 2H), 4.85-4.70 (m, 1H), 4.49-4.27 (m, 1H), 3.65-3.36 (m, 2H), 2.31-2.10 (m, 1H), 2.05-1.77 (m, 3H), 1.63-1.16 (m, 8H), 0.96-0.79 (m, 6H); 75 MHz $^{13}$C NMR ($CDCl_3$) at 50 $^o$C δ 172.7, 154.5, 135.8, 128.5, 128.2, 127.9, 75.0, 66.5, 58.8, 46.7, 36.4, 30.9, 23.4, 18.4, 13.9; IR (neat) 2957, 2934, 2873, 1746, 1698, 1406, 1336, 1162, 1114, 1086, 982, 737, 696 $cm^{-1}$; HRMS (ES) calcd. $C_{26}H_{29}NO_4Na$ $(M + Na)^+$ 370.1994, obsd. 370.1995.



***Preparation of (S)-2-benzyl 1-(2,4-dimethylpentan-3-yl) pyrrolidine-1,2-dicarboxylate (SI-5)***. This compound was synthesized using the method for **SI-4** to yield the desired compound **SI-5** (420 mg, 70% yield) as clear viscous oil: $R_f$ = 0.41 (33% EtOAc/hexanes, stained with $KMnO_4$); $[\alpha]^{23}_D$ -42.5 (c = 0.51, $CHCl_3$); 300 MHz $^1$H NMR ($CDCl_3$) at 50 $^oC$ δ 7.40-7.28 (m, 5H), 5.23-5.01 (m, 3H), 4.48-4.39 (m, 2H), 4.35 (dd, *J* = 8.8, 3.4 Hz, 1H), 3.67-3.38 (m, 2H), 2.32-2.11 (m, 1H), 2.05-1.77 (m, 2H), 1.68 (pent, *J* = 6.8 Hz, 1H), 0.92-0.74 (m, 12H); 75 MHz $^{13}$C NMR ($CDCl_3$) at 50 $^oC$ δ 172.7, 154.8, 135.5, 128.5, 128.2, 127.9, 83.7, 66.6, 58.6, 46.8, 30.9, 29.5, 23.4, 19.6, 17.1; IR (neat) 2962, 2936, 2876, 1745, 1699, 1455, 1404, 1191, 1115, 1086, 945, 751, 697 $cm^{-1}$; HRMS (ES) calcd. $C_{20}H_{29}NO_4Na$ $(M + Na)^+$ 340.1994, obsd. 370.1997.



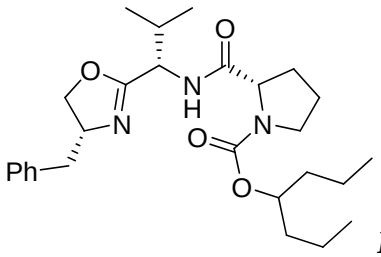
***Preparation of (S)-2-benzyl 1-(3-ethylpentan-3-yl) pyrrolidine-1,2-dicarboxylate (SI-6)***. This compound was synthesized using the method for **SI-4** to yield the desired compound **SI-6** (980 mg, 87% yield) as clear viscous oil: $R_f$ = 0.48 (33% EtOAc/hexanes, stained with PMA); $[\alpha]^{23}_D$ -43.0 (c = 0.67, $CHCl_3$); 400 MHz $^1$H NMR ($CDCl_3$) δ 7.38-7.28 (m, 5H), 5.19 (d, *J* = 5.1 Hz, 1H), 5.04 (d, *J* = 12.3 Hz, 1H), 4.27 (dd, *J* = 8.4, 3.1 Hz, 1H), 3.60-3.35 (m, 2H), 2.28-1.63 (m, 4H), 0.86-0.71 (m, 15H); 100 MHz $^{13}$C NMR ($CDCl_3$) δ 172.8, 153.3, 135.5, 128.4, 128.3, 127.9, 87.7, 66.6, 58.9, 46.3, 30.9, 26.9, 23.4, 7.6; IR (neat) 2969, 2880, 1745, 1694, 1661, 1592, 1519, 1500, 1453, 1397, 1336, 1163, 1122, 752, 696 $cm^{-1}$; HRMS (ES) calcd. $C_{20}H_{29}NO_4Na$ $(M + Na)^+$ 370.1994, obsd. 370.1992.



***Preparation of benzyl (S)-1-((R)-4-benzyl-4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamate (SI-7)***. To a stirring solution of Cbz-Val-OH (2.06 g, 8.19 mmol, 1 equiv.) and $CH_2Cl_2$ (33 mL), at -5 $^oC$, was slowly added *N*-methylmorpholine (1.08 mL, 9.83 mmol, 1.2 equiv.) via syringe. After the solution was stirred for 10 min at -5 $^oC$, isobutyl chloroformate (1.08 mL, 8.19 mmol, 1.0 equiv.) was added dropwise, via syringe, to the reaction mixture. After the solution was stirred for an additional 45 min at -5 $^oC$, H-D-Phenylalaninol (1.36 g, 8.99 mmol, 1.1 equiv.) was added in ca. three equal portions to the reaction mixture. The reaction mixture was then allowed to warm to room

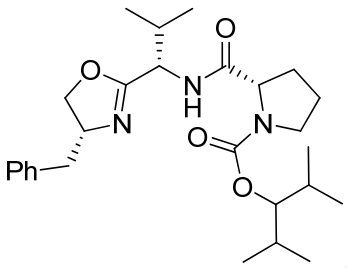
temperature. After 2 h, TLC analysis indicated complete consumption of starting material. The reaction was quenched by addition of 1 M HCl (15 mL) and diluted with $CH_2Cl_2$ (40 mL). The layers were separated, and the aqueous layer was removed. The organic layer was washed with $H_2O$ (3 x 20 mL) and brine (10 mL). The organic layer was dried over $Na_2SO_4$, filtered, and then concentrated under reduced pressure. The crude mixture was taken on without further purification.

To a stirring solution of the crude mixture in $CH_2Cl_2$ (60 mL) and triethylamine (40 mL), at -5 $^oC$, was slowly added *p*-toluenesulfonyl chloride (1.85 g, 9.83 mmol, 1.2 equiv.) in ca. three equal portions. After addition was complete the flask was removed from the cooling bath and the reaction mixture was allowed to warm to room temperature. After ca. 45 min, TLC analysis indicated complete conversion of the starting material to the *p*-toluenesulfonate. The reaction mixture was heated at reflux for 15 h. The reaction mixture was allowed to cool to room temperature before diluting with $CH_2Cl_2$ (25 mL). To this mixture was slowly added saturated aqueous $NaHCO_3$ (25 mL). The resulting organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL), $H_2O$ (20 mL) and brine (15 mL). The organic layer was dried over $Na_2SO_4$, filtered, and then concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 4.75 x 13 cm column, eluting first with 300 mL of 50% $Et_2O$/hexanes, followed by 35% acetone/hexanes, collecting 18 mL fractions. The product containing fractions were combined and concentrated under reduced pressure to give the desired Cbz protected oxazoline amine (2.52 g, 84% yield over two steps) as a white solid: mp 96-98 $^oC$; $R_f$ = 0.57 (35% acetone/hexanes, stained with phosphomolybdic acid); $[\alpha]^{23}_D$ -11.7 (c = 0.325, $CHCl_3$); 400 MHz $^1H$ NMR ($CDCl_3$) at 50 $^oC$ δ 7.37-7.17 (m, 10H), 5.39 (d, *J* = 8.8 Hz, 1H), 5.15 (d, *J* = 12.3 Hz, 1H), 4.44-4.35 (m, 2H), 4.23 (t, *J* = 8.8 Hz, 1H), 4.00 (t, *J* = 8.0 Hz, 1H), 3.08 (dd, *J* = 13.7, 5.1 Hz, 1H), 2.63 (dd, *J* = 13.7, 8.4 Hz, 1H), 2.11 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); 100 MHz $^{13}C$ NMR ($CDCl_3$) at 50 $^oC$ δ 166.7, 156.1, 137.6, 136.4, 129.2, 128.5, 128.4, 128.1, 128.0, 126.5, 72.2, 67.0, 66.9, 54.3, 41.7, 31.5, 18.8, 17.4; IR (thin film) 2977, 2935, 2863, 1382, 1123 $cm^{-1}$; HRMS (ES) calcd. $C_{22}H_{27}N_2O_3$ $(M + H)^+$ 367.2022, obsd. 367.2019.

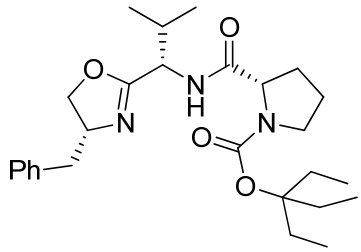



***Preparation of (S)-heptan-4-yl 2-((S)-1-((R)-4-benzyl-4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamoyl)pyrrolidine-1-carboxylate (1f)***. To a stirring solution of (*S*)-1-((heptan-4-yloxy)carbonyl)pyrrolidine-2-carboxylic acid (obtained by deprotection of the **SI-4** with 10 mol % Pd/C at 1 atm $H_2$ for 5 h) (141 mg, 0.55 mmol, 1 equiv.) and $CH_2Cl_2$ (3 mL), at -5 $^oC$, was slowly added *N*-methylmorpholine (72 μL, 0.66 mmol, 1.2 equiv.) via syringe. After the solution was stirred for 20 min at -5 $^oC$, isobutyl chloroformate (72 μL, 0.55 mmol, 1.0 equiv.) was added dropwise, via syringe, to the reaction mixture. After the solution was stirred for an additional 45 min at -5 $^oC$, the free oxazoline amine (140 mg, 0.60 mmol, 1.1 equiv.),

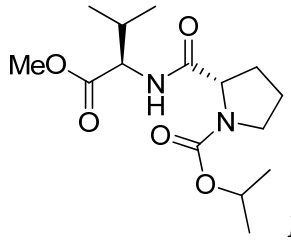
obtained by deprotection of the **SI-7** shown above (10 mol % Pd/C at 1 atm $H_2$ for 5 h), was added dropwise to the reaction mixture as a solution in $CH_2Cl_2$ (0.5 mL). The reaction mixture was then allowed to warm to room temperature. After 3 h, TLC analysis indicated complete consumption of starting material. The reaction was quenched by addition of 1 M HCl (1 mL) and diluted with $CH_2Cl_2$ (6 mL). The layers were separated, and the aqueous layer was removed. The organic layer was washed with $H_2O$ (3 x 5 mL) and brine (5 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 2 x 15 cm column, eluting first with 200 mL of 50% EtOAc/hexanes, followed by 40% acetone/hexanes, collecting 9 mL fractions. The product containing fractions were combined and concentrated under reduced pressure to give the desired ligand (119 mg, 46% yield) as a clear colorless oil: $R_f$ = 0.30 (66% EtOAc/hexanes, stained with PMA); $[\alpha]^{23}_D$ -36.7 (c = 0.39, $CHCl_3$); 400 MHz $^1$H NMR ($CDCl_3$) at 50 $^o$C δ 7.29 (t, *J* = 7.2 Hz, 1H), 7.21 (d, *J* = 9.2 Hz, 2H), 7.19 (d, *J* = 6.8 Hz, 2H), 4.83 (t, *J* = 5.6 Hz, 1H), 4.57 (dd, *J* = 8.6, 5.6 Hz, 1H), 4.42-4.29 (m, 2H), 4.20 (t, *J* = 8.8 Hz, 1H), 3.97 (t, *J* = 8.2 Hz, 1H), 3.58-3.33 (m, 2H), 3.12 (dd, *J* = 13.9, 5.1 Hz, 1H), 2.62 (dd, *J* = 13.9, 8.9 Hz, 1H), 2.44-1.80 (m, 4H), 1.63-1.21 (m, 7H), 0.97-0.85 (m, 14H); 100 MHz $^{13}$C NMR ($CDCl_3$) at 50 $^o$C δ 171.4, 166.3, 156.3, 137.8, 129.3, 128.5, 126.5, 75.6, 72.1, 67.1, 60.3 52.4, 46.9, 41.7, 36.6, 31.6, 27.8, 24.5, 18.5, 17.7, 14.0; IR (neat) 3314, 2958, 2933, 2872, 1690, 1664, 1533, 1412, 1190, 1116, 982, 702 cm$^{-1}$; HRMS (ES) calcd. $C_{27}H_{41}N_3O_4Na$ (M + Na)$^+$ 494.2995, obsd. 494.2990.




***Preparation of (S)-2,4-dimethylpentan-3-yl 2-((S)-1-((R)-4-benzyl-4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamoyl)pyrrolidine-1-carboxylate (1g)***. This compound was synthesized using the method for **1f** to yield the desired ligand (221 mg, 48% yield) as a clear colorless oil: $R_f$ = 0.32 (35% acetone/hexanes, stained with PMA); $[\alpha]^{23}_D$ -76.4 (c = 0.31, $CHCl_3$); 400 MHz $^1$H NMR ($CDCl_3$) at 50 $^o$C δ 7.48-7.11 (m, 5H), 4.57 (dd, *J* = 7.8, 5.5 Hz, 1H), 4.50 (t, *J* = 5.8 Hz, 1H), 4.43-4.28 (m, 2H), 4.22-4.08 (m, 2H), 3.10 (dd, *J* = 13.7, 5.1 Hz, 1H), 2.60 (dd, *J* = 13.7, 8.6 Hz, 1H), 2.17-1.80 (m, 6H), 0.96-0.82 (m, 18H); 100 MHz $^{13}$C NMR ($CDCl_3$) at 50 $^o$C δ 170.9, 166.2, 156.9, 137.9, 129.2, 128.5, 126.5, 84.3, 72.1, 67.1, 60.3, 52.5, 41.7, 31.6, 29.7, 20.9, 19.7, 18.8, 17.8, 17.4, 14.1; IR (neat) 3319, 2964, 2934, 2875, 1688, 1664, 1530, 1409, 1214, 1118, 751 cm$^{-1}$; HRMS (ES) calcd. $C_{27}H_{41}N_3O_4Na$ (M + Na)$^+$ 494.2995, obsd. 494.2994.

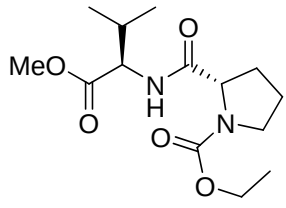


***Preparation of (S)-3-ethylpentan-3-yl 2-((S)-1-((R)-4-benzyl-4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamoyl)pyrrolidine-1-carboxylate (1h)***. This compound was synthesized using the method for **1f** to yield the desired ligand (285 mg, 60% yield) as a colorless wax: $R_f$ = 0.26 (66% EtOAc/hexanes, stained with ninhydrine); $[\alpha]^{23}_D$ -46.5 (c = 0.48, $CHCl_3$); 300 MHz $^1$H NMR ($CDCl_3$) at 50 $^o$C δ 7.34-7.15 (m, 5H), 4.58 (dd, *J* = 6.3, 4.5 Hz, 1H), 4.43-4.27 (m, 2H), 4.20 (t, *J* = 8.9 Hz, 1H), 3.96 (t, *J* = 7.8 Hz, 1H), 3.53-3.32 (m, 2H), 3.11 (dd, *J* = 14.1, 5.4 Hz, 1H), 2.62 (dd, *J* = 14.1, 8.9 Hz, 1H), 2.43-1.72 (m, 11H), 0.91 (d, *J* = 6.8 Hz, 6H), 0.84 (t, *J* = 7.3 Hz, 9H); 75 MHz $^{13}$C NMR ($CDCl_3$) at 50 $^o$C δ 171.7, 166.2, 154.9, 137.8, 129.2, 128.4, 126.4, 87.9, 72.0, 67.0, 60.0, 52.3, 46.9, 41.7, 31.6, 27.2, 24.4, 18.7, 17.7, 7.7; IR (neat) 3275, 2966, 2940, 2879, 1678, 1651, 1547, 1453, 1401, 1123, 978, 916, 700 cm$^{-1}$; HRMS (ES) calcd. $C_{27}H_{41}N_3O_4Na$ $(M + Na)^+$ 494.2995, obsd. 494.2990.

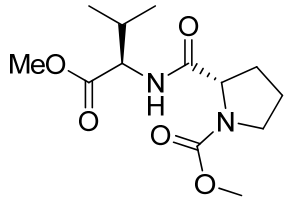


***Preparation of (S)-isopropyl 2-((R)-1-methoxy-3-methyl-1-oxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (SI-8)***. To a stirring solution of (*S*)-1-(isopropoxycarbonyl)pyrrolidine-2-carboxylic acid (103 mg, 0.51 mmol, 1 equiv.) in $CH_2Cl_2$ (2 mL), at -5 $^o$C, was slowly added *N*-methylmorpholine (84 μL, 0.76 mmol, 1.5 equiv.) via syringe. After the solution was stirred for 20 min at -5 $^o$C, isobutyl chloroformate (67 μL, 0.51 mmol, 1 equiv.) was added drop-wise, via syringe, to the reaction mixture. After the solution was stirred for an additional 30 min at -5 $^o$C, *N*-methylmorpholine (64 μL, 0.58 mmol, 1.15 equiv.) was added slowly, via syringe, to the reaction mixture. This was followed by the addition of *R*-valine methyl ester hydrochloride (94 mg, 0.56 mmol, 1.1 equiv.) in ca. three equal portions to the reaction mixture. The reaction mixture was then allowed to warm to room temperature. After 2 h, TLC analysis indicated complete consumption of starting material. The reaction was quenched by addition of 1 M HCl (5 mL) and diluted with $CH_2Cl_2$ (5 mL). The layers were separated, and the aqueous layer was removed. The organic layer was washed with $H_2O$ (3 x 10 mL), brine (5 mL). The organic layer was dried over $Na_2SO_4$, filtered, and then concentrated under reduced pressure. Purification was accomplished by mixed solvent recrystallization (1:4, $Et_2O$:hexanes) to yield **SI-8** as colorless crystals (138 mg, 86% yield): mp 85-86 $^o$C; $R_f$ = 0.40 (66% EtOAc/hexanes, stained with $KMnO_4$); $[\alpha]^{23}_D$ -81.8$^o$ (c = 2.89, $CHCl_3$); 500 MHz $^1$H NMR ($CDCl_3$) at 50 $^o$C δ 4.96 (pent, *J* = 6.3 Hz, 1H), 4.53 (dd, *J* = 8.8, 4.9 Hz, 1H), 4.36 (d, *J* = 7.8 Hz, 1H), 3.72 (s, 3H), 3.57-3.36 (m, 2H), 2.35-1.84 (m, 5H), 1.27 (t, *J* = 5.4 Hz, 6H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); 125 MHz $^{13}$C NMR ($CDCl_3$) at 50 $^o$C δ 172.3, 172.1, 155.9, 69.4, 60.8, 57.2,

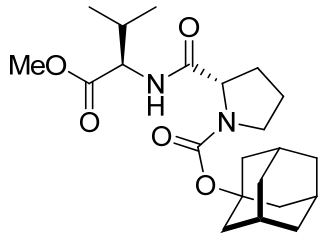
52.0, 47.2, 30.8, 29.4, 24.2, 22.3, 19.1, 17.8; IR (neat) 3262, 3070, 2973, 1742, 1710, 1659, 1552, 1412, 1202, 1176, 1143, 1122, 768 $cm^{-1}$; HRMS (ES) calcd. $C_{15}H_{27}N_2O_5$ $(M + H)^+$ 315.1920, obsd. 315.1919.



***Preparation of (S)-ethyl 2-((R)-1-methoxy-3-methyl-1-oxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (SI-9)***. This compound was synthesized using similar methods shown above for the synthesis of **SI-8** to yield **SI-9** as colorless crystals (408 mg, 91% yield): mp 39-41 $^oC$; $R_f$ = 0.31 (66% EtOAc/hexanes, stained with $KMnO_4$); $[\alpha]^{23}_D$ -74.5 (c = 2.75, $CHCl_3$); 500 MHz $^1H$ NMR ($CDCl_3$) at 50 $^oC$ δ 4.53 (dd, *J* = 8.8, 4.9 Hz, 1H), 4.37 (d, *J* = 6.3 Hz, 1H), 4.25-4.13 (m, 2H), 3.73 (s, 3H), 3.58-3.42 (m, 2H), 2.35-1.85 (m, 5H), 1.28 (t, *J* = 7.3 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); 125 MHz $^{13}C$ NMR ($CDCl_3$) at 50 $^oC$ δ 172.3, 172.0, 156.2, 61.9, 61.0, 57.2, 52.0, 47.3, 31.3, 29.3, 24.2, 19.1, 17.7, 14.8; IR (neat) 3316, 2966, 2878, 1744, 1697, 1536, 1422, 1381, 1347, 1267, 1205, 1120, 772 $cm^{-1}$; HRMS (ES) calcd. $C_{14}H_{25}N_2O_5$ $(M + H)^+$ 301.1763, obsd. 301.1758.

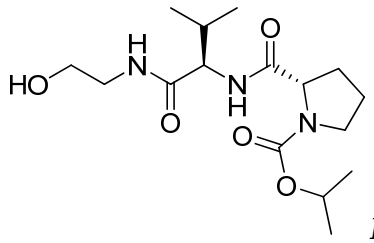


***Preparation of (S)-methyl 2-((R)-1-methoxy-3-methyl-1-oxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (SI-10)***. This compound was synthesized using similar methods shown above for the synthesis of **SI-8** to yield **SI-10** as colorless crystals (370 mg, 86% yield): mp 59-62 $^oC$; $R_f$ = 0.26 (66% EtOAc/hexanes, stained with $KMnO_4$); $[\alpha]^{23}_D$ -81.5 (c = 3.26, $CHCl_3$); 500 MHz $^1H$ NMR ($CDCl_3$) at 50 $^oC$ δ 4.52 (dd, *J* = 10.1, 5.2 Hz, 1H), 4.35 (bs, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.58-3.41 (m, 2H), 2.32-1.85 (m, 5H), 0.95 (d, *J* = 10.0 Hz, 3H), 0.89 (d, *J* = 10.1 Hz, 3H); 125 MHz $^{13}C$ NMR ($CDCl_3$) at 50 $^oC$ δ 172.3, 171.9, 156.5, 61.0, 57.2, 47.4, 31.3, 29.5, 24.2, 19.1, 17.7; IR (neat) 3317, 2962, 2878, 1743, 1704, 1535, 1452, 1383, 1203, 773 $cm^{-1}$; HRMS (ES) calcd. $C_{13}H_{23}N_2O_5$ $(M + H)^+$ 287.1607, obsd. 287.1611.

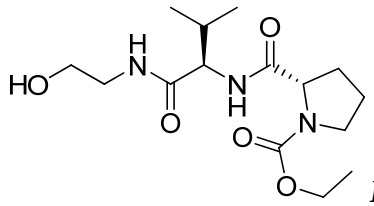


***Preparation of (S)-(1-adamantyl) 2-((R)-1-methoxy-3-methyl-1-oxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (SI-11)***. This compound was synthesized using similar methods shown above for the synthesis of **SI-8** to yield **SI-11** as colorless crystals (249 mg, 88% yield): mp 113-115 $^oC$; $R_f$ = 0.44 (66% EtOAc/hexanes, stained with $KMnO_4$); $[\alpha]^{23}_D$ -42.1 (c = 1.07, $CHCl_3$); 500 MHz $^1H$

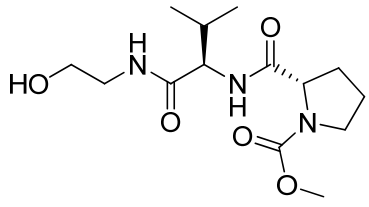
NMR ($CDCl_3$) at 50 °C δ 4.52 (dd, *J* = 8.8, 4.9 Hz, 1H), 4.32 (d, *J* = 5.9 Hz, 1H), 3.72 (s, 3H), 3.53-3.32 (m, 2H), 2.34-1.81 (m, 14H), 1.66 (bs, 6H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); 125 MHz $^{13}C$ NMR ($CDCl_3$) at 50 °C δ 172.4, 80.5, 60.6, 57.3, 52.1, 47.3, 42.0, 36.3, 31.2, 30.6, 24.2, 19.2, 17.9; IR (neat) 3313, 2912, 1744, 1696, 1536, 1398, 1353, 1300, 1203, 1123, 1056, 769 $cm^{-1}$; HRMS (ES) calcd. $C_{22}H_{34}N_2O_5Na$ $(M + Na)^+$ 429.2365, obsd. 429.2371.



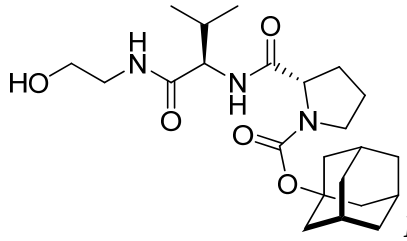
***Preparation of (S)-isopropyl 2-((R)-1-(2-hydroxyethylamino)-3-methyl-1-oxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (SI-12)***. To a stirring solution of **SI-8** (141 mg, 0.45 mmol, 1 equiv.), toluene (800 µL), and tetrahydrofuran (800 µL), was added 2-amino ethanol (137 µL, 2.28 mmol, 5 equiv.) via syringe. After 3 d at reflux the mixture was diluted with $CHCl_3$ (10 mL). The organic layer was then washed with $H_2O$ (3 x 10 mL) and brine (10 mL). The organic layer was dried over $Na_2SO_4$, filtered, and then concentrated under reduced pressure. Purification was accomplished by mixed solvent recrystallization (1:5, $CH_2Cl_2$:hexanes) to yield a white solid (141 mg, 91% yield): mp 185-187 °C; $R_f$ = 0.43 (10% MeOH/$CH_2Cl_2$, $KMnO_4$); $[\alpha]^{23}_D$ +1.6 (c = 0.49, $CHCl_3$); 500 MHz $^1H$ NMR ($CDCl_3$) at 50 °C δ 4.52 (dd, *J* = 8.8, 4.9 Hz, 1H), 4.32 (d, *J* = 5.9 Hz, 1H), 3.72 (s, 3H), 3.53-3.32 (m, 2H), 2.34-1.81 (m, 14H), 1.66 (bs, 6H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); 125 MHz $^{13}C$ NMR ($CDCl_3$) at 50 °C δ 172.4, 80.5, 60.6, 57.3, 52.1, 47.3, 42.0, 36.3, 31.2, 30.6, 24.2, 19.2, 17.9; IR (neat) 3285, 2966, 2872, 1664, 1638, 1546, 1421, 1383, 1345, 1231, 1173, 1109, 930, 768 $cm^{-1}$; HRMS (ES) calcd. $C_{16}H_{29}N_3O_5Na$ $(M + Na)^+$ 366.2005, obsd. 366.2005.



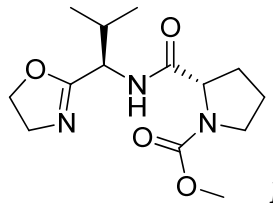
***Preparation of (S)-ethyl 2-((R)-1-(2-hydroxyethylamino)-3-methyl-1-oxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (SI-13)***. This compound was synthesized using similar methods shown above for the synthesis of **SI-12** to yield a colorless solid (86% yield): mp 170-173 °C; $R_f$ = 0.48 (10% MeOH/$CH_2Cl_2$, $KMnO_4$); $[\alpha]^{23}_D$ +2.8 (c = 0.88, $CHCl_3$); 400 MHz $^1H$ NMR ($CDCl_3$) at 50 °C δ 7.12 (bs, 1H), 6.60 (d, *J* = 8.6 Hz, 1H), 4.30 (dd, *J* = 8.6, 5.9 Hz, 1H), 4.19 (t, *J* = 4.7 Hz, 1H), 4.14 (d, *J* = 7.0 Hz, 1H), 4.10 (d, *J* = 7.4 Hz, 1H), 3.71-3.32 (m, 6H), 2.52-1.80 (m, 5H), 1.25 (t, *J* = 7.4 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H); 100 MHz $^{13}C$ NMR ($CDCl_3$) at 50 °C δ 172.8, 171.6, 156.1, 61.9, 61.8, 61.0, 58.7, 47.2, 42.7, 29.9, 24.6, 19.4, 17.4, 14.6; IR (neat) 3281, 2956, 2871, 1703, 1668, 1638, 1547, 1421, 1381, 1346, 1232, 1174, 1150, 1067, 768 $cm^{-1}$; HRMS (ES) calcd. $C_{15}H_{27}N_3O_5Na$ $(M + Na)^+$ 352.1848, obsd. 352.1840.



***Preparation of (S)-methyl 2-((R)-1-(2-hydroxyethylamino)-3-methyl-1-oxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (SI-14)***. This compound was synthesized using similar methods shown above for the synthesis of **SI-12** to yield a colorless solid (84% yield): mp 154-156 $^{o}$C; $R_f$ = 0.36 (10% MeOH/$CH_2Cl_2$, $KMnO_4$); $[\alpha]^{23}_D$ +8.6 (c = 0.42, $CHCl_3$); 400 MHz $^1$H NMR ($CDCl_3$) at 50 $^{o}$C δ 7.07 (bs, 1H), 6.47 (d, *J* = 7.4 Hz, 1H), 4.36-4.14 (m, 2H), 3.77-3.64 (m, 5H), 3.61-3.33 (m, 4H), 2.54-1.82 (m, 5H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H); 100 MHz $^{13}$C NMR ($CDCl_3$) at 50 $^{o}$C δ 172.7, 171.5, 61.9, 61.2, 52.9, 47.2, 42.7, 29.8, 24.6, 19.4, 17.3; IR (neat) 3478, 3291, 2954, 2869, 1692, 1660, 1632, 1544, 1459, 1391, 1337, 1122, 1092, 770 cm$^{-1}$; HRMS (ES) calcd. $C_{14}H_{25}N_3O_5Na$ $(M + Na)^+$ 338.1692, obsd. 338.1694.

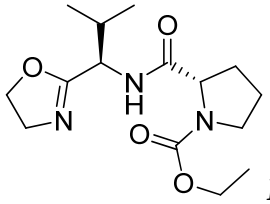


***Preparation of (S)-(1-adamantyl) 2-((R)-1-(2-hydroxyethylamino)-3-methyl-1-oxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (SI-15)***. This compound was synthesized using similar methods shown above for the synthesis of **SI-12** to yield a white solid (86% yield): mp 206-208 $^{o}$C; $R_f$ = 0.45 (10% MeOH/$CH_2Cl_2$, $KMnO_4$); $[\alpha]^{23}_D$ -18.8 (c = 0.32, $CHCl_3$); 400 MHz $^1$H NMR ($CDCl_3$) at 50 $^{o}$C δ 7.02 (bs, 1H), 6.53 (d, *J* = 8.6 Hz, 1H), 4.36-4.10 (m, 2H), 3.69 (d, *J* = 4.7 Hz, 2H), 3.55-3.30 (m, 4H), 2.45-1.79 (m, 14H), 1.66 (bs, 6H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H); 100 MHz $^{13}$C NMR ($CDCl_3$) at 50 $^{o}$C δ 172.9, 171.9, 80.6, 62.2, 60.8, 58.7, 47.3, 42.7, 41.8, 36.2, 30.9, 29.5, 24.5, 19.4; IR (neat) 3395, 3328, 3274, 2964, 2909, 2851, 1680, 1661, 1644, 1571, 1526, 1419, 1352, 1299, 1131, 1056, 921, 631 cm$^{-1}$; HRMS (ES) calcd. $C_{23}H_{37}N_3O_5Na$ $(M + Na)^+$ 358.2631, obsd. 358.2636.

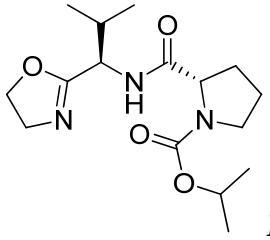


***Preparation of (S)-methyl 2-((R)-1-(4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamoyl)pyrrolidine-1-carboxylate (3a)***. This compound was synthesized using similar methods shown above for the synthesis of **3b** to yield a colorless solid (74% yield): mp 98-102 $^{o}$C; $R_f$ = 0.43 (10% MeOH/$CH_2Cl_2$, $KMnO_4$); $[\alpha]^{23}_D$ -63.2 (c = 0.22, $CHCl_3$); 300 MHz $^1$H NMR ($CDCl_3$) at 50 $^{o}$C δ 6.68 (bs, 1H), 4.60 (dd, *J* = 9.3, 5.4 Hz, 1H), 4.37-4.18 (m, 3H), 3.81 (t, *J* = 9.3 Hz, 2H), 3.72 (s, 3H), 3.63-3.38 (m, 2H), 2.28-1.74 (m, 5H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); 75 MHz $^{13}$C NMR ($CDCl_3$) at 50 $^{o}$C δ 171.5, 166.9, 77.2, 67.9, 61.1, 54.1, 52.7, 52.4, 47.3,

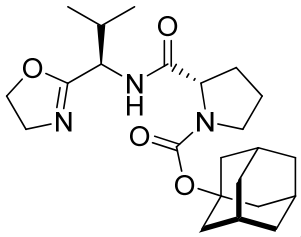
31.5, 24.0, 18.8, 17.6; IR (neat) 3333, 2957, 2887, 1704, 1657, 1531, 1451, 1382, 1168, 985, 769 $cm^{-1}$; HRMS (ES) calcd. $C_{14}H_{23}N_3O_4Na$ $(M + Na)^+$ 320.1586, obsd. 320.1590.



***Preparation of (S)-ethyl 2-((R)-1-(4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamoyl)pyrrolidine-1-carboxylate (3b)***. This compound was synthesized using similar methods shown above for the synthesis of **3b** to yield a colorless solid (82% yield): mp 72-75 $^oC$; $R_f$ = 0.22 (50% Acetone/Hexanes, $KMnO_4$); $[\alpha]^{23}_D$ -69.2 (c = 0.13, $CHCl_3$); 300 MHz $^1H$ NMR ($CDCl_3$) at 50 $^oC$ δ 6.74 (bs, 1H), 4.57 (dd, *J* = 9.3, 5.4 Hz, 1H), 4.36-4.06 (m, 5H), 3.79 (t, *J* = 9.8 Hz, 2H), 3.59-3.35 (m, 2H), 2.25-1.77 (m, 5H), 1.23 (t, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H); 75 MHz $^{13}C$ NMR ($CDCl_3$) at 50 $^oC$ δ 171.6, 166.8, 155.8, 77.2, 67.8, 61.6, 60.9, 54.0, 52.4, 47.1, 31.5, 23.9, 18.7, 17.5, 14.6; IR (neat) 3210, 2963, 2911, 2873, 1682, 1660, 1542, 1467, 1449, 1379, 1344, 1236, 1124, 985, 959, 770 $cm^{-1}$; HRMS (ES) calcd. $C_{15}H_{25}N_3O_4Na$ $(M + Na)^+$ 334.1743, obsd. 334.1738.

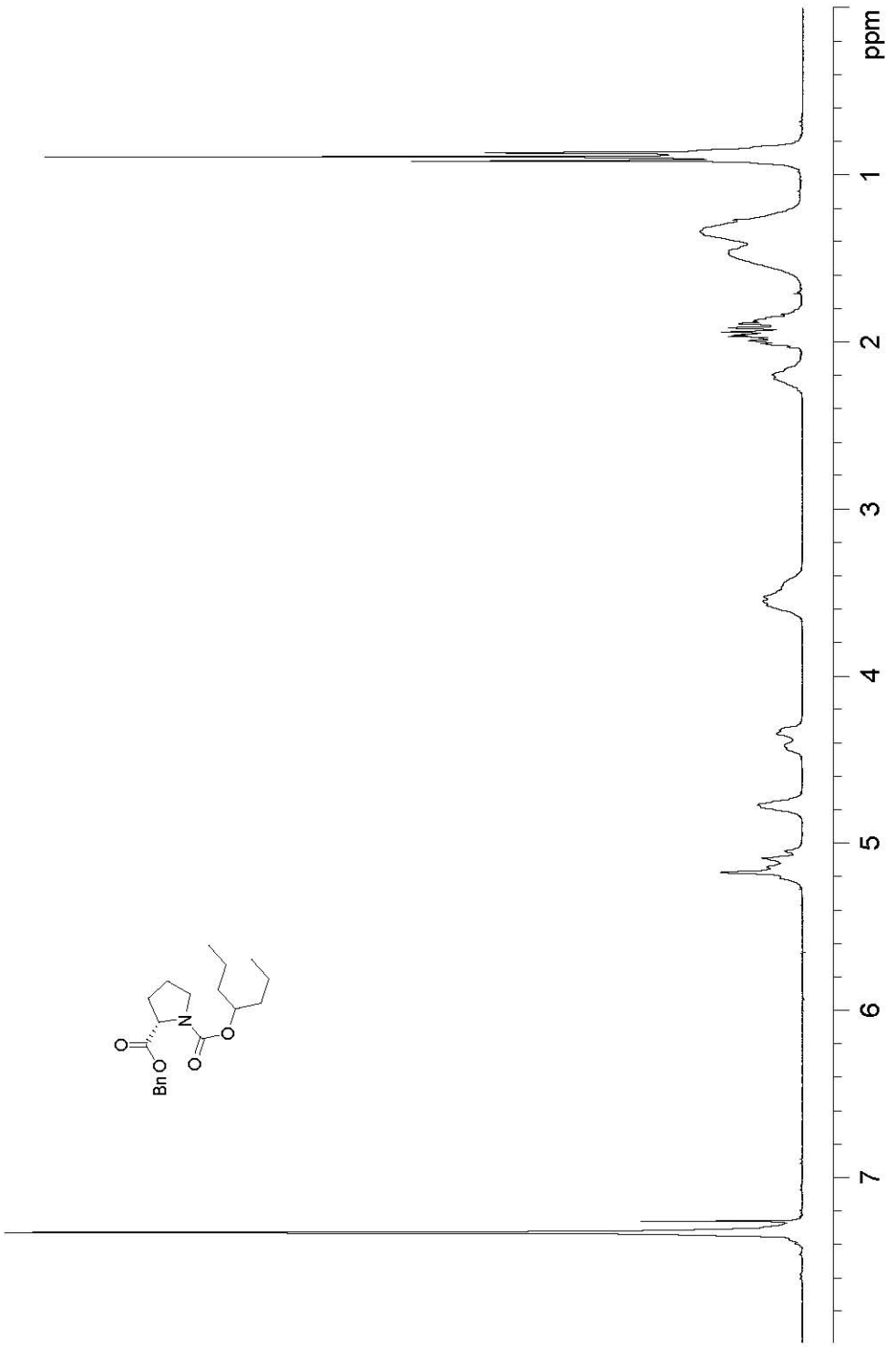


***Preparation of (S)-isopropyl 2-((R)-1-(4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamoyl)pyrrolidine-1-carboxylate (3c)***. To a stirring solution of **SI-12** (117 mg, 0.34 mmol, 1 equiv.) and tetrahydrofuran (2.25mL) was added triphenylphosphine (108 mg, 0.41 mmol, 1.2 equiv.) in one portion. This was followed by dropwise addition of diisopropyl azodicarboxylate (86 μL, 0.41 mmol, 1.2 equiv.) via syringe, to the reaction mixture. The reaction mixture was allowed to clear between drops. The progress of the reaction was monitored by TLC analysis. After 2 h of stirring the mixture was concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 1.5 x 12 cm column, eluting with 75 mL or 35% EtOAc/Hexanes followed by 40% Acetone/Hexanes, collecting 9 mL fractions. The product containing fractions were combined and concentrated under reduced pressure. The solid was then recrystallized by mixed solvent recrystallization (1:4, acetone:hexanes) to yield a colorless solid (97 mg, 88% yield): mp 112-114 $^oC$; $R_f$ = 0.31 (50% Acetone/Hexanes, ninhydrine) $[\alpha]^{23}_D$ -71.7 (c = 0.29, $CHCl_3$); 500 MHz $^1H$ NMR ($CDCl_3$) at 50 $^oC$ δ 4.88 (sept, *J* = 6.3 Hz, 1H), 4.54 (dd, *J* = 8.8, 4.9 Hz, 1H), 4.34-4.25 (m, 1H), 4.20 (sext, *J* = 9.3 Hz, 2H), 3.76 (t, *J* = 9.8 Hz, 2H), 3.53-3.27 (m, 2H), 2.26-1.76 (m, 5H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.19 (d, *J* = 6.3 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); 125 MHz $^{13}C$ NMR ($CDCl_3$) at 50 $^oC$ δ 172.1, 167.2, 155.9, 69.5, 68.2, 61.2, 54.5, 52.8, 47.5, 31.9, 31.2, 29.7, 24.3, 22.6, 22.5, 19.2, 18.0; IR (neat) 3213, 3045, 2960, 2874, 1687, 1657, 1549, 1418, 1380, 1209, 1110, 933, 769, 697 $cm^{-1}$; HRMS (ES) calcd. $C_{16}H_{27}N_3O_4Na$ $(M + Na)^+$ 343.1899, obsd. 348.1908.



***Preparation of (S)-(1-adamantyl) 2-((R)-1-(4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamoyl)pyrrolidine-1-carboxylate (3e)***. This compound was synthesized using similar methods shown above for the synthesis of **3b** to yield a colorless solid (75% yield): mp 116-119 $^{o}$C; $R_f$ = 0.33 (50% Acetone/Hexanes, $KMnO_4$); $[\alpha]^{23}_D$ -78.5 (c = 0.26, $CHCl_3$); 400 MHz $^1$H NMR ($CDCl_3$) at 50 $^{o}$C δ 4.60 (dd, *J* = 8.0, 5.7 Hz, 1H), 4.36-4.17 (m, 3H), 3.81 (t, *J* = 9.4 Hz, 2H), 3.54-3.30 (m, 2H), 2.31-1.77 (m, 14H), 1.65 (bs, 6H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H); 100 MHz $^{13}$C NMR ($CDCl_3$) at 50 $^{o}$C δ 171.9, 166.9, 154.7, 80.2, 67.8, 60.9, 54.1, 52.4, 47.0, 41.8, 36.3, 31.6, 31.0, 24.0, 18.9, 17.8; IR (neat) 3282, 2907, 2850, 1691, 1655, 1555, 1394, 1353, 1299, 1208, 1058, 982, 768 cm$^{-1}$; HRMS (ES) calcd. $C_{23}H_{35}N_3O_4Na$ $(M + Na)^+$ 440.2525, obsd. 440.2518.

**Preparation of homoallylic alcohols**. To a 1.5 dram vial was added $CrCl_3$ (7.9 mg, 0.05 mmol, 0.1 equiv.), Mn(0) (325 mesh) (55mg, 1.0 mmol, 2 equiv.), **2a** (17 mg, 0.05 mmol, 0.1 equiv.). The vial was fitted with a permeable Teflon cap and charged with tetrahydrofuran (2.5 mL) and allowed to stir. After c.a. 2 min, triethylamine (15 μL, 0.1 mmol, 0.2 equiv.) and chlorotrimethylsilane (255 μL, 2 mmol, 4 equiv.) were added to the reaction mixture. After the solution had stirred for 20 min and the color had changed to a deep blue/purple color, allyl bromide (85 μL, 1.0 mmol, 2 equiv.) was added to the reaction mixture. After 30 min, carbonyl (0.5 mmol, 1 equiv.) was added and the mixture was allowed to stir at room temperature. After 24 h, the reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (1.5 mL). Take care to add $NaHCO_3$ solution dropwise as a large amount of gas evolves. After stirring for 20 min, the mixture was passed through a Celite® plug, eluting with diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and then concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 2 x 15 cm column, eluting with 8% EtOAc/hexanes, collecting 9 mL fractions. The product containing fractions were combined and concentrated under reduced pressure to give the desired homoallylic alcohol as a colorless oil (64-97% yield): The enantiomeric excess of acetophenone allylation was determined by HPLC analysis (Chiralcel OJ-H, hexanes/*i*-PrOH = 97/3, flow rate = 1.0 mL/min): $t_{major}$ = 9.6 min (*R*), $t_{minor}$ = 11.5 min (*S*).[5] The enantiomeric excess of benzaldehyde allylation was determined by HPLC analysis (Chiralcel OD, hexanes/*i*-PrOH = 98/2, flow rate = 1.0 mL/min): $t_{major}$ = 15.9 min (R), $t_{minor}$ = 18.4 min (S).[1] The enantiomeric excess of hydrocinnamaldehyde allylation was determined by HPLC analysis (Chiralcel OD, hexanes/*i*-PrOH = 98/2, flow rate = 1.0 mL/min): $t_{major}$ = 19.3 min (S), $t_{minor}$ = 34.5 min (R).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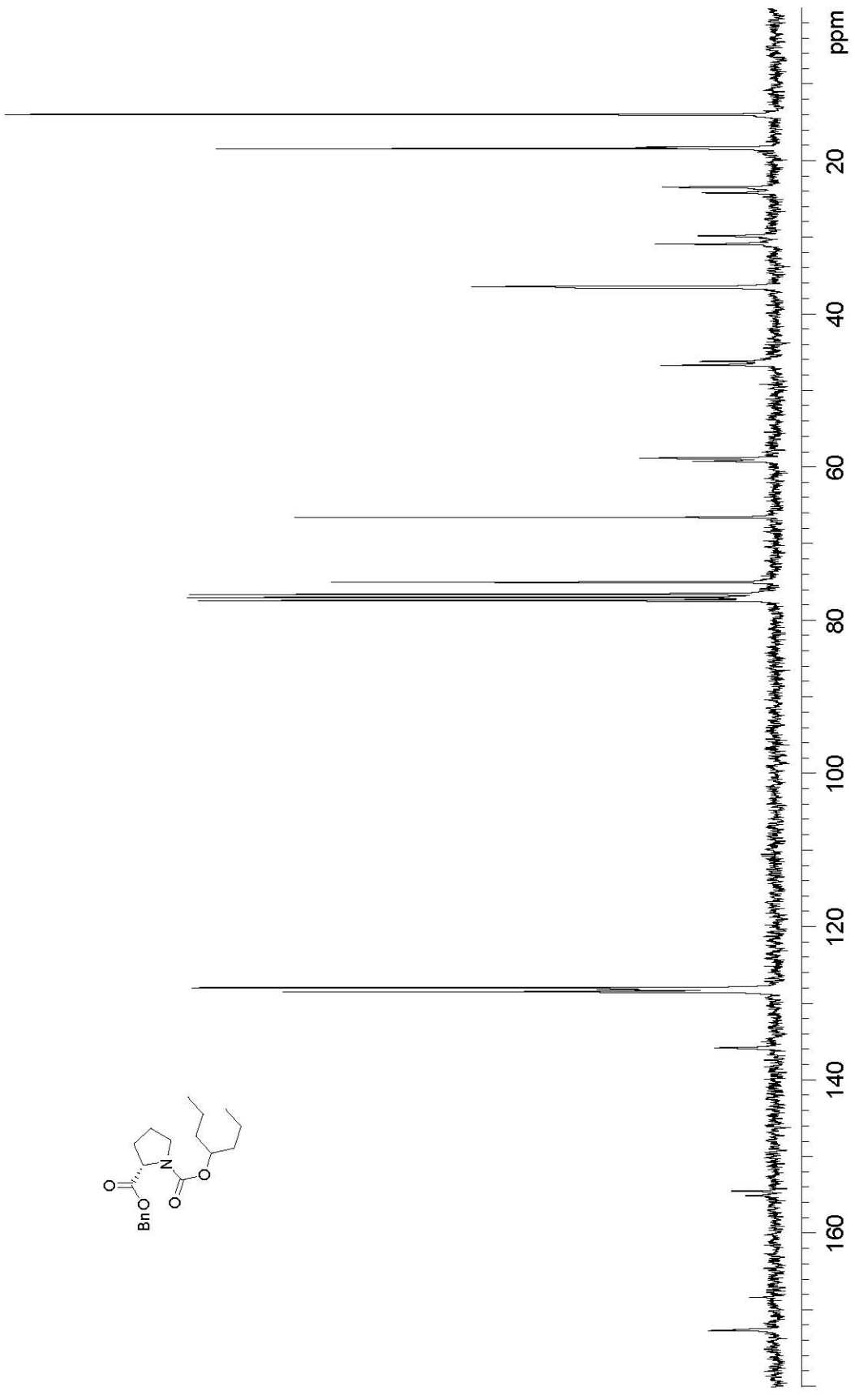
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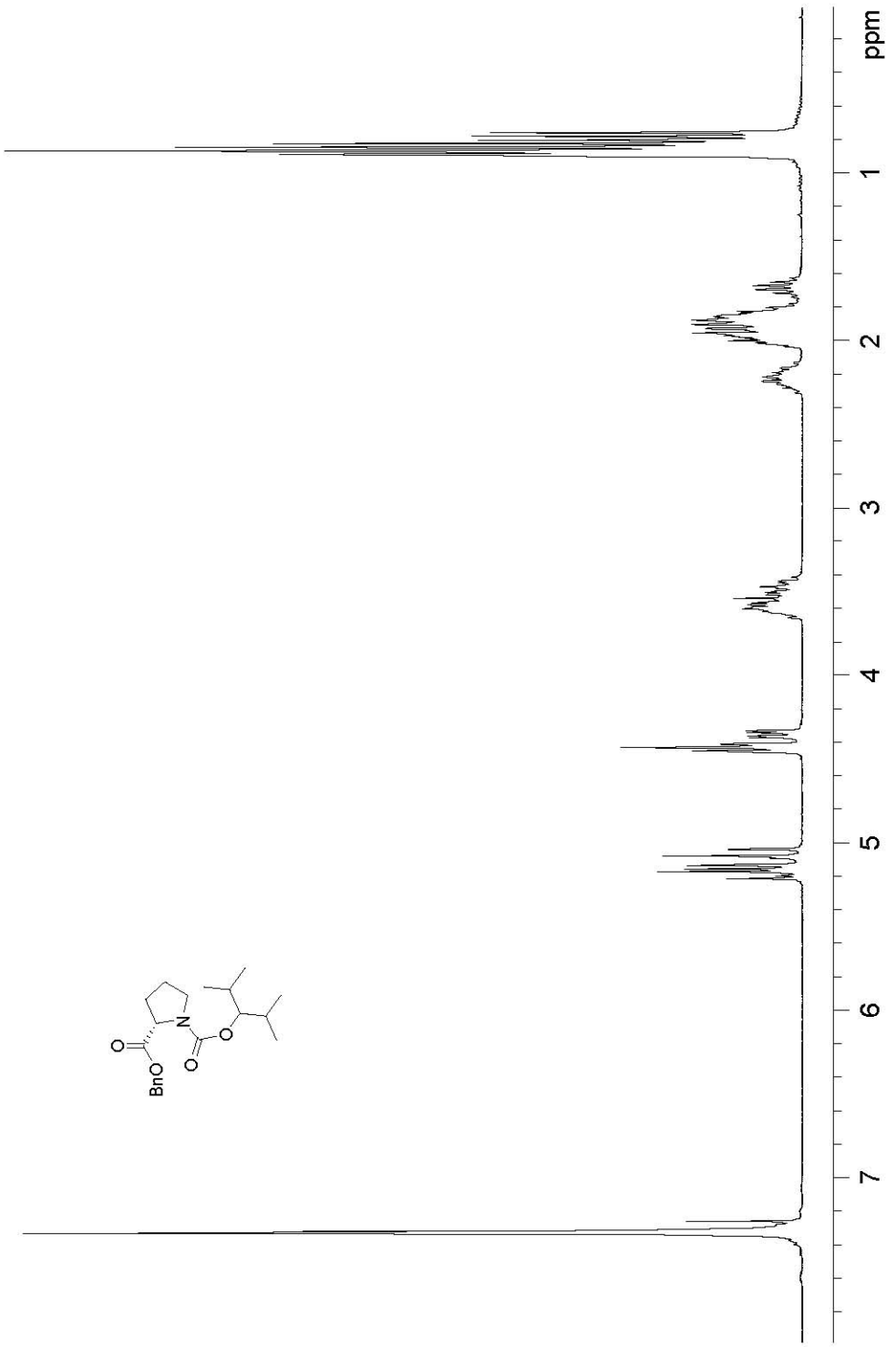
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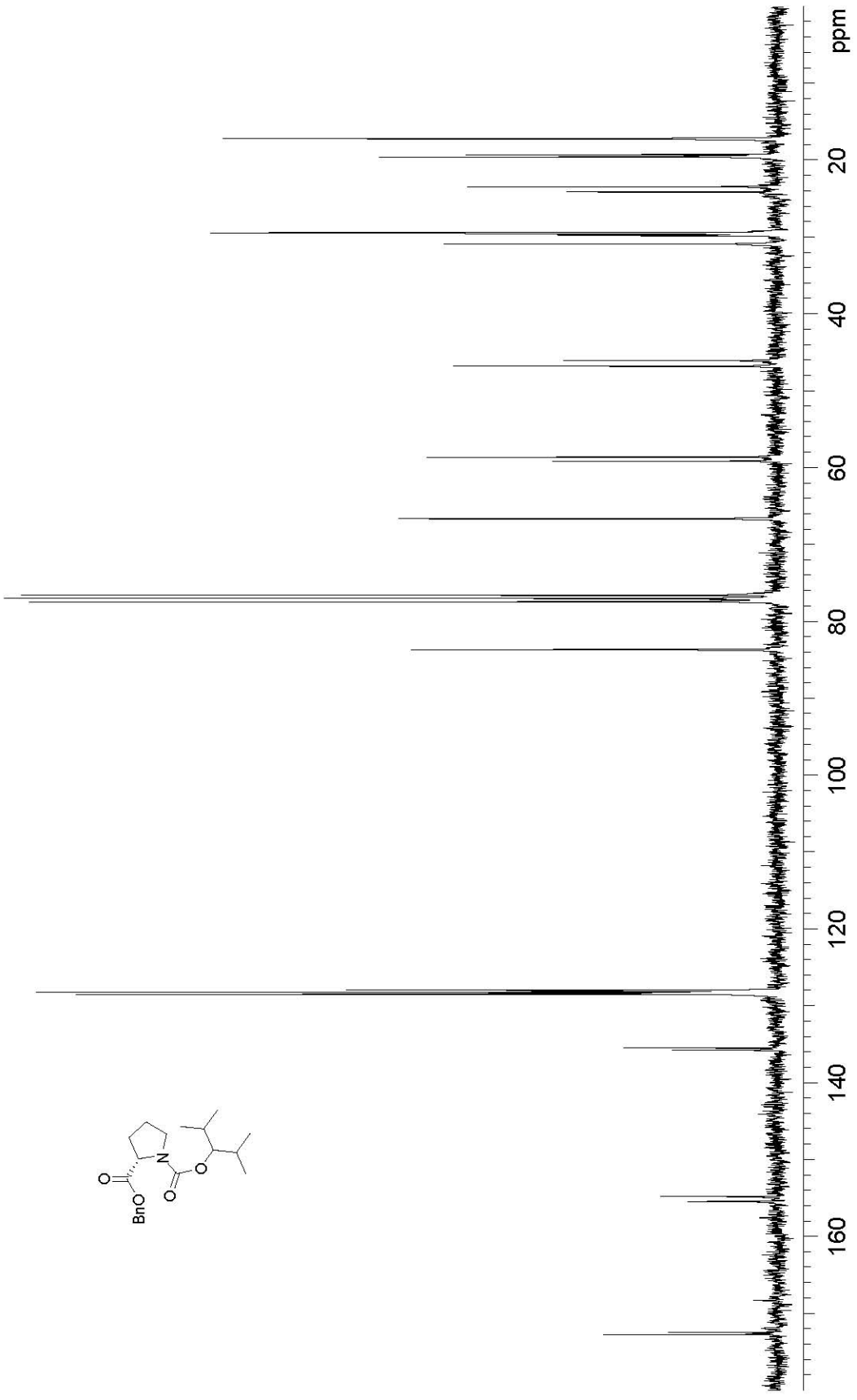
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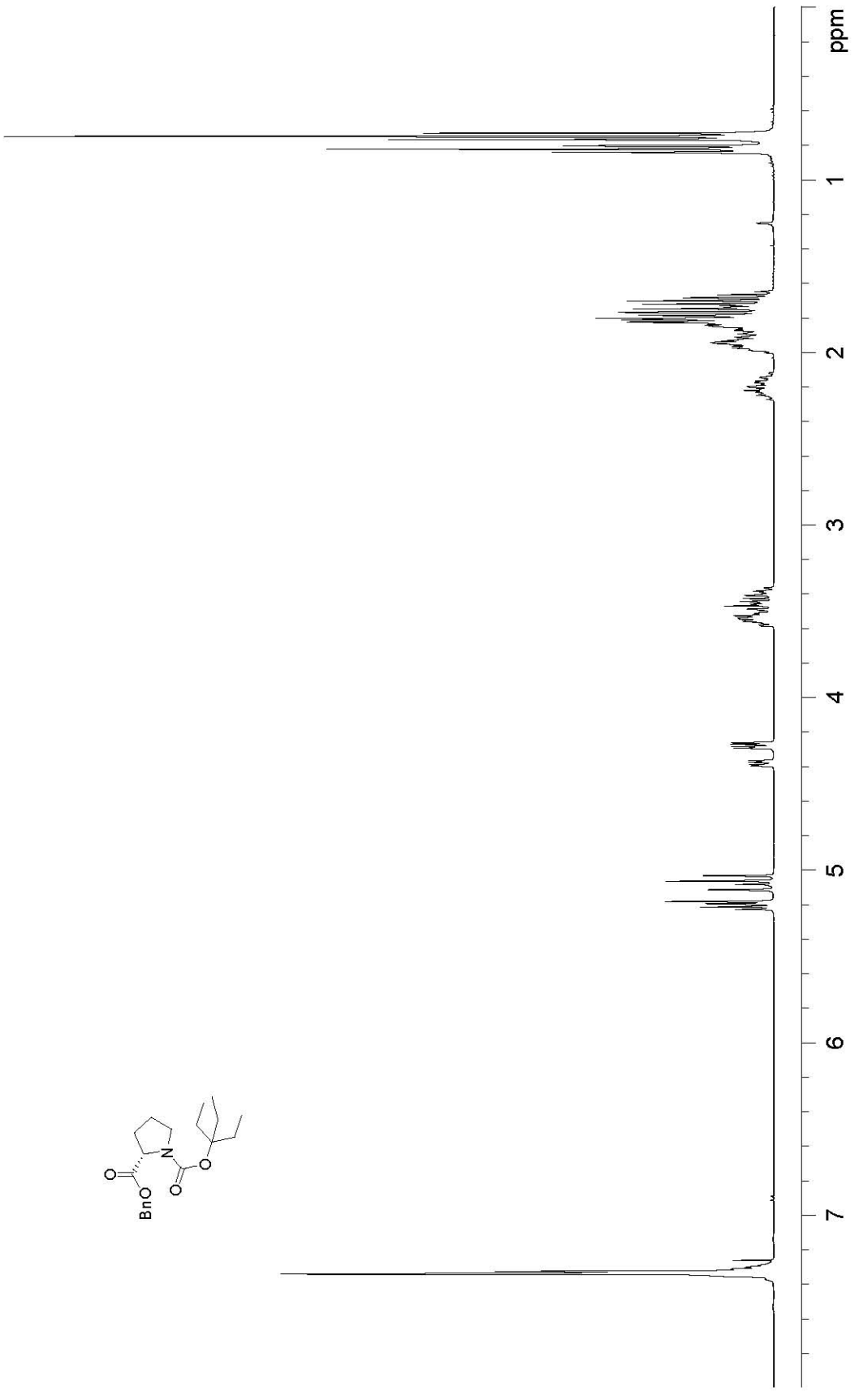
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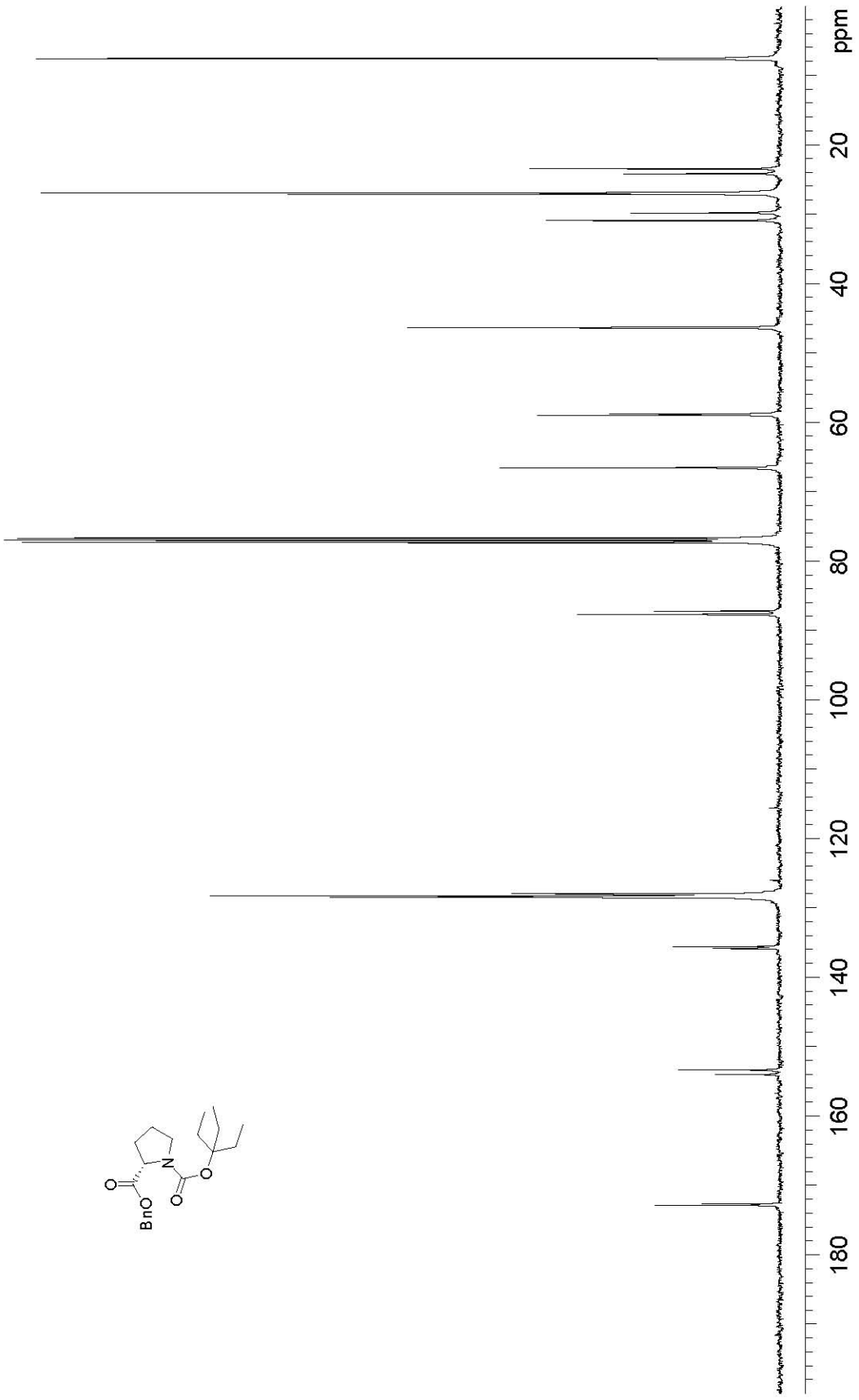
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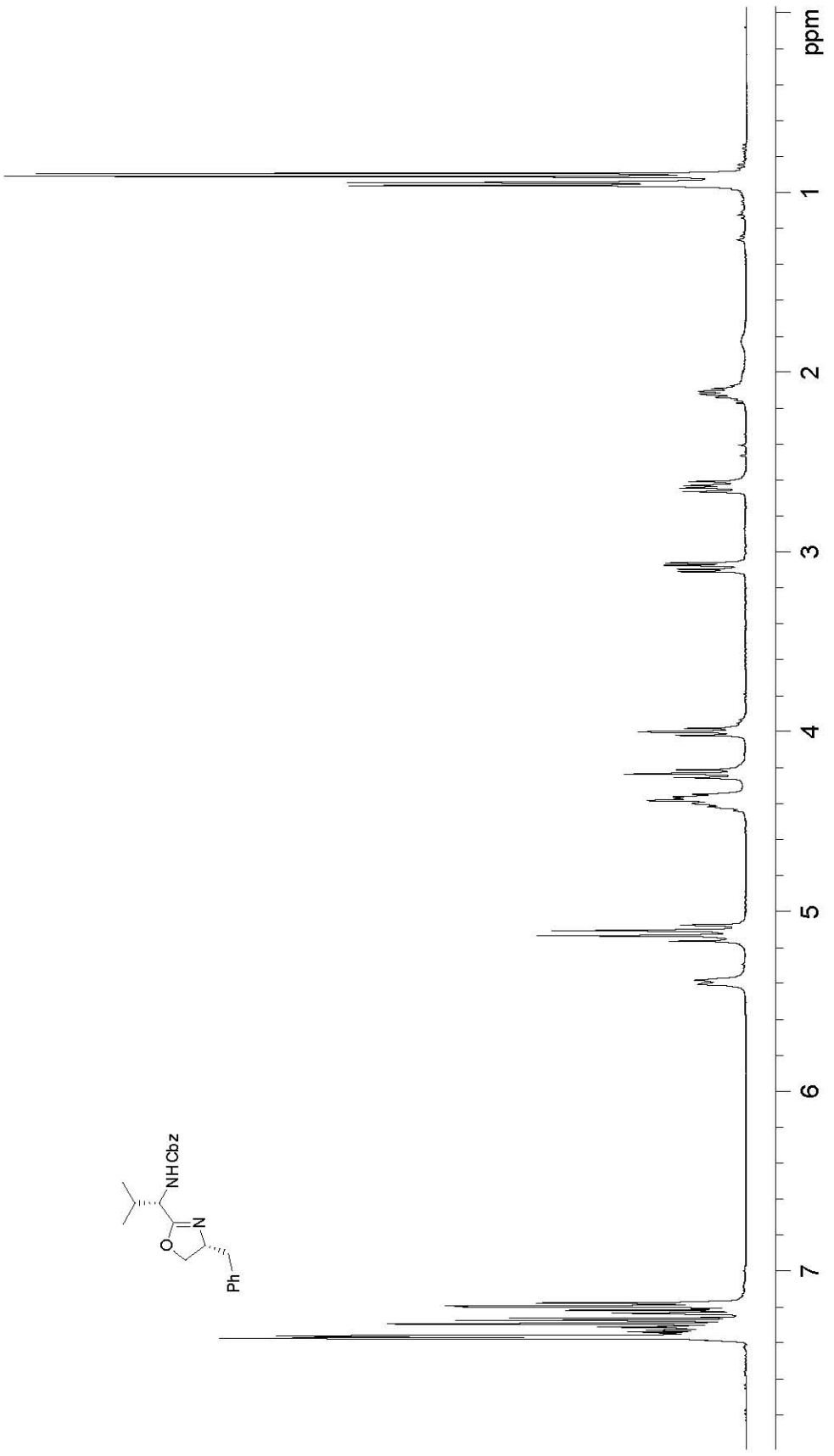
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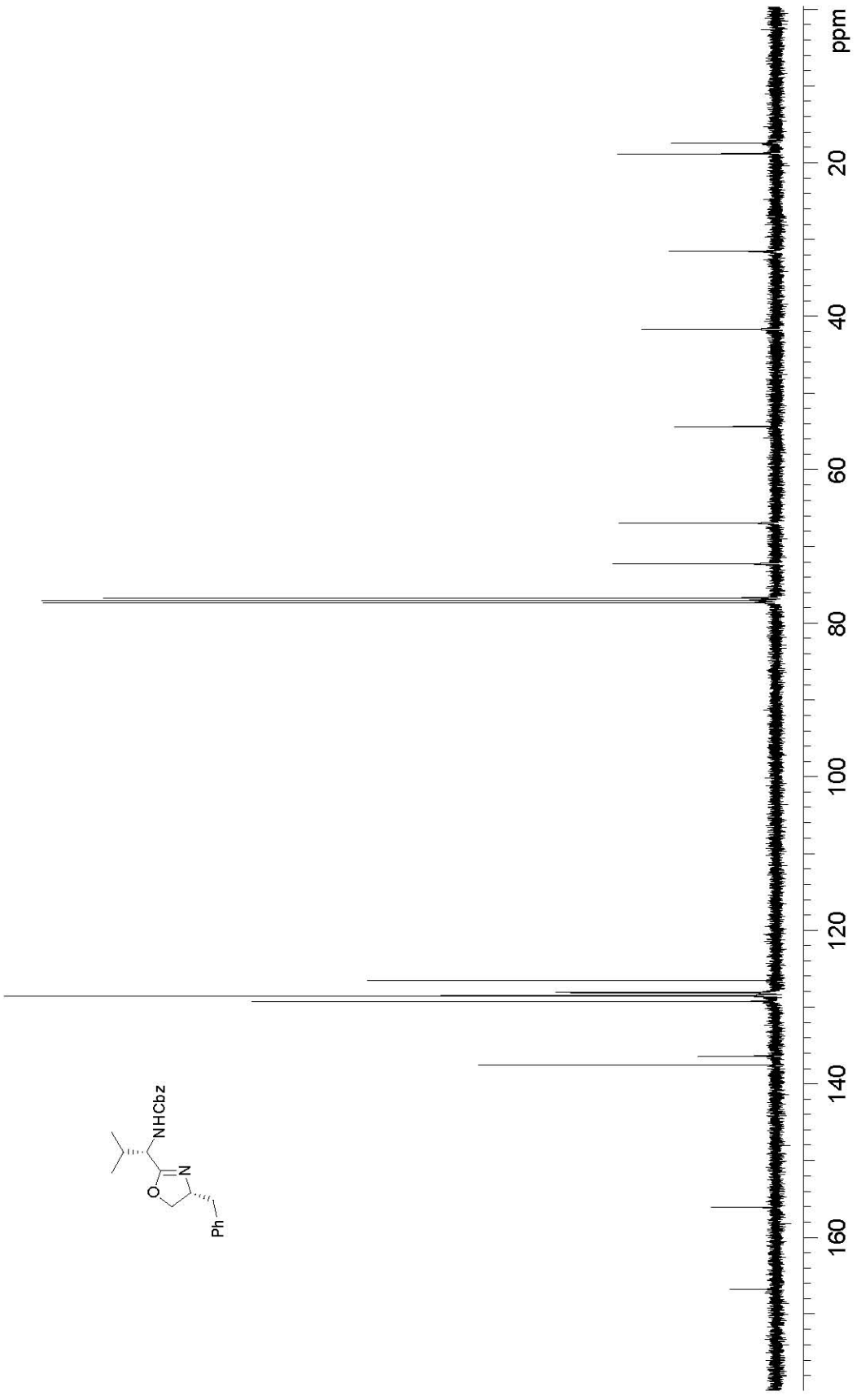
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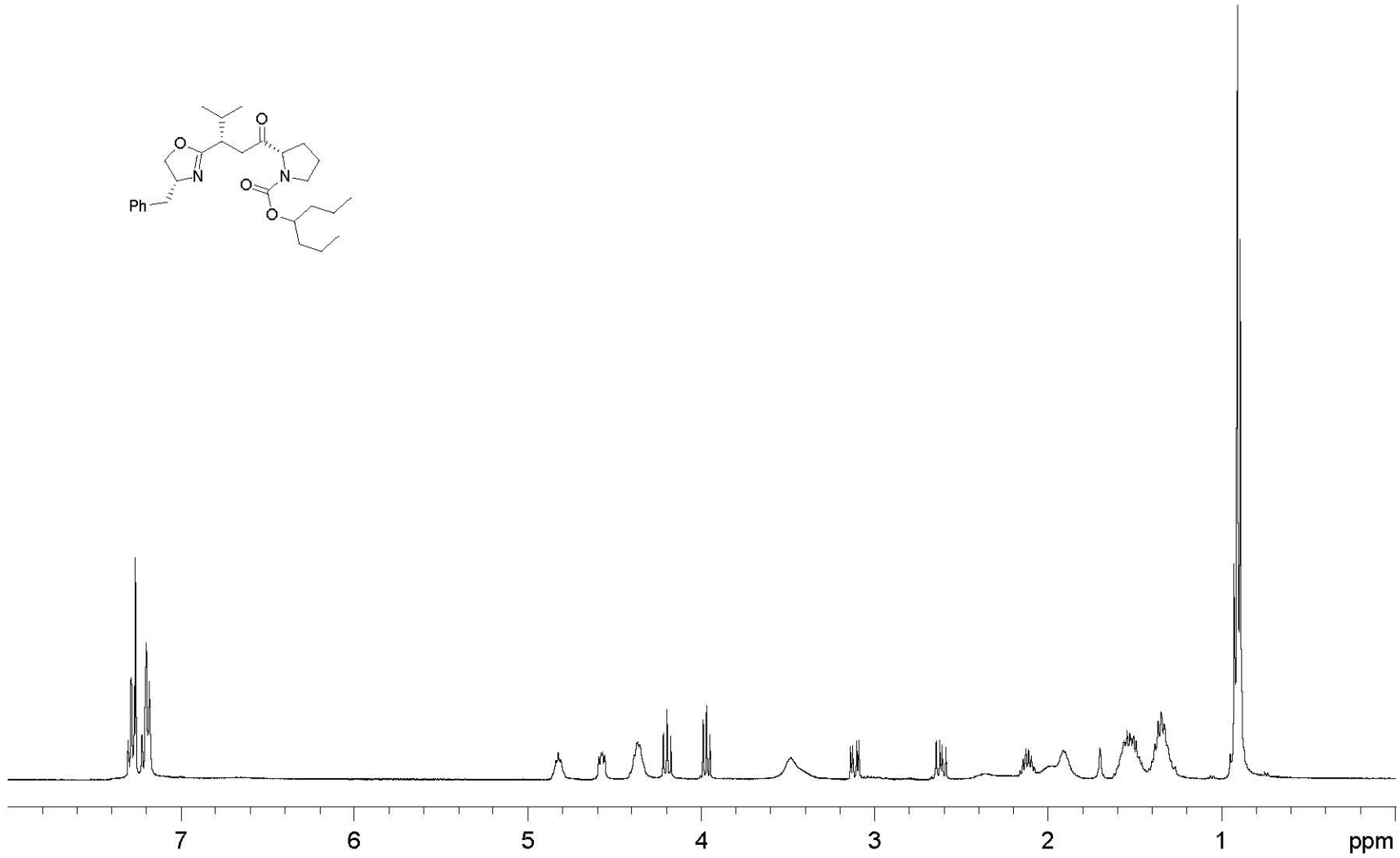
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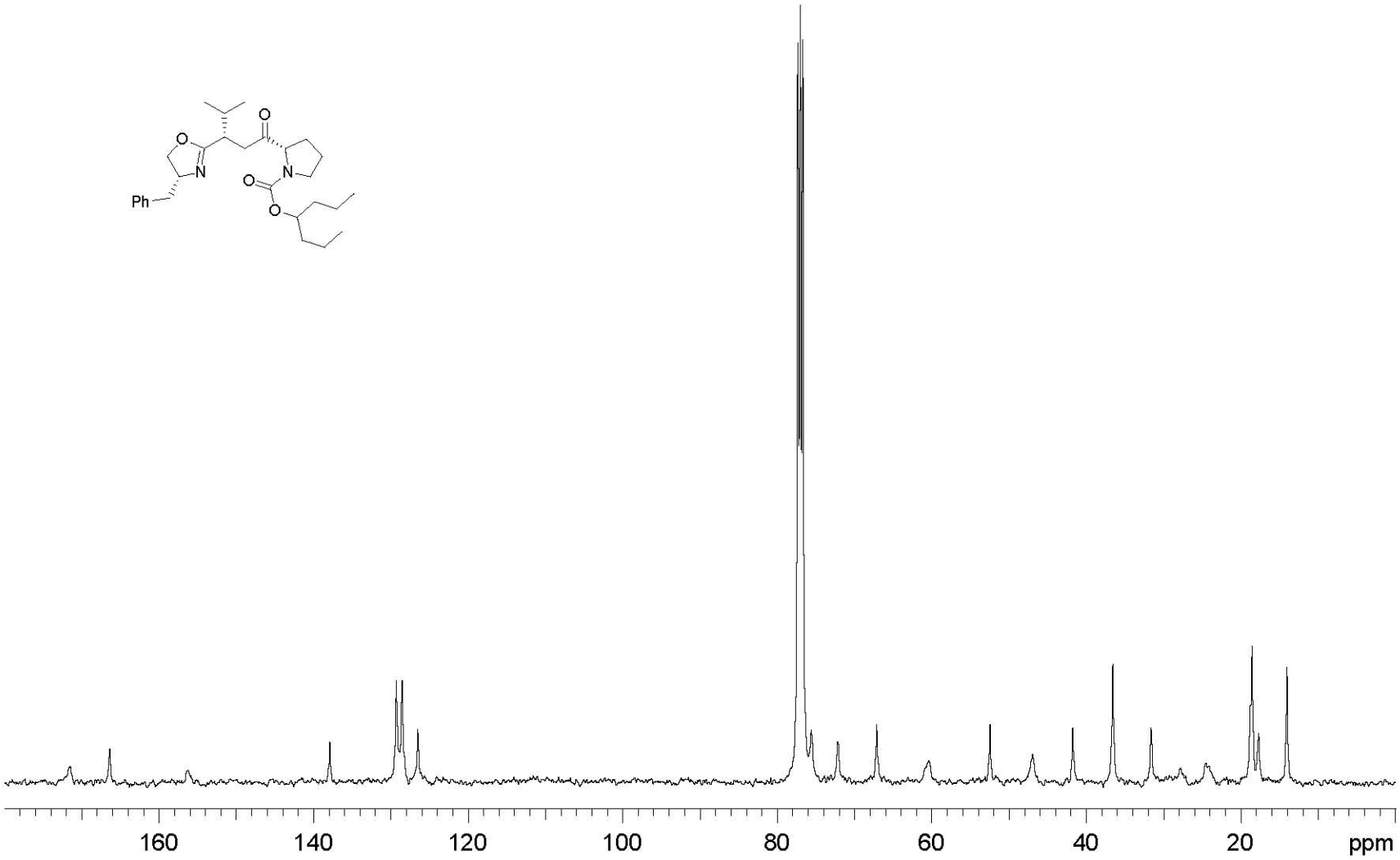
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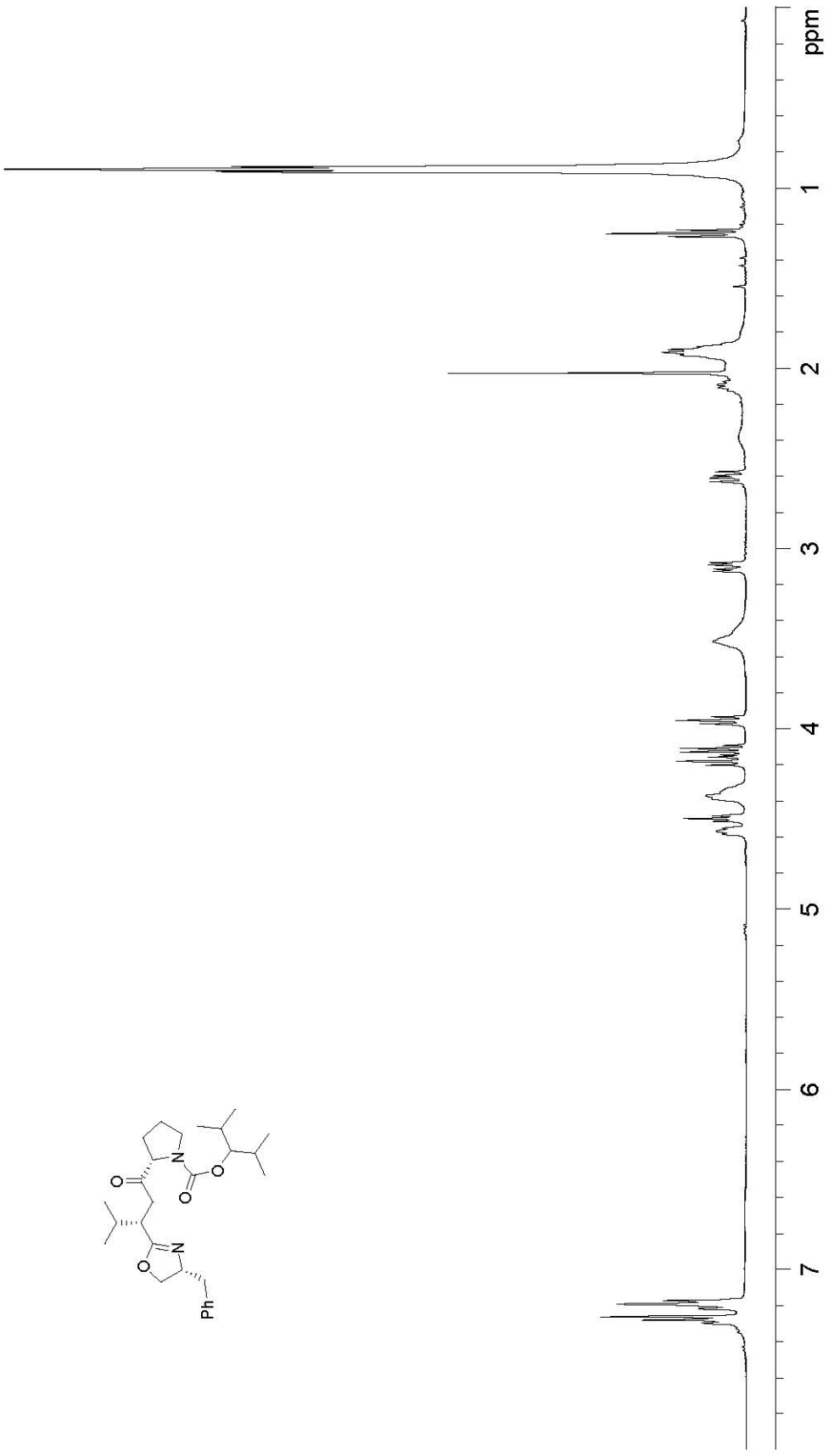
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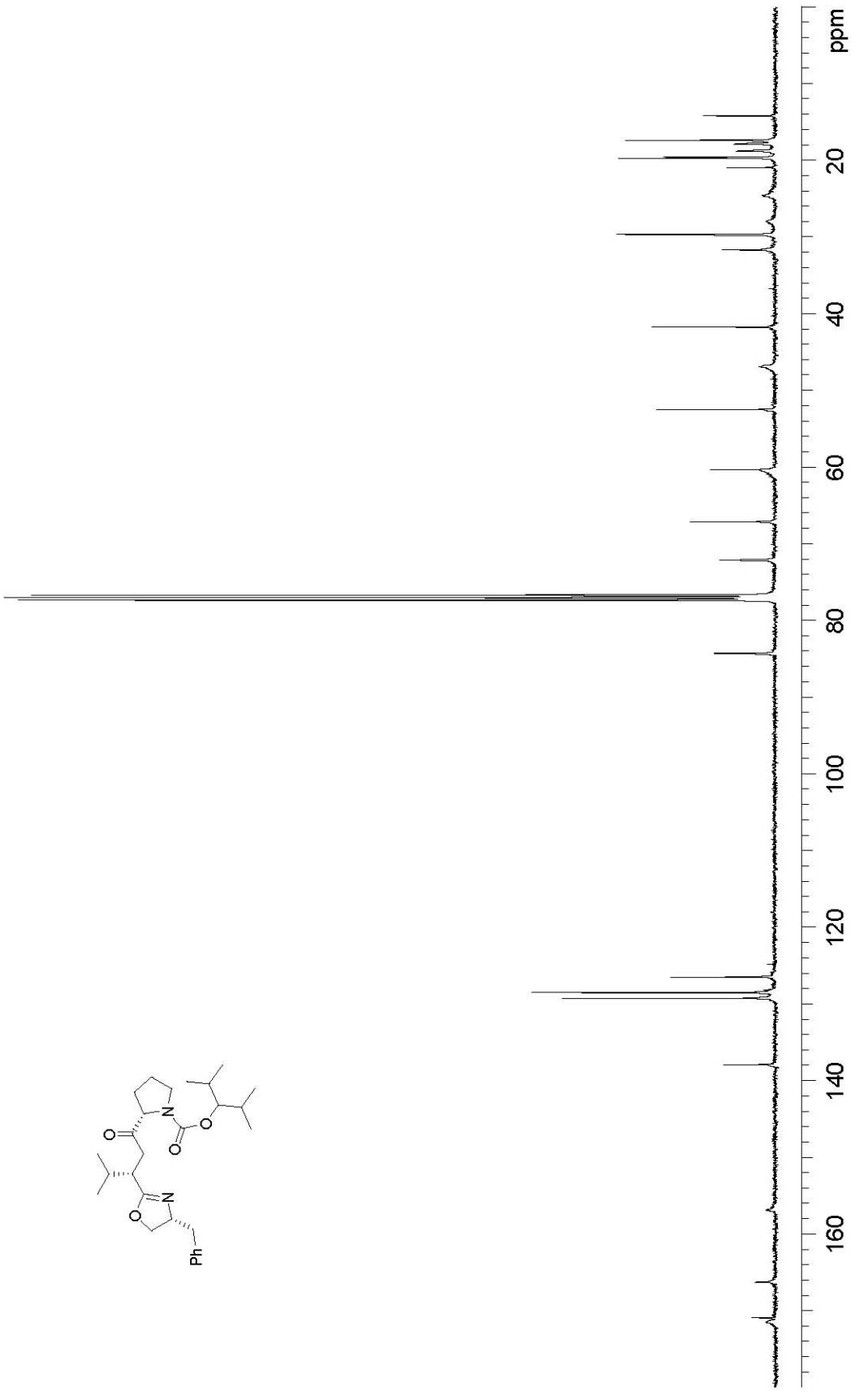
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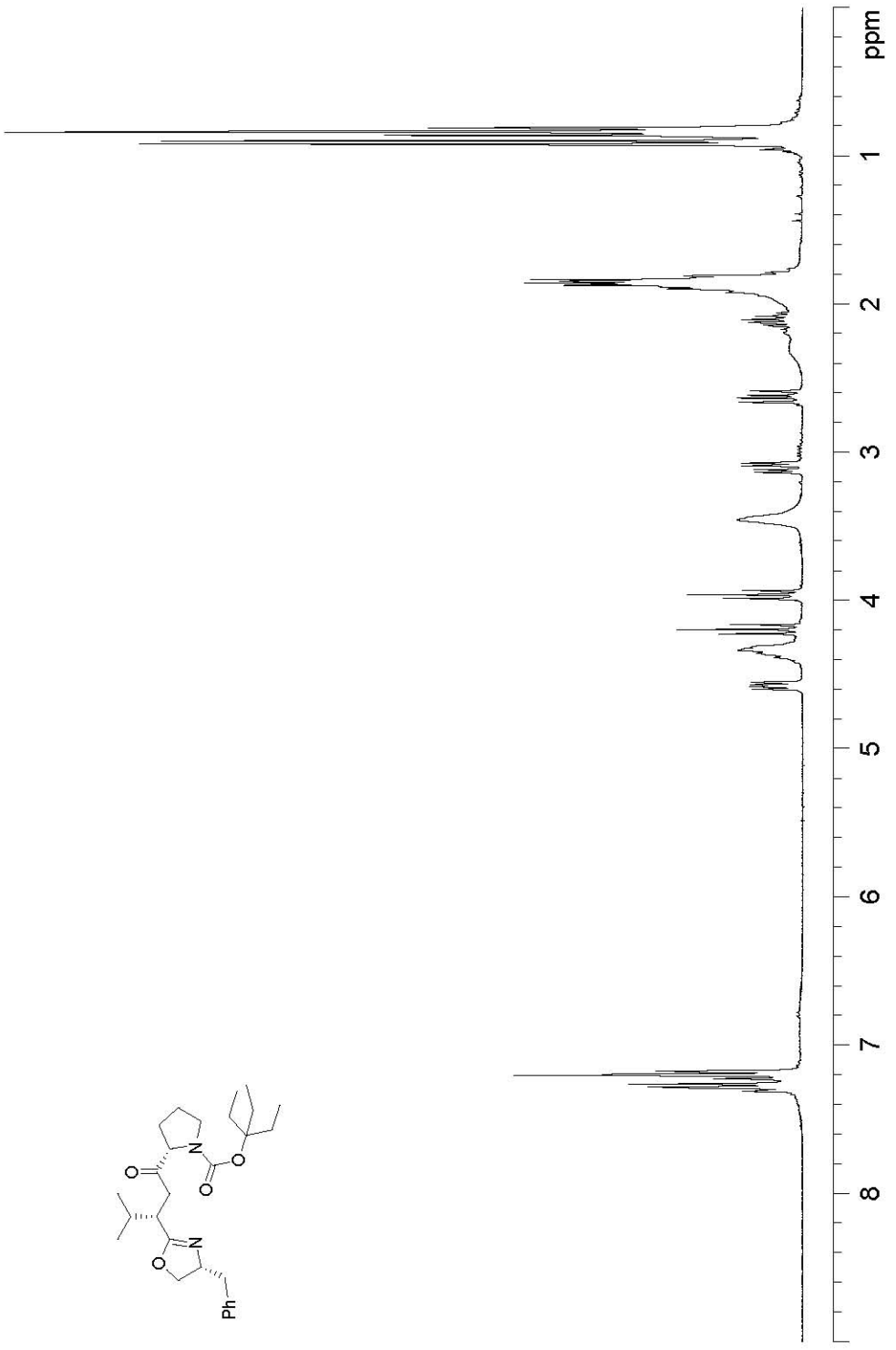
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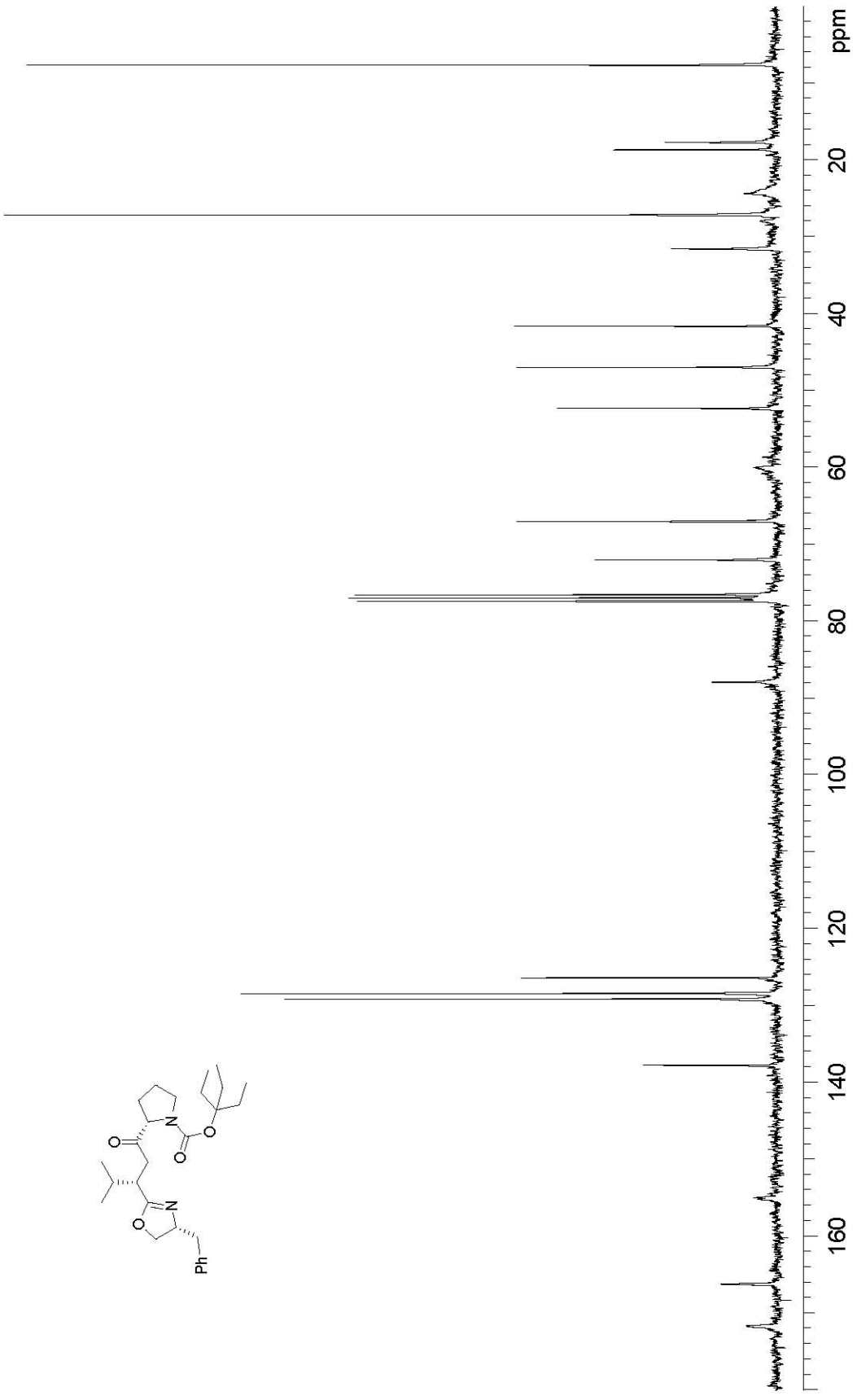
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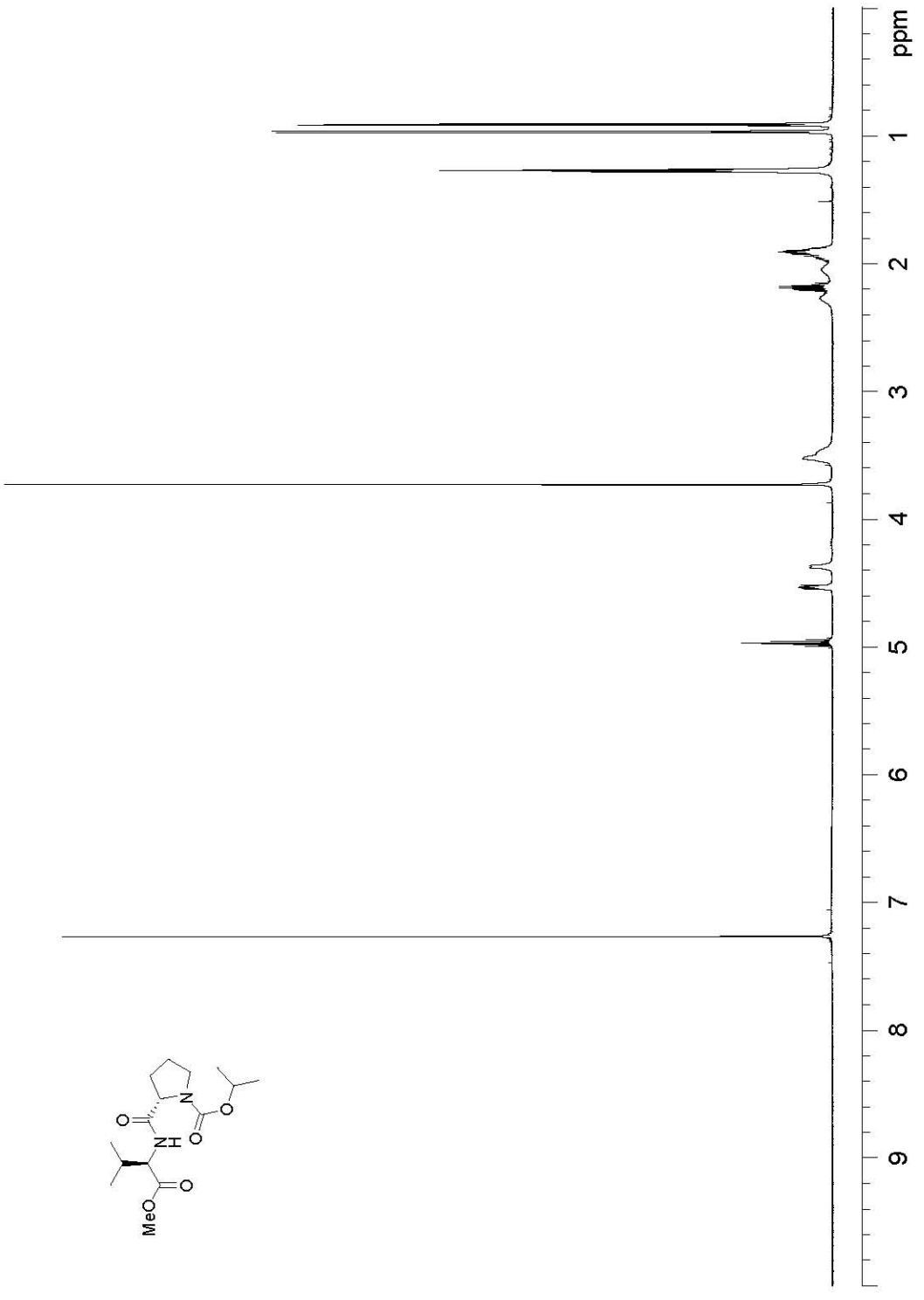
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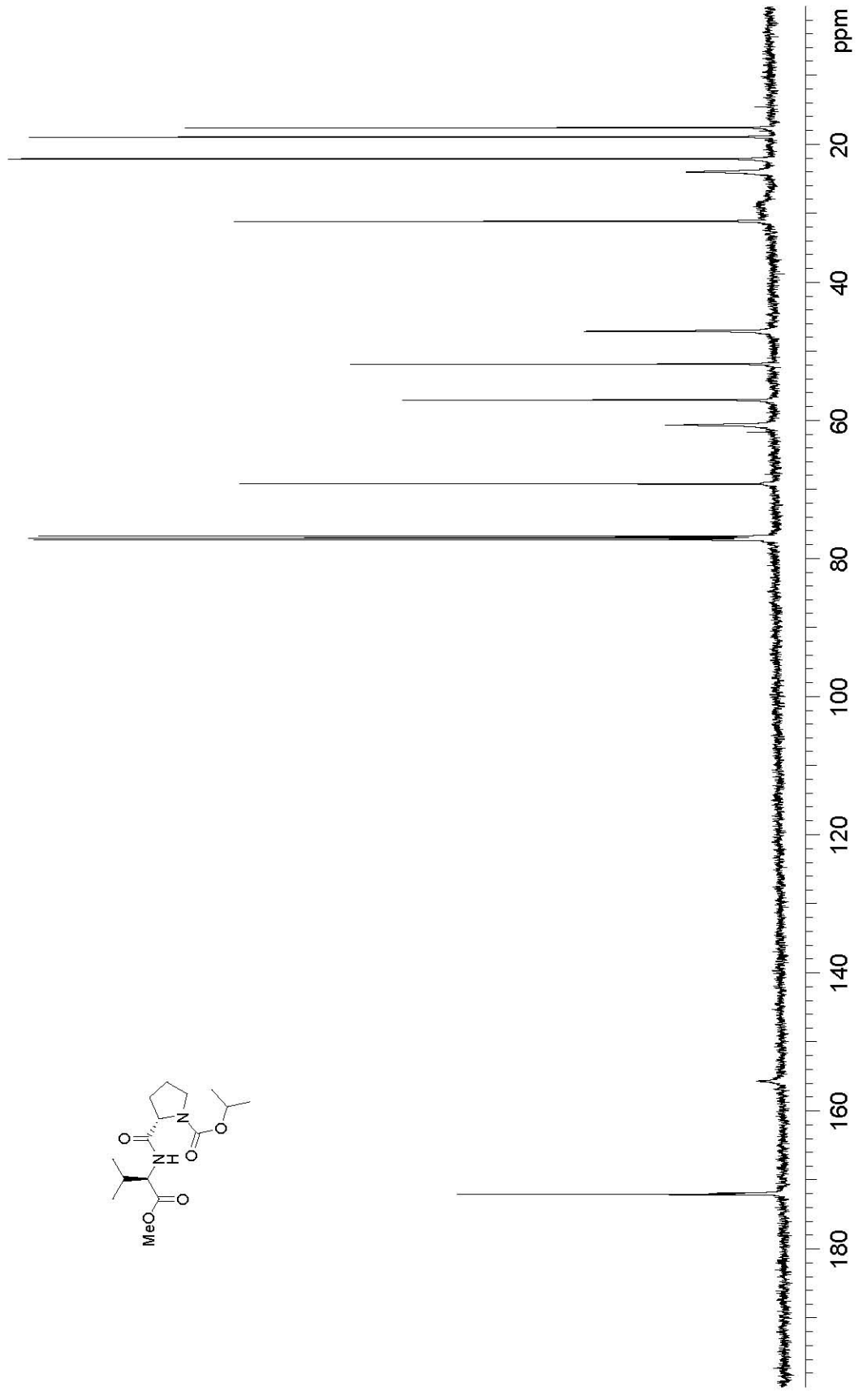
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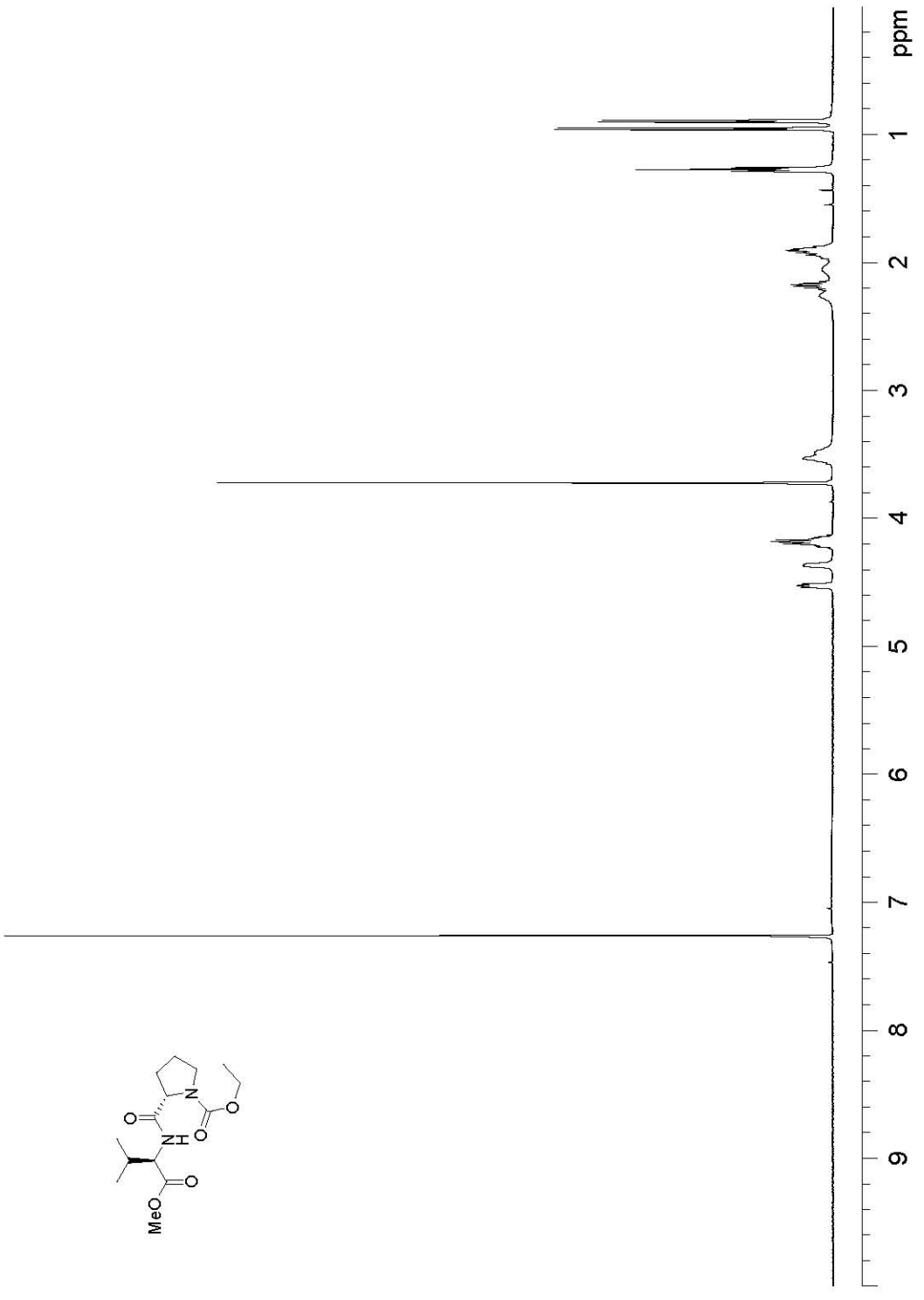
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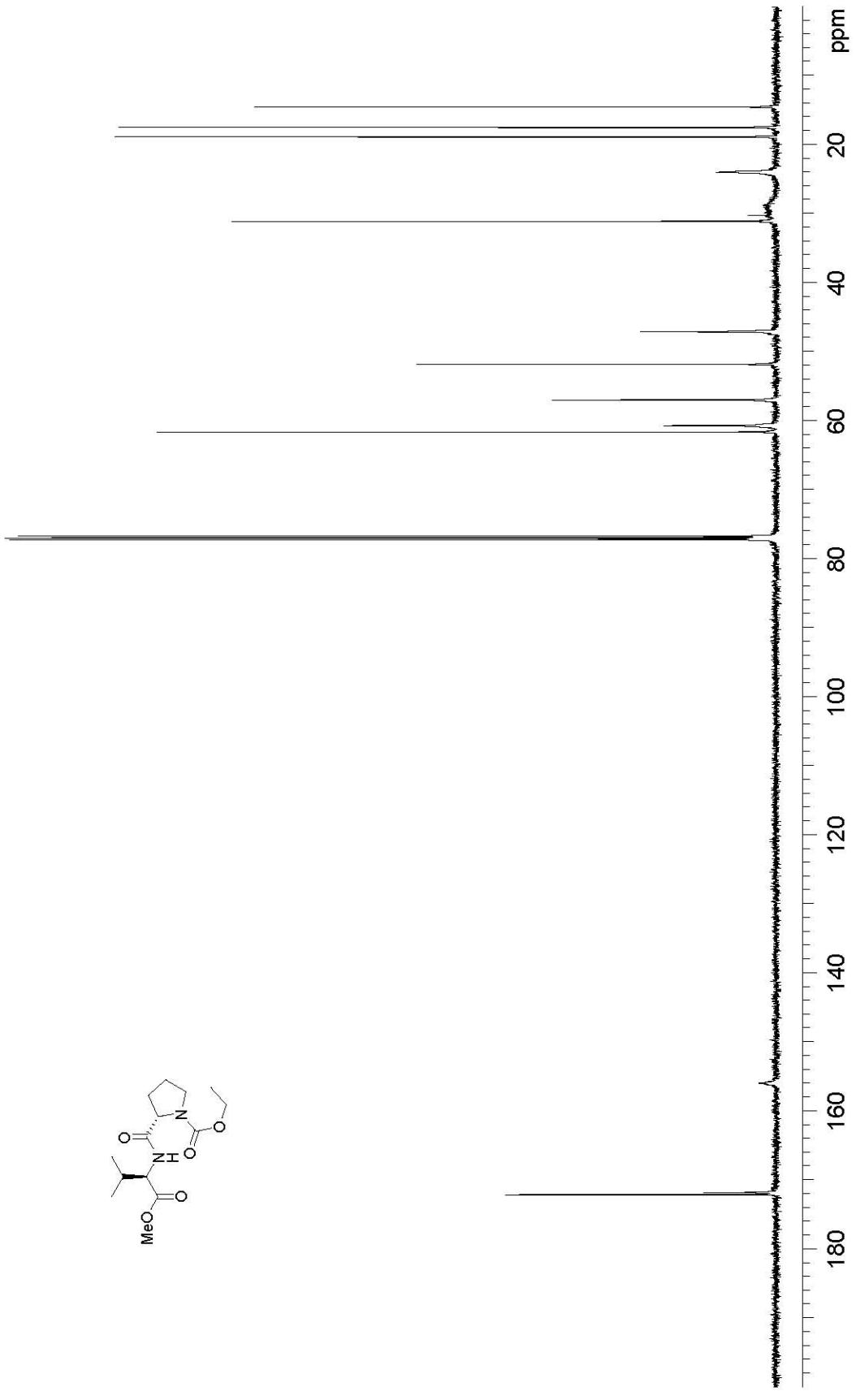
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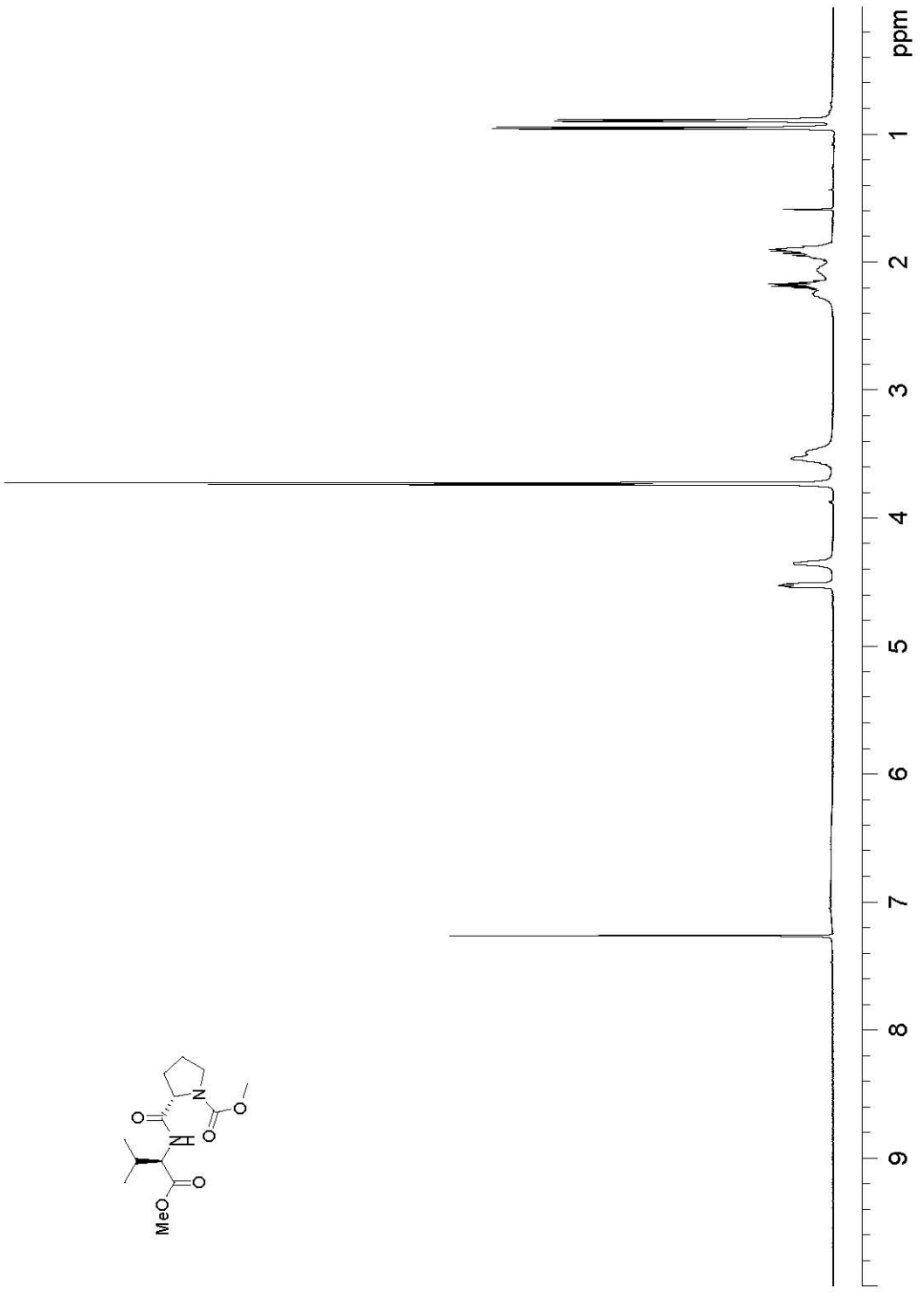
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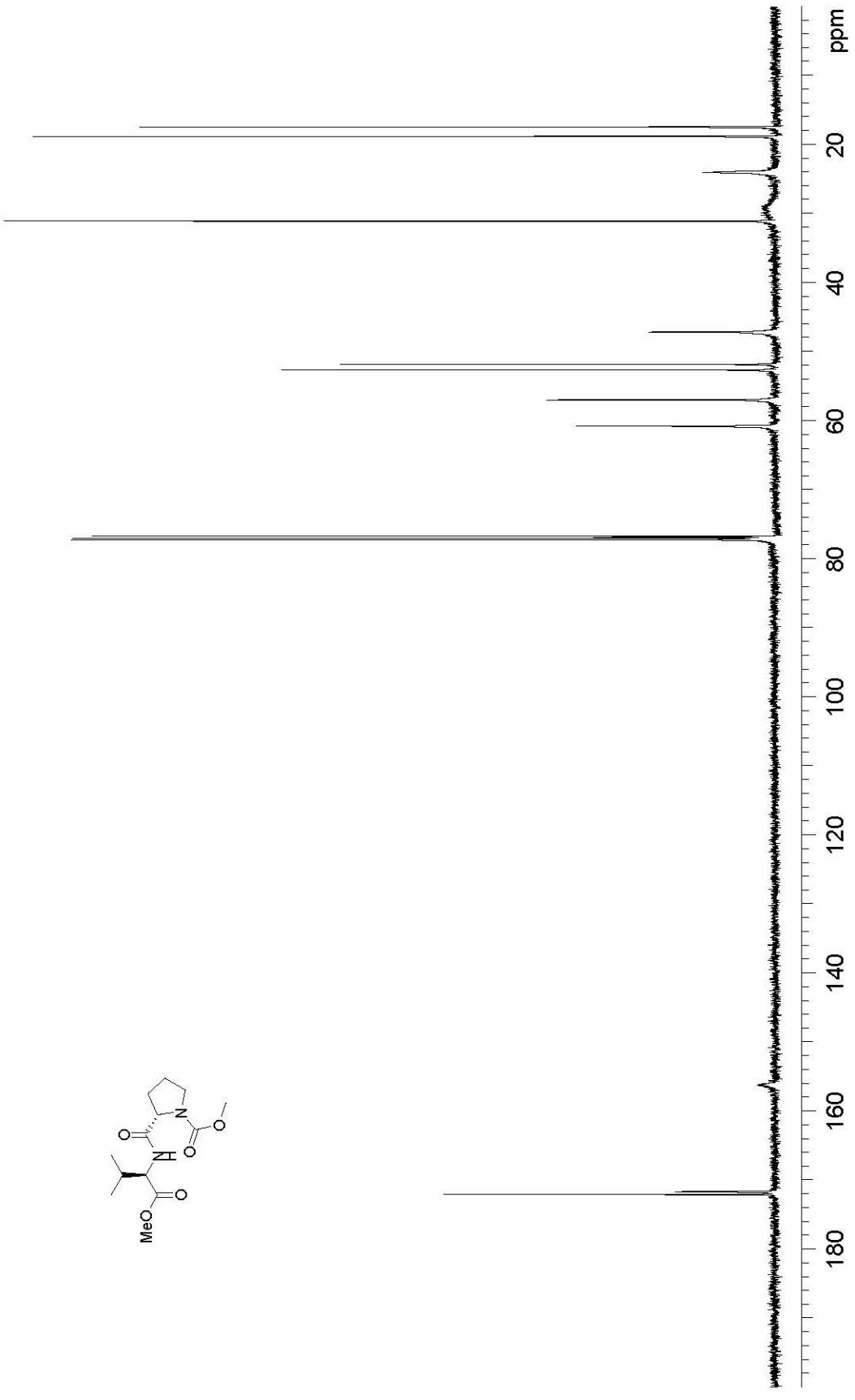
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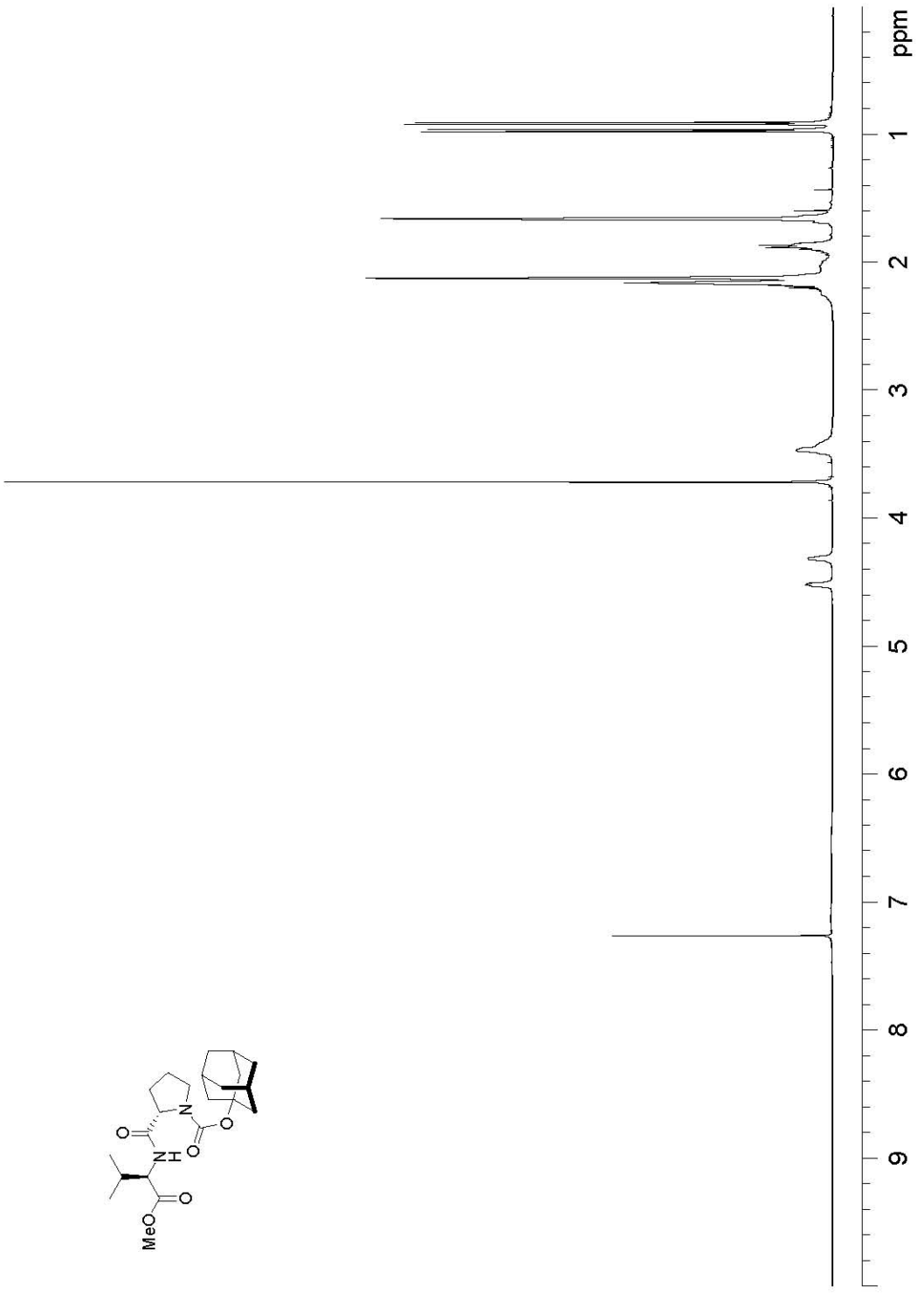
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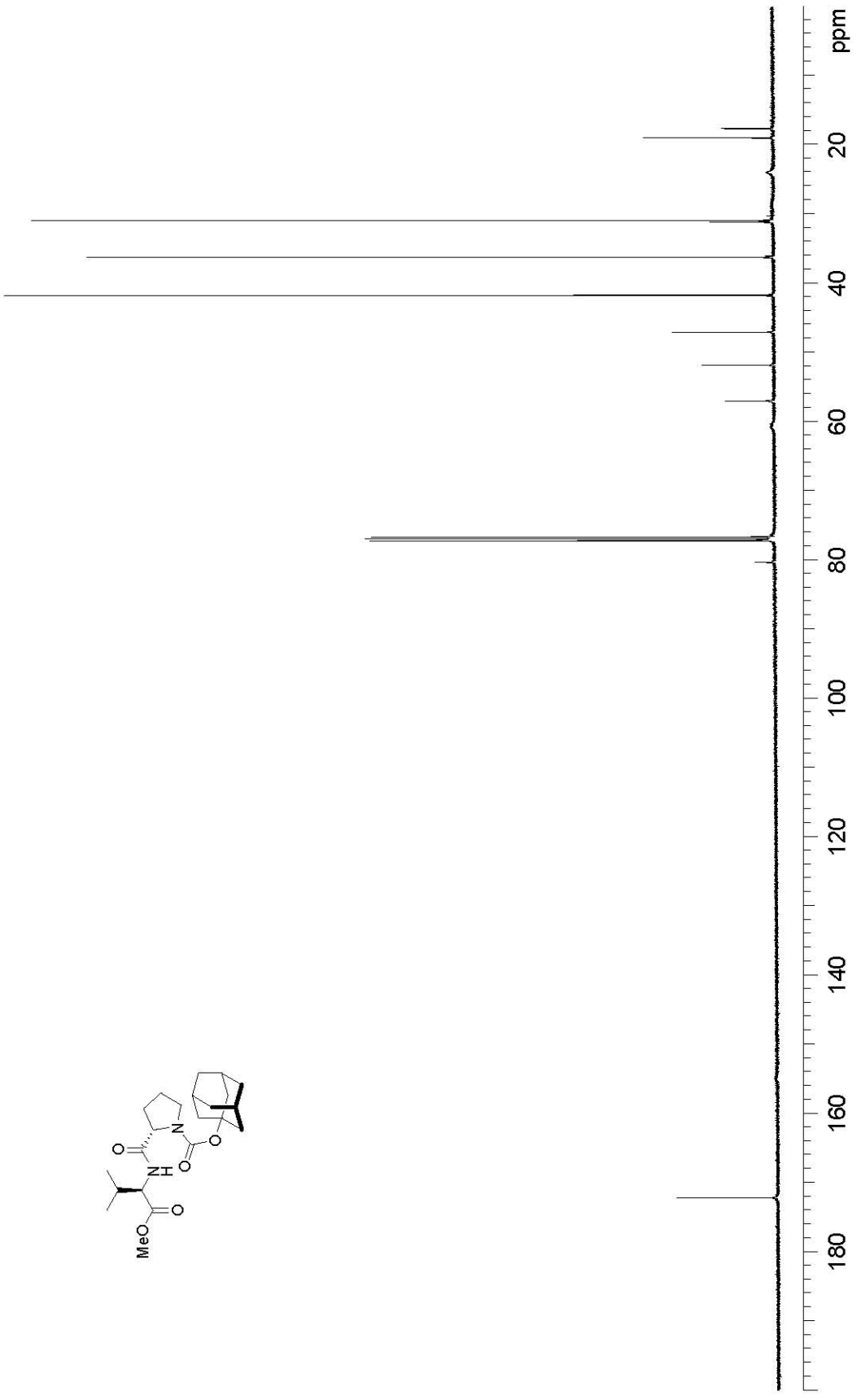
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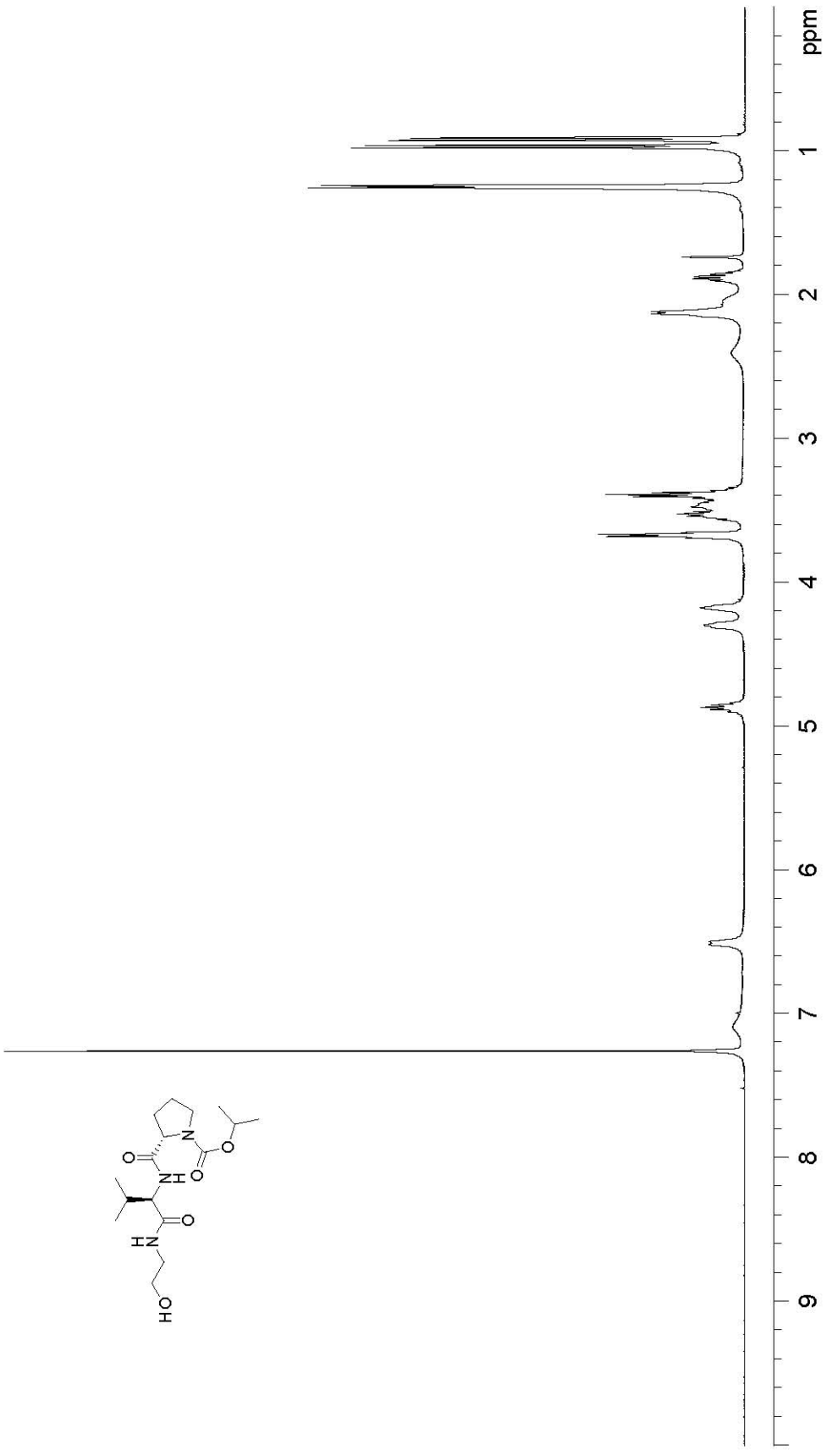
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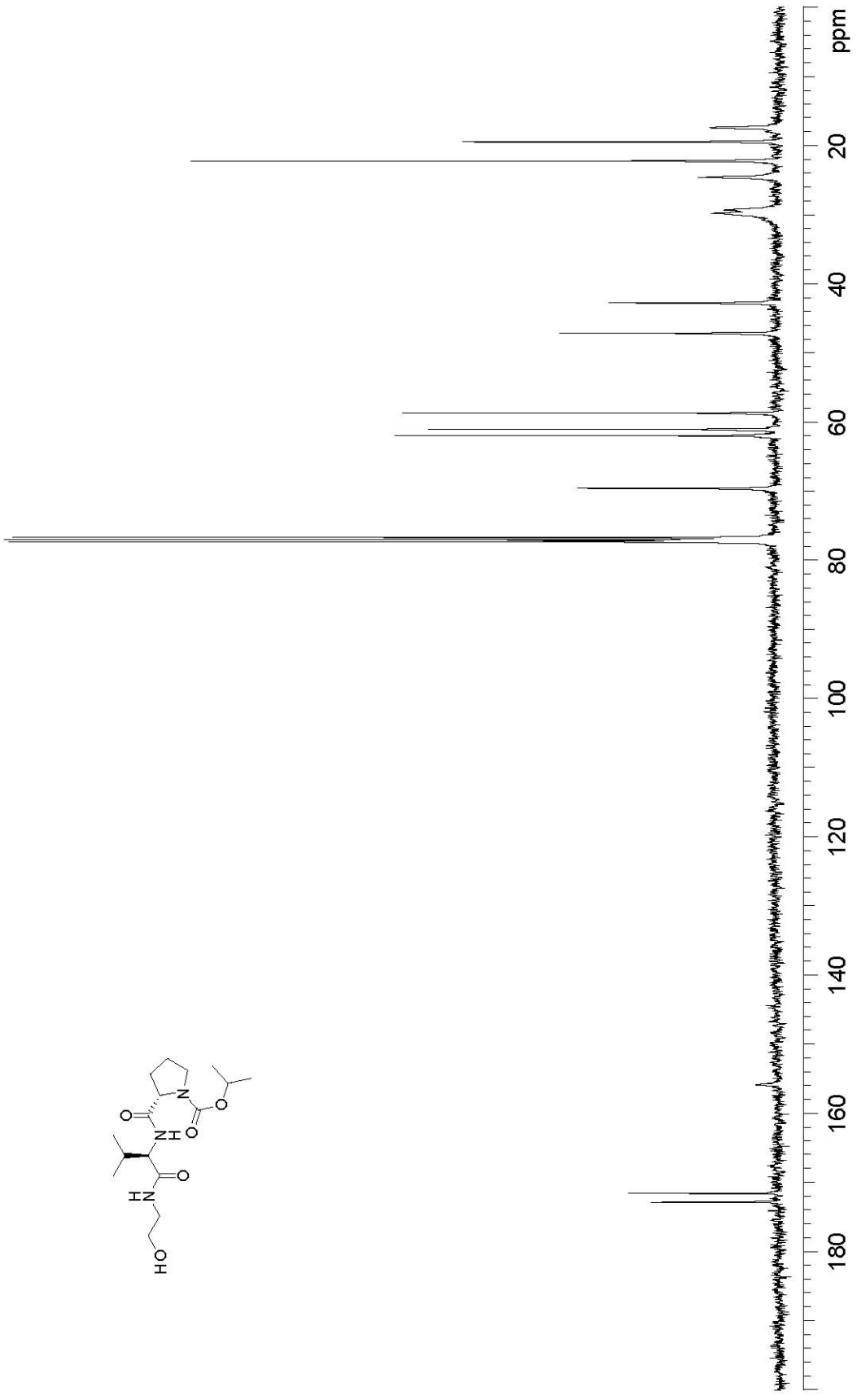
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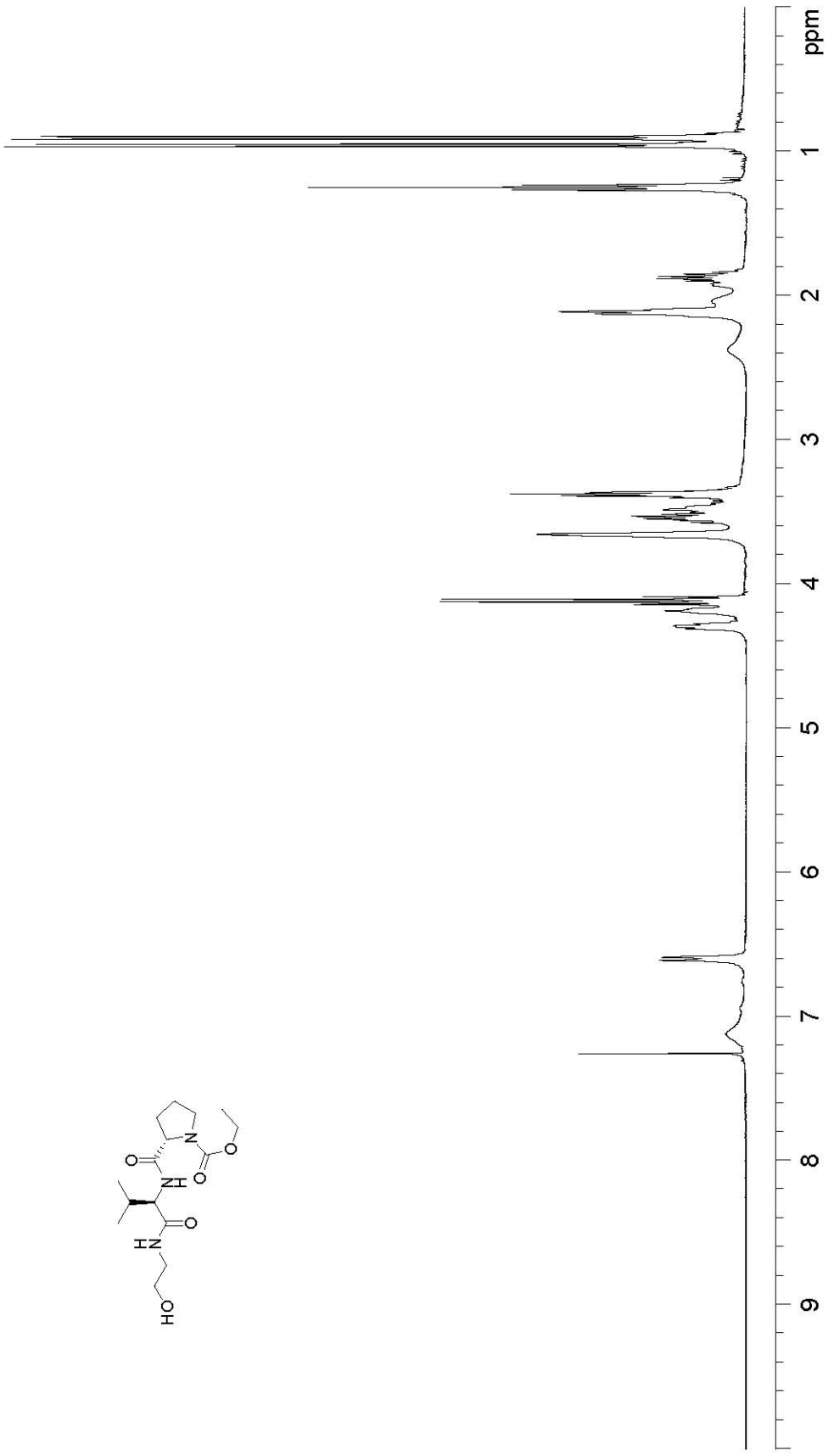
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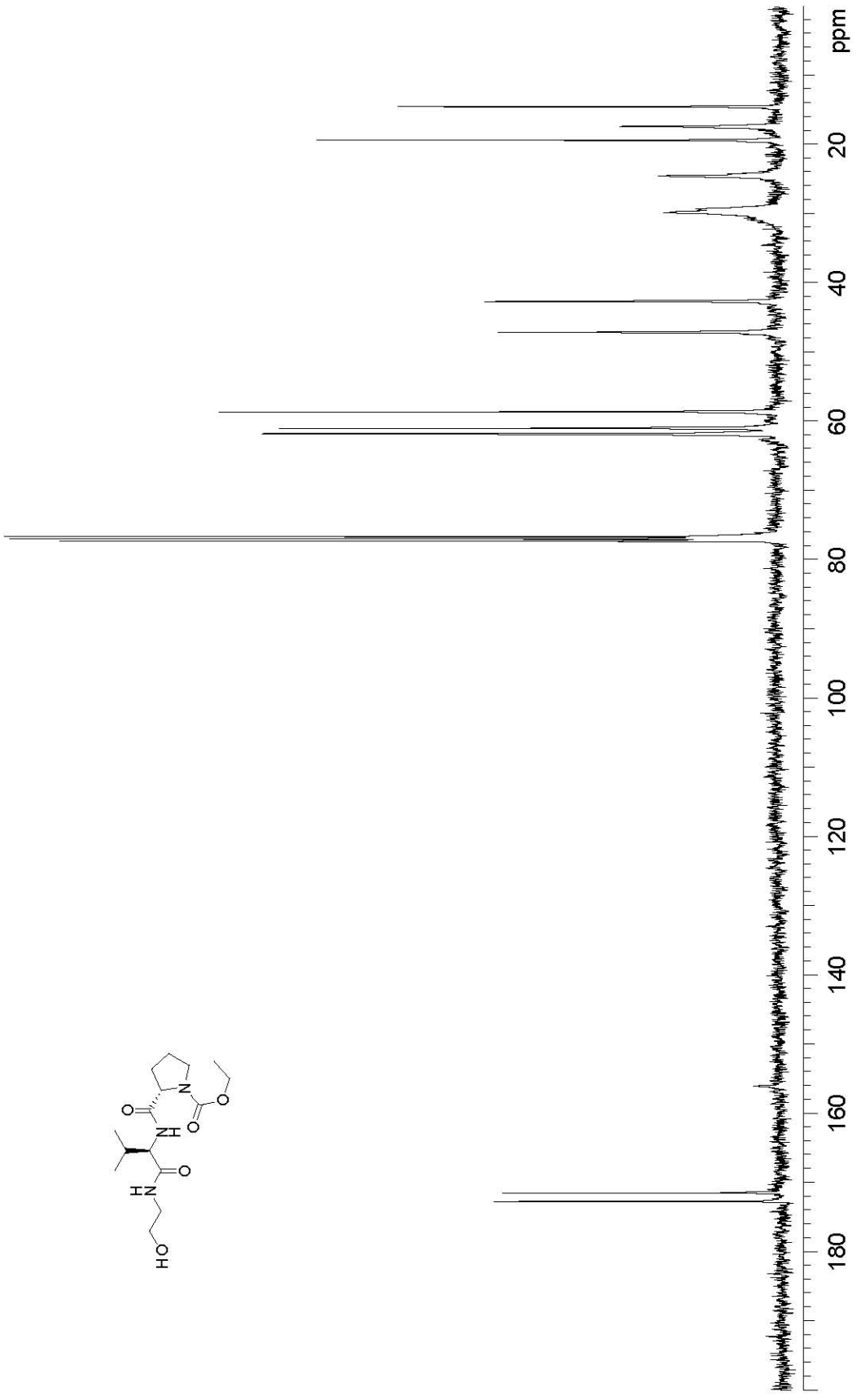
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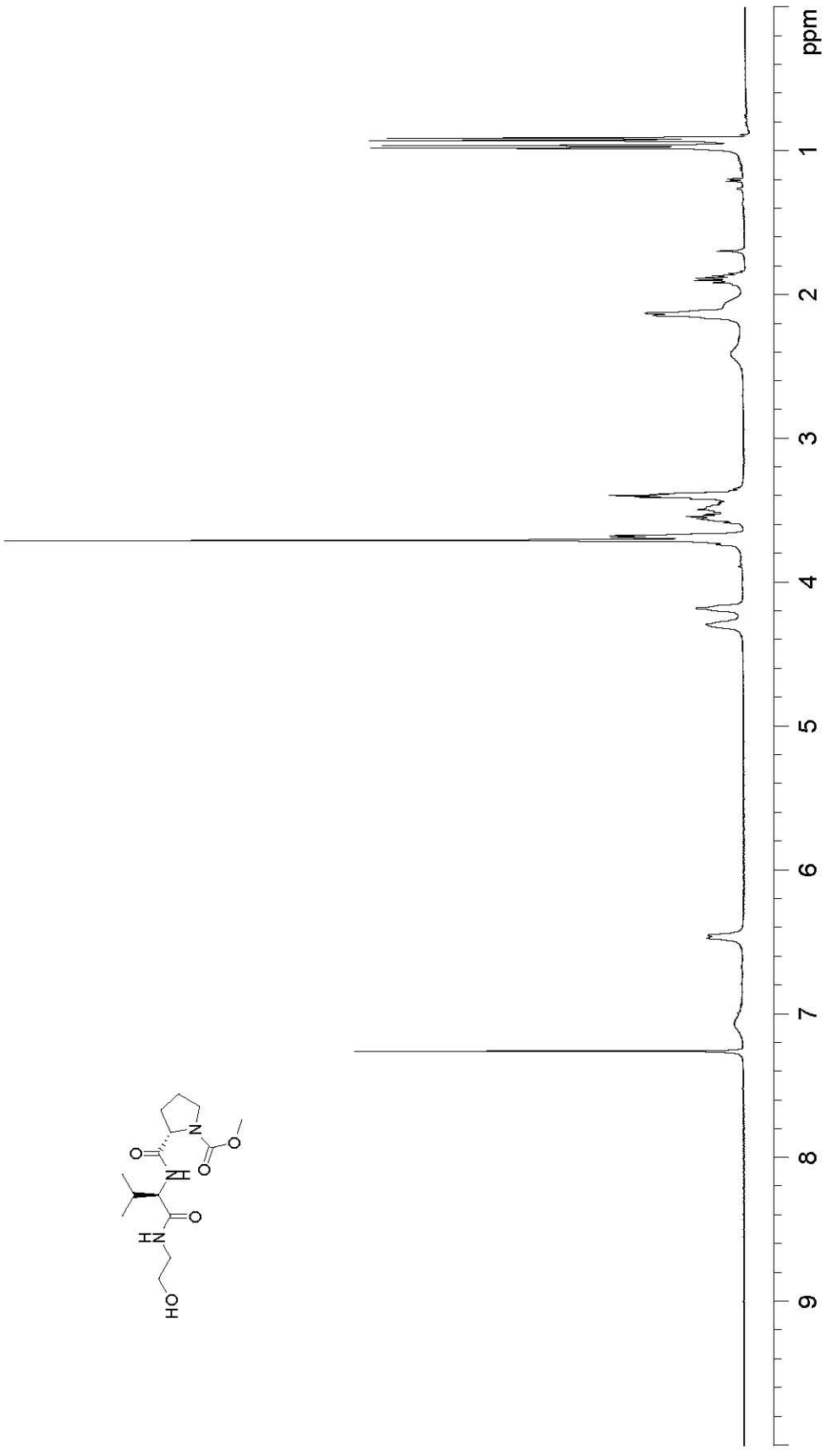
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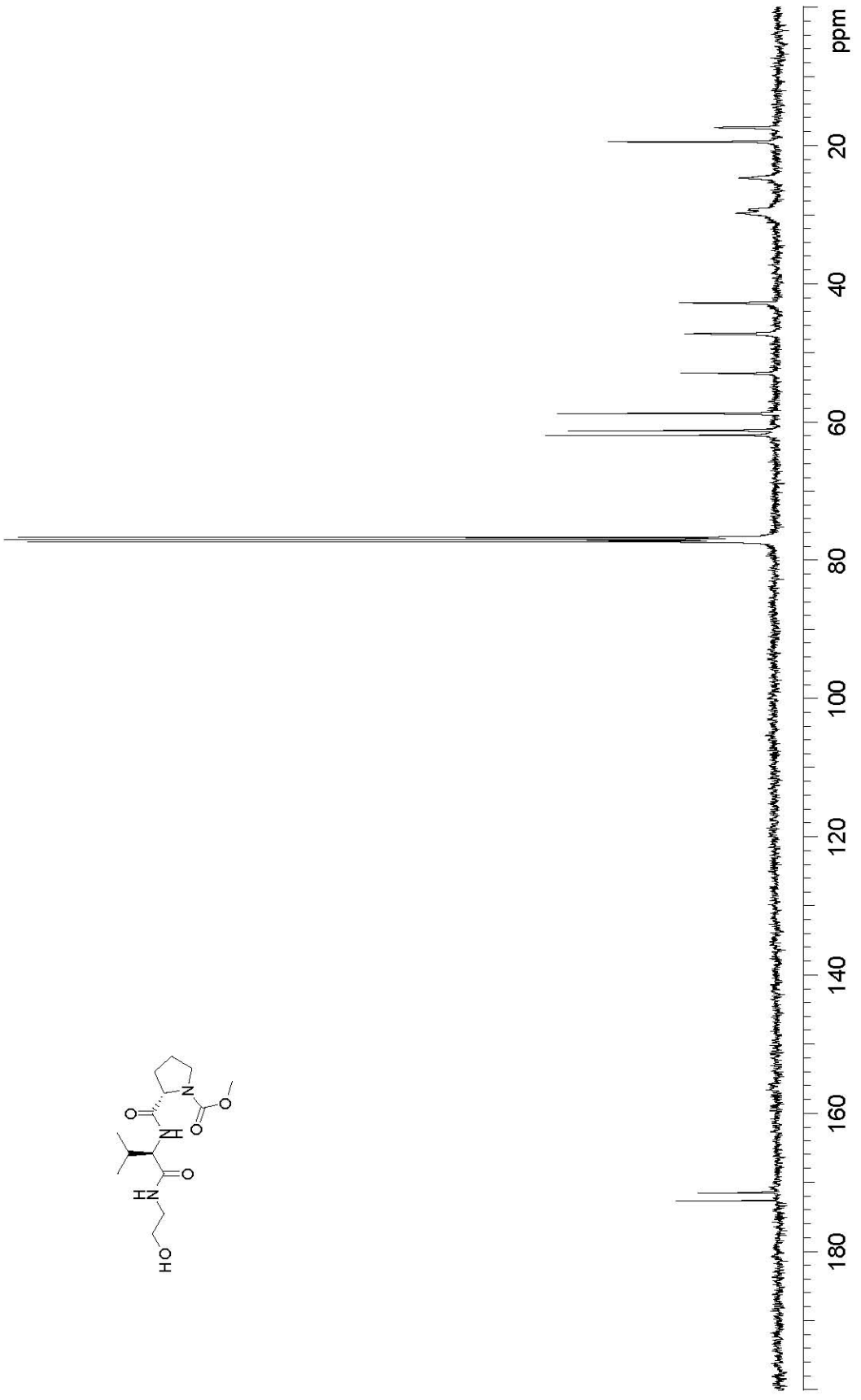
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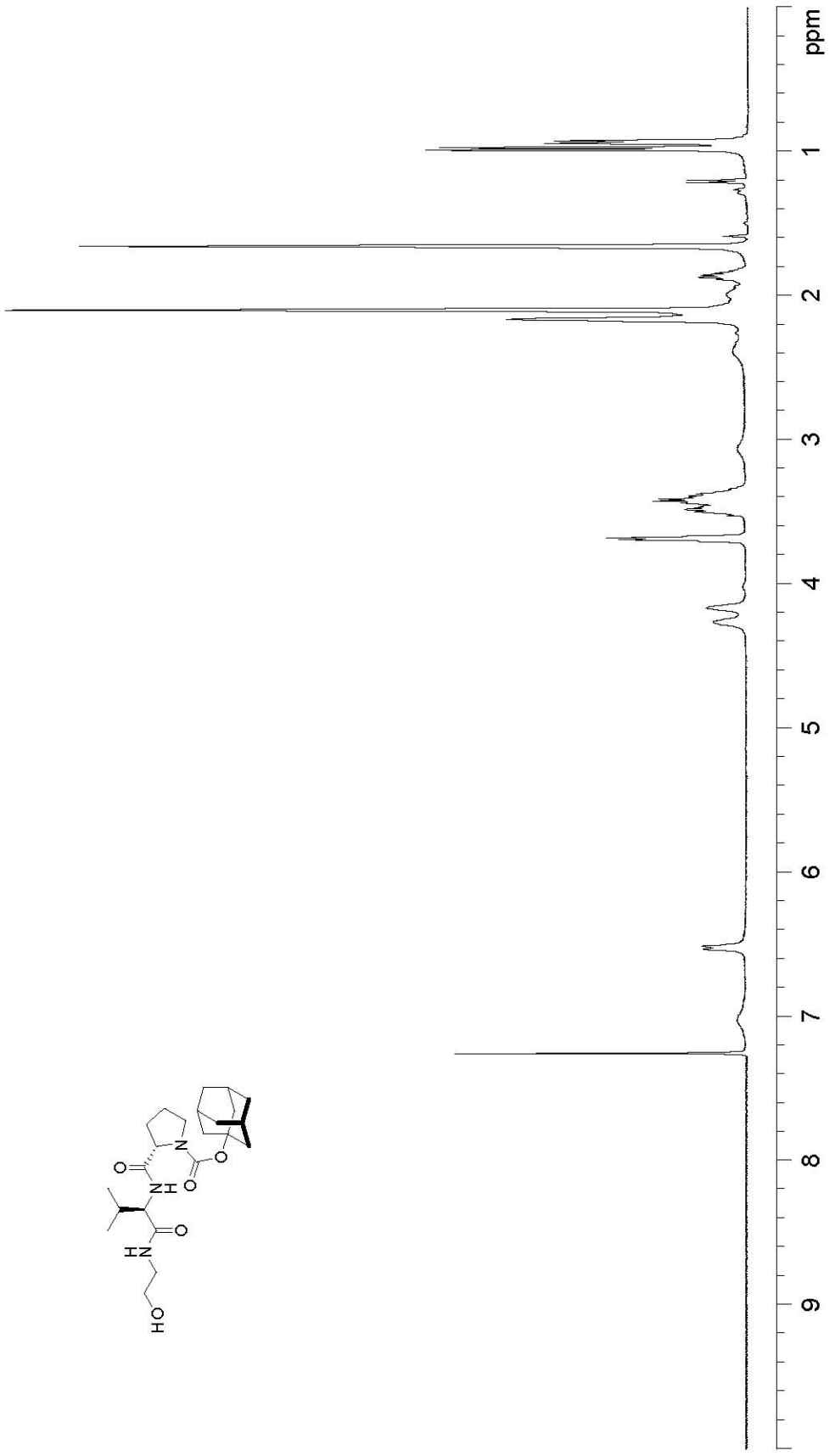
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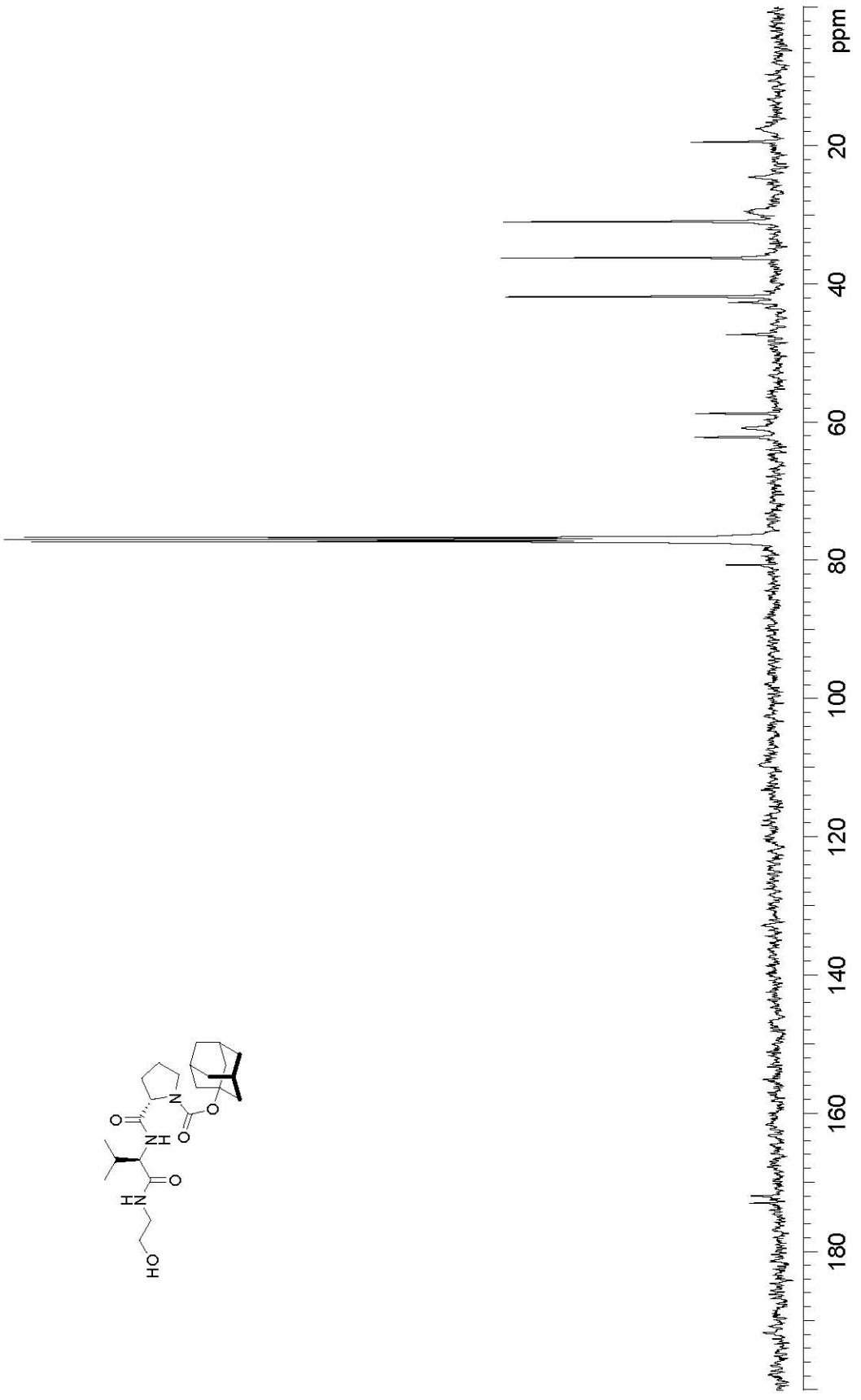
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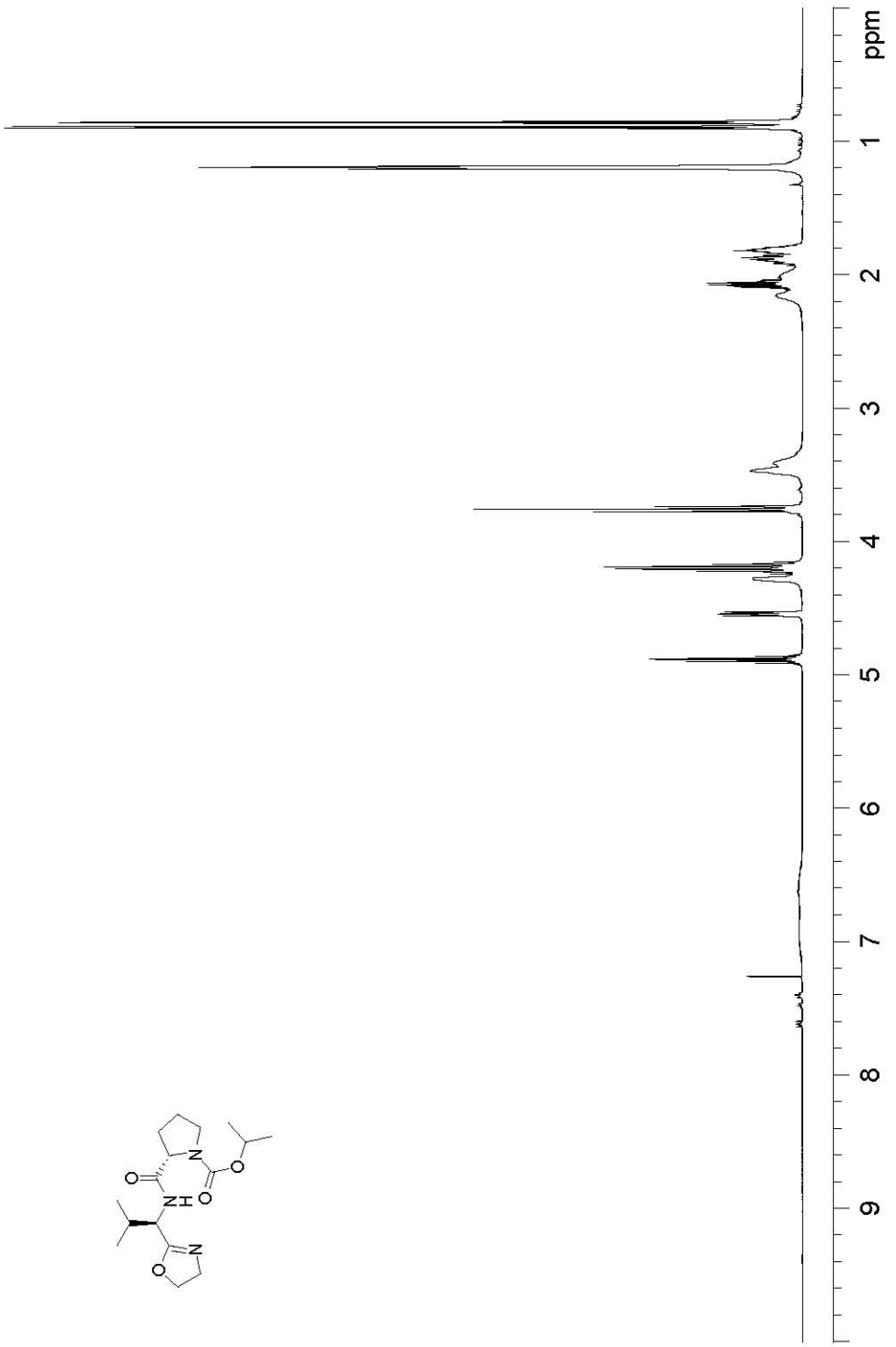
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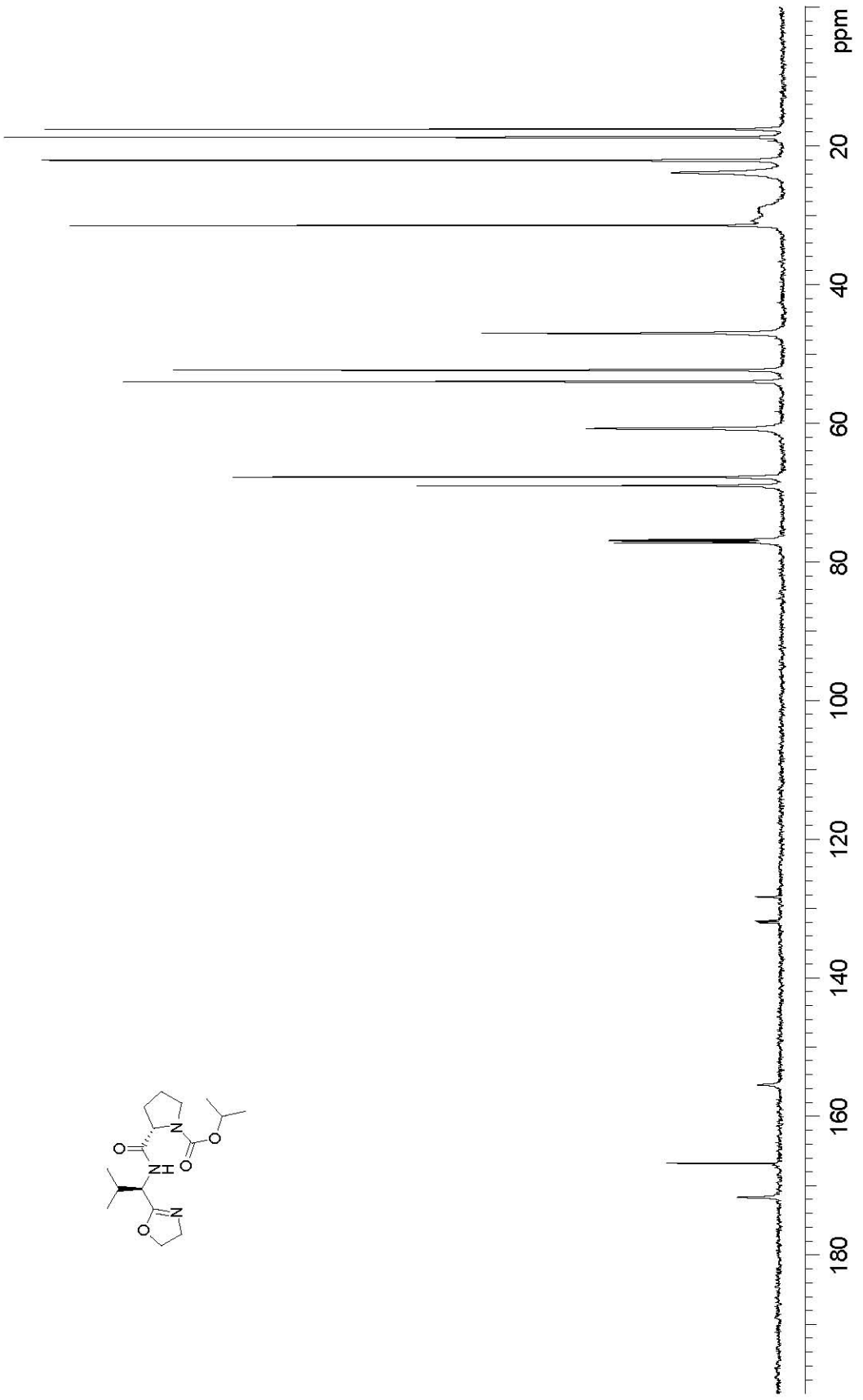
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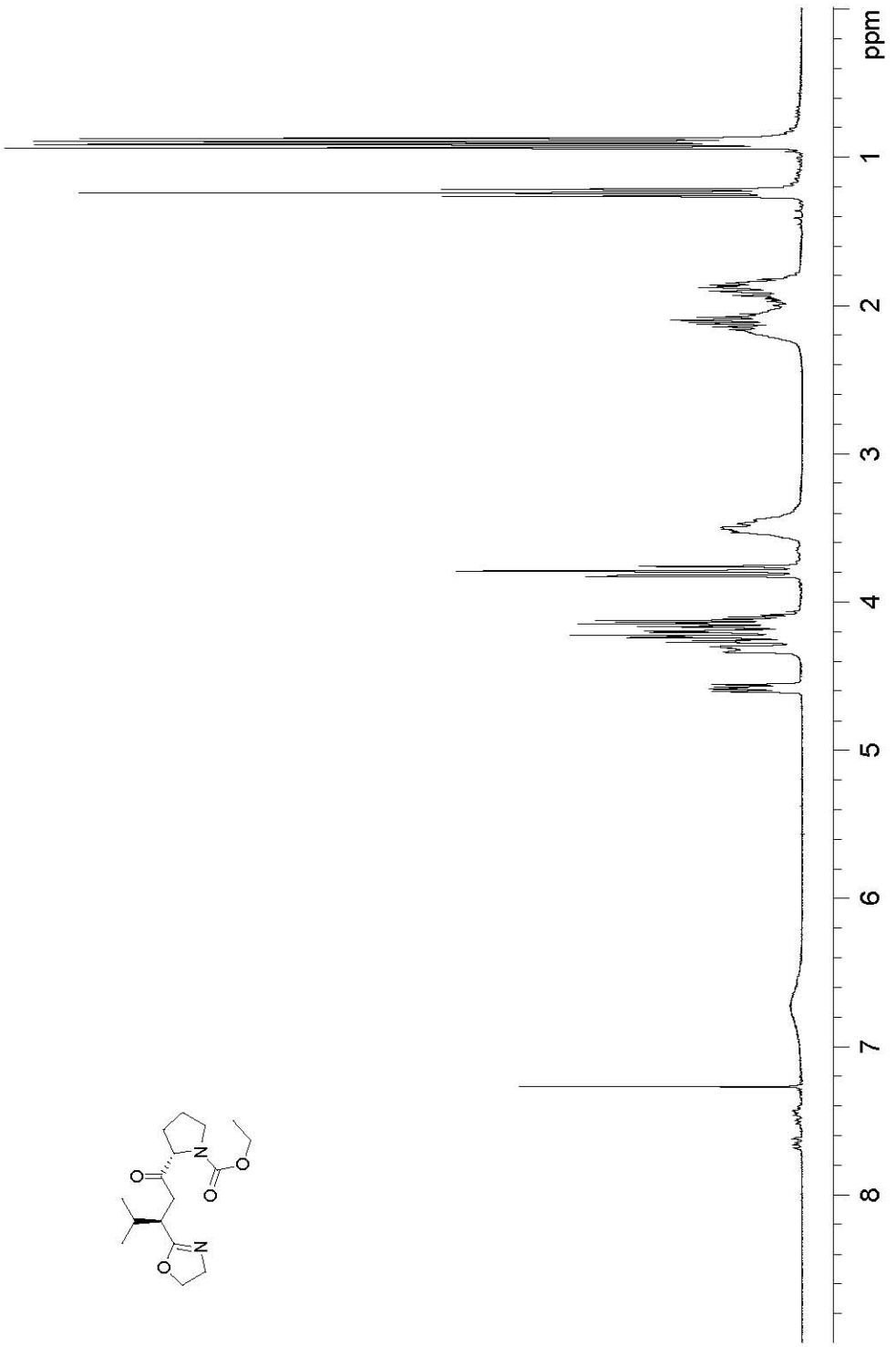
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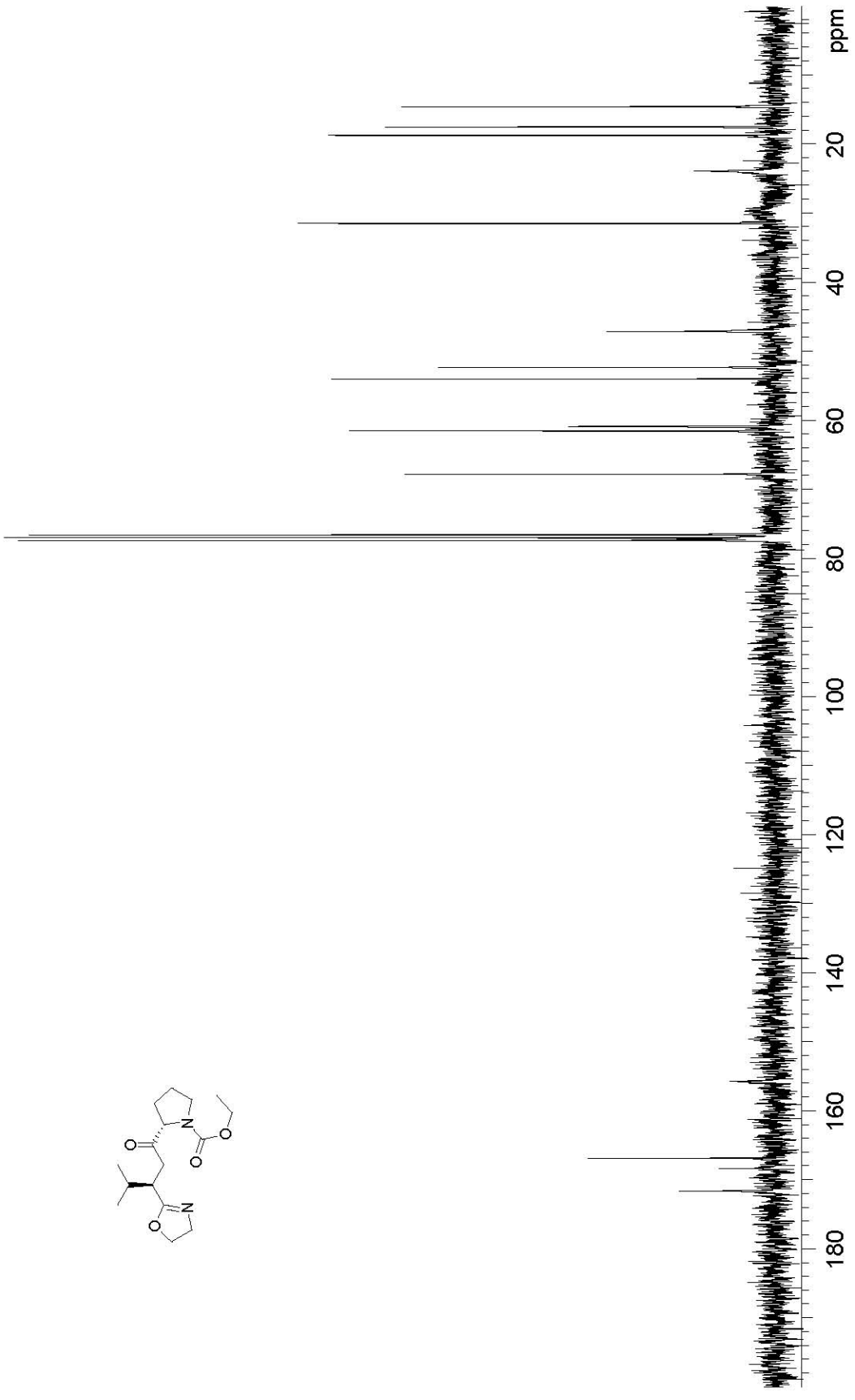
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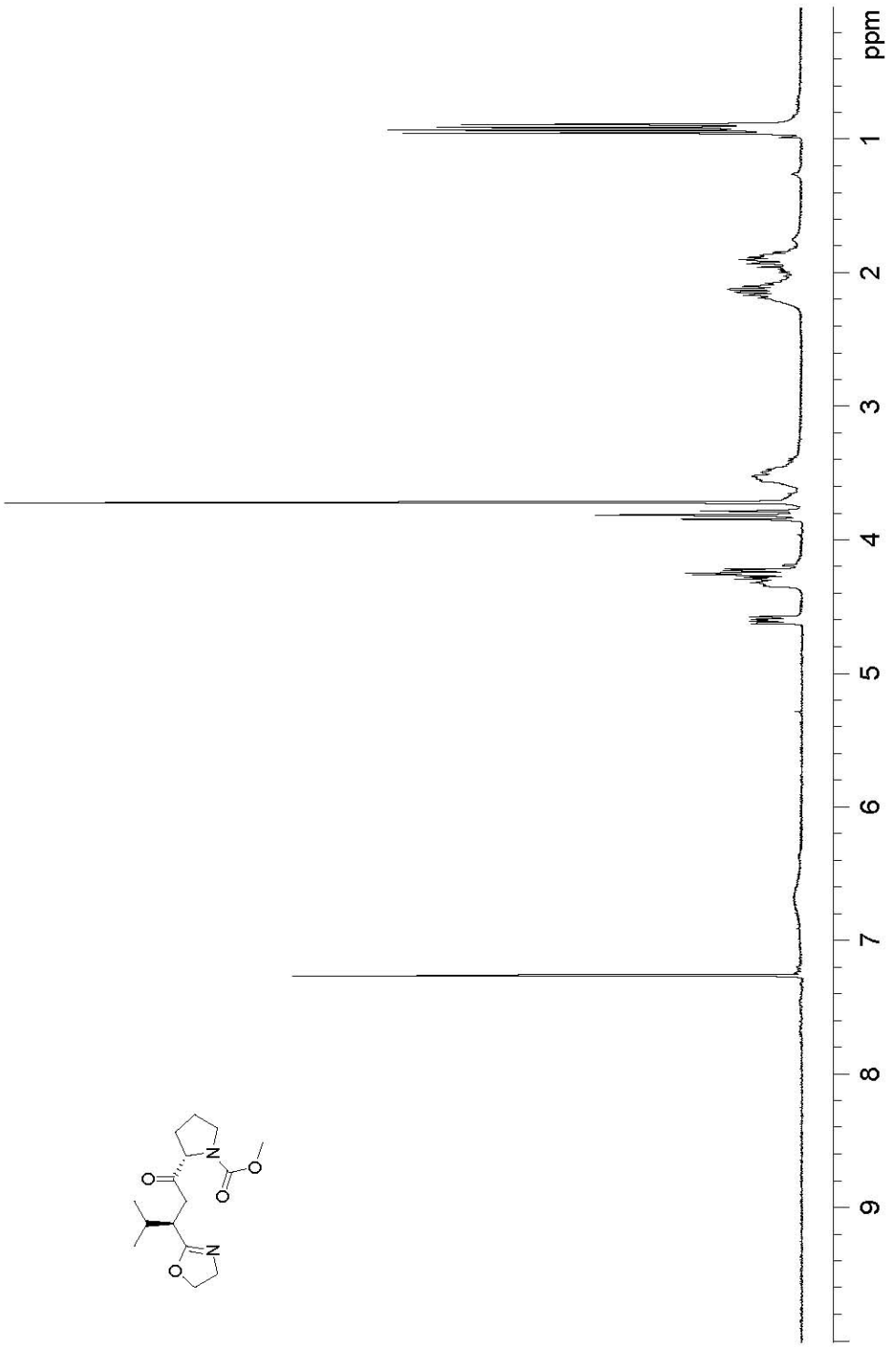
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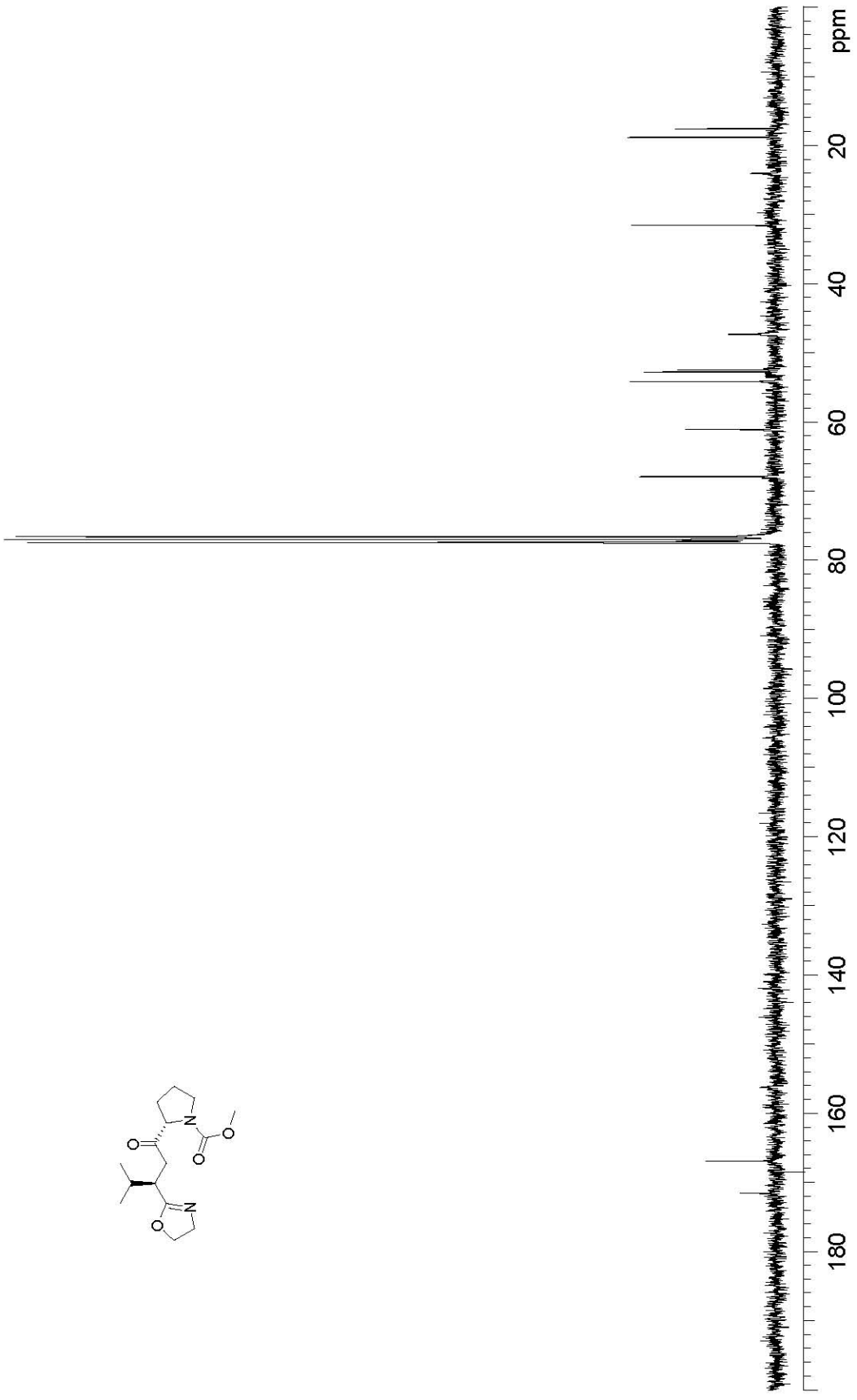
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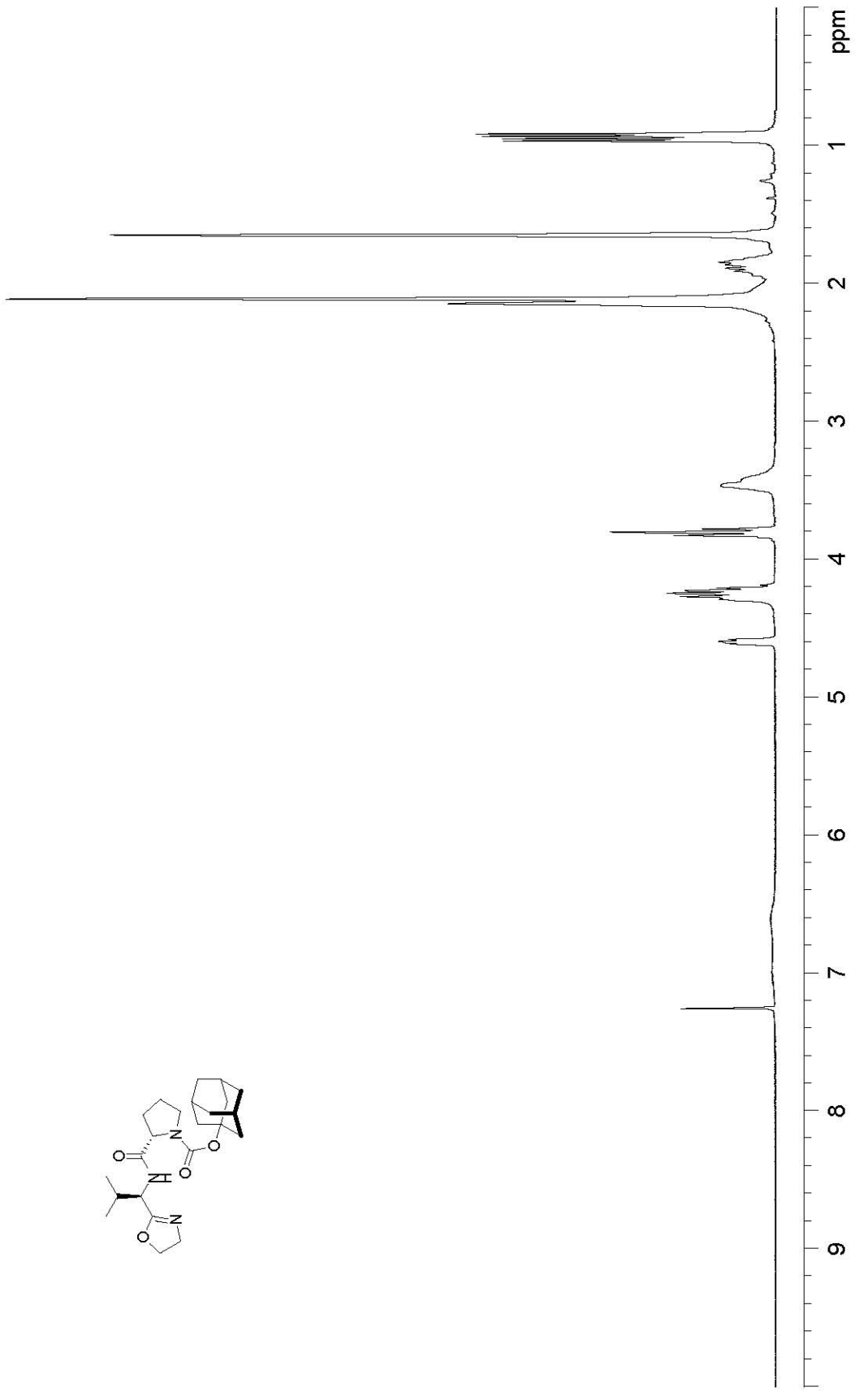
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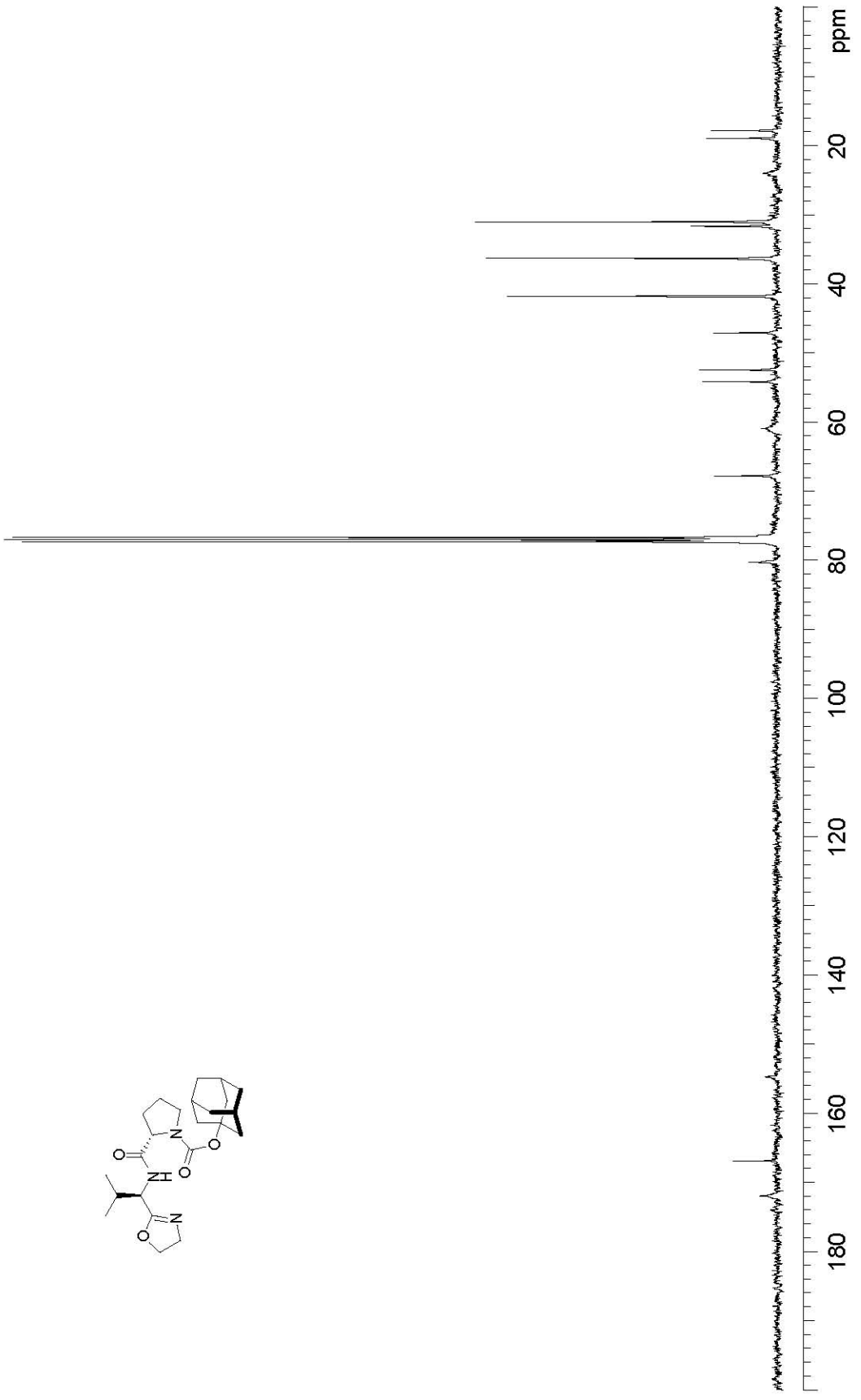
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**References:**

(1)Miller, J. J.; Rajaram, S.; Pfaffenroth, C.; Sigman, M. S. *Tetrahedron* **2009**, *65*, 3110-3119.
(2) Miller, J. J.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 771-774.