Supporting Information

EFFICIENT SYNTHESIS OF METHYL (S)-4-(1-METHYLPYRROLIDIN-2-YL)-3-OXOBUTANOATE AS THE KEY INTERMEDIATE FOR TROPANE ALKALOID BIOSYNTHESIS WITH OPTICALLY ACITVE FORM

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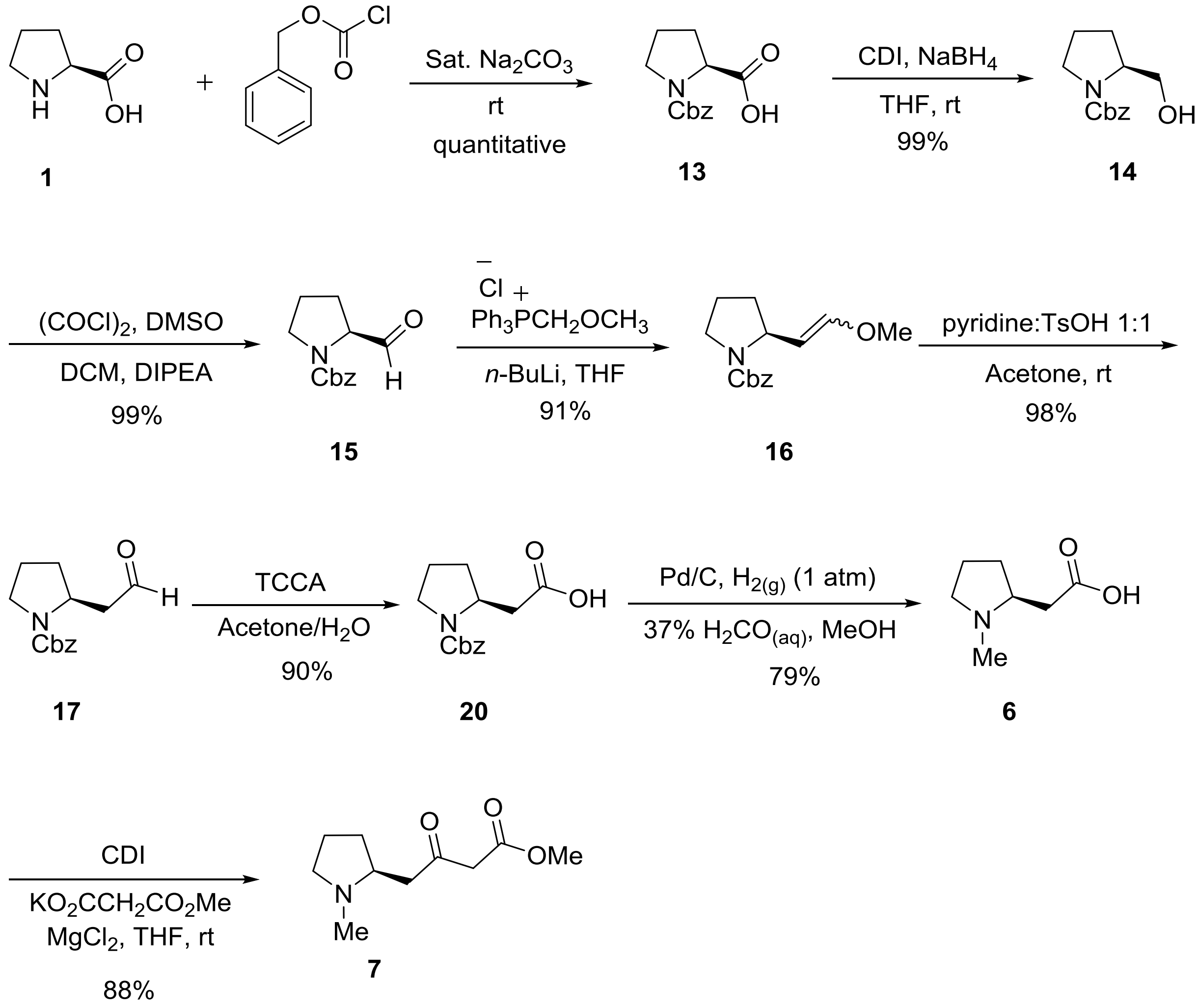
General Information

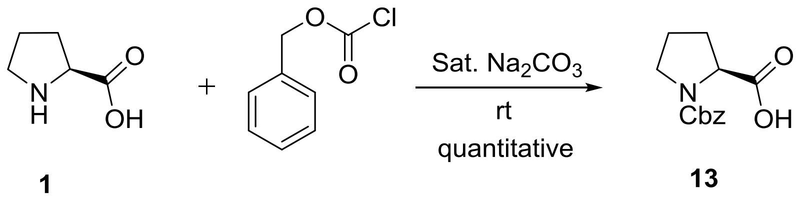
Reagents were used as obtained from commercial suppliers without further purification unless otherwise specified. ACS grade hexanes, ethyl acetate, dichloromethane and methanol were used for column chromatography. Thin layer chromatography (TLC) was performed on Alumina coated silica plates from Agela Technologies and visualization was performed with UV lamp or potassium permanganate staining solution followed by heating using a hotgun or iodine on silica. Column chromatography was performed on silica gel, siliaFlash P60 40-63µm (230-400 mesh) purchased from Silicycle. Chloroform-*d* was purchased from Cambridge Isotope Laboratories. Optical rotations were determined with AUTOPOL IV automatic polarimeter purchased from Rudolph research analytical. ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL 400 MHz. Chemical shifts are given in parts per million (ppm) referenced to solvent residual proton resonance (δ = 7.26 for $CHCl_3$) and solvent carbon resonance (δ = 77.0 for $CHCl_3$). LC-MS analysis was done on LCQ FLEET(Electro spray ionization and ion trap) from Thermo Scientific.

Reaction Scheme



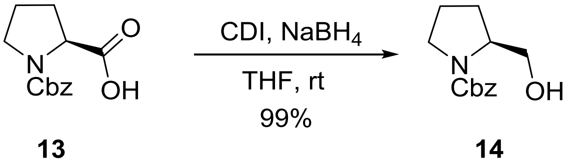
Experimental Procedures:

Synthesis of ((benzyloxy)carbonyl)-L-proline (13)



In 150 mL of saturated Na_2CO_3 solution, L-proline (5 g, 43.43 mmol, 1 eq) is dissolved and benzyl chloroformate (6.82 mL, 47.78 mmol, 1.1 eq) is added in a dropwise manner to the above solution at 0 °C. The reaction mixture is stirred at room temperature for 3 h. CH_2Cl_2 is added to the reaction mixture and the aqueous layer is separated to which 2N HCl is added till pH drops to 2. Then the product is extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated to afford **13** as yellow. Yield 10.825 g, quantitative. $[\alpha]_D^{25}$ = -105.3 (*c* 1g/100mL, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.68-11.39 (s, 1H), 7.45-7.27 (m, 5H), 5.27-5.07 (m, 2H), 4.52-4.29 (m, 1H), 3.69-3.40 (m, 2H), 2.34-1.81 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 178.27, 176.66, 155.69, 154.38, 136.39, 128.46, 128.34, 128.07, 127.89, 127.84, 127.60, 67.43, 67.09, 59.21, 58.57, 46.86, 46.57, 30.83, 29.36, 24.22, 23.39. MS (ESI): *m/z* calcd for $[C_{13}H_{15}NO_4 + H]^+$: 250, found: 250. Spectroscopic data agree with literature[1].

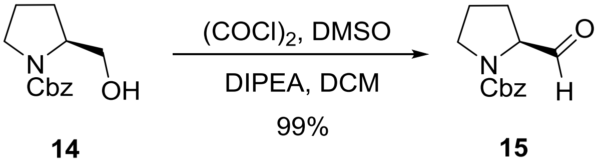
Synthesis of benzyl (*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (14)



13 **14**

To a stirred solution of **13** (10.825 g, 43.43 mmol, 1 eq) in THF was added 1,1'-carbonyldiimidazole (9.365 g, 57.76 mmol, 1.33) and the reaction mixture is stirred for 15 min at room temperature. $NaBH_4$ (2. 743 g, 72.52 mmol, 1.67 eq) in 60 mL H_2O is added slowly and let it stir for 30 min. Reaction mixture is quenched with 1N HCl till the pH drops to 2 and the solution is extracted with EtOAc. The combined extracts were washed with $NaHCO_3$, brine, dried over $MgSO_4$ and passed through a short pad of silica to afford yellow oil. Yield 10.116 g, 99%. $[\alpha]_D^{25}$ = -40.1 (*c* 1g/100mL, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.27 (m, 5H), 5.16-5.06 (m, 2H), 4.34-4.03 (bs, 1H), 4.01-3.86 (m, 1H), 3.71-3.57 (d, *J* = 5.2 Hz, 2H), 3.55-3.44 (m, 1H), 3.42-3.32 (m, 1H), 2.04-1.71 (bm, 3H), 1.68-1.55 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 156.88, 136.37, 128.37, 127.92, 127.75, 67.06, 66.51, 60.48, 47.15, 28.37, 23.86. MS (ESI): *m/z* calcd for $[C_{13}H_{17}NO_3 + H]^+$: 236, found: 236. Spectroscopic data agree with literature[2].

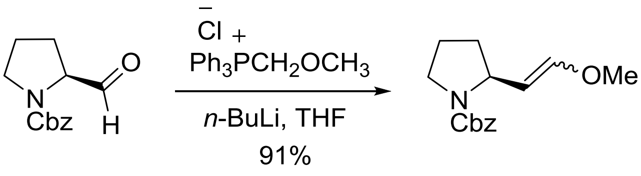
Synthesis of benzyl (*S*)-2-formylpyrrolidine-1-carboxylate (15)



14 **15**

A 100 mL flame-dried Schlenk flask under nitrogen atmosphere was charged with oxalyl chloride (1.64 mL, 19.12 mmol, 1.5 eq) and 60 mL dry DCM and cooled to -78 °C using dry ice/acetone. DMSO (2.71 mL, 38.25 mmol, 3.0 eq) was added dropwise, and the reaction was stirred for 15 min. A solution of **14** (3.00 g, 12.75 mmol, 1.0 eq) in 20 mL dry DCM was added dropwise, and the reaction was stirred for 1 h. DIPEA (12 mL) was added, and the reaction was stirred for an additional hour at -78 °C, followed by slow warming until the temperature reached -10 °C. Saturated NH_4Cl was slowly added to quench, and the reaction was brought to room temperature. The organic layer was washed twice with additional saturated NH_4Cl, dried over $MgSO_4$, filtered, and evacuated to afford 1**5** as yellow oil. Cooling in the fridge overnight afforded pale yellow crystals which did not melt upon warming to room temperature. Yield 2.94 g, 99%. $[\alpha]_D^{25} = -24$ (*c* 1g/100ml, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.53$ (d, *J* = 4.0 Hz, 1H), 7.34 – 7.25 (m, 5H), 5.15 – 5.06 (m, 2H), 4.31 – 4.10 (m, 1H), 3.57 – 3.43 (m, 2H), 2.10 – 1.76 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 199.79$, 155.09, 154.23, 136.22, 136.01, 128.25, 127.85, 127.69, 66.97, 65.02, 64.62, 47.04, 46.46, 27.49, 26.32, 24.22, 23.43. MS (ESI): *m/z* calcd for $[C_{13}H_{15}NO_3 + H]^+$: 234, found: 234. Spectroscopic data agree with literature[3].

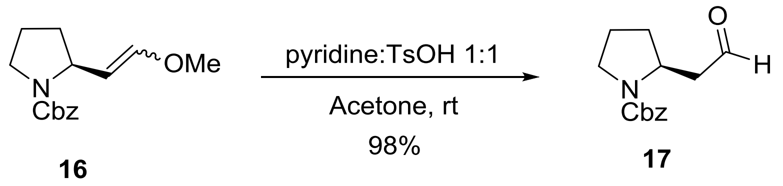
Synthesis of benzyl (S)-2-(2-methoxyvinyl)pyrrolidine-1-carboxylate (16)



15 **16**

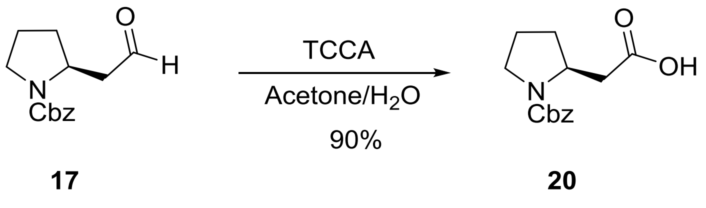
A 500 mL round-bottom flask under nitrogen atmosphere was charged with (methoxymethyl)triphenylphosphonium chloride (8.729 g, 25.46 mmol, 2 eq) and 150 mL dry THF and cooled to 0 °C. *n*-Butyllithium (9.67 mL, 2.5 M, 24.19 mmol, 1.9 eq) was added dropwise, and the reaction was stirred at 0 °C for 1 h. A solution of **15** (2.97 g, 12.73 mmol, 1.0 eq) in 20 mL dry THF was added dropwise and the reaction was stirred for an additional hour at 0 °C. The reaction mixture was quenched with saturated NH_4Cl at 0 °C, diluted with DCM and extracted with DCM. The combined organic layers were separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel using 10% EtOAC/hexanes as the solvent afforded **16** as an otherwise clean mixture of cis and trans isomers as colorless oil. Yield 3.027 g, 91%. $[\alpha]_D^{25} = -5$ (*c* 1g/100ml, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.27 (m, 5H), 6.42 (d, *J* = 6.8 Hz, 0.57H, *trans* isomer), 5.84 (d, *J* = 5.1 Hz, 0.27H, *cis* isomer), 5.23 – 4.99 (m, 2H), 4.82 – 4.72 (m, 0.3 H, *cis* isomer), 4.71 – 4.64 (m, 0.7H, *trans* isomer), 4.45 – 4.23 (m, 1H), 3.70 – 3.32 (bm, 5H), 2.13 – 1.97 (m, 1H), 1.96 – 1.76 (m, 2H), 1.73-1.64 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 154.96, 154.48, 149.16, 146.36, 145.77, 141.13, 137.06, 136.91, 128.28, 128.24, 127.72, 127.66, 127.24, 126.76, 108.70, 108.18, 103.60, 103.04, 66.31, 64.92, 59.75, 59.46, 55.90, 52.74, 52.11, 46.22, 33.34, 32.73, 32.44, 24.09, 23.54, 23.37, 22.83. MS (ESI): *m/z* calcd for $[C_{15}H_{19}NO_3 + H]^+$: 262, found: 262.

Synthesis of benzyl (*S*)-2-(2-oxoethyl)pyrrolidine-1-carboxylate (17)



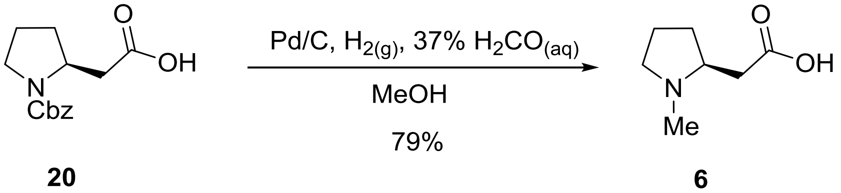
A 250 mL round-bottom flask was charged with 100 mL acetone, pyridine (1.01 mL, 12.62 mmol, 1.1 eq), and tosic acid (2.402 g, 12.62 mmol, 1.1 eq) and was stirred until homogeneous. **16** (3 g, 11.48 mmol, 1 eq) was added, and the reaction was stirred overnight at room temperature. Roughly 80% of the solvent was evacuated, followed by dilution with DCM. The organic layer was washed twice with saturated NH_4Cl solution. The combined organic layers were dried over $MgSO_4$, filtered, and evacuated to afford **1**7 as colorless oil. Yield, 2.782 g, 98%. $[\alpha]_D^{25}$ = -9 (*c* 1g/100ml, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.78 (brs, 0.6H), 9.66 (brs, 0.4H), 7.40 – 7.27 (m, 5H), 5.18 – 5.08 (m, 2H), 4.36 – 4.26 (m, 1H), 3.53 – 3.37 (m, 2H), 3.03 – 2.76 (m, 1H), 2.55 – 2.45 (m, 1H), 2.19 – 2.07 (m, 1H), 1.93 – 1.80 (m, 2H), 1.73 – 1.60 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 200.71, 154.78, 136.61, 128.36, 128.01, 127.86, 127.73, 66.66, 52.85, 52.10, 49.08, 48.42, 46.64, 46.26, 31.84, 31.05, 23.60, 22.82. MS (ESI): *m/z* calcd for $[C_{14}H_{17}NO_3 + H]^+$: 248, found: 248. Spectroscopic data are in agreement with literature[4].

Synthesis of (*S*)-2-(1-((benzyloxy)carbonyl)pyrrolidine-2-yl)acetic acid (20)



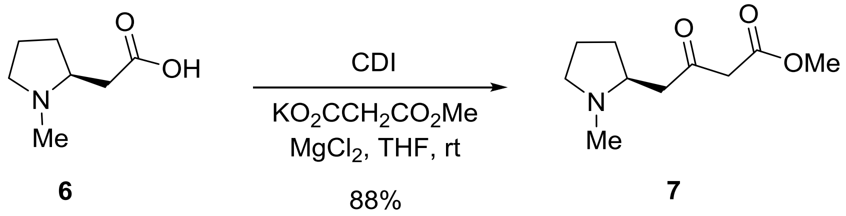
A 250 mL round-bottom flask was charged with 55 mL water, 125 mL acetone, and **17** (2.5 g, 10.10 mmol, 1.0 eq). TCCA (2.584 g, 11.12 mmol, 1.1 eq) was added, and the reaction was stirred overnight at room temperature. The reaction mixture was diluted with DCM and washed twice with brine. The combined organic layers were dried over $MgSO_4$, filtered and evacuated to afford **20** as yellow crystalline solid. Yield, 2.391 g, 90%. $[\alpha]_D^{25}$ = -3.5 (*c* 1g/100ml, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 10.60 - 9.99 (bs, 1H), 7.45 – 7.27 (m, 5H), 5.21 –5.07 (m, 2H), 4.29 – 4.20 (m, 1H), 3.50 – 3.39 (m, 2H), 3.11 – 2.78 (m, 1H), 2.45 – 2.30 (m, 1H), 2.18 – 2.04 (m, 1H), 1.95 – 1.73 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 176.53, 154.87, 136.59, 128.42, 127.92, 127.80, 66.81, 54.31, 53.75, 46.74, 46.42, 38.95, 38.25, 31.29, 30.72, 23.44, 22.66. MS (ESI): *m/z* calcd for $[C_{14}H_{17}NO_4 + H]^+$: 264, found: 264.[5]

Synthesis of (*S*)-2-(1-methylpyrrolidin-2-yl)acetic acid (6)



A 50 mL Schlenk flask was charged with **20** (2 g, 7.60 mmol), 10% Pd/C (200 mg, 10 Wt%), and 20 mL MeOH. 1.45 mL of 37% aqueous formaldehyde solution was added, and the reaction was placed under hydrogen atmosphere (balloon) and stirred for 16 h at room temperature. Filtration of the reaction mixture, followed by solvent evacuation afforded **6** as white amorphous solid. Yield 0.859 g, 79%. Mp = 119 °C. $[\alpha]_D^{25}$ = -45 (*c* 1g/100ml, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.50 – 3.41 (m, 1H), 3.17 – 3.07 (m, 1H), 2.58 (s, 3H), 2.67 – 2.40 (m, 3H), 2.21 – 2.09 (m, 1H), 1.98 – 1.65 (bm, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 174.81, 64.39, 55.45, 39.17, 36.55, 30.10, 21.82. MS (ESI): *m/z* calcd for $[C_7H_{13}NO_2 + Na]^+$: 166, found: 166.[6]

Synthesis of Methyl (*S*)-4-(1-methylpyrrolidin-2-yl)-3-oxobutanoate (7)



1, 1’-Carbonyldiimidazole (622 mg, 3.84 mmol, 1.1 eq) was taken in a 10 mL flame-dried Schlenk flask which was under nitrogen atmosphere. The shlenk was charged with N-methylamino acid **6** (500 mg, 3.49 mmol, 1.0 eq) in THF (0.5 M) and the reaction was stirred for 3 h at room temperature. Then methyl potassium malonate (818 mg, 5.23 mmol, 1.5 eq) and $MgCl_2$ (398 mg, 4.19 mmol, 1.2 eq) were added to the above solution and the reaction mixture was stirred for 16 hours. Water is added to the reaction mixture and extracted with EtOAc. The crude oil was dissolved in CH_2Cl_2 and was directly loaded onto a silica gel. Flash column with 5% MeOH in DCM afforded the target compound as yellow oil. Yield 612 mg, 88%. $[\alpha]_D^{25}$ = -70 (*c* 1g/100mL, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 3H), 3.53 (s, 2H), 3.44 – 3.33 (m, 1H), 3.26 – 3.15 (m, 1H), 3.11 – 2.98 (bs, 1H), 2.91 – 2.80 (m, 1H), 2.53 (s, 3H), 2.57 – 2.44 (m, 1H), 2.30 – 2.17 (m, 1H), 2.03 – 1.80 (bm, 2H), 1.74 – 1.60 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 200.59, 167.36, 62.80, 56.32, 52.51, 49.09, 45.24, 40.25, 30.76, 29.68, 22.04. *m/z* calcd for $[C_{10}H_{17}NO_3 + H]^+$: 200, found: 200.

References

1. D. S. Bose, M. Idrees, I. K. Todewale, N. M. Jakka, and J. V. Rao, *Eur. J. Med. Chem.,* 2012, **50**, 27.
2. A. Quintard, C. Bournaud, and A. Alexakis, *Chem. Eur. J.,* 2008, **14**, 7504.
3. S. E. Denmark, J. P. Edwards, T. Weber, and D. W. Piotrowski, *Tetrahedron: Asymmetry*, 2010, **21**, 1278.

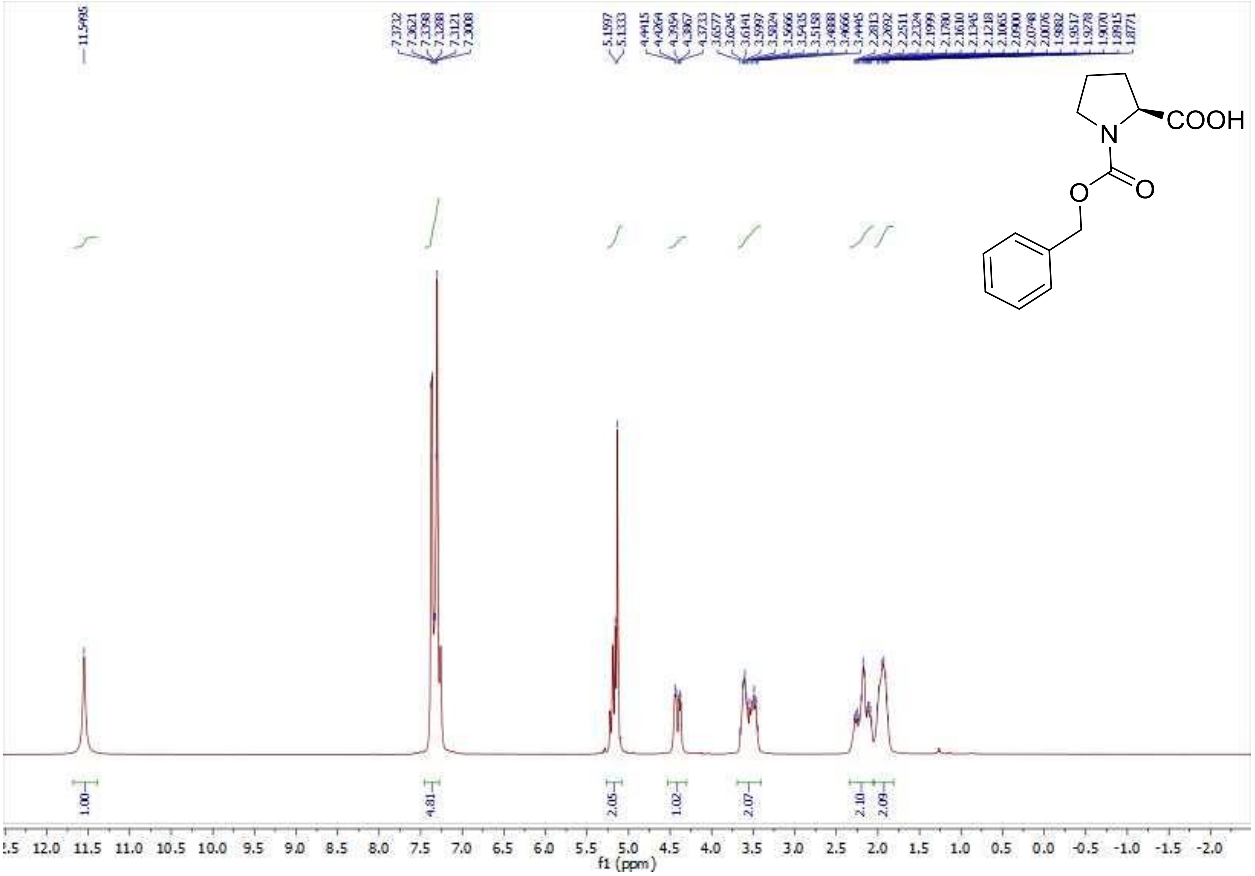
4. H. Konno, S. Kusumoto, S. Kanai, Y. Yamahana, K. Nosaka, and K. Akaji, *Heterocycles*, 2006, **68**, 2579.

5. T. Aoyama, and T. Shioiri, *Chem. Pharm. Bull.*, 1981, **29**, 3249.

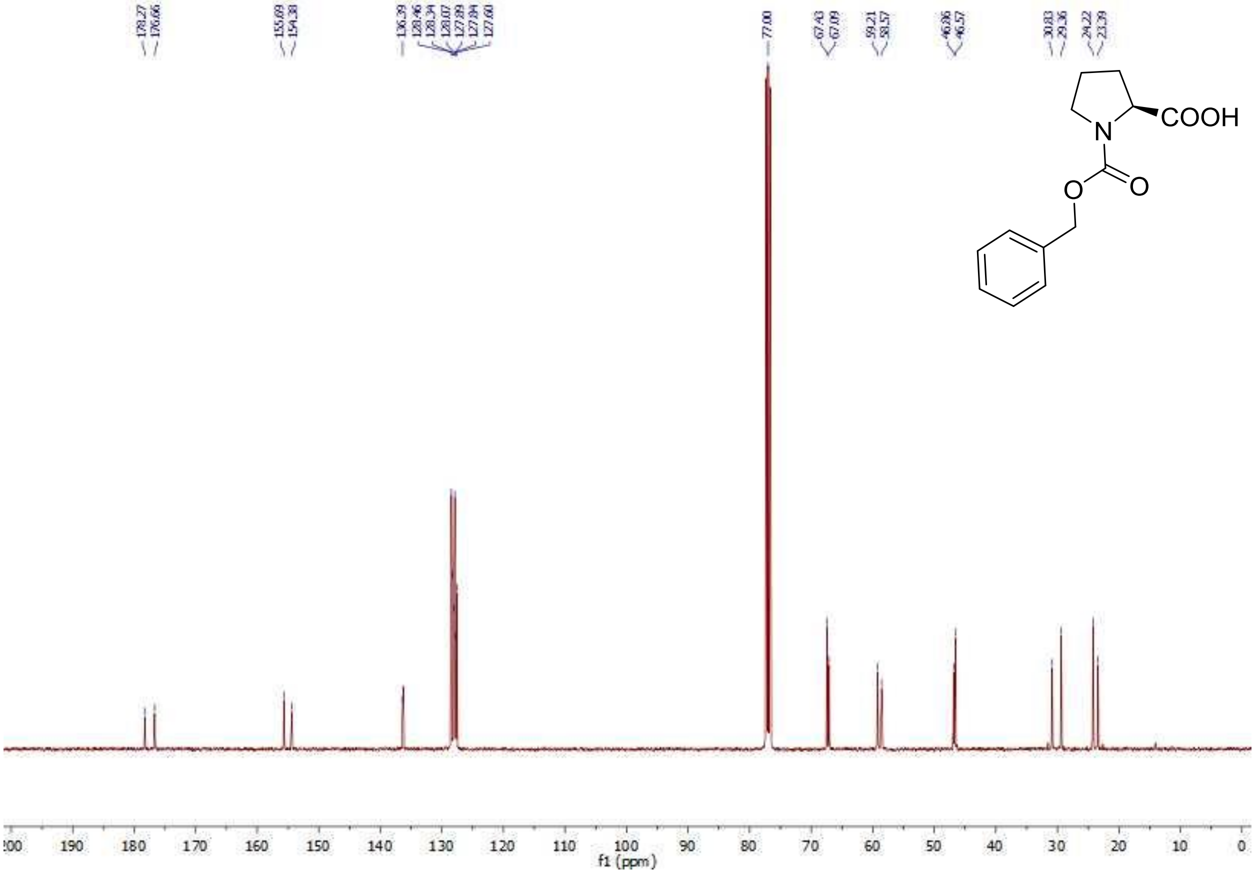
6. E. Leete, J. A. Bjorklund, M. M. Couladis, and S. H. Kim, *J. Am. Chem. Soc.*, 1991, **113**, 9286.

NMR Spectra

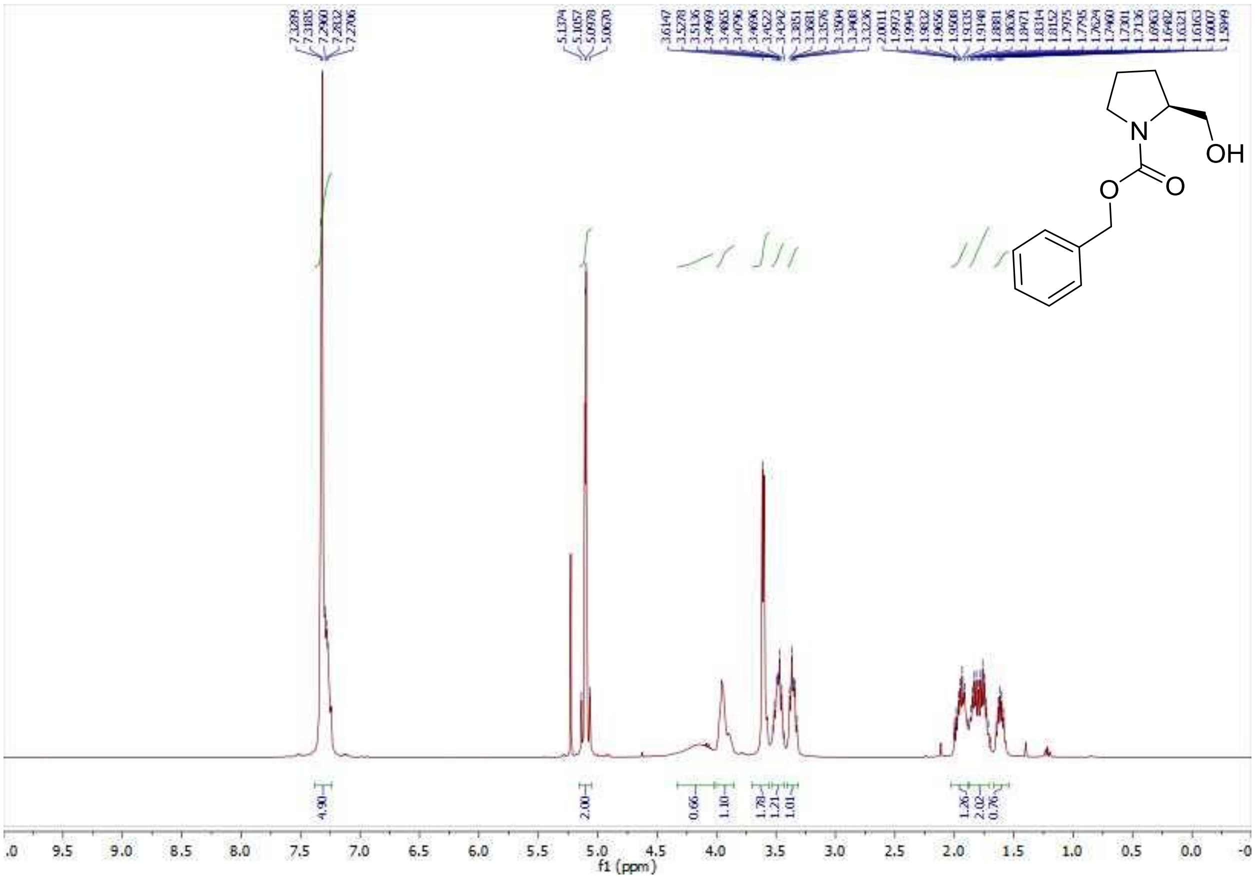
^{1}H NMR Spectrum of Compound 13



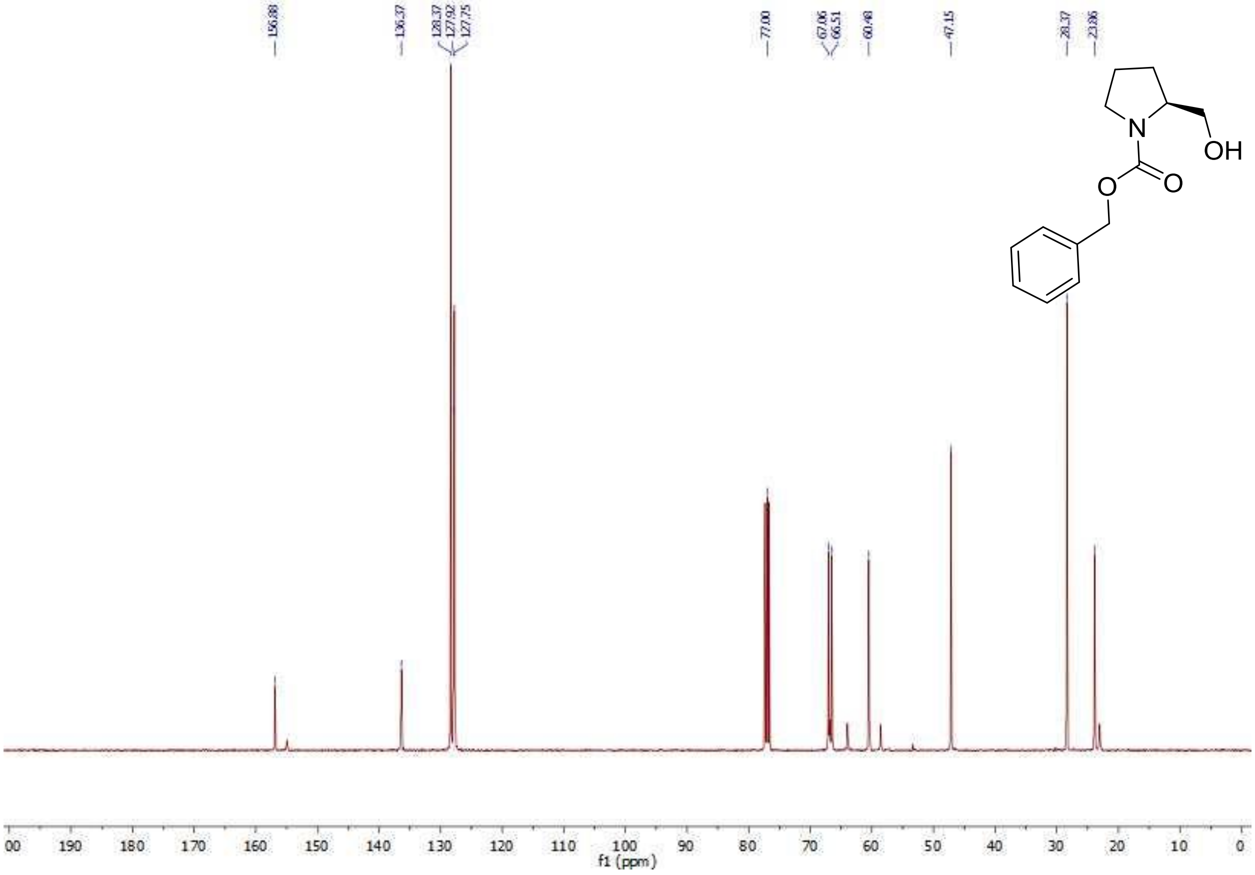
^{13}C NMR Spectrum of Compound 13



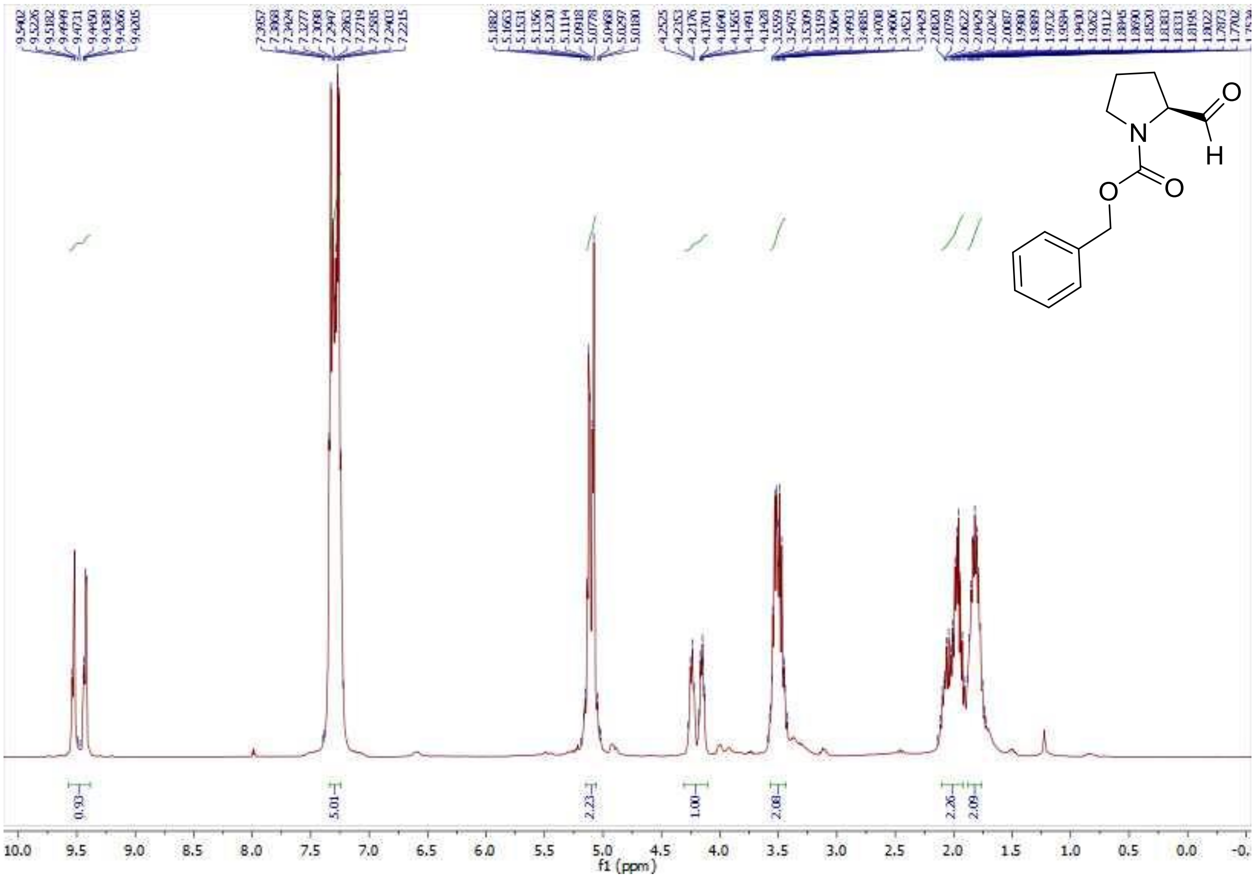
^{1}H NMR Spectrum of Compound 14



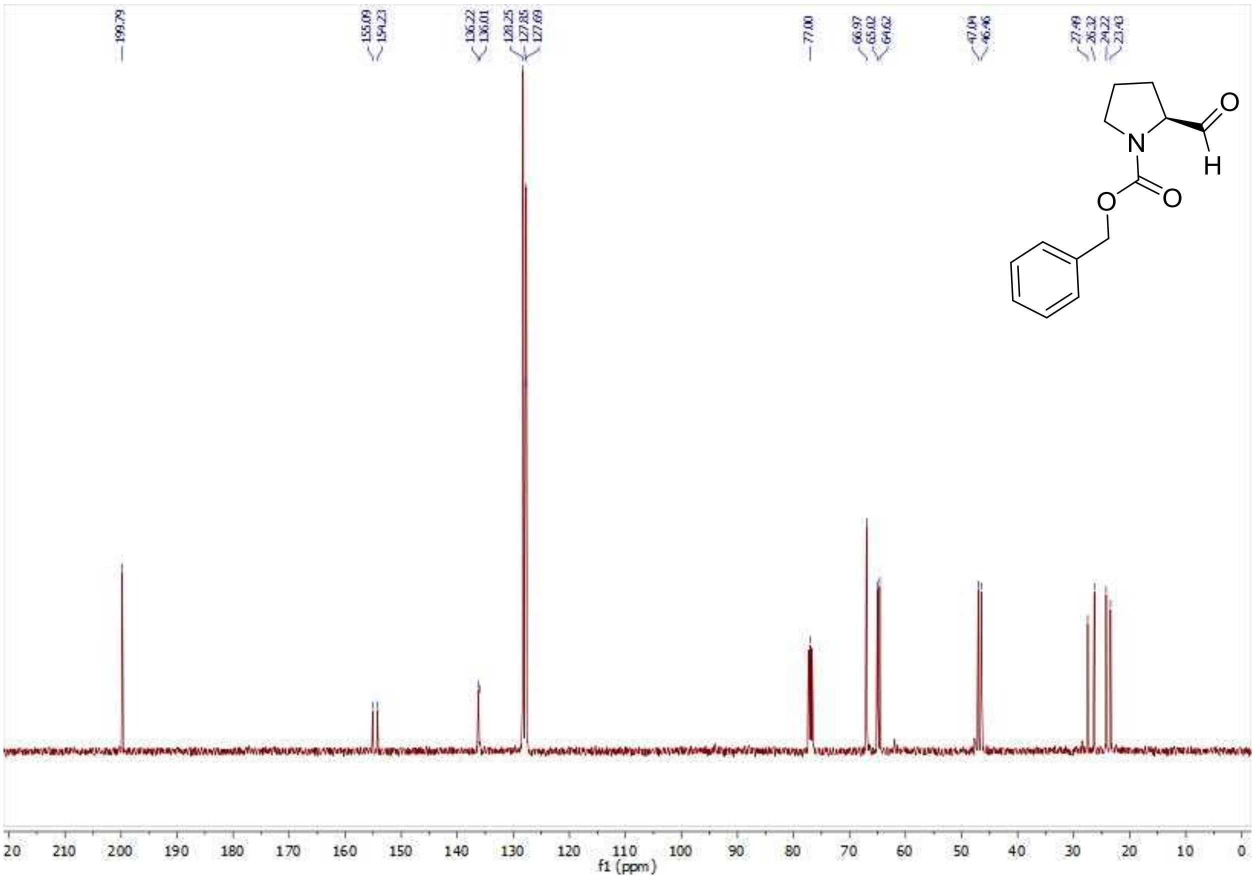
^{13}C NMR Spectrum of Compound 14



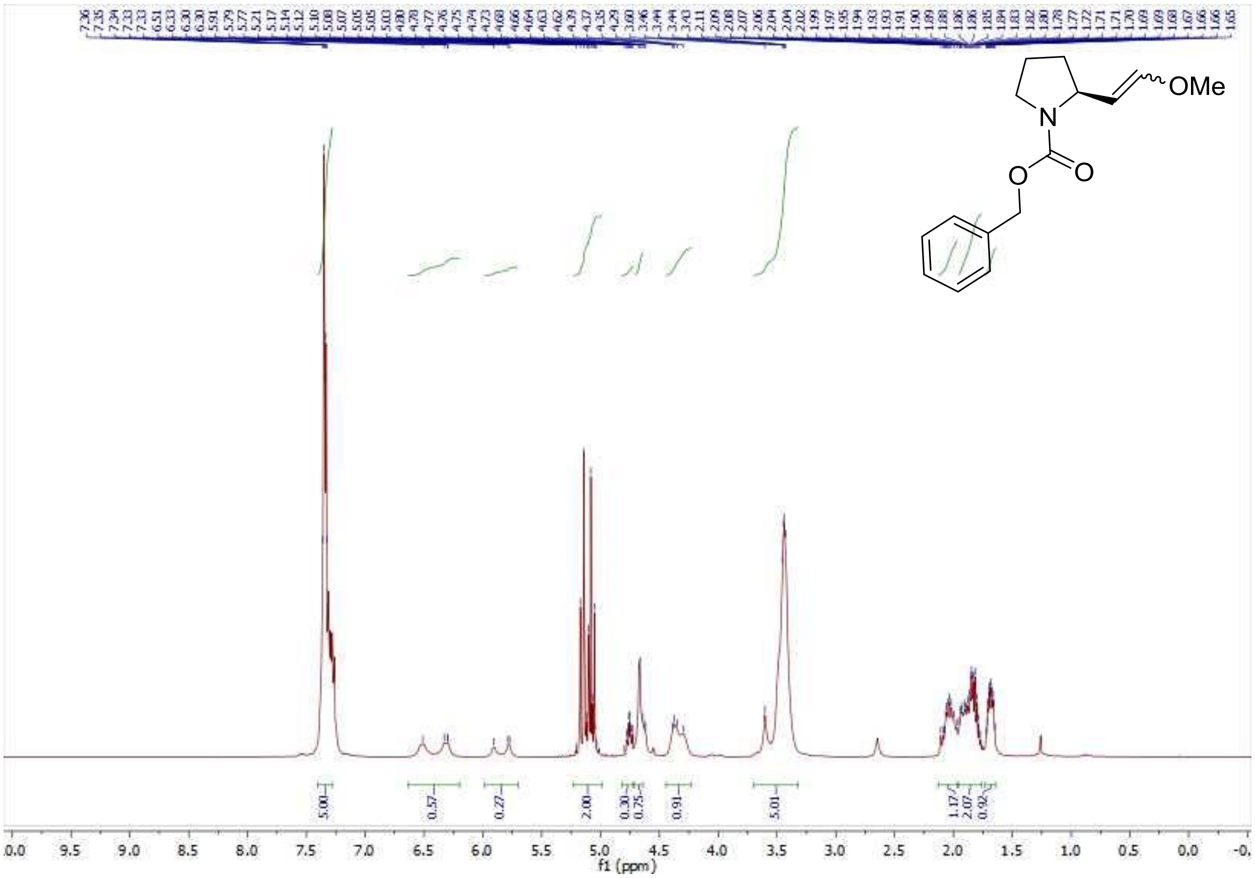
^{1}H NMR Spectrum of Compound 15



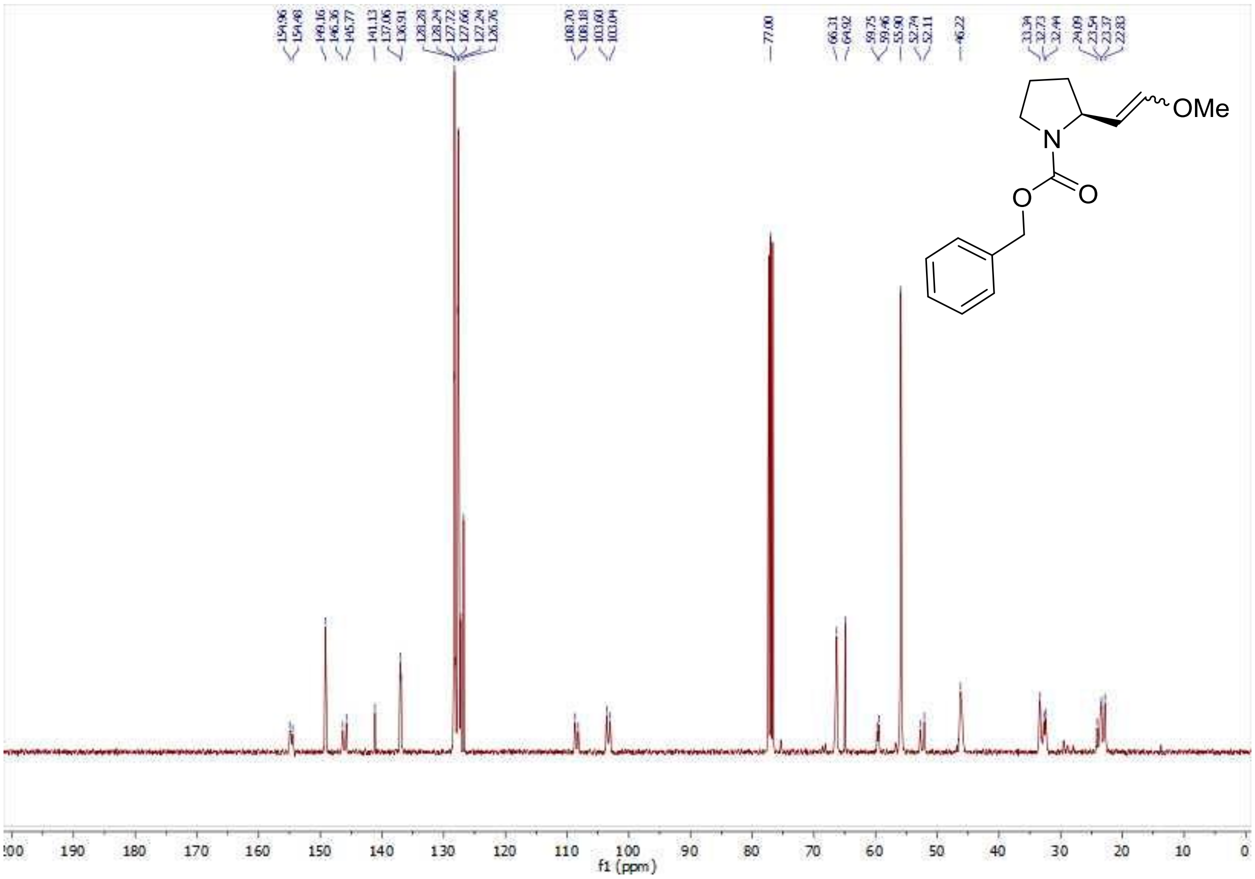
^{13}C NMR Spectrum of Compound 15



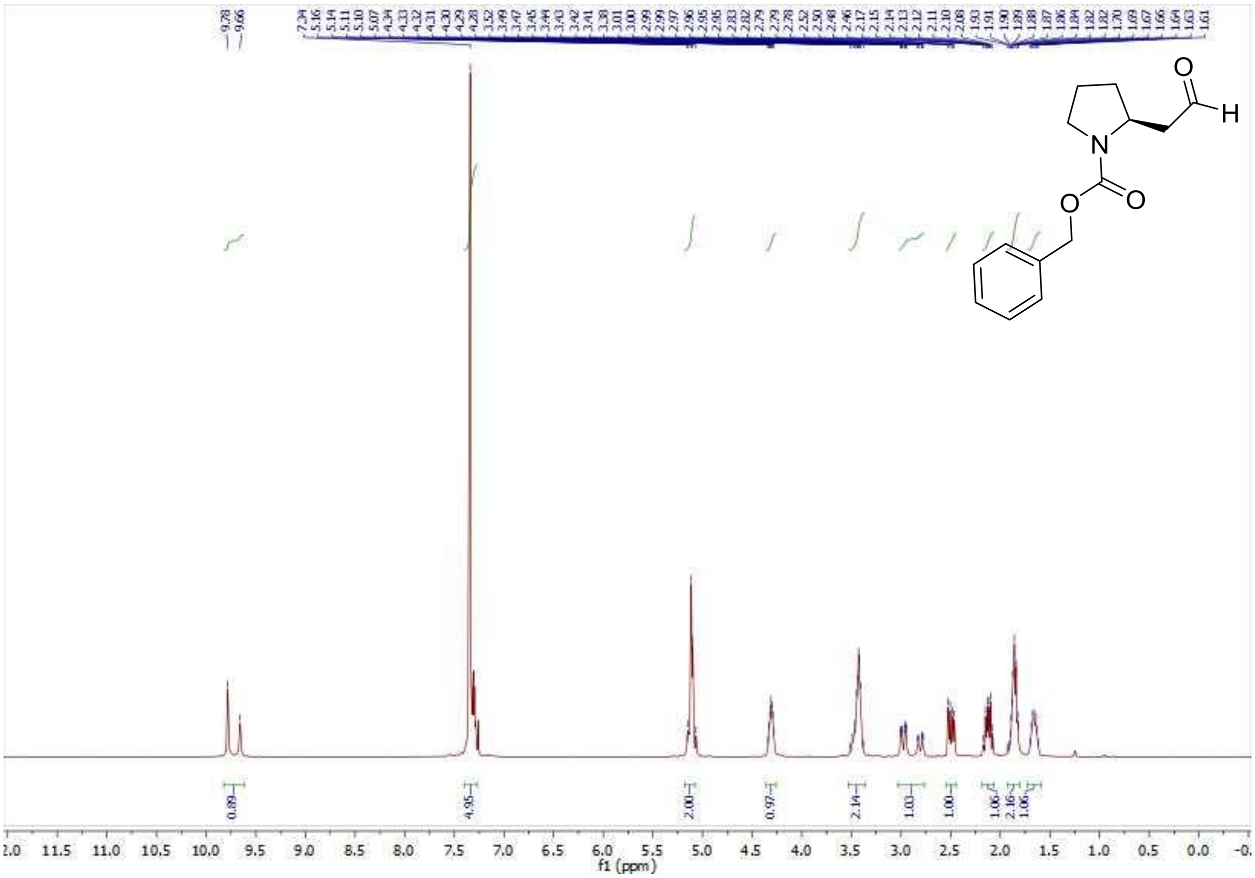
^{1}H NMR Spectrum of Compound 16



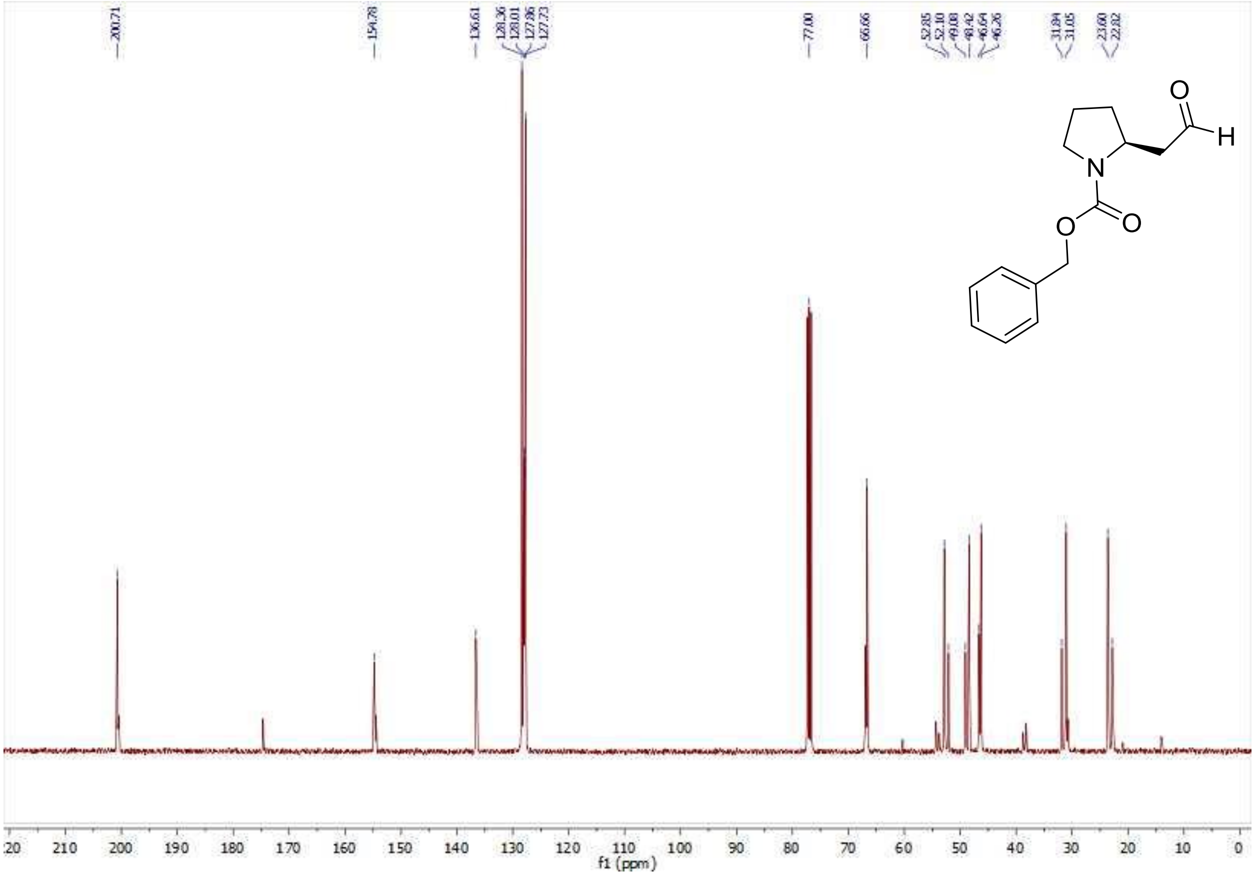
^{13}C NMR Spectrum of Compound 16



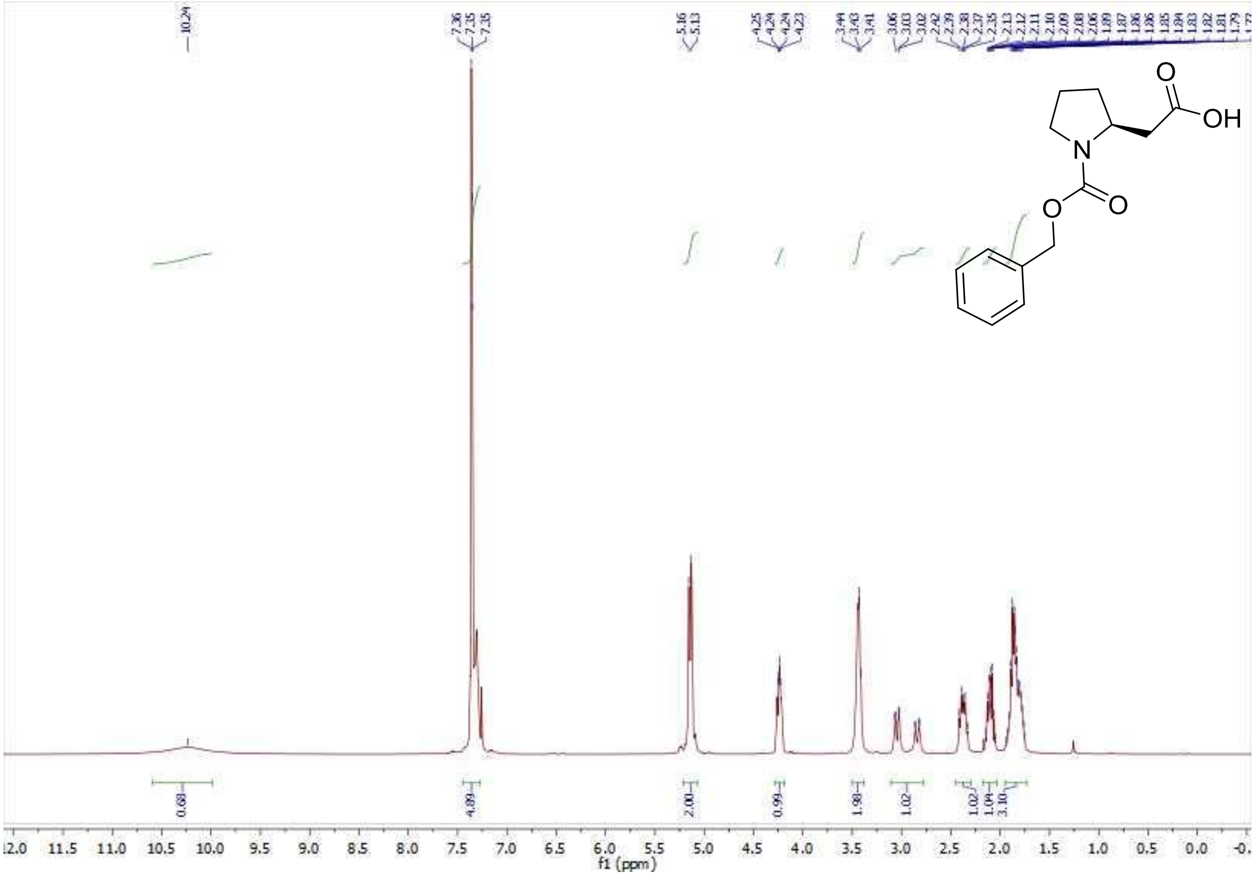
^{1}H NMR Spectrum of Compound 17



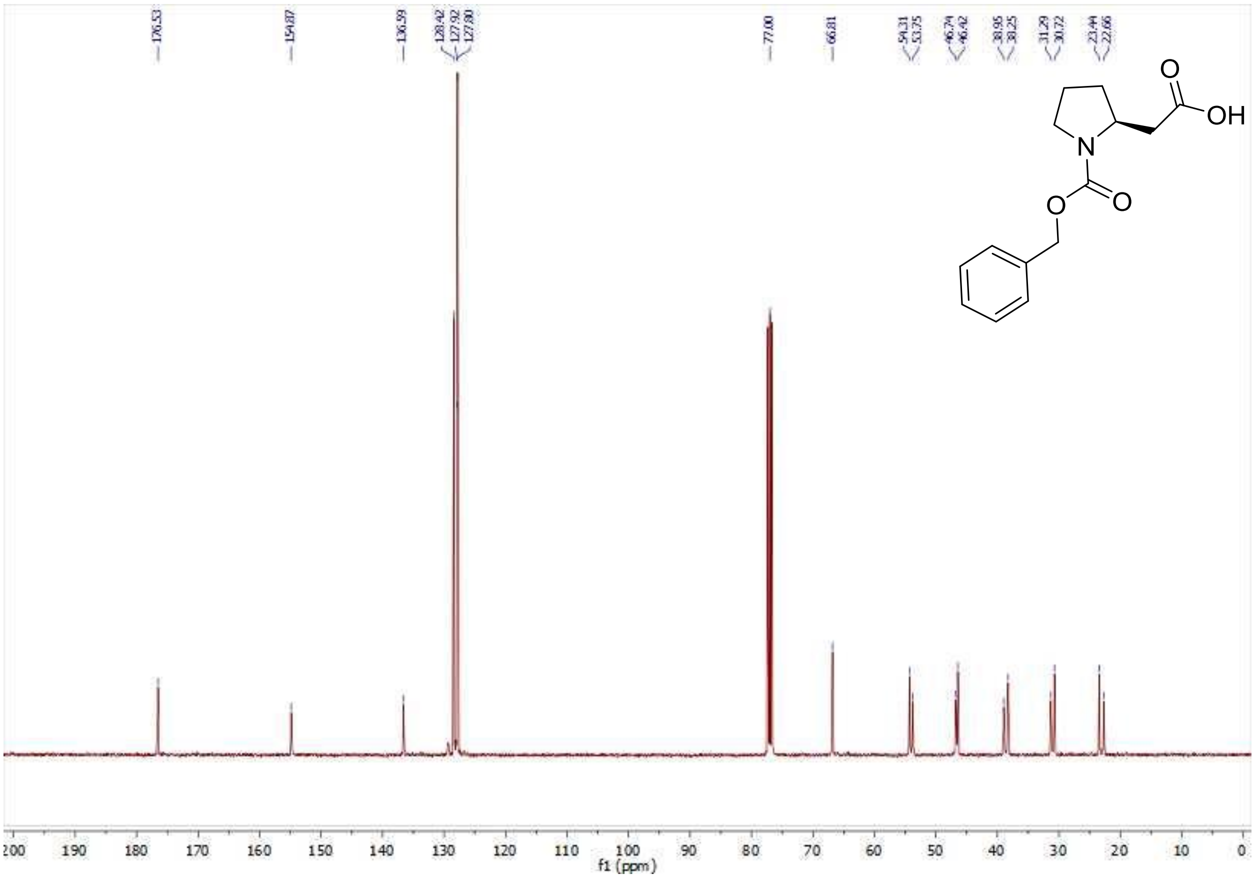
^{13}C NMR Spectrum of Compound 17



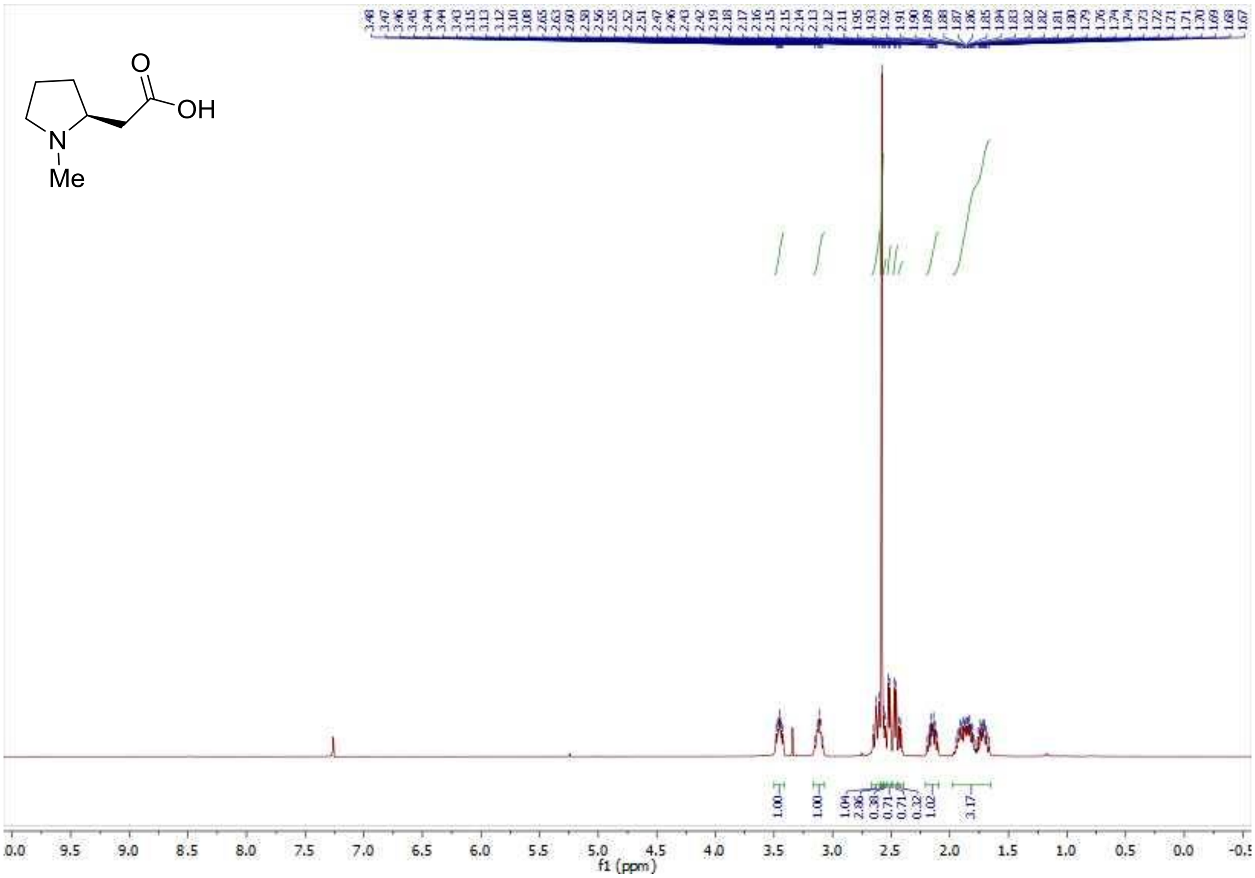
^{1}H NMR Spectrum of Compound 20



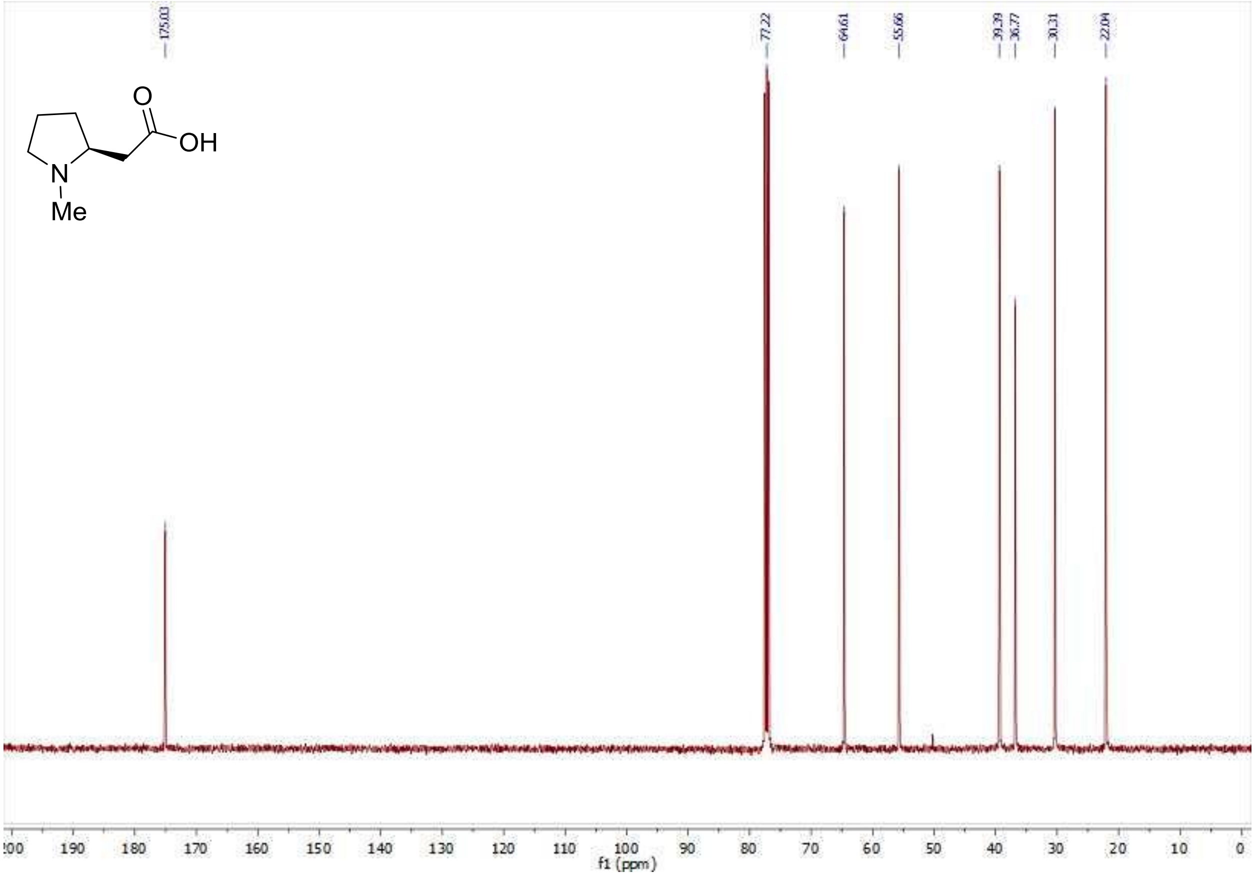
^{13}C NMR Spectrum of Compound 20



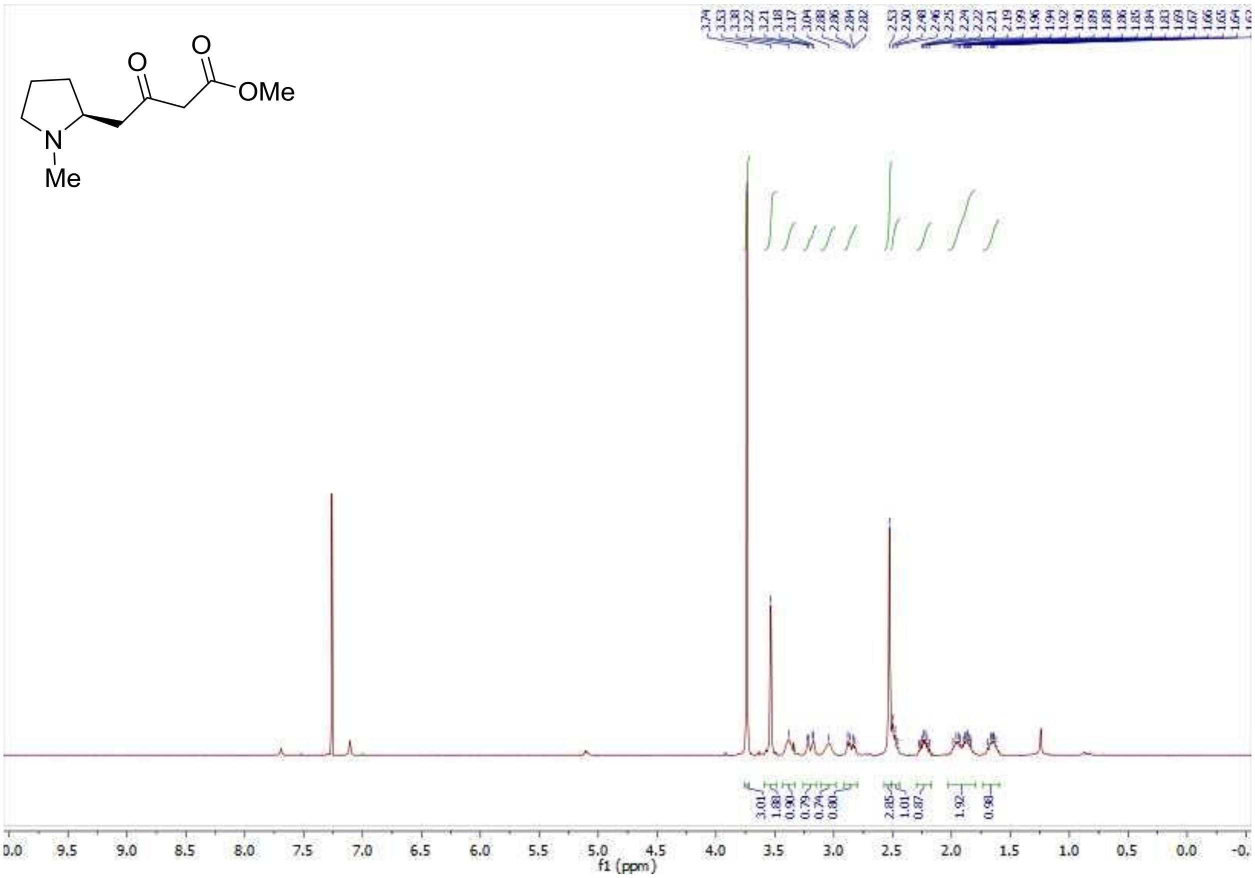
^{1}H NMR Spectrum of Compound 6



^{13}C NMR Spectrum of Compound 6



^{1}H NMR Spectrum of Compound 7



^{13}C NMR Spectrum of Compound 7