Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supplementary Information

Syntheses of (–)-Pelletierine and (–)-Homopipecolic Acid

Wen-Hua Chiou,* Guei-Tang Chen, Chien-Lun Kao and Yu-Kai Gao

wchiou@dragon.nchu.edu.tw

Department of Chemistry, National Chung Hsing University, Taichung 402 Taiwan, R.O.C.

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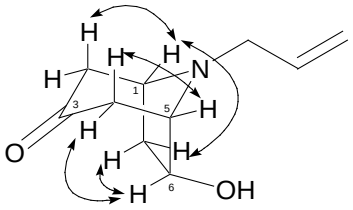
General Methods:

All NMR spectra were recorded on a Varian 600 MHz NMR spectrometer. For each compound, full assignment of all ^{13}C peaks was achieved on the basis of the data from gradient HSQC, gradient HMBC and gradient COSY from regular NMR experiments, as well as assignment of most ^{1}H peaks. The relationship of some ^{1}H peaks has been further confirmed by ROESY spectroscopy. Melting points were measured on a Büchi 535 melting point apparatus and uncorrected. High-resolution mass spectrometry (HRMS) analyses and X-ray crystallography were conducted at the Instrument Center of National Chung Hsing University. The specific rotation values were recorded by Perkin-Elmer PE-241 polarimeter. GC-MS analyses were performed on an HP 5890 Series GC system equipped with an Rtx-®-5MS capillary column (50 m X 0.25 mm, 0.5 μm). TLC analyses were performed on Merck DC-alufolien with Kieselgel 60F-254, and were visualized with UV light, iodine chamber, 10% sulfuric acid or 10% PMA solution. Purifications were performed by flash chromatography on silica gel 60 (Merck, 230-400 mesh ASTM).

Materials: Chemicals, reagents and solvents were purchased from Sigma Aldrich Company or Acros Organic Fischer Company. The reagents were used as received. Dichloromethane, pyridine, triethylamine, acetonitrile, DMSO and methanol were dried and distilled over calcium hydride under nitrogen before use. Ether was dried and distilled over sodium-benzophenone ketyl under nitrogen before use. THF was dried and distilled over potassium metal under nitrogen before use. Toluene and benzene were dried and distilled over sodium metal under nitrogen or argon before use. The reaction flasks were dried in a 110 °C oven and allowed to cool to room temperature in a desiccator over "*Drierite*" (calcium sulfate) and assembled under nitrogen or argon atmosphere.

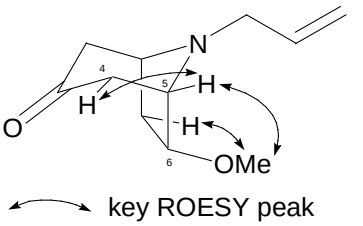
A solution of 2,5-dimethoxyfuran (4.70 mL, 38.8 mmol, 1.0 equiv.) in HCl (3 N, 70 mL) was allowed to be stirred at room temperature for 1 h, followed by addition of NaOH solution (6 N, 35 mL) to neutralize excess acid. The hydrolyzed furan solution was added to an acetate buffer solution, prepared by mixing acetonedicarboxylic acid (10.00 g, 68.4 mmol), allylamine (5.80 mL, 77.3 mmol), $NaOAc{\cdot}3H_2O$ (15.00 g, 110 mmol) in water (200 mL). The solution was allowed to be stirred at room temperature overnight. The reaction may be monitored by GC-MS. Upon completion of the reaction, K_2CO_3 (6.25 g, 45 mmol) and NaCl (6.25 g, 107 mmol) were added and stirred for 1 h to quench the reaction. The reaction mixture was partitioned with CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (50 mL X 10) again. The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure to give a crude product (~ 5.1 g). The residue was purified by flash chromatography on silica gel, using ethyl acetate/n-hexane/triethylamine (1/3/0.03) as the eluant to give tropanol **1a** (R_f = 0.10, 3.20 g, 17.7 mmol, 46%) and methyl ether **1b** (R_f = 0.40, 1.12 g, 5.74 mmol, 15%) as colorless oil.

***N*-allyl-6-hydroxy-3-tropanone (1a):** ^{1}H-NMR (600 MHz, 25 ^{o}C, $CDCl_3$, δ): 1.95 (dd, *J* = 7.2, 14.4 Hz, 1H, H-7-exo), 2.02 (dd, *J* = 7.2, 14.4 Hz, 1H, H-7-endo), 2.07 (d, *J* = 16.2 Hz, 1H, H-2-eq), 2.18 (d, *J* = 16.2 Hz, 1H, H-4-eq), 2.57-2.62 (m, 2H, H-2-ax and H-4-ax), 2.96 (br, 1H, -OH), 3.41-3.48 (m, 3H, H-5 and NC<u>H</u>$_2$), 3.65 (brs, 1H, H-1), 4.05 (brs, 1H, H-6), 5.15 (d, *J* = 10.2 Hz, 1H, -CH=C<u>H</u>$_2$), 5.25 (dd, *J* = 1.8, 16.8 Hz, 1H, -CH=C<u>H</u>$_2$), 5.93 (tdd, *J* = 6.0, 10.2, 16.8 Hz, 1H, -C<u>H</u>=CH$_2$); ^{13}C-NMR (150 MHz, 25 ^{o}C, $CDCl_3$, δ): 40.7 (t, C-7), 41.9 (t, C-4), 44.3 (t, C-2), 51.1 (t, N<u>C</u>H$_2$), 56.8 (d, C-1), 66.0 (d, C-5), 74.8 (d, C-6), 117.3 (t, -CH=<u>C</u>H$_2$),

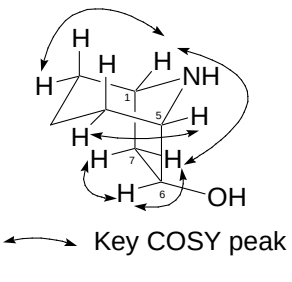


135.2 (d, -<u>C</u>H=CH$_2$), 208.2 (s, C-3); EI-HRMS (m/z): [M]$^+$ calcd for $C_{10}H_{15}NO_2^+$, 181.1103; found, 181.1109 (Δ = 3.3 ppm). GC-MS condition: initial temperature: 50 ^{o}C, heating rate 10 ^{o}C per min to 280 ^{o}C and keeping the temperature for 2 min. t_R: 16.65 min.

***N*-allyl-6-methoxy-3-tropanone (1b):** ^{1}H-NMR (600 MHz, 25 ^{o}C, $CDCl_3$, δ): 2.00 (dd, *J* = 7.2, 14.4 Hz, 1H, H-7-endo), 2.06 (dd, *J* = 7.2, 13.8 Hz, 1H, H-7-exo), 2.14 (d, *J* = 15.6 Hz, 1H, H-2-eq), 2.21 (d, *J* = 16.2 Hz, 1H, H-4-eq), 2.58-2.74 (m, 2H, H-2-ax and H-4-ax), 3.25 (s, 3H, OC<u>H</u>$_3$), 3.39-3.47 (m, 2H, NC<u>H</u>$_2$ X2), 3.62 (brs, 1H, H-5), 3.65-3.70 (m, 2H, H-1 and H-6), 5.16 (d, *J* = 9.6 Hz, 1H, -CH=C<u>H</u>$_2$), 5.25 (d, *J* = 17.4 Hz, 1H, -CH=C<u>H</u>$_2$), 5.98 (tdd, *J* = 6.6, 10.2, 16.8 Hz, 1H, -C<u>H</u>=CH$_2$); ^{13}C-NMR (150 MHz, 25 ^{o}C, $CDCl_3$, δ): 37.3 (t, C-7), 44.2 (t, C-4), 46.1 (t, C-2), 53.0 (t, N<u>C</u>H$_2$), 56.8 (q, O<u>C</u>H$_3$), 57.8 (d, C-1), 62.7 (d, C-5), 85.1 (d, C-6), 117.4 (t, -CH=<u>C</u>H$_2$), 135.7 (d, -<u>C</u>H=CH$_2$), 208.6 (s, C-3); EI-HRMS (m/z): [M]$^+$ calcd for $C_{11}H_{17}NO_2^+$, 195.1259; found, 195.1251 (Δ = 4.1 ppm). GC-MS condition: initial temperature: 50 ^{o}C, heating rate 10 ^{o}C per min to 280 ^{o}C and keeping the temperature for 2 min. t_R: 15.83 min.



6-tropanol (2): A mixture of tropanol **1a** (2.37 g, 13.1 mmol, 1.0 equiv.) and hydrazine monohydrate (5.7 mL, 118 mmol) in EtOH (24 mL) was heated under reflux condition for 1.5 h. The reaction mixture was concentrated under reduced pressure to a brown syrup. After addition with powdered KOH (6.67 g, 118 mmol), the mixture



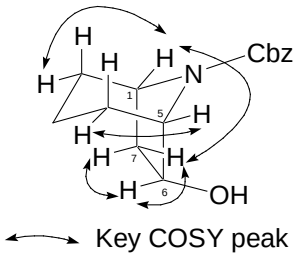
was heated at 130 ^{o}C for 1 h, 160 ^{o}C for 1 h and 180 ^{o}C for 2.5 h. When the reaction mixture has been cool down, water (25 mL) were added to quench the reaction. The solution was partitioned with CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (70 mL X5). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure to give a crude product (~2.0 g). The crude product was purified by flash chromatography on silica gel, using MeOH/$CHCl_3$/Et_3N (R_f = 0.10, 1/9/0.05) as the eluant to give titled product **2** as a white solid (1.36 g, 10.7 mmol, 82%): mp: 70-73 ^{o}C, ^{1}H-NMR (600 MHz, 25 ^{o}C, $CDCl_3$, δ): 1.35-1.41 (m, 2H, H-2 and H-3), 1.51-1.69 (m, 4H,H-2, H-3 and H-4 X2), 1.80 (dd, *J* = 7.2, 13.8 Hz, 1H, H-7 exo), 2.16 (dd, *J* = 7.2, 13.8 Hz, 1H, H-7 endo), 3.33 (brs, 1H, H-5), 3.70 (brs, 1H, H-1), 4.24 (dd, *J* = 2.4, 7.8 Hz, 1H, H-6), 4.46-4.56 (br, 2H, -OH and NH); ^{13}C-NMR (150 MHz, 25 ^{o}C, $CDCl_3$, δ): 17.2 (t, C-3), 28.5 (t, C-4), 30.4 (t, C-2), 40.5 (t, C-7), 55.4 (d, C-1), 63.6 (d, C-5), 74.4 (d, C-6); EI-HRMS (m/z): $[M]^+$ calcd for $C_7H_{13}NO^+$, 127.0997; found, 127.1000 (Δ = 2.4 ppm).

Resolution: To a solution of 6-tropanol (1.27 g, 10.0 mmol) in methanol (50 ml) was added L-tartaric acid (1.51 g, 10.0 mmol). The solution became cloudy immediately, and was heated up until the solution was clear, and the resulting solution was allowed to stand at room temperature overnight. The salt was separated as crystals, and was able to be collected and washed with a small amount cold methanol. The crystals (~700 mg) was dissolved in methanol (30 mL), and repeated the previous manipulation mentioned above, yielding new crystals (~ 400 mg). The recrystallization procedure was repeated again to give white crystals (233 mg): mp: 164-168 ^{o}C $[\alpha]_D^{25}$ +18.1° (*c*: 1.0, H_2O).

A CH_2Cl_2 solution (10 mL) of the salt was partitioned with NaOH solution (6 N, 10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL X5). The combined CH_2Cl_2

solution was washed with brine (5 mL), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure to give a white solid product (+)-**2** (103 mg, 0.81 mmol): mp: 69-73 ^oC, $[\alpha]_D^{25}$ +16.1° (*c*: 1.0, CH_2Cl_2).

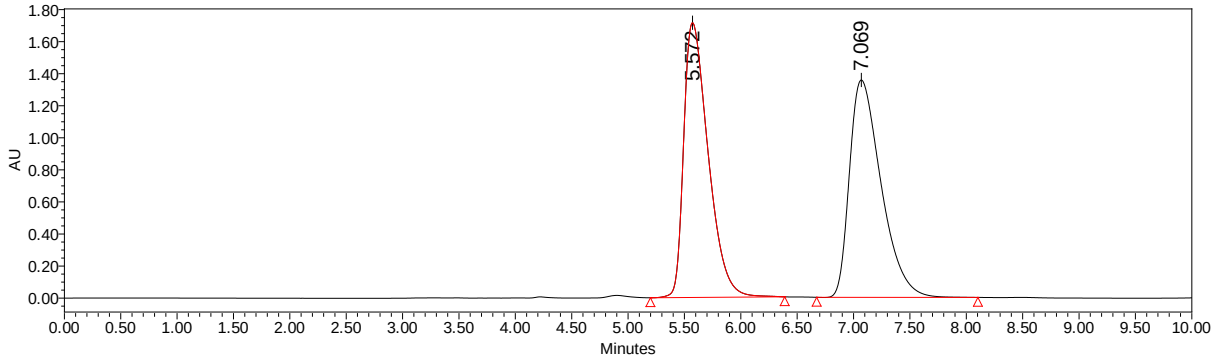
(1*R*, 5*S*, 6*S*)-*N*-Benzyloxycarbonyl-6-tropanol ((+)-3): To a THF solution (12 mL) of 6-tropanol (**2**, 468 mg, 3.68 mmol, 1.0 eq.) and K_2CO_3 (1.02 g, 7.38 mmol, 2.0 eq.) in an ice bath, was added benzyl chloroformate (0.58 mL, 4.06 mmol, 1.1 eq.). The solution was allowed to be stirred at room temperature overnight (~16 h).



Upon completion of the reaction, the reaction mixture was partitioned with CH_2Cl_2 (15 mL) and water (10 mL). The aqueous layer was extracted with dichloromethane (15 mL X 5). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure to give a crude product. The crude product was purified by flash chromatography on silica gel using ethyl acetate/n-hexane (R_f = 0.11, EtOAc/n-hex = 1/1) as the eluant to give product **3** as a colorless oil (958 mg, 3.66 mmol, 99%): $[\alpha]_D^{28}$ +12.2° (*c*: 0.5, CH_2Cl_2); ^{1}H-NMR (600 MHz, 25 ^oC, $CDCl_3$, δ): 1.34-1.39 (m, 1H, H-2), 1.45-1.60 (m, 3H, H-3 X 2 and H-4), 1.63-1.75 (m, 2H, H-2 and H-4), 1.88 (dd, *J* = 8.4, 14.4 Hz, 1H, H-7), 2.10 (br, 1H, -OH), 2.17 (dd, *J* = 7.2, 14.4 Hz, 1H, H-7), 4.07 (brs, 1H, H-5), 4.29 (dd, *J* = 2.4, 7.2 Hz, 1H, H-6), 4.43 (d, *J* = 7.2 Hz, 1H, H-1), 5.15 (s, 2H, -OC$\underline{H_2}$Ph), 7.28-7.32 (m, 1H, H-4 in Ph), 7.33-7.37 (m, 4H, H-2 and H-3 in Ph); ^{13}C-NMR (150 MHz, 25 ^oC, $CDCl_3$, δ): 17.1 (t, C-3), 27.6 (t, C-4), 29.5 (t, C-2), 40.2 (t, C-7), 54.7 (d, C-1), 63.3 (d, C-5), 66. 7 (t, -O$\underline{C}H_2$Ph), 74.5 (d, C-6), 127.8 (d, C-2 in Ph), 127.9 (d, C-4 in Ph), 128.4 (d, C-3 in Ph), 136.8 (s, C-1 in Ph), 154.3 (s,

N-CO-O); EI-HRMS (m/z): $[M]^+$ calcd for $C_{15}H_{19}NO_3^+$, 261.1365; found, 261.1367 (Δ = 0.8 ppm).

HPLC condition: Chiralcel OD, 250 mm X 4.6 mm, 5 μm; Mobile phase A: IPA : n-Hex=1:2(v/v); Mobile phase B: n-Hexane; isocratic, 60% A : 40% B; flow rate 1.0 mL per min; detection UV 215 nm, t_R: 5.6 min for (+)-**3**, 7.1 min for (–)-**3.**



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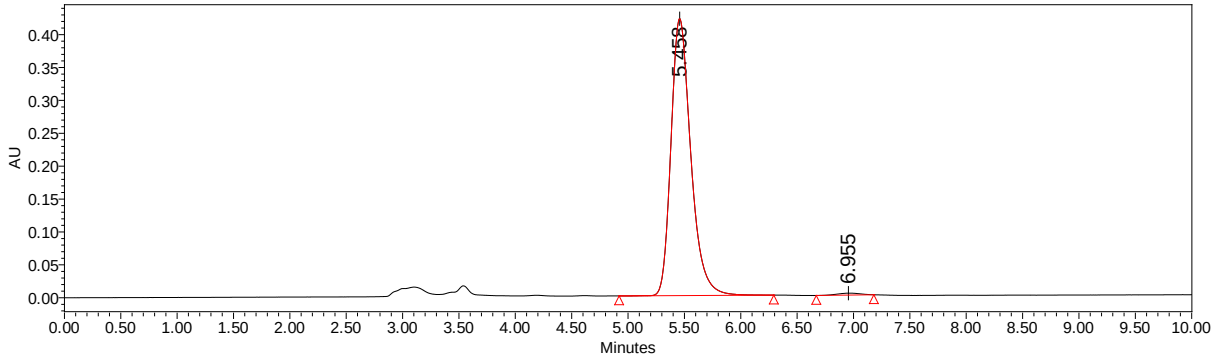

	Retention Time	Area	% Area	Height
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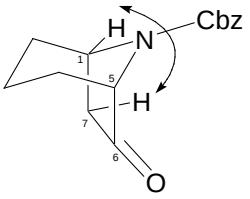
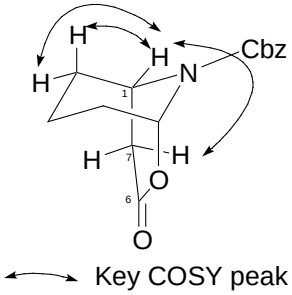
2	6.955	41364	0.80	2952

(1*R*, 5*S*)-*N*-Benzyloxycarbonyl 6-tropanone ((+)-4): To a solution of alcohol **3** (1.721 g, 6.58 mmol, 1.00 eq.) in acetone (65 mL) in an ice bath, an aqueous $NaHCO_3$ solution (5%, 32 mL), KBr (392 mg, 3.29 mmol, 0.5 eq.), and tetramethylpiperidine nitroxyl free radical (TEMPO, 206 mg, 1.32 mmol, 0.20 eq.) were added. Then, a bleach solution (13%, 10 mL, ~ 3 eq.) was added dropwise via a syringe over 5 min. The solution became white cloudy. After stirring for 1 h in an ice bath, additional $NaHCO_3$ (5%, 32 mL) and additional bleach (13%, 10 mL) were added. The reaction mixture was stirred in an ice bath for another 1 h. Concentration of the reaction mixture under reduced pressure to remove volatile substances gave a clean aqueous solution. The solution was acidified with an aqueous $KHSO_4$ solution (1 M) in an ice bath until pH became 2~3. The aqueous solution was extracted with ethyl acetate (80 mL). The resulting aqueous layer was extracted with ethyl acetate (30 mL X 5). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and then concentrated to give a product. The residue was purified by flash chromatography on silica gel, using ethyl acetate/n-hexane (R_f = 0.53, EtOAc/n-hex = 1/1) as the eluant to give the titled compound **3** as a colorless oil (1.593 g, 6.14 mmol, 93%)**:** $[\alpha]_D^{25}$ +126.2° (*c*: 1.00, $CHCl_3$); ^{1}H-NMR (600 MHz, 40 ^{o}C, $CDCl_3$, δ): 1.56-1.60 (m, 1H, H-2), 1.67-1.63 (m, 2H, H-3 X 2), 1.76-1.90 (m, 2H, H-4 X 2), 1.98 (brs, 1H, H-2), 2.21 (d, *J* = 18.0 Hz, 1H, H-7), 2.65 (dd, *J* = 7.2, 18.0 Hz, 1H, H-7), 4.15 (brs, 1H, H-5), 4.69 (brs, 1H, H-1), 5.18 (s, 2H, -OC$\underline{H}_2$Ph), 7.29-7.33 (m, 1H, H-4 in Ph), 7.34-7.37 (m, 4H, H-2 and H-3 in Ph); ^{13}C-NMR (150 MHz, 40 ^{o}C, $CDCl_3$, δ): 16.8 (t, C-3), 27.3 - 28.9 (br, 2C, C-2 and C-4), 42.5 (t, C-7), 52.4 (d, C-1), 60.9 (d, C-5), 67.1 (t, -O$\underline{C}H_2$Ph), 127.9 (d, C-2 in Ph), 128.1 (d, C-3 in Ph), 128.5 (d, C-4 in Ph), 136.3 (s, C-1

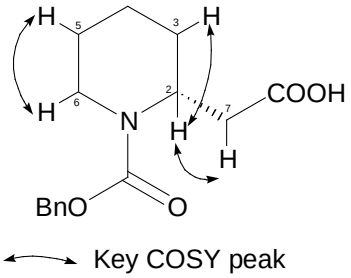


in Ph), 153.5 (s, N-CO-O), 213.1 (s, C-6); EI-HRMS (m/z): $[M]^+$ calcd for $C_{15}H_{17}NO_3^+$, 259.1208; found, 259.1201 (Δ = 2.7 ppm).

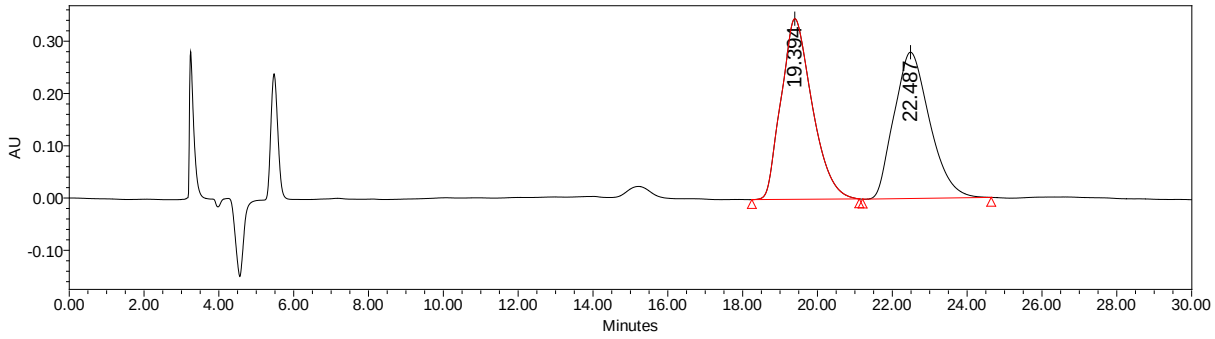
(1*R*, 5*R*)-9-Benzyloxycarbonylamino-2-oxo-1-oxabicyclo[3.3.1]nonane ((–)-5): To a mixture of ketone **4** (519 mg, 2.00 mmol, 1.00 eq.) and Na_2HPO_4 (570 mg, 4.02 mmol, 2.0 eq.) in CH_2Cl_2 (40 mL), was added *meta*-chloroperoxybenzoic acid (*m*CPBA 70-75%, 460 mg, ~1.0 equiv.). The solution was allowed to be stirred for 12 h at room temperature. Upon completion of the reaction (R_f = 0.10, EtOAc/n-hex = 1/1), the reaction mixture was washed with saturated $NaHCO_{3(aq)}$ (40 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL X 5). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure to give a light yellow colorless oil (562 mg). The product was used directly without further purification: $[\alpha]_D^{25}$ –23.6° (*c*: 1.00, C_6H_6); ^{1}H-NMR (600 MHz, 25 ^{o}C, $CDCl_3$, δ): 1.72-1.80 (m, 4H, H-2, H-3 X2 and H-4), 1.84-1.90 (m, 1H, H-2), 2.08-2.16 (m, 1H, H-4), 2.46 (d, *J* = 18.6 Hz, 1H, H-7), 2.92 (brs, 1H, H-7), 4.60 (brs, 1H, H-1), 5.17 (d, *J* = 12.0 Hz, 1H, -OC$\underline{H}_2$Ph), 5.21 (d, *J* = 12.0 Hz, 1H, -OC$\underline{H}_2$Ph), 6.33 (brs, 1H, H-5), 7.34-7.39 (m, 5H, $C_6\underline{H}_5$-); ^{13}C-NMR (150 MHz, 25 ^{o}C, $CDCl_3$, δ): 13.7 (t, C-3), 29.4 (t, C-2), 29.9 (t, C-4), 34.3 (t, C-7), 45.0 (d, C-1), 68.1 (t, -O$\underline{C}H_2$Ph), 82.5 (d, C-5), 128.1 (d, C-2 in Ph), 128.4 (d, C-4 in Ph), 128.5 (d, C-3 in Ph), 135.4 (s, C-1 in Ph), 153.4 (s, N-$\underline{C}$O-O), 168.8 (s, C-6); EI-HRMS (m/z): $[M]^+$ calcd for $C_{15}H_{17}NO_4^+$, 275.1158; found, 275.1149 (Δ = 3.3 ppm).



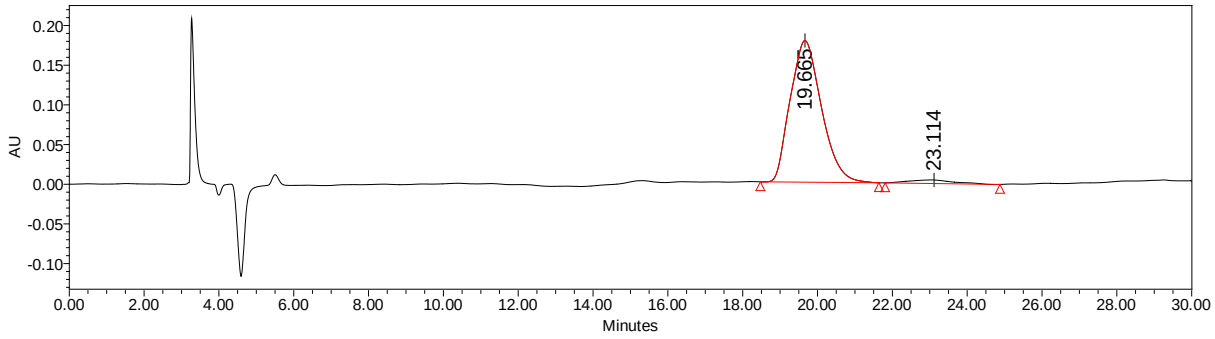
(2*R*)-*N*-Benzyloxycarbonyl-2-piperidinylacetic acid ((+)-6): To a CH_2Cl_2 solution (20 mL) of crude lactone **5** (562 mg) at -78 ^oC, was added dropwise triethylsilane (Et_3SiH, 960 μL, 6.01 mmol, 3.0 equiv), followed by boron trifluoride etherate ($BF_3{\cdot}OEt_2$, 760 μL, 6.00 mmol, 3.0 equiv). The reaction mixture was allowed to be stirred at -78 ^oC overnight (~ 16 h). Upon completion of the reaction, a saturated $NaHCO_3$ solution (12 mL) was slowly added into the reaction mixture so that the temperature was kept below -60 ^oC, and then warmed up to room temperature. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (15 mL X 5). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 and then concentrated under reduced pressure to give a crude residue. The crude product was purified by flash chromatography on silica gel using ethyl acetate/n-hexane (R_f = 0.41, pure EtOAc) as the eluant to give titled compound **6** as a colorless solid (484 mg, 1.75 mmol, 87% over two steps). Further purification was carried out by recrystallization within ethyl acetate/n-hexane, yielding white needle crystals: mp: 72-74 ^oC, $[\alpha]_D^{25}$ +2.8° (*c*: 1.9, $CHCl_3$); ^{1}H-NMR (600 MHz, 25 ^oC, $CDCl_3$, δ): 1.39-1.45 (m, 1H, H-5), 1.49-1.56 (m, 1H, H-4), 1.62-1.71 (m, 4H, H-3 X 2, H-4 and H-5), 2.61 (dd, *J* = 8.4, 15.0 Hz, 1H, H-7), 2.65 (dd, *J* = 7.2, 15.0 Hz, 1H, H-7), 2.86 (t, *J* = 13.2 Hz, 1H, H-6), 4.08 (brs, 1H, H-6), 4.78-4.84 (m, 1H, H-2), 5.12 (s, 2H, -OC<u>H</u>$_2$Ph), 7.28-7.32 (m, 1H, H-4' in Ph), 7.34-7.37 (m, 4H, H-2' and H-3' in Ph), 8.40-9.60 (br, -COO<u>H</u>); ^{13}C-NMR (150 MHz, 25 ^oC, $CDCl_3$, δ): 18.7 (t, C-4), 25.1 (t, C-5), 28.2 (t, C-3), 35.0 (t, C-7), 39.6 (t, C-6), 47.9 (d, C-2), 67.2 (t, -O<u>C</u>H_2Ph), 127.7 (d, C-2 in Ph), 127.9 (d, C-4 in Ph), 128.4 (d, C-3 in Ph), 136.6 (s, C-1 in Ph), 155.4 (s, N-<u>C</u>O-O), 176.6 (s, C-8); EI-HRMS (m/z): $[M]^+$ calcd for $C_{15}H_{19}NO_4^+$, 277.1314; found, 277.1312 (Δ = 0.8 ppm).



HPLC condition: Chiralcel OD, 250 mm X 4.6 mm, 5 μm; Mobile phase A: IPA : n-Hex = 1:5 (v/v), + 0.5% TFA; Mobile phase B: 0.5% TFA in n-Hex; isocratic, 20% A : 80% B; flow rate 1.0 mL per min; detection UV 215 nm, t_R: 19.4 min for (+)-**6**, 22.5 min for (–)-**6.**

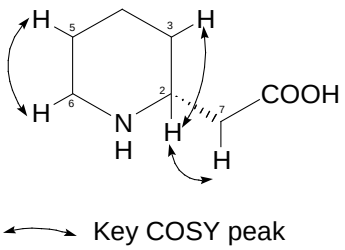


	Retention Time	Area	% Area
1	19.394	19847058	51.77
2	22.487	18486481	48.23

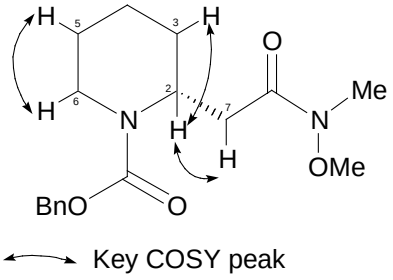


	Retention Time	Area	% Area	Height	Int Type
1	19.665	10347162	96.50	178562	bb
2	23.114	375442	3.50	4508	bb

(*R*)-Homopipecolic Acid ((–)-7): A hydrochloric acid solution (6 N, 1 mL) of the acid **6** (8.1 mg, 0.029 mmol, 1.00 equiv) was stirred under reflux for 1 h, and then concentrated under reduced pressure to give the residue. Reflux of the crude product in EtOH (0.5 mL) and propylene oxide (0.05 mL), and then concentrated under reduced pressure to give the titled product as light yellow oil (4.0 mg, 0.028 mmol, 96%): $[\alpha]_D^{25}$ –24.0° (*c*: 0.4, H_2O) (lit. $[\alpha]_D^{25}$ –24.0° (*c*: 0.4, H_2O); ^{1}H-NMR (600 MHz, 25 ^{o}C, D_2O, δ): 1.51-1.59 (m, 2H, H-3 and H-5), 1.63-1.69 (m, 1H, H-4), 1.87-1.94 (m, 2H, H-4 and H-5), 1.95-1.99 (m, 1H, H-3), 2.65 (d, *J* = 6.6 Hz, 2H, H-7), 3.05 (t, *J* = 13.2 Hz, 1H, H-6), 3.42-3.49 (m, 2H, H-2 and H-6); ^{13}C-NMR (150 MHz, 25 ^{o}C, D_2O, δ): 21.5 (t, C-4), 21.9 (t, C-5), 28.1 (t, C-3), 38.7 (t, C-7), 44.8 (t, C-6), 54.0 (d, C-2), 175.8 (s, C-8). HRMS-FAB (*m/z*): $[M]^+$ calcd for $C_7H_{13}NO_2$, 143.0946; found, 143.0940, (Δ: 4.2 ppm).

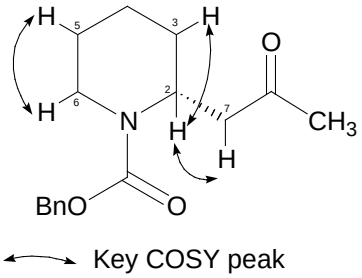


(*R*)-*N*-methyl-*N*-methoxy-(*N'*-Benzyloxycarbonyl-2-piperidinyl)acetamide ((+)-8): A CH_2Cl_2 (0.5 mL) suspension of acid **6** (139 mg, 0.50 mmol, 1.0 equiv.), EDC (106 mg, 0.55 mmol, 1.1 equiv.), HOBt (100 mg, 0.65 mmol, 1.3 equiv.), dimethoxyhydroxyamine hydrochloride (54 mg, 0.55 mmol, 1.1 equiv.) and *N*-methylpiperidine (67 μL, 0.55 mmol, 1.1 equiv.) was allowed to stir overnight (~ 16 h) under nitrogen. The reaction mixture was partitioned with CH_2Cl_2 (5 mL) and saturated $NaHCO_3$ solution (3 mL). The organic layer was washed with saturated NH_4Cl solution (3 mL). The aqueous solution was extracted with CH_2Cl_2 (5 mL X2) again. The combined organic layers were washed with brine (3 mL), dried over



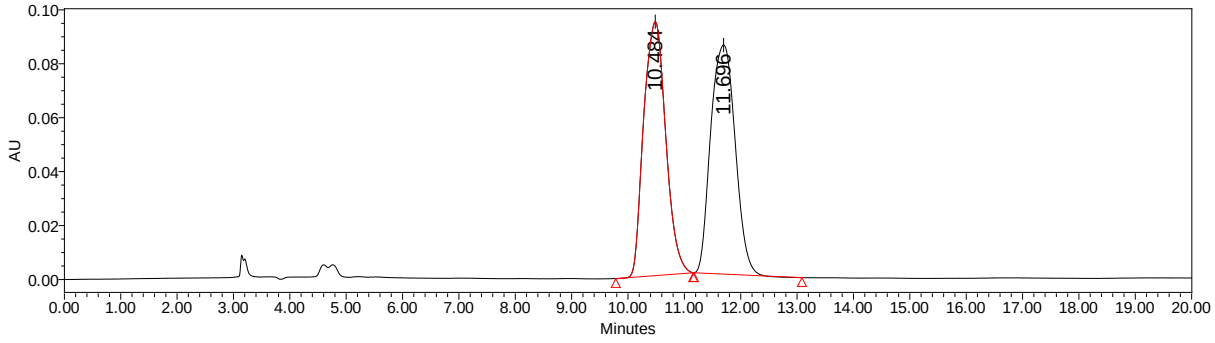
anhydrous Na_2SO_4, and then concentrated under reduced pressure to give a crude product. Purification of the crude product by flash chromatography on silica gel, using EtOAc/n-hexane (R_f = 0.25, EtOAc/n-hex = 1/1) as the eluant to afford the titled amide as a colorless oil (141 mg, 0.44 mmol, 88%): $[\alpha]_D^{25}$ +12.0° (*c*: 1.20, $CDCl_3$); ^{1}H-NMR (600 MHz, 25 ^{o}C, $CDCl_3$, δ): 1.38-1.45 (m, 1H, H-5), 1.52-1.59 (m, 1H, H-4), 1.59-1.72 (m, 4H, H-3 X 2, H-4 and H-5), 2.66 (brs, 1H, H-7), 2.72-2.76 (m, 1H, H-7), 2.91 (brs, 1H, H-6), 3.10 (s, 3H, NC$\underline{H}_3$), 3.62 (s, 3H, OC$\underline{H}_3$), 4.07 (brs, 1H, H-6), 4.81 (brs, 1H, H-2), 5.11 (s, 2H, -OC$\underline{H}_2$Ph), 7.26-7.30 (m, 1H, H-4' in Ph), 7.32-7.36 (m, 4H, H-2' and H-3' in Ph); ^{13}C-NMR (150 MHz, 25 ^{o}C, $CDCl_3$, δ): 18.8 (t, C-4), 25.2 (t, C-5), 28.2 (t, C-3), 32.0 (q, N$\underline{C}H_3$), 32.7 (t, C-7), 39.7 (t, C-6), 47.9 (d, C-2), 61.2(q, O$\underline{C}H_3$), 66.8 (t, -O$\underline{C}H_2$Ph), 127.71 (d, C-2 in Ph), 127.75 (d, C-4 in Ph), 128.3 (d, C-3 in Ph), 136.8 (s, C-1 in Ph), 155.2 (s, N-$\underline{C}$O-O), 171.9 (s, C-8); EI-HRMS (m/z): $[M]^+$ calcd for $C_{17}H_{24}N_2O_4^+$, 320.1736; found, 320.1738 (Δ = 0.6 ppm).

(*R*)-*N*-Benzyloxycarbonyl pelletierene ((+)-9): To a THF solution (10 mL) of Weinreb's amide **8** (190 mg, 0.59 mmol, 1.0 equiv.) in an ice bath, was slowly added a methylmagnesium bromide ether solution (3 M, 0.69 mL, 2.1 mmol, 3.5 equiv.). The reaction mixture was allowed to stir for 4 h in an ice bath, and at room temperature overnight under nitrogen. Upon completion of the reaction, the reaction mixture was evaporated and then partitioned with ether (10 mL) and saturated NH_4Cl solution (10 mL). The aqueous solution was extracted with ether (5 mL X5) again. The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure to give a crude yellow product. Purification of the crude product by flash chromatography on silica gel, using EtOAc/n-hexane (R_f = 0.26, EtOAc/n-hex = 1/3) as the eluant to afford the titled compound as a colorless oil (141 mg, 0.51 mmol, 86%): $[\alpha]_D^{25}$ +12.0° (*c*: 2.5, $CHCl_3$); ^{1}H-NMR (600 MHz, 25 ^{o}C, $CDCl_3$, δ): 1.35-1.44 (m, 1H, H-5), 1.46-1.53 (m, 1H, H-4), 1.55-1.68 (m, 4H, H-3 X 2, H-4 and H-5), 2.12 (brs, 3H, H-9), 2.62-2.71 (m, 2H, H-7 X2), 2.84 (t, *J* = 12.0 Hz, 1H, H-6), 4.03 (brs, 1H, H-6), 4.78 (brs, 1H, H-2), 5.08 (d, *J* = 12.0 Hz, 1H, -OC$\underline{H}_2$Ph), 5.11 (d, *J* = 12.0 Hz, 1H, -OC$\underline{H}_2$Ph), 7.27-7.31 (m, 1H, H-4' in Ph), 7.32-7.35 (m, 4H, H-2' and H-3' in Ph); ^{13}C-NMR (150 MHz, 25 ^{o}C, $CDCl_3$, δ): 18.7 (t, C-4), 25.1 (t, C-5), 28.2 (t, C-3), 29.9 (q, C-9), 39.7 (t, C-6), 44.1 (t, C-7), 47.4 (d, C-2), 67.0 (t, -O$\underline{C}H_2$Ph), 127.71 (d, C-2 in Ph), 127.84 (d, C-4 in Ph), 128.4 (d, C-3 in Ph), 136.6 (s, C-1 in Ph), 155.2 (s, N-$\underline{C}$O-O), 206.8 (s, C-8); EI-HRMS (m/z): $[M]^+$ calcd for $C_{16}H_{21}NO_3^+$, 275.1521; found, 275.1526 (Δ = 1.8 ppm).

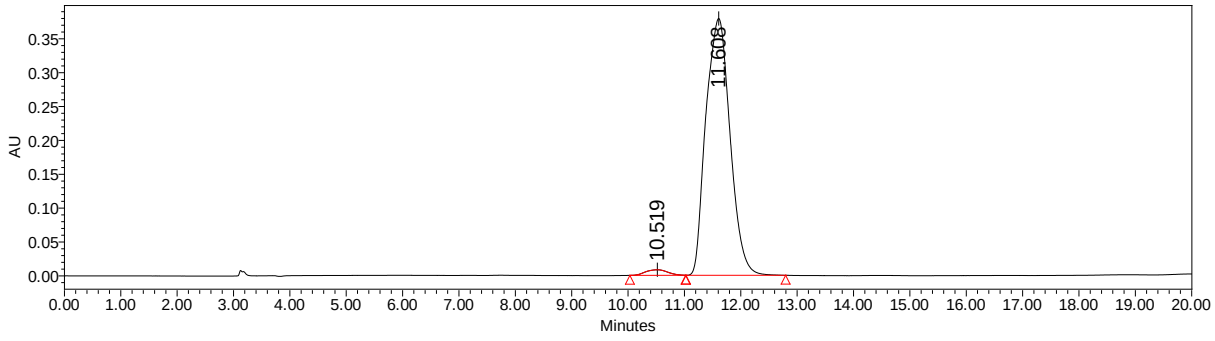


HPLC condition: Chiralcel OD, 250 mm X 4.6 mm, 5 μm; Mobile phase A: IPA: n-Hex =1 : 5 (v/v); Mobile phase B: n-Hex; isocratic, 40% A : 60% B; flow rate 1.0 mL per min; detection UV 215 nm, t_R: 11.6 min for (+)-**9**; 10.5 min for (–)-**9**

Injection of racemate:



	Retention Time	Area	% Area
1	10.484	2561286	49.88
2	11.696	2573575	50.12



	Retention Time	Area	% Area	Height	Int Type
1	10.519	222264	1.93	8171	bb
2	11.608	11293734	98.07	379166	bb

(*R*)-Pelletierine ((–)-10): To an ethyl acetate solution (2 mL) of carbamate **9** (30 mg, 0.11 mmol, 1.0 equiv.), was added Pd on carbon (2%, 12 mg, 2 mmol%). The reaction suspension was allowed to stir for 5 h under hydrogen balloon. Upon completion of the reaction, the suspension was filtered by celite to remove the catalyst. The filtrate solution was concentrated under reduced pressure to give a crude oil. (14 mg, 0.099 mmol, 91%, R_f = 0.02, pure EtOAc): $[\alpha]_D^{25}$ –19.6° (*c*: 0.7, EtOH); ^{1}H-NMR (600 MHz, 25 ^{o}C, $CDCl_3$, δ): 1.21 (dq, *J* = 3.0, 12.0 Hz, 1H, H-3), 1.36 (tq, *J* = 3.6, 12.6 Hz, 1H, H-4), 1.46 (tq, *J* = 4.2, 12.6 Hz, 1H, H-5), 1.57-1.62 (m, 2H, H-3 and H-5), 1.74-1.77 (m, 1H, H-4), 2.12 (s, 3H, H-9), 2.55 (dd, *J* = 4.2, 18.0 Hz, 1H, H-7), 2.61 (dd, *J* = 7.8, 17.4 Hz, 1H, H-7), 2.66 (dt, *J* = 2.4, 12.0 Hz, 1H, H-6), 2.99-3.02 (m, 1H, H-2), 3.02-3.08 (m, 1H, H-6), 3.62 (br, 1H, NH); ^{13}C-NMR (150 MHz, 25 ^{o}C, $CDCl_3$, δ): 24.2 (t, C-4), 25.3 (t, C-5), 30.6 (q, C-9), 31.8 (t, C-3), 46.4 (t, C-6), 49.9 (t, C-7), 52.4 (d, C-2), 208.1 (s, C-8); EI-HRMS (m/z): $[M]^+$ calcd for $C_8H_{15}NO^+$, 141.1154; found, 141.1160 (Δ = 4.3 ppm).

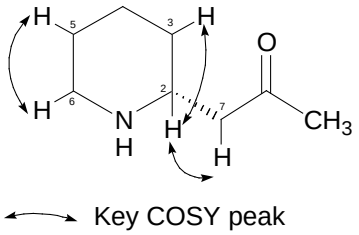


Table 1. Crystal data and structure refinement for KCATAM.

Identification code	kcatam	
Empirical formula	C11 H19 N O7	
Formula weight	277.27	
Temperature	297(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 7.1563(10) Å	α= 90°.
	b = 8.3628(12) Å	β= 98.637(2)°.
	c = 10.5833(15) Å	γ = 90°.
Volume	626.19(15) $Å^3$	
Z	2	
Density (calculated)	1.471 Mg/m^3	
Absorption coefficient	0.123 mm^{-1}	
F(000)	296	
Crystal size	0.30 x 0.20 x 0.20 mm^3	
Theta range for data collection	1.95 to 25.98°.	
Index ranges	-8<=h<=8, -7<=k<=10, -13<=l<=9	
Reflections collected	3552	
Independent reflections	2243 [R(int) = 0.0273]	
Completeness to theta = 25.98°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	1.00000 and 0.96400	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2243 / 1 / 193	
Goodness-of-fit on F^2	1.063	
Final R indices [I>2sigma(I)]	R1 = 0.0344, wR2 = 0.0965	
R indices (all data)	R1 = 0.0353, wR2 = 0.0981	
Absolute structure parameter	0.4(9)	
Extinction coefficient	0.054(8)	
Largest diff. peak and hole	0.195 and -0.236 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for KCATAM. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N	-6150(2)	3448(2)	-2370(1)	27(1)
O(1)	-2996(2)	987(2)	-2560(2)	46(1)
C(1)	-6330(2)	1679(2)	-2522(2)	30(1)
C(2)	-8287(3)	1335(2)	-3223(2)	36(1)
C(3)	-8626(3)	2128(3)	-4533(2)	43(1)
C(4)	-7947(3)	3847(3)	-4478(2)	41(1)
C(5)	-6001(2)	4000(2)	-3692(2)	33(1)
C(6)	-4561(3)	2828(3)	-4078(2)	42(1)
C(7)	-4763(3)	1301(2)	-3317(2)	35(1)
O(2)	-2902(2)	5220(2)	-1521(2)	48(1)
O(3)	-3074(2)	7721(2)	-2223(1)	43(1)
O(4)	706(2)	4951(2)	-1620(1)	36(1)
O(5)	569(2)	7338(2)	330(1)	39(1)
O(6)	4160(2)	7426(2)	-16(1)	53(1)
O(7)	3461(2)	7762(2)	-2108(1)	39(1)
C(8)	-2202(2)	6457(2)	-1849(2)	30(1)
C(9)	-72(2)	6476(2)	-1859(2)	27(1)
C(10)	930(2)	7674(2)	-909(2)	28(1)
C(11)	3036(2)	7610(2)	-959(2)	31(1)

Table 3. Bond lengths [Å] and angles [°] for KCATAM.

N-C(1)	1.492(2)
N-C(5)	1.493(2)
N-H(0A)	0.93(2)
N-H(0B)	0.89(3)
O(1)-C(7)	1.416(2)
O(1)-H(1A)	0.8200
C(1)-C(2)	1.511(2)
C(1)-C(7)	1.533(2)
C(1)-H(1B)	0.9800
C(2)-C(3)	1.524(3)
C(2)-H(2A)	0.9700
C(2)-H(2B)	0.9700
C(3)-C(4)	1.515(3)
C(3)-H(3A)	0.9700
C(3)-H(3B)	0.9700
C(4)-C(5)	1.517(3)
C(4)-H(4B)	0.9700
C(4)-H(4C)	0.9700
C(5)-C(6)	1.522(3)
C(5)-H(5B)	0.9800
C(6)-C(7)	1.528(3)
C(6)-H(6A)	0.9700
C(6)-H(6B)	0.9700
C(7)-H(7A)	0.9800
O(2)-C(8)	1.222(3)
O(3)-C(8)	1.261(2)
O(4)-C(9)	1.399(2)
O(4)-H(4A)	0.75(3)
O(5)-C(10)	1.402(2)
O(5)-H(5A)	0.85(3)
O(6)-C(11)	1.194(2)
O(7)-C(11)	1.303(2)
O(7)-H(7B)	0.88(4)
C(8)-C(9)	1.526(2)

C(9)-C(10)	1.520(2)
C(9)-H(9A)	0.9800
C(10)-C(11)	1.516(2)
C(10)-H(10A)	0.9800

C(1)-N-C(5)	102.86(13)
C(1)-N-H(0A)	114.5(15)
C(5)-N-H(0A)	111.3(14)
C(1)-N-H(0B)	113.0(18)
C(5)-N-H(0B)	101.6(16)
H(0A)-N-H(0B)	112(2)
C(7)-O(1)-H(1A)	109.5
N-C(1)-C(2)	107.49(15)
N-C(1)-C(7)	101.85(14)
C(2)-C(1)-C(7)	113.08(15)
N-C(1)-H(1B)	111.3
C(2)-C(1)-H(1B)	111.3
C(7)-C(1)-H(1B)	111.3
C(1)-C(2)-C(3)	111.91(16)
C(1)-C(2)-H(2A)	109.2
C(3)-C(2)-H(2A)	109.2
C(1)-C(2)-H(2B)	109.2
C(3)-C(2)-H(2B)	109.2
H(2A)-C(2)-H(2B)	107.9
C(4)-C(3)-C(2)	111.81(16)
C(4)-C(3)-H(3A)	109.3
C(2)-C(3)-H(3A)	109.3
C(4)-C(3)-H(3B)	109.3
C(2)-C(3)-H(3B)	109.3
H(3A)-C(3)-H(3B)	107.9
C(3)-C(4)-C(5)	111.35(16)
C(3)-C(4)-H(4B)	109.4
C(5)-C(4)-H(4B)	109.4
C(3)-C(4)-H(4C)	109.4
C(5)-C(4)-H(4C)	109.4
H(4B)-C(4)-H(4C)	108.0

N-C(5)-C(4)	107.38(14)
N-C(5)-C(6)	101.48(14)
C(4)-C(5)-C(6)	113.67(17)
N-C(5)-H(5B)	111.3
C(4)-C(5)-H(5B)	111.3
C(6)-C(5)-H(5B)	111.3
C(5)-C(6)-C(7)	106.00(14)
C(5)-C(6)-H(6A)	110.5
C(7)-C(6)-H(6A)	110.5
C(5)-C(6)-H(6B)	110.5
C(7)-C(6)-H(6B)	110.5
H(6A)-C(6)-H(6B)	108.7
O(1)-C(7)-C(1)	113.13(15)
O(1)-C(7)-C(6)	107.84(16)
C(1)-C(7)-C(6)	104.59(15)
O(1)-C(7)-H(7A)	110.4
C(1)-C(7)-H(7A)	110.4
C(6)-C(7)-H(7A)	110.4
C(9)-O(4)-H(4A)	110(2)
C(10)-O(5)-H(5A)	106.3(17)
C(11)-O(7)-H(7B)	109(2)
O(2)-C(8)-O(3)	126.48(15)
O(2)-C(8)-C(9)	117.61(16)
O(3)-C(8)-C(9)	115.88(15)
O(4)-C(9)-C(10)	110.23(14)
O(4)-C(9)-C(8)	111.06(15)
C(10)-C(9)-C(8)	112.03(13)
O(4)-C(9)-H(9A)	107.8
C(10)-C(9)-H(9A)	107.8
C(8)-C(9)-H(9A)	107.8
O(5)-C(10)-C(11)	110.45(13)
O(5)-C(10)-C(9)	110.57(14)
C(11)-C(10)-C(9)	109.06(13)
O(5)-C(10)-H(10A)	108.9
C(11)-C(10)-H(10A)	108.9
C(9)-C(10)-H(10A)	108.9

O(6)-C(11)-O(7)	124.78(15)
O(6)-C(11)-C(10)	121.56(15)
O(7)-C(11)-C(10)	113.66(13)

Symmetry transformations used to generate equivalent atoms:

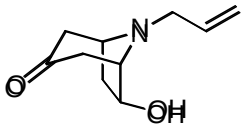
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for KCATAM. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

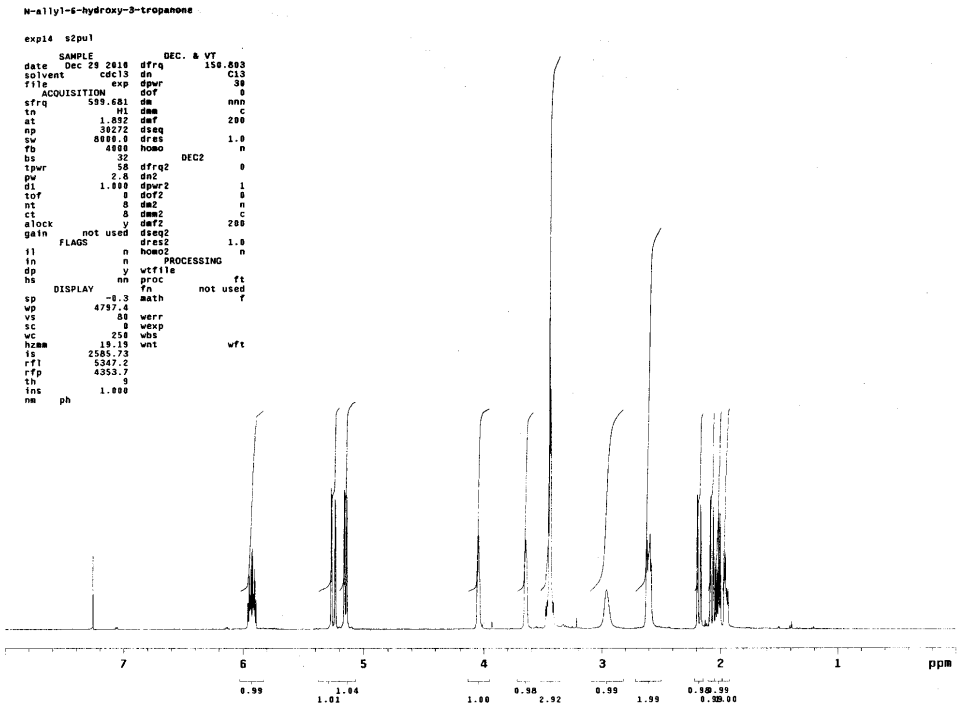
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N	24(1)	28(1)	29(1)	-3(1)	4(1)	1(1)
O(1)	34(1)	40(1)	62(1)	-2(1)	4(1)	6(1)
C(1)	31(1)	28(1)	32(1)	1(1)	5(1)	0(1)
C(2)	33(1)	34(1)	40(1)	0(1)	2(1)	-5(1)
C(3)	43(1)	51(1)	34(1)	-5(1)	-5(1)	0(1)
C(4)	45(1)	44(1)	32(1)	7(1)	2(1)	6(1)
C(5)	37(1)	29(1)	35(1)	2(1)	11(1)	1(1)
C(6)	44(1)	45(1)	42(1)	0(1)	19(1)	4(1)
C(7)	34(1)	33(1)	40(1)	-6(1)	8(1)	4(1)
O(2)	27(1)	41(1)	76(1)	5(1)	4(1)	-7(1)
O(3)	25(1)	45(1)	58(1)	12(1)	8(1)	4(1)
O(4)	30(1)	29(1)	53(1)	-1(1)	16(1)	1(1)
O(5)	29(1)	58(1)	30(1)	-10(1)	7(1)	-2(1)
O(6)	30(1)	92(1)	35(1)	-7(1)	-2(1)	6(1)
O(7)	24(1)	55(1)	40(1)	11(1)	8(1)	1(1)
C(8)	22(1)	36(1)	32(1)	-3(1)	3(1)	-3(1)
C(9)	23(1)	32(1)	27(1)	-1(1)	6(1)	0(1)
C(10)	23(1)	29(1)	33(1)	-3(1)	5(1)	0(1)
C(11)	24(1)	31(1)	37(1)	-4(1)	4(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for KCATAM.

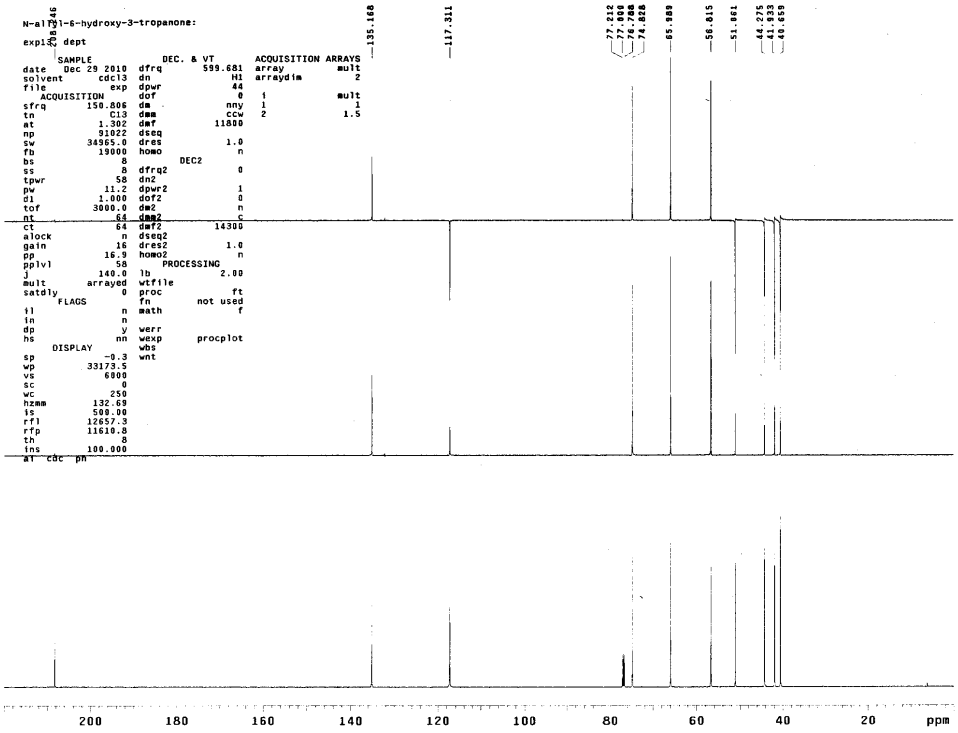
	x	y	z	U(eq)
H(0A)	-7160(30)	3940(30)	-2060(20)	34(5)
H(0B)	-5040(40)	3750(30)	-1950(20)	46(6)
H(1A)	-3072	169	-2144	69
H(1B)	-6110	1136	-1692	36
H(2A)	-9218	1719	-2717	43
H(2B)	-8449	188	-3324	43
H(3A)	-7968	1531	-5118	52
H(3B)	-9966	2101	-4862	52
H(4B)	-8834	4508	-4104	49
H(4C)	-7906	4229	-5339	49
H(5B)	-5537	5103	-3692	40
H(6A)	-3292	3257	-3874	51
H(6B)	-4817	2614	-4988	51
H(7A)	-5136	405	-3896	42
H(4A)	70(40)	4450(30)	-1270(20)	41(7)
H(5A)	1630(40)	7080(30)	760(30)	50(7)
H(7B)	4690(50)	7680(60)	-2080(40)	93(11)
H(9A)	144	6800	-2715	32
H(10A)	464	8749	-1151	34

^{1}H NMR of **1a:**

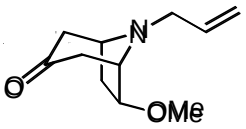


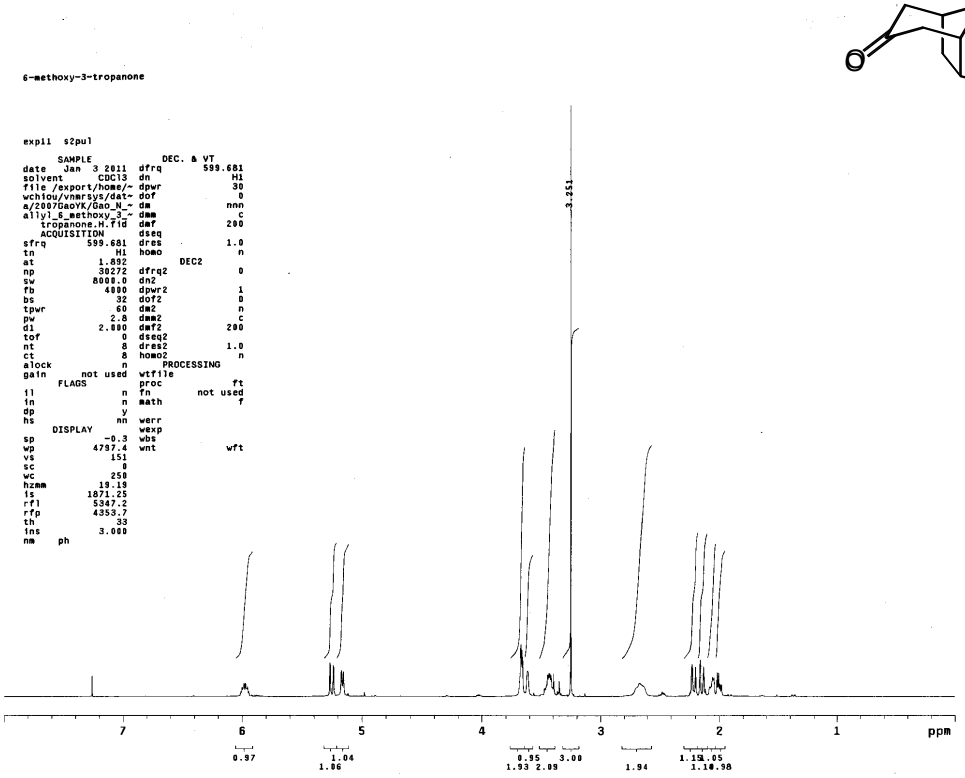


^{13}C NMR of **1a:**

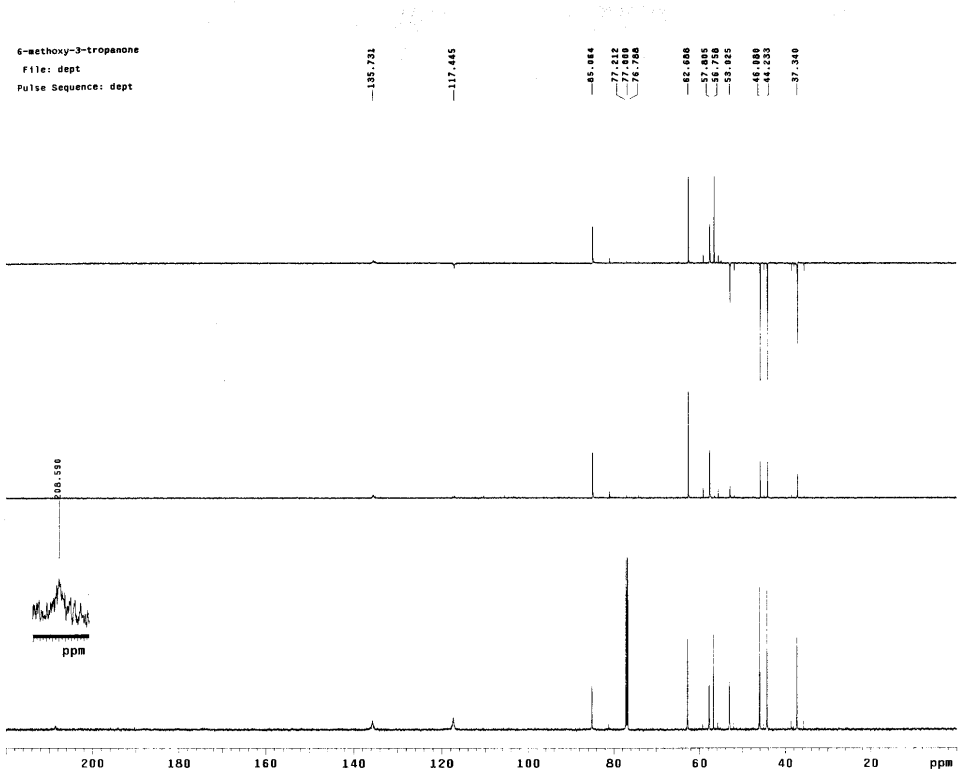


^{1}H NMR of **1b:**

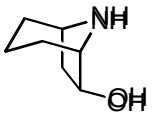


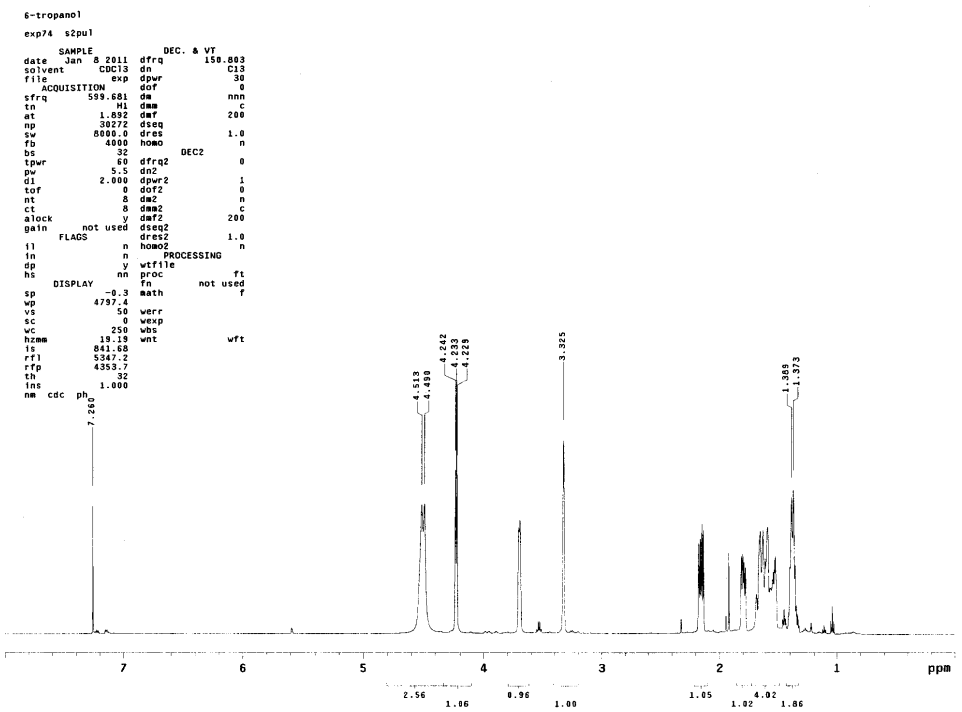


^{13}C NMR of **1b:**

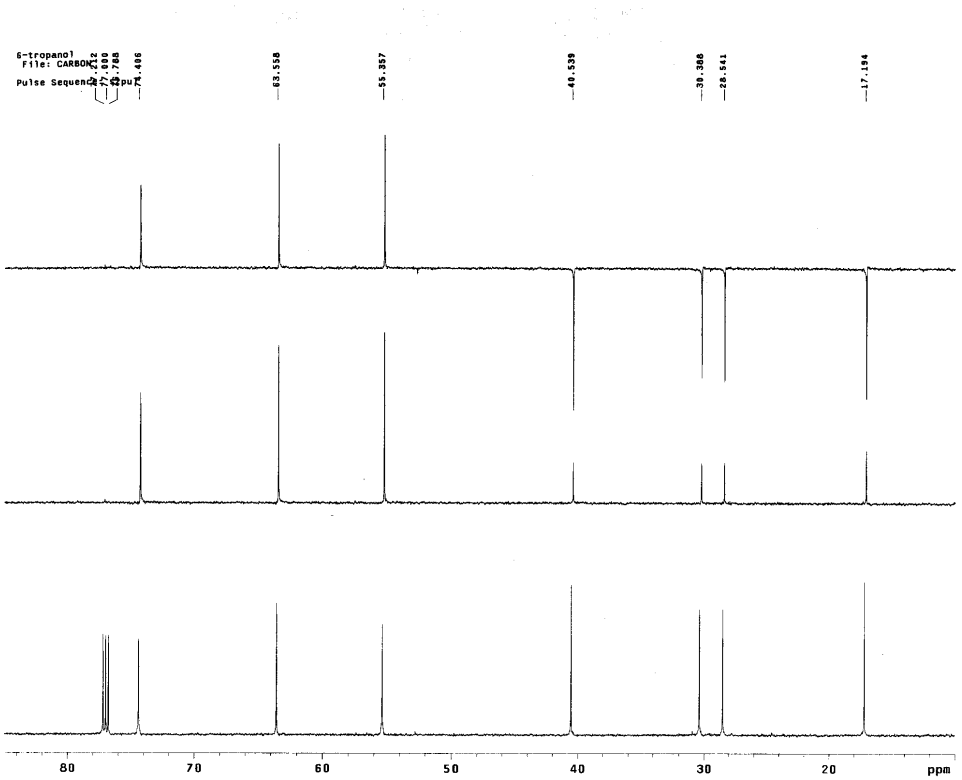


^{1}H NMR of (+)-**2:**

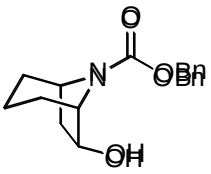


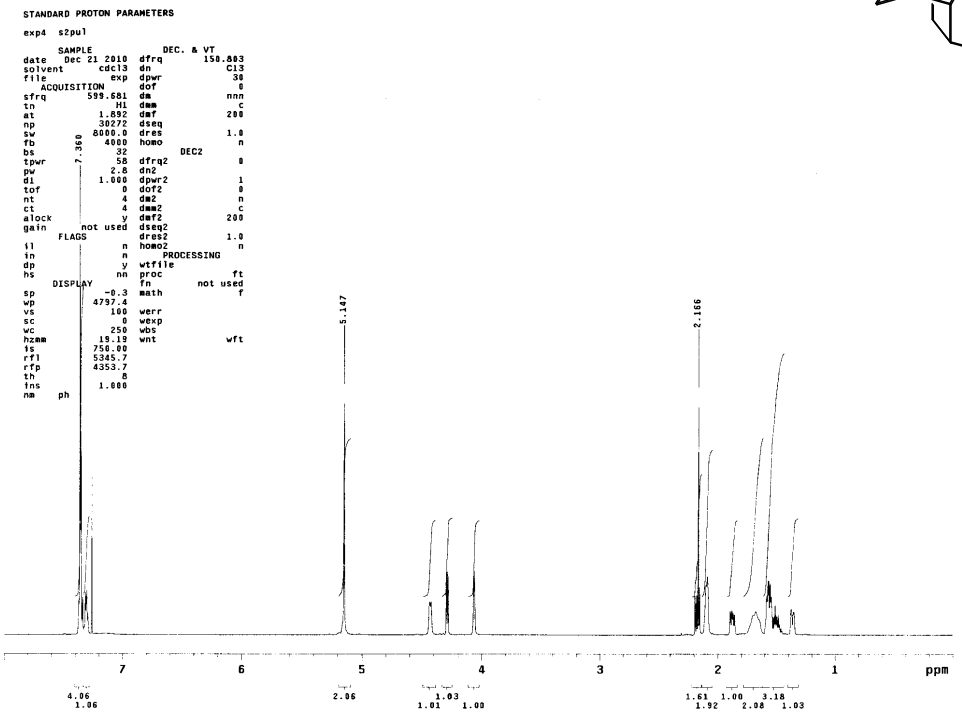


^{13}C NMR of (+)-**2**

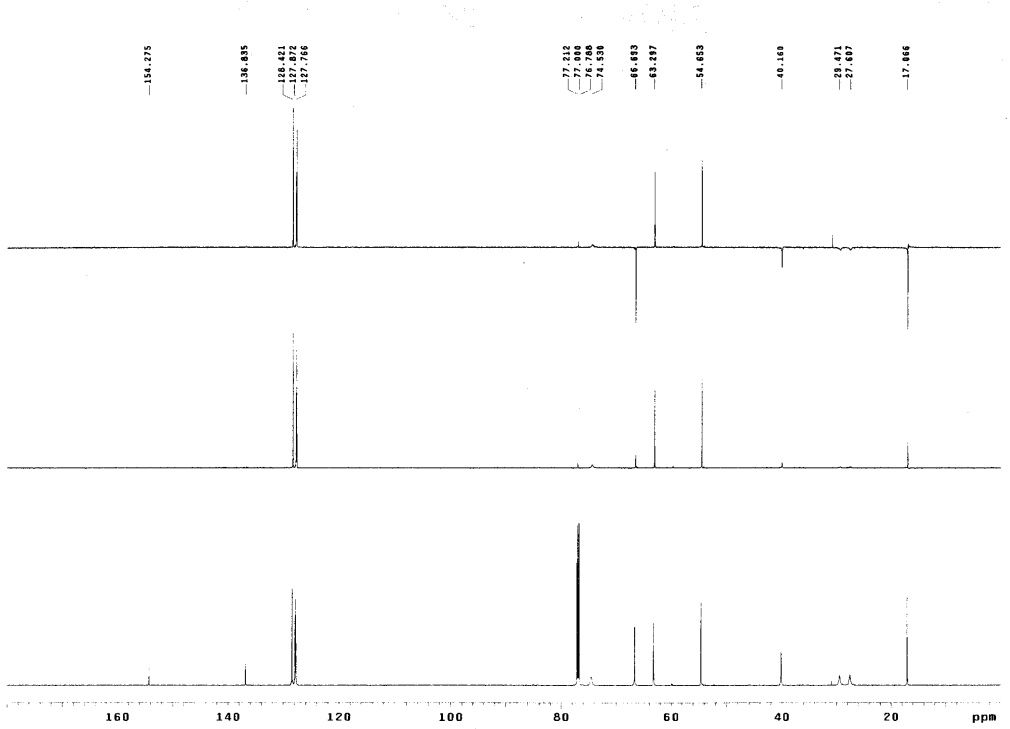


^{1}H NMR of (+)-**3:**

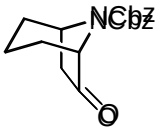


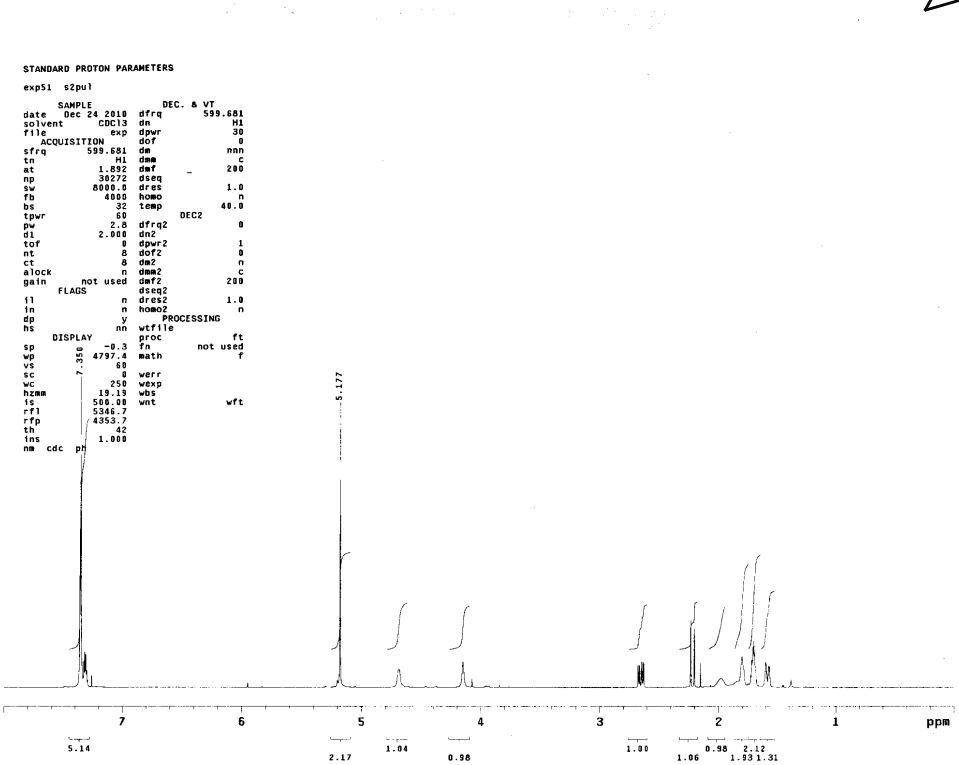


^{13}C NMR of (+)-**3**

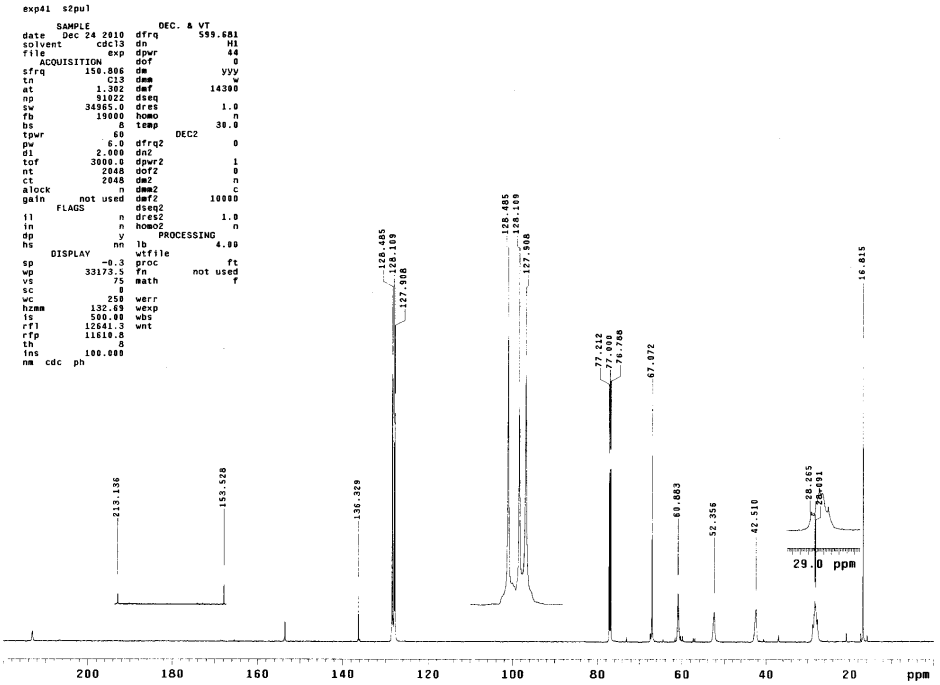


^{1}H NMR of (+)-**4**:

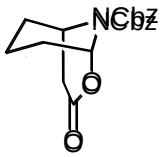


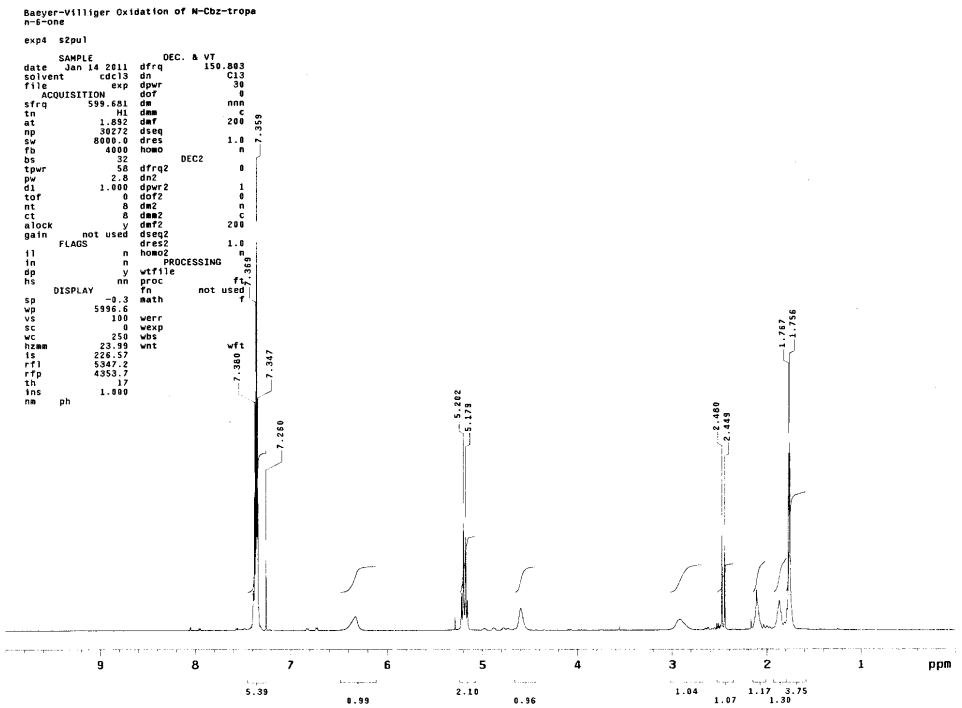


^{13}C NMR of (+)-**4**:

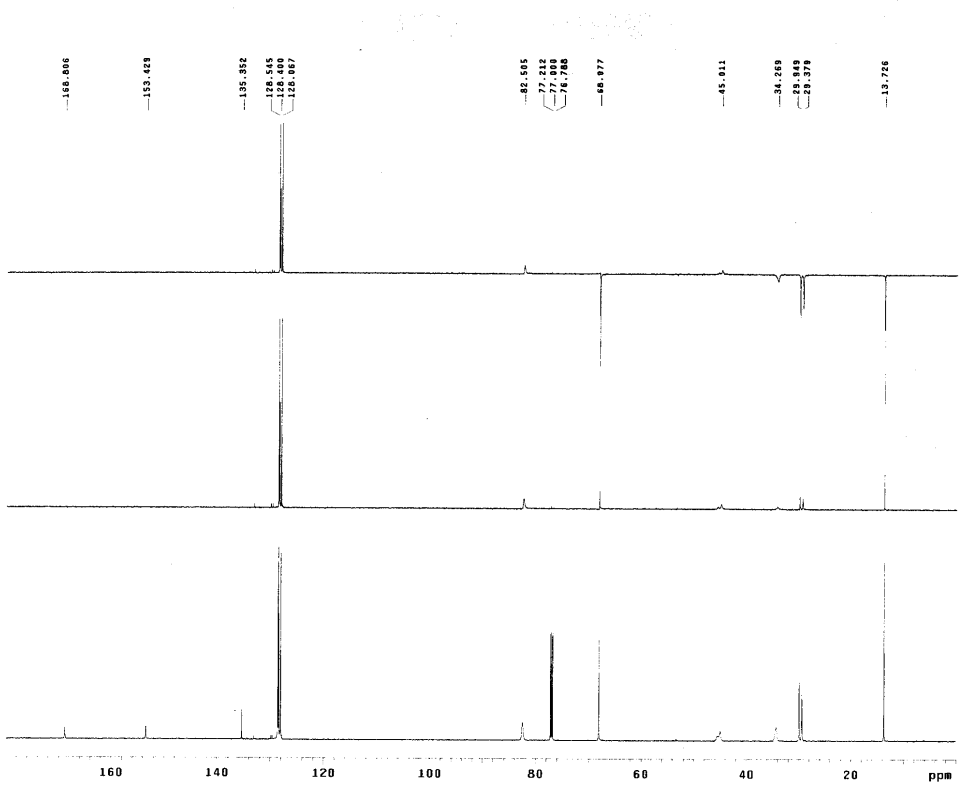


^{1}H NMR of (–)-**5:**

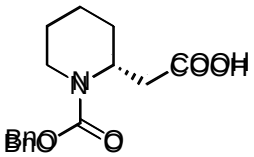


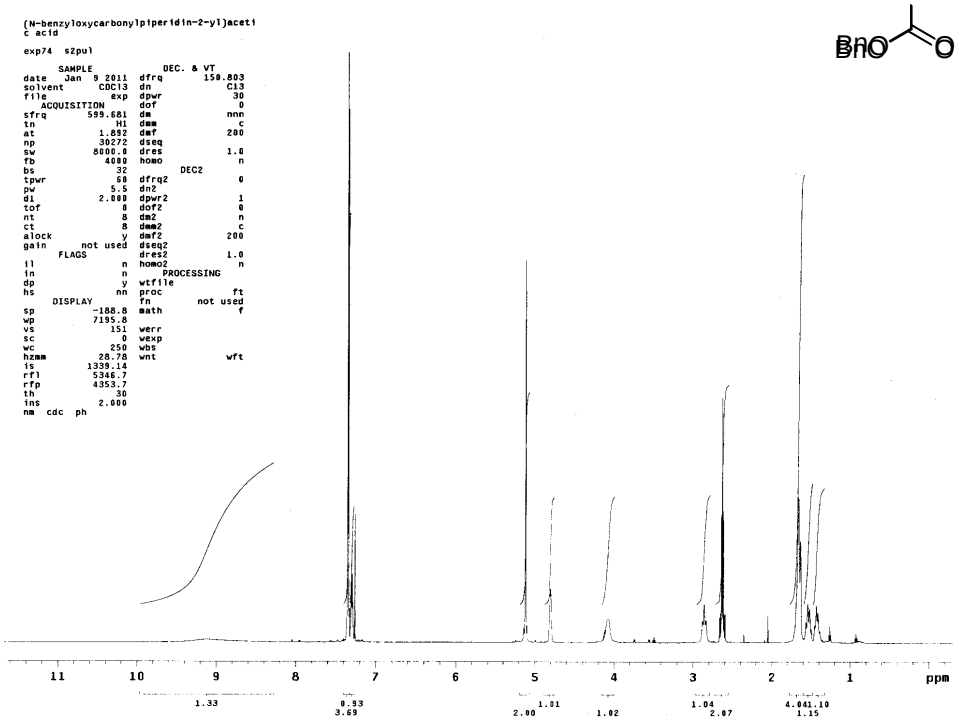


^{13}C NMR of (–)-**5:**

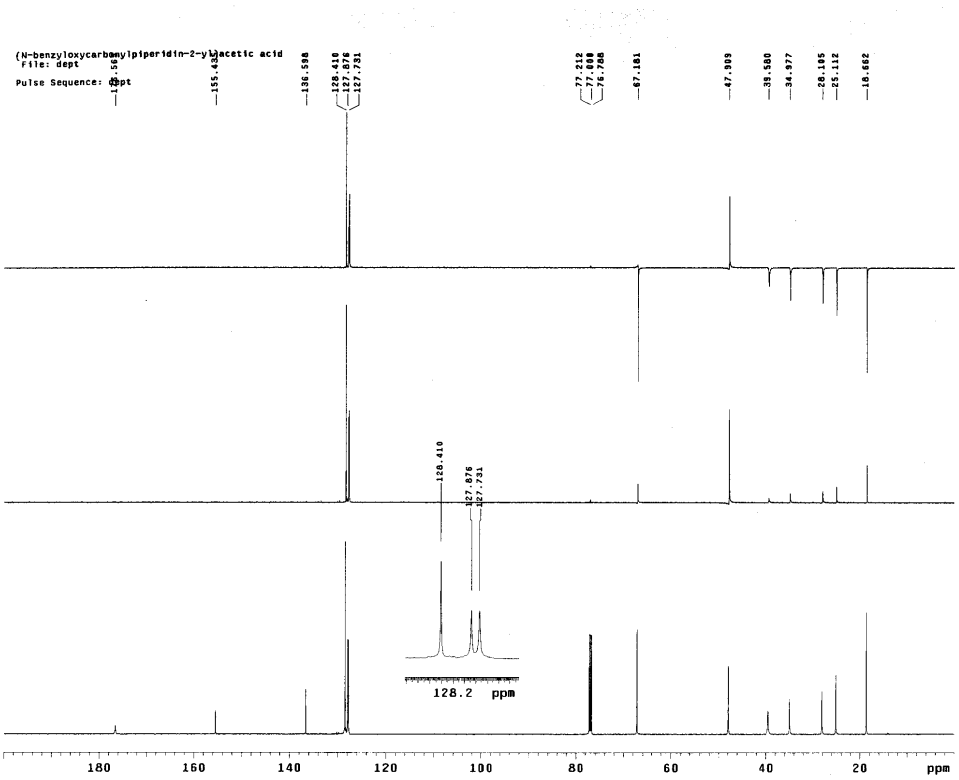


^{1}H NMR of (+)-**6**:

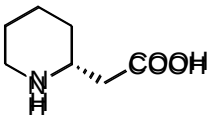


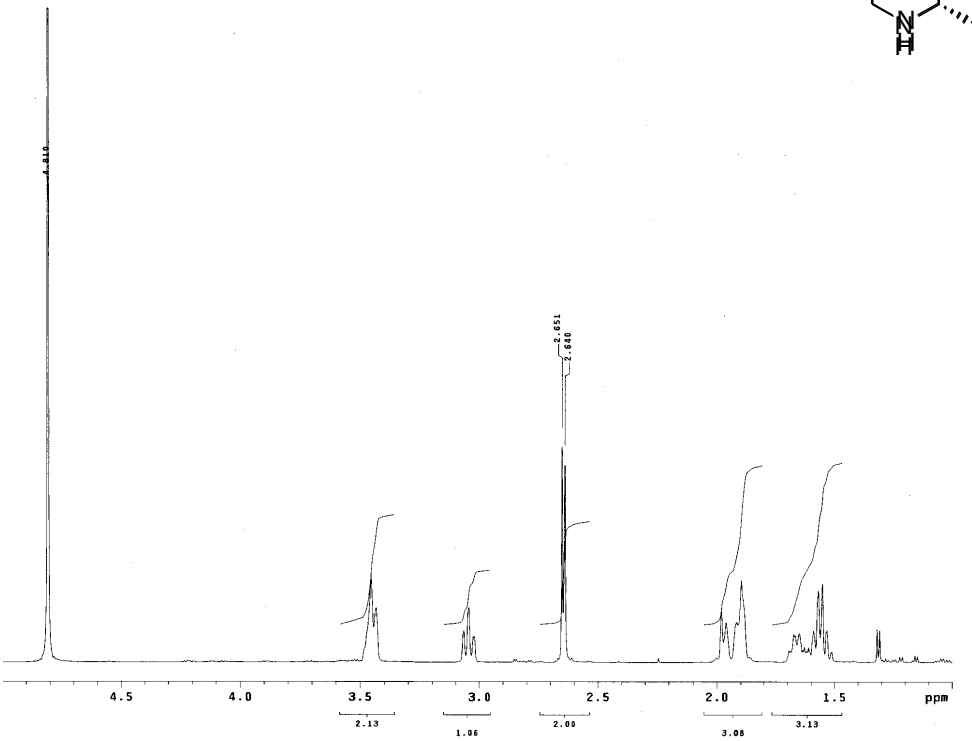


^{13}C NMR of (+)-**6**:

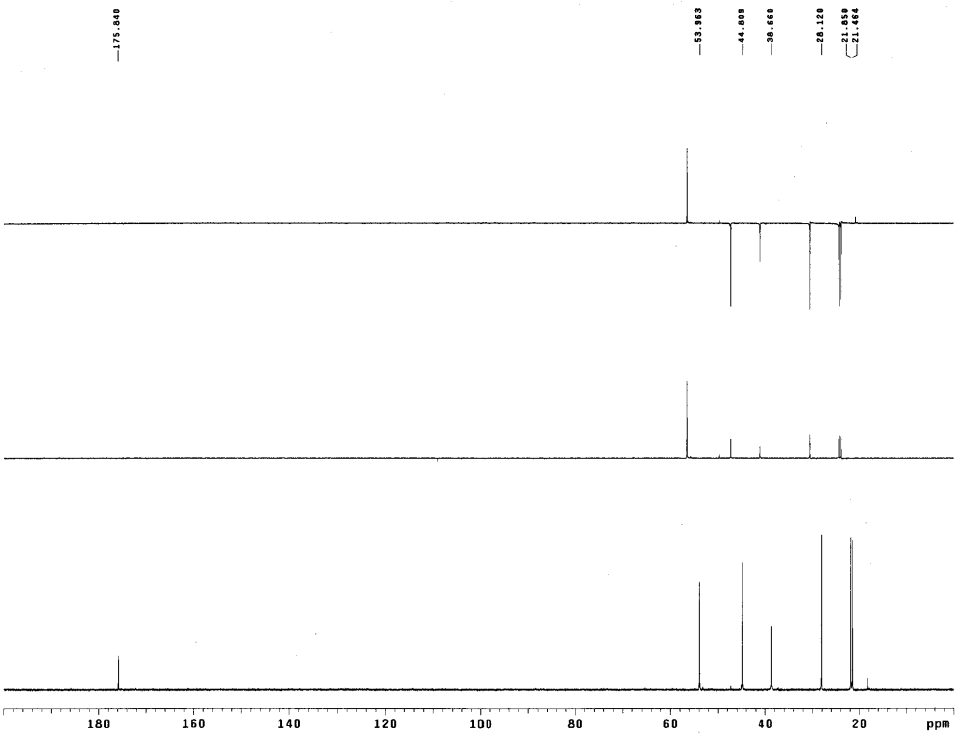


^{1}H NMR of (–)-**7:**

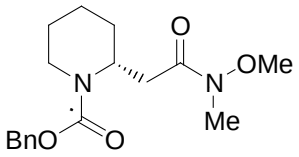


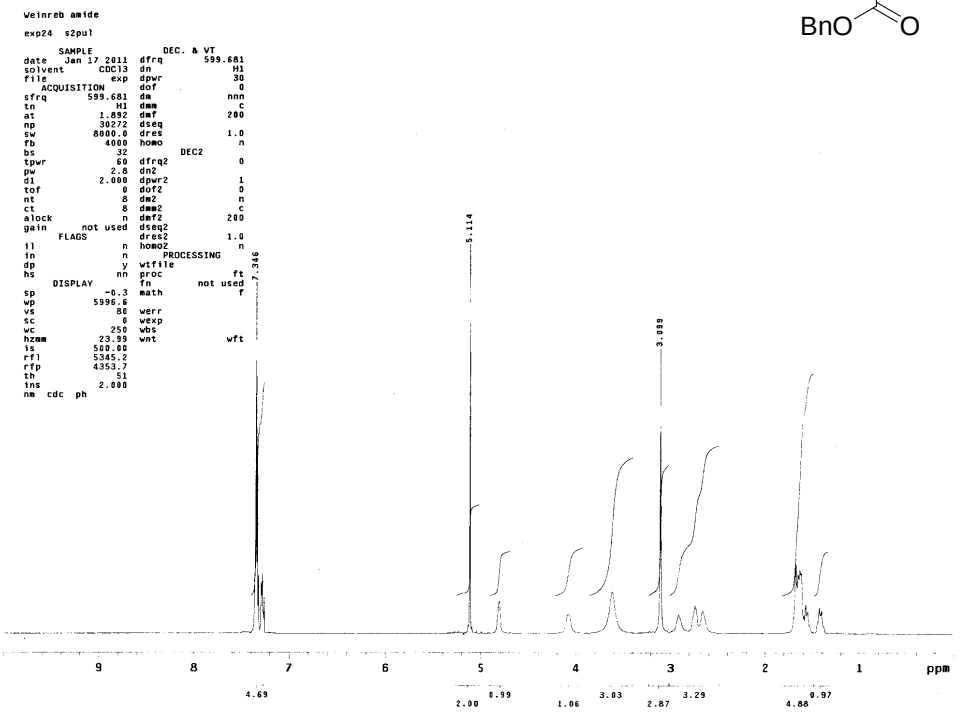


^{13}C NMR of (–)-**7:**

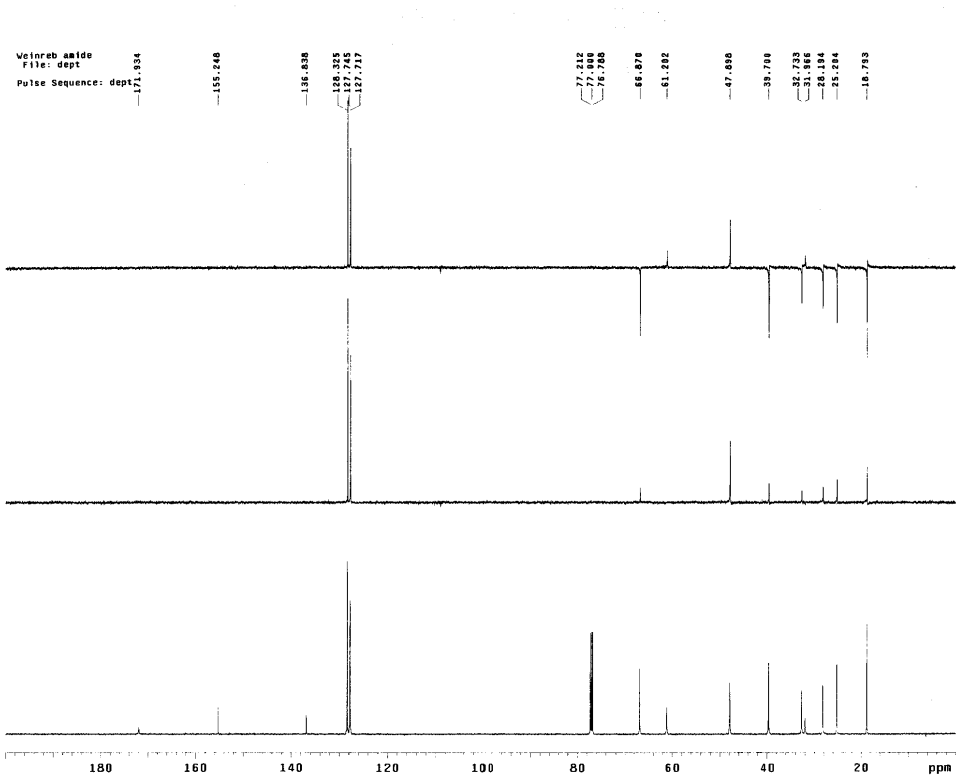


^{1}H NMR of (+)-**8**:

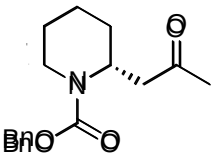


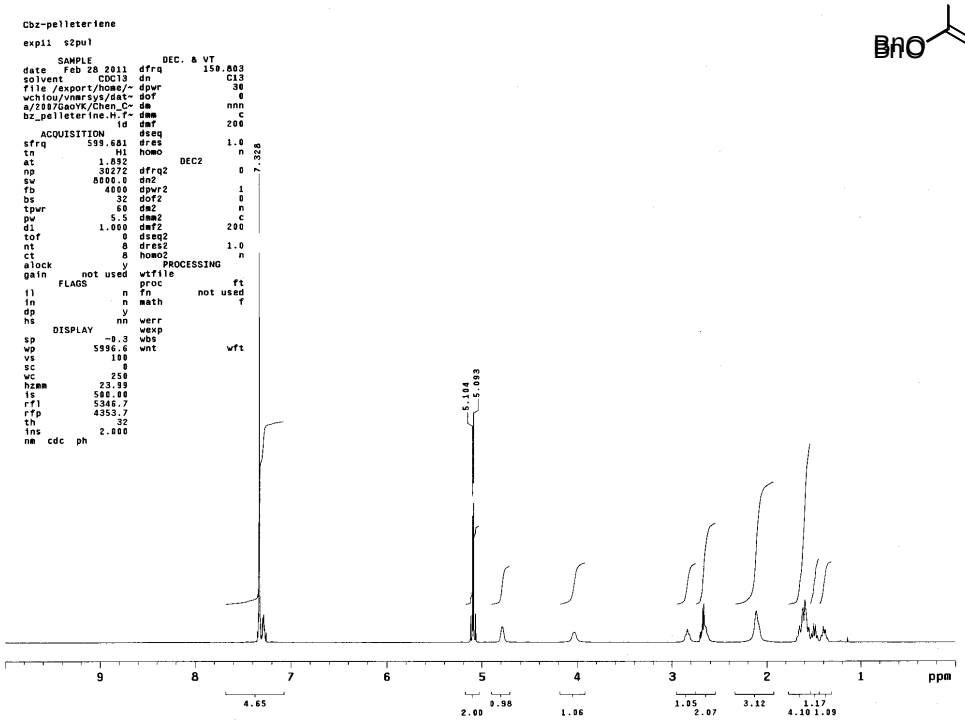


^{13}C NMR of (+)-**8**:

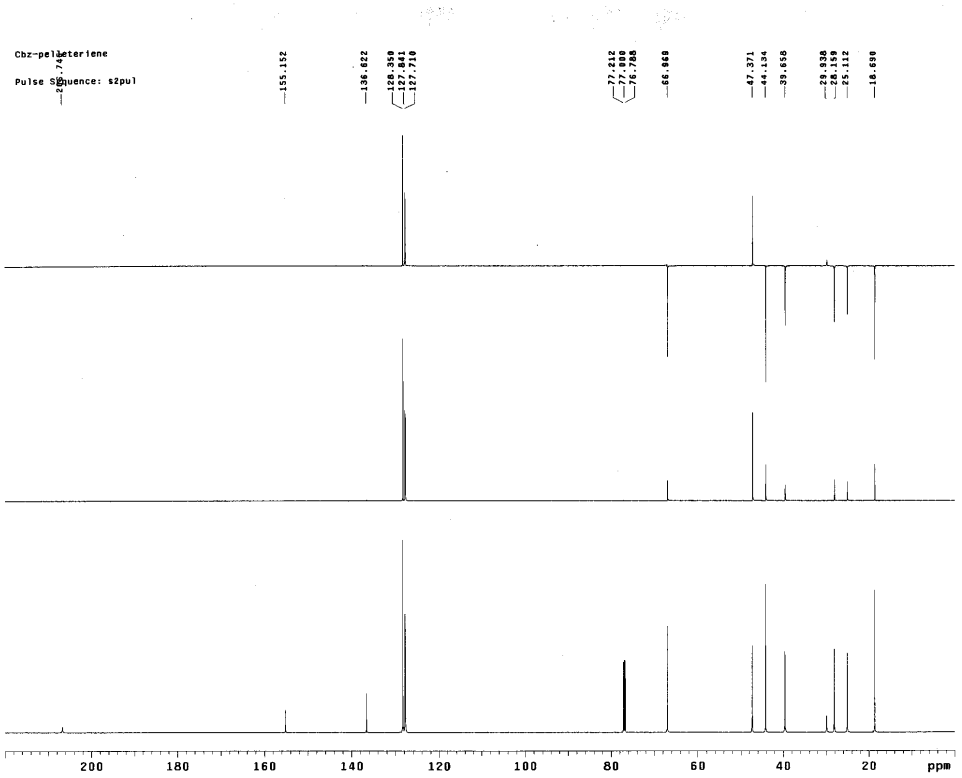


^{1}H NMR of (+)-**9**:

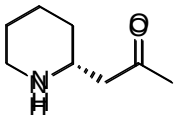


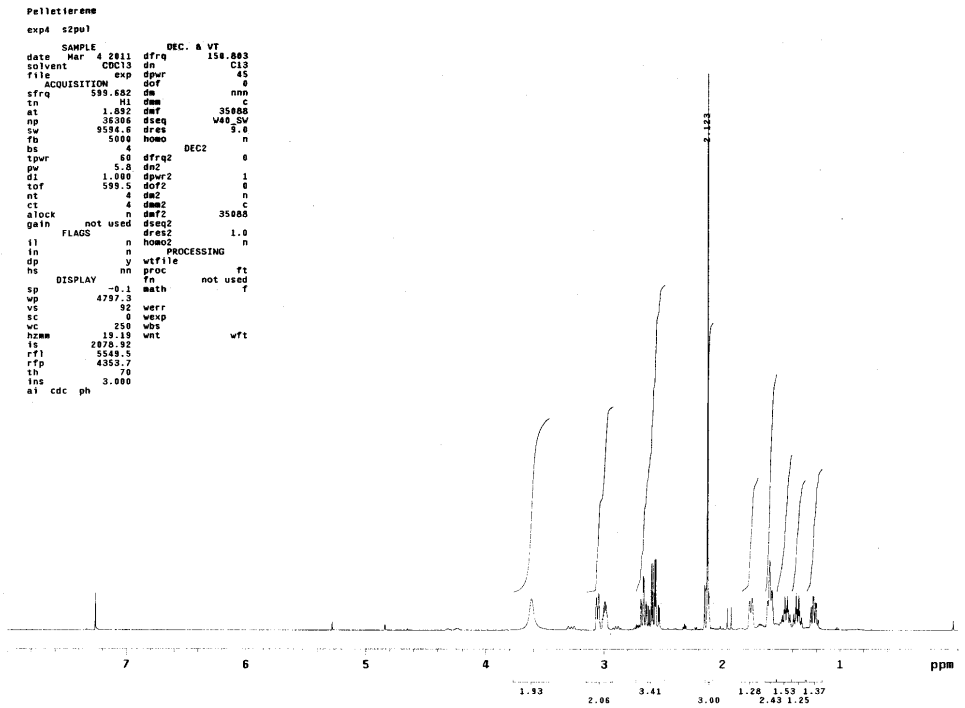


^{13}C NMR of (+)-**9**:



^{1}H NMR of (–)-**10:**





^{13}C NMR of (–)-**10:**