Proline-β^3-Amino-acid Dipeptides as Efficient Catalysts for Enantioselective Direct Aldol Reaction in Aqueous Medium

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1. General

Inorganics, organic reagents, and solvents were commercial pure compounds and used without further purification. TLC analyses were performed using silica gel plates (silica gel 60 F-254) visualized by UV light, iodine, and ninhydrin spray. Column chromatography was carried out on silica gel (70-230 mesh). ^{1}H and ^{13}C NMR spectra were recorded on 500, 400, and 200 MHz spectrometers: chemical shifts in ppm (δ) and J coupling constants in Hz, solvent $CDCl_3$ unless otherwise specified. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; m, multiplet; b, broad signal. Chiral HPLC analysis were performed by Daicel ChiralPak IC column (250 x 4.6 mm) and DAD UV detector. Optical rotations were measured at λ = 589 nm (1.0 dm cell) solvent $CHCl_3$ unless otherwise specified. All compounds for which analytical and spectroscopic data are quoted were homogeneous by TLC and HPLC. All new compounds were characterized on the basis of one- and two-dimensional NMR experiments including COSY and HSQC. *Abbreviations*. Boc: tert-butyloxycarbonyl; DCC: *N*,*N*-dicyclohexylcarbodiimide; HOBt: *N*-hydroxybenzotriazole.

The notation (#/S) indicates intermediates not mentioned in the manuscript.

2. Starting β^3-amino acid methyl esters

β^3-HPhg-OMe

β^3-HPhe-OMe

[S. Capone, A. Guaragna, G. Palumbo, S. Pedatella, *Tetrahedron* 2005, *61*, 6675-6579]

β^3-HLeu-OMe

β^3-HTyr(Bn)-OMe

[R. Caputo, E. Cassano, L. Longobardo, G. Palumbo, *Tetrahedron* 1995, *51*, 12337-12350.]

β^3-HCys(Bn)-OMe

[K. Mang'era, H. Vanbilloen, B. Cleynhens, T. de Groot, G. Bormans, A. Verbruggen, K. Verbeke, *Nucl. Med .Biol.* 2000, *27*, 781-789.]

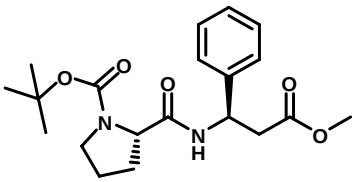
β^3-HTrp-OMe (9/S)

Prepared according to R. Caputo, E. Cassano, L. Longobardo, G. Palumbo, *Tetrahedron* 1995, *51*, 12337-12350: glassy oil, $[\alpha]_D^{25}$ = 1.6 (c = 3.0). ^{1}H NMR (500 MHz): δ 2.64-2.72 (m, 2H, H-2), 3.00 (dd, J = 14.4, J = 6.9, 1H, Ha-4), 3.07 (dd, J = 14.4, J = 7.4, 1H, Hb-4), 3.56 (s, 3H, OMe), 3.70-3.78 (m, 1H, H-3), 6.97-7.42 (m, 5H, H-Ar), 8.28 (bs, 1H, NH). ^{13}C NMR (125 MHz): δ 28.3, 35.1, 49.5,

52.4, 111.5, 118.7, 119.9, 122.6, 124.0, 126.5, 128.3, 136.3, 172.1. Calculated for $C_{13}H_{16}N_2O_2$ (232.28): C, 67.22%; H, 6.94%; N, 12.06%; found: C, 67.25%; H, 6.90%; N, 12.01%.

3. Experimental procedures

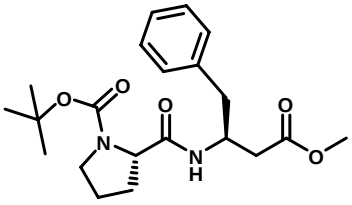
3.1. Coupling reactions of Boc-proline and β[3]-HAaa methyl esters.



(*3R*)-3-[(*2S*)-1-(*tert*-butyloxycarbonyl)tetrahydro-1H-2-pyrrolyl]carboxamido-3-phenylpropanoic acid methyl ester (10/S).

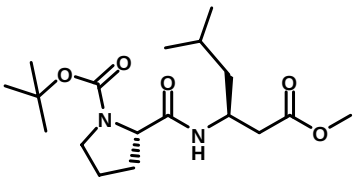
To a solution of *tert*-butyloxycarbonyl-L-proline (0.46 mmol) in dry CH_2Cl_2 (3 mL), HOBt (0.92 mmol) was added at 0° C. The mixture was stirred for 30 min. Then DCC (0.50 mmol) in dry CH_2Cl_2 (1 mL) and protected β-amino acids (0.42 mmol) in the same solvent (2 mL) were added. The reaction mixture was stirred at 0° C for 12 h, then concentrated under reduced pressure. The resulting mixture was diluted with EtOAc (20 mL). The organic layer was washed with saturated aq $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and after removal of solvent under reduced pressure, the residue was purified by silica gel chromatography to give the title protected dipeptide. Yield 85%. Oil, $[\alpha]_D^{25}$ = –54.1 (*c* = 1.1). ^{1}H NMR (400 MHz, CD_3OD)**:** δ 1.43 (bs, 9H, Boc), 1.79-1.99 (m, 3H, H-4' and Ha-3'), 2.09-2.18 (m, 1H, Hb-3'), 2.79-2.90 (m, 2H, H-2), 3.35-3.52 (m, 2H, H-5'), 3.65 (s, 3H, OMe), 4.05-4.09 (m, 1H, H-2'), 5.25-5.35 (m, 1H, H-3), 7.18-7.32 (m, 5H, H-Ar), 8.25 (bd, *J* = 5.7, 1H, NH). ^{13}C NMR (125 MHz, CD_3OD): δ 26.6, 26.8, 32.2, 41.5, 47.9, 50.5, 50.9, 61.6, 79.7, 128.0, 128.6, 129.2, 142.5, 149.9, 172.7, 176.0. Calculated for $C_{20}H_{28}N_2O_5$ (376.45): C, 63.81%; H, 7.50%; N, 7.44%; found: C, 63.78%; H, 7.46%; N, 7.46%.

Under the same conditions the following compounds were prepared:



(*3S*)-3-[(*2S*)-1-(tert-butyloxycarbonyl)tetrahydro-1H-2-pyrrolyl]carboxamido-4-phenylbutanoic acid methyl ester (11/S).

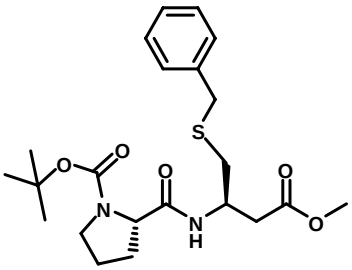
Yield 87%. Oil, $[\alpha]_D^{25}$ = –48.2 (*c* = 1.2, acetone). ^{1}H NMR (400 MHz)**:** δ 1.44 (bs, 9H, Boc), 1.55-1.98 (m, 4H, H-4' and H-3'), 2.45-2.60 (m, 2H, H-2), 2.88-2.92 (m, 2H, CH_2-Ph), 3.24-3.44 (m, 2H, H-5'), 3.69 (s, 3H, OMe), 4.08-4.27 (m, 1H, H-2'), 4.45-4.55 (m, 1H, H-3), 7.14-7.34 (m, 5H, H-Ar). ^{13}C NMR (125 MHz): δ 23.1, 23.8, 26.5, 35.6, 38.0, 45.1, 47.3, 49.8, 59.4, 78.5, 124.9, 126.7, 127.3, 135.9, 155.0, 169.6, 170.0. Calculated for $C_{21}H_{30}N_2O_5$ (390.47): C, 64.59%; H, 7.74%; N, 7.17%; found: C, 64.56%; H, 7.71%; N, 7.21%.



(*3S*)-3-[(*2S*)-1-(*tert*-butyloxycarbonyl)tetrahydro-1H-2-pyrrolyl]carboxamido-5-methylhexanoic acid methyl ester (12/S).

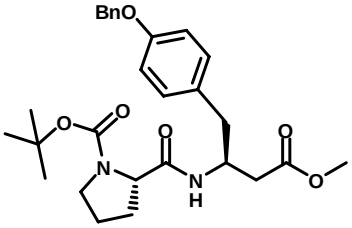
Yield 83%. Oil, $[\alpha]_D^{25}$ = –66.4 (*c* = 0.4, acetone). ^{1}H NMR (400 MHz)**:** δ 0.90 (d, *J* = 6.3, 6H, H-6 and CH_3), 1.08-1.38 (m, 2H, H-4), 1.45 (s, 9H, Boc), 1.50-1.58 (m, 1H, H-5), 1.69-1.92 (m, 3H, H-4' and Ha-3'), 2.03-2.15 (m, 1H, Hb-3'), 2.42-2.58 (m, 2H, H-2), 3.22-3.57 (m, 2H, H-5'), 3.66 (s, 3H, OMe), 4.19-4.39 (m, 2H, H-2' and H-3). ^{13}C NMR (50 MHz): δ 21.9, 23.0, 25.1, 28.3, 39.1, 43.1, 44.1, 47.0,

60.1, 51.6, 80.3, 156.1, 172.0, 186.4. Calculated for $C_{18}H_{32}N_2O_5$ (356.46): C, 60.65%; H, 9.05%; N, 7.86%; found: C, 60.68%; H, 9.00%; N, 7.90%.



(*3R*)-4-(benzylsulfanyl)-3-[(*2S*)-1-(*tert*-butyloxycarbonyl)tetrahydro-1H-2-pyrrolyl]carboxamidobutanoic acid methyl ester (13/S).

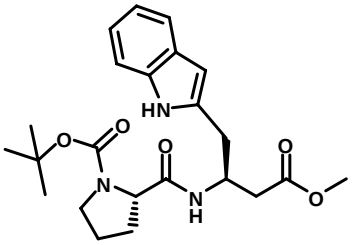
Yield 86%. Oil, $[\alpha]_D^{25}$ = –29.3 (*c* = 1.1, acetone). ^{1}H NMR (400 MHz)**:** δ 1.40 (bs, 9H, Boc), 1.78-2.18 (m, 4H, H-4' and H-3'), 2.49-2.76 (m, 4H, H-4 and H-2), 3.29-3.51 (m, 2H, H-5'), 3.63 (s, 3H, OMe), 3.73 (s, 2H, SCH_2-Ph), 4.11-4.40 (m, 2H, H-2' and H-3), 7.18–7.35 (m, 5H, H-Ar). ^{13}C NMR (50 MHz): δ 24.4, 28.3, 34.8, 36.0, 36.8, 44.8, 47.0, 51.7, 60.4, 80.4, 127.0, 128.5, 129.0, 138.1, 155.8, 171.6, 175.4. Calculated for $C_{22}H_{32}N_2O_5S$ (436.46): C, 60.53%; H, 7.39%; N, 6.42%; found: C, 60.49%; H, 7.41%; N, 6.44%.



(*3S*)-4-[4-(benzyloxy)phenyl]-3-[(*2S*)-1-(tert-butyloxycarbonyl)tetrahydro-1H-2-pyrrolyl]carboxamidobutanoic acid methyl ester (14/S).

Yield 85%. Oil, $[\alpha]_D^{25}$ = – 44.5 (*c* = 0.1, acetone). ^{1}H NMR (500 MHz)**:** δ 1.44 (bs, 9H, Boc), 1.65-1.75 (m, 2H, H-4'), 1.82-198 (m, 2H, H-3'), 2.44-2.57 (m, 2H, H-2), 2.76-2.86 (m, 2H, CH_2-Ph), 3.22-3.44

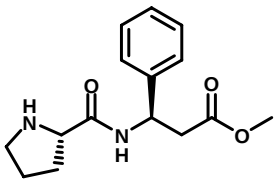
(m, 2H, H-5'), 3.68 (s, 3H, OMe), 4.10-4.27 (m, 1H, H-2'), 4.40-4.51 (m, 1H, H-3), 5.00-5.07 (m, 2H, OCH_2-Ph), 6.85-7.45 (m, 9H, H-Ar). ^{13}C NMR (125 MHz): δ 24.8, 25.5, 28.2, 33.8, 37.2, 46.9, 49.0, 51.6, 60.3, 69.8, 80.1, 113.1, 114.7, 127.3, 127.8, 128.4, 130.0, 136.9, 157.4, 157.8, 171.8, 175.1. Calculated for $C_{28}H_{36}N_2O_6$ (496.60): C, 67.72%; H, 7.31%; N, 5.64%; found: C, 67.76%; H, 7.35%; N, 5.62%.



(*3S*)-3-[(*2S*)-1-(*tert*-butyloxycarbonyl)tetrahydro-1H-2-pyrrolyl]carboxamido-4-(1H-3-indolyl)butanoic acid methyl ester (15/S).

Yield 90%. Oil, $[\alpha]_D^{25}$ = –48.7(*c* = 1.3, acetone). ^1H NMR (400 MHz)**:** δ 1.39 (s, 9H, Boc), 160-1.67 (m, 3H, H-4' and Ha-3'), 1.90-1.95 (m, 1H, Hb-3'), 2.49-2.54 (m, 2H, H-2), 2.98-3.15 (m, 2H, H-4), 3.20-3.25 (m, 2H, H-5'), 3.67 (s, 3H, OMe), 4.09-4.22 (m, 1H, H-2'), 4.56-4.69 (m, 1H, H-3), 6.62 (bs, 1H, NH), 7.05-7.64 (m, 5H, H-Ar), 8.19 (bs, 1H, NH). ^{13}C NMR (50 MHz): δ 25.6, 28.3, 29.7, 30.4, 31.9, 37.4, 46.6, 46.9, 51.6, 61.3, 80.2, 111.1, 111.6, 118.7, 119.6, 122.1, 122.7, 127.7, 136.2, 159.6, 172.0, 176.0. Calculated for $C_{23}H_{31}N_3O_5$ (429.51): C, 64.32%; H, 7.27%; N, 9.78%; found: C, 64.28%; H, 7.22%; N, 9.76%.

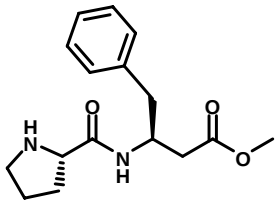
3.2. Boc removal from *N*-terminal proline



(*3R*)-3-phenyl-3-[(*2S*)tetrahydro-1H-2-pyrrolylcarboxamido]propanoate (*2S*,*3S*)-methyl 3-amino-2-(*tert*-butoxycarbonylamino)-3-phenylpropanoic acid methyl ester (1a).

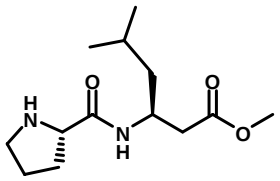
Formic acid (0.7 mL) was slowly added to the *N*-proline protected dipeptide (0.1 mmol), at 0° C under magnetic stirring. The mixture was left to raise to room temperature and stirred for 12 h. Formic acid was then evaporated and the reaction mixture was neutralized with aq ammonia at 0° C. The product was extracted with CH_2Cl_2 and the organic layer, after washing with brine and drying (Na_2SO_4), was concentrated under reduced pressure to get an oil residue. The residue was purified by flash column chromatography on silica gel. Yield 89%. Oil, $[\alpha]_D^{25} = -23.2$ (c = 0.9, acetone). ^{1}H NMR (500 MHz, CD_3OD)**:** δ 1.64-1.83 (m, 3H, H-4' and Ha-3'), 2.03-2.19 (m, 1H, Hb-3'), 2.79-3.05 (m, 4H, H-2 and H-5'), 3.61 (s, 3H, OMe), 3.65-3.74 (m, 1H, H-2'), 5.31-5.36 (m, 1H, H-3), 7.21-7.42 (m, 5H, H-Ar). ^{13}C NMR (50 MHz, CD_3OD): δ 26.8, 32.1, 41.5, 48.1, 51.2, 52.2, 61.6, 127.8, 128.2, 129.2, 142.4, 172.9, 176.2. Calculated for $C_{15}H_{20}N_2O_3$ (276.33): C, 65.20%; H, 7.30%; N, 10.14%; found: C, 65.24%; H, 7.27%; N, 10.16%.

Under the same conditions the following compounds were prepared:



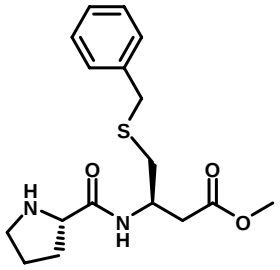
(*3S*)-4-phenyl-3-[(*2S*)tetrahydro-1H-2-pyrrolylcarboxamido]butanoic acid methyl ester (1b).

Yield 90%. Oil, $[\alpha]_D^{25}$ = –48.7 (*c* = 1.0, acetone). ^{1}H NMR (500 MHz)**:** δ 1.87-2.11 (m, 3H, H-4' and Ha-3'), 2.26-2.44 (m, 1H, Hb-3'), 2.48-2.56 (m, 2H, H-4), 2.79 (dd, *J* = 13.6, *J* = 7.4, 1H, Ha-2), 2.93 (dd, *J* = 13.6, *J* = 7.5, 1H, Hb-2), 3.30-3.43 (m, 2H, H-5'), 3.63 (s, 3H, OMe), 4.39-4.49 (m, 1H, H-3), 4.50-4.58 (m, 1H, H-2'), 7.11-7.31 (m, 5H, H-Ar), 8.05 (bs, 1H, NH). ^{13}C NMR (125 MHz): δ 24.0, 29.5, 37.2, 39.8, 46.3, 48.8, 51.7, 59.4, 126.7, 128.5, 129.1, 137.1, 167.7, 171.6. Calculated for $C_{16}H_{22}N_2O_3$ (290.36): C, 66.18%; H, 7.64%; N, 9.65%; found: C, 66.23%; H, 7.61%; N, 9.69%.



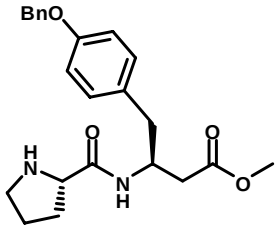
(*3S*)-5-methyl-3-[(*2S*)tetrahydro-1H-2-pyrrolylcarboxamido]hexanoic acid methyl ester (1c).

Yield 86%. Oil, $[\alpha]_D^{25}$ = –50.6 (*c* = 0.9, acetone). ^{1}H NMR (400 MHz)**:** δ 0.87 (d, *J* = 6.5, 6H, H-6 and CH_3), 1.31-1.46 (m, 1H, Ha-4), 1.48-1.75 (m, 2H, Hb-4 and H-5), 1.97-2.21 (m, 3H, H-4' and Ha-3'), 2.32-2.57 (m, 3H, Hb-3' and H-2), 3.39-3.50 (m, 2H, H-5'), 3.64 (s, 3H, OMe), 4.25-4.29 (m, 1H, H-3), 4.57-4.61 (m, 1H, H-2'), 7.91 (bs, 1H, NH). ^{13}C NMR (100 MHz): δ 21.8, 22.7, 24.3, 24.7, 29.6, 39.1, 42.9, 45.7, 46.4, 51.7, 59.4, 167.9, 171.8. Calculated for $C_{13}H_{24}N_2O_3$ (256.34): C, 60.91%; H, 9.44%; N, 10.93%; found: C, 60.88%; H, 9.41%; N, 10.96%.



(*3R*)-4-(benzylsulfanyl)-3-[(*2S*)tetrahydro-1H-2-pyrrolylcarboxamido]butanoic acid methyl ester (1d).

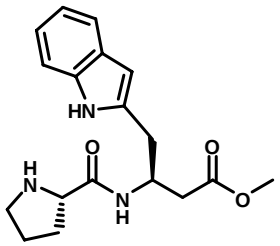
Yield 90%. Oil, $[\alpha]_D^{25}$ = –41.1 (*c* = 0.7, acetone). ^{1}H NMR (400 MHz, CD_3OD)**:** δ 1.98-2.10 (m, 3H, H-4' and Ha-3'), 2.36-2.43 (m, 1H, Hb-3'), 2.56 (dd, *J* = 15.6, *J* = 8.6, 1H, Ha-2), 2.65 (d, *J* = 7.0, 2H, H-4), 2.73 (dd, *J* = 15.6, *J* = 4.9, 1H, Hb-2), 3.29-3.43 (m, 2H, H-5'), 3.64 (s, 3H, OMe), 3.76 (s, 2H, CH_2Ph), 4.17-4.22 (m, 1H, H6), 4.35-4.61 (m, 1H, H-3), 7.18–7.38 (m, 5H, H-Ar). ^{13}C NMR (100 MHz, CD_3OD): δ 25.0, 31.2, 36.1, 36.9, 38.9, 47.4, 47.8, 52.3, 61.1, 128.1, 129.5, 130.0, 139.6, 169.3, 172.9. Calculated for $C_{17}H_{24}N_2O_3S$ (336.45): C, 60.69%; H, 7.19%; N, 8.33%; found: C, 60.71%; H, 7.16%; N, 8.38%.



(*3S*)-4-[4-(benzyloxy)phenyl]-3-[(*2S*)tetrahydro-1H-2-pyrrolylcarboxamido]butanoic acid methyl ester (1e).

Yield 90%. Oil, $[\alpha]_D^{25}$ = –29.3 (*c* = 1.1, acetone). ^{1}H NMR (500 MHz)**:** 1.89-2.07 (m, 3H, H-4' and Ha-3'), 2.26-2.41 (m, 2H, Hb-3'), 2.44-2.57 (m, 2H, H-4), 2.72 (d, *J* = 14.1, *J* = 8.0, 1H, Ha-2), 2.86 (d, *J* = 14.1, *J* = 5.8, 1H, Hb-2), 3.29-3.41 (m, 2H, H-5'), 3.61 (s, 3H, OMe), 4.32-4.43 (m, 1H, H-2'), 4.48-4.59 (m, 1H, H-3), 4.97-5.04 (d, *J* = 7.3, 2H, OCH_2-Ph), 6.80-7.40 (m, 9H, H-Ar), 7.97 (bd, *J* = 7.3, NH). ^{13}C NMR (50 MHz): δ 24.4, 30.0, 37.3, 39.0, 46.3, 49.0, 51.7, 59.5, 69.9, 114.9, 127.5, 127.9,

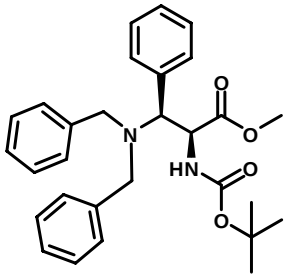
128.5, 129.5, 130.2, 137.0, 157.7, 168.7, 171.8. Calculated for $C_{23}H_{28}N_2O_4$ (396.48): C, 69.67%; H, 7.12%; N, 7.07%; found: C, 69.67%; H, 7.08%; N, 7.11%.



(*3S*)-4-(1H-3-indolyl)-3-[(2*S*)tetrahydro-1H-2-pyrrolylcarboxamido]butanoic acid methyl ester (1f).

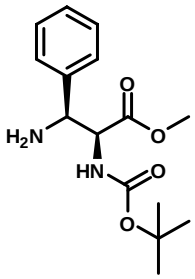
Yield 90%. Oil, $[\alpha]_D^{25} = -36.7$ (c = 0.4, Acetone). ^{1}H NMR (500 MHz)**:** δ 1.80-1.99 (m, 3H, H-4' and Ha-3'), 2.24-2.37 (m, 1H, Hb-3'), 2.55-2.66 (m, 2H, H-4), 2.94-3.06 (m, 1H, Ha-2), 3.16-3.33 (m, 3H, Hb-2 and H-5'), 3.65 (s, 3H, OMe), 4.35-4.45 (m, 1H, H-2'), 4.55-4.65 (m, 1H, H-3), 6.96-7.68 (m, 5H, H-Ar), 7.80-7.92 (m, 1H, NH), 8.33-8.44 (m, 1H, NH). ^{13}C NMR (50 MHz): δ 24.3, 29.7, 30.1, 38.4, 46.5, 47.9, 51.8, 59.5, 111.0, 111.5, 118.5, 119.5, 122.1, 123.1, 127.3, 136.0, 168.1, 171.8. Calculated for $C_{18}H_{23}N_3O_3$ (329.39): C, 65.63%; H, 7.04%; N, 12.76%; found: C, 65.66%; H, 7.02%; N, 12.71%.

3.3. Synthesis of C-2-substituted β^3-HPhg-OMe



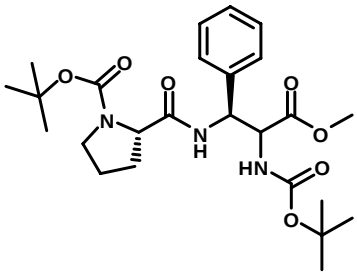
(*2S*,*3S*)-2-(*tert*-butoxycarbonylamino)-3-(dibenzylamino)-3-phenylpropanoic acid methyl ester (3).

To a stirred solution of (*2S*,*3S*)-2-amino-3-(dibenzylamino)-3-phenylpropanoic acid methyl ester [S. Capone, A. Guaragna, G. Palumbo, S. Pedatella, *Tetrahedron* **2005**, *61*, 6675–6579] (1.2 mmol) in 1M NaOH (2.6 mL) at 0° C, $(Boc)_2O$ (1.6 mmol) in dioxane (1.2 mL) was added slowly. The reaction mixture was left overnight, then was quenched with a solution $NaHSO_4$ (2 mL) and extracted with EtOAc. The organic layer was washed with brine until neutral, dried (Na_2SO_4), and the solvents evaporated under reduced pressure. Chromatography on silica gel (hexane/EtOAc, 8:2) afforded the oily pure title compound (Yield 92%), $[\alpha]_D^{25}$ = 50.7 (*c* = 1.5). ^{1}H NMR (500 MHz)**:** δ 1.23 (s, 9H, Boc), 3.02 (d, *J* = 13.0, 2H, CH_2-Ph), 3.82 (s, 3H, OMe), 3.90-4.03 (m, 3H, CH_2-Ph and H-3), 4.55 (bd, *J* = 7.9, 1H, NH), 5.06-5.18 (m, 1H, H-2), 7.18-7.49 (m, 15H, H-Ar). ^{13}C NMR (50 MHz): δ 28.0, 45.3, 52.1, 53.8, 64.7, 73.1, 127.1, 128.2, 128.9, 129.8, 138.8, 139.4, 140.1, 169.8, 171.2. Calculated for $C_{29}H_{34}N_2O_4$ (474.59): C, 73.39%; H, 7.22%; N, 5.90%; found: C, 73.43%; H, 7.25%; N, 5.86%.



(*2S*,*3S*)-methyl 3-amino-2-(*tert*-butoxycarbonylamino)-3-phenylpropanoic acid methyl ester (4).

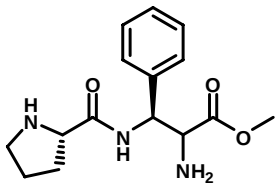
A magnetically stirred solution of *N*,*N*-dibenzylated β^3-amino acid (0.6 mmol) in glacial AcOH (15 mL) was treated with hydrogen over 30% Pd/C catalyst (69 mg) for 2 h at 50° C, under a slightly positive pressure (~3 bar). The mixture was then filtered through Celite® and washed with MeOH (20 mL). After removal of the solvents under reduced pressure, the residue was purified by silica gel chromatography. Yield 95%. Oil, $[\alpha]_D^{25}$ = 29.0 (*c* = 0.9). ^{1}H NMR (500 MHz)**:** δ 1.41 (s, 9H, Boc), 3.65 (s, 3H, OMe), 4.45-4.53 (m, 1H, H-3), 4.61-4.70 (m, 1H, H-2), 5.18-5.26 (m, 1H, NH), 7.11-7.46 (m, 5H, H-Ar). ^{13}C NMR (125 MHz): δ 28.9, 52.3, 54.3, 55.0, 79.9, 128.3, 128.5, 130.0, 137.7, 139.8, 169.4, 172.1. Calculated for $C_{15}H_{22}N_2O_4$ (294.35): C, 61.21%; H, 7.53%; N, 9.52%; found: C, 61.26%; H, 7.49%; N, 9.50%.



(*2S*,*3S*)-2-(*tert*-butyloxycarbonylamino)-3-[(*2S*)-1-(*tert*-butyloxycarbonyl)tetrahydro-1H-2-pyrrolyl]carboxamido-3-phenylpropanoic acid methyl ester (5).

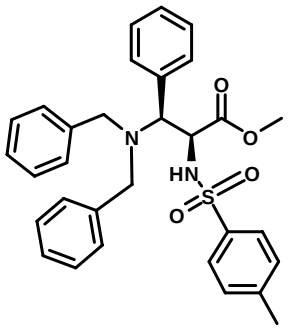
Yield 85%. Oil, $[\alpha]_D^{25}$ = 12.2 (*c* = 0.9, MeOH). ^{1}H NMR (500 MHz)**:** δ 1.45 (s, 9H, Boc), 1.49 (s, 9H, Boc), 1.64-2.10 (m, 4H, H-4' and H-3'), 3.32-3.53 (m, 2H, H-5'), 3.64 (s, 3H, OMe), 4.32-4.40 (m, 1H, H-2'), 4.69-4.80 (m, 1H, H-3), 5.43-5.55 (m, 1H, H-2), 7.04-7.35 (m, 5H, H-Ar), 8.18-8.30 (m, 1H,

NH), 8.30-8.39 (m, 1H, NH). ^{13}C NMR (125 MHz): δ 24.4, 28.0, 28.3, 29.5, 46.8, 52.1, 55.0, 57.1, 60.1, 80.0, 114.7, 126.4, 127.5, 128.1, 156.7, 158.3, 172.1, 175.7. Calculated for $C_{25}H_{37}N_3O_7$ (491.58): C, 61.08%; H, 7.59%; N, 8.55%; found: C, 61.21%; H, 7.32%; N, 8.60%.



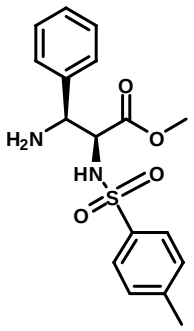
(*2S*,*3S*)-2-amino-3-phenyl-3-[(*2S*)tetrahydro-1H-2-pyrrolylcarboxamido]propanoic acid methyl ester (1g).

Yield 82%. Oil, $[\alpha]_D^{25}$ = 9.7 (*c* = 0.9, MeOH). ^{1}H NMR (500 MHz, CD_3OD)**:** δ 2.01-2.17 (m, 3H, H-4' and Ha-3'), 2.41-2.52 (m, 1H, Hb-3'), 3.37-3.46 (m, 2H, H-5'), 3.81 (s, 3H, OMe), 4.27-4.41 (m, 2H, H-2 and H-2'), 5.44 (bd, *J* = 7.63, H-3), 7.37-7.50 (m, 5H, H-Ar). ^{13}C NMR (125 MHz, CD_3OD): δ 25.2, 31.5, 47.8, 54.0, 56.1, 58.1, 61.4, 129.1, 131.4, 136.9, 169.9, 170.1. Calculated for $C_{15}H_{21}N_3O_3$ (291.35): C, 61.84%; H, 7.27%; N, 14.42%; found: C, 61.88%; H, 7.26%; N, 14.40%.



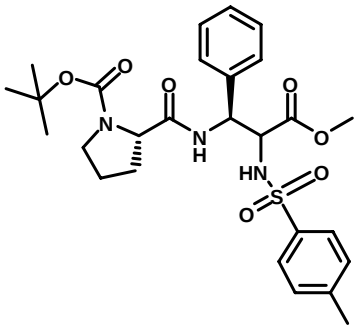
(*2S*,*3S*)-3-(dibenzylamino)-2-[(4-methylphenyl)sulfonamido]-3-phenylpropan ic acid methyl ester (6).

To a solution of (*2S*,*3S*)-2-amino-3-(dibenzylamino)-3-phenylpropanoic acid methyl ester [S. Capone, A. Guaragna, G. Palumbo, S. Pedatella, *Tetrahedron* **2005**, *61*, 6675–6579] (0.7 mmol) dissolved in H_2O/THF (3:1) cesium carbonate (2.2 mmol) and 4-toluenesulfonyl chloride (2.2 mmol) were added at r.t.. The reaction mixture, stirred for 2 h, was extracted with EtOAc. The organic layer was washed with brine until neutral, dried (Na_2SO_4), and the solvents evaporated under reduced pressure. Flash chromatography on silica gel (hexane/EtOAc, 85:15) afforded the oily pure title compound (Yield 81%). $[\alpha]_D^{25}$ = 31.5 (*c* = 4.5, acetone). ^{1}H NMR (400 MHz)**:** δ 2.42 (s, 3H, CH_3), 2.93 (d, *J* = 13.5, 2H, CH_2-Ph), 3.49 (s, 3H, OMe), 3.85 (d, *J* = 13.5, 2H, CH_2-Ph), 3.91 (d, *J* = 10.6, 1H, H-3), 4.56-4.68 (m, 2H, H-2 and NH), 6.98-7.55 (m, 19H, H-Ar). ^{13}C NMR (125 MHz): δ 21.4, 49.8, 51.9, 53.7, 56.9, 64.2, 127.0, 127.3, 128.0, 128.1, 128.7, 129.3, 129.5, 131.2, 136.0, 138.3, 143.5, 170.7. Calculated for $C_{31}H_{32}N_2O_4S$ (528.66): C, 70.43%; H, 6.10%; N, 5.30%; found: C, 70.46%; H, 6.09%; N, 5.33%.



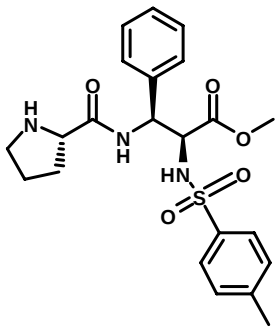
(*2S*,*3S*)-3-amino-2-[(4-methylphenyl)sulfonamido]-3-phenylpropanoic acid methyl ester (7).

The title compound was obtained by the corresponding *N*,*N*-dibenzylated β^3-amino acid under the conditions reported. Yield 80%. Oil, $[\alpha]_D^{25}$ = 3.6 (*c* = 1.4, acetone). ^{1}H NMR (500 MHz)**:** δ 2.39 (s, 3H, CH_3), 3.37 (s, 3H, OMe), 4.19 (d, *J* = 4.6, 1H, H-3), 4.33 (d, *J* = 4.6, 1H, H-2), 7.12-7.72 (m, 9H, H-Ar). ^{13}C NMR (125 MHz): δ 19.7, 50.4, 55.5, 59.6, 124.6, 125.5, 126.3, 126.6, 126.8, 127.8, 134.6, 138.0, 141.9, 168.0. Calculated for $C_{17}H_{20}N_2O_4S$ (348.42): C, 58.60%; H, 5.79%; N, 8.04%; found: C, 58.57%; H, 5.81%; N, 8.07%.



(*2S*,*3S*)-2-(4-methylphenylsulfonamido)-3-[(*2S*)-1-(*tert*-butyloxycarbonyl)tetrahydro-1H-2-pyrrolyl]carboxamido-3-phenylpropanoic acid methyl ester (8).

Yield 83%. Oil, $[\alpha]_D^{25}$ = –40.3 (*c* = 2.1, acetone). ^{1}H NMR (500 MHz)**:** δ 1.48 (s, 9H, Boc), 1.82-2.15 (m, 4H, H-4' and H-3'), 2.41 (s, 3H, CH_3), 3.32-3.60 (m, 5H, OMe and H-5'), 4.20-4.59 (m, 2H, H-2' and H-2), 5.23-5.36 (m, 1H, H-3), 5.76-5.96 (bs, 1H, NH), 7.15-7.78 (m, 9H, H-Ar), 8.40 (bs, 1H, NH). ^{13}C NMR (125 MHz): δ 21.4, 25.6, 28.4, 29.6, 47.2, 52.3, 54.4, 58.8, 60.6, 80.7, 126.7, 127.3, 128.6, 129.6, 136.1, 143.6, 156.1, 169.9, 171.8. Calculated for $C_{27}H_{35}N_3O_7S$ (545.65): C, 59.43%; H, 6.47%; N, 7.70%; found: C, 59.40%; H, 6.49%; N, 7.66%.



(*2S*,*3S*)-2-(4-methylphenylsulfonamido)-3-phenyl-3-((*S*)-pyrrolidine-2-carboxamido)propanoic acid methyl ester (1h).

Yield 80%. Oil, $[\alpha]_D^{25}$ = –3.8 (*c* = 0.1, acetone). ^{1}H NMR (400 MHz)**:** δ 1.65-1.76 (m, 2H, H-4'), 1.80-1.93 (m, 1H, Ha-3'), 2.10-2.20 (m, 1H, Hb-3'), 2.38 (s, 3H, CH_3), 2.90-3.10 (m, 2H, H-5'), 3.46 (s, 3H, OMe), 3.83 (dd, *J* = 9.1, *J* = 5.6, 1H, H-2'), 4.37 (d, *J* = 3.9, 1H, H-2), 5.37 (dd, *J* = 8.8, *J* = 3.9, 1H, H-3), 7.16-7.69 (m, 9H, H-Ar), 8.72 (d, *J* = 8.8, 1H, NH). ^{13}C NMR (100 MHz): δ 21.4, 25.9, 30.2, 47.1,

52.5, 53.7, 58.6, 60.5, 126.9, 127.3, 128.4, 128.7, 129.6, 135.6, 135.7, 143.8, 169.0, 175.0. Calculated for $C_{22}H_{27}N_3O_5S$ (445.53): C, 59.31%; H, 6.11%; N, 9.43%; found: C, 59.34%; H, 6.13%; N, 9.42%.

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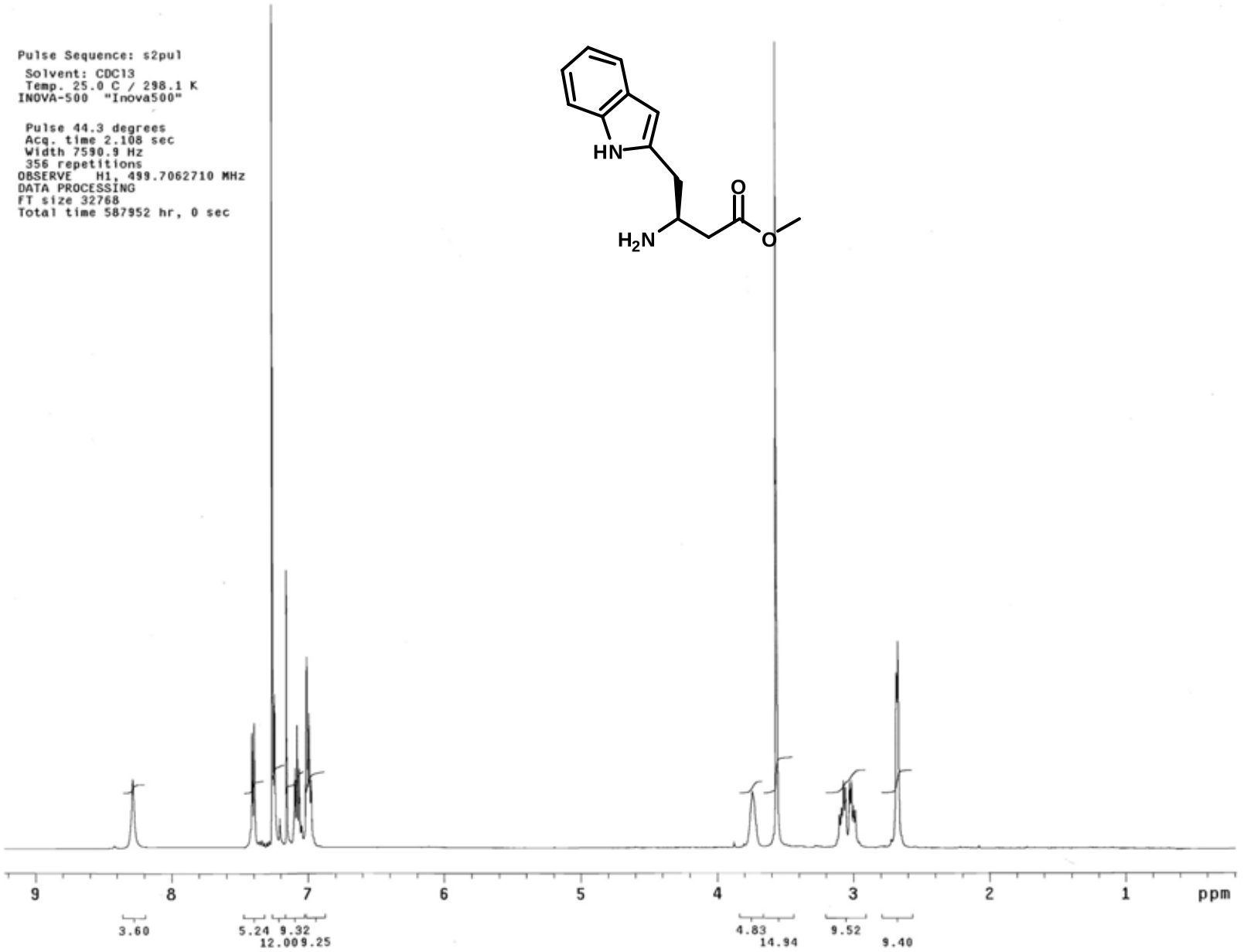
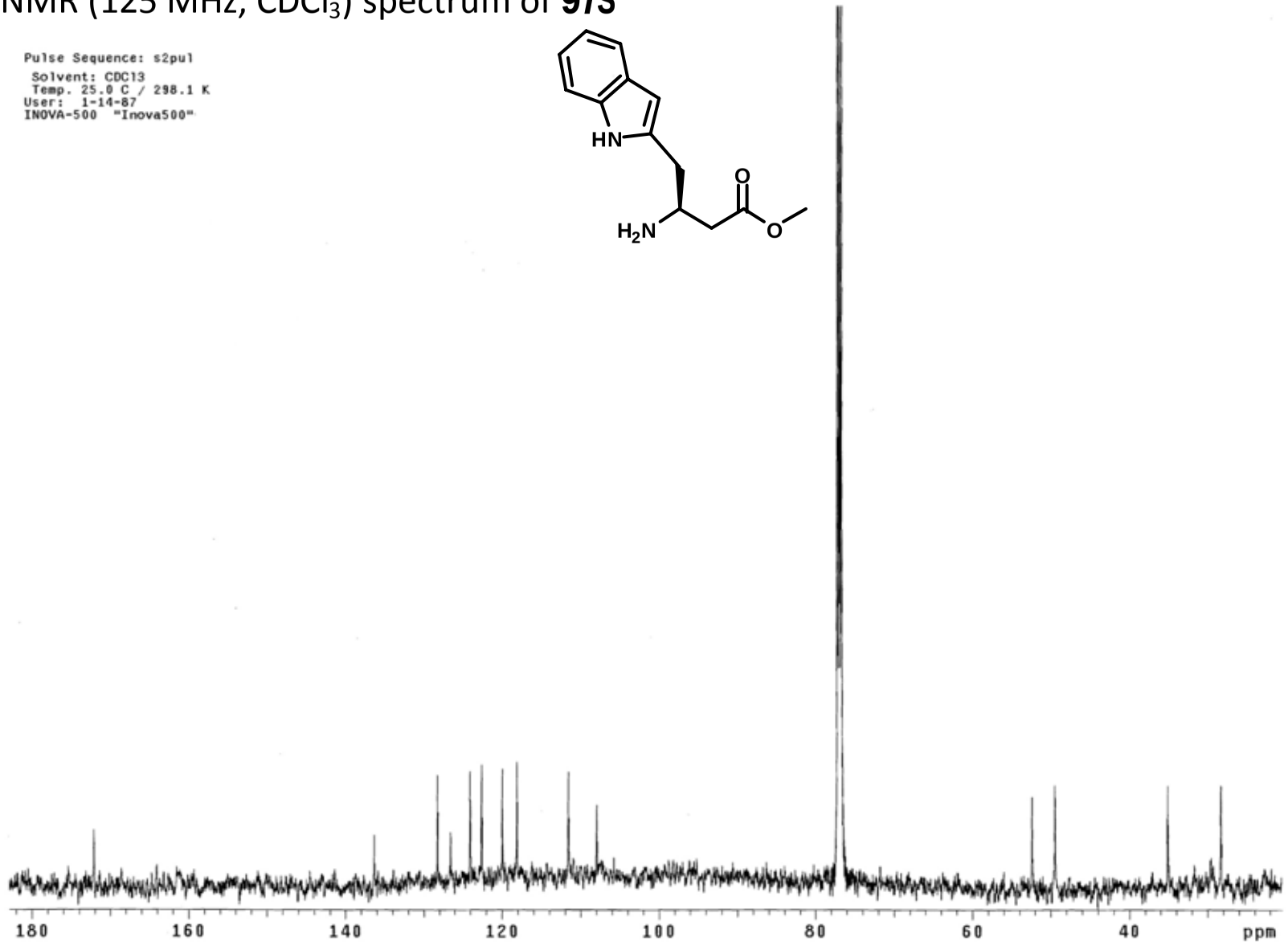
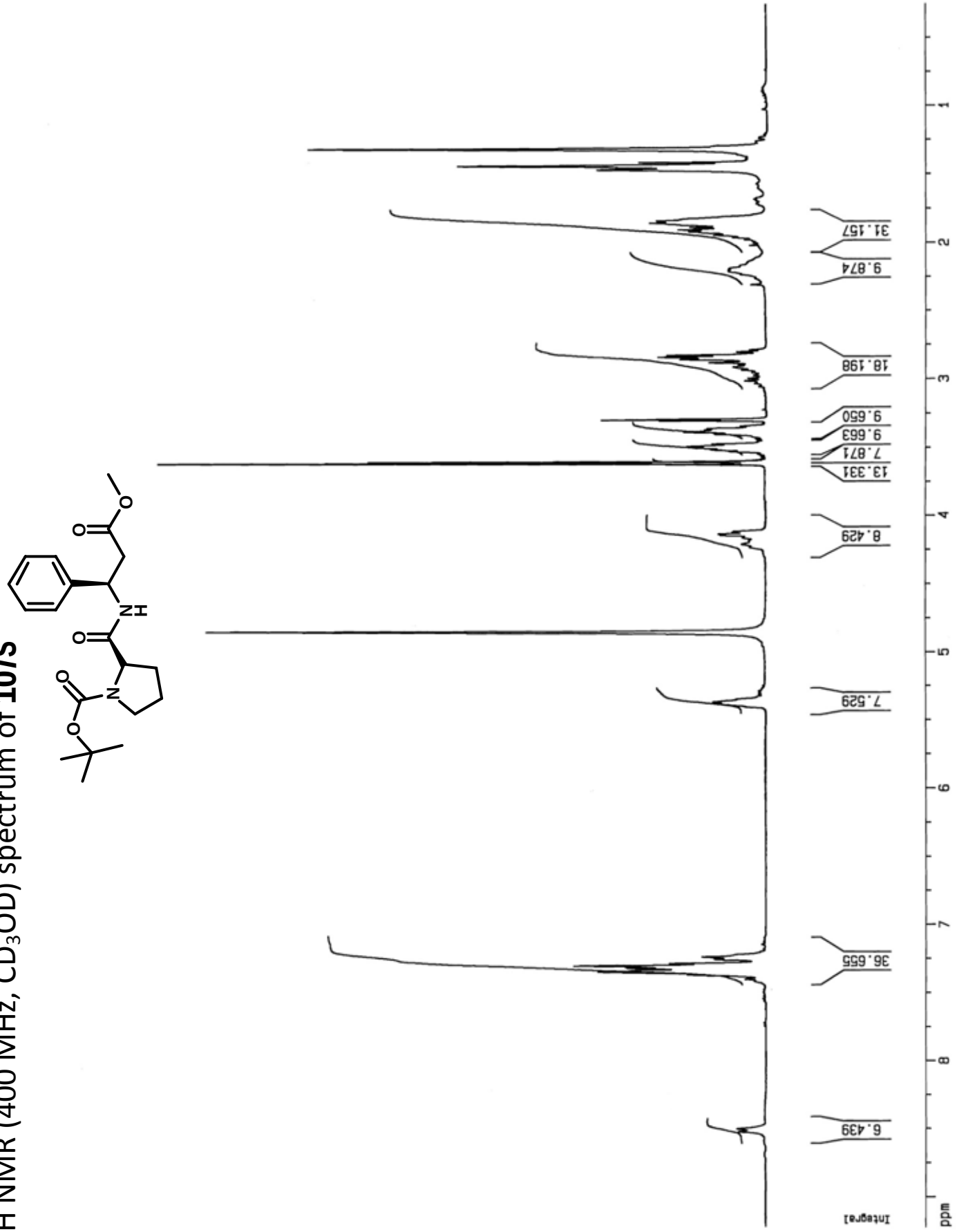
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **9*I*S**



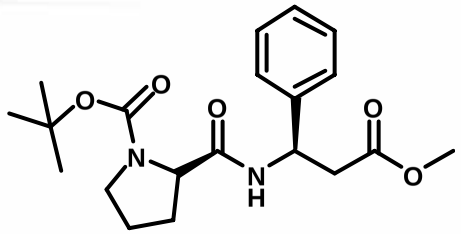
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **9*I*S**



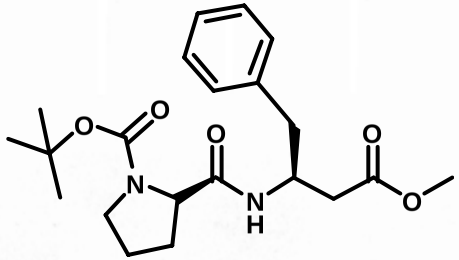
^{1}H NMR (400 MHz, CD_3OD) spectrum of **10/S**

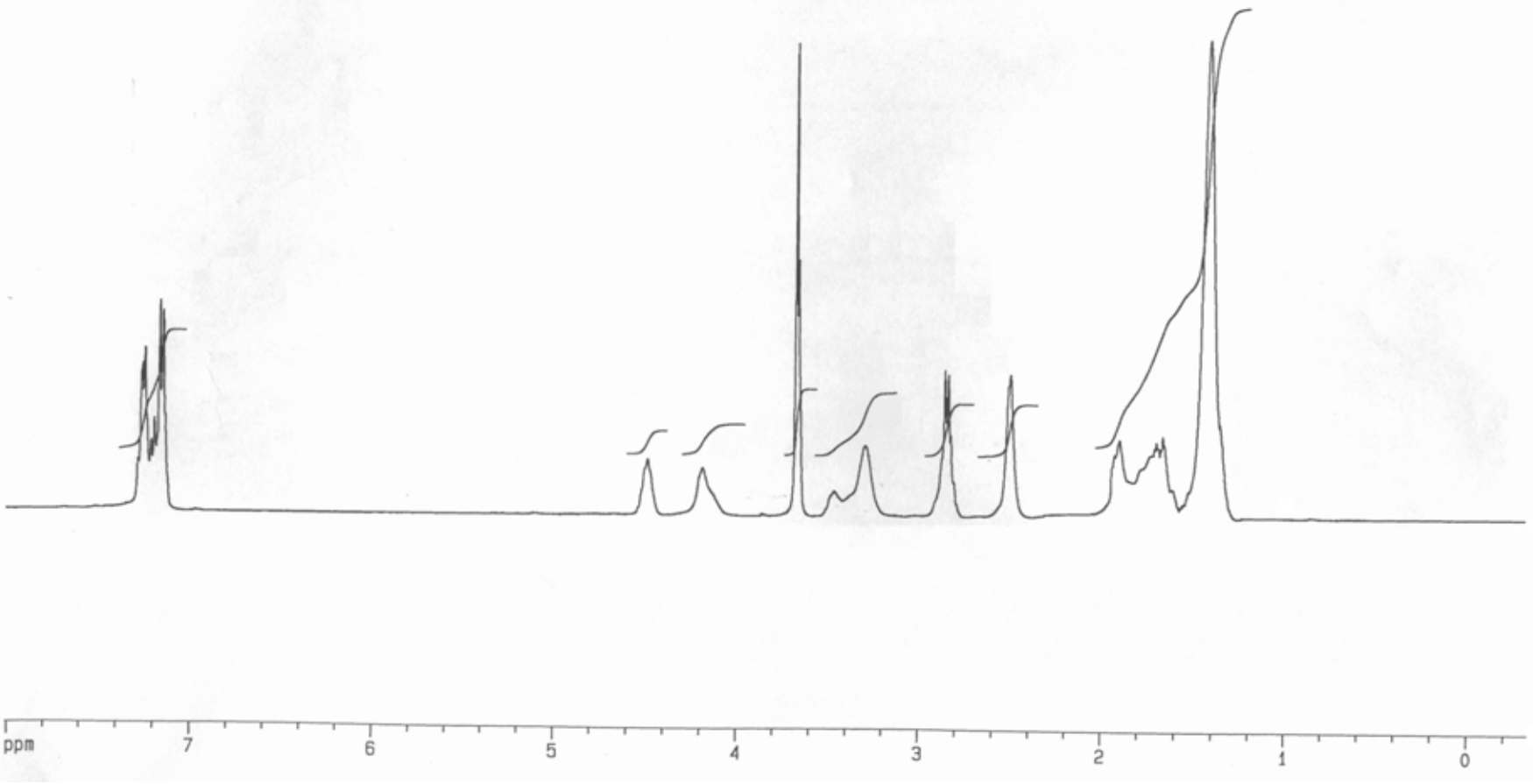


^{13}C NMR (125 MHz, CD_3OD) spectrum of **10/S**

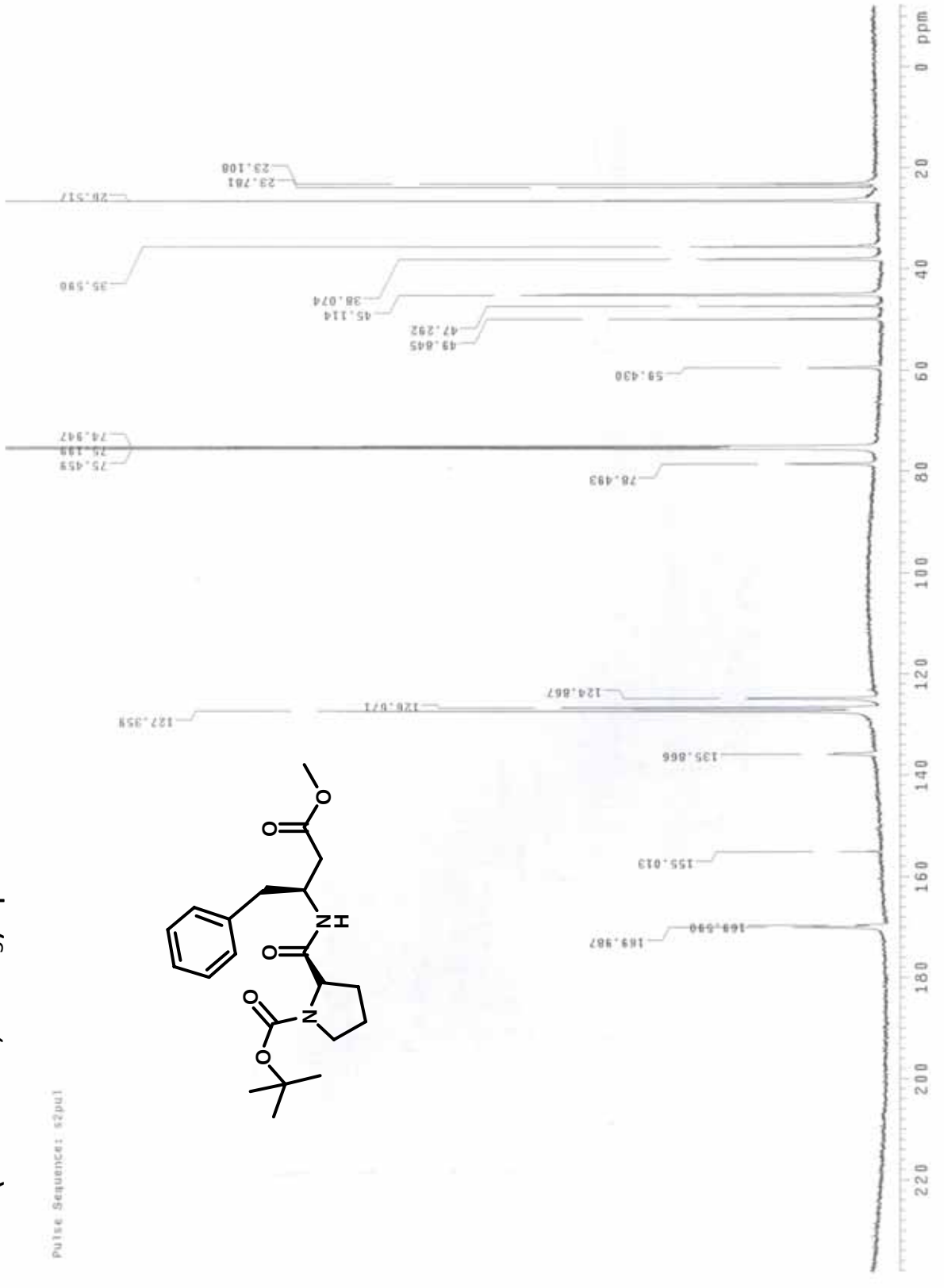


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **11/S**

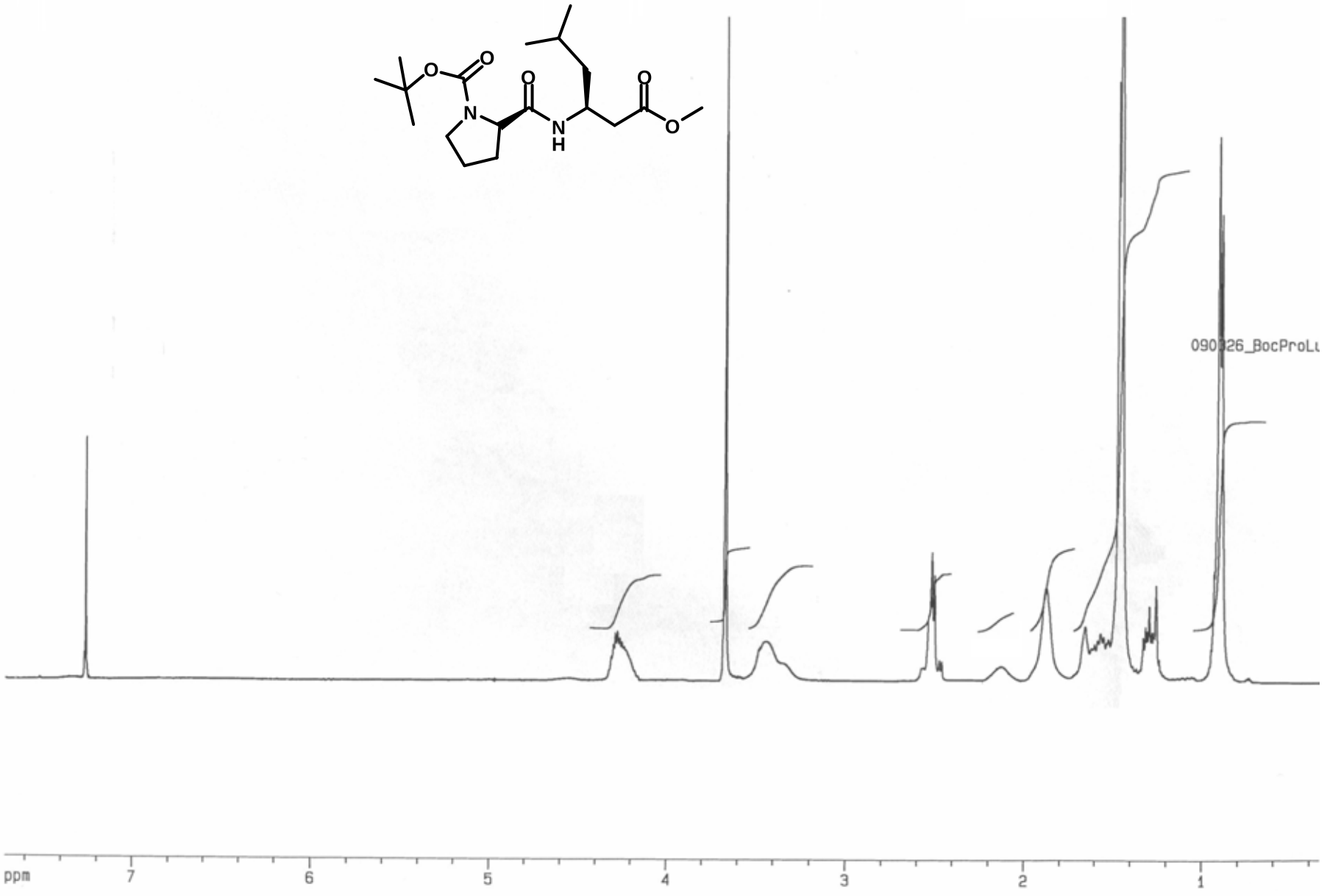




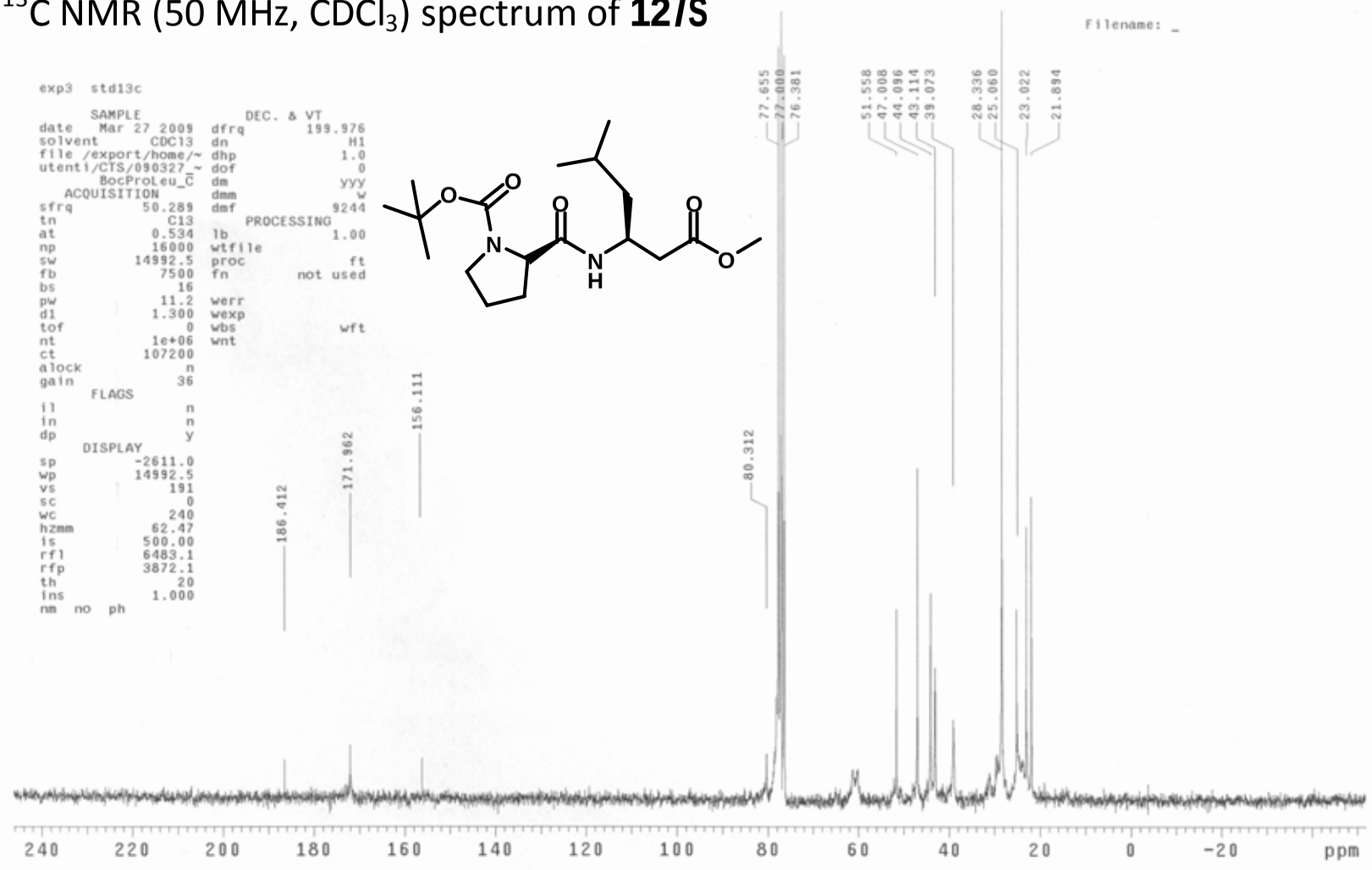
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **11/S**



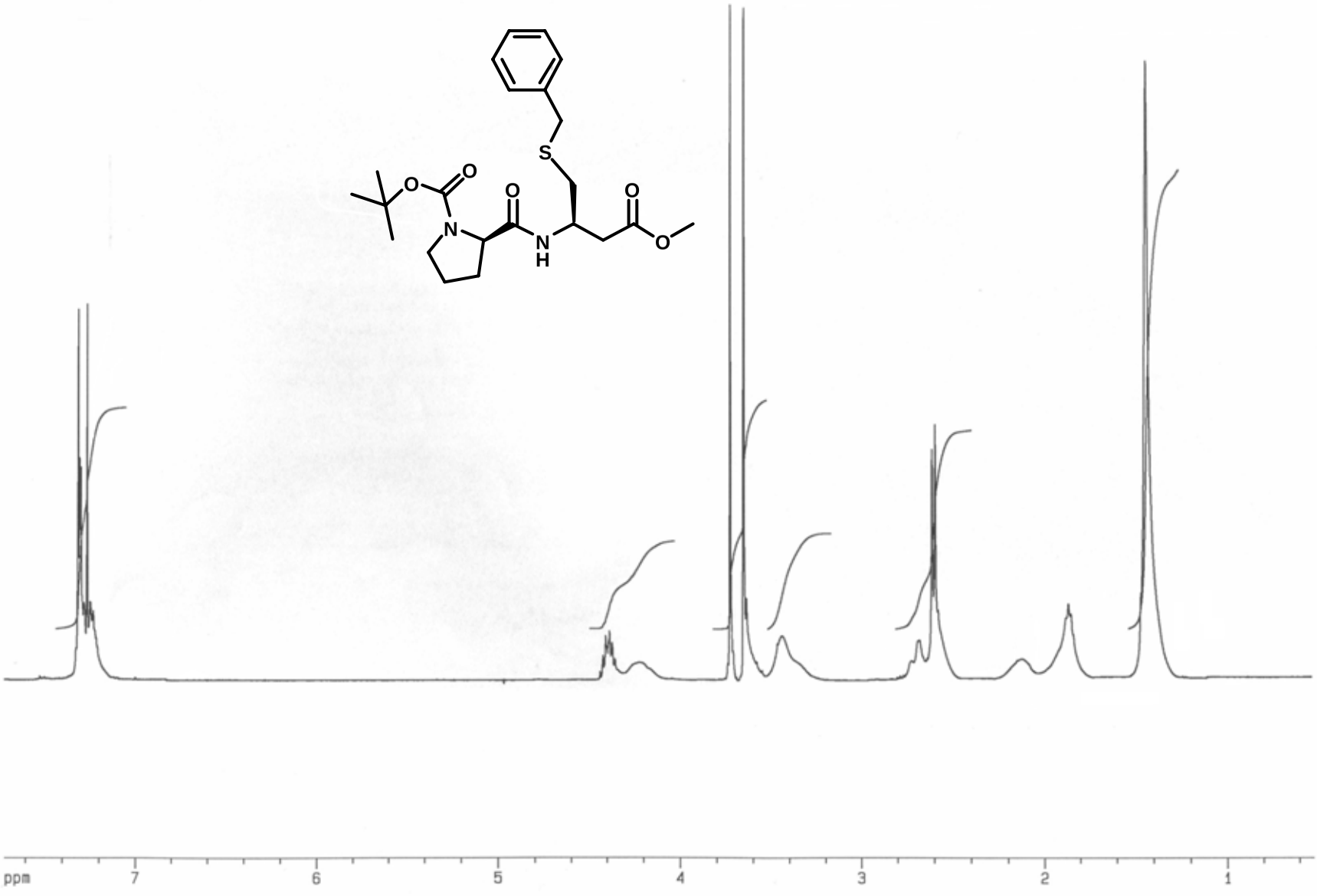
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **12/*S***



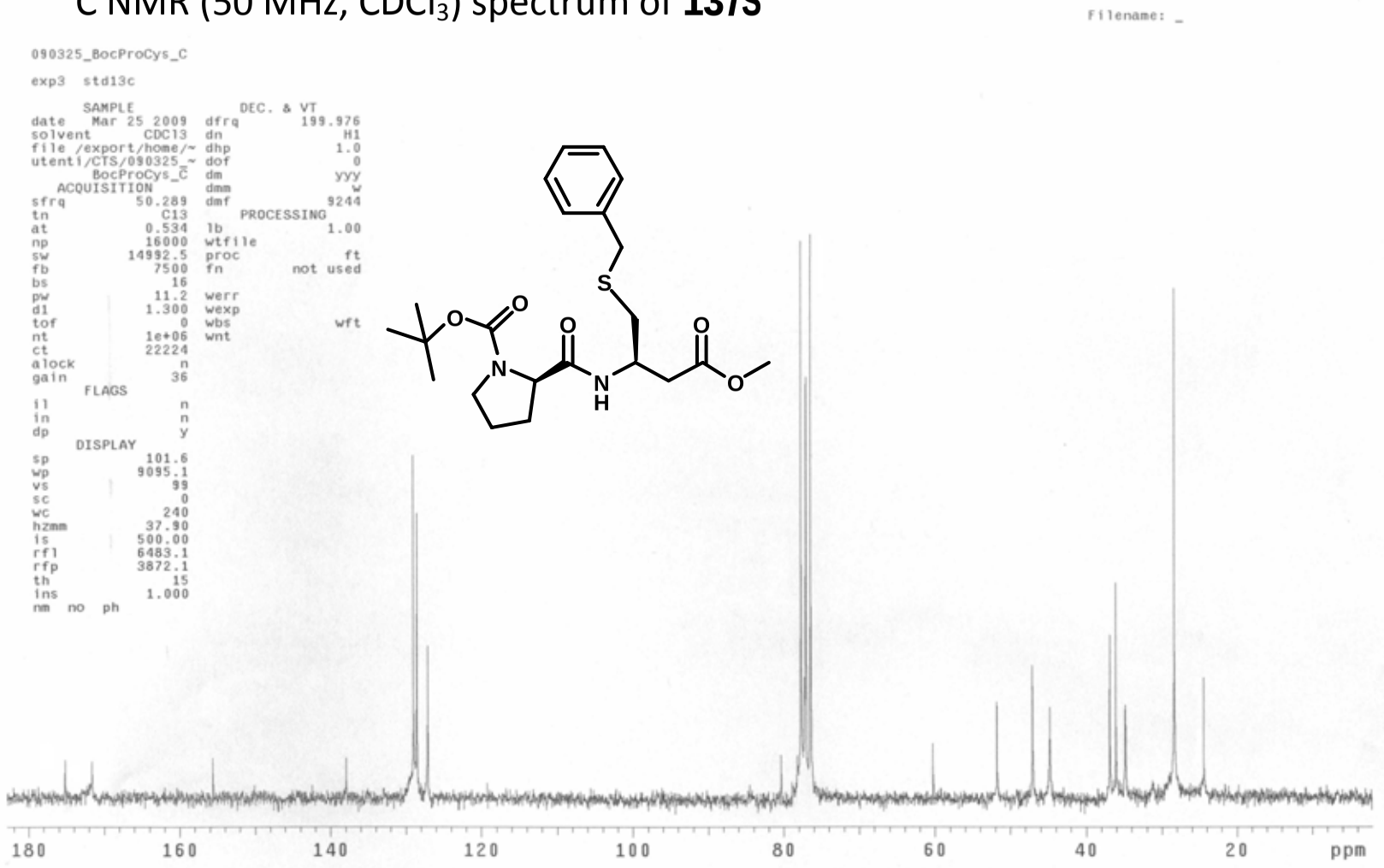
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **12/*S***



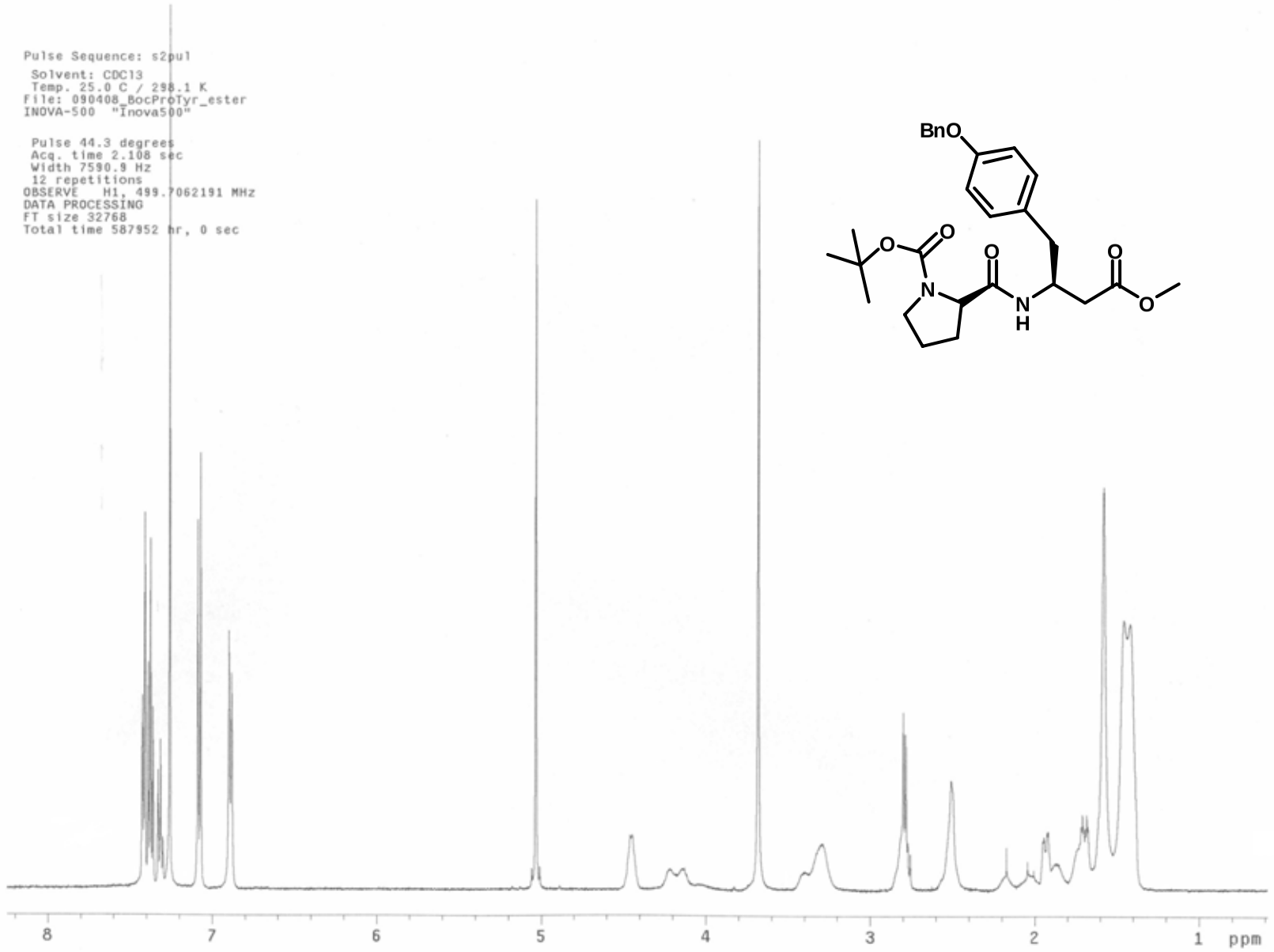
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **13/S**



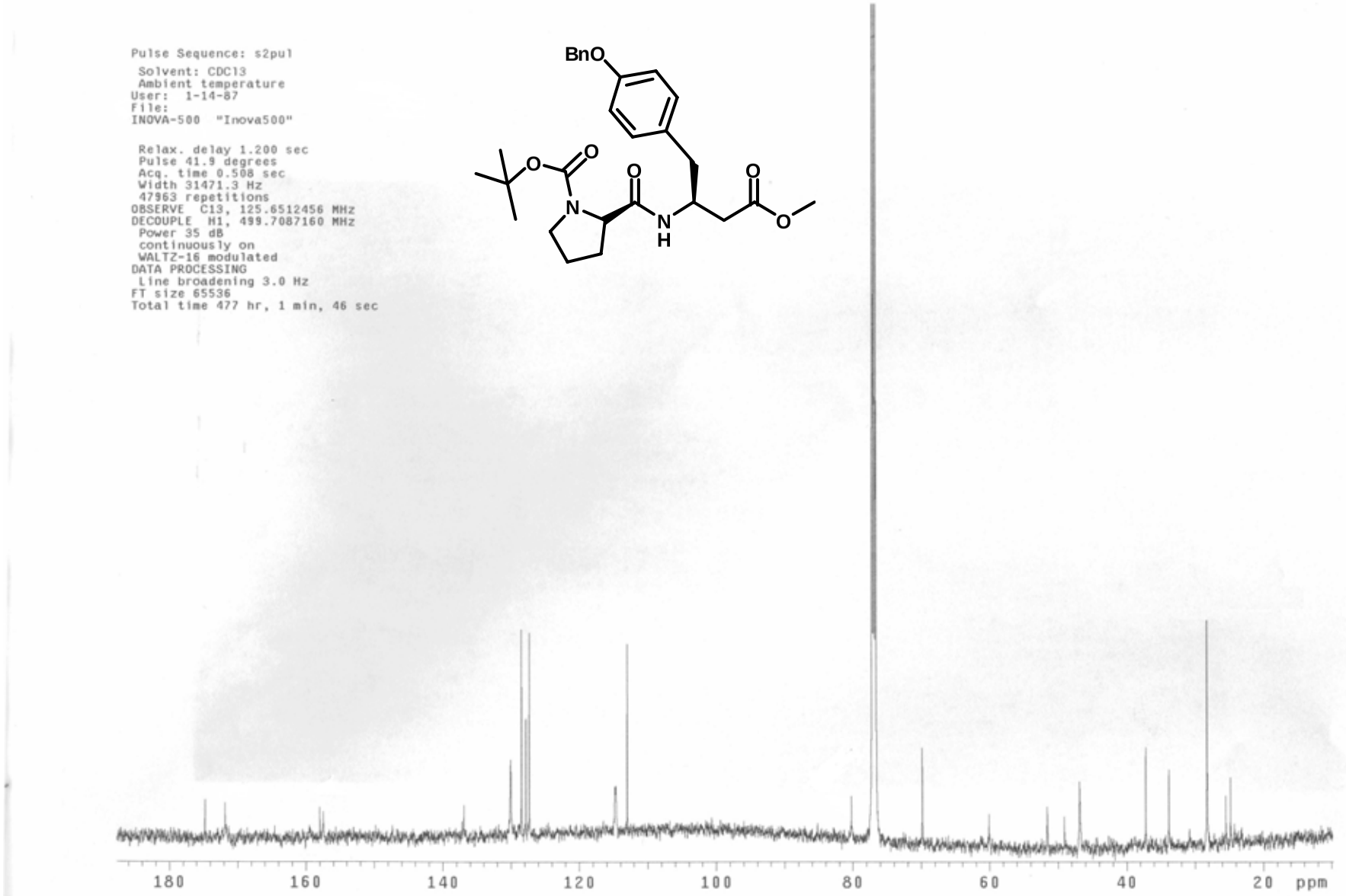
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **13/*S***



^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **14/S**

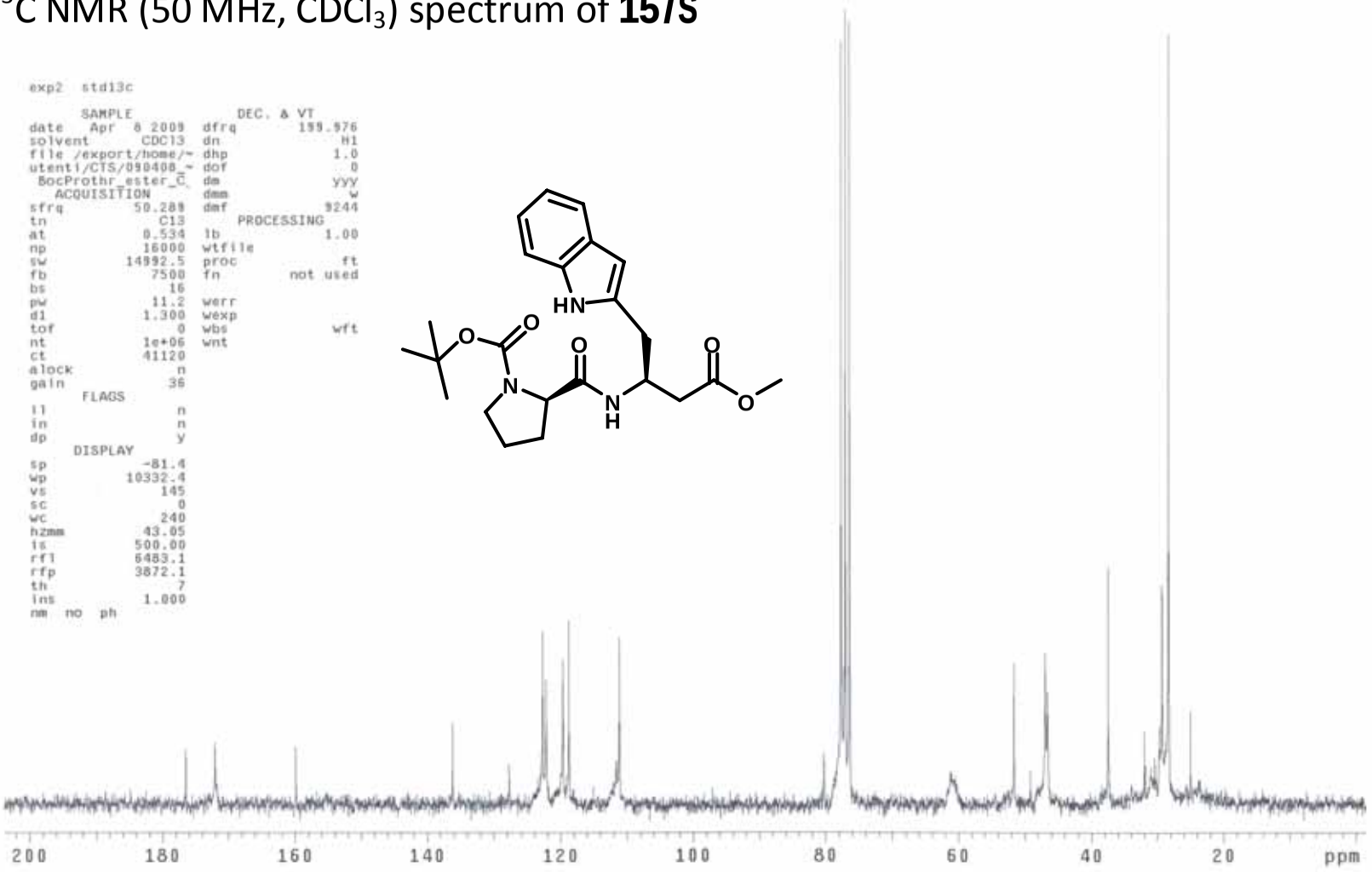


^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **14/S**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **15/S**

^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **15/S**



^{1}H NMR (500 MHz, CD_3OD) spectrum of **1a**

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 Solvent: CD3OD
 Temp. 25.0 C / 298.1 K
INOVA-500  "Inova500"

 Pulse 44.3 degrees
 Acq. time 1.784 sec
 Width 5871.6 Hz
 16 repetitions
OBSERVE    H1, 499.7081908 MHz
DATA PROCESSING
FT size 32768
Total time 2 min, 59 sec
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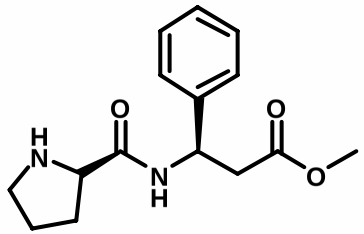
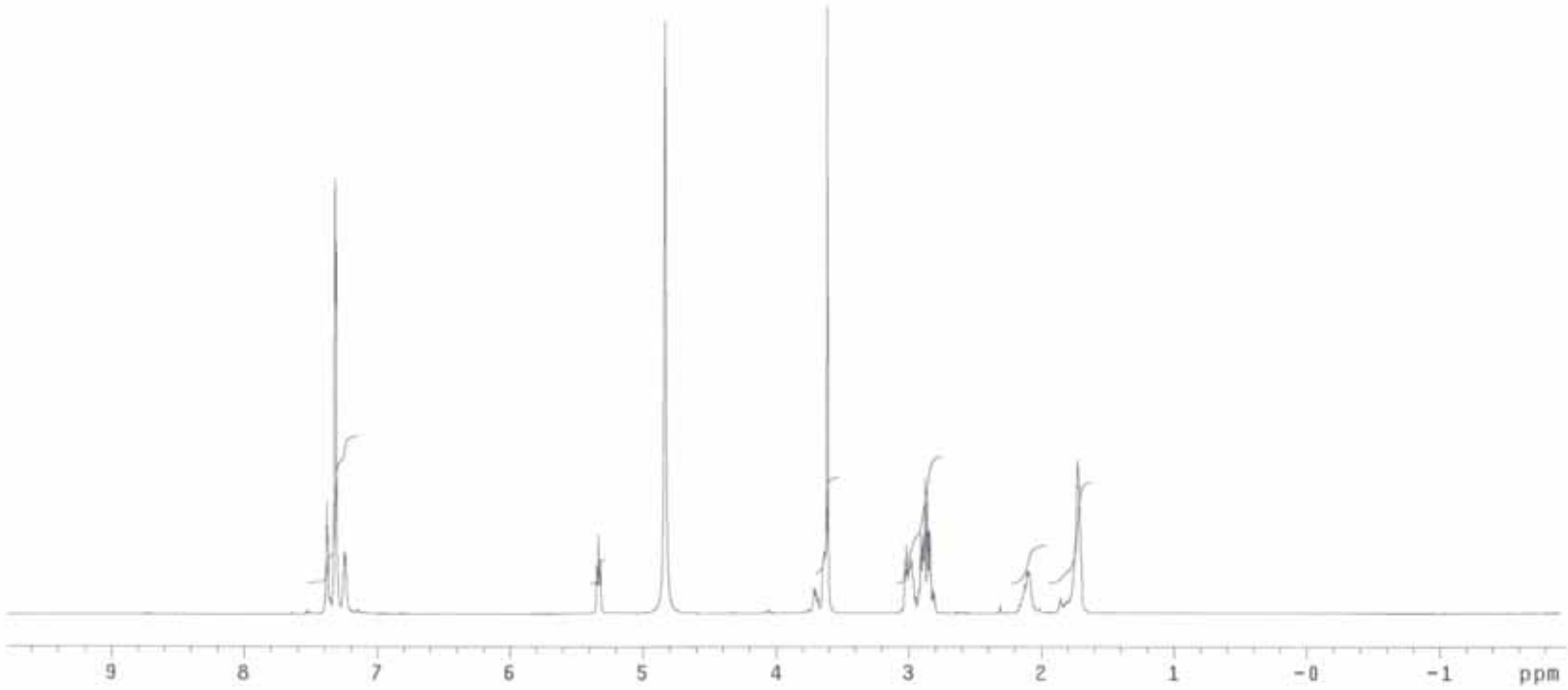
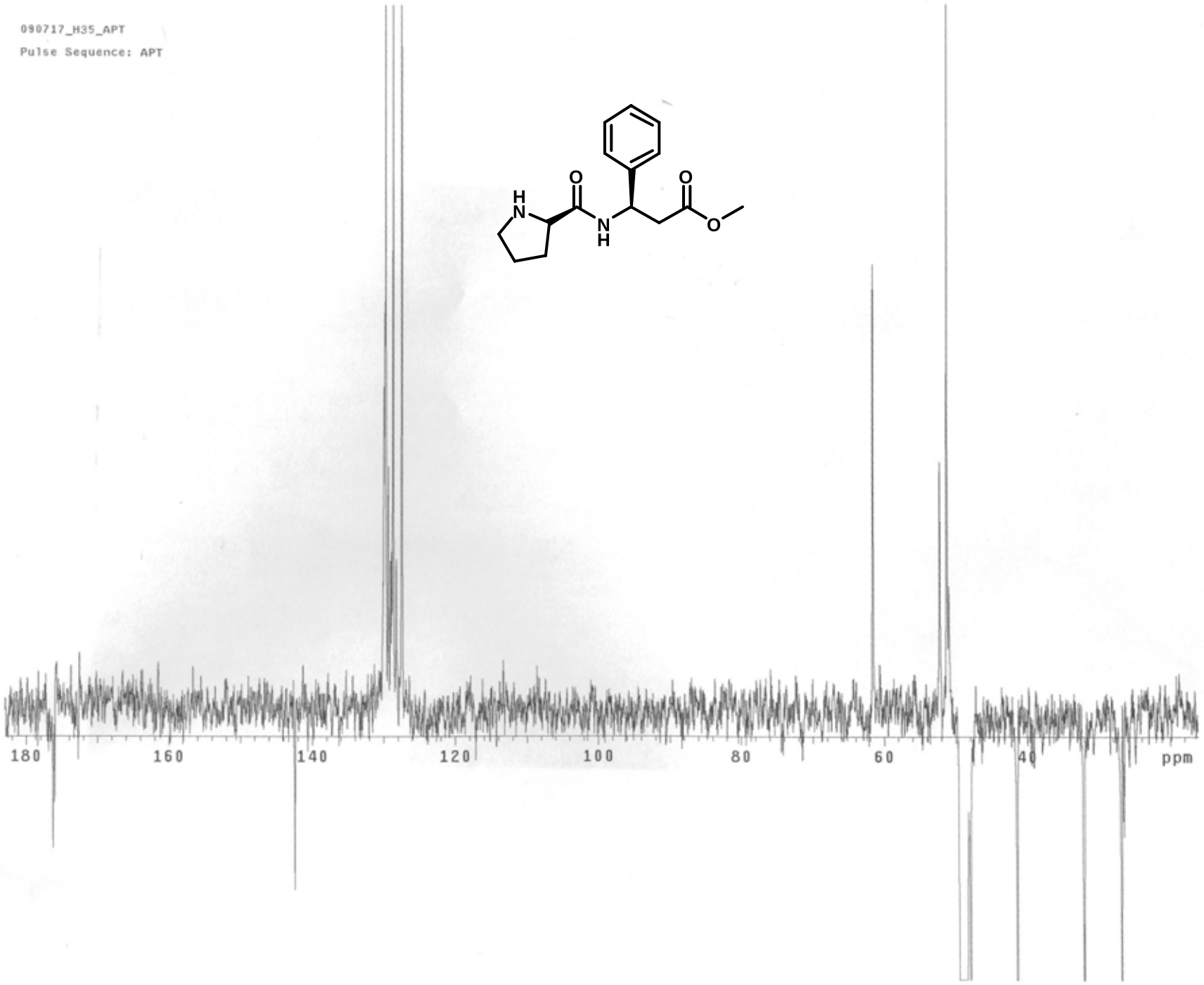
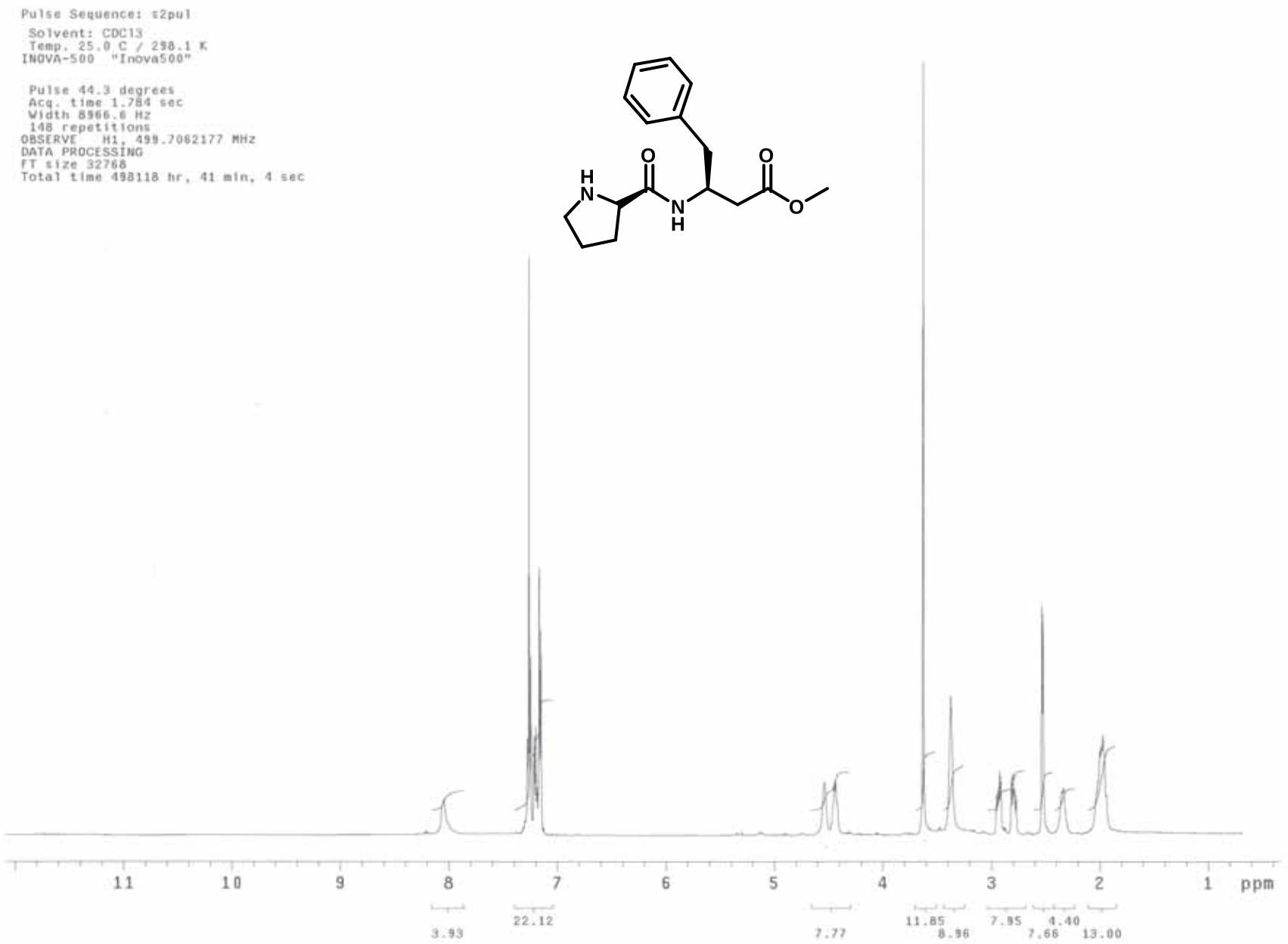




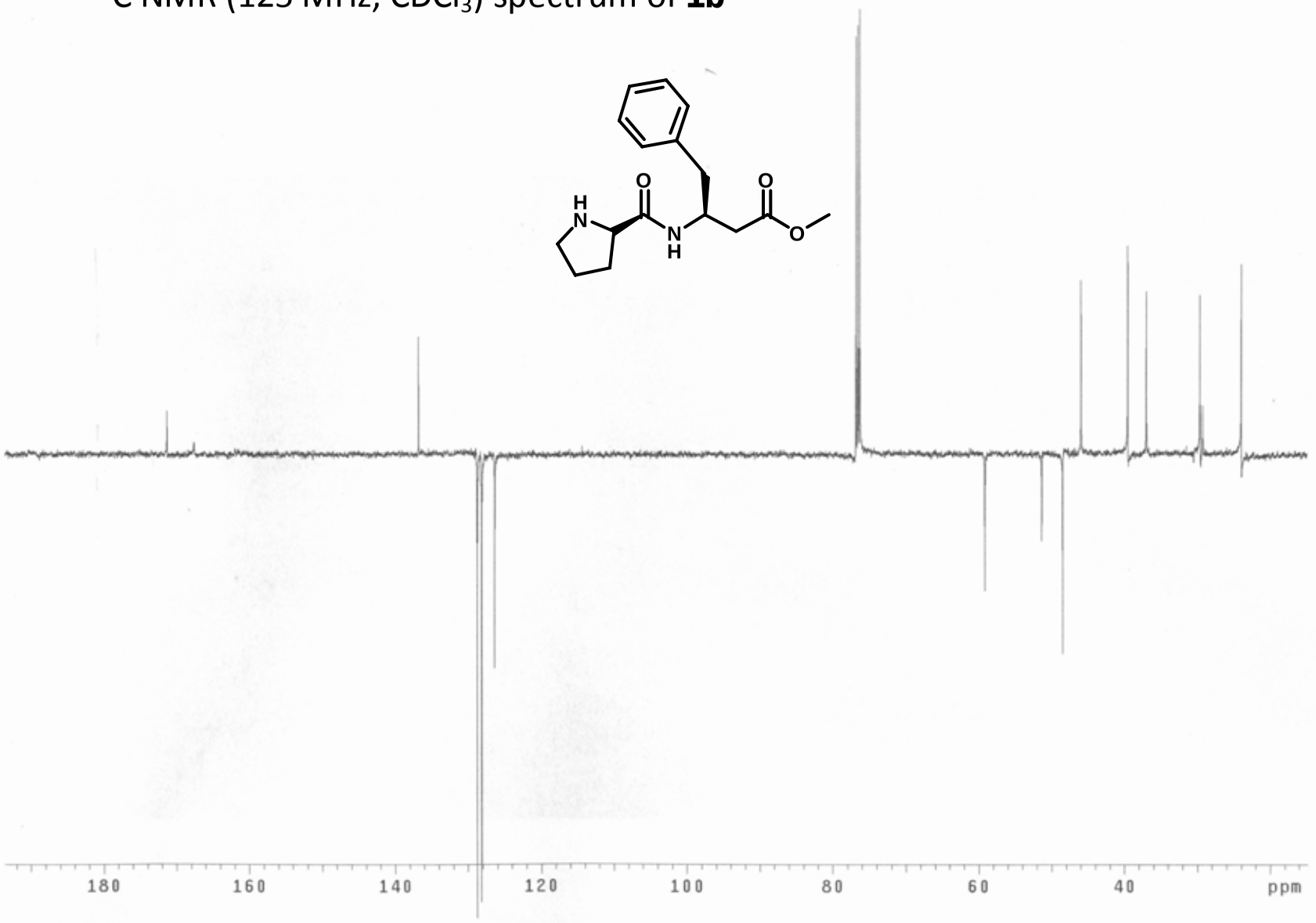
^{13}C NMR (50 MHz, CD_3OD) spectrum of **1a**



^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **1b**

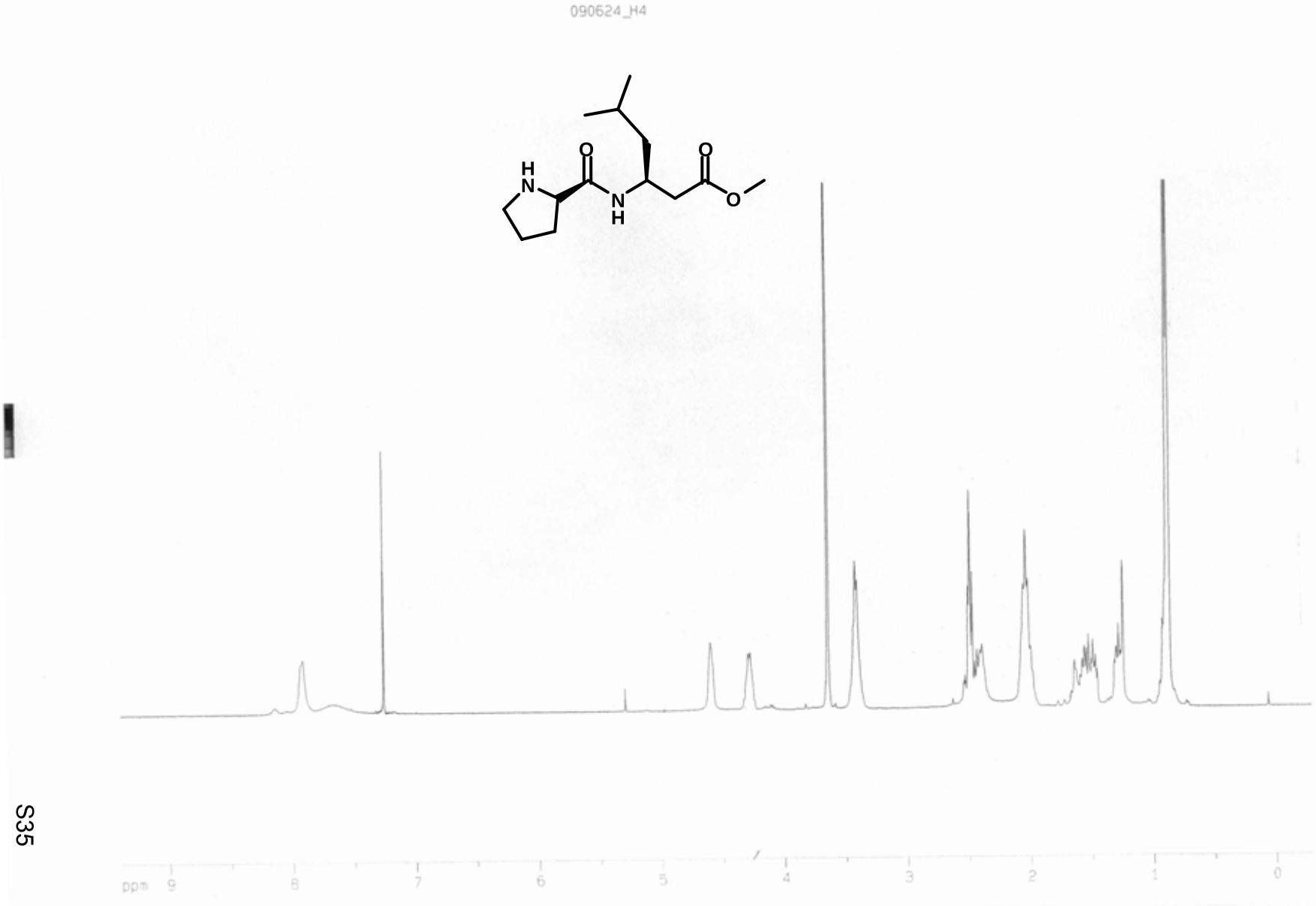


^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **1b**

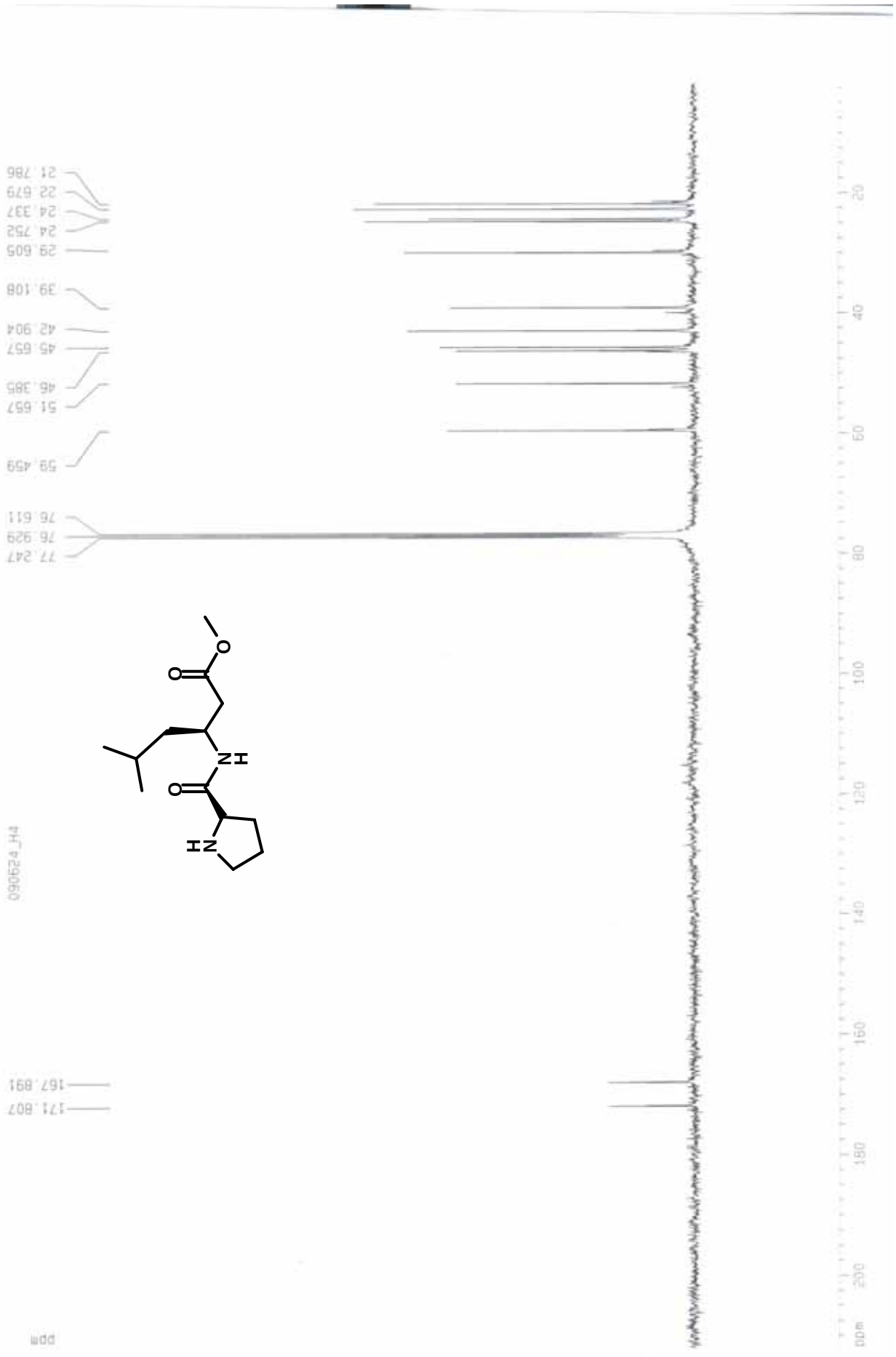


PULSE SEQUENCE: APT Relax. delay 1.200 sec 1st pulse 90.0 degrees 2nd pulse 138.1 degrees Acq. time 0.254 sec Width 31471.3 Hz 1000000000 repetitions	OBSERVE C13, 125.6512831 DECOUPLE H1, 499.7087160 Power 35 dB on during acquisition WALTZ-16 modulated	DATA PROCESSING Line broadening 3.0 Hz FT size 65536 Total time 403944.4 hours			090514_H18_APT Pulse Sequence: APT Solvent: CDCl3 Temp. 25.0 C / 298.1 K User: 1-14-87 File: 090414_H18_APT INOVA-500 "Inova500"

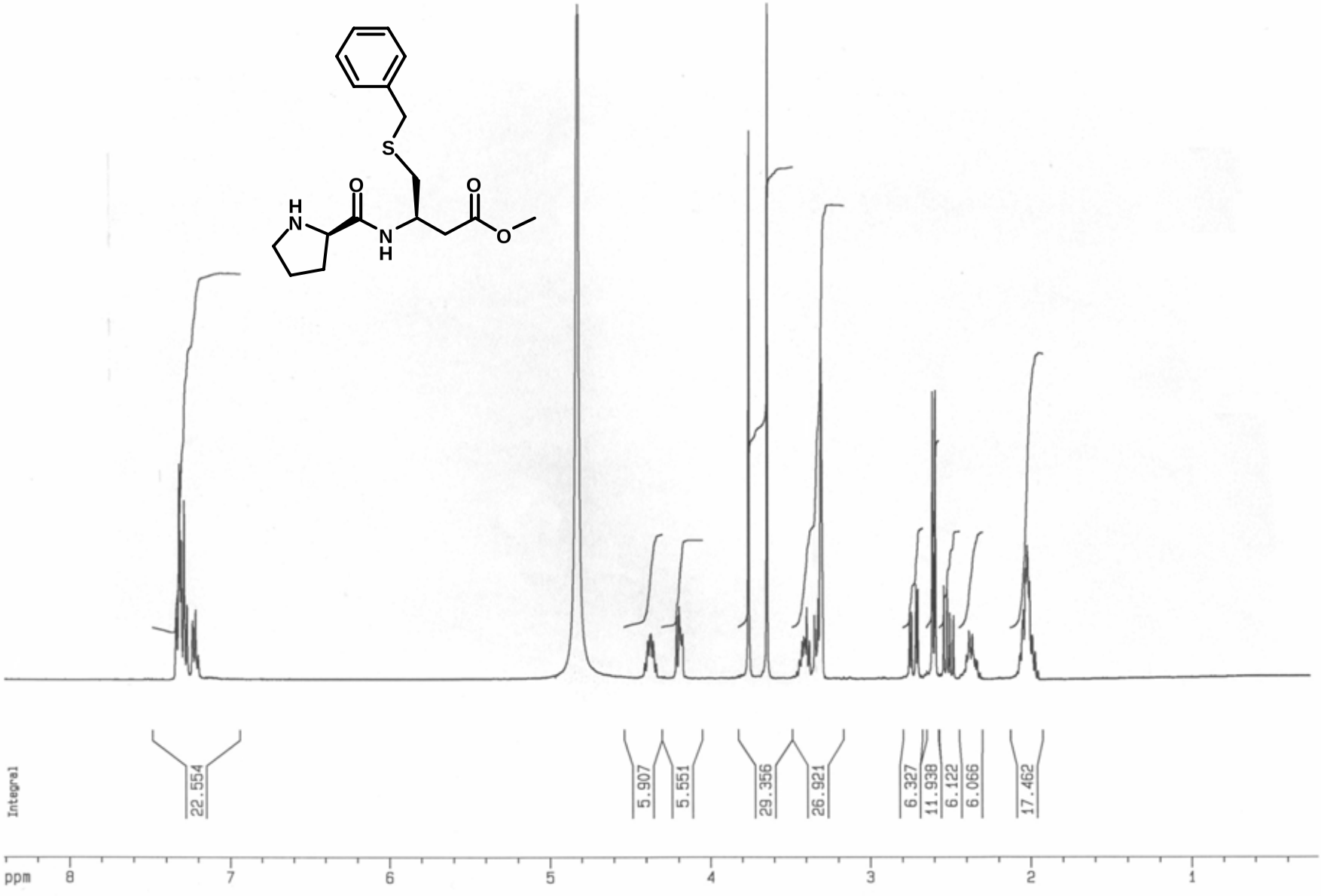
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **1c**



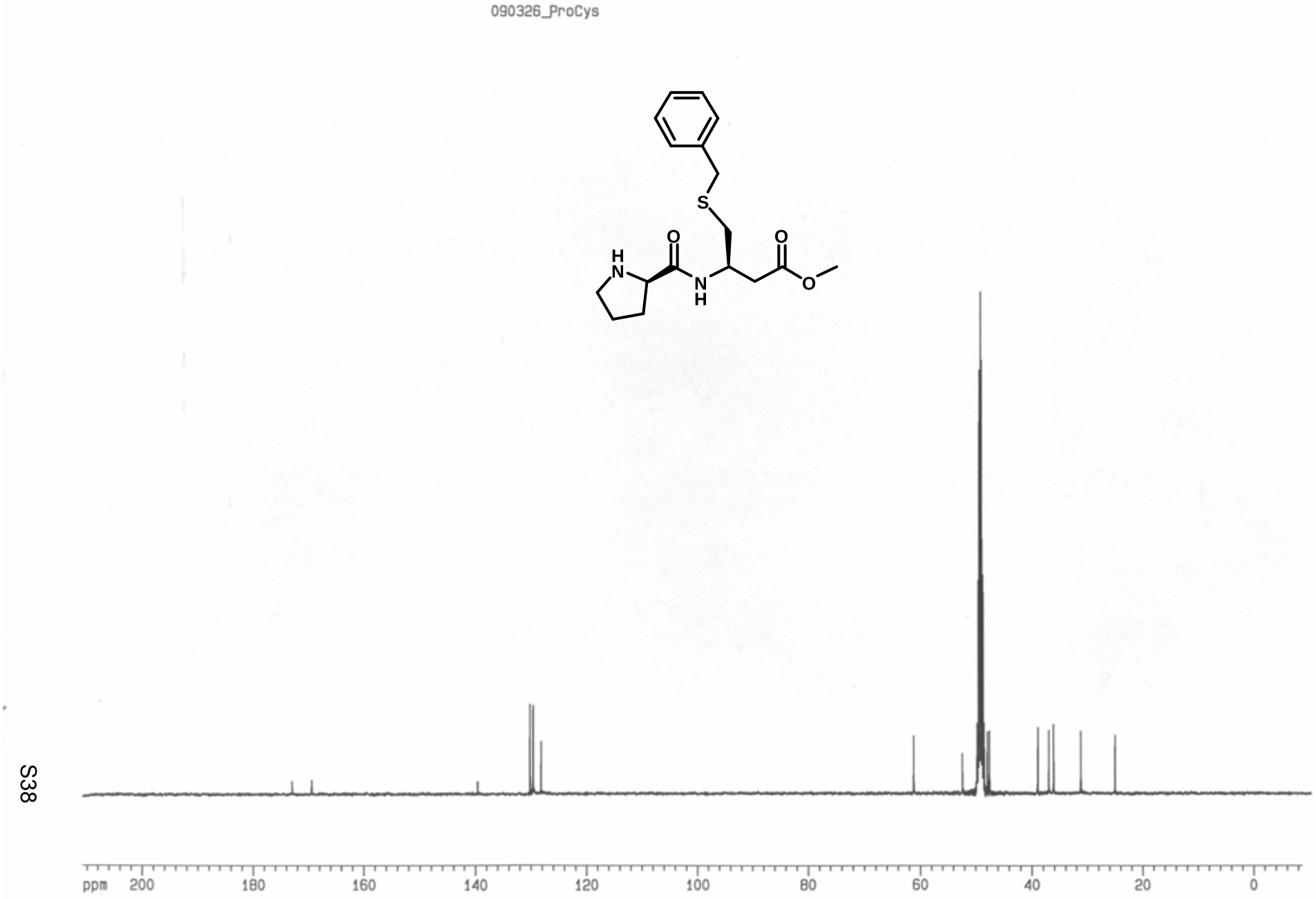
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **1c**



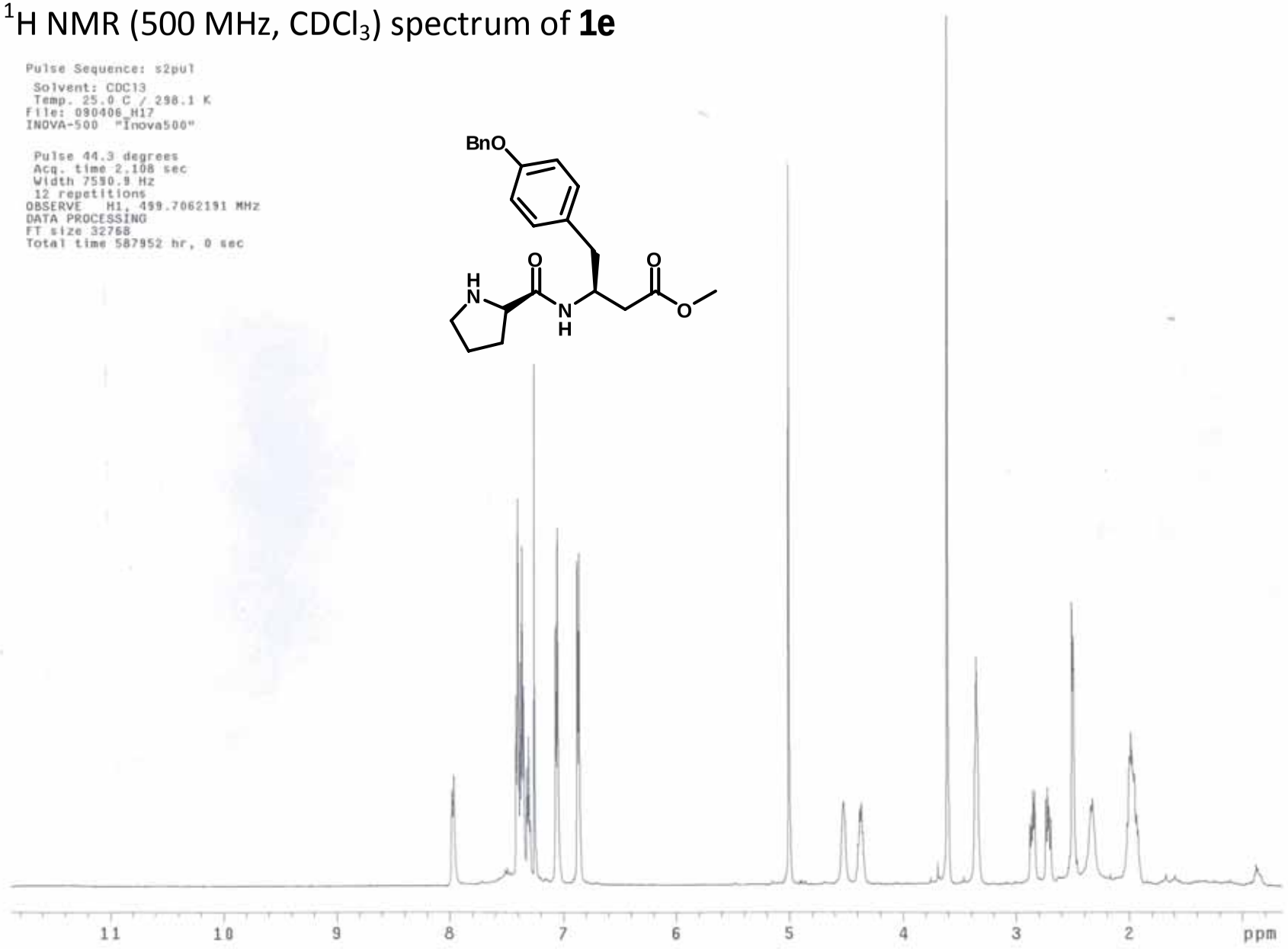
^{1}H NMR (400 MHz, CD_3OD) spectrum of **1d**



^{13}C NMR (100 MHz, CD_3OD) spectrum of **1d**



^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **1e**



^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **1e**

```
exp1  std13c

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date    Apr  6 2009
solvent       CDCl3
file /export/home/~
utenti/CTS/JEXP090~
        406_H16_C
   ACQUISITION
sfrq         50.289
tn              C13
at              0.534
np              16000
sw           14992.5
fb               7500
bs                 16
pw               11.2
d1              1.300
tof                0
nt              1e+06
ct              24517
alock               n
gain               36
      FLAGS
il                  n
in                  n
dp                  y
     DISPLAY
sp            -2611.0
wp            14992.5
vs                 51
sc                  0
wc                240
hzmm            13.77
is             500.00
rfl            6483.1
rfp            8872.1
th                 15
ins             1.000
nm  no  ph

      DEC. & VT
dfrq          199.976
dn                 H1
dhp                1.0
dof                  0
dm                 yyy
dmm                  w
dmf               9211
     PROCESSING
lb                1.00
wtfile
proc                ft
fn          not used
werr
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wbs               wft
wnt
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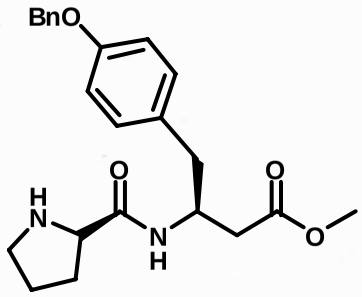
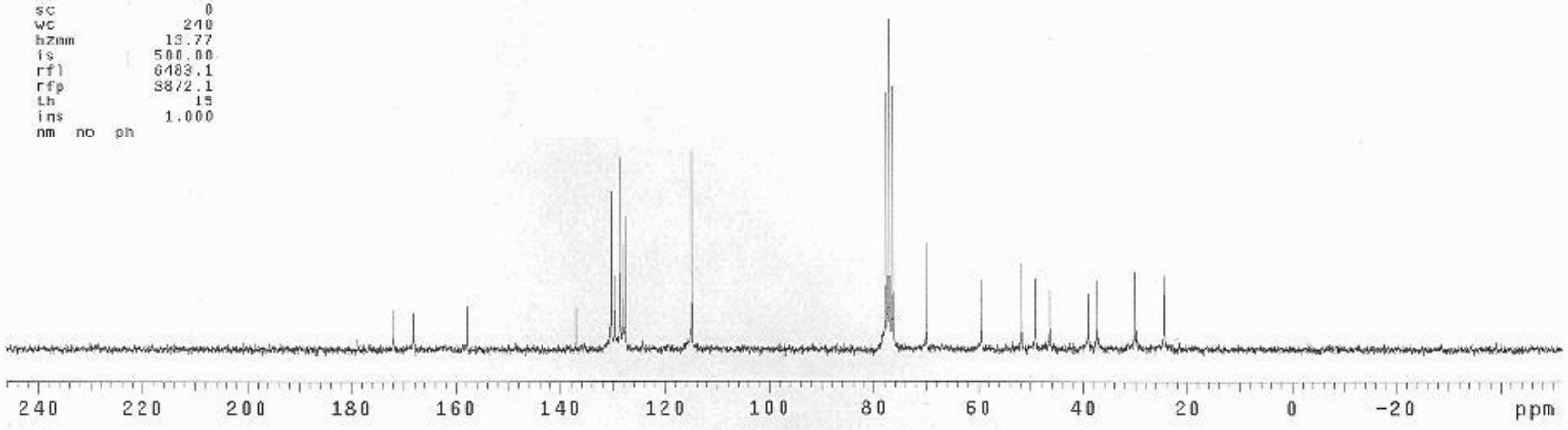
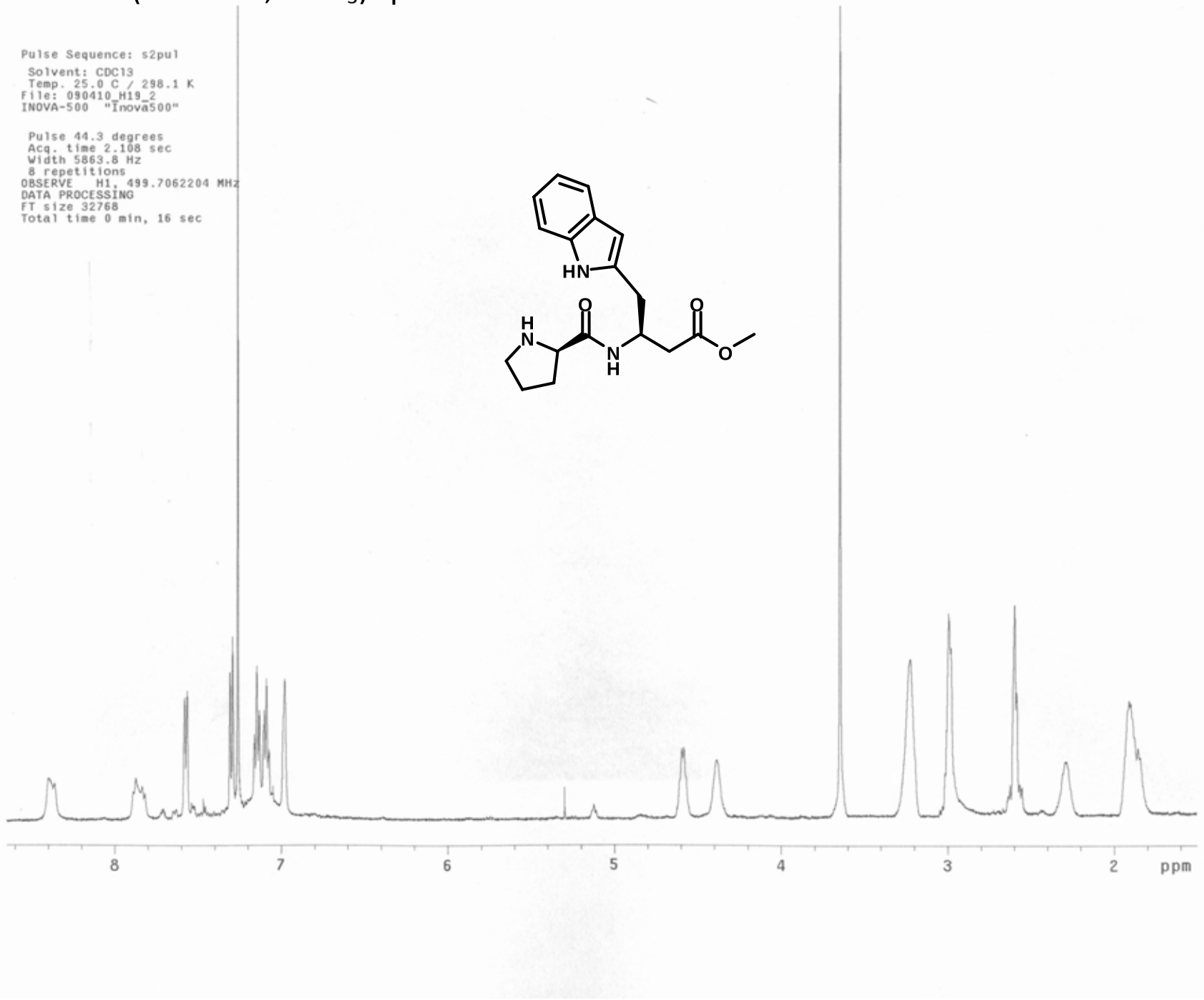
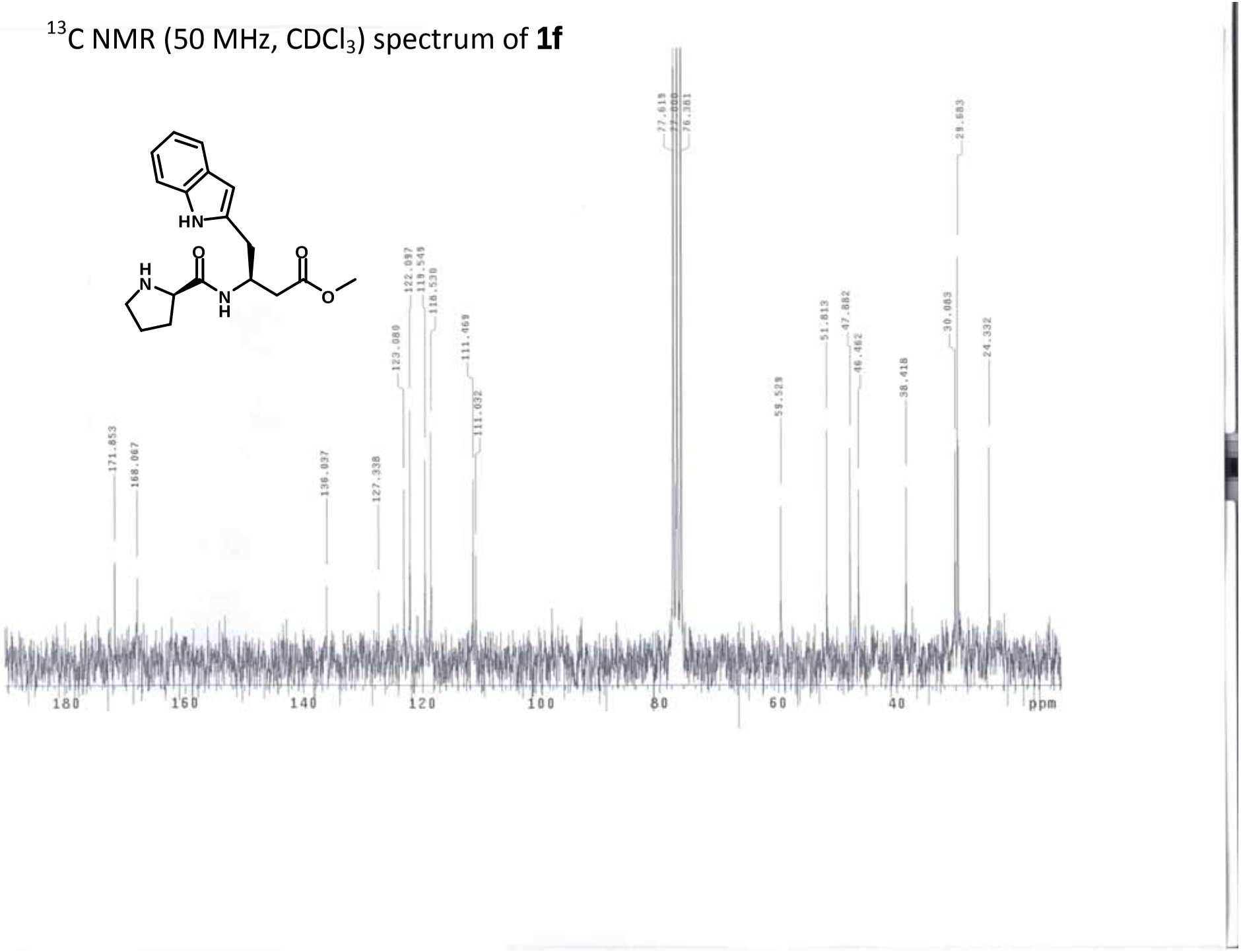




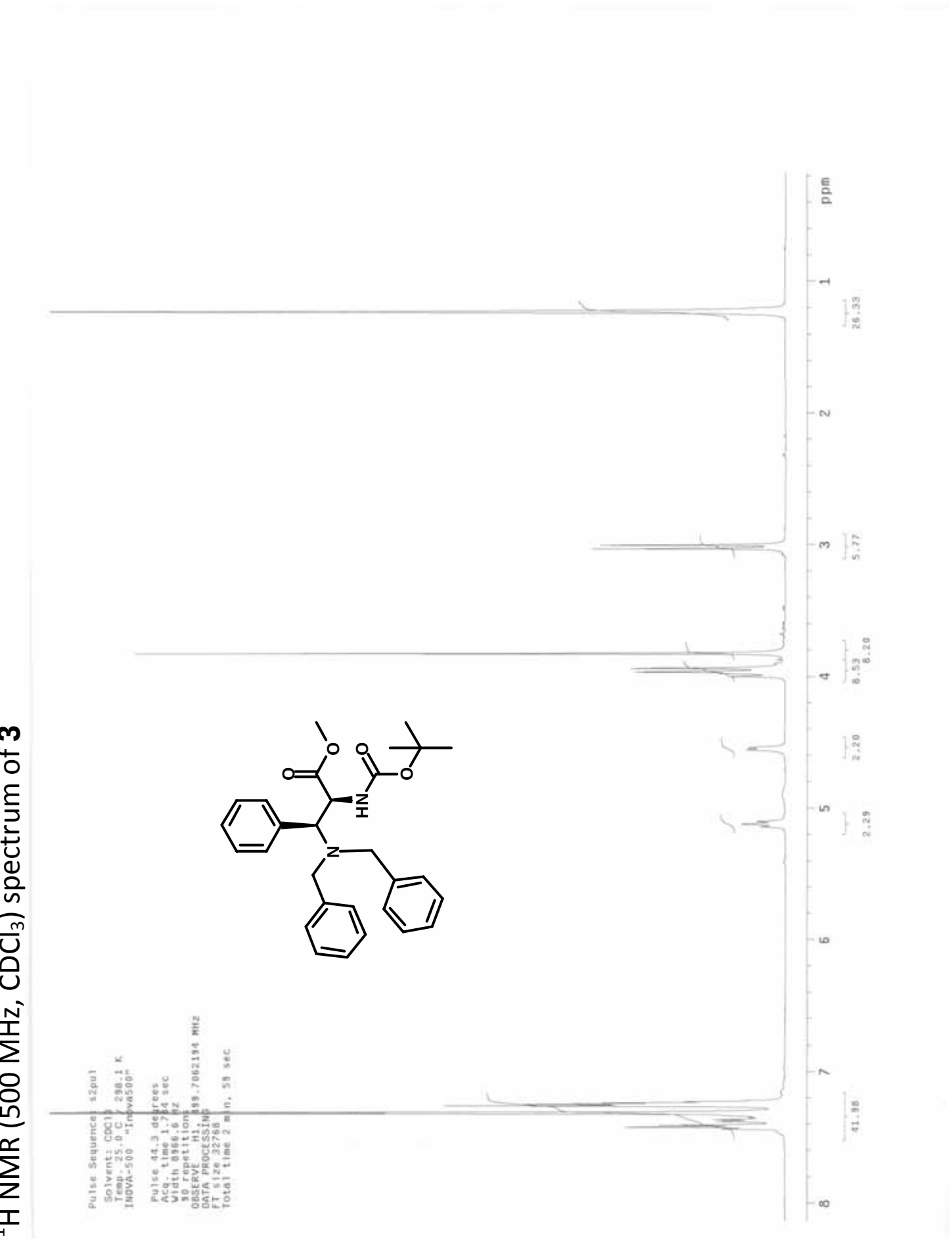
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **1f**



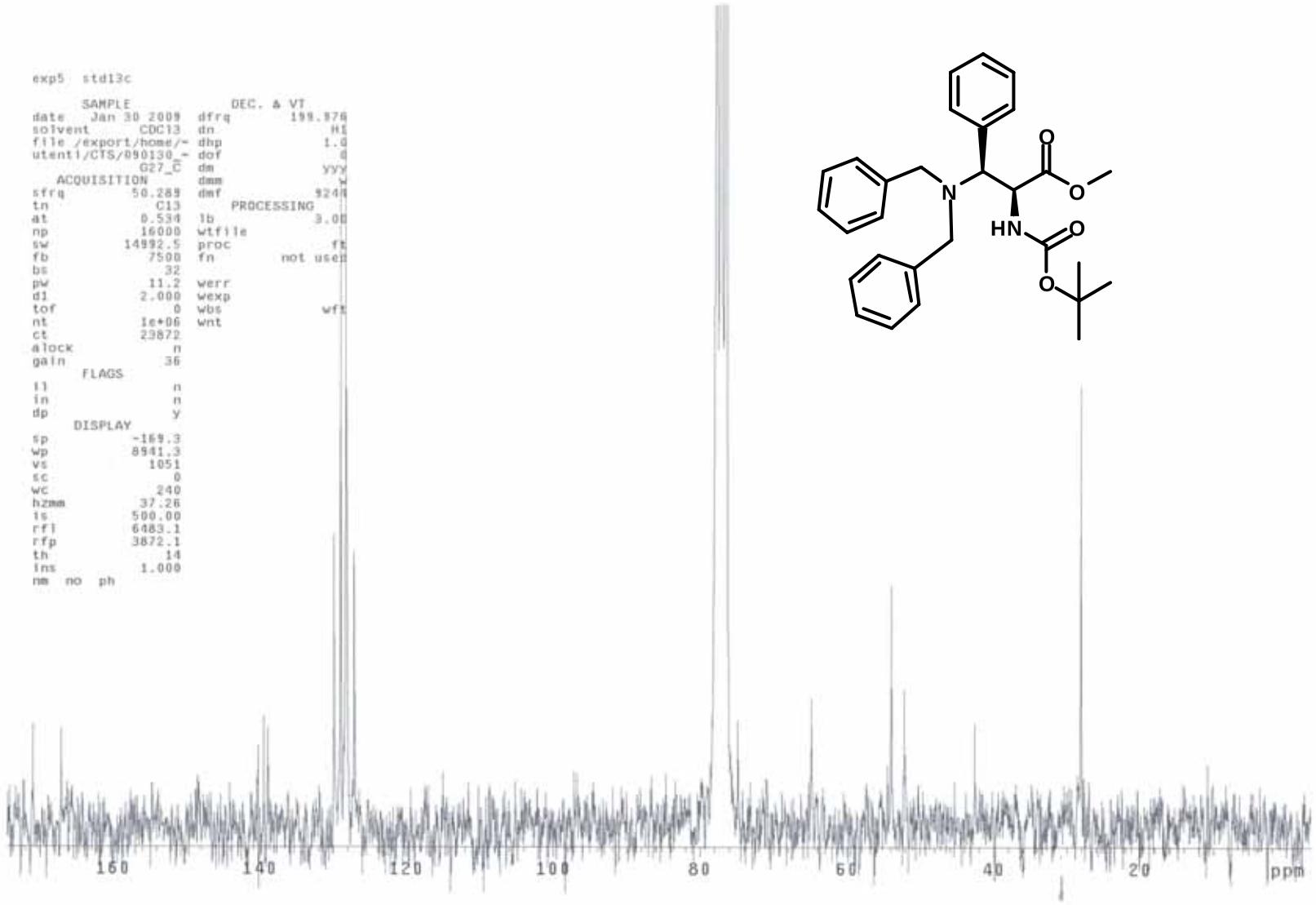
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **1f**



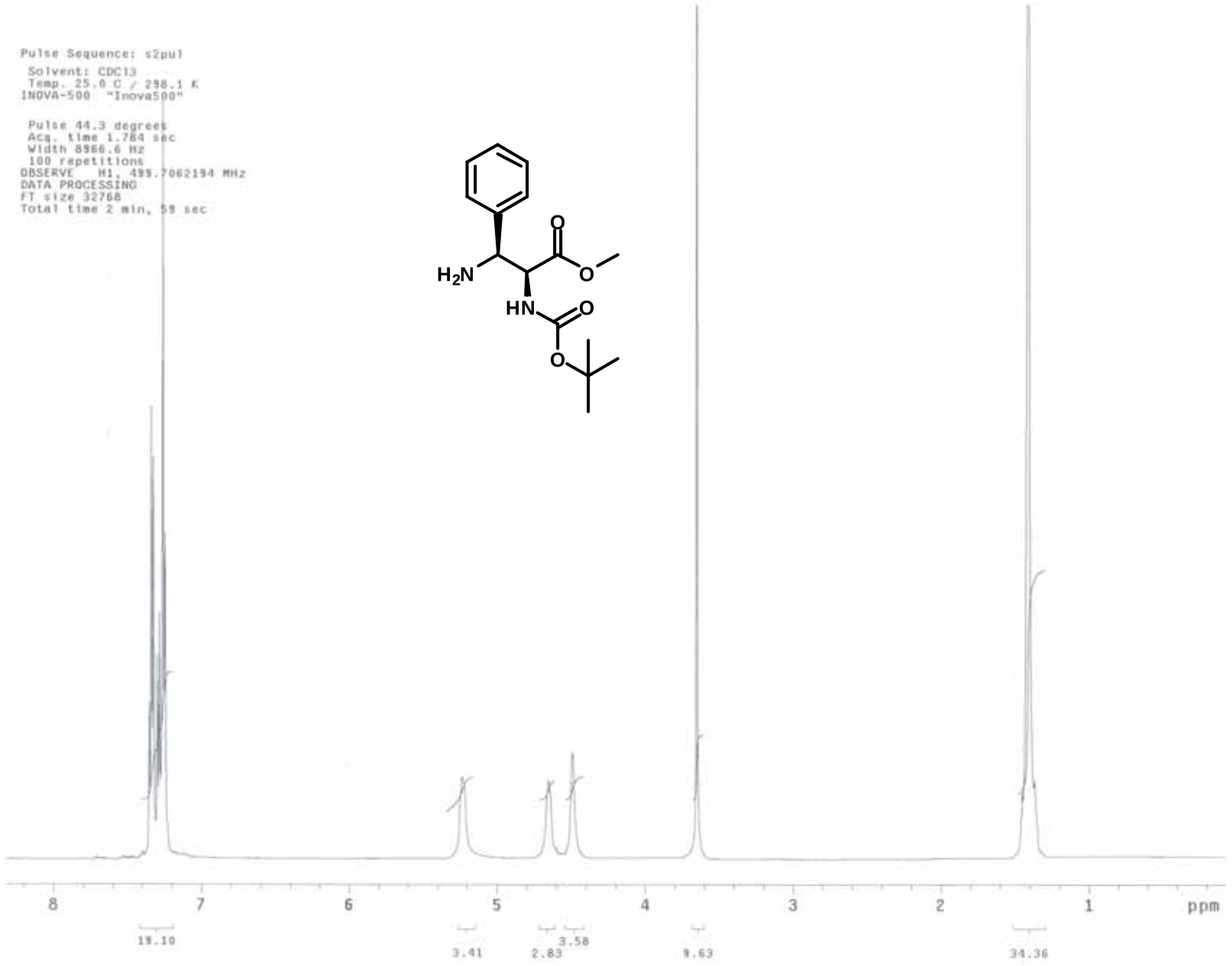
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **3**



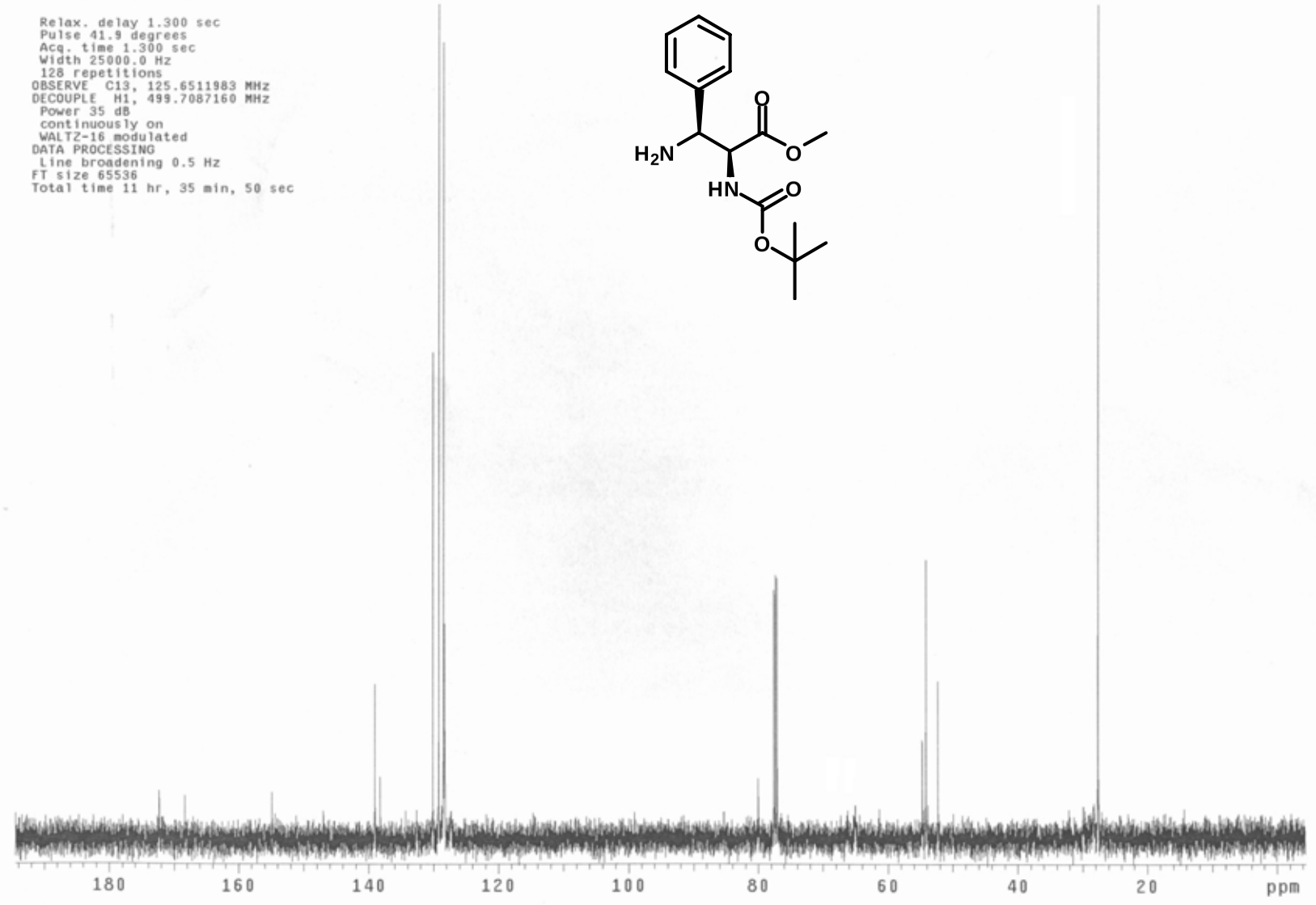
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **3**



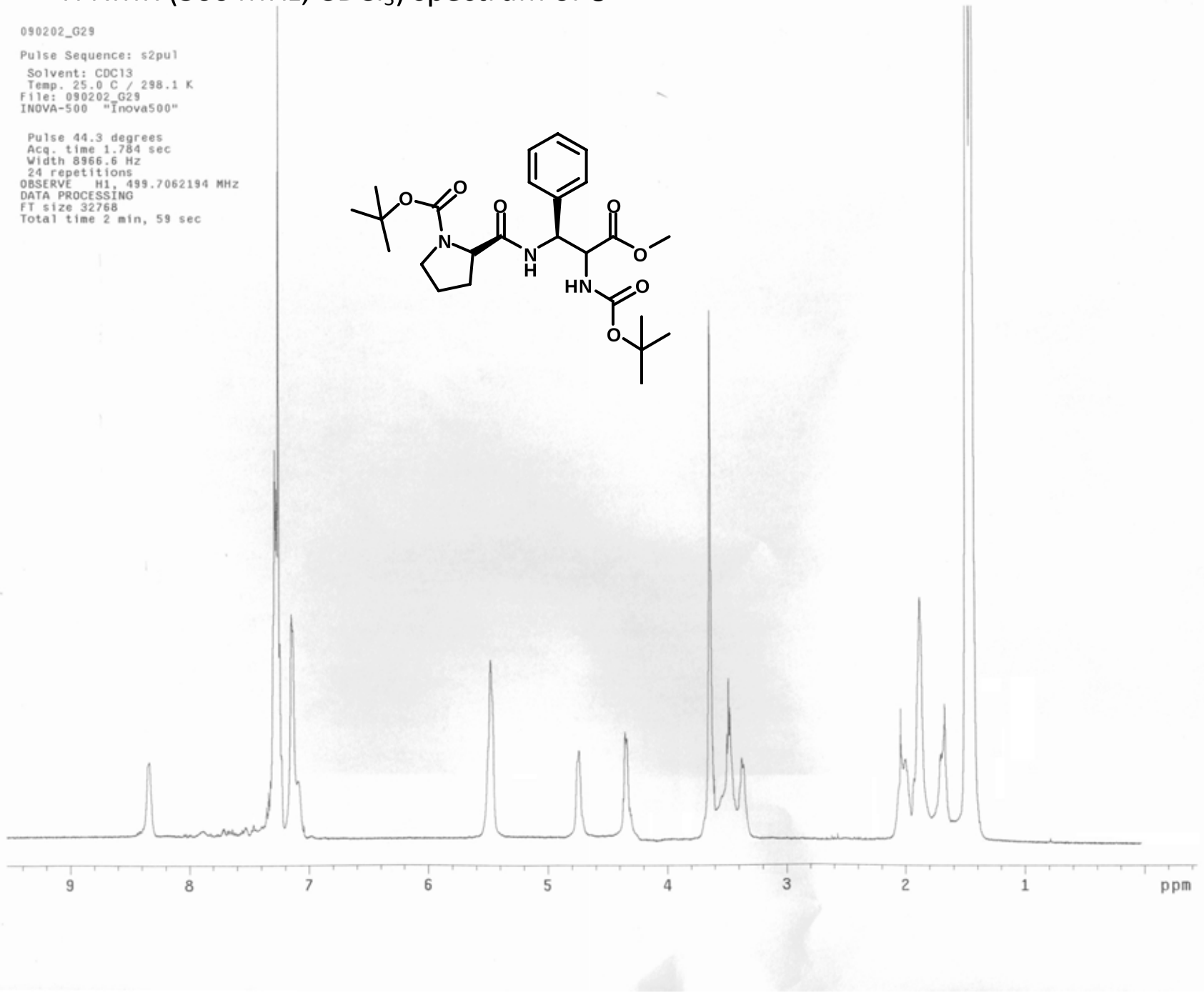
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **4**



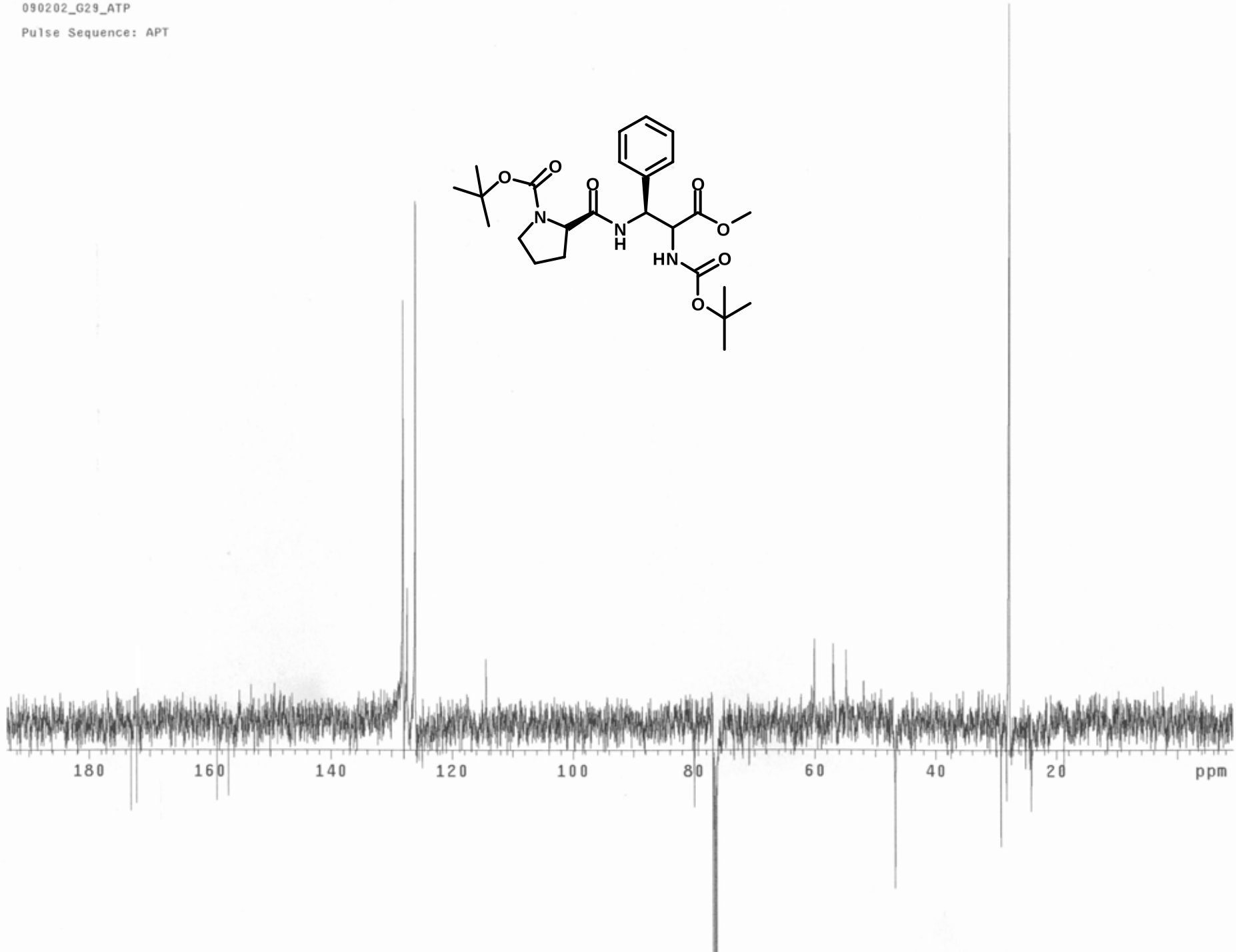
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **4**



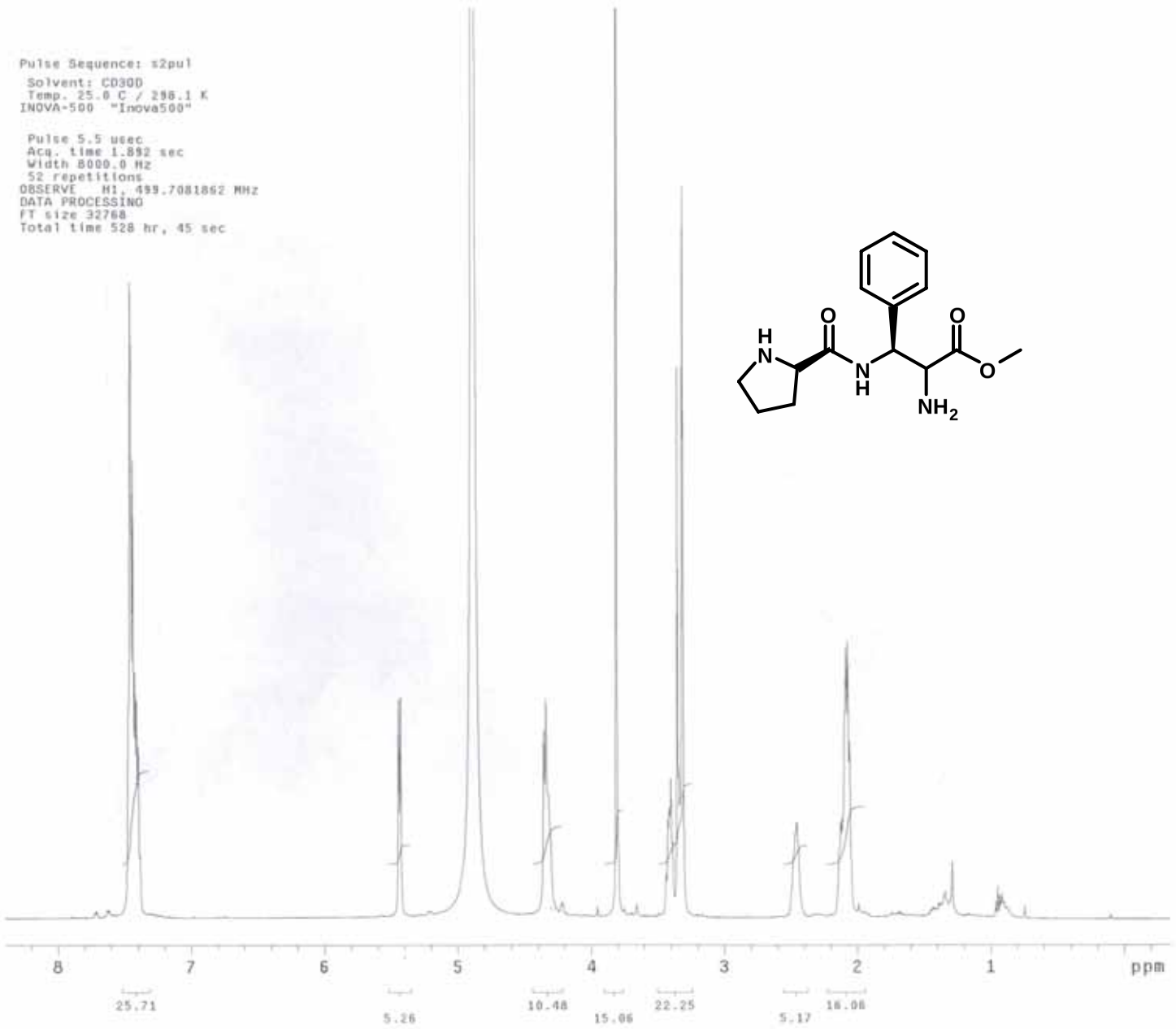
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **5**



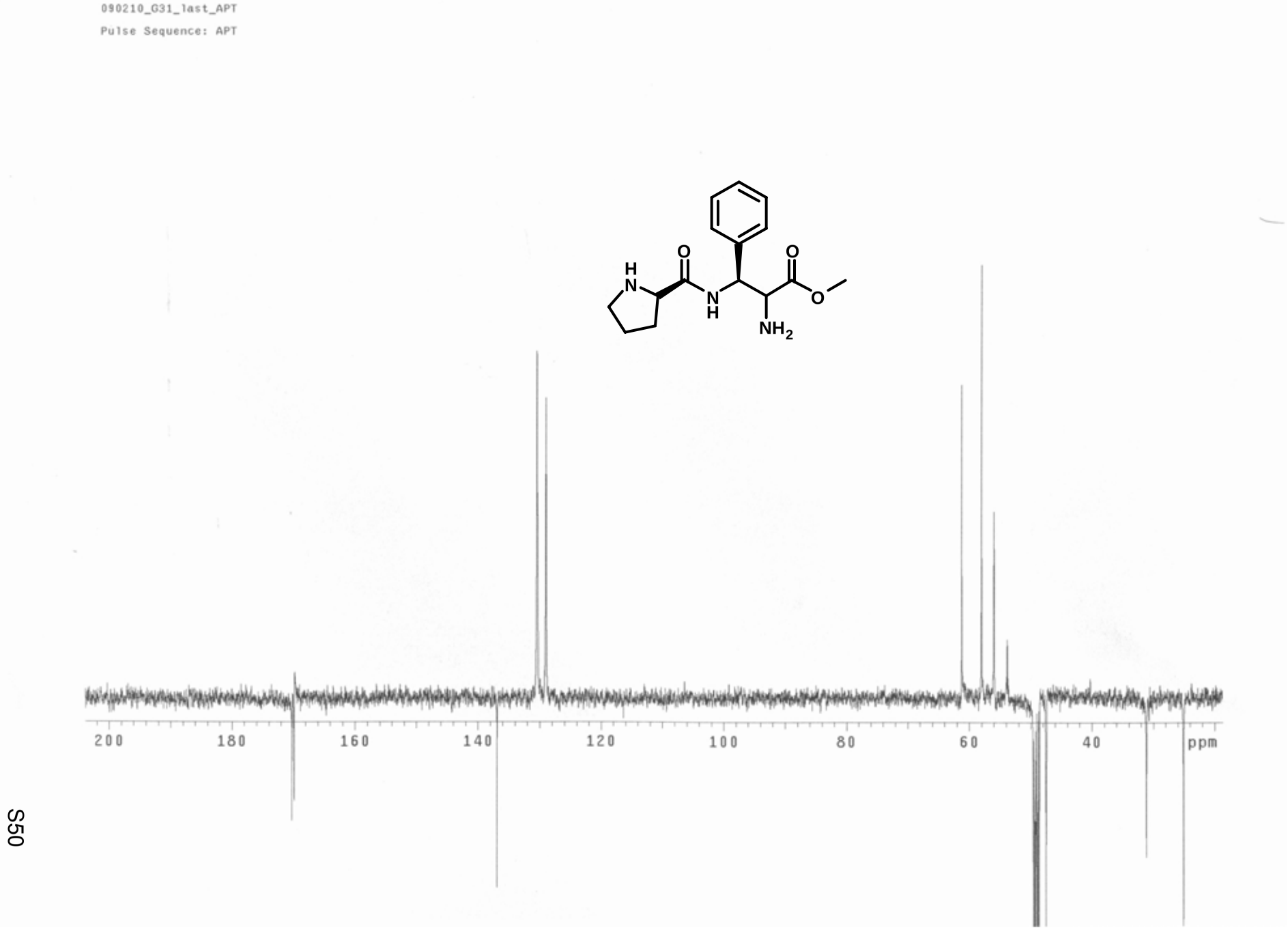
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **5**



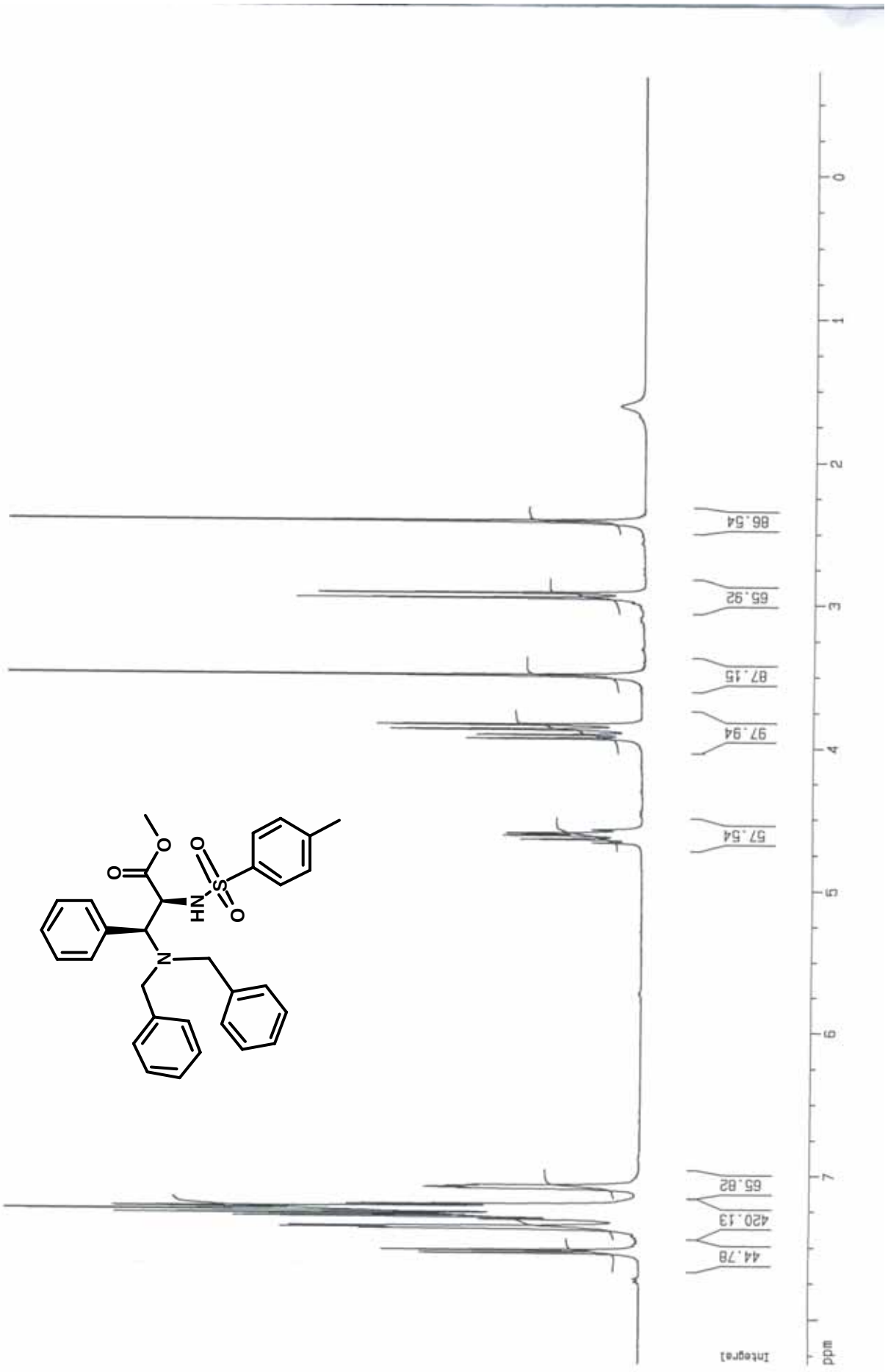
^{1}H NMR (500 MHz, CD_3OD) spectrum of **1g**



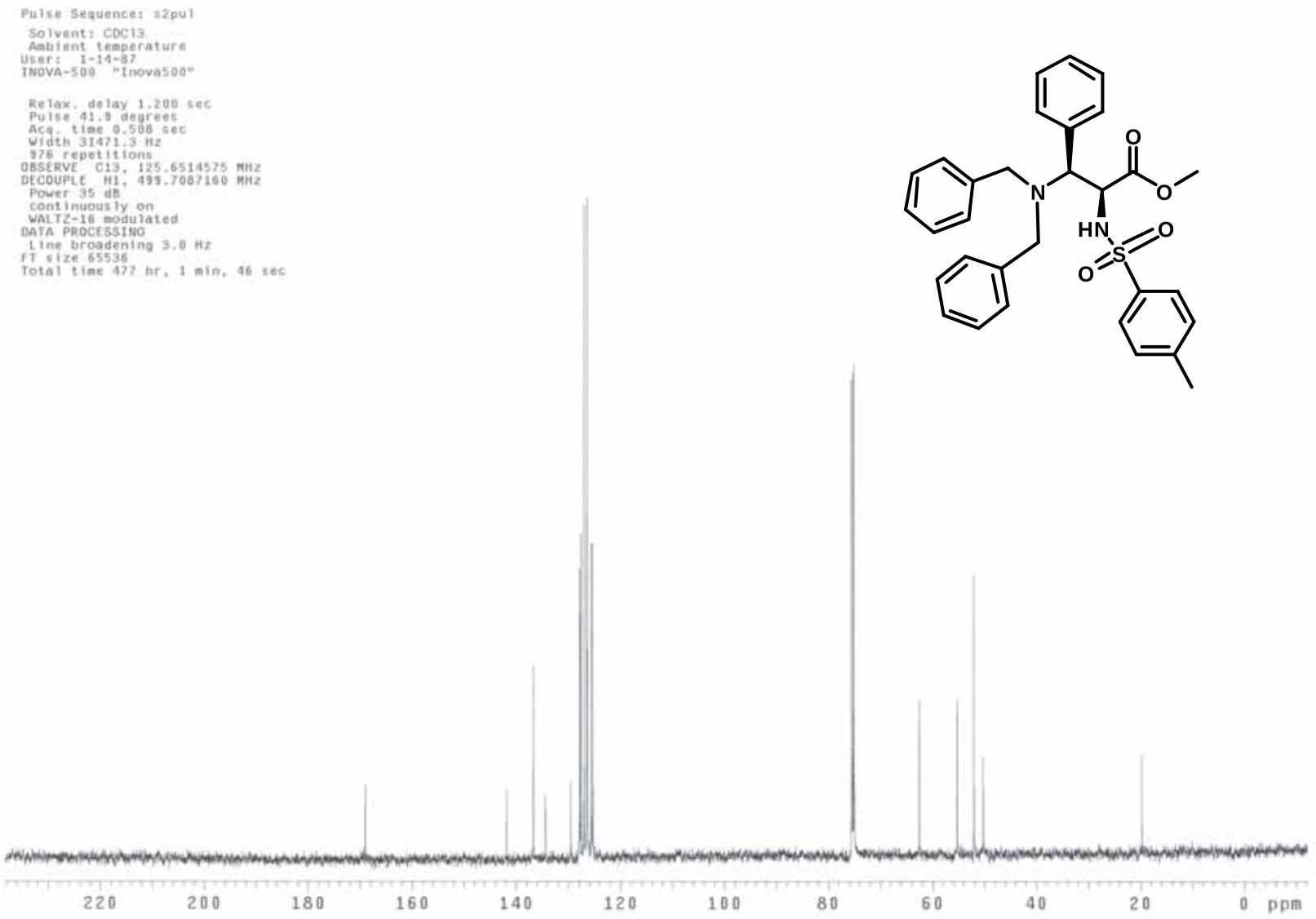
^{13}C NMR (125 MHz, CD_3OD) spectrum of **1g**



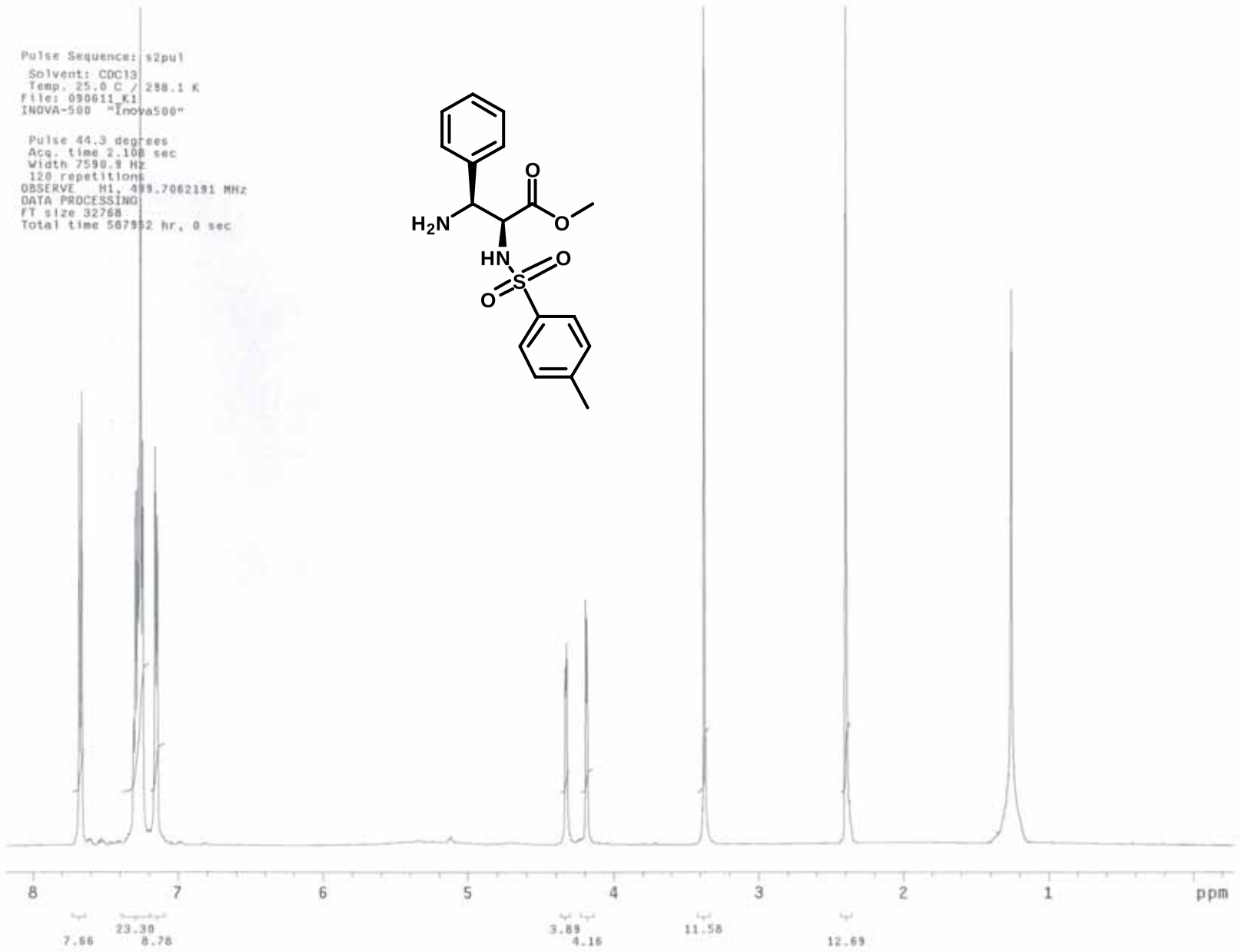
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **6**



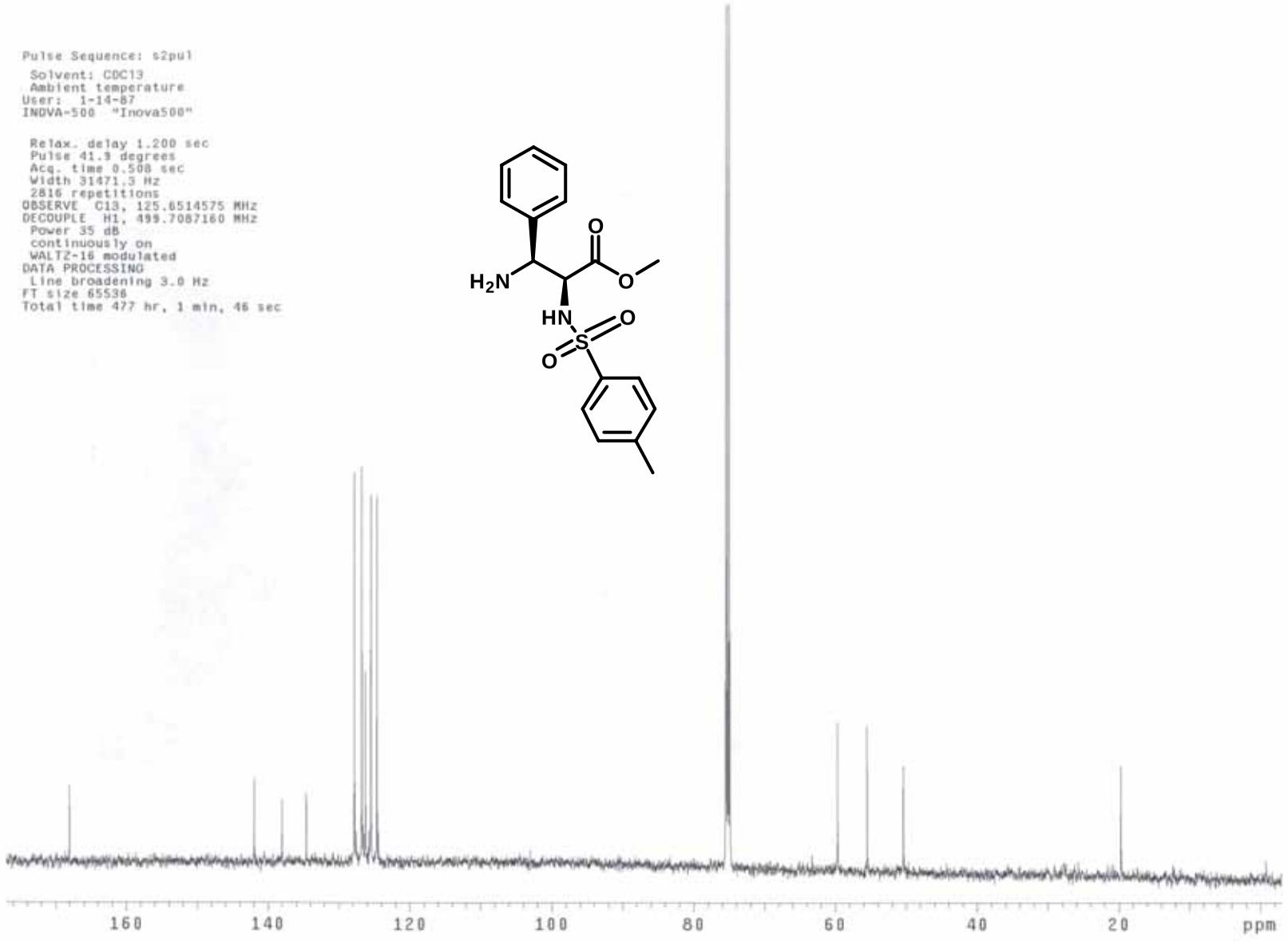
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **6**



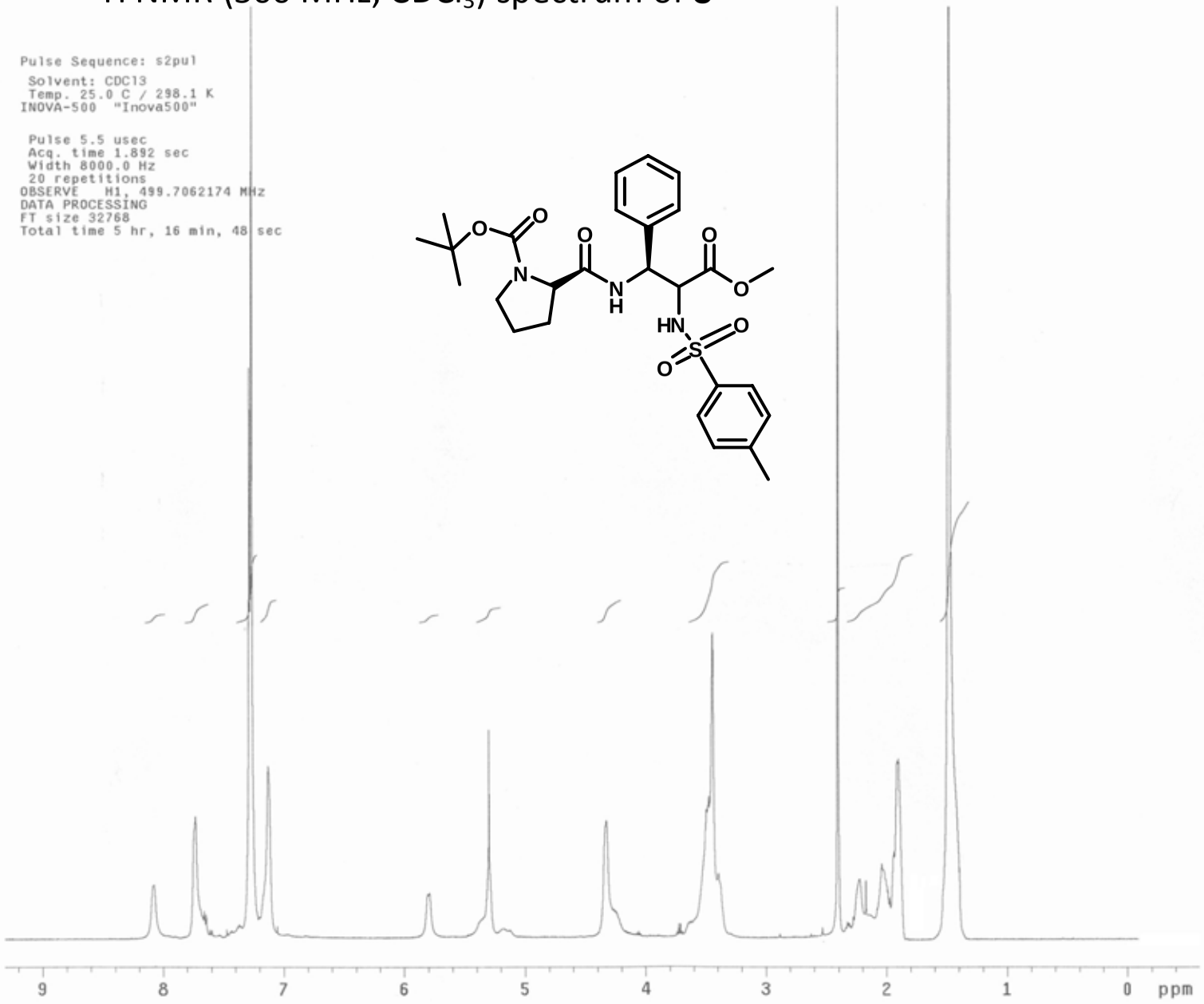
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **7**



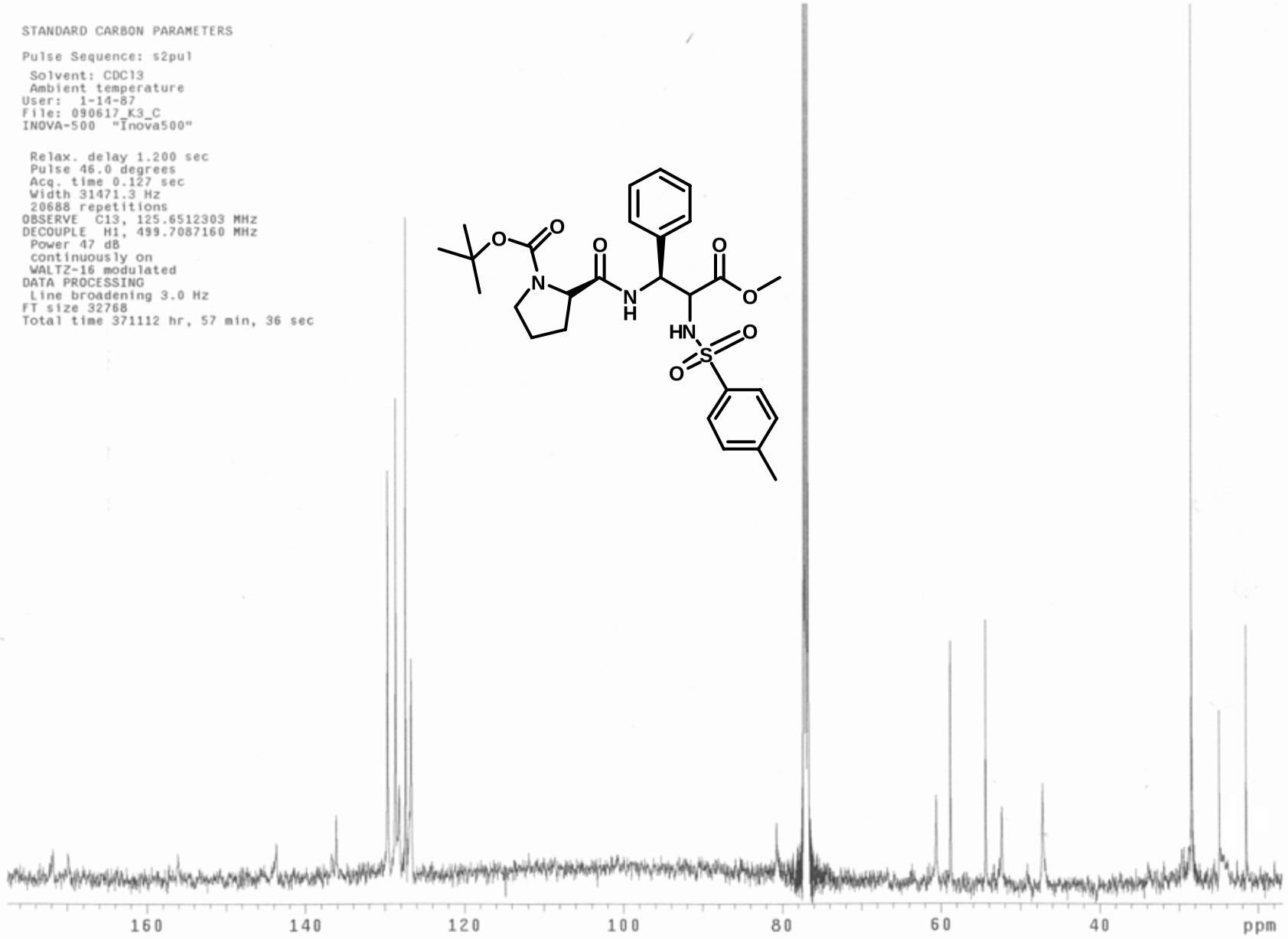
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **7**



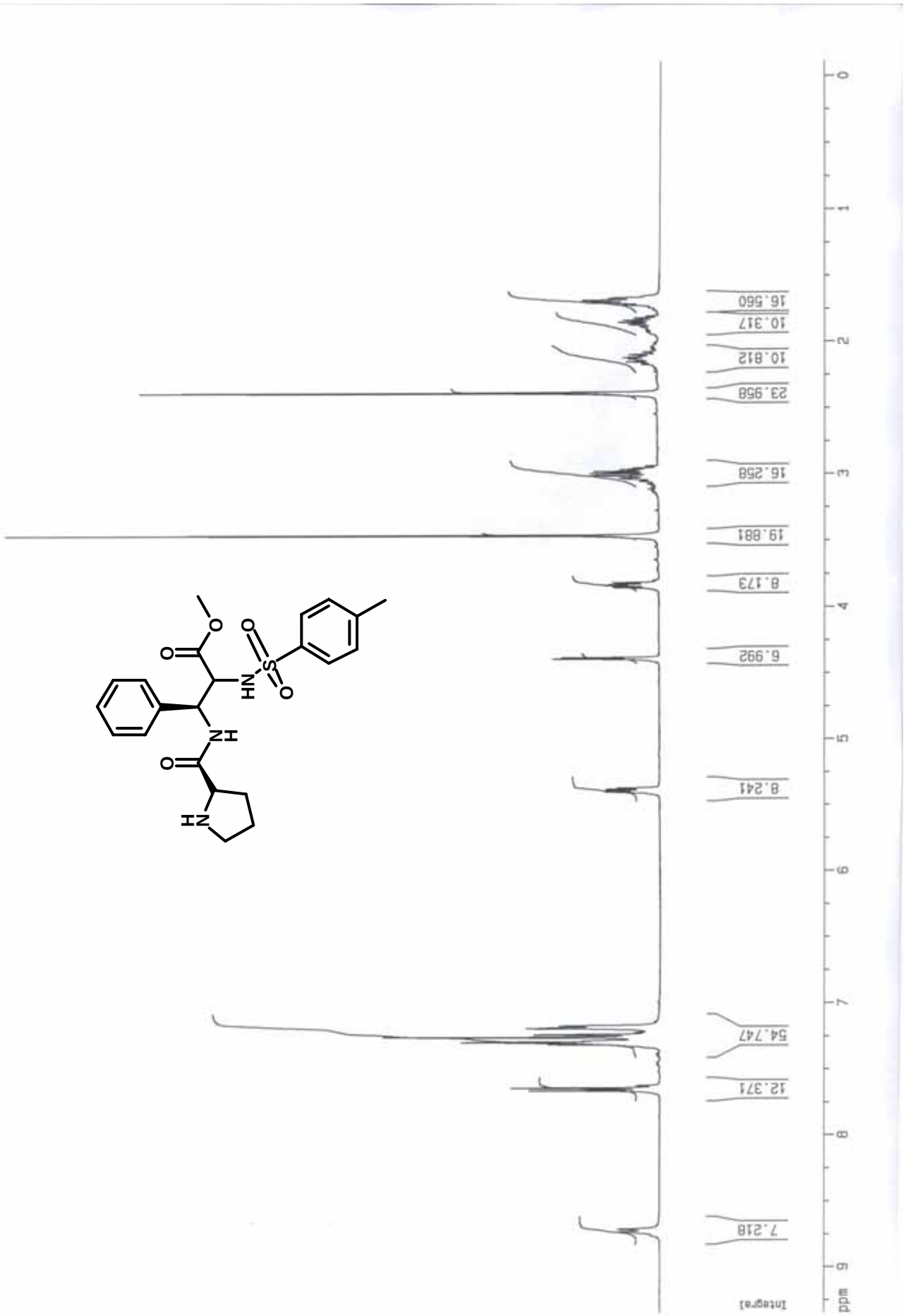
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **8**



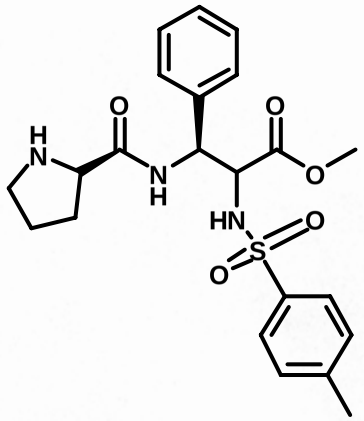
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **8**

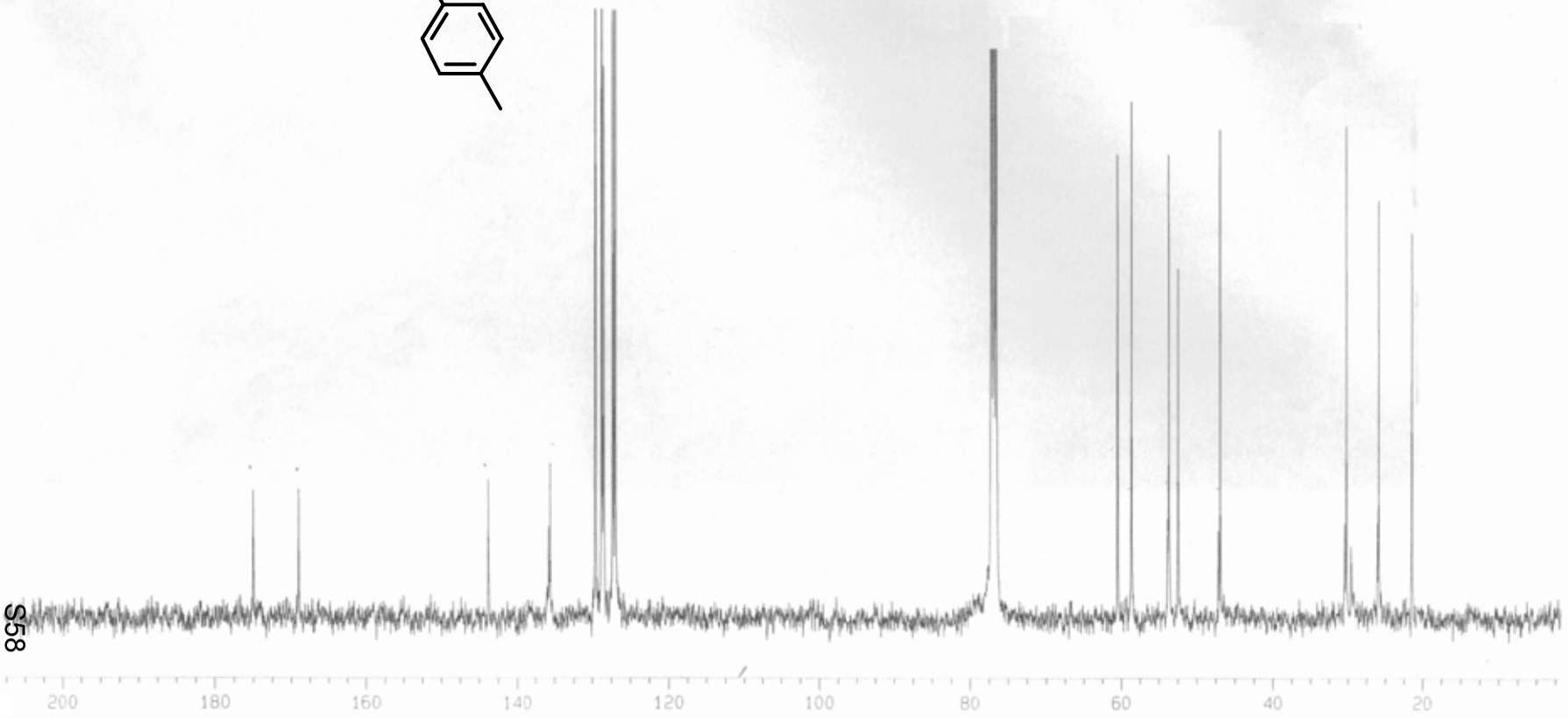


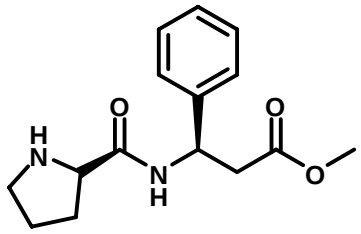
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **1h**



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **1h**

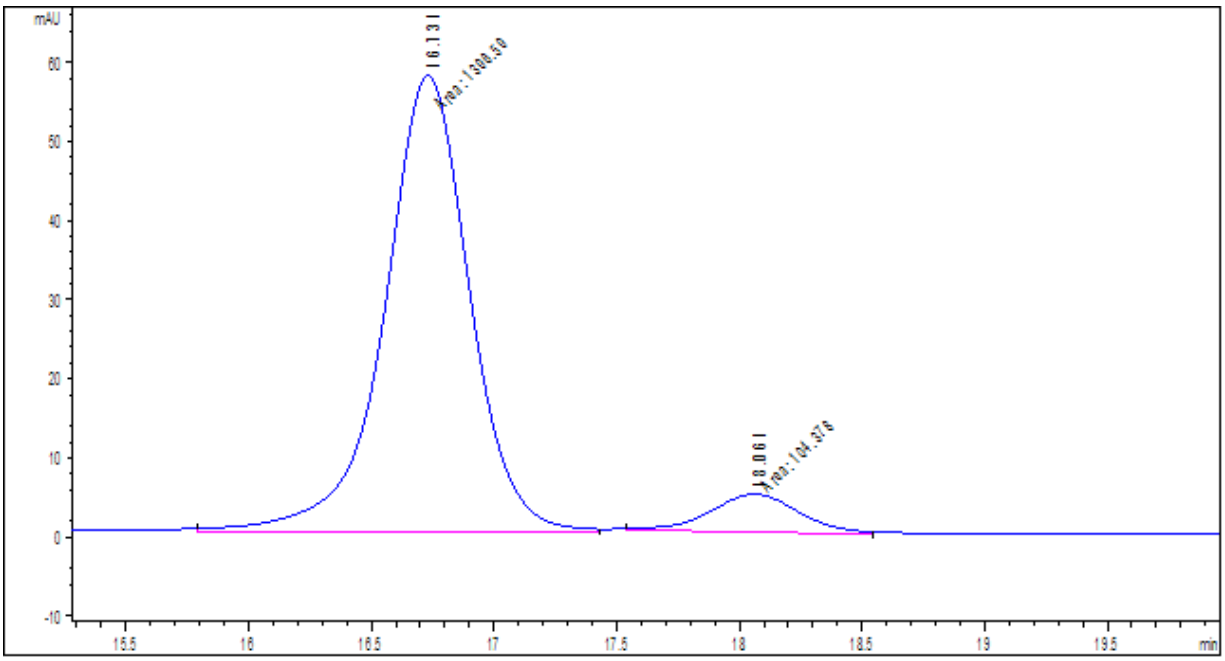




Catalyst  10 mol % in THF, 25° C, 48h

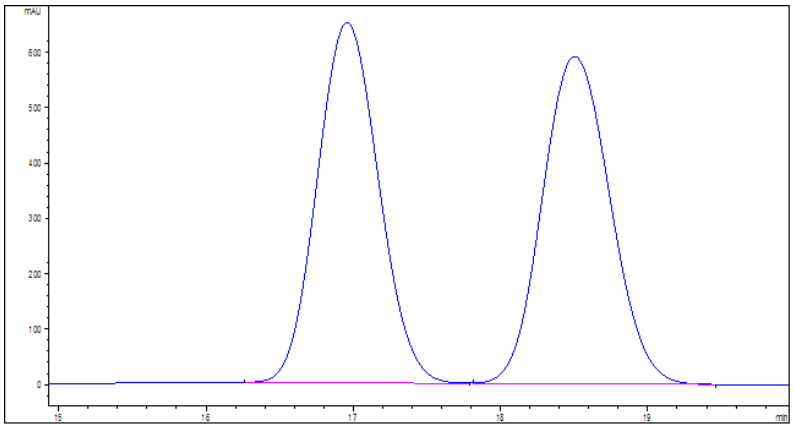
Column DAICEL CHIRALPAK IC; flow 1.2 mL/min hexane/ethanol/dichloromethane 85:4:11 Signal: DAD1 B Wavelength=264.10 nm

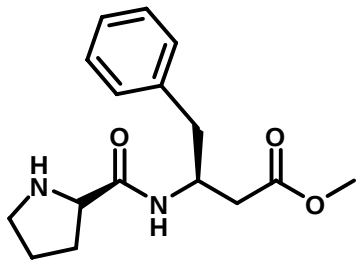
Data File C:\CHEM32\1\DATA\H9\H9.D HPLC1100 03/04/2009 14:51:34 daniele



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.731	MM	0.4032	1396.58801	57.73474	93.0459
2	18.061	MM	0.3902	104.37838	4.45868	6.9541
Totals :				1500.96639	62.19342	

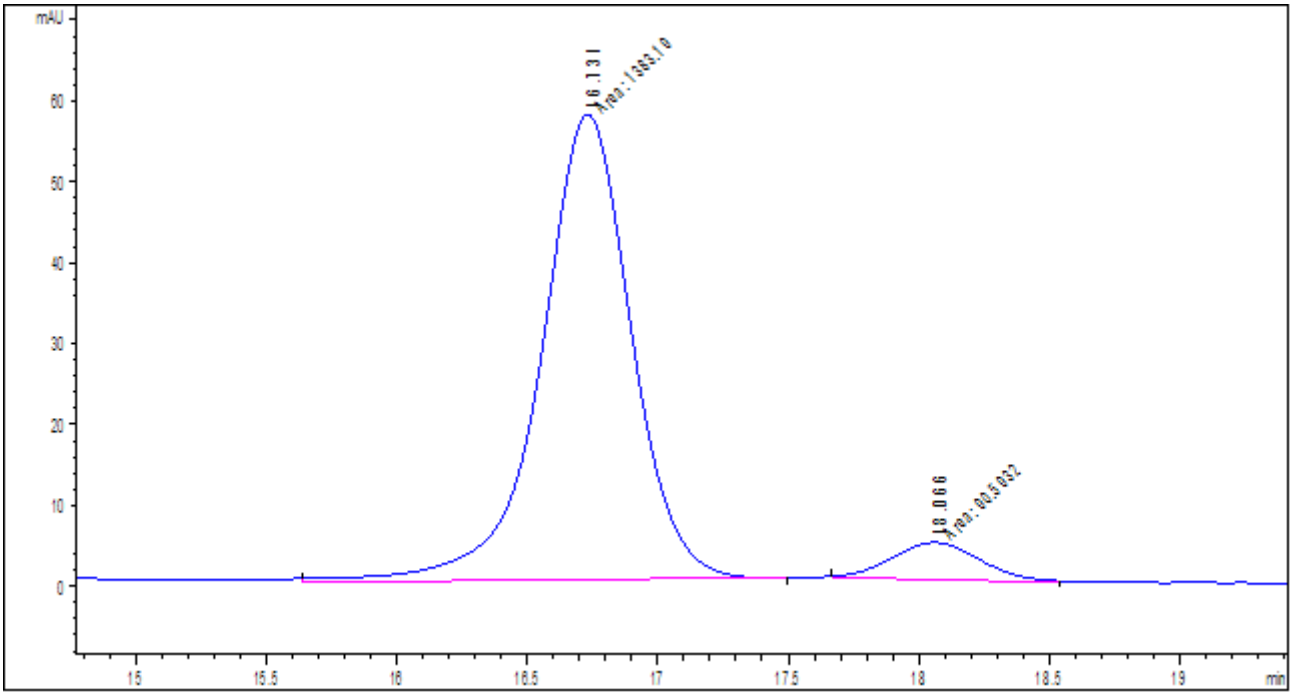
Racemic Mixture



Catalyst  10 mol % in brine, 25° C, 48h

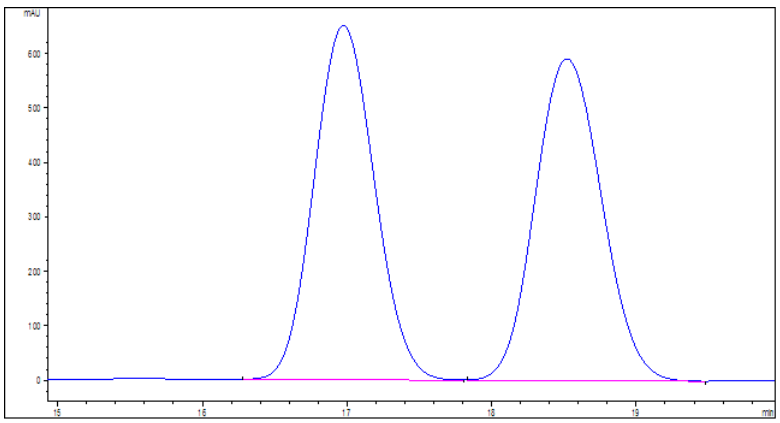
Column DAICEL CHIRALPAK IC; flow 1.2 mL/min hexane/ethanol/dichloromethane 85:4:11 Signal: DAD1 B Wavelength=264.10 nm

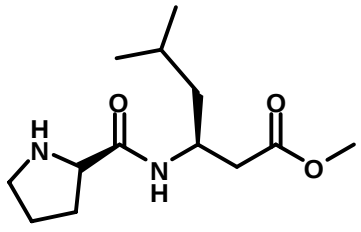
Data File C:\CHEM32\1\DATA\H10\H10.D HPLC1100 31/03/2009 15:58:05 daniele



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.731	MM	0.4008	1383.19336	57.51449	93.8530
2	18.066	MM	0.3561	90.59321	4.23998	6.1470
Totals :				1473.78657	61.75447	

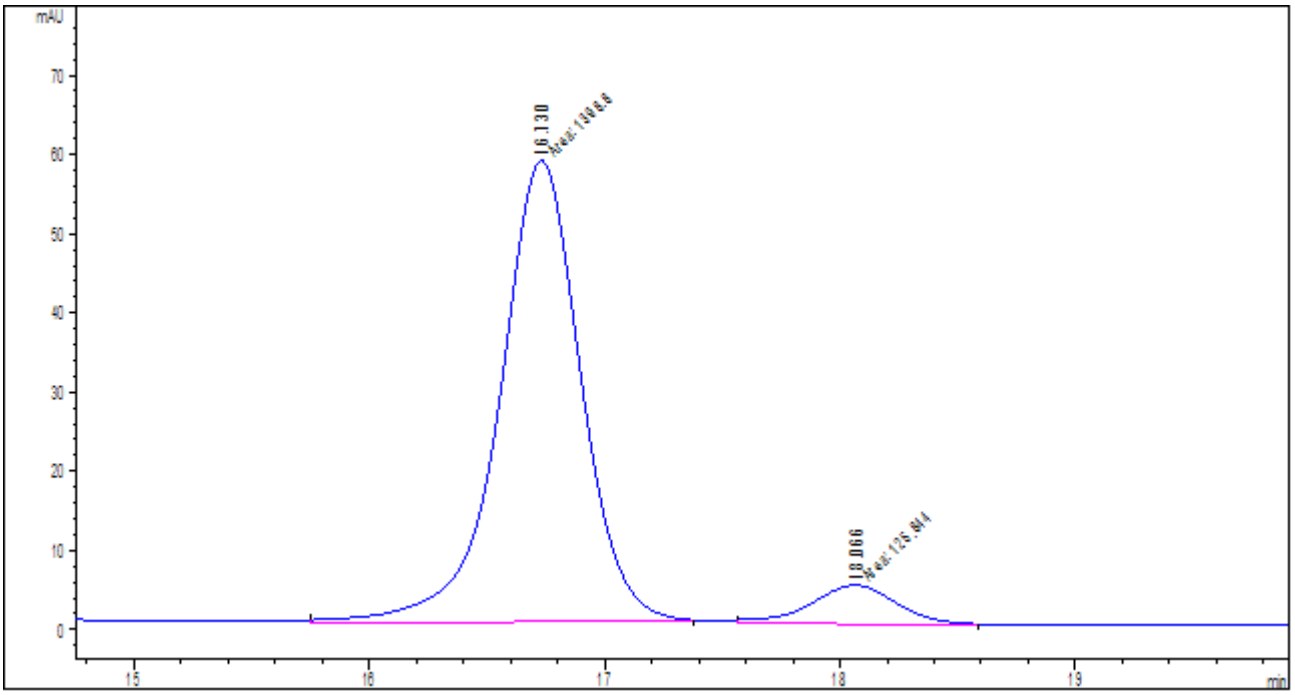
Racemic Mixture



Catalyst  10 mol % in water, 25° C, 48h

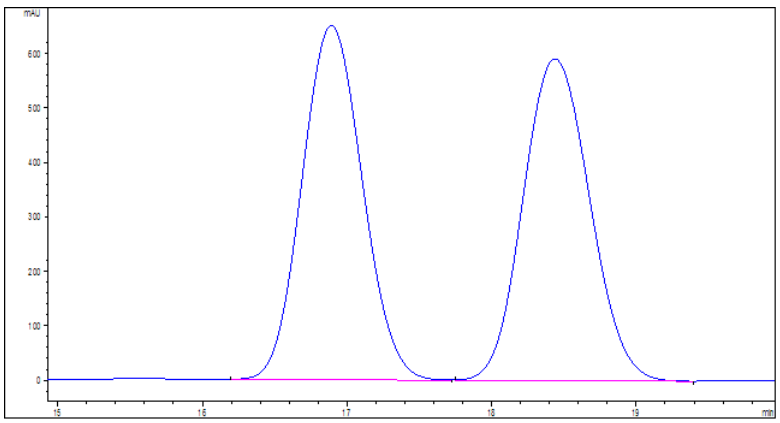
Column DAICEL CHIRALPAK IC; flow 1.2 mL/min hexane/ethanol/dichloromethane 85:4:11 Signal: DAD1 B Wavelength=264.10 nm

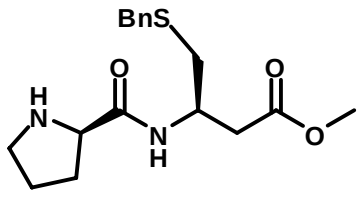
Data File C:\CHEM32\1\DATA\H15\H15.D HPLC1100 19/05/2009 17:07:45 daniele



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.730	MM	0.4001	1398.80408	58.27502	91.7460
2	18.066	MM	0.4267	125.84443	4.91516	8.2540
Totals :				1524.64851	63.19018	

Racemic Mixture

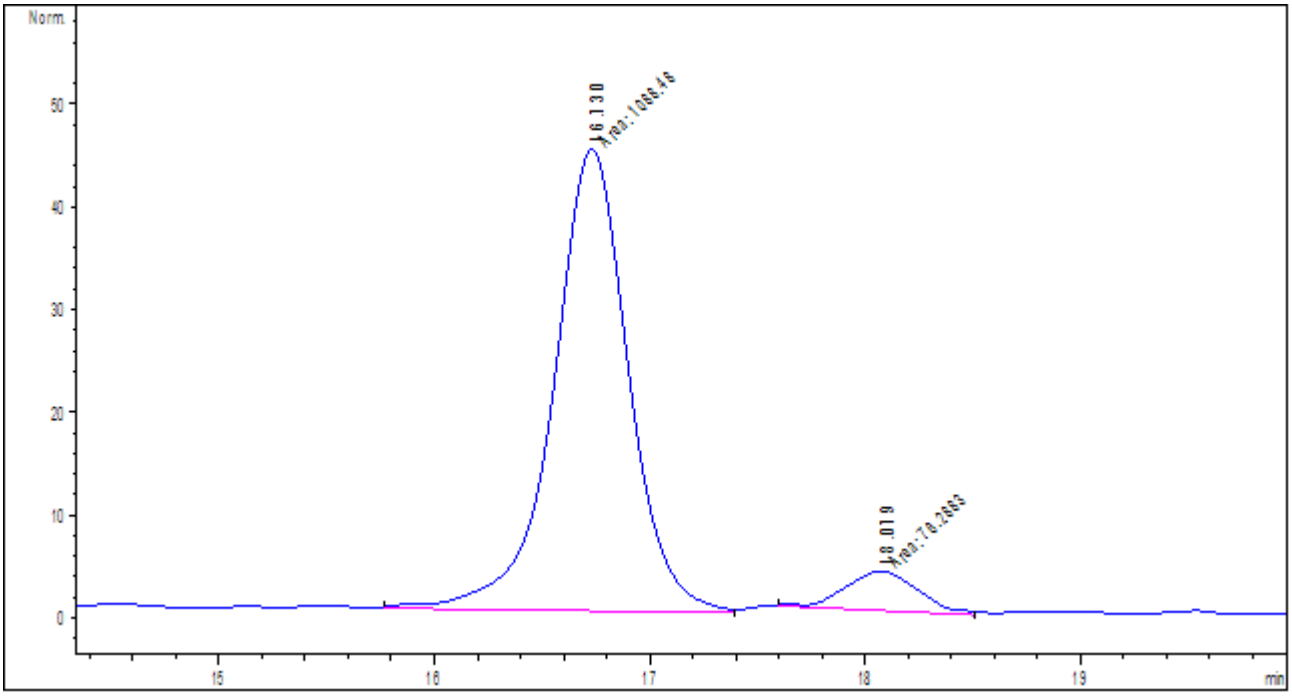


Catalyst 

10 mol % in water, 25° C, 48h

Column DAICEL CHIRALPAK IC; flow 1.2 mL/min hexane/ethanol/dichloromethane 85:4:11 Signal: DAD1 B Wavelength=264.10 nm

Data File C:\CHEM32\1\DATA\H23\H23.D HPLC1100 09/04/2009 12:13:29 daniele



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.730	MM	0.4036	1088.47888	44.94388	93.4503
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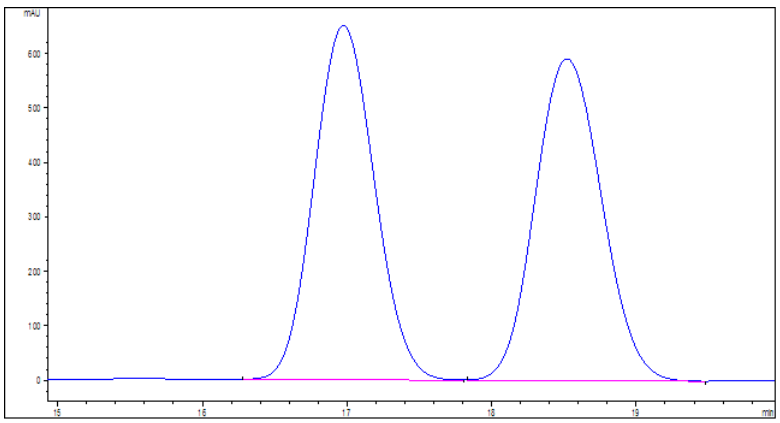
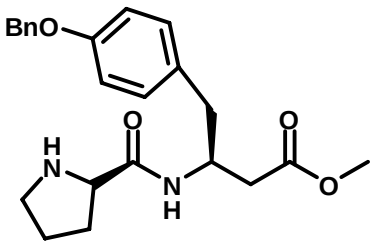
Totals :				1164.76716	48.54662	

Racemic Mixture

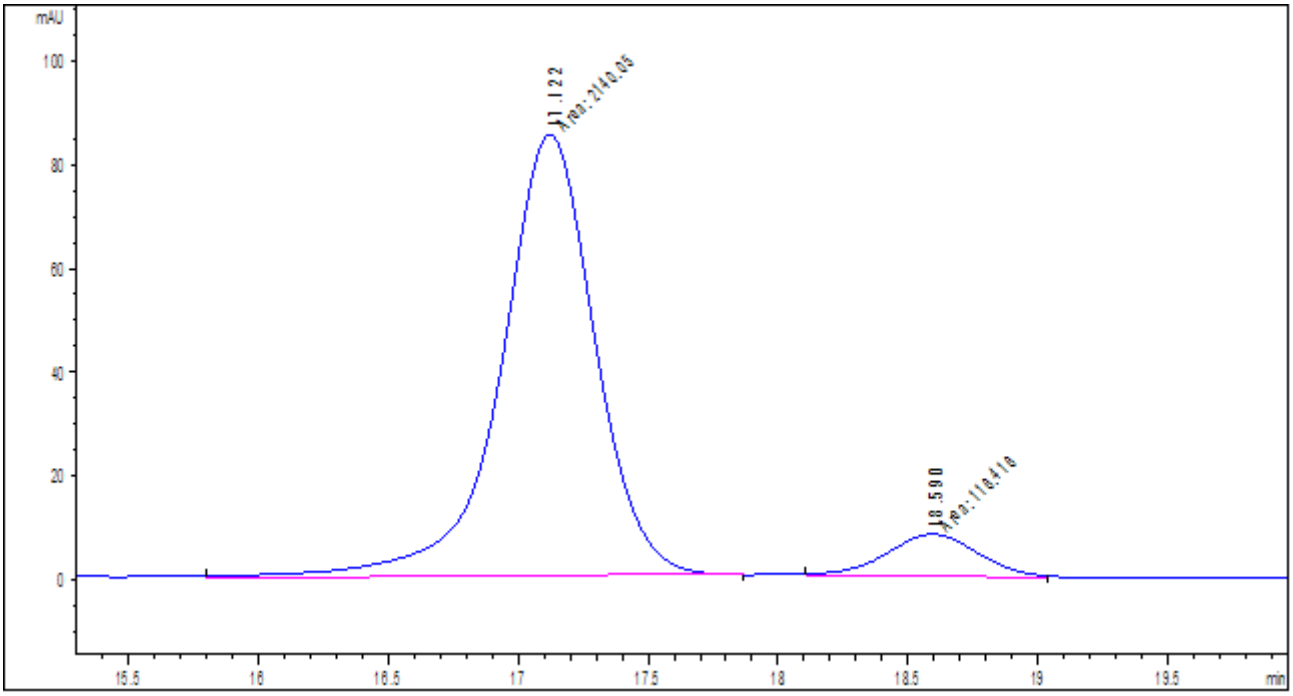




Catalyst 10 mol % in water, 25° C, 48h

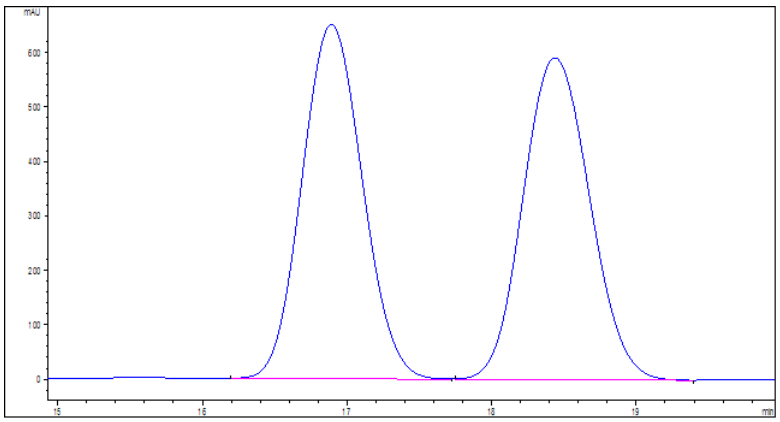
Column DAICEL CHIRALPAK IC; flow 1.2 mL/min hexane/ethanol/dichloromethane 85:4:11 Signal: DAD1 B Wavelength=264.10 nm

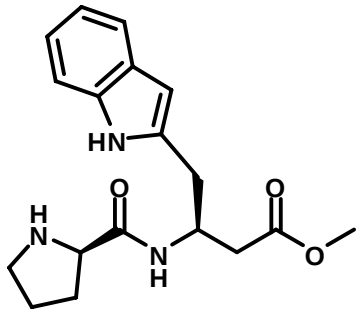
Data File C:\CHEM32\1\DATA\H24\H24.D HPLC1100 17/04/2009 09:44:15 daniele



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.122	MM	0.4189	2140.04785	85.14655	94.8408
2	18.590	MM	0.3094	116.41602	6.27075	5.1592
Totals :				2256.46387	91.41729	

Racemic Mixture

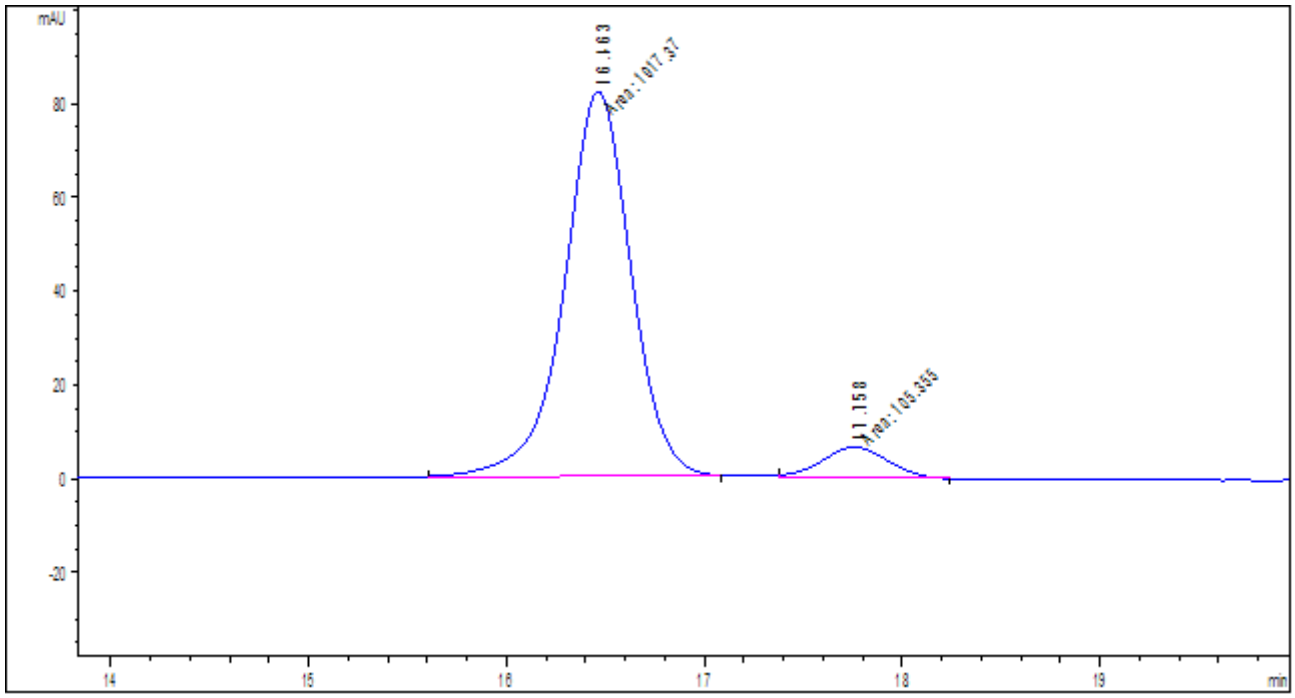




Catalyst 10 mol % in brine, 25° C, 48h

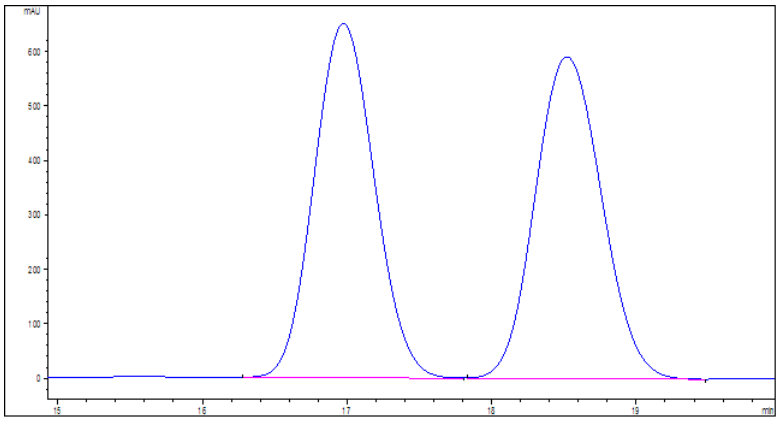
Column DAICEL CHIRALPAK IC; flow 1.2 mL/min hexane/ethanol/dichloromethane 85:4:11 Signal: DAD1 B Wavelength=264.10 nm

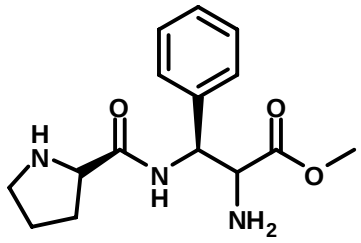
Data File C:\CHEM32\1\DATA\H25\H25.D HPLC1100 17/04/2009 15:48:55 daniele



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.463	MM	0.3892	1917.37134	82.10417	94.7914
2	17.758	MM	0.3194	105.35524	5.49720	5.2086
Totals :				2022.72658	87.60137	

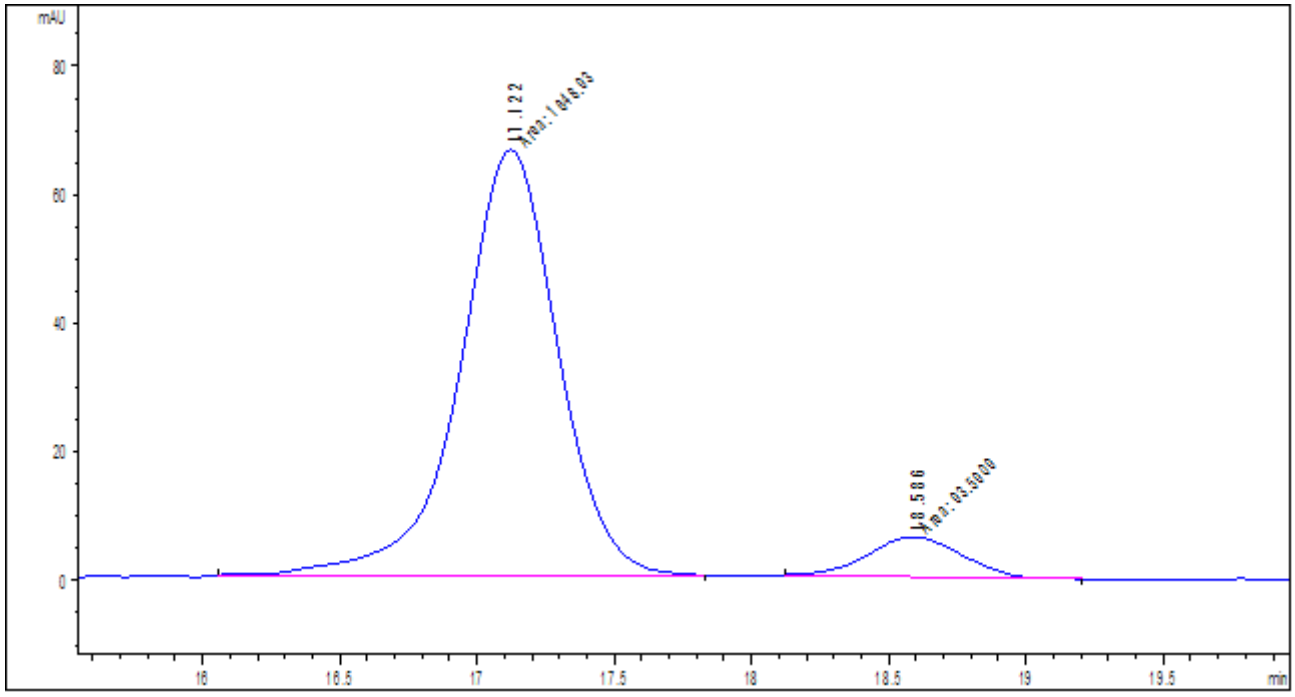
Racemic Mixture



Catalyst  10 mol % in brine, -16° C, 48h

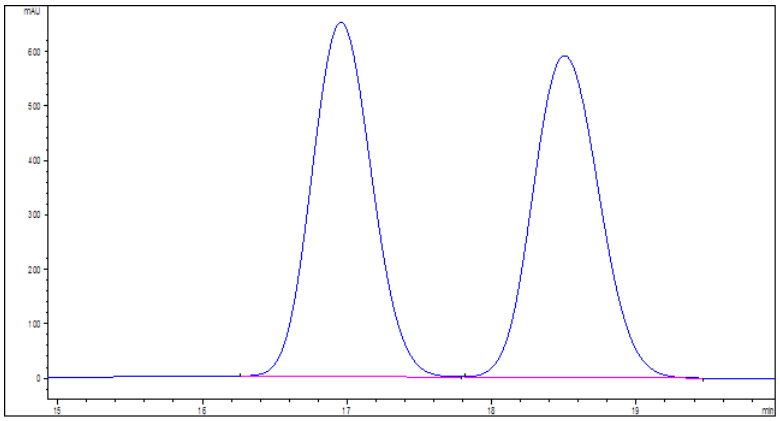
Column DAICEL CHIRALPAK IC; flow 1.2 mL/min hexane/ethanol/dichloromethane 85:4:11 Signal: DAD1 B Wavelength=264.10 nm

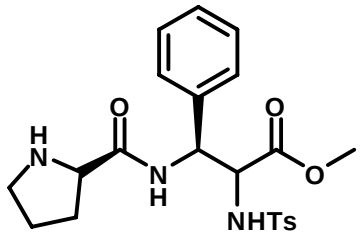
Data File C:\CHEM32\1\DATA\H30\H30.D HPLC1100 26/06/2009 17:44:12 daniele



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.122	MM	0.4149	1648.93323	66.23879	94.6290
2	18.586	MM	0.3172	93.59091	4.91690	5.3710
Totals :				1742.52414	71.15569	

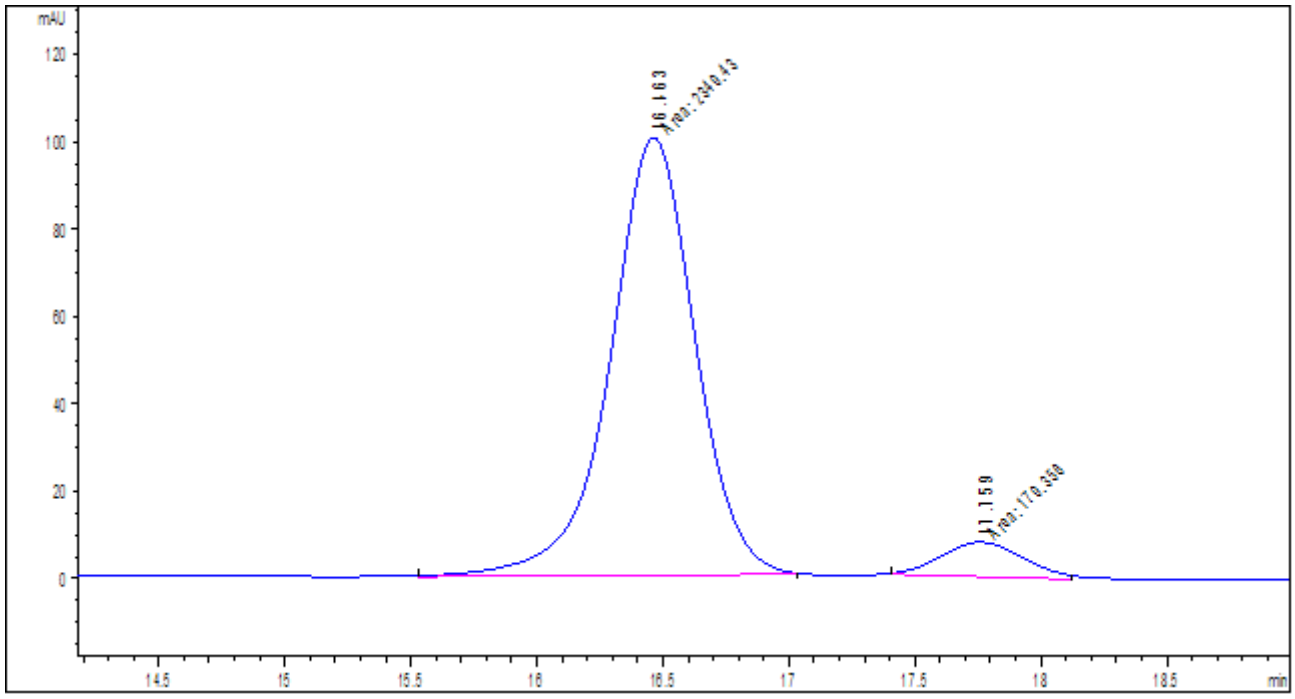
Racemic Mixture



Catalyst  3 mol % in brine, -16° C, 48h

Column DAICEL CHIRALPAK IC; flow 1.2 mL/min hexane/ethanol/dichloromethane 85:4:11 Signal: DAD1 B Wavelength=264.10 nm

Data File C:\CHEM32\1\DATA\H41\H41.D HPLC1100 07/07/2009 15:12:06 daniele



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.463	MM	0.3903	2349.42993	100.31687	92.9074
2	17.759	MM	0.3767	179.35573	7.93549	7.0926
Totals :				2528.78566	108.25236	

Racemic Mixture