Supporting Information

Direct Asymmetric *anti*-Mannich-Type Reactions Catalyzed by a Designed Amino Acid

Susumu Mitsumori,[†] Haile Zhang,[†] Paul Ha-Yeon Cheong,[§] K. N. Houk,*[§] Fujie Tanaka,*[†] and Carlos, F. Barbas, III*[†]

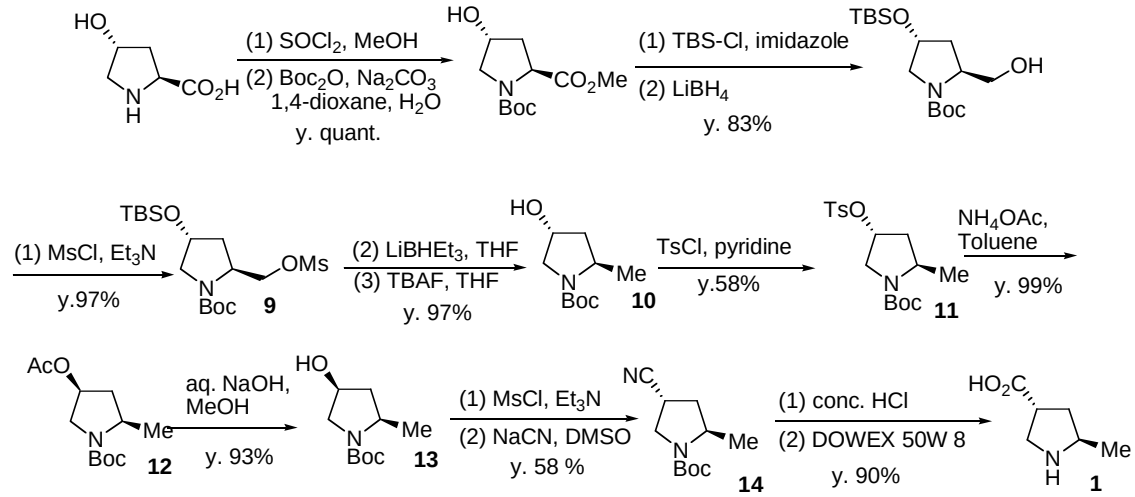
[†] The Skaggs Institute for Chemical Biology and the Departments of Chemistry and Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

[§] Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569

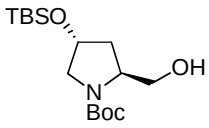
General: Moisture sensitive reactions were carried out under an argon atmosphere. For thin layer chromatography (TLC), silica gel plates VWR GL60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), and conc. H_2SO_4 (60 mL) in H_2O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), and acetic acid (10 mL) in ethanol (900 mL) followed by heating. Flash column chromatography was performed using Bodman silica gel 32-63, 60Å. ^1H NMR and ^{13}C NMR spectra were recorded on INOVA-400 or Mer-300. Proton chemical shifts are given in δ relative to tetramethylsilane (δ 0.00 ppm) in $CDCl_3$ or to the residual proton signals of the deuterated solvent in CD_3OD (δ 3.35 ppm). Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.00 ppm) or CD_3OD (δ 49.00 ppm). High-resolution mass spectra were recorded on an Agilent ESI-TOF mass spectrometer. Enantiomeric excesses were determined by chiral-phase HPLC using a Hitachi instrument. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

Synthesis of catalyst 1 (Scheme S1).

Scheme S1

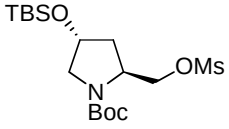


(2*S*,4*R*)-*tert*-Butyl 4-(*tert*-butyldimethylsilyloxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate.[S1]



This compound was synthesized from *trans*-4-hydroxy-L-proline by the reported procedures.[S1] ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.87 (s, 9H), 1.47 (s, 9H), 1.96 (m, 1H), 1.98 (s, 1H), 3.34 (dd, *J* = 4.0, 14.6Hz, 1H), 3.42 (d, *J* = 12.0Hz, 1H), 3.55 (m, 1H), 3.71 (m, 1H), 4.11 (m, 1H), 4.27 (m, 1H), 4.91 (dd, *J* = 0.8 Hz, 12.0 Hz, 1H).

(2*S*,4*R*)-*tert*-Butyl 4-(*tert*-butyldimethylsilyloxy)-2-((methylsulfonyloxy)methyl)pyrrolidine-1-carboxylate (9).



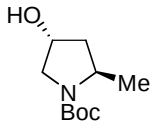
9

To a solution of (2*S*,4*R*)-*tert*-butyl 4-(*tert*-butyldimethylsilyloxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (6.50 g, 19.6 mmol) and Et_3N (5.5 mL, 39.2 mmol) in CH_2Cl_2 (80 ml) was added MsCl (2.3 mL, 29.4 mmol) at 4 °C.[S1] After stirring for 3 h at the same temperature, the mixture was poured into water and extracted with AcOEt. The organic layers were combined, washed

(S1) Rosen, T.; Chu, D. T. W.; Lico, I. M.; Fernandes, P. B.; Marsh, K.; Shen, L.; Cepa, V. G.; Pernet, A. G. *J. Med. Chem.* **1988**, *31*, 1598.

with brine, dried over Na_2SO_4, and concentrated in vacuo to afford **9** (7.80 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.87 (s, 9H), 1.58 (s, 9H), 2.04 (m, 1H), 3.00 (s, 3H), 3.36 (d, *J* = 1.2Hz, 2H), 3.51 (m, 1H), 4.18 (m, 1H), 4.29 (m, 1H), 4.37 (m, 1H), 4.55 (m, 1H).

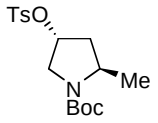
(2*R*,4*R*)-*tert*-Butyl 4-hydroxy-2-methylpyrrolidine-1-carboxylate (10).



10

To a solution of compound **9** (7.80 g, 24.7 mmol) in THF (20 mL) was slowly added 1 M $LiBHEt_3$ in THF solution (76.2 mL) at 4 °C and the mixture was allowed to warm to room temperature. After stirring for 2.5 h, the mixture was quenched with crushed-ice and extracted with AcOEt.[S1] The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated. The residue was dissolved in THF (100 mL) and 1 M *n*-Bu_4NF solution was added at 4 °C.[S1] After stirring for 16 h, the mixture was poured into water and extracted with AcOEt. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/AcOEt = 3:1 – 2:1) to afford **10** (3.70 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (m, 3H), 1.47 (s, 9H), 1.55 (br, 1H), 1.74 (m, 1H), 2.10 (m, 1H), 3.44-3.49 (m, 2H), 4.00 (m, 1H), 4.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.20, 28.43, 42.44, 51.56, 54.28, 69.43, 79.34, 155.14. HRMS: calcd for $C_{10}H_{19}NO_3$ (MNa^+) 224.1257, found 224.1255.

(2*R*,4*R*)-*tert*-Butyl 2-methyl-4-(tosyloxy)pyrrolidine-1-carboxylate (11).

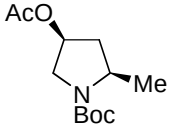


11

To a solution of compound **10** (1.30 g, 6.46 mmol) in pyridine (10 mL) was added TsCl (2.22 g, 11.6 mmol) at 4 °C and the mixture was allowed to warm to room temperature.[S2] After stirring for 30 h, the mixture was poured into 2 N HCl solution and extracted with AcOEt. The organic layers were combined, washed with sat. $NaHCO_3$ solution and brine, dried over Na2SO4, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/AcOEt = 10:1 – 6:1) to afford **11** (1.33 g, 58%). 1H NMR (400 MHz, $CDCl_3$): δ 1.21 (d, *J* = 6.0, 3H), 1.44 (s, 9H), 1.74 (m, 1H), 2.26 (m, 1H), 2.46 (s, 3H), 3.41 (m, 1H), 3.62 (d, *J* = 13.2 Hz, 1H), 3.96 (m, 1H), 4.97 (m, 1H), 7.35 (d, *J* = 12.0 Hz, 2H), 7.78 (d, *J* = 12.0 Hz, 2H).

(S2) (a) Bridges, R. J.; Stanley, M. S.; Anderson, M. W.; Cotman, C. W.; Chamberlin, A. R.. *J. Med. Chem*. **1991**, *34*, 717. (b) Heindl, C.; Hubner, H.; Gmeiner, P. *Tetrahedron: Asymmetry* **2003**, *14*, 3141.

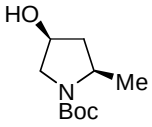
(2*R*,4*S*)-*tert*-Butyl 4-acetoxy-2-methylpyrrolidine-1-carboxylate (12).



12

To a solution compound **11** (1.35 g, 3.80 mmol) in toluene (15 mL) was added NH_4OAc (1.49 g, 4.94 mmol).[S2] After reflux for 4 h, the mixture was cooled to room temperature, poured into water, and extracted with AcOEt. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified flash column chromatography (hexane/AcOEt = 10:1) to afford **12** (0.91 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (d, *J* = 5.2 Hz, 3H), 1.47 (s, 9H), 1.77 (dd, *J* = 0.4Hz, 14.0 Hz, 1H), 2.07 (s, 3H), 2.30 (m, 1H), 3.46 (m, 1H), 3.65 (m, 1H), 3.97 (m, 1H), 5.23 (m, 1H).

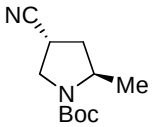
(2*R*,4*S*)-*tert*-Butyl 4-hydroxy-2-methylpyrrolidine-1-carboxylate (13).



13

To a solution of compound **12** (0.910 g, 3.74 mmol) in MeOH (5 mL) and THF (1 mL) was added 2 N NaOH solution (5.6 mL, 11.2 mmol) at room temperature.[S2b,S3] After stirring for 30 min, the mixture was poured into water and extracted with AcOEt. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford **13** (0.703 g, 93%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (d, *J* = 6.4 Hz, 3H), 1.47 (s, 9H), 1.59 (d, *J* = 3.2Hz, 1H), 1.67 (d, *J* = 13.6 Hz, 1H), 2.26 (m, 1H), 3.35 (dd, *J* = 2.0 Hz, 12.0 Hz, 1H), 3.63 (m, 1H), 3.91(m, 1H), 4.41(m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.77, 28.51, 41.53, 52.49, 54.75, 77.21, 79.22, 154.52. HRMS: calcd for $C_{10}H_{19}NO_3$ (MNa^+) 224.1257, found 224.1262.

(2*R*,4*R*)-*tert*-Butyl 4-cyano-2-methylpyrrolidine-1-carboxylate (14).



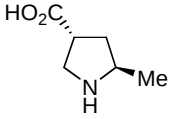
14

To a solution of compound **13** (0.70 g, 3.48 mmol) and Et_3N (0.97 mL, 6.96 mmol) in CH_2Cl_2 (10 mL) was added MsCl (0.40 mL, 5.22 mmol) at 4 °C.[S2] After stirring for 3 h at the same

(S3) Zhao, X.; Hoesl, C. E.; Hoefner, G. C.; Wanner, K. T. *Eur. J. Med. Chem.* **2005**, *40*, 231.

temperature, the mixture was poured into water and extracted with AcOEt. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give the mesylated compound (0.97 g, 100%). Without further purification, this residue was dissolved in DMSO (10 mL) and NaCN (0.256 g, 5.22 mmol) was added.[S2] This mixture was stirred at 80 °C for 20 h. The mixture was treated with sat. $NaHCO_3$ and extracted with AcOEt. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/AcOEt = 6:1) to give **14** (0.422 g, 58%). ^{1}H NMR (400MHz, $CDCl_3$): δ 1.20 (d, *J* = 8.4 Hz, 3H), 1.47 (s, 9H), 1.97 (m, 1H), 2.36 (m, 1H), 3.13 (m, 1H), 3.64-3.72 (m, 2H), 4.06 (br, 1H). ^{13}C NMR (100MHz, $CDCl_3$): δ 20.18, 26.11, 28.32, 36.73, 48.98, 52.00, 80.02, 119.88, 153.59. HRMS: calcd for $C_{11}H_{18}N_2O_2$ (MNa^+) 233.1260, found 233.1257.

(3*R*,5*R*)-5-Methyl-3-pyrrolidinecarboxylic acid (1).

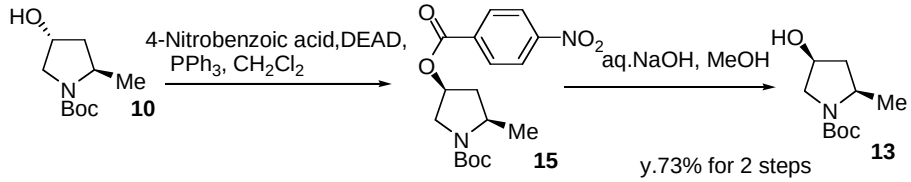


1

A solution of compound **14** (0.42 g, 2.00 mmol) in conc. HCl (4.2 mL) was refluxed for 2 h. The mixture was concentrated in vacuo. The resulting colorless solid was dissolved in water and the solution was loaded to Dowex 50WX8-100 ion-exchange resin (H^+ form, activated with 0.01 M HCl). The resin was washed with water then eluted with 1 M ammonium hydroxide. The eluted fractions were lyophilized to afford **1** (0.232 g, 90%) as a colorless solid. ^{1}H NMR (400 MHz, CD_3OD): δ 1.41 (d, *J* = 8.4 Hz, 3H), 1.90 (m, 1H), 2.43 (m, 1H), 3.11 (m, 1H), 3.44 (dd, *J* = 8.0 Hz, 11.6Hz, 1H), 3.56 (dd, *J* = 5.6 Hz, 11.6 Hz, 1H), 3.78 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 17.5, 37.6, 45.9, 49.3, 56.8, 179.7. HRMS: calcd for $C_6H_{11}NO_2$ (MH^+) 130.0863, found 130.0868. $[\alpha]^{25}_D$ +10.3 (c 0.58, MeOH).

Another route from 10 to 13 (Scheme S2).

Scheme S2

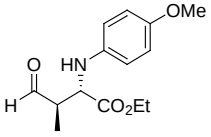


To a solution of compound **10** (0.70 g, 3.48 mmol) and PPh_3 (1.37 g, 5.22 mmol) in CH_2Cl_2 (7 mL) was added DEAD (0.91 mL, 5.22 mmol) at 4°C.[S3] The resulting mixture was stirred for 10 min and then 4-nitrobenzoic acid (1.62 g, 5.22 mmol) was added. This mixture was allowed to

warm up to room temperature and stirred for 16 h. The reaction mixture was quenched with 2 N NaOH solution and extracted with AcOEt. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography to give **15** (0.885 g, 73 %) as a pale yellow solid. Compound **15**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (d, *J* = 0.4 Hz, 3H), 1.48 (s, 9H), 1.96 (d, *J* = 14.4 Hz, 1H), 2.47 (m, 1H), 3.64-3.83 (m, 2H), 4.11 (m, 1H), 5.55 (m, 1H), 8.21 (d, *J* = 8.0 Hz, 2H), 8.31 (d, *J* = 8.0 Hz, 2H). Compound **15** (0.885 g, 2.51 mmol) was dissolved in MeOH (5 mL) and THF (5 mL) and 2 N NaOH solution was added at room temperature. After stirring for 30min, the mixture was poured into water and extracted with AcOEt. The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give compound **13** (0.52 g, 100%) as a colorless solid.

General procedure for the Mannich-type reaction between *N*-PMP protected α-imino ethyl glyoxylate and aldehyde donors (Table 1). *N*-PMP-protected α-imino ethyl glyoxylate (0.25 mmol, 1 equiv) was dissolved in anhydrous DMSO (2.5 mL) and aldehyde (0.5 mmol, 2 equiv) was added, followed by catalyst **1** (0.0125 mmol, 0.05 equiv). After stirring for 0.5-3 h at room temperature, the mixture was worked up by addition of aqueous saturated ammonium chloride solution and extracted with AcOEt (three or four times). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (10-15% AcOEt/hexane) to afford the corresponding Mannich addition product. When the catalyst loading was 1 or 2 mol%, the reaction was performed using *N*-PMP-protected α-imino ethyl glyoxylate (0.5 mmol, 1 equiv), aldehyde (1.0 mmol, 2 equiv), and catalyst **1** (0.005 or 0.01 mmol, 0.01 or 0.02 equiv) in DMSO (5 mL). The reactions were performed in a closed system (a vial with a cap). An inert atmosphere of nitrogen or argon was not necessary for the reactions.

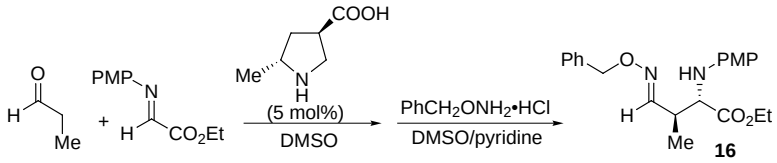
Ethyl (2*S*,3*R*)-3-formyl-2-(*p*-methoxyphenylamino)butanoate (2).



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$), 1.23 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 2.85-2.92 (m, 1H, C*H*CHO), 3.74 (s, 3H, OC*H*$_3$), 4.09 (brd, *J* = 8.4 Hz, 1H, N*H*PMP), 4.14-4.23 (m, 2H, OC*H*$_2$CH$_3$), 4.34-4.37 (brdd, *J* = 6.0 Hz, 8.8 Hz, 1H, C*H*NHPMP), 6.66 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.78 (d, *J* = 9.0 Hz, 2H, Ar*H*), 9.73 (d, *J* = 1.2 Hz, 1H, CHC*H*O).

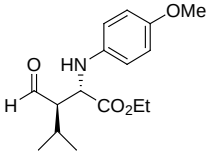
^{13}C NMR (100 MHz, $CDCl_3$): δ 201.9, 171.8, 153.2, 140.1, 115.6, 114.9, 61.6, 58.6, 55.7, 48.5, 14.2, 9.9. HRMS: calcd for $C_{14}H_{20}NO_4$ (MH^+) 266.1387, found 266.1382.

Ethyl (*E*)-3-benzyloxyiminomethyl-2-(*p*-methoxyphenylamino)butanoate (16).



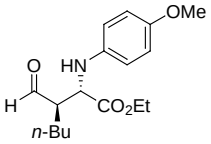
A mixture of *N*-PMP-protected α-imino ethyl glyoxylate (0.5 mmol, 1 equiv), an aldehyde donor (1.0 mmol, 2 equiv), and catalyst **1** (0.025 mmol, 0.05 equiv) in DMSO (5 mL) was stirred for 1h at room temperature. To the mixture, *O*-benzylhydroxylamine hydrochloride (1.3 mmol) and pyridine (0.5 mL) were added. The mixture was stirred for an additional 4 h at room temperature, filtered through Celite, and concentrated in vacuo. The residue was purified by flash column chromatography to afford oxime **16**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$), 1.21 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 2.86-2.95 (m, 1H, CH$_3$C*H*CH=N), 3.74 (s, 3H, OC*H*$_3$), 3.91-3.98 (m, 2H, N*H*C*H*CO$_2$Et), 4.14 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$CH$_3$), 5.07 (s, 2H, C*H*$_2$Ph), 6.55 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.75 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.31-7.44 (m, 6H, Ar*H* and C*H*=N). ^{13}C NMR (100 MHz, $CDCl_3$): δ172.5, 152.8, 151.8, 140.8, 137.6, 128.4, 128.2, 127.8, 115.2, 114.8, 75.7, 61.3, 61.2, 55.7, 37.5, 14.7, 14.2. HRMS: calcd for $C_{21}H_{27}N_2O_4$ (MH^+) 371.1965, found 371.1966. HPLC (Daicel Chairalcel AD, hexane/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm): t_R (*anti* major enantiomer) = 66.6 min, t_R (*anti* minor enatiomer) = 57.8 min.

Ethyl (2*S*,3*R*)-3-formyl-2-(*p*-methoxyphenylamino)-4-methylpentanoate (3).



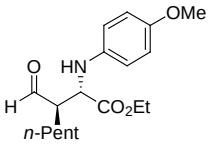
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 1.12 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 1.21 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 2.02-2.18 (m, 1H, C*H*(CH$_3$)$_2$), 2.57-2.63 (m, 1H, C*H*CHO), 3.74 (s, 3H, OC*H*$_3$), 4.00 (brs, 1H, N*H*PMP), 4.15 (q, *J* = 6.9 Hz, 2H, OC*H*$_2$CH$_3$), 4.35 (d, *J* = 7.8 Hz, 1H, C*H*NHPMP), 6.66 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.77 (d, *J* = 9.0 Hz, 2H, Ar*H*), 9.75 (d, 1H, *J* = 3.3 Hz, CHC*H*O). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.2, 172.8, 153.2, 140.4, 115.9, 114.8, 61.3, 59.6, 57.2, 55.6, 27.5, 21.2, 19.2, 14.1. HRMS: calcd for $C_{16}H_{24}NO_4$ (MH^+) 294.1700, found 294.1701. HPLC (Daicel Chairalcel AS-H, hexane/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm): t_R (*anti* major enantiomer, (2*S*,3*R*)-**3**) = 24.0 min, t_R (*anti* minor enatiomer, (2*R*,3*S*)-**3**) = 49.3 min. $[\alpha]^{25}_D$ –35.4 (c 1.8, $CHCl_3$).

Ethyl (2*S*,3*R*)-3-formyl-2-(*p*-methoxyphenylamino)octanoate (4).



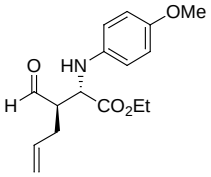
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (m, 3H, $CH_2CH_2CH_3$), 1.23 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.25-1.80 (m, 6H), 2.75 (m, 1H, C*H*CHO), 3.74 (s, 3H, OCH_3), 4.03 (brs, 1H, N*H*PMP), 4.18 (dq, *J* = 0.9 Hz, 7.2 Hz, 2H, OCH_2CH_3), 4.26 (brd, *J* = 6.3 Hz, 1H, C*H*NHPMP), 6.65 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.78 (d, *J* = 9.0 Hz, 2H, Ar*H*), 9.65 (d, *J* = 2.4 Hz, 1H, CHC*H*O). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.3, 172.2, 153.2, 140.3, 115.7, 114.8, 61.5, 58.1, 55.7, 53.9, 29.4, 25.4, 22.6, 14.2, 13.8. HRMS: calcd for $C_{17}H_{26}NO_4$ (MH^+) 308.1856, found 308.1852. HPLC (Daicel Chairalcel AS-H, hexane/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm): t_R (*anti* major enantiomer, (2*S*,3*R*)-**4**) = 24.4 min, t_R (*anti* minor enatiomer, (2*R*,3*S*)-**4**) = 28.5 min. $[\alpha]^{25}_D$ –11.0 (c 1.4, $CHCl_3$).

Ethyl (2*S*,3*R*)-3-formyl-2-(*p*-methoxyphenylamino)heptanoate (5).



^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.8 Hz, 3H, CH_2CH_3), 1.23 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.24-1.78 (m, 8H), 2.72-2.78 (m, 1H, C*H*CHO), 3.74 (s, 3H, OCH_3), 4.03 (brd, *J* = 6.4 Hz, 1H, N*H*PMP), 4.18 (dq, *J* = 1.6 Hz, 7.2 Hz, 2H, OCH_2CH_3), 4.26 (m, 1H, C*H*NHPMP), 6.65 (d, *J* = 9.2 Hz, 2H, Ar*H*), 6.78 (d, *J* = 9.2 Hz, 2H, Ar*H*), 9.65 (d, *J* = 2.4 Hz, 1H, CHC*H*O). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.3, 172.2, 153.1, 140.3, 115.7, 114.8, 61.5, 58.1, 55.6, 53.9, 31.6, 27.0, 25.6, 22.3, 14.1, 13.9. HRMS: calcd for $C_{18}H_{27}NO_4$ (MH^+) 322.2013, found 322.2007. HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm): t_R (*anti* major enantiomer, (2*S*,3*R*)-**5**) = 21.5 min, t_R (*anti* minor enatiomer, (2*R*,3*S*)-**5**) = 24.9 min. $[\alpha]^{25}_D$ –11.9 (c 1.3, $CHCl_3$).

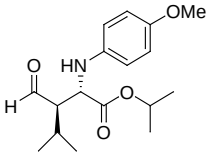
Ethyl (2*S*,3*R*)-3-formyl-2-(*p*-methoxyphenylamino)hex-5-enoate (6).



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 2.37-2.59 (m, 2H, $CH_2CH{=}CH_2$), 2.94-2.99 (m, 1H, C*H*CHO), 3.74 (s, 3H, OCH_3), 4.08 (brd, *J* = 10.0 Hz, 1H,

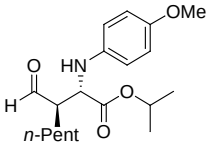
N*H*PMP), 4.18 (dq, *J* = 0.8 Hz, 7.2 Hz, 2H, OC*H*$_2$CH$_3$), 4.28 (m, 1H, C*H*NHPMP), 5.12-5.17 (m, 2H, CH=C*H*$_2$), 5.77-5.88 (m, 1H, C*H*=CH$_2$*)*, 6.65 *(*d, *J* = 9.2 Hz, 2H, Ar*H)*, 6.77 (d, *J* = 9.2 Hz, 2H, Ar-*H)*, 9.69 *(*d, *J* = 1.6 Hz, 1H, CHC*H*O). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.9, 172.2, 153.1, 140.5, 134.3, 118.2, 115.8, 114.8, 61.6, 57.7, 55.6, 53.1, 30.0, 14.1. HRMS: calcd for $C_{16}H_{22}NO_4$ (MH^+) 292.1543, found 292.1537. HPLC (Daicel Chairalcel AS-H, hexane/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm): t_R (*anti* major enantiomer, (2*S*,3*R*)-**6**) = 30.2 min, t_R (*anti* minor enatiomer, (2*R*,3*S*)-**6**) = 38.5 min. $[\alpha]^{25}_D$ +21.5 (c 1.0, $CHCl_3$).

Isopropyl (2*S*,3*R*)-3-formyl-2-(*p*-methoxyphenylamino)-4-methylpentanoate (7).



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (d, *J* = 6.8 Hz, 3H, CCHC*H*$_3$), 1.12 (d, *J* = 6.8 Hz, 3H, CCHC*H*$_3$), 1.16 (d, *J* = 6.4 Hz, 3H, OCHC*H*$_3$), 1.19 (d, *J* = 6.4 Hz, 3H, OCHC*H*$_3$), 2.04-2.14 (m, 1H, CC*H*(CH$_3$)$_2$), 2.54-2.58 (m, 1H, C*H*CHO), 3.73 (s, 3H, OC*H*$_3$), 3.90 (brs, 1H, N*H*PMP), 4.32 (d, *J* = 8.0 Hz, 1H, C*H*NHPMP), 4.96 (m, 1H, OC*H*(CH$_3$)$_2$), 6.66 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.76 (d, *J* = 8.8 Hz, 2H, Ar*H*), 9.73 (d, *J* = 3.6 Hz, 1H,CHC*H*O). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.2, 172.2, 153.2, 140.4, 115.9, 114.7, 69.1, 59.6, 57.4, 55.6, 27.5, 21.7, 21.6, 21.2, 19.1. HRMS: calcd for $C_{17}H_{25}NO_4$ (MH^+) 308.1856, found 308.1859. HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm), t_R (*anti* major enantiomer, (2*S*,3*R*)-**7**) = 19.1 min, t_R (*anti* minor enatiomer, (2*R*,3*S*)-**7**) = 50.7 min. $[\alpha]^{25}_D$ –34.7 (c 2.3, $CHCl_3$).

Isopropyl (2*S*,3*R*)-3-formyl-2-(*p*-methoxyphenylamino)heptanoate (8).



^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.9Hz, 3H, C*H*$_3$), 1.18 (d, *J* = 6.4 Hz, 3H, OCHC*H*$_3$), 1.21 (d, *J* = 6.4 Hz, 3H, OCHC*H*$_3$), 1.25-1.76 (m, 8H), 2.69-2.74 (m, 1H, C*H*CHO), 3.74 (s, 3H, OC*H*$_3$), 4.02 (d, *J* = 10.0 Hz, 1H, N*H*PMP), 4.24 (dd, 1H, *J* = 6.8 Hz, 10.0 Hz, 1H, C*H*NHPMP), 4.98-5.08 (m, 1H, OC*H*CH$_3$), 6.65 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.77 (d, *J* = 8.8 Hz, 2H, Ar*H*), 9.65 (d, *J* = 2.6 Hz, 1H,CHC*H*O). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.2, 171.6, 153.1, 140.3, 115.7, 114.8, 69.4, 58.2, 55.6, 53.9, 31.7, 27.0, 25.6, 22.3, 21.7, 21.7, 13.9. HRMS: calcd for $C_{19}H_{29}NO_4$ (MH^+) 336.2169, found 336.2174. HPLC (Daicel Chiralpak OJ-H, hexane/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm); t_R (*anti* major enantiomer, (2*S*,3*R*)-**8**) = 29.9 min, t_R (*anti* minor enatiomer, (2*R*,3*S*)-**8**) = 27.7 min. $[\alpha]^{25}_D$ –20.3 (c 1.5, $CHCl_3$).

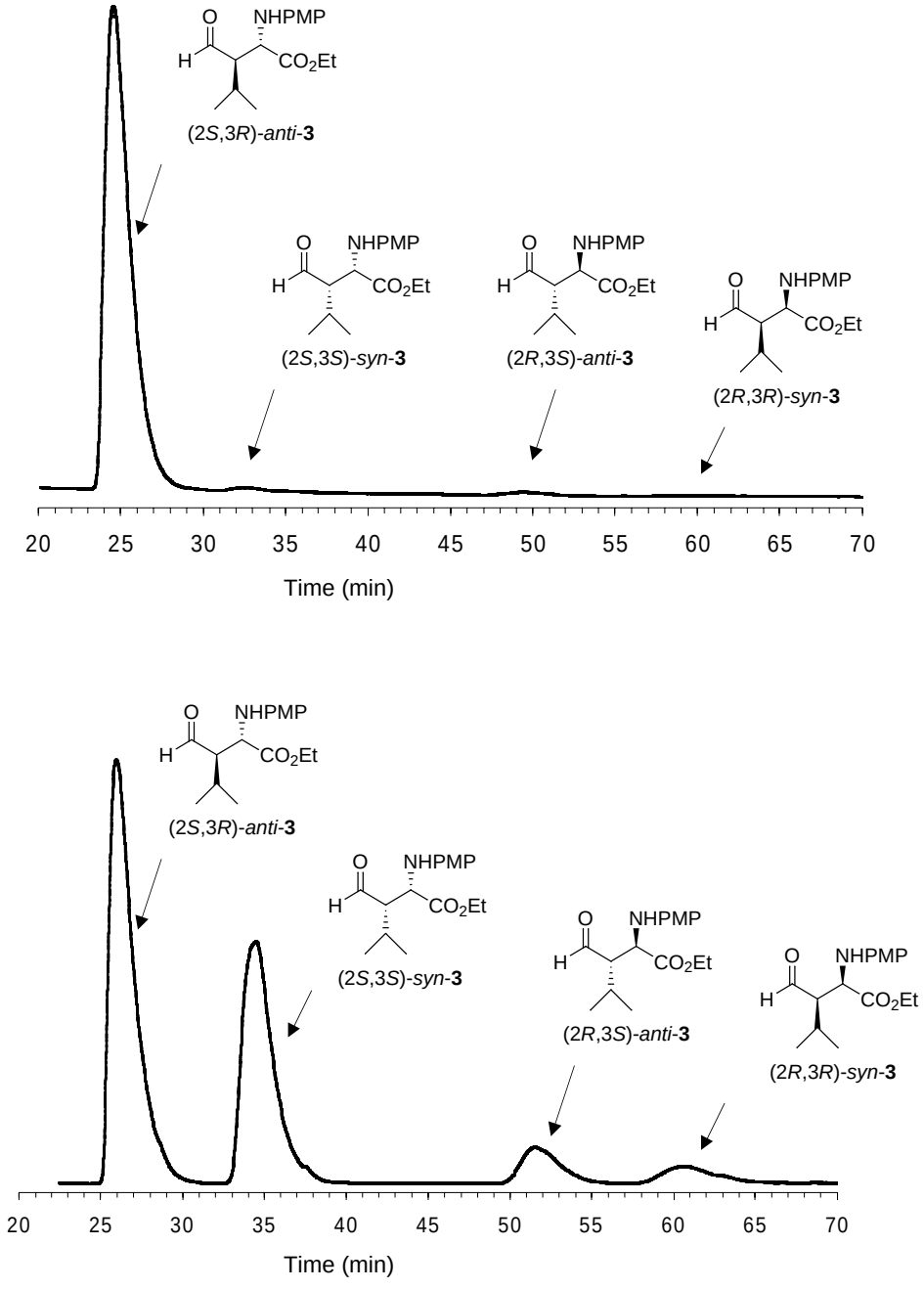
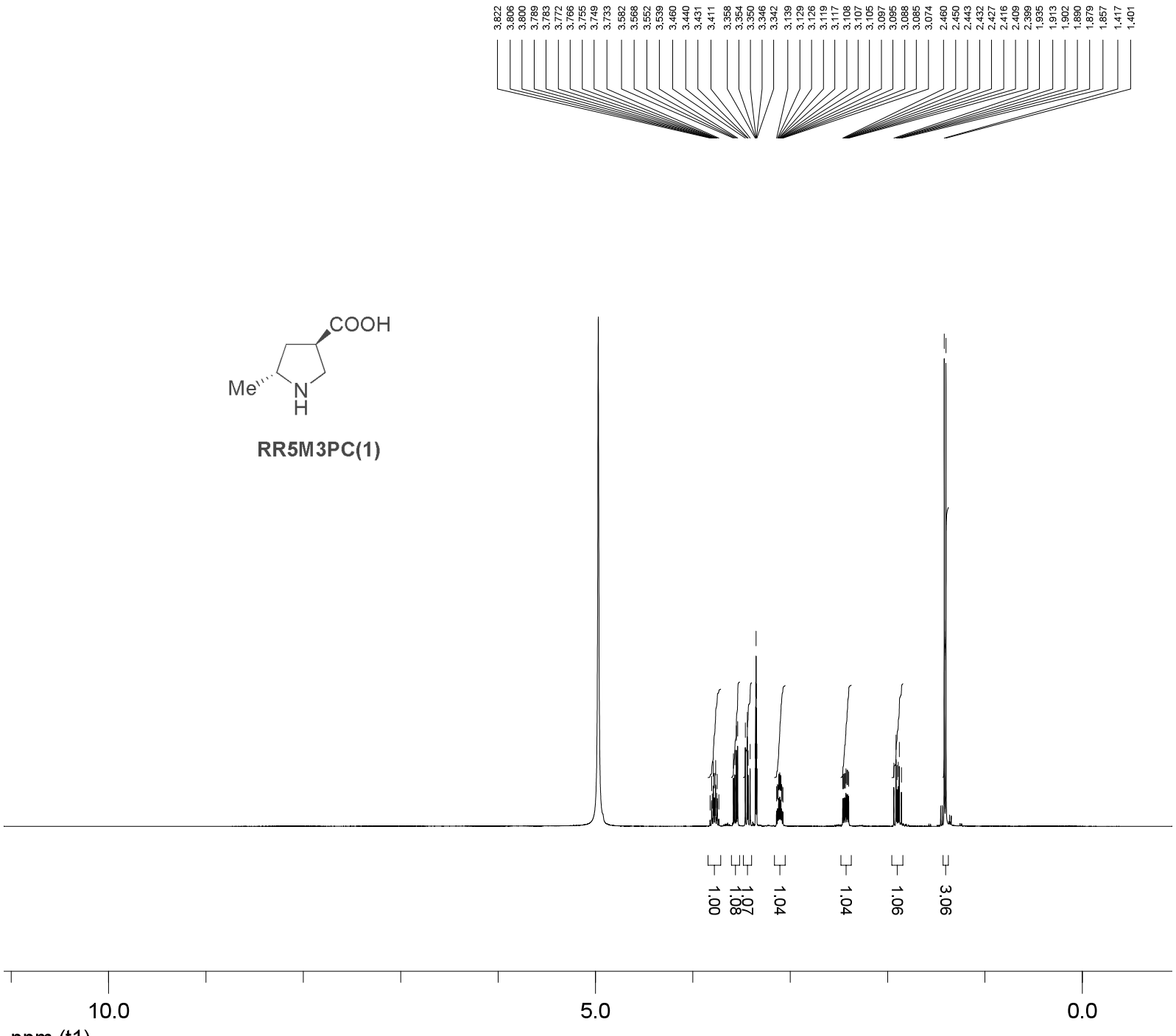


Figure S1. HPLC charts of the Mannich product **3** generated by the **1**-catalyzed reaction (upper chart) and of a mixture of the diastereomers and enantiomers of **3** (lower chart).



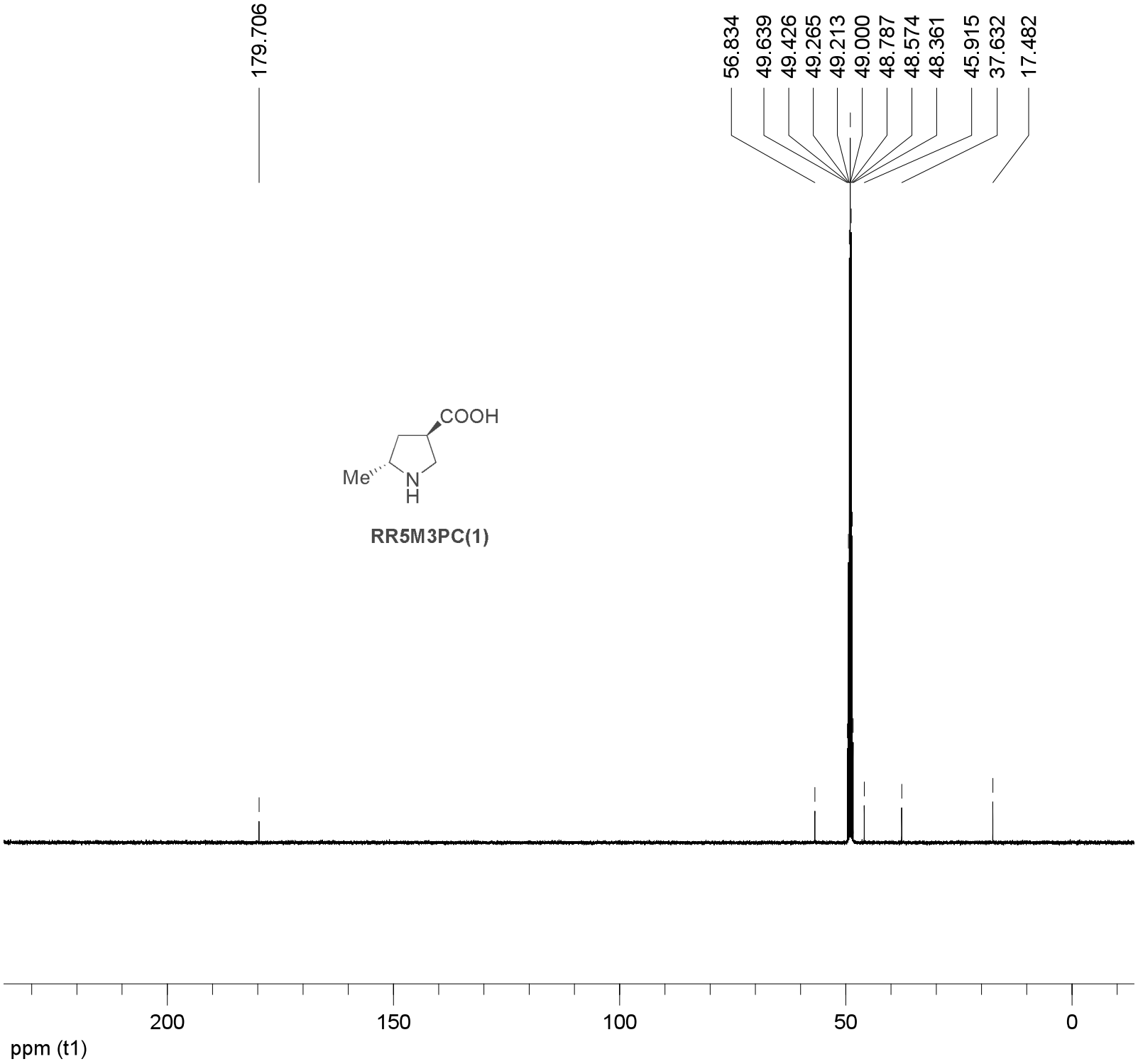
Date:
11 Oct 2005
Document's Title:
catalyst.fid.mrc

Spectrum Title:
susumu278-01_30Aug2005

Frequency (MHz):
(f1) 399.740
Original Points Count:
(f1) 17959
Actual Points Count:
(f1) 65536
Acquisition Time (sec):
(f1) 3.7440
Spectral Width (ppm):
(f1) 12.000
Pulse Program:
Unknown
Temperature:
29

Number of Scans:
128

Acq. Date:
Aug 30 2005



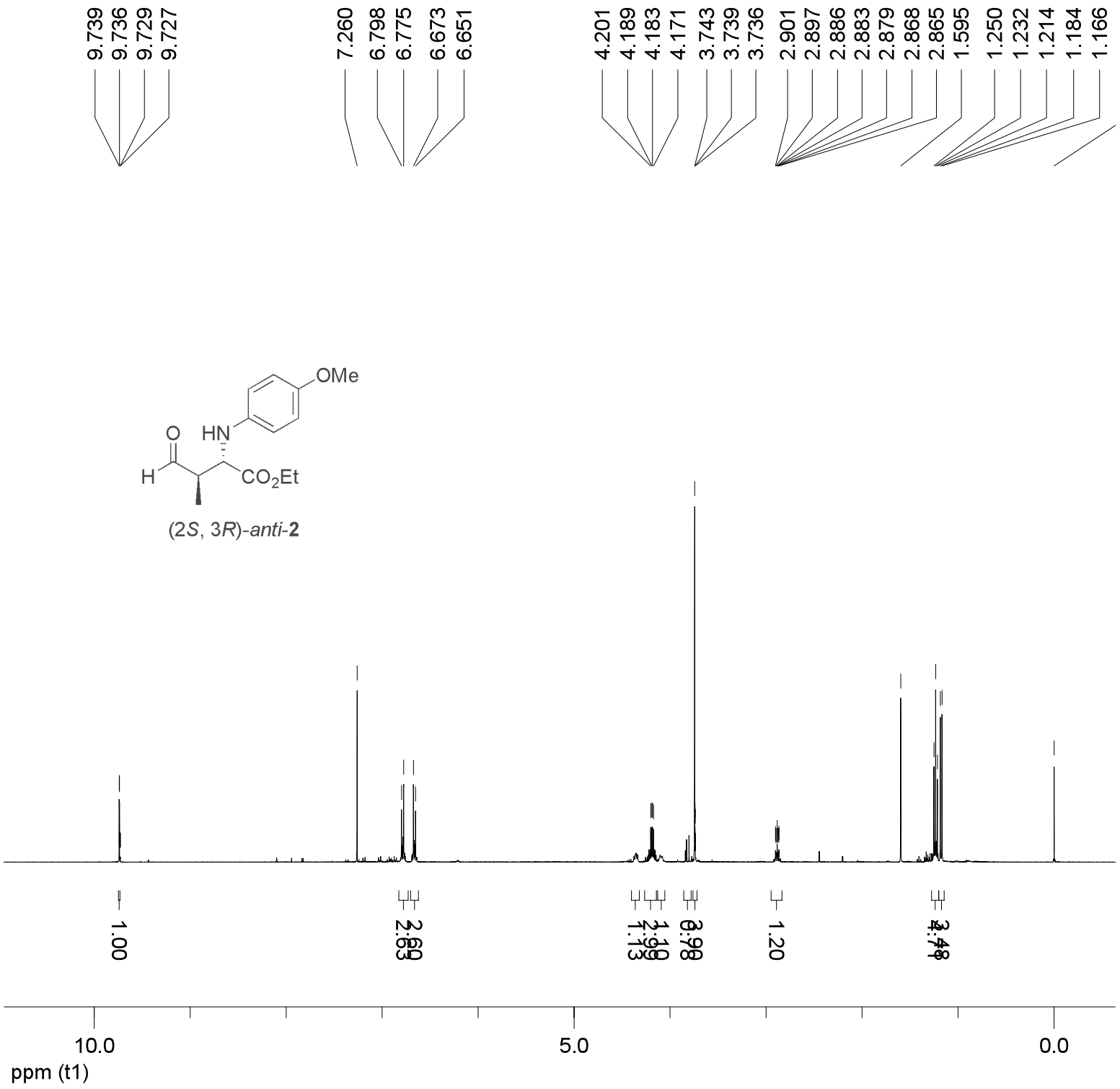
Date:
11 Oct 2005
Document's Title:
catalyst(carbon13).fid.mrc

Spectrum Title:
susumu278-01_31Aug2005

Frequency (MHz):
(f1) 100.525
Original Points Count:
(f1) 30135
Actual Points Count:
(f1) 65536
Acquisition Time (sec):
(f1) 1.1994
Spectral Width (ppm):
(f1) 249.944
Pulse Program:
Unknown
Temperature:
29

Number of Scans:
512

Acq. Date:
Aug 31 2005



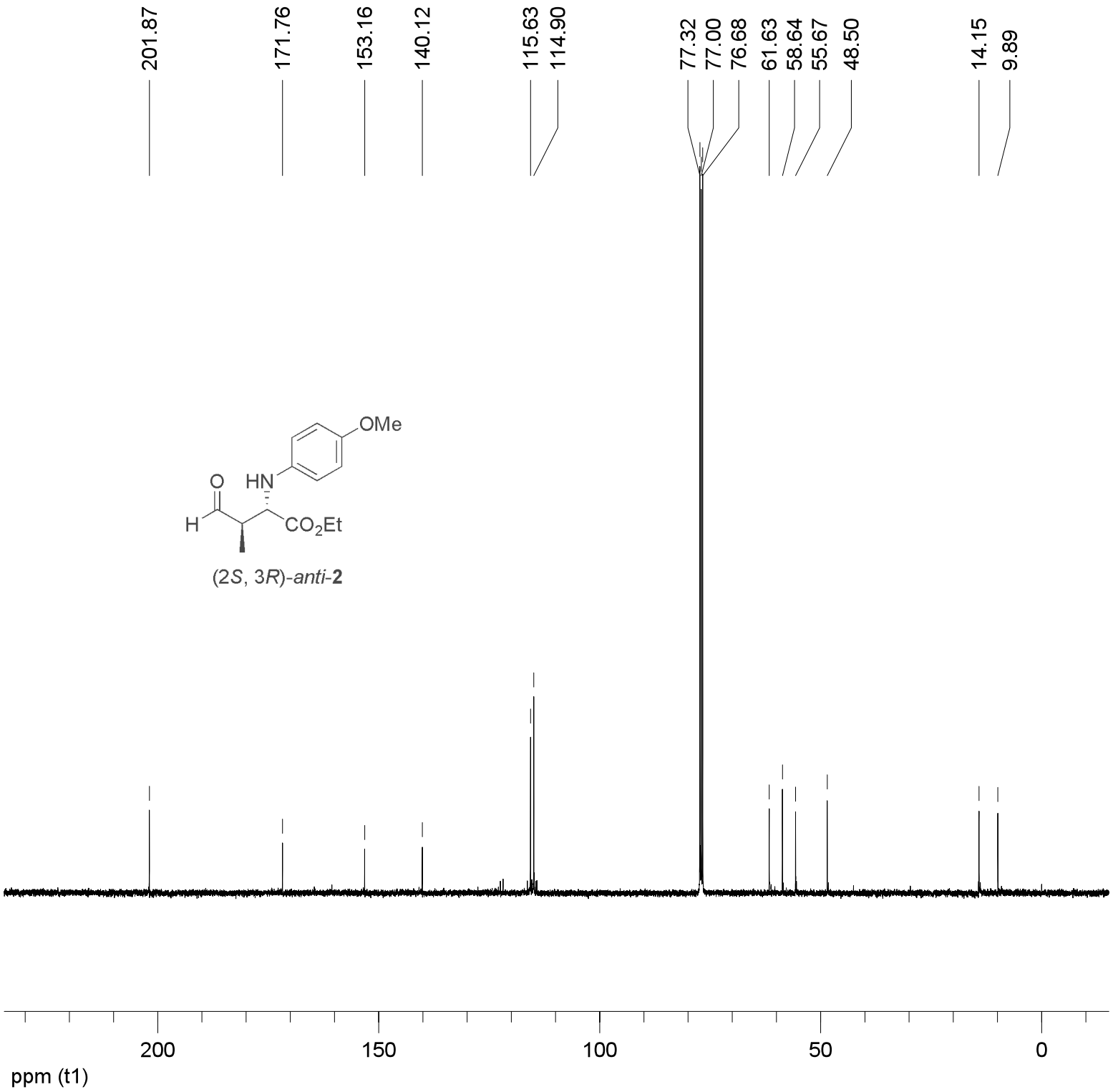
Date:
16 Sep 2005
Document's Title:
Me.mrc

Spectrum Title:
ZHL-1203A_08Sep2005

Frequency (MHz):
(f1) 399.739
Original Points Count:
(f1) 23946
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 3.7440
Spectral Width (ppm):
(f1) 16.000
Pulse Program:
Unknown
Temperature:
29

Number of Scans:
8

Acq. Date:
Sep 8 2005



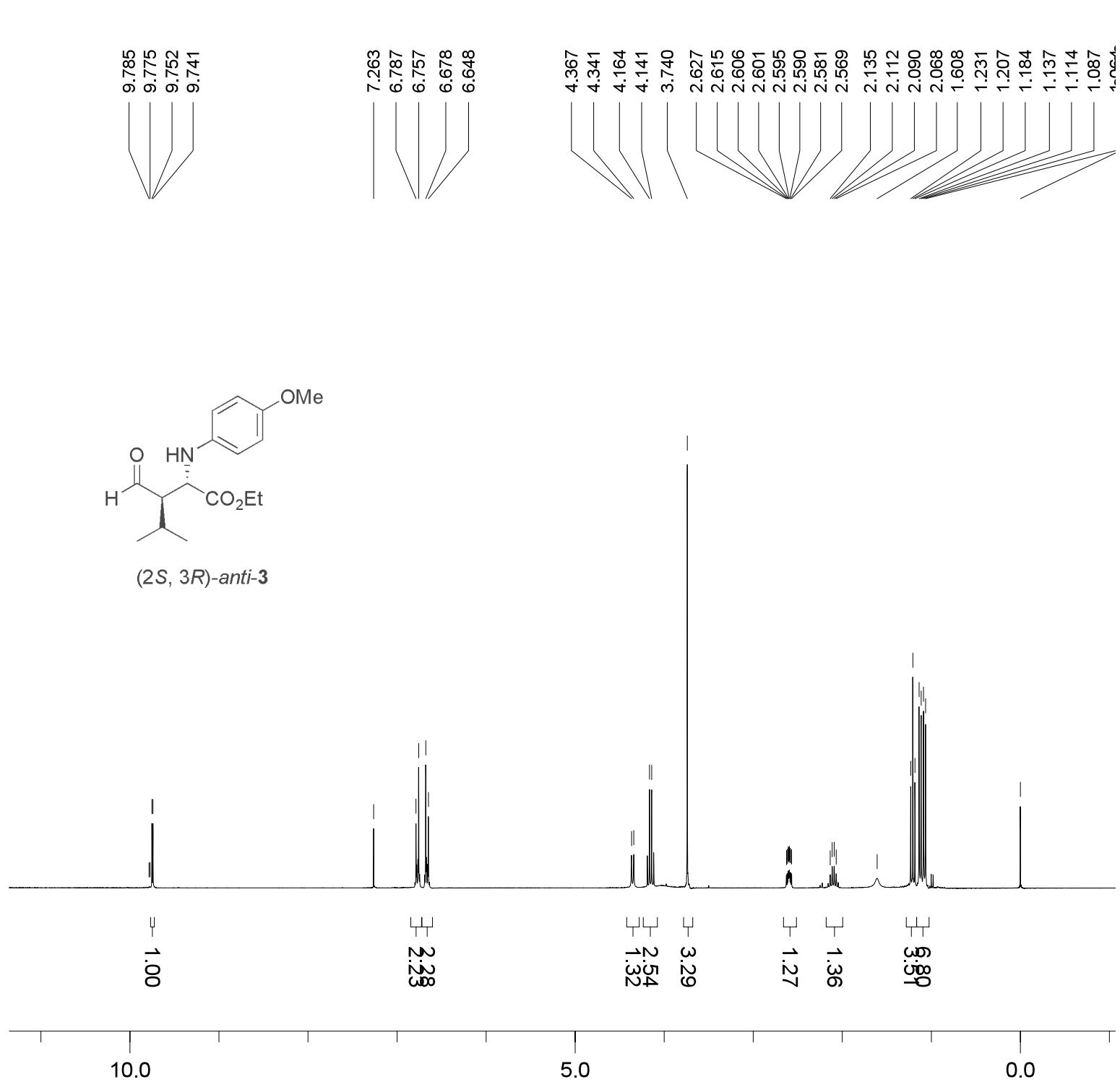
Date:
10 Oct 2005
Document's Title:
Me-car.mrc

Spectrum Title:
ZHL-1203ACar_08Sep2005

Frequency (MHz):
(f1) 100.525
Original Points Count:
(f1) 30135
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 1.1994
Spectral Width (ppm):
(f1) 249.945
Pulse Program:
Unknown
Temperature:
29

Number of Scans:
2000

Acq. Date:
Sep 8 2005



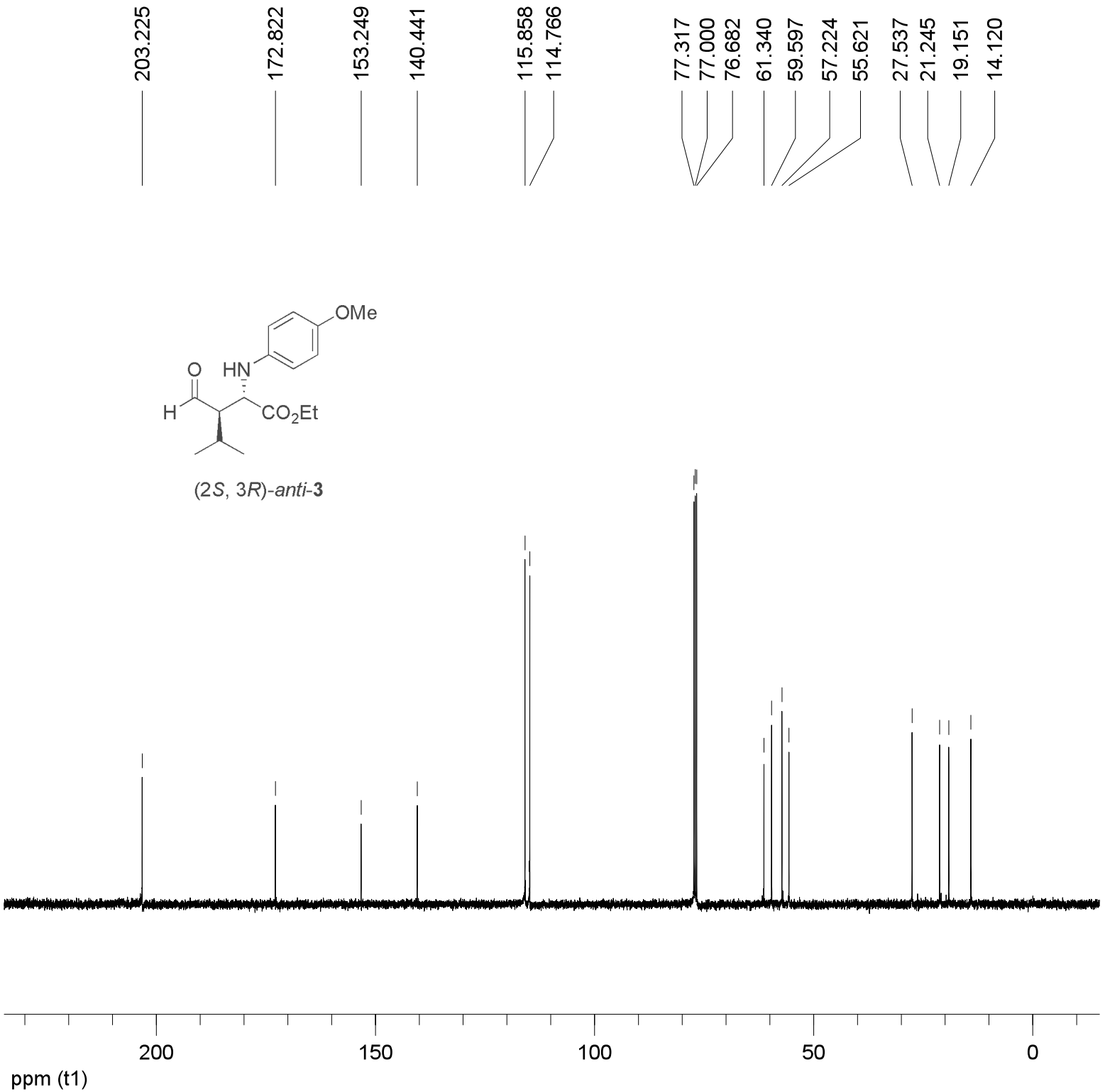
Date:
16 Sep 2005
Document's Title:
iPr.mrc

Spectrum Title:
ZHL-1194sec_02Sep2005

Frequency (MHz):
(f1) 300.143
Original Points Count:
(f1) 9596
Actual Points Count:
(f1) 16384
Acquisition Time (sec):
(f1) 1.9979
Spectral Width (ppm):
(f1) 16.003
Pulse Program:
Unknown
Temperature:
25

Number of Scans:
40

Acq. Date:
Sep 2 2005



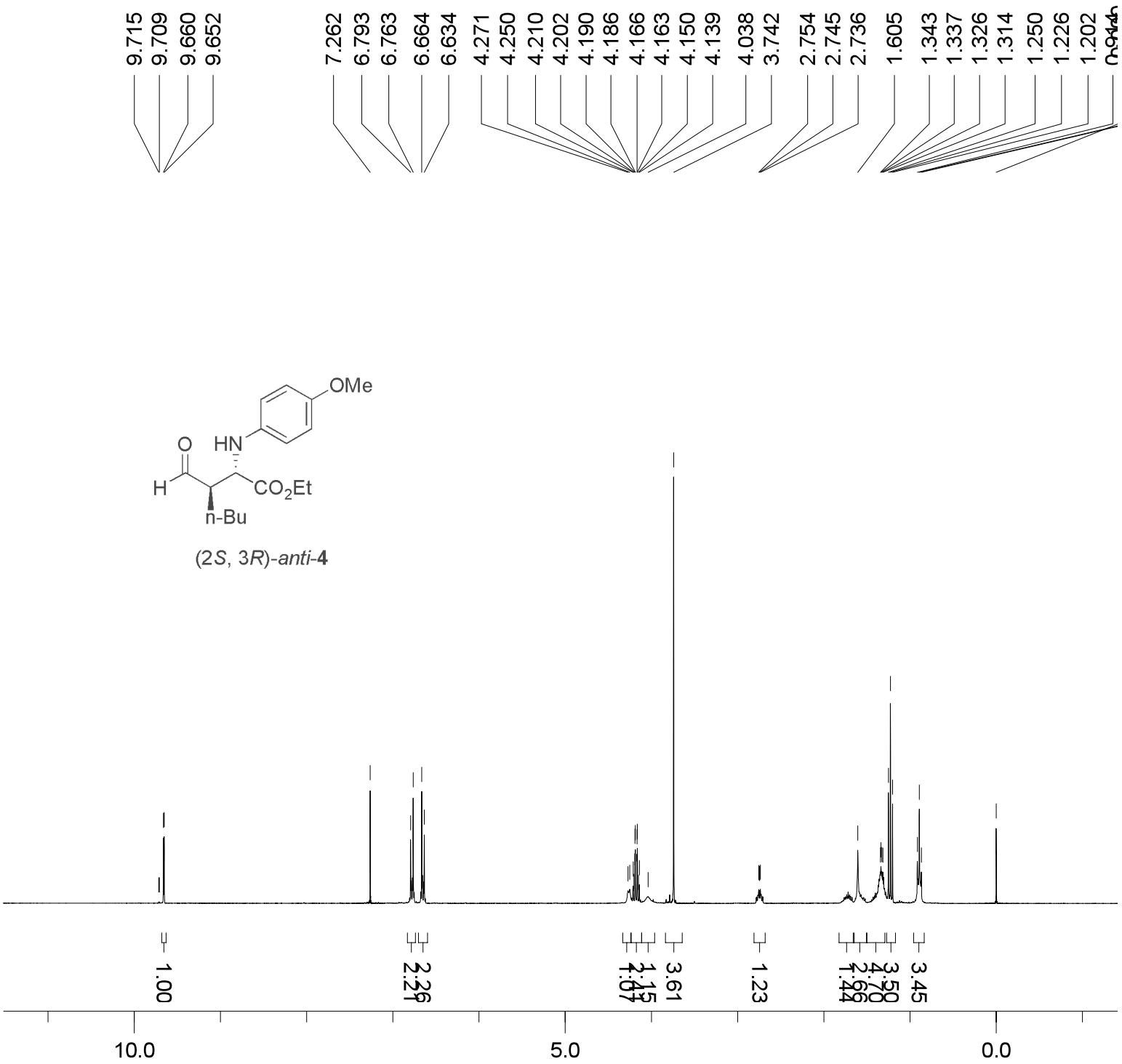
Date:
10 Oct 2005
Document's Title:
iPr-car.mrc

Spectrum Title:
ZHL-1194car_01Sep2005

Frequency (MHz):
(f1) 100.525
Original Points Count:
(f1) 30135
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 1.1994
Spectral Width (ppm):
(f1) 249.945
Pulse Program:
Unknown
Temperature:
29

Number of Scans:
256

Acq. Date:
Sep 1 2005



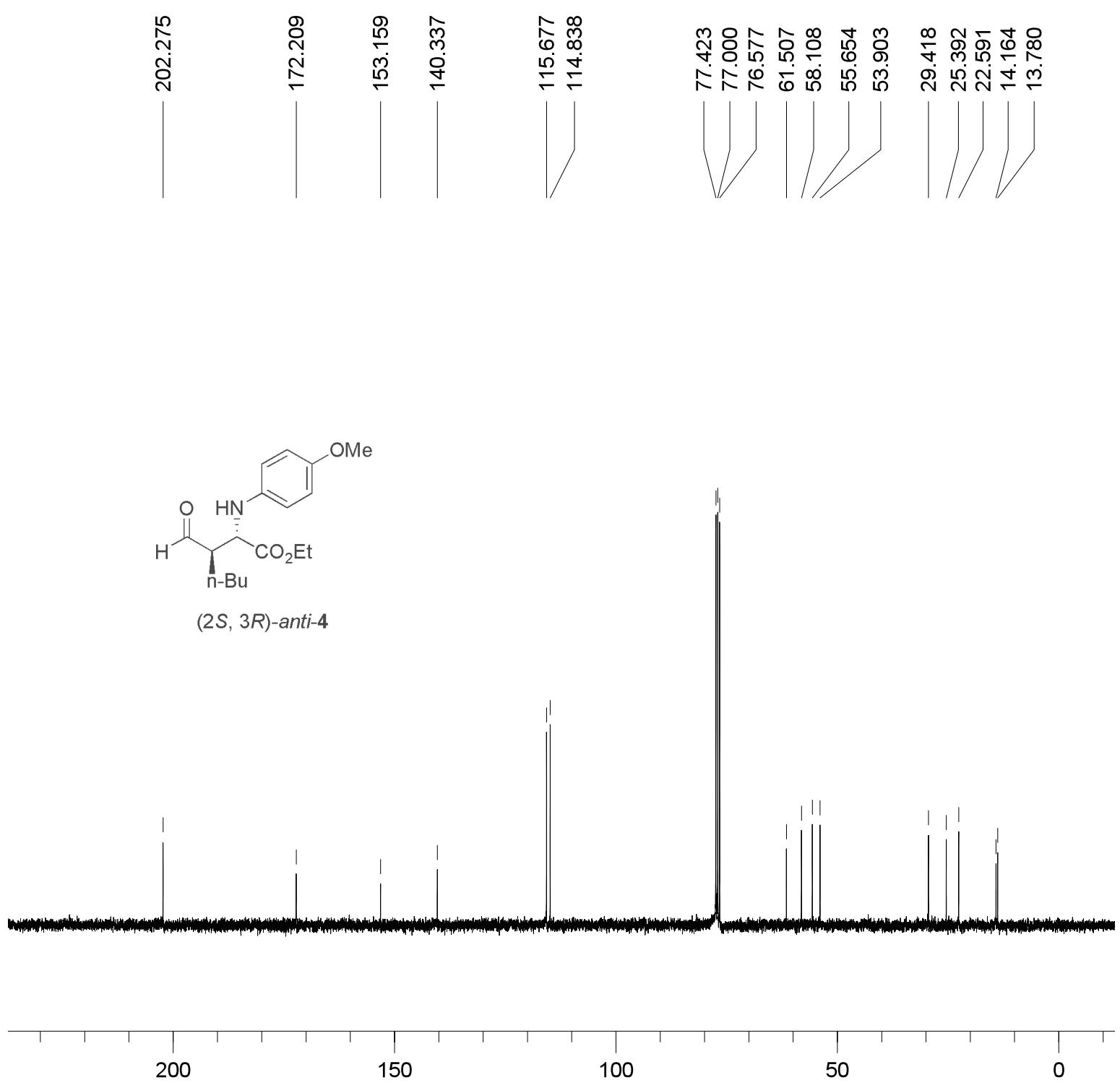
Date:
16 Sep 2005
Document's Title:
Bu.mrc

Spectrum Title:
ZHL-1201A-b1_07Sep2005

Frequency (MHz):
(f1) 300.143
Original Points Count:
(f1) 9596
Actual Points Count:
(f1) 16384
Acquisition Time (sec):
(f1) 1.9979
Spectral Width (ppm):
(f1) 16.003
Pulse Program:
Unknown
Temperature:
25

Number of Scans:
40

Acq. Date:
Sep 7 2005



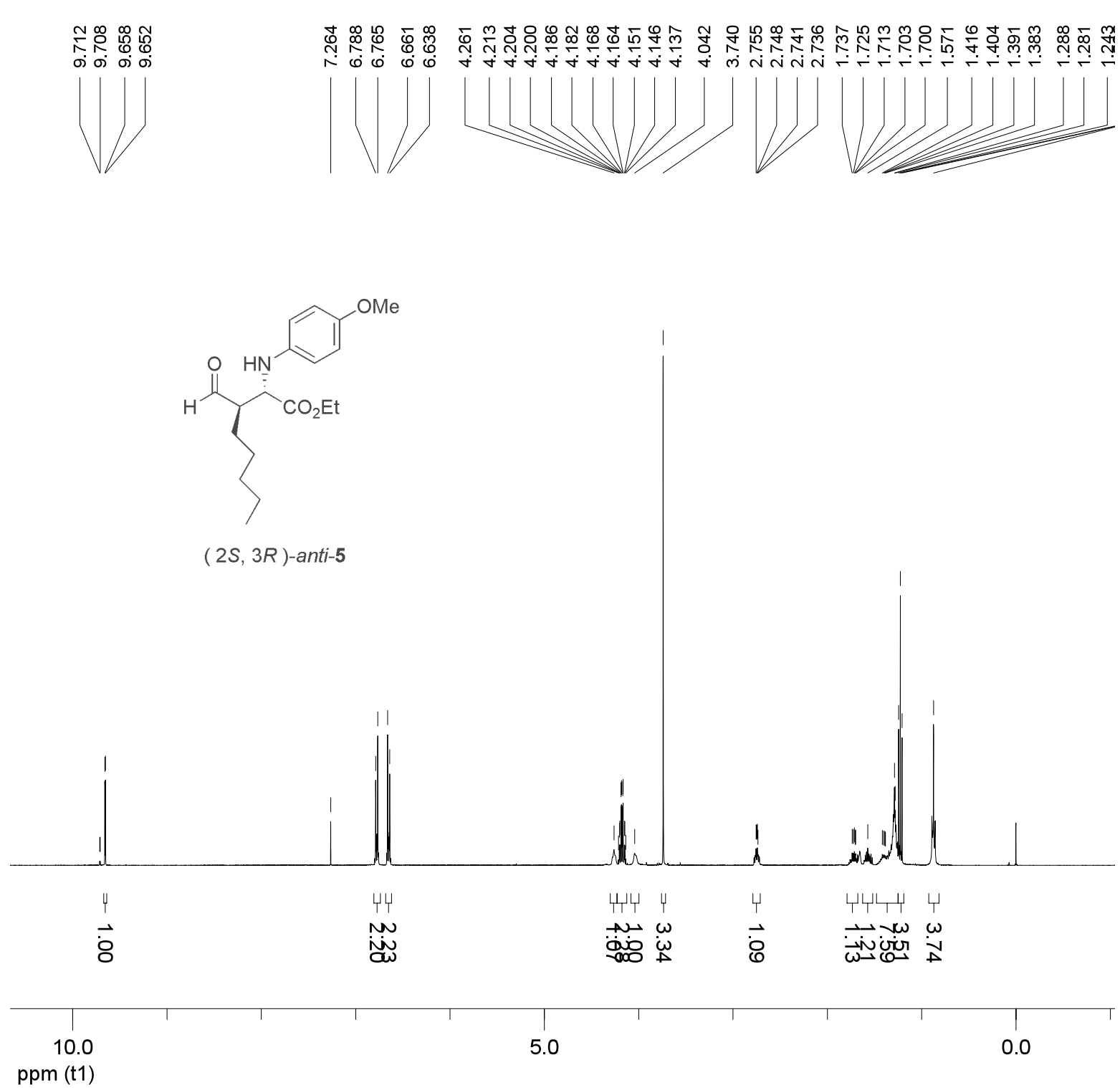
Date:
16 Sep 2005
Document's Title:
ZHL-1201-Acar.mrc

Spectrum Title:
ZHL-1201-Ab1car_07Sep2005

Frequency (MHz):
(f1) 75.479
Original Points Count:
(f1) 34246
Actual Points Count:
(f1) 65536
Acquisition Time (sec):
(f1) 1.8150
Spectral Width (ppm):
(f1) 249.976
Pulse Program:
Unknown
Temperature:
25

Number of Scans:
1000

Acq. Date:
Sep 7 2005



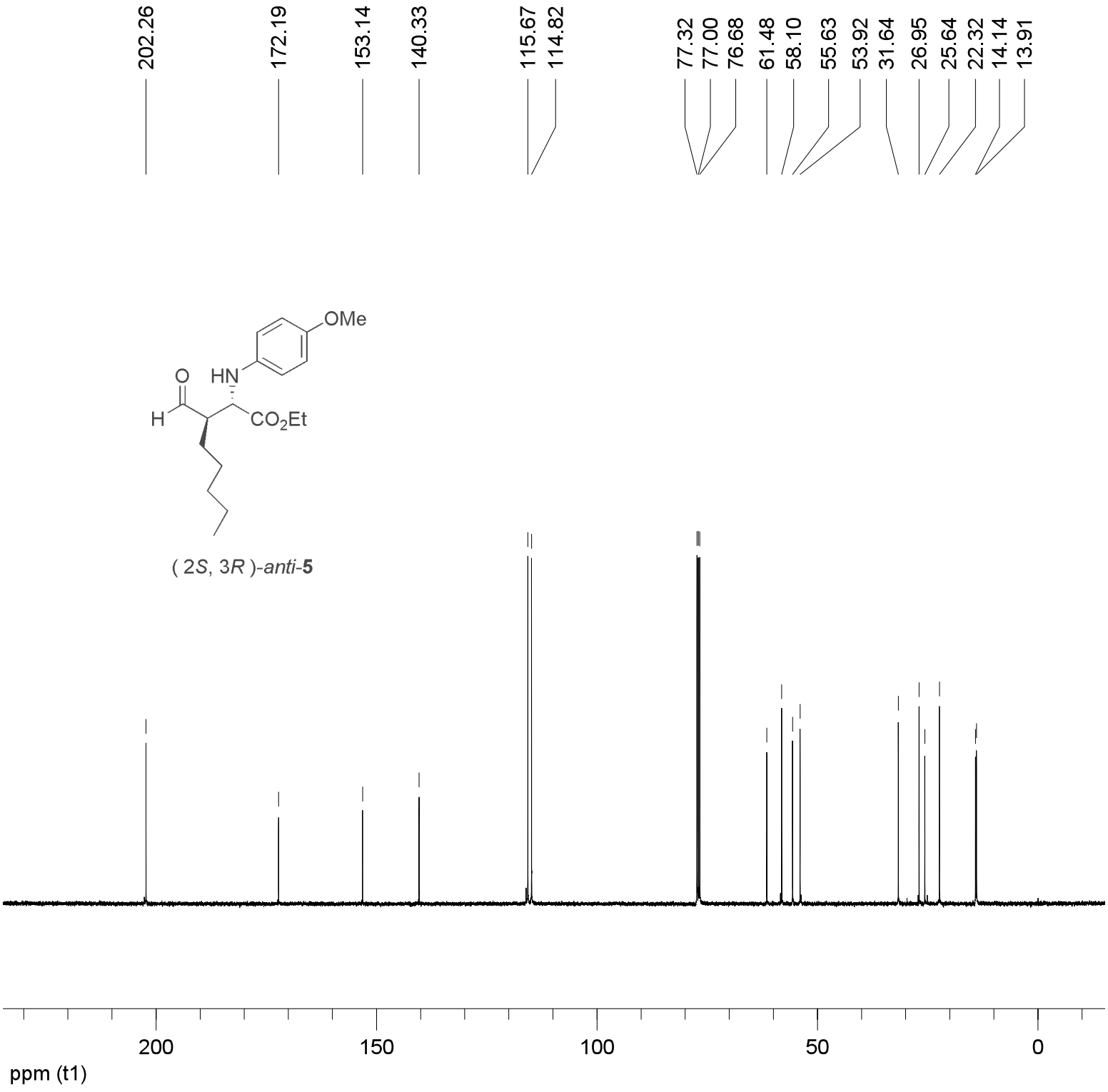
Date:
17 Sep 2005
Document's Title:
pent.mrc

Spectrum Title:
ZHL-1197-5789_06Sep2005

Frequency (MHz):
(f1) 399.739
Original Points Count:
(f1) 23946
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 3.7440
Spectral Width (ppm):
(f1) 16.000
Pulse Program:
Unknown
Temperature:
29

Number of Scans:
8

Acq. Date:
Sep 6 2005



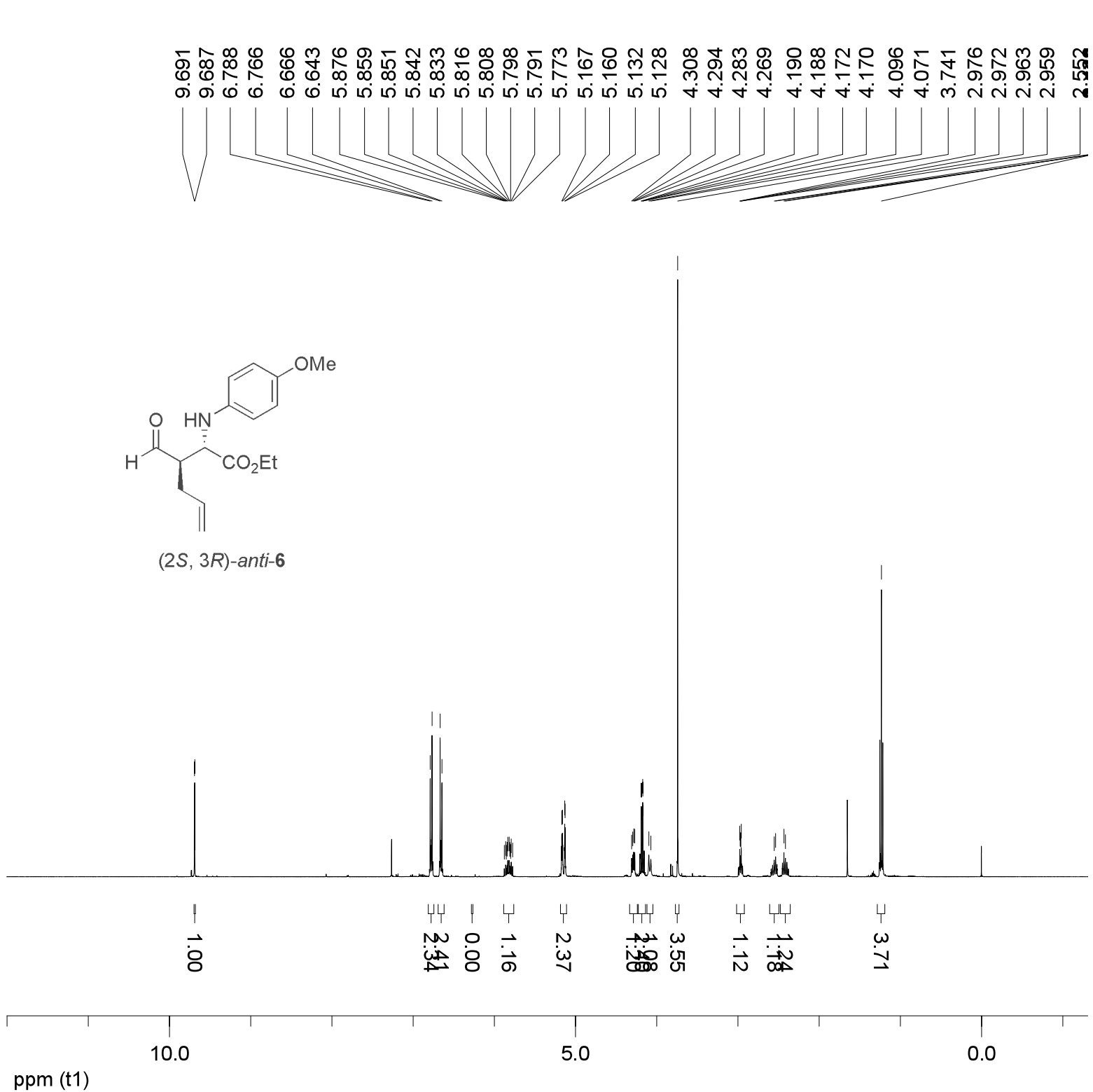
Date:
10 Oct 2005
Document's Title:
pent- car.mrc

Spectrum Title:
ZHL-1197-5789car_06Sep2005

Frequency (MHz):
(f1) 100.525
Original Points Count:
(f1) 30135
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 1.1994
Spectral Width (ppm):
(f1) 249.945
Pulse Program:
Unknown
Temperature:
29

Number of Scans:
1000

Acq. Date:
Sep 6 2005



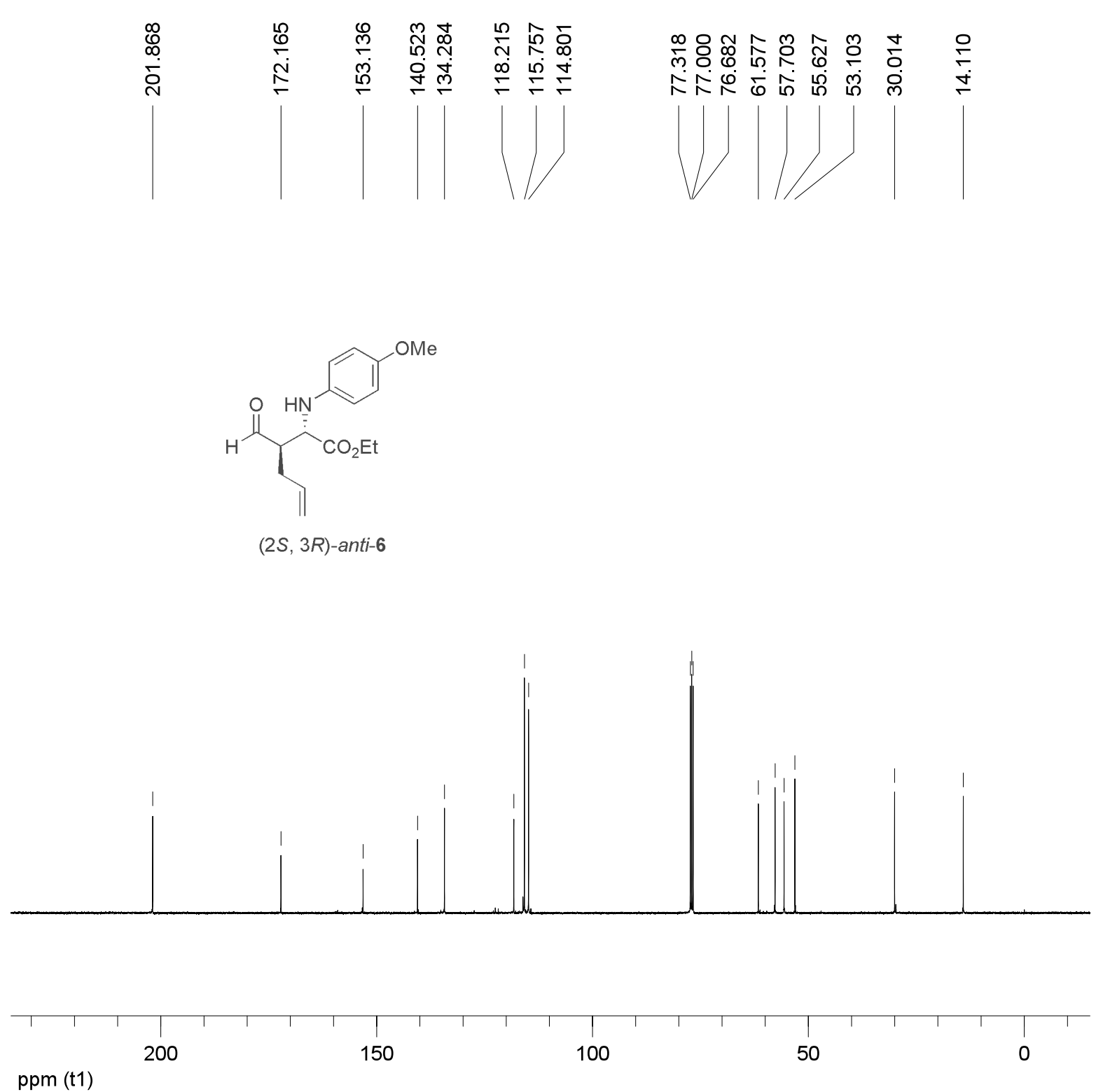
Date:
17 Sep 2005
Document's Title:
e-for JACS.mrc

Spectrum Title:
ZHL-1209-d1-d4_11Sep2005

Frequency (MHz):
(f1) 399.739
Original Points Count:
(f1) 23946
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 3.7440
Spectral Width (ppm):
(f1) 16.000
Pulse Program:
Unknown
Temperature:
29

Number of Scans:
8

Acq. Date:
Sep 11 2005



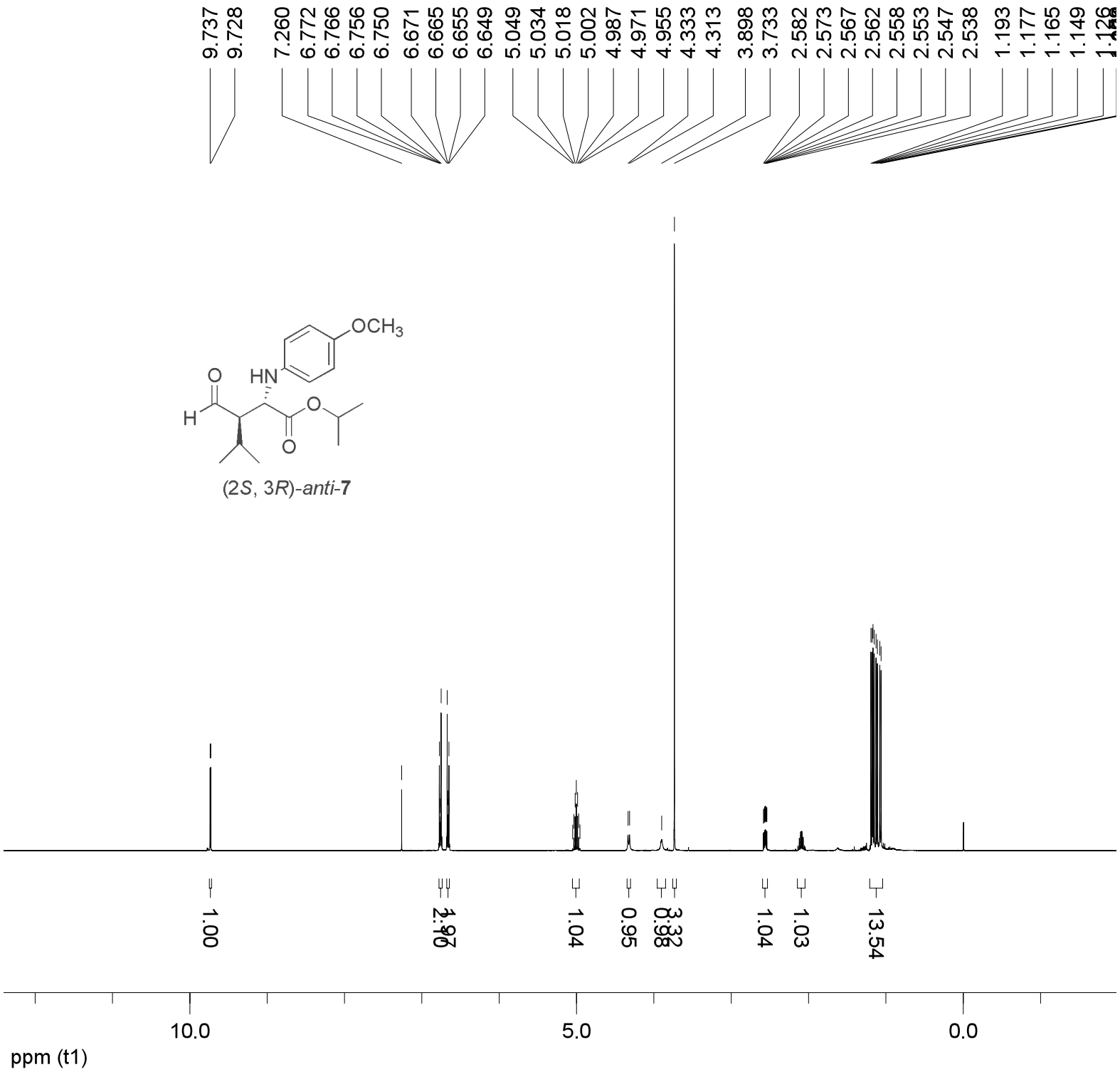
Date:
10 Oct 2005
Document's Title:
e-car.mrc

Spectrum Title:
ZHL-1209-d1d4car_11Sep2005

Frequency (MHz):
(f1) 100.525
Original Points Count:
(f1) 30135
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 1.1994
Spectral Width (ppm):
(f1) 249.945
Pulse Program:
Unknown
Temperature:
29

Number of Scans:
2000

Acq. Date:
Sep 11 2005



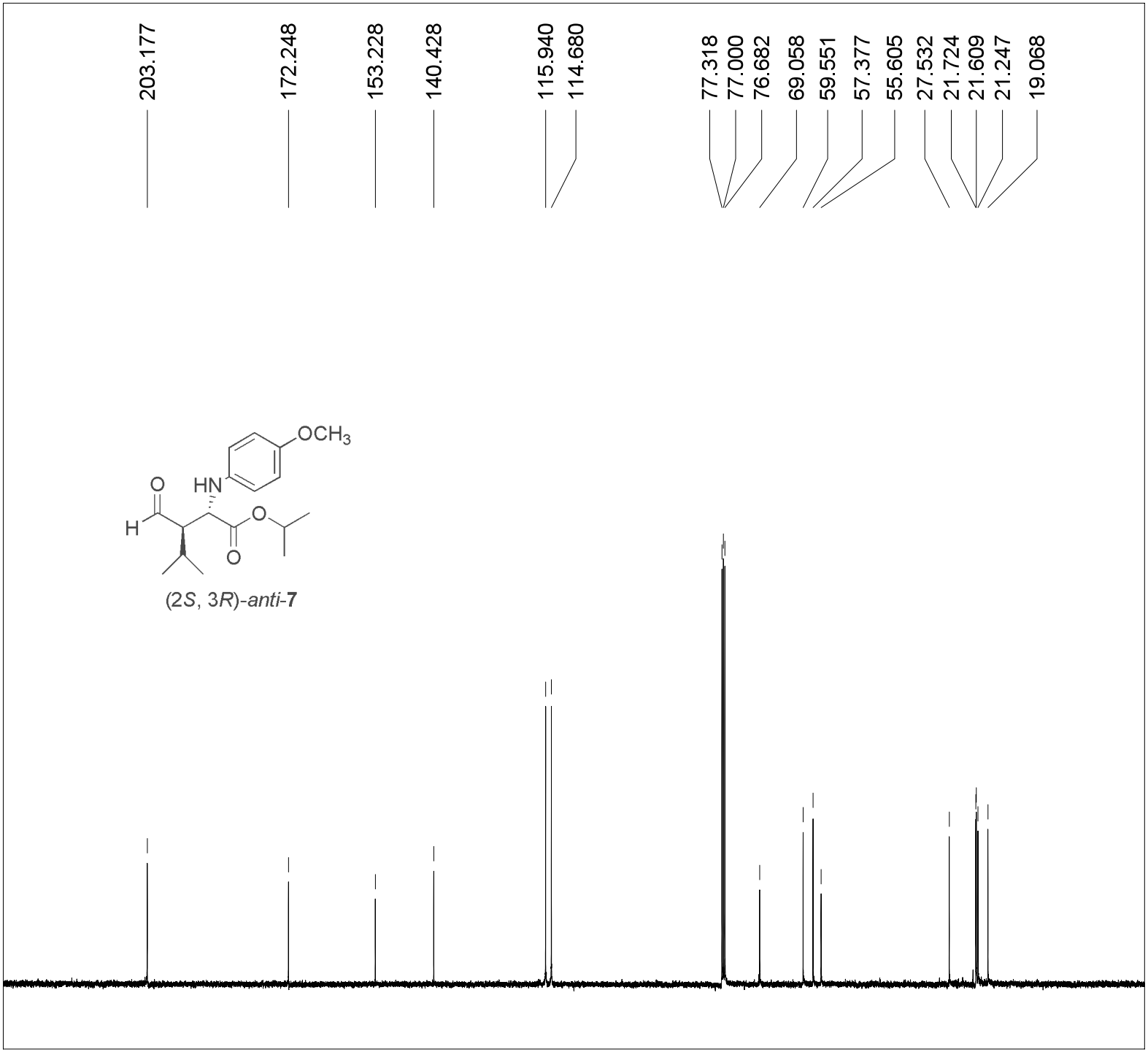
Date:
21 Nov 2005
Document's Title:
ZHL-1287.mrc

Spectrum Title:
ZHL-1287-ipr_19Nov2005

Frequency (MHz):
(f1) 399.739
Original Points Count:
(f1) 23946
Actual Points Count:
(f1) 65536
Acquisition Time (sec):
(f1) 3.7440
Spectral Width (ppm):
(f1) 16.000
Pulse Program:
Unknown
Temperature:
29

Number of Scans:
8

Acq. Date:
Nov 19 2005



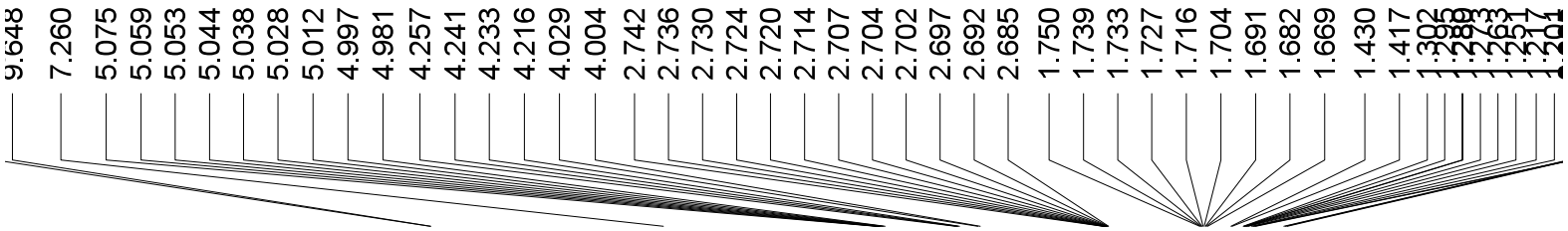
Date:
21 Nov 2005
Document's Title:
ZHL-1284car.mrc

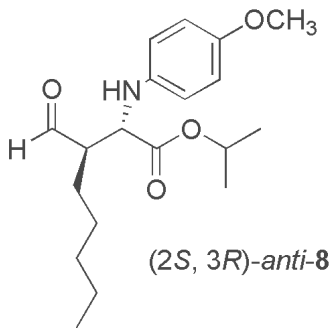
Spectrum Title:
ZHL-1284car_18Nov2005

Frequency (MHz):
(f1) 100.525
Original Points Count:
(f1) 30135
Actual Points Count:
(f1) 65536
Acquisition Time (sec):
(f1) 1.1994
Spectral Width (ppm):
(f1) 249.945
Pulse Program:
Unknown
Temperature:
29

Number of Scans:
5000

Acq. Date:
Nov 18 2005





(2*S*, 3*R*)-*anti*-**8**

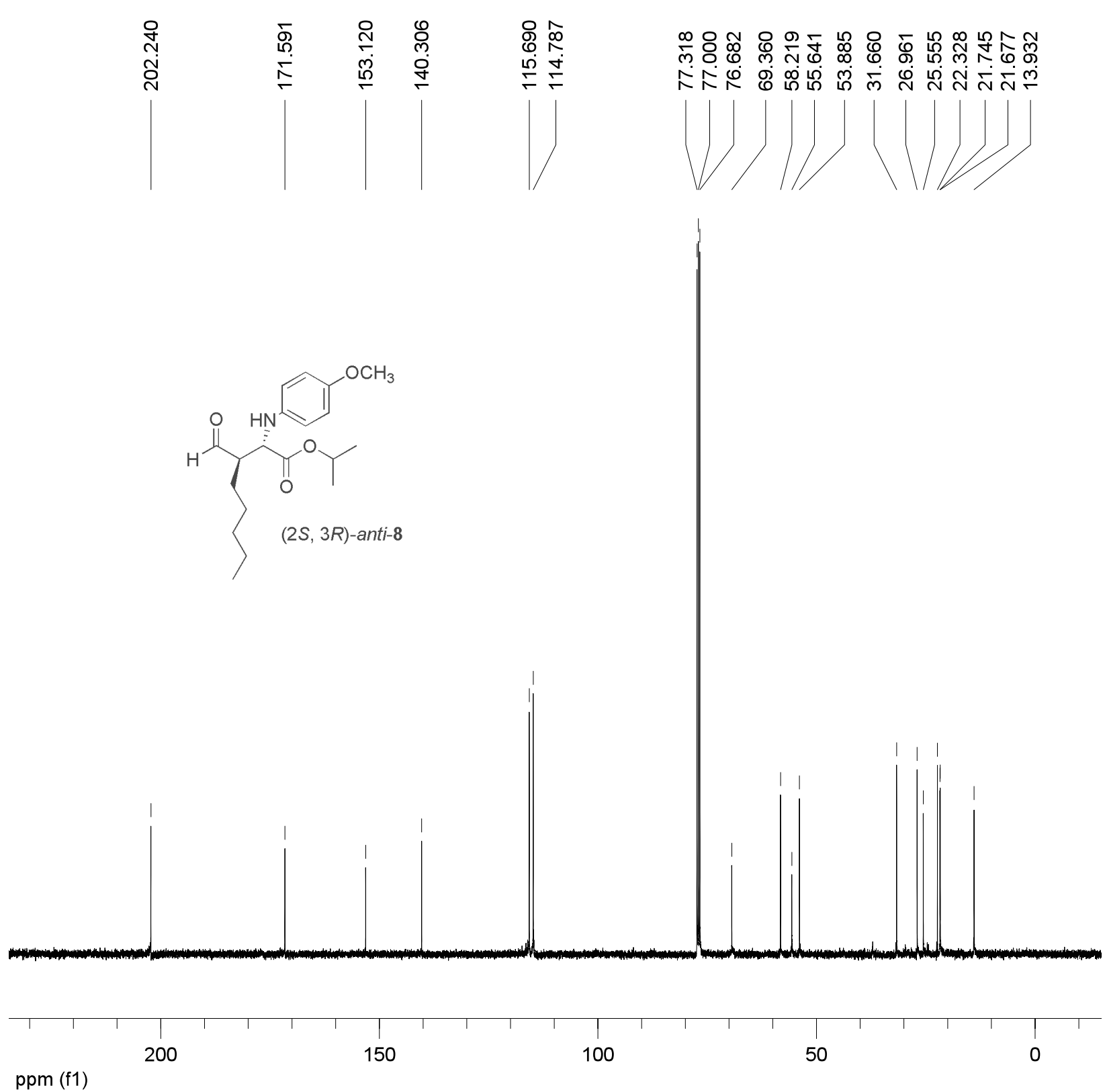
Date:
21 Nov 2005
Document's Title:
ZHL-1288-pent-H.mrc

Spectrum Title:
ZHL-1287-pent_19Nov2005

Frequency (MHz):
(f1) 399.739
Original Points Count:
(f1) 23946
Actual Points Count:
(f1) 65536
Acquisition Time (sec):
(f1) 3.7440
Spectral Width (ppm):
(f1) 16.000
Pulse Program:
Unknown
Temperature:
29

Number of Scans:
8

Acq. Date:
Nov 19 2005



Date:
21 Nov 2005
Document's Title:
ZHL-1288-pentcar.mrc

Spectrum Title:
ZHL-1288car_19Nov2005

Frequency (MHz):
(f1) 100.525
Original Points Count:
(f1) 30135
Actual Points Count:
(f1) 65536
Acquisition Time (sec):
(f1) 1.1994
Spectral Width (ppm):
(f1) 249.945
Pulse Program:
Unknown
Temperature:
29

Number of Scans:
2000

Acq. Date:
Nov 19 2005