The Direct Organocatalytic Asymmetric Mannich-Reaction – Unmodified Aldehydes as Nucleophiles

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General. Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates 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), conc. H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating or by treatment with a solution of p-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed using silica gel (particle size 0.040-0.063 mm). For ^{1}H NMR and chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants *J* are given in Hz. The spectra were recorded in $CDCl_3$ or CD_3OD as solvents at room temperature, TMS served as internal standard (δ = 0 ppm) for ^{1}H NMR, and $CDCl_3$ was used as internal standard (δ = 77.0 ppm) for ^{13}C NMR. Optical rotations were recorded at λ=589 nm (1 dm cell). High resolution mass spectra were recorded on a FTMS mass spectrometer with a DHB-matrix.

Typical experimental procedure for the catalytic asymmetric Mannich-type reaction with propionaldehyde and preformed aldimines: Anhydrous DMF (3 mL) was added to a vial containing the corresponding aldimine (0.5 mmol) and proline (30 mol%) and placed in a 4 ºC cold room. The reaction was initiated by slow addition (0.2 μL/min) of a pre-cooled mixture of propionaldehyde (5.0 mmol) in anhydrous DMF (2 mL) with syringe pump at 4 ºC. After 14-15h of total reaction time the reaction mixture was diluted with anhydrous Et_2O (2 mL) and the temperature decreased to at 0 ºC followed by reduction with $NaBH_4$ (400 mg). for 10 minutes. Next, the reaction mixture was poured into a vigorously stirred bi-phasic solution of Et_2O and saturated aqueous NH_4Cl solution (or alternatively sodium phosphate buffer pH=7.2). The organic layer was separated and the aqueous phase was extracted thoroughly with ethyl acetate.

saturated aqueous NH_4Cl solution (or alternatively sodium phosphate buffer pH=7.2). The organic layer was separated and the aqueous phase was extracted thoroughly with ethyl acetate. The combined organic phases were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired β-amino alcohols. The enantiomeric excesses of the products were determined by HPLC analysis using chiral stationary phases.

Typical three-component one-pot experimental procedure for the catalytic asymmetric Mannich-type reaction of aldehydes and *p*-anisidine: To a vial containing the acceptor aldehyde (0.5 mmol), *p*-anisidine (0.5 mmol), proline (30 mol%) and anhydrous DMF (3 mL) was added the corresponding donor aldehyde (5.0 mmol) in anhydrous DMF (2 mL) at 4 ºC with syringe pump. After 15-16h of total reaction time the temperature was decreased to 0ºC followed by dilution with anhydrous Et_2O (2 mL) and reduction with $NaBH_4$ (400 mg) for 10 minutes. Next, the reaction mixture was poured into a vigorously stirred bi-phasic solution of Et_2O and saturated aqueous NH_4Cl solution (or alternatively sodium phosphate buffer pH=7.2). The organic layer was separated and the aqueous phase was extracted thoroughly with ethyl acetate. The combined organic phases were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired β-amino alcohols. The enantiomeric excesses of the products were determined by HPLC analysis using chiral stationary phases.

Typical experimental procedure for the formation of self-Mannich products: To a vial containing *p*-anisidine (0.5 mmol), L-proline (30 mol%) in DMF (5 mL) was added aldehyde (4 mmol) at - 15 ˚C and stirred for 7 h. After completion of the reaction, the mixture was diluted with ether (2 mL) and treated with $NaBH_4$ (400 mg) at 0 ˚C for 10 minutes. The reaction mixture was poured into a half saturated NH_4Cl solution and ether under vigorous stirring, the layers were separated and the aqueous phase was extracted thoroughly with ether. The combined organic phases were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired amino alcohols.

Experimental protocol for studying the water effect on Mannich-reaction with α-imino ethyl glyoxylate **(Table 3)**: A mixture of heptanal (0.75 mmol) α-imino ethyl glyoxylate (0.5 mmol), and L-proline (0.05 mmol) in the indicated dioxane-H_2O mixture (5 mL) was stirred for 16–24 h at r.t. The mixture was worked up by the addition of saturated NH_4Cl and extracted with EtOAc. The combined organic layer was washed with saturated NaCl, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography (EtOAc-hexanes) to afford **5**. The enantiomeric excess of *syn*-**5** was determinedd by HPLC. HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 99:1, flow rate 1.0 mL/min, 254 nm): 25.8 min (*anti*-major enantiomer), 28.7 min (*anti*-minor enantiomer), 30.9 min ((*S*,*S*)-**5**), 46.9 min ((*R*,*R*)-**5**).

Experimental protocol for studying the water effect on Mannich-reaction with preformed aromatic imines **(Table 5)**: A solution of propionaldehyde (2.5 mmol) in the indicated DMF-H_2O mixture (2 mL) was slowly added to a mixture of imine (0.5 mmol) and L-proline (0.15 mmol) in the indicated DMF-H_2O mixture (3 mL) over 5 h at 0 °C and the mixture was stirred for 1 h at the same temperature. When the solvent of the Mannich reaction includes H_2O (for entries 3–8), the mixture was added to saturated NH_4Cl and extracted with EtOAc. The

combined organic layers were washed with saturated NaCl and concentrated. The residue in EtOAc (10 mL) was cooled to 0°C and $NaBH_4$ (200 mg, 5.3 mmol) was added to the mixture. After 30 min, the mixture was added to a mixture of ice and saturated NH4Cl and extracted with EtOAc. The combined organic layer was washed with saturated NaCl, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography (EtOAc-hexanes) to afford **11**. For entries 1 and 2, the Mannich-type reaction mixture was diluted with Et_2O (2 mL) and $NaBH_4$ (200 mg, 5.3 mmol) was added to the mixture at 0 °C. The same work up and purification as that of entries 3–8 afforded **11**. The enantiomeric excess of *syn*-**11** was determined by HPLC analysis.

Ethyl (2S,3S)-6-tert-Butyldimethylsilyloxy-3-formyl-2-(p-methoxyphenylamino)-hexanoate (**6**): ^{1}H NMR (~1.5:1-mixture of diastereomers): 0.04 (s, 6H), 0.89 (s, 9H), 1.22-1.26 (m, 3H), 1.50-1.95 (m, 4H), 2.78 (m, 1H), 3.61 (m, 2H), 3.74 (s, 3H, OMe), 3.97 (bs, 1H), 4.06 (bs, 1H), 4.16 (m, 2H), 4.27 (m, 1H), 4.34 (m, 1H), 6.65 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 9.66 (s, 1H), 9.72 (s, 1H); ^{13}C NMR: 14.4, 18.5, 22.0, 26.1, 30.5, 30.8, 53.7, 53.9, 55.7, 55.9, 58.7, 61.8, 62.6, 62.7, 115.0, 115.1, 116.0, 116.3, 140.6, 140.7, 153.4, 13.6, 172.4, 172.6, 202.5, 202.8; HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 99:1, flow rate 0.7 mL/min, λ = 254 nm): major diastereomer: t_R (major) = 9.49 min; t_R (minor) = 12.49 min; HR-MS: 446.2339; $C_{22}H_{37}NO_5SiNa^+$ (calcd 446.2333)

Ethyl (2S,3S,4S)-4,8-dimethyl-3-formyl-2-(p-methoxyphenylamino)-non-7-enoate (**7**): ^{1}H NMR: 1.13-1.23 (m, 6H), 1.53-1.72 (m, 7H), 1.85-2.22 (m, 4H), 2.64 (m, 1H), 3.74 (s, 3H, OMe), 3.84 (bs, 1H), 4.16 (m, 2H), 4.33 (m, 1H), 5.03 (m, 1H), 6.67 (d, J = 8.6 Hz, 2H), 6.77 (d, J = 8.6 Hz, 2H), 9.75 (m, 1H); ^{13}C NMR: 14.4, 17.7, 17.9, 25.8, 25.9, 30.8, 34.3, 55.9, 57.1, 59.2, 61.7, 115.1, 116.1, 123.9, 132.5, 140.5, 153.4, 173.0, 203.8; HR-MS: 384.2145; $C_{21}H_{31}NO_4Na^+$ (calcd 384.2145)

(2S,3S)-2-Methyl-3-(4-methoxyphenylamino)-3-(4-nitrophenyl)-propan-1-ol (**11**): ^{1}H NMR ($CDCl_3$): δ = 0.91 (d, 3H, J = 7.0 Hz); 2.21 (m, 1H); 3.64 (m, 2H), 3.67 (s, 3H, OMe); 4.65 (d, 1H, J = 4.0 Hz); 6.42 (d, 2H, J = 8.8 Hz); 6.68 (d, 2H, J = 8.8 Hz);); 7.51 (d, 2H, J = 8.8 Hz); 8.17 (d, 2H, J = 8.8 Hz); ^{13}C NMR (CD_3OD): δ = 11.9, 41.6, 56.0, 60.8, 66.0; 115.0, 115.1, 123.9, 128.3, 141.0, 147.3, 150.6, 152.6; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm): major isomer: t_R = 36.10 min; minor isomer: t_R = 21.49 min; $[\alpha]_D$ = -65.2 (c=0.2, MeOH); HR-MS: 317.1496; $C_{17}H_{20}NO_2$ ($M+H^+$: calcd 317.1496).

*Anti/syn-**11** (from SMP-reaction):* HPLC (Daicel Chiralpak OD-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, 254 nm): 28.0 min ((*S*,*S*)-**11**), 31.4 min ((*R*,*R*)-**11**), 35.6 min (anti), 50.0 min (anti); ^{1}H NMR (400 MHz, $CDCl_3$) (*syn*:*anti* = 1:1, * donates the *anti*-diastereomer) δ 0.89 (d, J = 7.0 Hz, 3H* x 1/2), 0.90 (d, J = 7.0 Hz, 3H x 1/2), 2.12 (m, 1H* x 1/2), 2.21 (m, 1H x 1/2), 3.67 (s, 3H), 3.63–3.74 (m, 2H), 4.38 (d, *J* = 7.0 Hz, 1H* x 1/2), 4.65 (d, *J* = 3.8 Hz, 1H x 1/2), 6.43 (d, *J* = 8.8 Hz, 2H x 1/2), 6.44 (d, *J* = 8.8 Hz, 2H* x 1/2), 6.67 (d, *J* = 8.8 Hz, 2H* x 1/2), 6.68 (d, *J* = 8.8 Hz, 2H x 1/2), 7.48 (d, *J* = 8.8 Hz, 2H* x 1/2), 7.51 (d, *J* = 8.8 Hz, 2H x 1/2), 8.16 (d, *J* = 8.8 Hz, 2H* x 1/2), 8.17 (d, *J* = 8.8 Hz, 2H x 1/2). ^{13}C (100 MHz, $CDCl_3$) (*syn*:*anti* = 1:1) 11.6, 14.4, 41.0, 55.6, 60.4, 65.6, 66.2, 114.6, 114.7, 115.3, 123.6, 123.7, 128.0, 140.5, 140.7, 146.9, 147.0, 150.4, 152.2, 152.5

(2S,3S)-2-Methyl-3-(4-methoxyphenylamino)-3-(4-cyanophenyl)-propan-1-ol (**12**): ^{1}H NMR (CD_3OD): δ = 0.85 (d, 3H, J = 7.0 Hz); 1.98 (m, 1H); 3.32 (dd, 1H), 3.45 (dd, 1H) 3.67 (s, 3H, OMe); 4.47 (d, 1H, J = 4.0 Hz); 6.38 (d, 2H, J = 8.8 Hz); 6.68 (d, 2H, J = 8.8 Hz);); 7.44 (d, 2H, J = 8.0 Hz); 7.54 (d, 2H, J = 8.0 Hz); ^{13}C NMR (CD_3OD): δ = 12.3, 43.4, 56.1, 60.7, 65.5; 115.6, 115.7, 129.5, 133.1, 143.2, 151.3, 153.1; HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, 254 nm): 34.8 min ((*S*,*S*)-**12**), 42.5 min ((*R*,*R*)-**12**). $[\alpha]_D$ = +11.2 (c=1, $CHCl_3$); HR-MS: 297.1597; $C_{18}H_{20}N_2O_2$ ($M+H^+$: calcd 297.1583).

(2S,3S)-2-Methyl-3-(4-methoxyphenylamino)-3-(4-bromophenyl)-propan-1-ol (**13**): ^{1}H NMR (CD_3OD): δ = 0.94 (d, 3H, J = 7.3 Hz); 2.03 (m, 1H); 3.37 (dd, 1H), 3.55 (dd, 1H) 3.62 (s, 3H, OMe); 4.43 (d, 1H, J = 5.1 Hz); 6.47 (d, 2H, J = 9.2 Hz); 6.61 (d, 2H, J = 8.8 Hz);); 7.25 (d, 2H, J = 8.4 Hz); 7.40 (d, 2H, J = 8.4 Hz); ^{13}C NMR (CD_3OD): δ = 12.7, 43.6, 56.3, 60.8, 65.8; 115.7, 115.9, 130.6, 132.3, 143.7, 144.1, 153.2; HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, 254 nm): 22.5 min ((*S*,*S*)-**13**), 27.5 min ((*R*,*R*)-**13**). $[\alpha]_D$ = -38.9 (c=0.6, $CHCl_3$); HR-MS: 350.0753; $C_{17}H_{20}BrNO_2$ ($M+H^+$: calcd 350.0753).

(2S,3S)-2-Methyl-3-(4-methoxyphenylamino)-3-(4-chlorophenyl)-propan-1-ol (**14**): ^{1}H NMR (CD_3OD): δ = 0.93 (d, 3H, J = 7.0 Hz); 2.02 (m, 1H); 3.38 (m, 1H), 3.53 (m, 1H); 3.67 (s, 3H, OMe); 4.45 (d, 1H, J = 4.8 Hz); 6.47 (d, 2H, J = 8.4 Hz); 6.62 (d, 2H, J = 9.2Hz);); 7.25 (d, 2H, J = 8.4 Hz); 7.31 (d, 2H, J = 8.4 Hz); ^{13}C NMR (CD_3OD): δ = 12.7, 43.6, 56.3, 60.7, 65.8, 115.7, 115.9, 129.3, 130.2, 133.3, 143.6, 153.1; HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, 254 nm): 22.0 min ((*S*,*S*)-**14**), 25.4 min ((*R*,*R*)-**14**). $[\alpha]_D$ = +11.2 (c=1, $CHCl_3$); HR-MS: 305.1173; $C_{17}H_{20}ClNO_2$ (M^+: calcd 305.1182).

(2S,3S)-2-Methyl-3-(4-methoxyphenylamino)-3-phenylpropan-1-ol (**15**): ^{1}H NMR (CD_3OD): δ = 0.95 (d, 3H, J = 7.0 Hz); 2.05 (m, 1H); 3.38 (dd, 1H), 3.56 (dd, 1H) 3.62 (s, 3H, OMe); 4.43 (d, 1H, J = 4.0 Hz); 6.38 (d, 2H, J = 8.8 Hz); 6.50 (d, 2H, J = 8.8 Hz); 7.12 (m, 1H); 7.24 (m, 2H); 7.31 (d, 2H, J = 7.7 Hz) ^{13}C NMR (CD_3OD): δ = 12.8, 43.7, 56.3, 61.4, 66.0; 115.7, 116.0, 127.7, 128.6,129.3, 143.9, 144.6, 151.9, 153.1, 157.7; HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 98:2, flow rate 1.0 mL/min, 254 nm): 52.5 min ((*S*,*S*)-**15**), 57.5 min ((*R*,*R*)-**15**). $[\alpha]_D$ = -6.2. (c=1, MeOH); HR-MS: 272.1647; $C_{17}H_{21}NO_2$ ($M+H^+$: calcd 272.1645).

(2S,3S)-2-Methyl-3-(4-methoxyphenylamino)-3-(3-bromophenyl)-propan-1-ol (**16**): ^{1}H NMR (CD_3OD): δ = 0.85 (d, 3H, J = 7.0 Hz); 1.98 (m, 1H); 3.32 (dd, 1H), 3.45 (dd, 1H) 3.54 (s, 3H, OMe); 4.35 (d, 1H, J = 5.9 Hz); 6.39 (d, 2H, J = 9.2 Hz); 6.52 (d, 2H, J = 9.2 Hz);); 7.15 (dd, 2H, J = 8.1 Hz, J = 7.5 Hz); 7.21 (m, 2H); 7.42 (bs, 1H); ^{13}C NMR (CD_3OD): δ = 12.5, 43.5, 56.2, 60.6, 65.7; 115.6, 115.7, 127.3, 130.6, 130.8, 131.6, 147.0, 147.6, 153.0; HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, 254 nm): 21.0 min ((*S*,*S*)-**16**), 25.4 min ((*R*,*R*)-**16**). $[\alpha]_D$ = -28.6 (c=1.7, MeOH); HR-MS: 350.0753; $C_{17}H_{20}BrNO_2$ ($M+H^+$: calcd 350.0753).

(2S,3S)-2-Methyl-3-(4-methoxyphenylamino)-3-phenylpropan-1-ol and (2R,3S)-2-Methyl-3-(4-methoxyphenylamino)-3-phenylpropan-1-ol (syn/anti-**15**) A 1.1:1 diasteromeric mixture of *anti* and *syn* (*3S*)-methyl-2-methyl-3-(4-methoxyphenylamino)-3-phenylpropanoate (0.1 mmol) in THF (5mL) was reduced by addition of $LiAlH_4$ (1 mmol) at 0°C. After 4h at this reaction time the reaction was left to attain room temperature and quenched after 24 h by addition of

$Na_2SO_4 \cdot 10H_2O$ and filtered through Celite. Next, the filtrate was diluted with ethyl ether and washed with brine. The organic layer was separated and the aqueous phase was extracted thoroughly with ethyl acetate. The combined organic phases were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford β-amino alcohol **15** with a dr of (syn/anti=0.9:1). ^{1}H NMR (CD_3OD): (* denotes the anti-diastereomer) δ = 0.79 (d, 3H*, J = 7.0 Hz); 0.95 (d, 3H, J = 7.0 Hz); 2.05 (m, 1H, 1H*); 3.38 (dd, 1H), 3.56 (dd, 1H) 3.61 (d, 2 H*, J = 5.9 Hz); 3.62 (s, 3H, 3H*, OMe); 4.27 (d, 1H*, J =7.0 Hz); 4.43 (d, 1H, J = 4.0 Hz); 6.50 (dd, 2H, 2H*); 6.61 (dd, 2H, 2H*); 7.12 (m, 1H, 1H*); 7.24 (m, 2H, 2H*); 7.31 (m, 2H, 2H*) ^{13}C NMR (CD_3OD): δ = 12.8, 14.6, 42.8, 43.6, 56.2, 56.3, 61.4, 66.0, 66.3, 115.6, 115.7, 116.0, 116.5, 127.7, 127.9, 128.6, 129.2, 129.3, 143.9, 144.4, 153.2, 153.4; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm): major isomer: t_R = 14.02 min; minor isomer: t_R = 12.18 min; major isomer*: t_R = 15.55 min; minor isomer*: t_R = 13.55 min; HR-MS: 272.1647; $C_{17}H_{21}NO_2$ ($M+H^+$: calcd 272.1645).

(1S,2S)-2-Hydroxymethyl-1-(4-methoxyphenylamino)-1-(4-nitrophenyl)-heptane (**17**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82–1.50 (m, 11H), 2.03 (m, 1H), 2.7–3.1 (br, 1H), 3.68 (s, 3H), 3.64–3.75 (m, 3H), 4.70 (d, *J* = 3.5 Hz, 1H), 6.43 (d, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 8.17 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.4, 25.6, 27.4, 31.8, 46.4, 55.7, 60.6, 63.5, 114.7, 114.8, 123.6, 128.1, 140.7, 146.9, 150.2, 152.2. HRMS calcd for $C_{21}H_{29}N_2O_4$ (MH^+) 373.2122, found 373.2123. HPLC (Daicel Chiralpak OD-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, 254 nm): 42.3 min ((*S*,*S*)-**22**), 47.4 min ((*R*,*R*)-**22**), 38.5 min (anti), 55.9 min (anti).

(2S,3S)-2-Methyl-3-(4-methoxyphenylamino)-3-pentan-1-ol (**18**): ^{1}H NMR (CD_3OD): δ = 0.92 (t, 3H, J = 6.9 Hz), 0.95 (d, 3H, J = 7.7 Hz); 1.52 (m, 2H), 1.87 (m, 1H), 3.50 (dd, 1H), 3.66 (dd, 1H) 3.68 (s, 3H, OMe); 6.70 (d, 2H, J = 8.8 Hz); 6.81 (d, 2H, J = 8.8 Hz); ^{13}C NMR (CD_3OD): δ = 11.9, 12.3, 26.7, 40.0, 56.4, 58.8, 66.3, 115.9, 116.0, 145.3, 153.0; HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm): t_R = 26.76 min (major), t_R = 13.94 min (minor). $[\alpha]_D$ = +6.4. (c=1, MeOH); HR-MS: 224.1645; $C_{13}H_{21}NO_2$ ($M+H^+$: calcd 224.1645.1645).

(5S,6S)-5-Hydroxymethyl-6-(4-methoxyphenylamino)-undecane (**19**): ^{1}H NMR (400MHz, $CDCl_3$): δ 0.89 (m, 6H), 1.32 (m, 10H), 1.48 (m, 1H), 1.82 (m, 1H), 3.61(dt, 1H), 3.73 (m, 2H), 3.75 (s, 3H), 6.66 (m, 2H), 6.78 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$): δ 13.94, 13.97, 22.5, 22.9, 25.5, 26.5, 30.0, 31.3, 31.7, 41.4, 55.6, 58.7, 64.7, 114.7, 116.1, 141.7, 152.6; MALDI-FTMS calcd for $C_{19}H_{34}NO_2$ (MH^+) 308.2584, found 308.2578. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 95:1, flow rate 1.0 mL/min, λ = 254 nm): t_R = 82.80 min (major), t_R = 51.79 min (minor).

(7S,8S)-7-Hydroxymethyl-8-(4-methoxyphenylamino)-pentadecane (**20**): ^{1}H NMR (400 MHz, $CDCl_3$) (a diastereomer mixture of 3:1, * donates the minor diastereomer) δ 0.82–1.85 (m, 37H), 3.20 (br, 2H), 3.30–3.36 (m, 1H* x1/4), 3.38–3.44 (m, 1H x 3/4), 3.62–3.83 (m, 2H), 3.73 (s, 3H), 6.61 (d, *J* = 8.8 Hz, 2H* x 1/4), 6.65 (d, *J* = 8.8 Hz, 2H x 3/4), 6.75 (d, *J* = 8.8 Hz, 2H* x 1/4), 6.76 (d, *J* = 8.8 Hz, 2H x 3/4). ^{13}C NMR (125 MHz, $CDCl_3$) (a diastereomer mixture of 3:1, * donates the minor diastereomer) δ 14.1, 22.6, 25.9, 26.9, 27.9, 29.2, 29.3, 29.5, 29.6, 29.9, 31.4, 31.6, 31.8, 31.9, 41.5, 55.7, 58.9, 64.9, 114.8, 116.2, 141.6, 152.8. MALDI-FTMS calcd

for $C_{27}H_{50}NO_2$ (MH^+) 420.3836, found 420.3850. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm): t_R = 14.44 min (major), t_R = 6.00 min (minor).

(4S,5S)-4-Hydroxymethyl-5-(4-methoxyphenylamino)-nona-1,8,-diene (**21**): ^{1}H NMR ($CDCl_3$): δ 1.61 (m, 2H), 1.92 (m, 1H), 2.10 (m, 4H), 3.02 (brs, 2H), 3.49 (h, 1H), 3.69 (s, 1H), 3.70 (d, *J* = 1.6 Hz, 1H), 3.73 (s, 3H), 4.94-5.06 (m, 2H), 5.04-5.11 (m, 2H), 5.72-5.88 (m, 2H), 6.30 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 30.81, 30.88, 31.4, 42.0, 55.6, 56.6, 64.0, 114.8, 115.0, 115.6, 116.5, 136.8, 138.0, 141.6, 152.4; HRMS for $C_{17}H_{25}NO_2$ ($M+H^+$): calcd 276.1958, obsd 276.1962; HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 95:1, flow rate 1.0 mL/min, λ = 254 nm): t_R = 82.80 min (major), t_R = 51.79 min (minor).

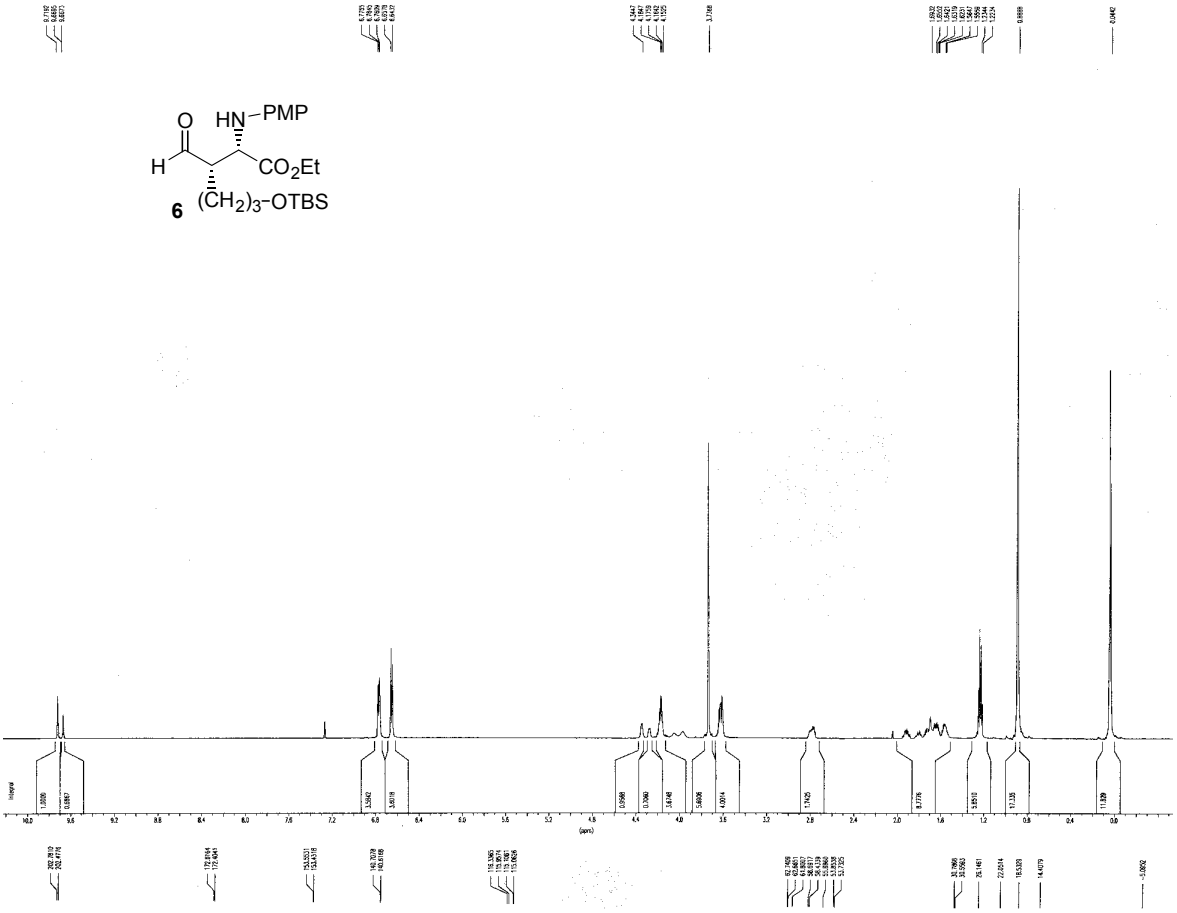
(3S,4S)-3-Hydroxymethyl-4-(4-methoxyphenylamino)-2,6-dimethyl-heptane (**22**): **Major diastereomer** (TLC down). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.34 (m, 1H), 1.46–1.62 (m, 2H), 1.70–1.81 (m, 2H), 3.20 (bs, 2H), 3.62 (m, 1H), 3.74 (s, 3H), 3.72–3.83 (m, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 21.7, 21.8, 24.0, 25.1, 26.9, 39.4, 47.6, 54.3, 54.3, 55.7, 62.8, 114.9, 115.6, 141.6, 152.6. MALDI-FTMS calcd for $C_{17}H_{30}NO_2$ (MH^+) 280.2271, found 280.2274. HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 95:3, flow rate 1.0 mL/min, λ = 254 nm): t_R = 27.23 min (major), t_R = 18.03 min (minor). **Minor diastereomer** (TLC up). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.28 (m, 1H), 1.45 (t, *J* = 6.8 Hz, 2H), 1.62 (m, 1H), 1.95 (m, 1H), 3.20 (bs, 2H), 3.55 (m, 2H), 3.74 (s, 3H), 3.79–3.89 (m, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 21.6, 22.7, 22.9, 24.6, 26.4, 44.4, 49.6, 54.8, 55.7, 61.4, 114.9, 115.0, 142.6, 152.0. MALDI-FTMS calcd for $C_{17}H_{30}HNO_2$ (MH^+) 280.2271, found 280.2274. HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 99:1, flow rate 1.0 mL/min, 254 nm): 24.6 min (minor enantiomer), 27.6 min (major enantiomer).

(2S,3S)-3-Hydroxymethyl-2-(p-methoxyphenylamino)-4-methyl-pentan-1-ol (**27**): A solution of **1** (1.46 g, 5 mmol; crude from previous reaction) in THF (100 mL) was cooled to 0°C and LAH (30 mL, 1M solution in THF) was added. After stirring for 30 min, the ice-bath was removed and the mixture was stirred for 1.5 h at room temperature. The mixture was quenched by careful addition of aqueous NH_4Cl solution, followed by 3M HCl, and then extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/ethyl acetate = 1:5) afforded diol **14** (1.12 g, 88%) as pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): 0.93 (d, J = 7.9 Hz, 3H), 1.02 (d, J = 7.9 Hz, 3H), 1.55 (m, 1H), 1.92 (m, 1H), 3.55 (m, 1H), 3.63 (m, 1H) 3.71-3.3.83 (m, 6H), 6.58 (d, J = 8.8 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): 20.1, 21.3, 25.9, 47.5, 55.2, 55.7, 59.1, 60.8, 115.0, 115.2, 141.1, 152.1; HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm): t_R (major) = 23.12 min; t_R (minor) = 26.64 min; HR-MS: 254.1752; $C_{14}H_{32}NO_3H^+$ (calcd 254.1751)

Ethyl (E)-(2S, 3S)-3-benzyloxyiminomethyl-2-(p-methoxyphenylamino)-4-methylpentanoate (**28**): *N*-PMP-Protected α-imino ethyl glyoxylate (0.5 mmol) was dissolved in anhydrous dioxane and isovaleraldyde (1.0 mmol) was added, followed by L-proline (20 mol%). The total volume of the reaction mixture was 5 mL. After stirring overnight at room temperature, *O*-benzyl-hydroxylamine hydrochloride (1.3 mmol) and pyridine (0.5 mL) were added directly to the

reaction mixture. The mixture was stirred for an additional 2h at room temperature, filtered through Celite, concentrated and the residue purified by column chromatography (silica, hexanes/ethyl acetate = 10/1) to afford oxime **28** (129 mg, 78%): ^{1}H NMR (500MHz, $CDCl_3$) δ = 0.89 (d, 3H, *J* = 6.6 Hz, CHC*H*$_3$), 1.04 (d, 3H, *J* = 6.6 Hz, CHC*H*$_3$), 1.16 (t, 3H, OCHC*H*$_3$), 2.12 (m, 1H), 2.40 (m, 1H), 3.69 (s, 3H, OC*H*$_3$), 3.81 (bs, 1H, ArN*H*CH), 4.05 (q, 2H, OC*H*$_2$CH$_3$), 4.14 (bs, 1H), 5.09 (s, 2H, PhC*H*$_2$), 6.48 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.71 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.25-7.40 (m, 6H, Ar*H* and *H*C=N); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 172.4, 152.8, 150.0, 140.3, 137.8, 128.3, 127.9, 127.6, 115.4, 114.6, 75.5, 60.8, 58.0, 55.5, 49.1, 27.3, 20.9, 19.4, 14.1; HPLC (Daicel Chiralpak AD, hexane/i-PrOH = 92:8, flow rate 1.0 mL/min, λ = 254 nm); t_R (major) = 12.52 min; t_R (minor) = 23.86 min; HRMS: Calcd for $C_{23}H_{30}N_2O_4$ ($M+H^+$): 399.2278, found: 399.2281.

Ethyl (E)-(2S,3S)-3-benzyloxyiminomethyl-2-(p-methoxyphenylamino)-octanoate (**29**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85–1.65 (m, 11H), 1.21 (t, *J* = 7.0 Hz, 3H), 2.70 (m, 1H), 3.73 (m, 3H), 3.88 (brd, *J* = 10.2 Hz, 1H), 4.02 (m, 1H), 4.08-4.17 (m, 2H), 5.10 (s, 2H), 6.51 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 7.28–7.40 (m, 6H). ^{13}C (100 MHz, $CDCl_3$) δ 14.0, 14.2, 22.4, 26.7, 28.8, 31.4, 42.8, 55.6, 60.6, 61.6, 75.6, 114.7, 115.6, 127.7, 128.1, 128.4, 137.8, 140.6, 151.6, 152.9, 172.4. HRMS calcd for $C_{25}H_{35}N_2O_4$ (MH^+) 427.2591, found 427.2601. HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 84:14, flow rate 1.0 mL/min, 254 nm): 6.6 min (*anti*), 9.5 min (*anti*), 10.3 min ((*S*,*S*)-enantiomer, major), 16.9 min ((*R*,*R*)-enantiomer, minor).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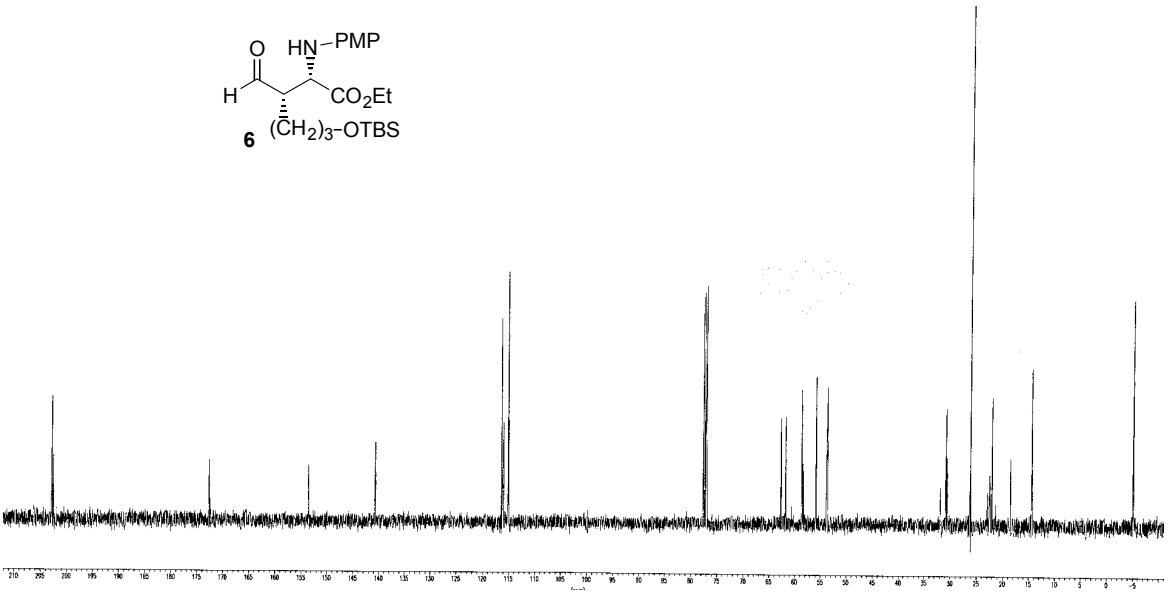
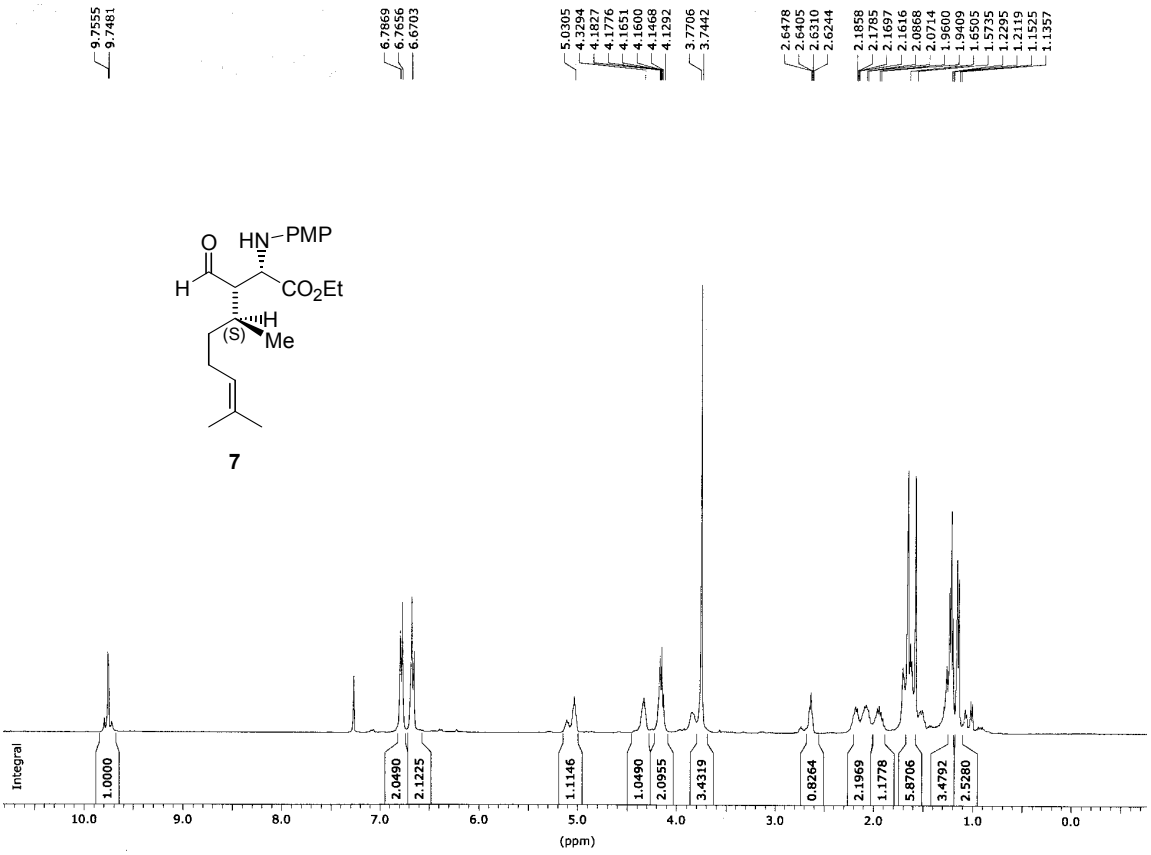
HN–PMP
H
CO2Et
(CH2)3–OTBS
6


O
HN–PMP
H
CO2Et
(CH2)3–OTBS
6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9.7481
6.7869
6.7656
6.6703
5.0305
4.3294
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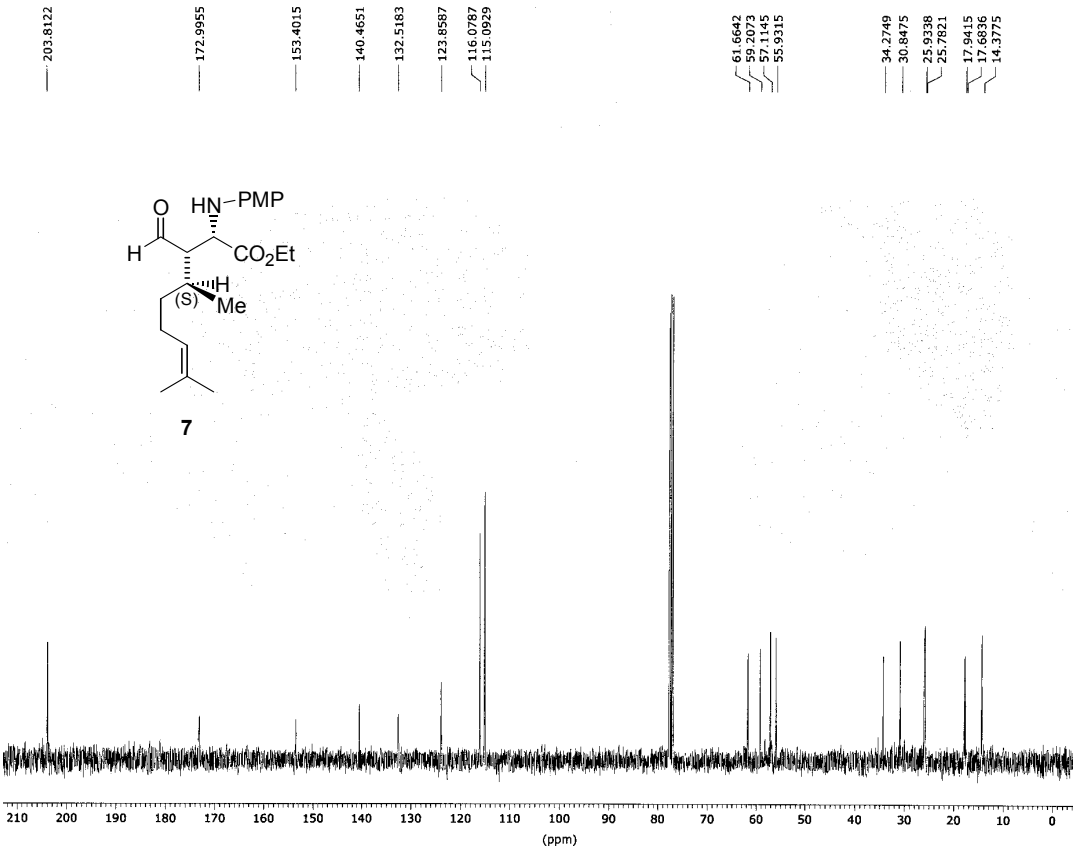
4.1776
4.1651
4.1600
4.1468
4.1292
3.7706
3.7442
2.6478
2.6405
2.6310
2.6244
2.1858
2.1785
2.1697
2.1616
2.0868
2.0714
1.9600
1.9409
1.6505
1.5735
1.2295
1.2119
1.1525
1.1357
O
HN–PMP
H
CO2Et
(S)
H
Me
7
Integral
1.0000
2.0490
2.1225
1.1146
1.0490
2.0955
3.4319
0.8264
2.1969
1.1778
5.8706
3.4792
2.5280
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)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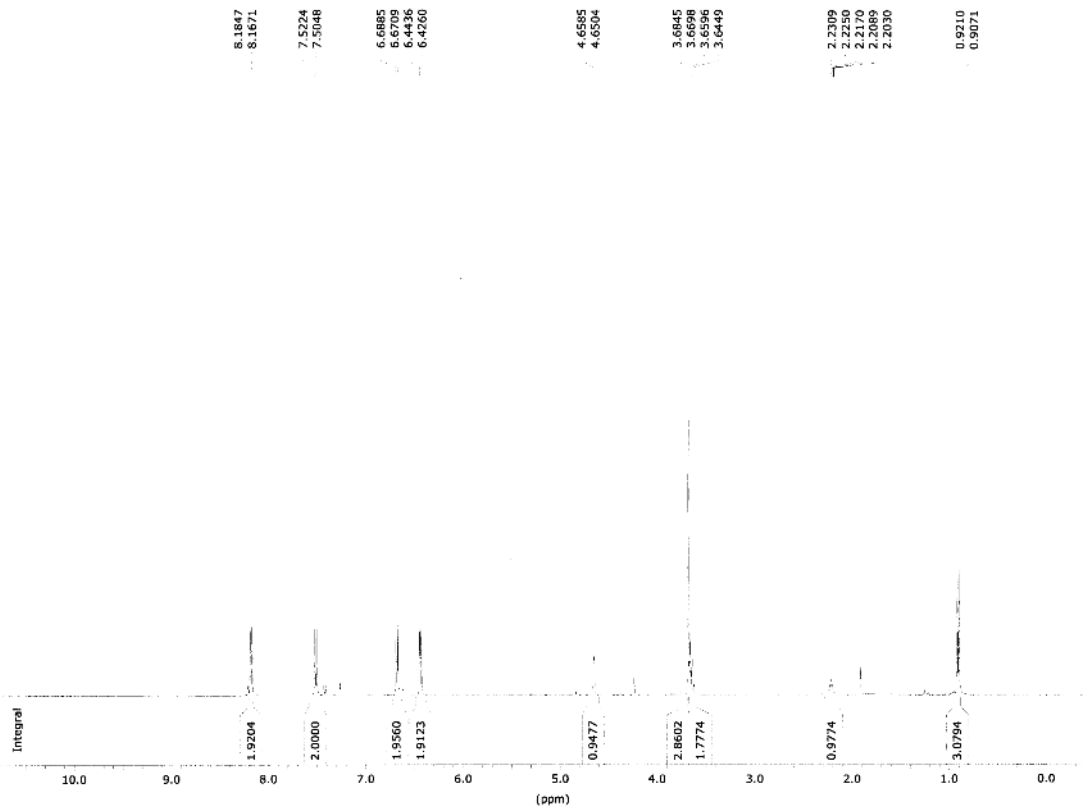
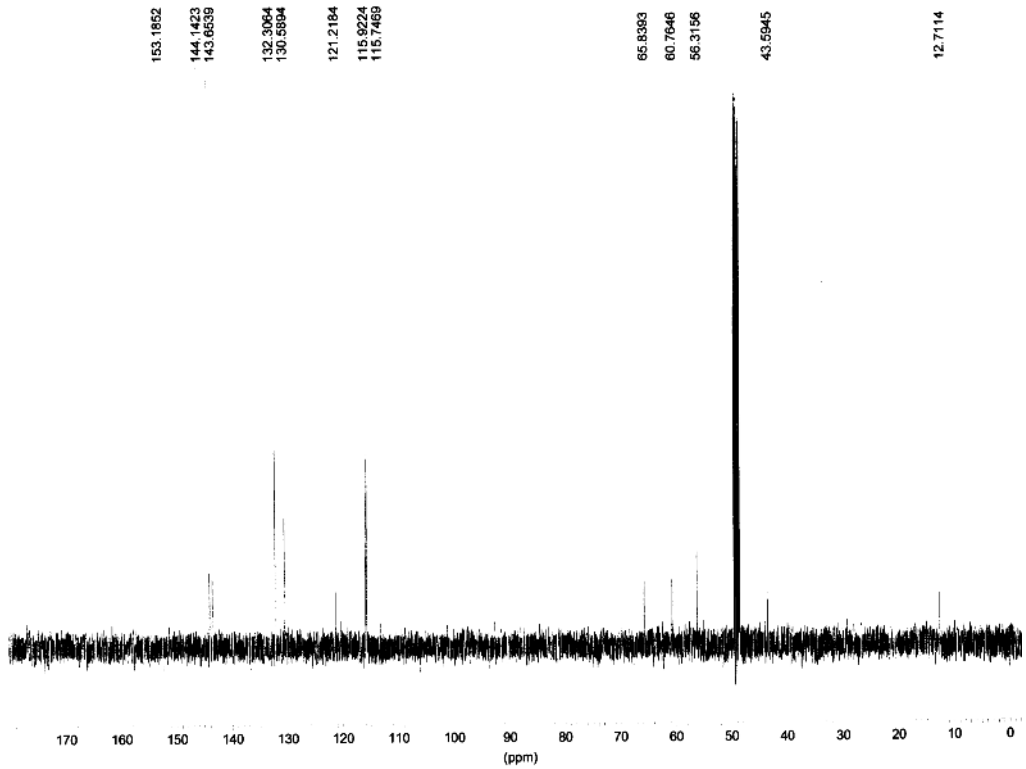
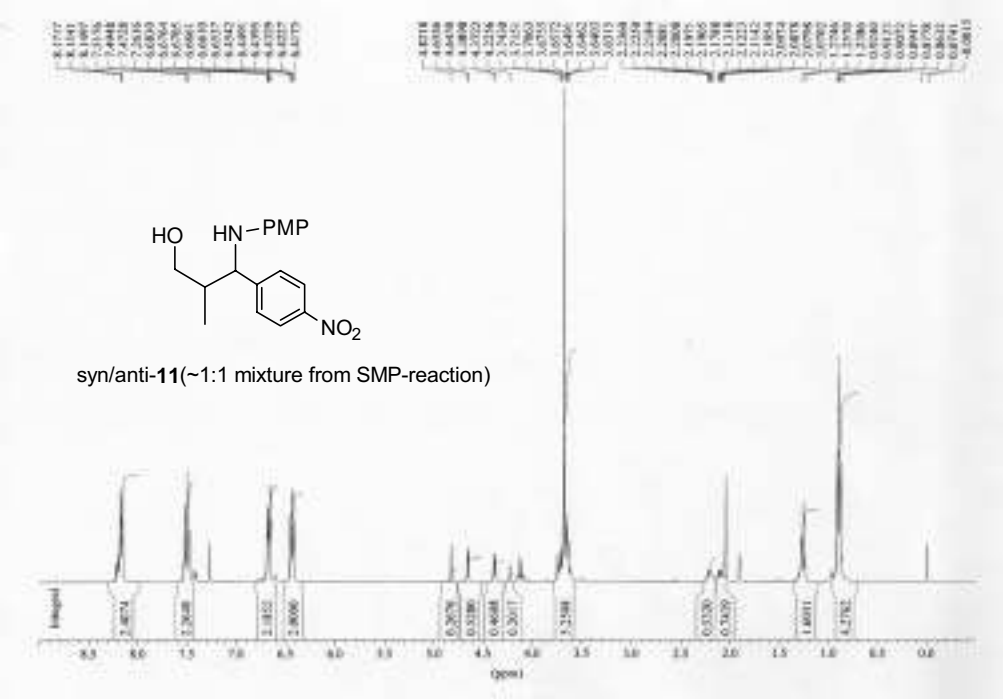
57.1145
55.9315
34.2749
30.8475
25.9338
25.7821
17.9415
17.6836
14.3775
O
HN–PMP
H
CO2Et
(S)
H
Me
7
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

^{1}H NMR (CDCl3) of compound **11**.

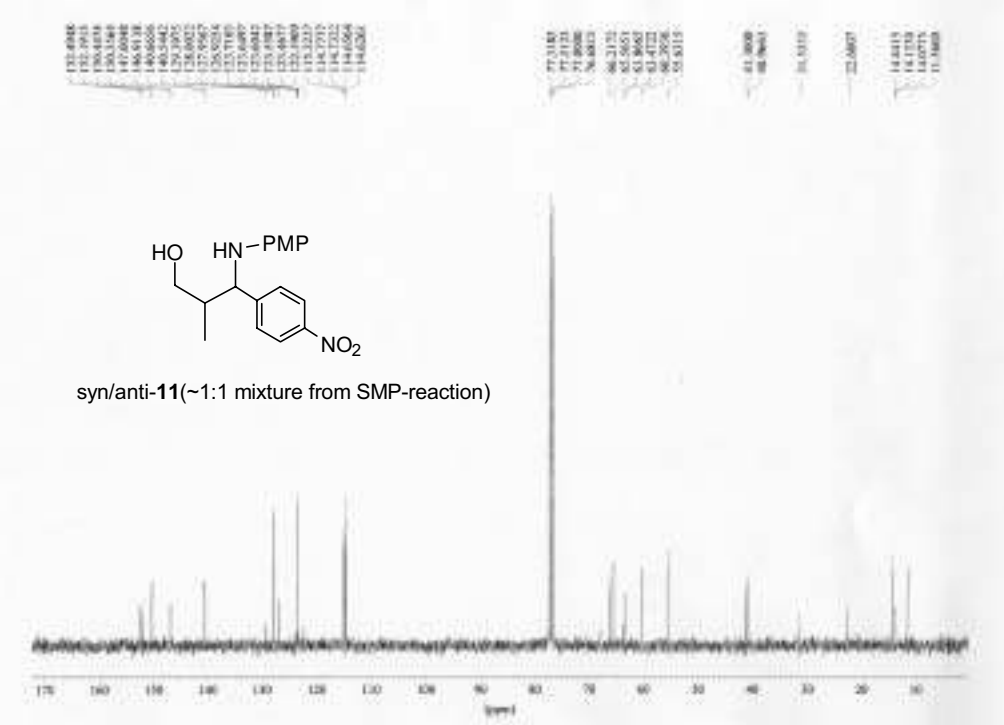


^{13}C NMR (CD3OD) of compound **11**.



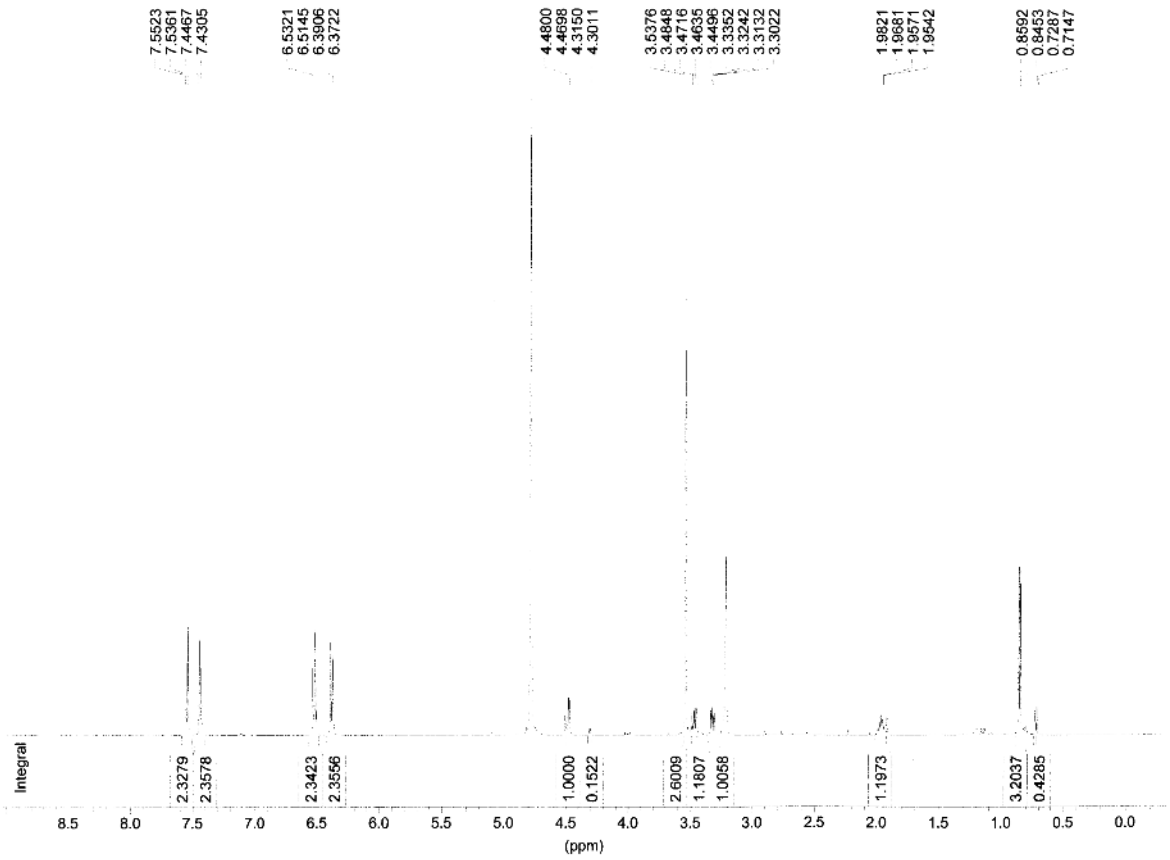


syn/anti-**11**(~1:1 mixture from SMP-reaction)

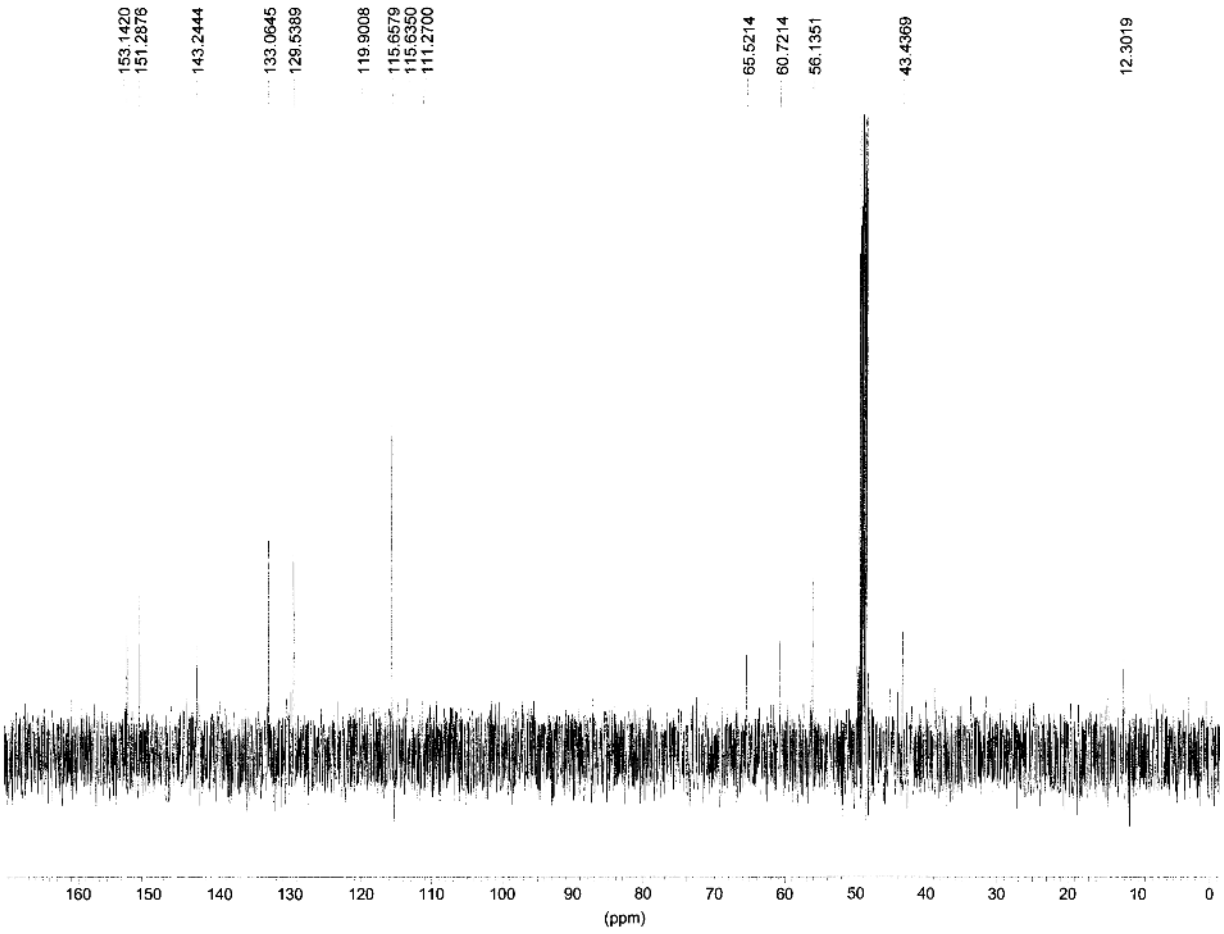


syn/anti-**11**(~1:1 mixture from SMP-reaction)

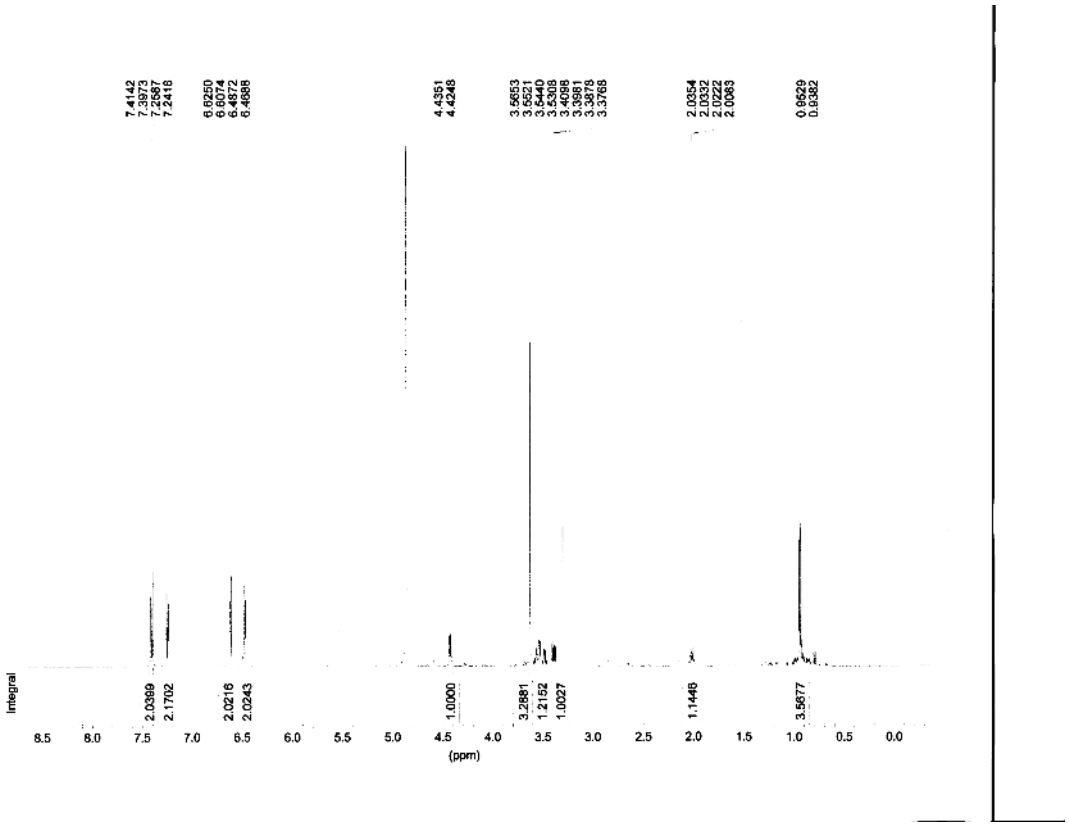
^{1}H NMR (CD_3OD) of compound **12**.



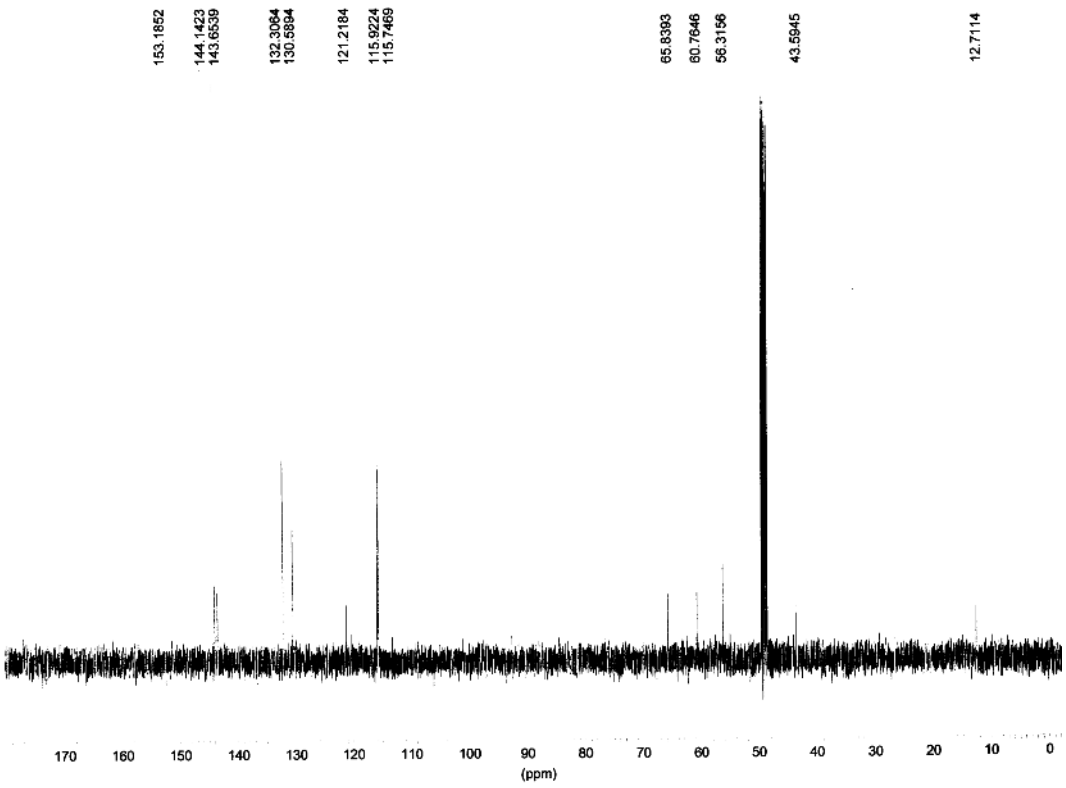
^{13}C NMR (CD_3OD) of compound **12**.



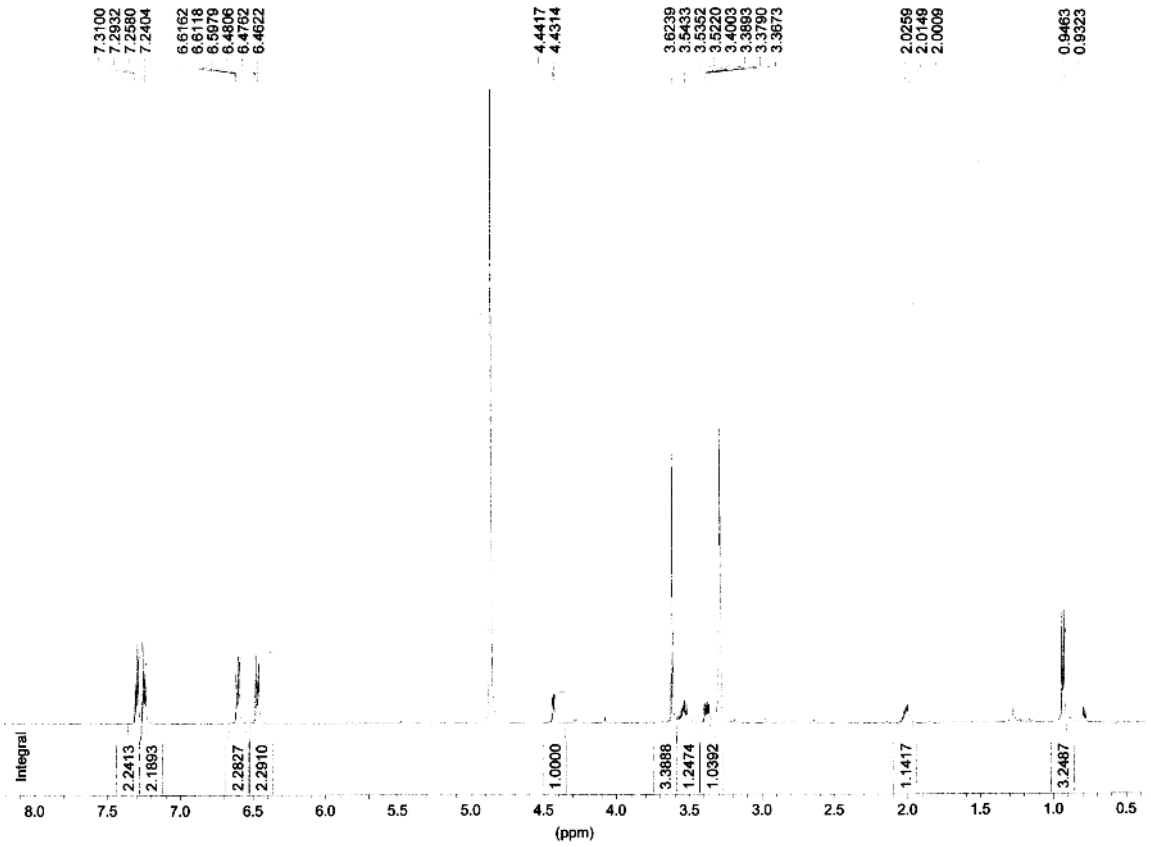
^{1}H NMR (CD_3OD) of compound **13**.



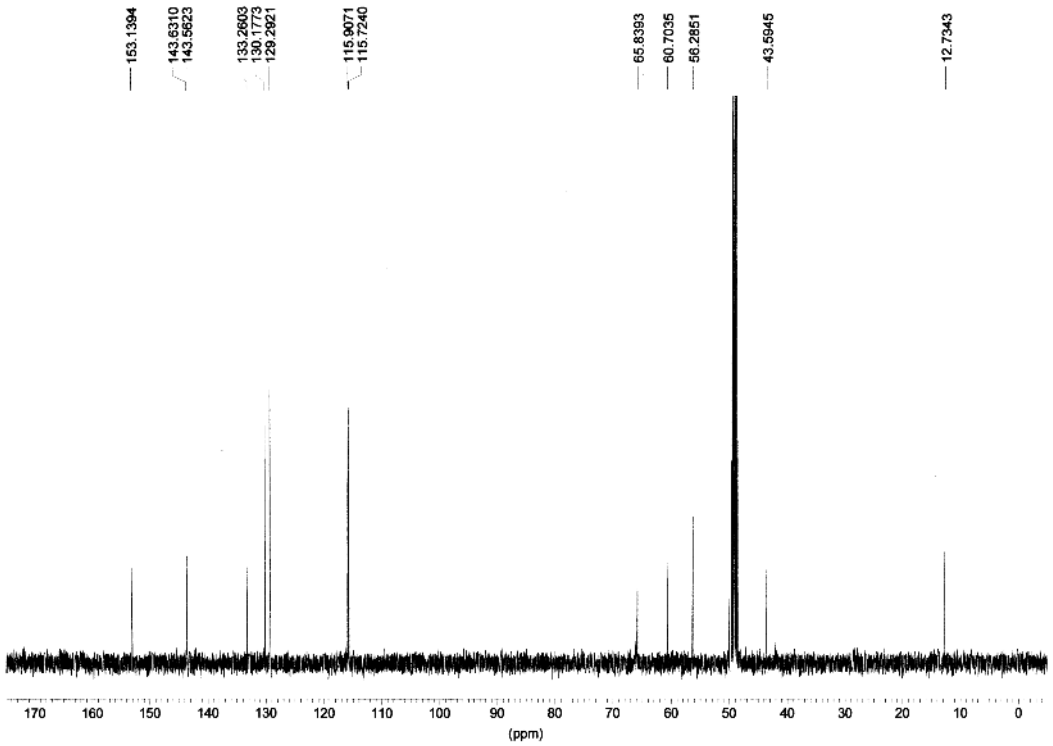
^{13}C NMR (CD_3OD) of compound **13**.



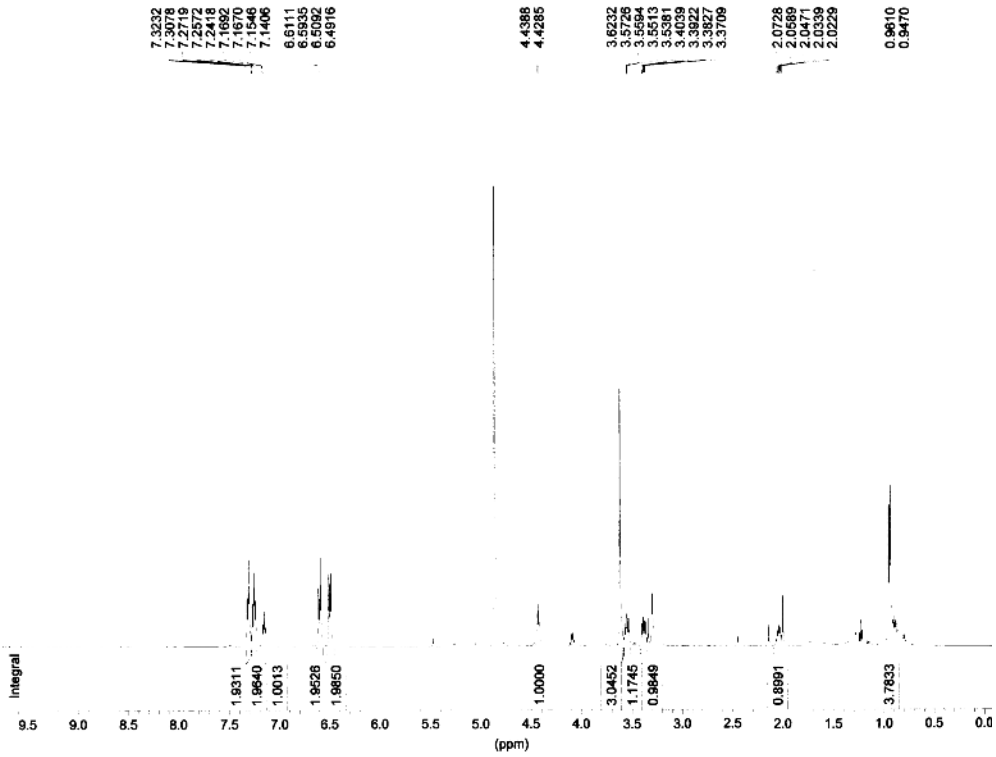
^{1}H NMR (CD_3OD) of compound **14**.



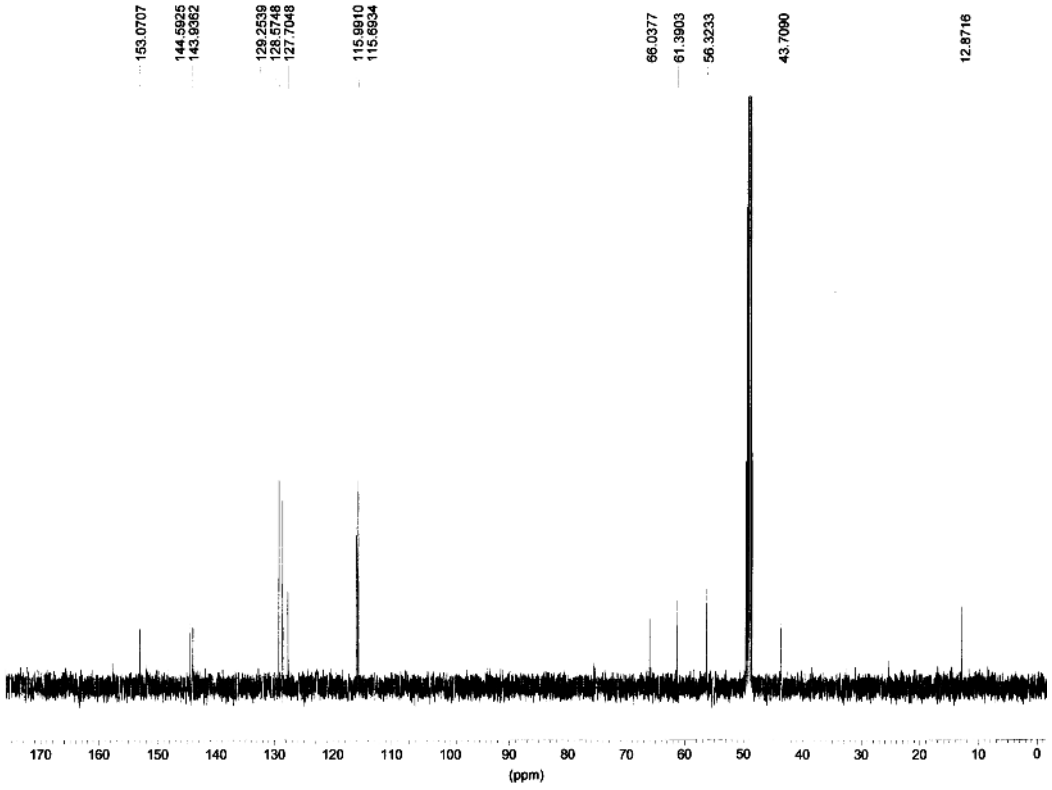
^{13}C NMR (CD_3OD) of compound **14**.



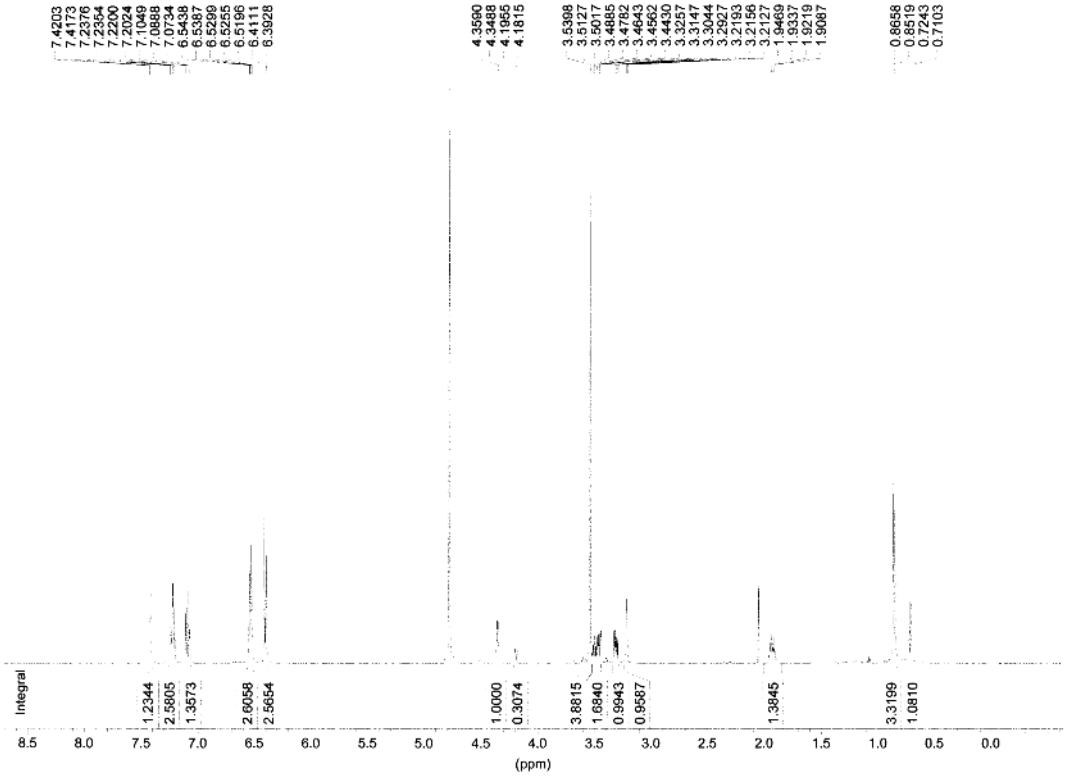
^{1}H NMR (CD_3OD) of compound **15**.



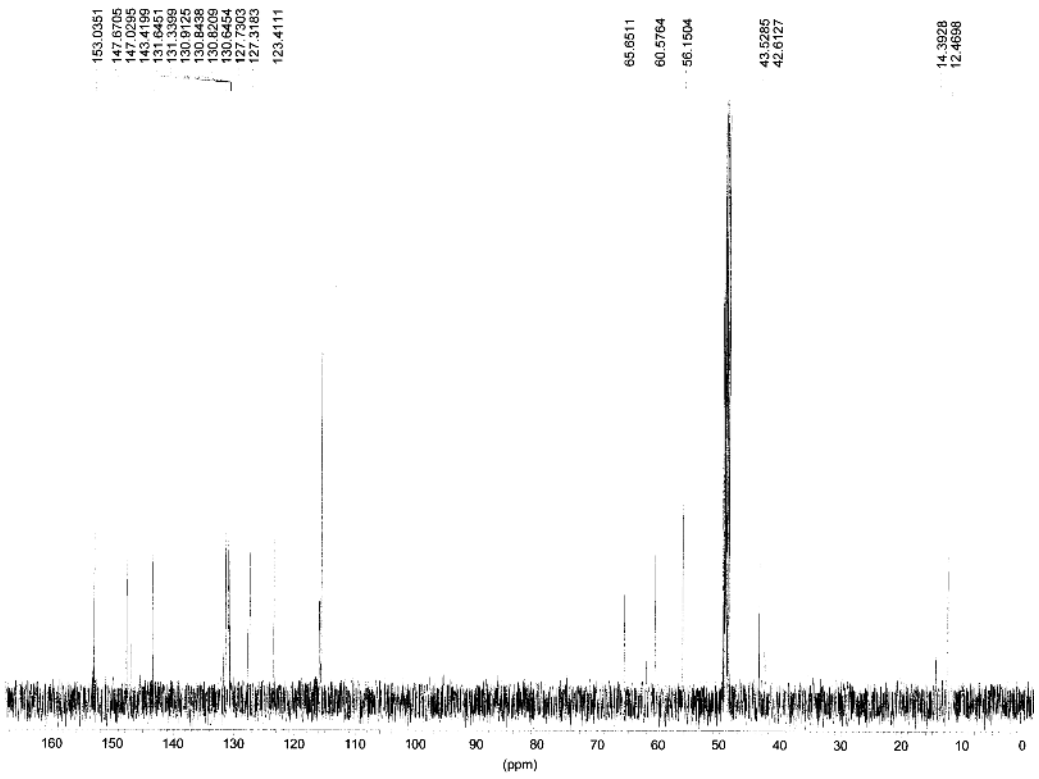
^{13}C NMR (CD_3OD) of compound **15**.

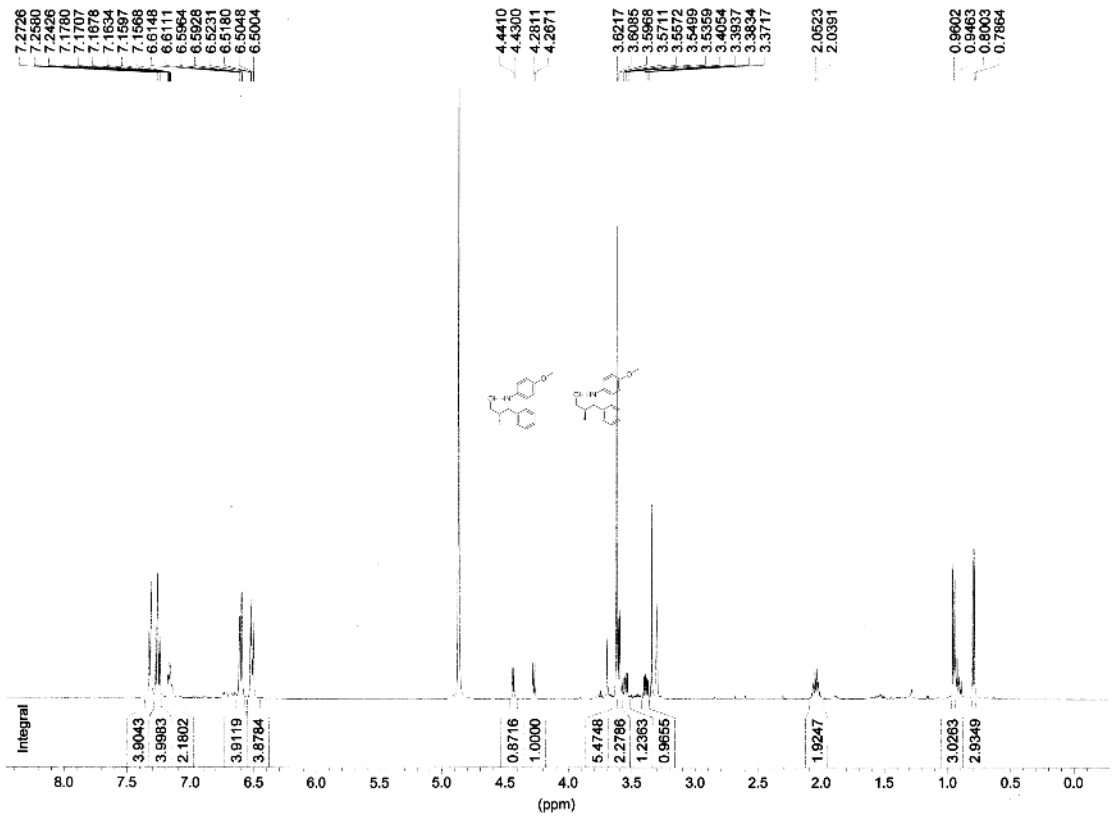


^{1}H NMR (CD_3OD) of compound **16** (syn/anti-3/1).



^{13}C NMR (CD_3OD) of compound **16** (syn/anti-3/1).




7.2726
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7.2426
7.1780
7.1707
7.1678
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7.1597
7.1568
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6.6111
6.5964
6.5928
6.5231
6.5180
6.5048
6.5004
4.4410
4.4300
4.2811
4.2671
3.6217
3.6085
3.5968
3.5711
3.5572
3.5499
3.5359
3.4054
3.3937
3.3834
3.3717
2.0523
2.0391
0.9602
0.9463
0.8003
0.7864
Integral
3.9043
3.9983
2.1802
3.9119
3.8784
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5.4748
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1.2363
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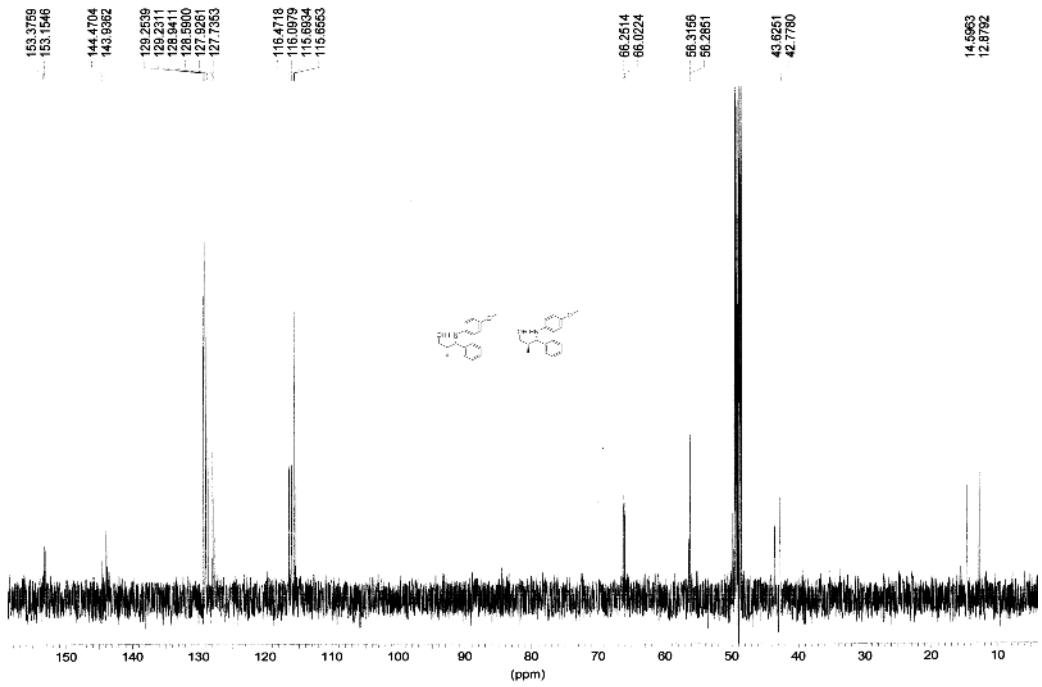
1.9247
3.0263
2.9349
(ppm)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127.9261
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116.0979
115.6934
115.6553
66.2514
66.0224
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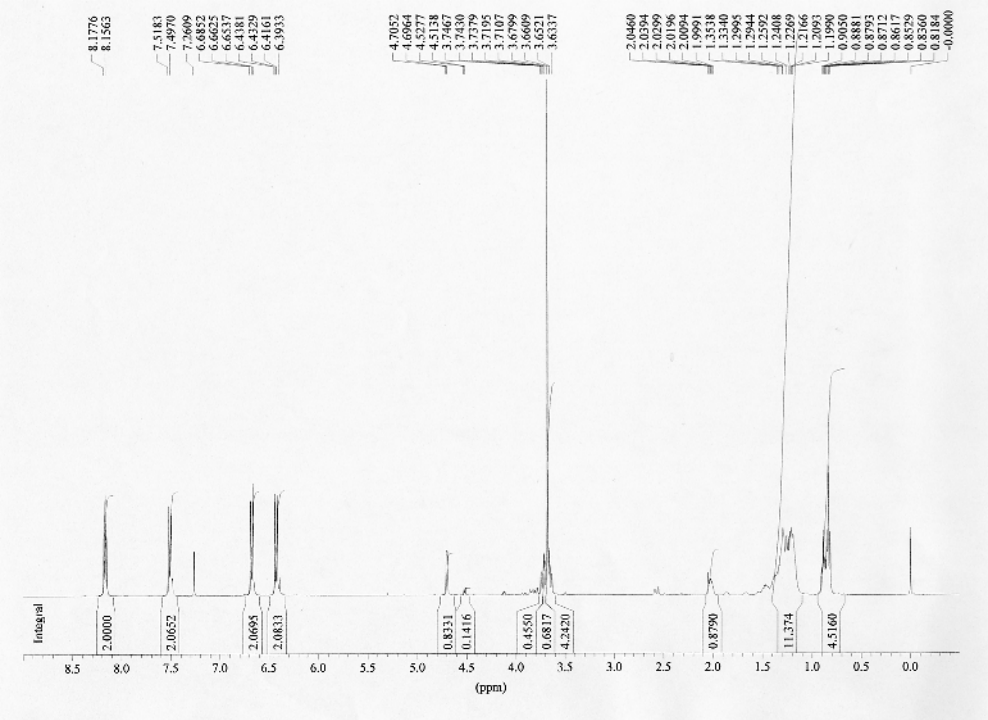
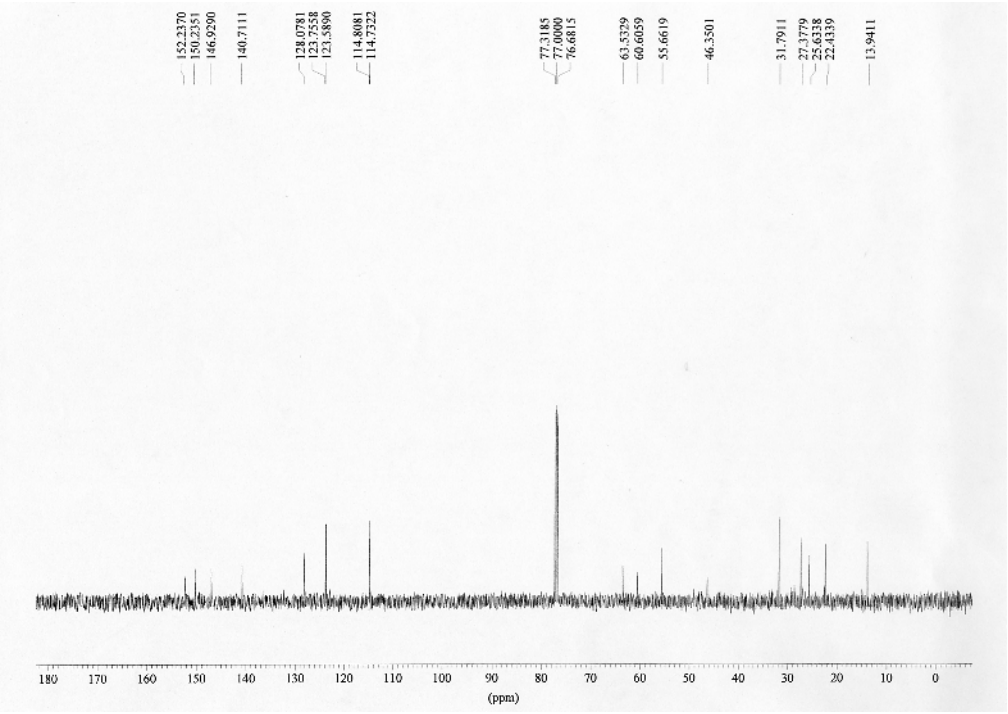
43.6251
42.7780
14.5963
12.8792
(ppm)

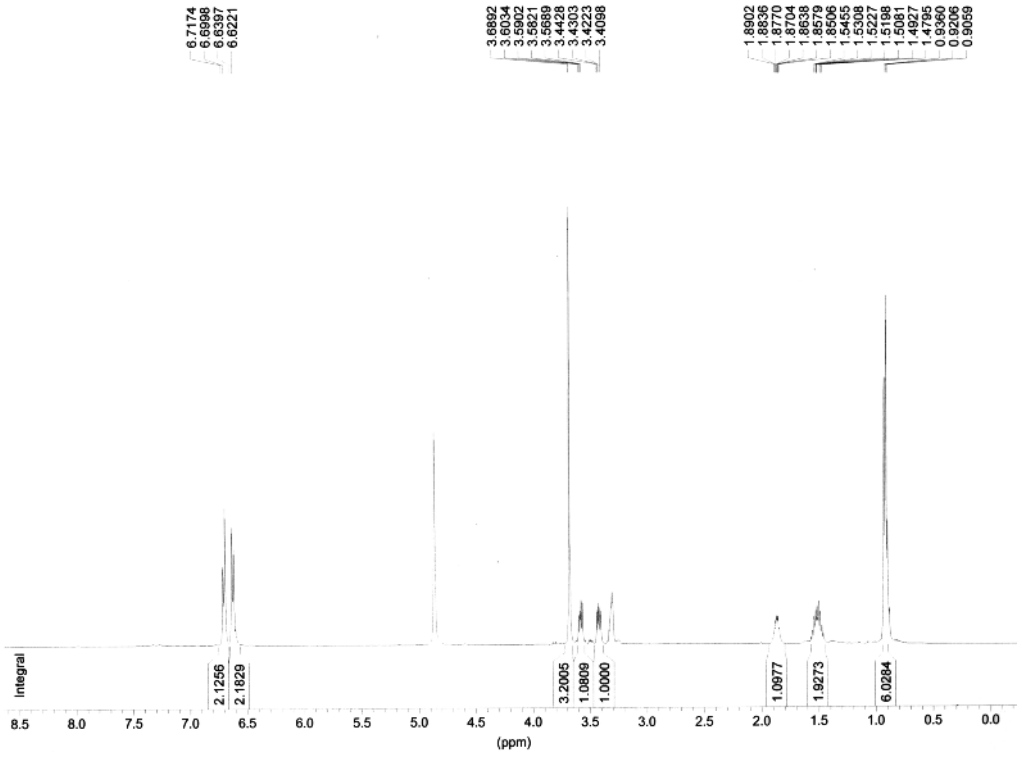
^{1}H NMR ($CDCl_3$) of compound **17**.



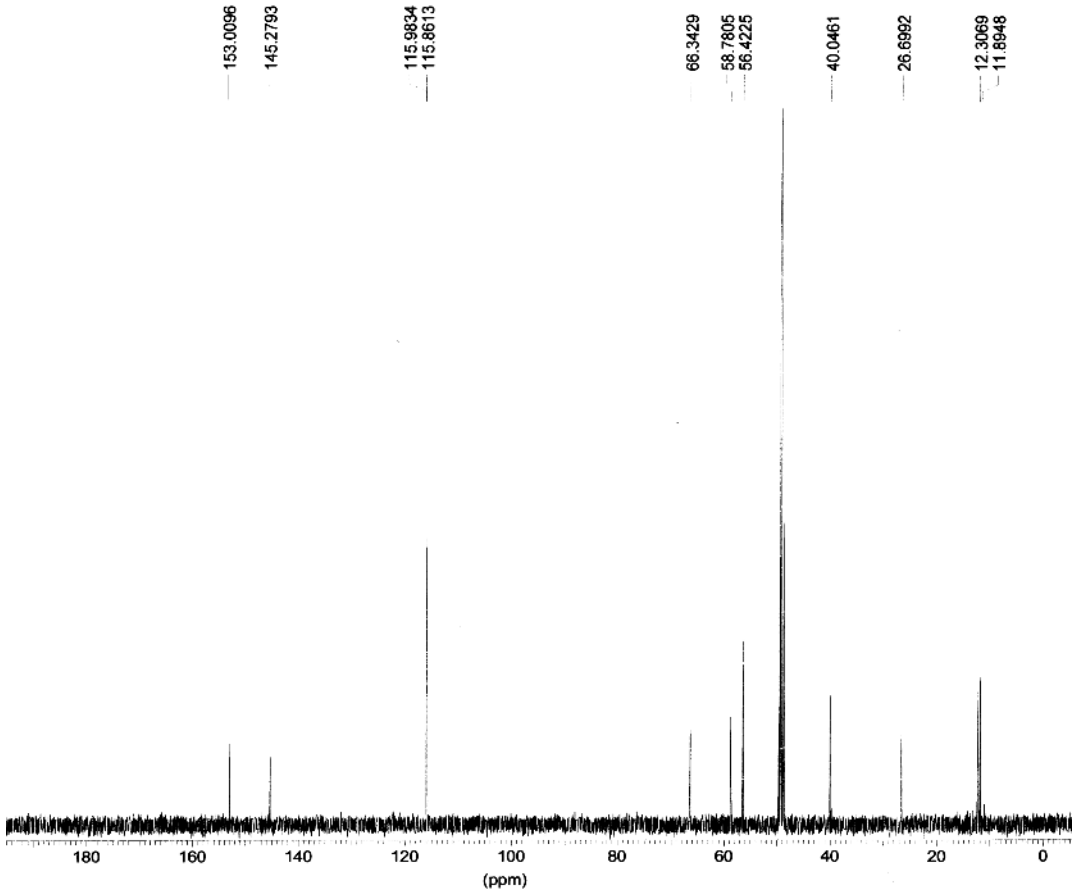
^{13}C NMR ($CDCl_3$) of compound **17**.



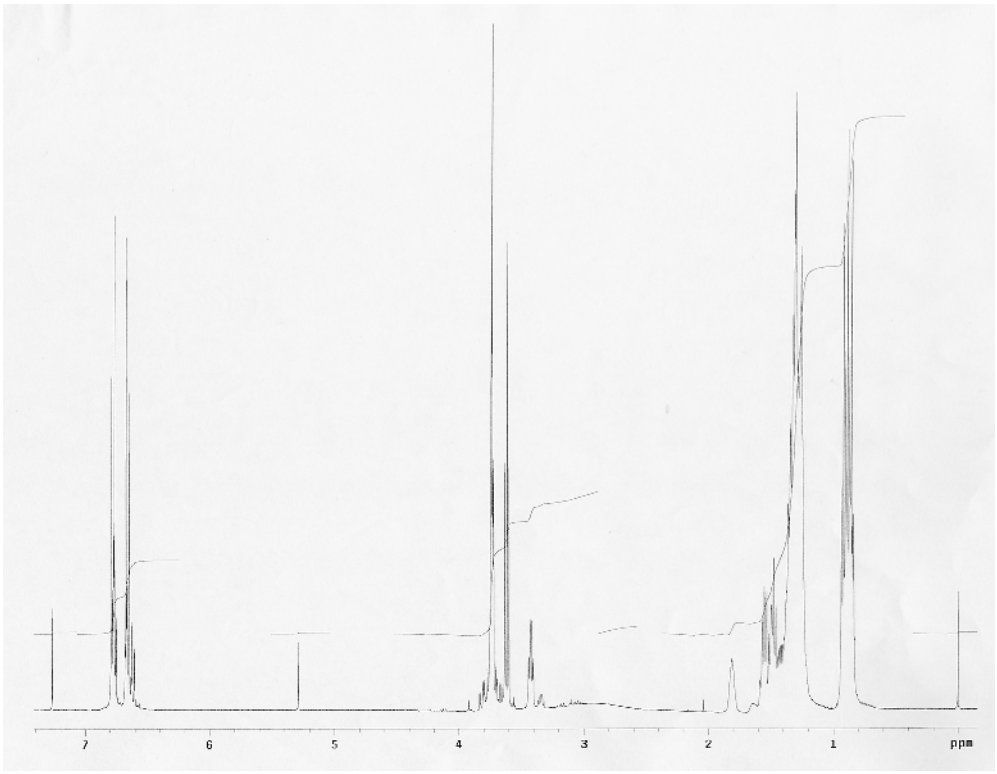
^{1}H NMR (CD_3OD) of compound **18**.



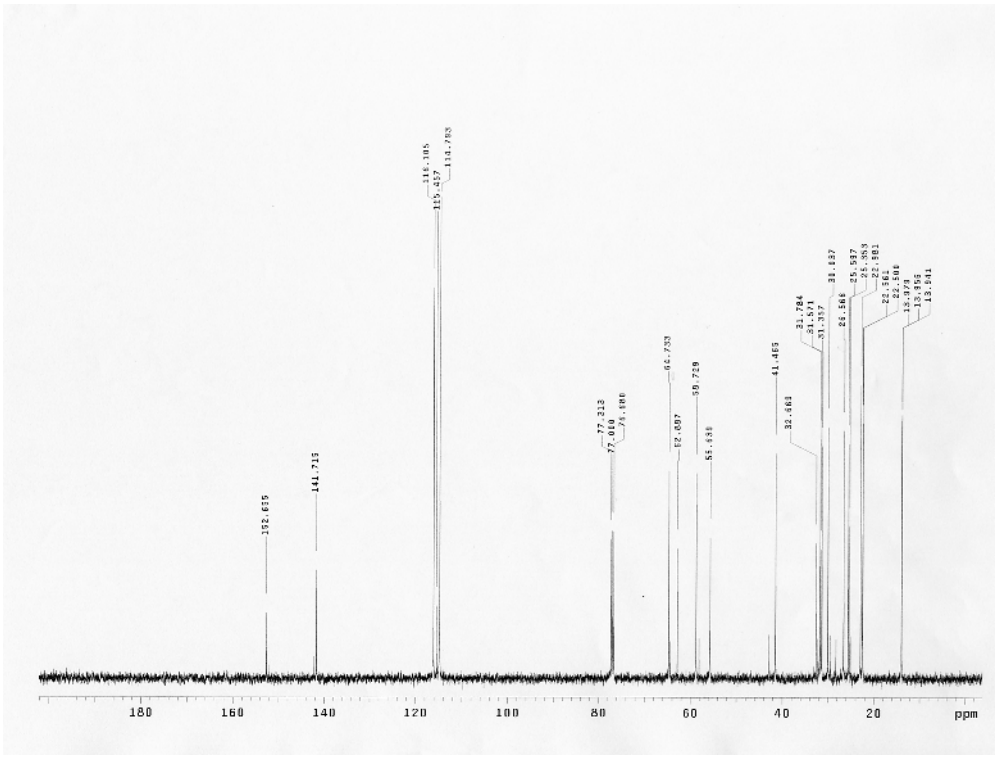
^{13}C NMR (CD_3OD) of compound **18**.



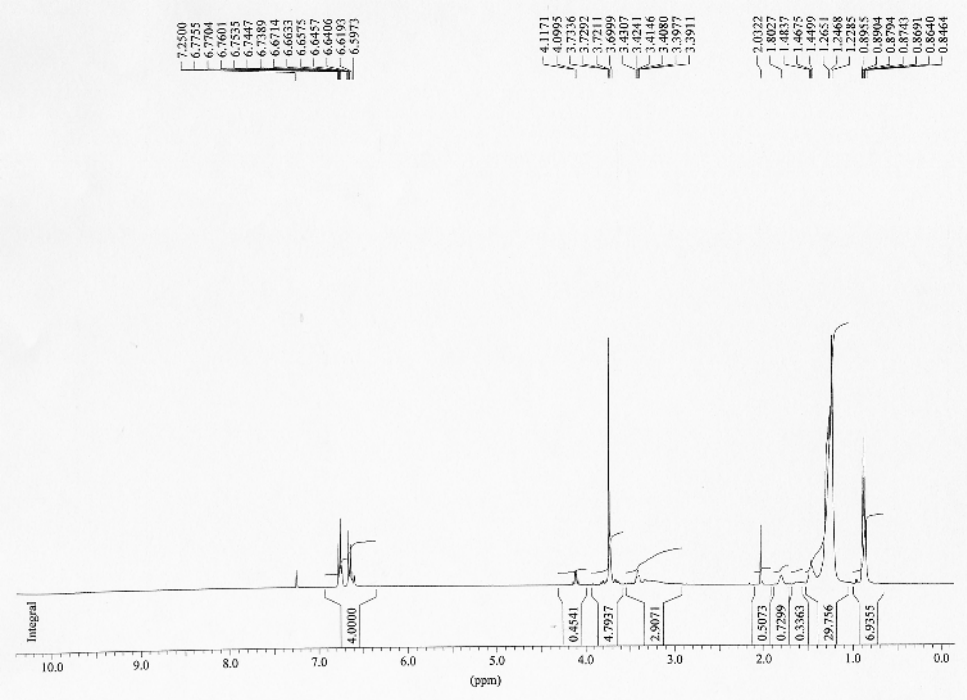
^{1}H NMR ($CDCl_3$) of compound **19**.



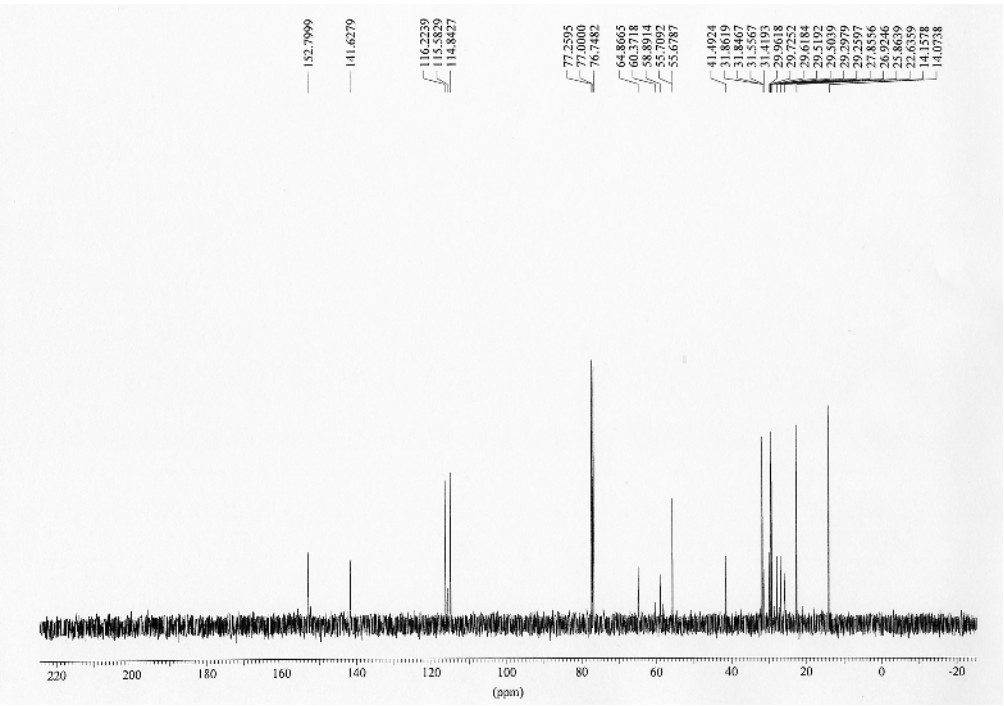
^{13}C NMR ($CDCl_3$) of compound **19**.



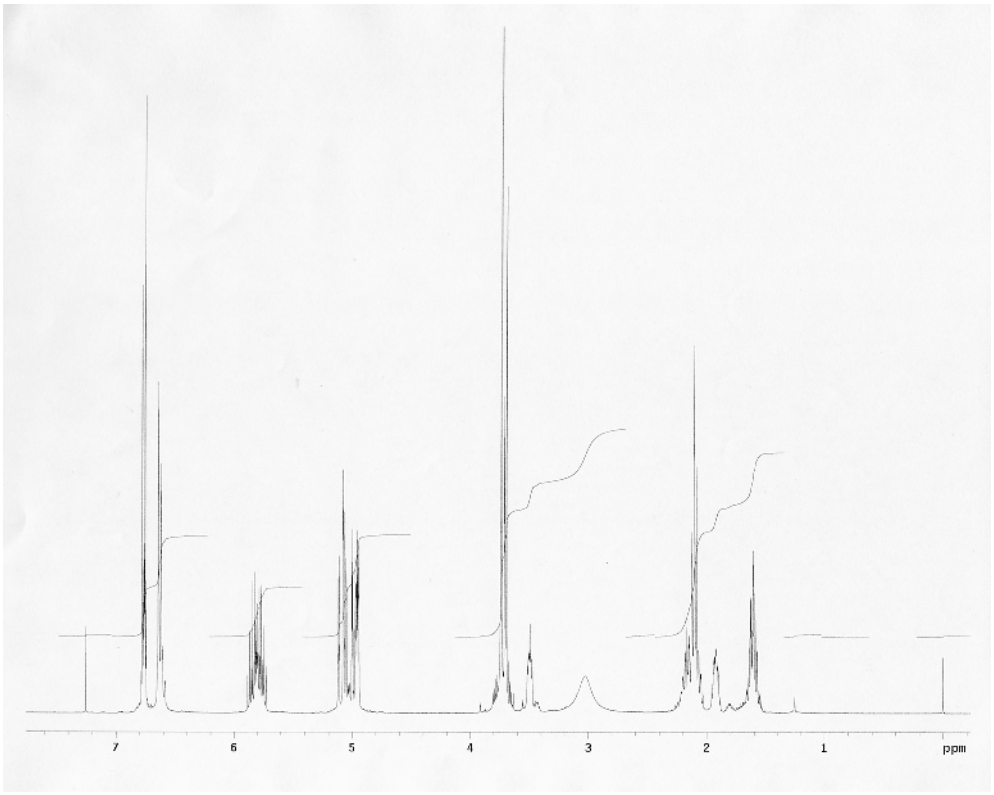
^{1}H NMR ($CDCl_3$) of compound **20**.



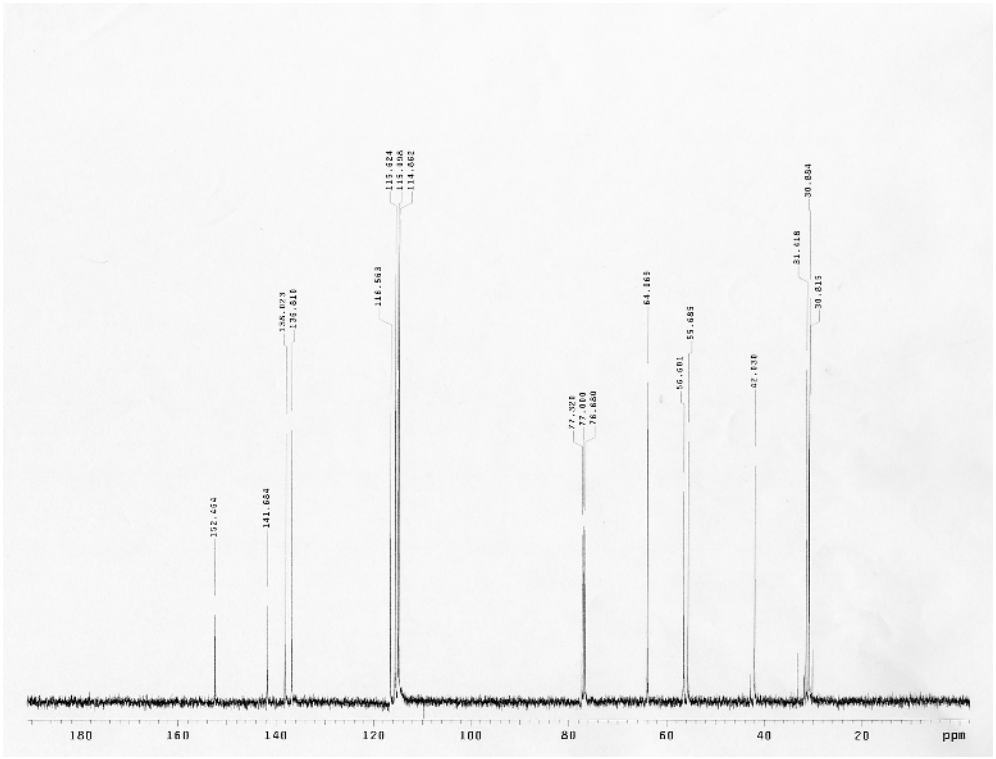
^{13}C NMR ($CDCl_3$) of compound **20**.



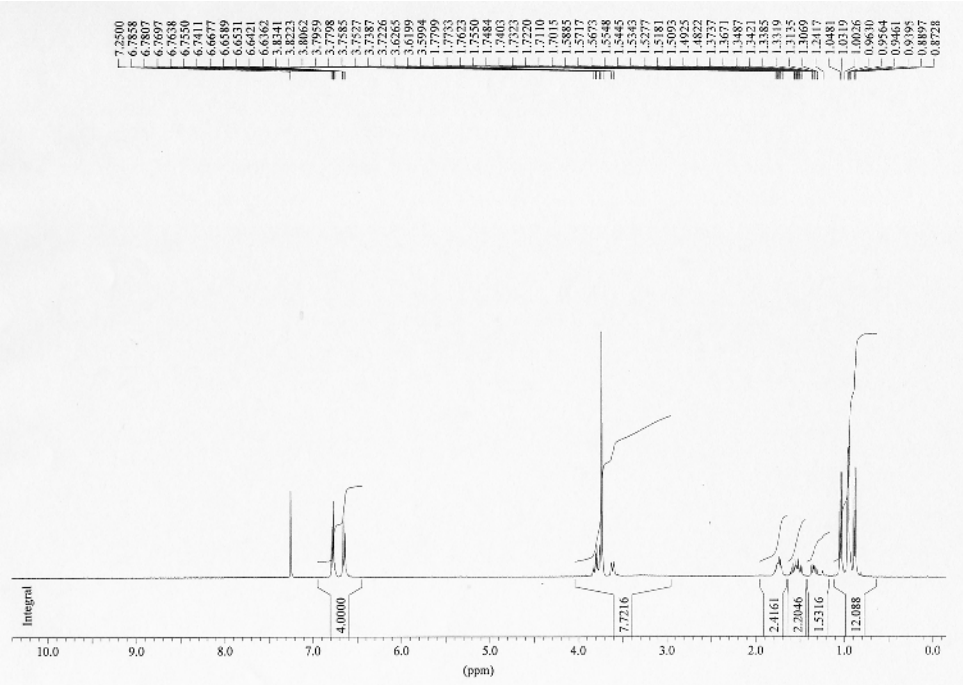
^{1}H NMR ($CDCl_3$) of compound **21**.



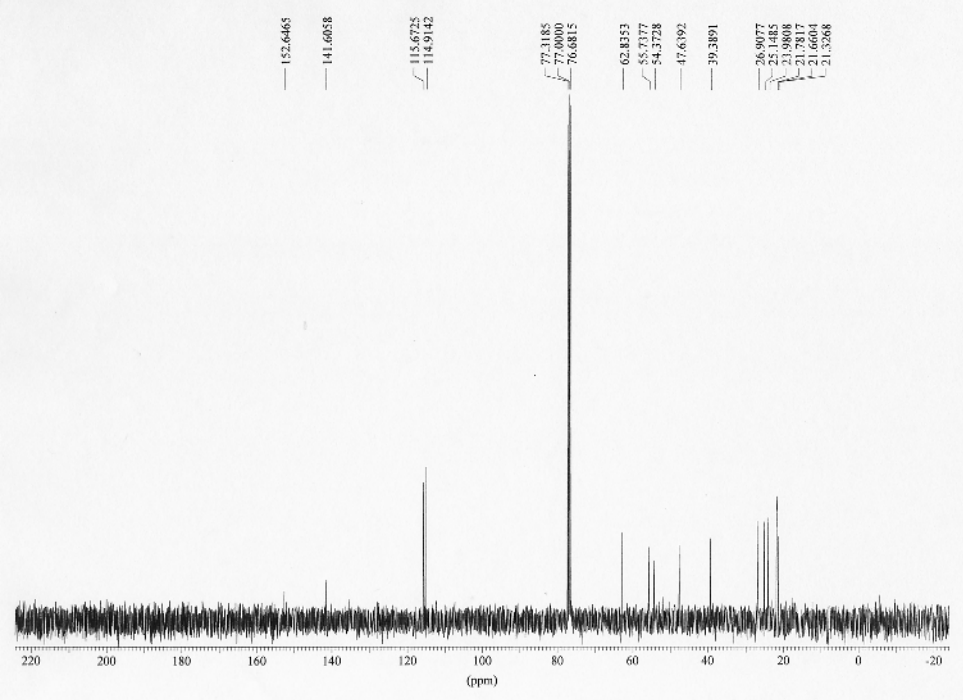
^{13}C NMR ($CDCl_3$) of compound **21**.



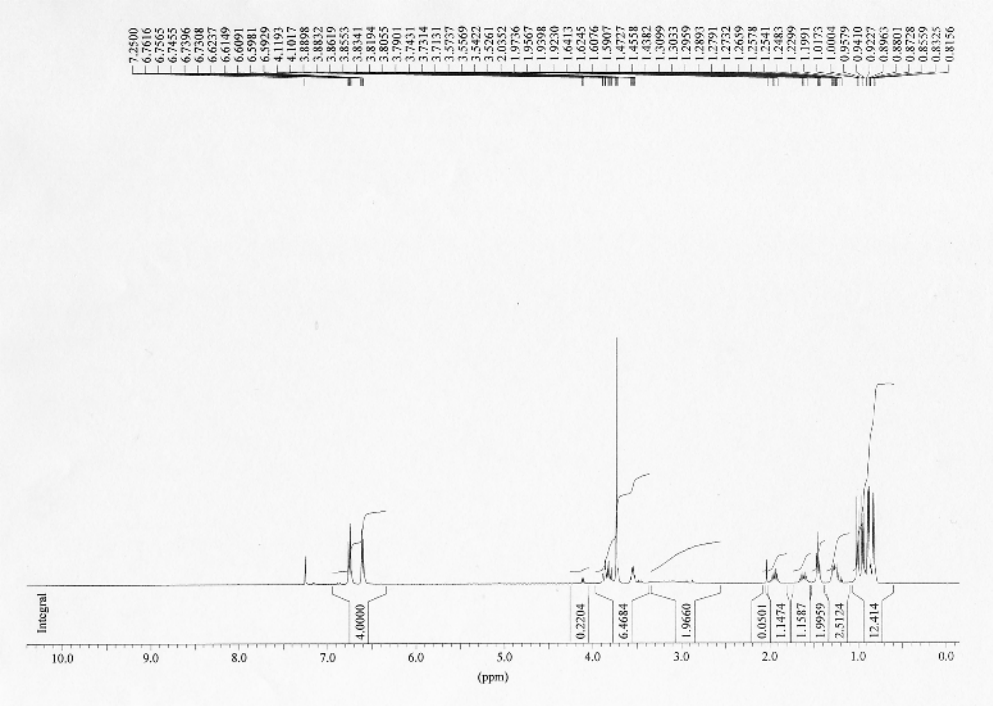
^{1}H NMR ($CDCl_3$) of compound **22** (major isomer).



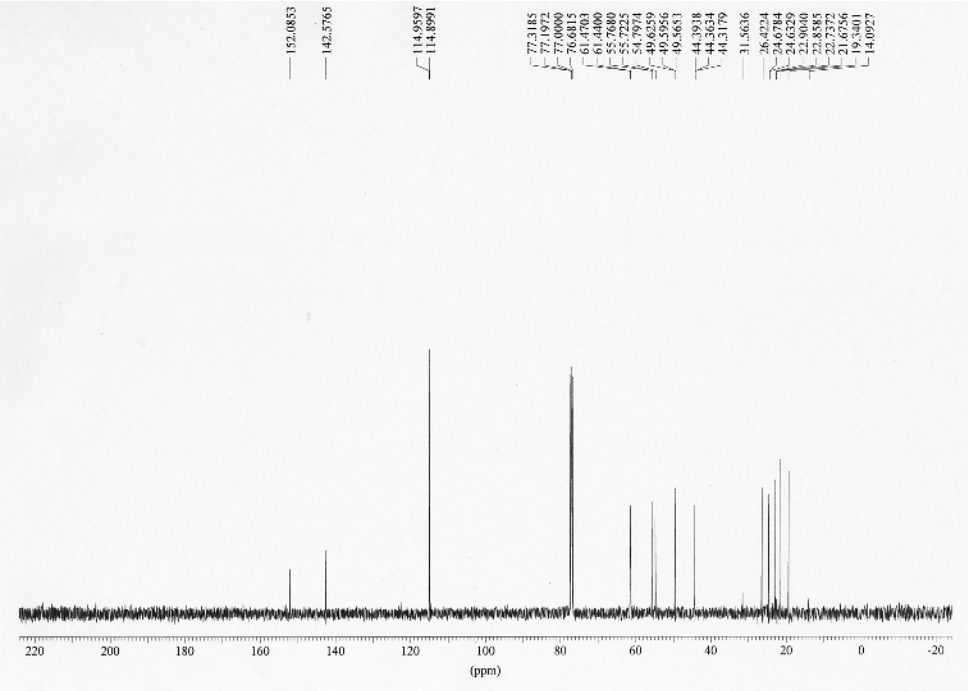
^{13}C NMR ($CDCl_3$) of compound **22** (major isomer)

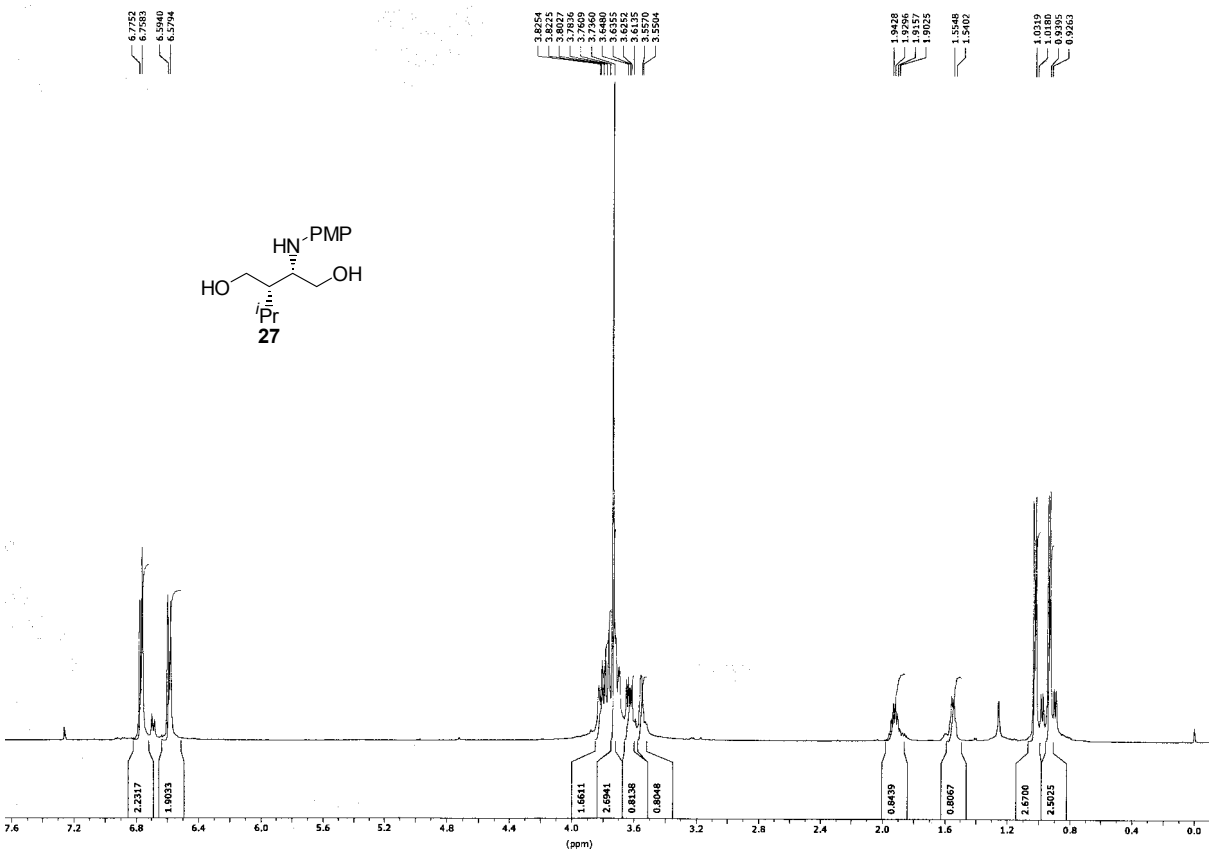


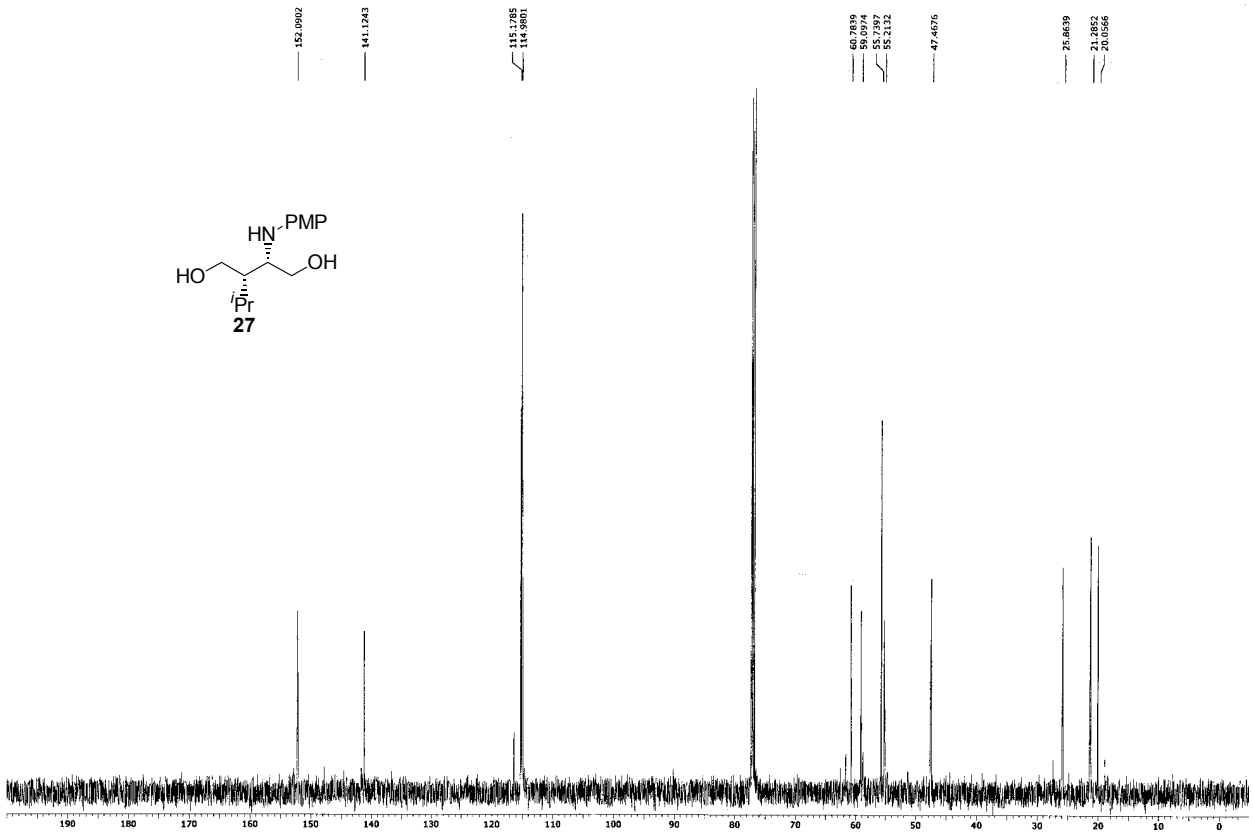
^{1}H NMR ($CDCl_3$) of compound **22** (minor isomer).

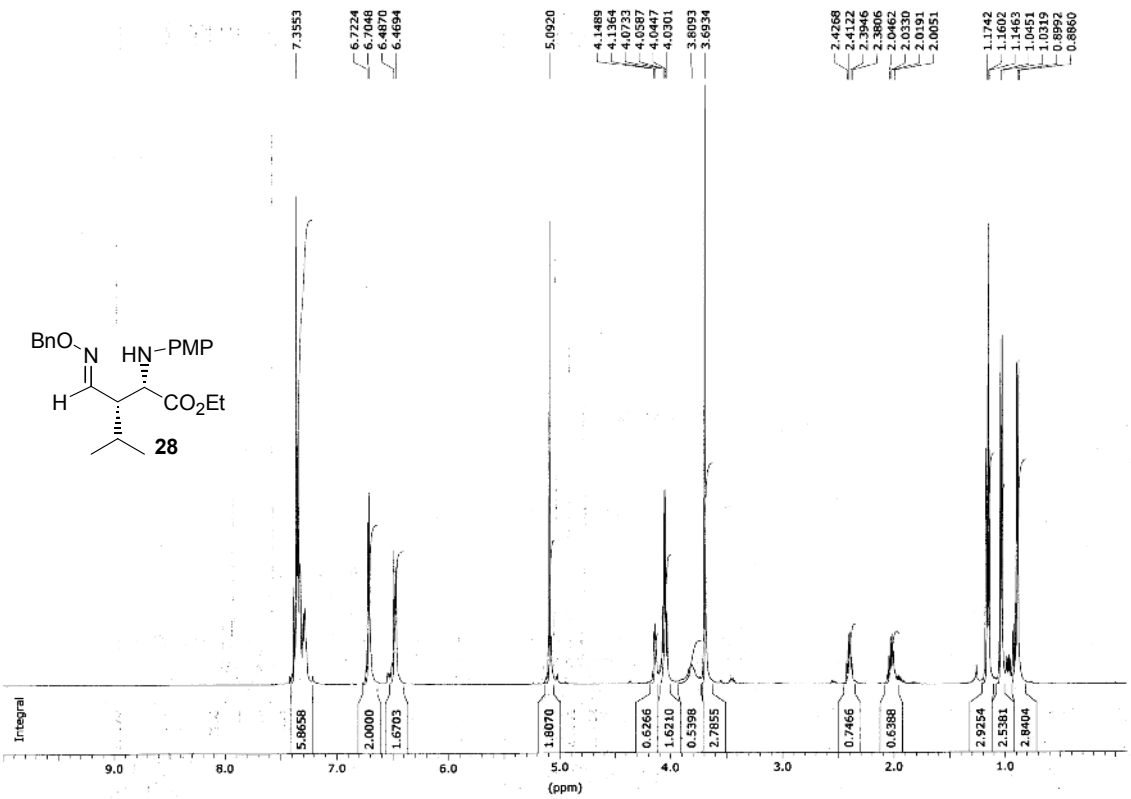


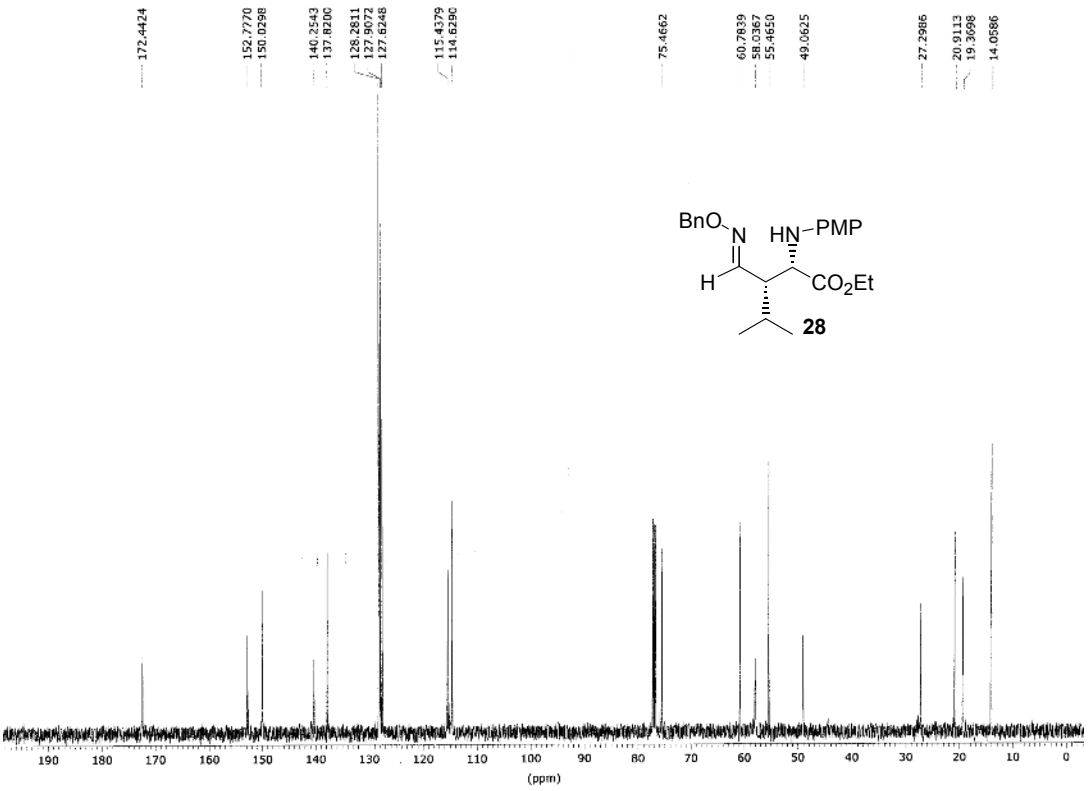
^{13}C NMR ($CDCl_3$) of compound **22** (minor isomer).

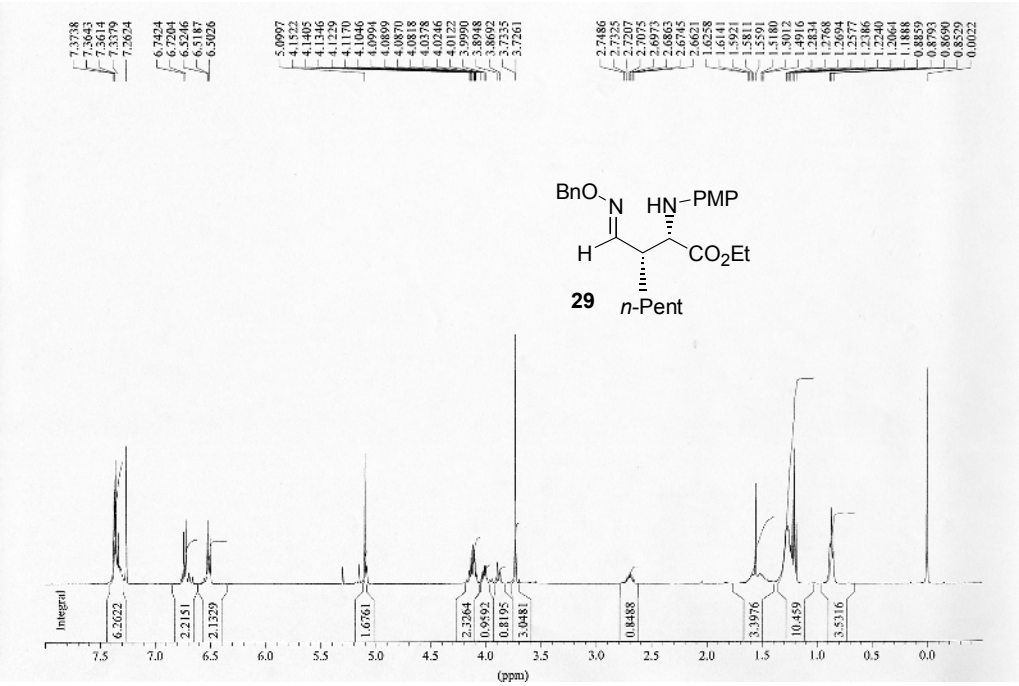


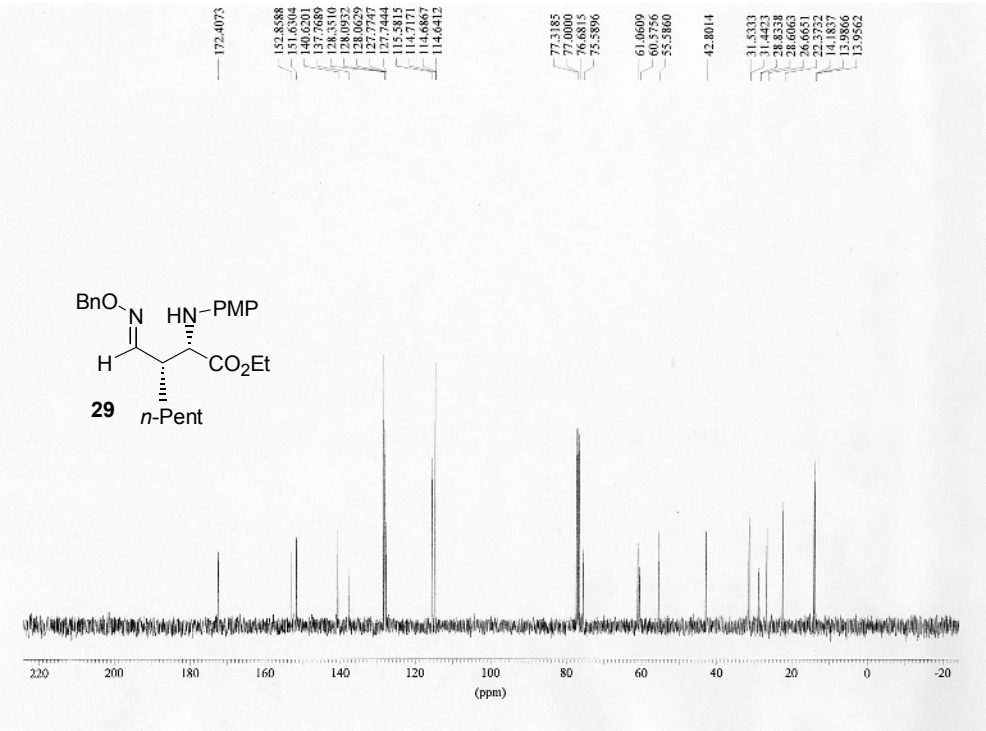

HN
PMP
HO
OH
iPr
27
(ppm)


HN
PMP
HO
OH
iPr
27


BnO
N
HN–PMP
H
CO2Et
28
Integral
(ppm)


BnO
N
HN–PMP
H
CO2Et
28
(ppm)


BnO
N
HN–PMP
H
CO2Et
29
n-Pent
Integral
6.2622
2.2151
2.1329
1.6761
2.3264
0.9592
0.8195
3.0481
0.8488
3.3976
10.459
3.5316
(ppm)


BnO
N
HN–PMP
H
CO2Et
29
n-Pent
(ppm)