SUPPORTING INFORMATION

Title: Tripeptide-catalyzed asymmetric aldol reacition between α-Ketoesters and acetone catalyzed under acidic cocatalyst-free Condition

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Content

1. General

Column chromatography was carried out on a column packed with silica-gel 60N spherical neutral size 40-50 μm. Preparative thin layer chromatography was conducted using PLC Silica gel (60 F_{254}, 1 mm). NMR spectra were recorded on a JEOL JNM-ECA600 spectrometer (1H, 600 MHz; 13C, 150 MHz). Chemical shifts of ^{1}H NMR and ^{13}C NMR signals reported δ ppm referenced to the solvent, an internal $SiMe_4$ or Sodium 3-(Trimethylsilyl)-1-propanesulfonate. HRMS were obtained at an ionization potential of 70 eV with a JEOL JMS-T100GCV spectrometer. Melting points were measured on AS ONE ATM-01 melting-point apparatus. Optical rotations were measured by JASCO P-1010 Polarimeter. HPLC analysis were performed with Daicel Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm) and Chiralpak OD-H column (25 cm × 4.6 mm × 5 μm). Absolute configurations of aldol adducts **4a** was determined by comparison between **4a'**s optical rotation and previous reported optical rotation.[1]

2. Materials

All reagents and solvents were purchased from commercial sources and used without purification. Amino ester hydrochlorides were synthesised by the literature methods.[2] **1a**–**h** were synthesised by previously reported method.[3]

3. Preparation of the tripeptide catalysts

Tripeptide catalyst were synthesised by the literature methods (Figure 1).[4]

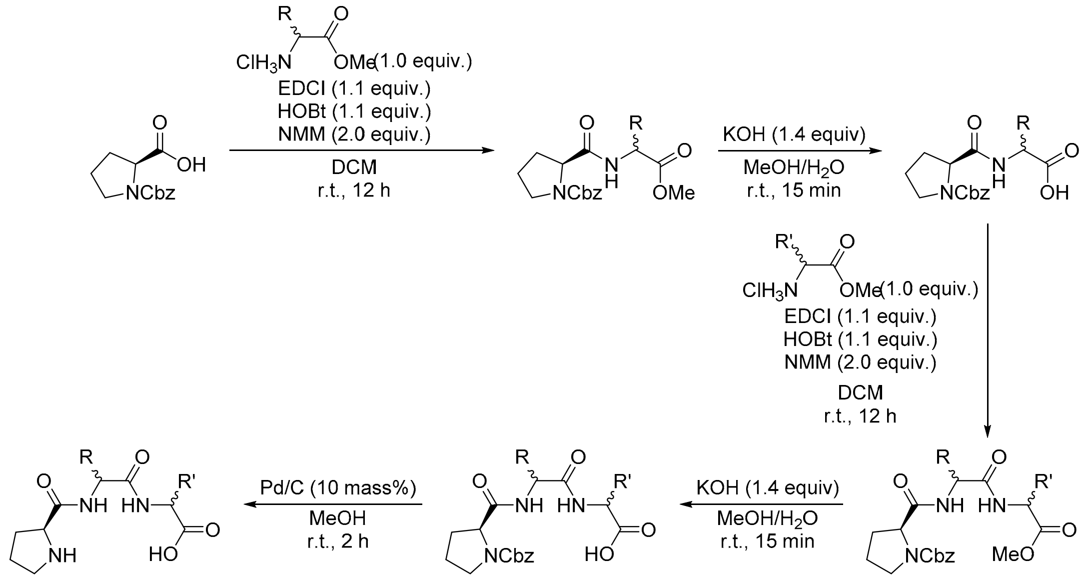
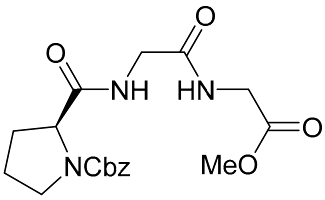


Figure 1. Synthesis of tripeptide catalysts

Condensation between Cbz-Pro-OH and amino ester hydrochloride: To a solution of Cbz-Pro-OH (20.0 mmol, 4.985 g) in CH_2Cl_2 (100 mL), Amino ester hydrochloride (20.0 mmol), HOBt (22.0 mmol, 2.973g), EDCI (22 mmol, 3.9 mL) and NMM (40 mmol, 4.4 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was concentrated under reduced pressure and was diluted by ethyl acetate. The mixture was washed with saturated aqueous $NaHCO_3$ (100 mL), 1M HCl_{aq} (100 mL) and brine. The organic phase was dried over Na_2SO_4. After removal of solvent under reduced pressure, the crude was purified through column chromatography on silica gel using *n*-hexane/ethyl acetate as eluent to give corresponding Cbz-protected dipeptide esters.

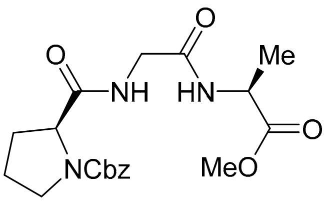
Hydrolysis of Cbz-protected peptide esters: To a solution of Cbz-protected peptide-esters (15.0 mmol) in MeOH (60 mL) and H_2O (30 mL), KOH (21.0 mmol, 1.168 g) was added at room temperature. The reaction mixture was stirred at room temperature for 15 min and the resulting mixture was concentrated under reduced pressure. The mixture was extracted with ethyl acetate. To the aqueous phase, 1M HCl_{aq} was added until pH 3. The aqueous phase was extracted with ethyl acetate. The organic phase was washed with brine and was dried over Na_2SO_4. After the removal of solvent under reduced pressure, corresponding Cbz-protected peptide was obtained.

Condensation of between Cbz-protected dipeptide and amino ester hydrochloride: To a solution of Cbz-protected dipeptide (10.0 mmol) in CH_2Cl_2 (100 mL), amino ester hydrochloride (10.0 mmol), HOBt (11.0 mmol, 1.483g), EDCI (11 mmol, 2.0 mL) and NMM (20 mmol, 2.2 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was concentrated under reduced pressure and was diluted by ethyl acetate. The mixture was washed with saturated aqueous $NaHCO_3$ (50 mL), 1M HCl_{aq} (50 mL) and brine. The Organic phase was dried over Na_2SO_4. After removal of solvent under reduced pressure, the crude was purified through column chromatography on silica gel using $CHCl_3$/MeOH as eluent to give corresponding Cbz-protected tripeptide esters.



Cbz-Pro-Gly-Gly-OMe

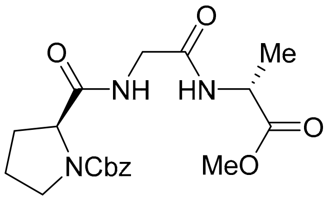
71% yield, ^{1}H NMR (600 MHz, DMSO-d$_6$, VT 100 °C) δ: 7.93 (1H, s), 7.83 (1H, s), 7.37-7.27 (5H, m), 5.09 (1H, d, J = 12.9 Hz), 5.06 (1H, d, J = 12.9 Hz), 4.30-4.20 (1H, m), 3.86 (2H, d, J = 5.8 Hz), 3.78 (1H, dd, J = 16.7, 5.8 Hz), 3.73 (1H, dd, J = 16.7, 5.3 Hz), 3.65 (3H, s), 3.53-3.42 (2H, m), 2.18-2.10 (1H, m), 1.97-1.87 (2H, m), 1.86-1.78 (1H, m). ^{13}C NMR (150 MHz, DMSO-d$_6$, VT 100 °C) δ: 172.2, 169.9, 169.1, 154.3, 137.0, 128.2, 127.5, 127.2, 66.1, 60.1, 51.5, 46.8, 42.1, 40.7, 30.3, 23.5. HRMS (EI): *m/z* cald for $C_{18}H_{23}N_3O_6$[M$^+$]: 377.1587; found: 377.1564. m.p. 104-105 °C; $[\alpha]_D^{30}$ = -28.2 (c = 0.11 in MeOH).



Cbz-Pro-Gly-Ala-OMe

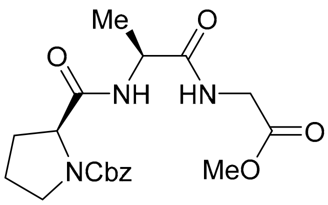
82% yield, ^{1}H NMR (600MHz, DMSO-d$_6$, VT 100 °C) δ: 7.93 (1H, s), 7.79 (1H, s), 7.37-7.28 (5H, m), 5.10 (1H, d, J = 12.9

Hz), 5.06 (1H, d, J = 12.9 Hz), 4.36-4.32 (1H, m), 4.27-4.25 (1H, m), 3.79-3.69 (2H, m), 3.65 (3H, s), 3.51-3.42 (2H, m), 2.18-2.10 (1H, m), 1.95-1.88 (2H, m), 1.85-1.79 (1H, m), 1.30 (3H, d, J = 7.2 Hz). ^{13}C NMR (150 MHz, DMSO-d_6, VT 100 °C) δ: 172.1, 171.7, 168.0, 153.7, 136.5, 127.7, 127.0, 126.7, 65.5, 59.6, 51.1, 47.1, 46.3, 41.6, 29.7, 23.0, 16.6. HRMS (EI): *m/z* cald for $C_{19}H_{25}N_3O_6[M^+]$: 391.1743; found: 391.1743. $[\alpha]_D^{30}$ = -46.2 (c = 0.43 in MeOH).



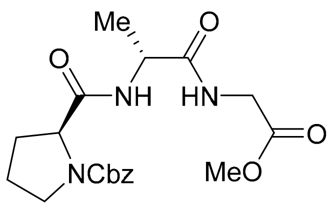
Cbz-Pro-Gly-D-Ala-OMe

89% yield, ^{1}H NMR (600 MHz, DMSO-d_6, VT 100 °C) δ: 7.90 (1H, s), 7.80 (1H, s), 7.37-7.28 (5H, m), 5.10 (1H, d, J = 12.7 Hz), 5.06 (1H, d, J = 12.7 Hz), 4.37-4.32 (1H, m), 4.27-4.24 (1H, m), 3.74 (2H, d, J = 5.8 Hz), 3.64 (3H, s), 3.53-3.48 (1H, m), 3.47-3.43 (1H, m), 2.17-2.11 (1H, m), 1.95-1.87 (2H, m), 1.85-1.79 (1H, m), 1.31 (3H, d, J = 7.2 Hz). ^{13}C NMR (150 MHz, DMSO-d_6, VT 100 °C) δ: 172.1, 171.6, 168.0, 153.8, 136.5, 127.7, 127.0, 126.7, 65.6, 59.7, 51.2, 47.1, 46.3, 41.6, 29.8, 23.0, 16.6. HRMS (EI): *m/z* cald for $C_{19}H_{25}N_3O_6[M^+]$: 391.1743; found: 391.1720. m.p. 132-133 °C; $[\alpha]_D^{30}$ = 47.5 (c = 0.43 in MeOH).



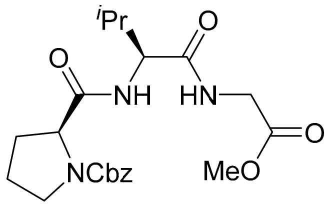
Cbz-Pro-Ala-Gly-OMe

90% yield, ^{1}H NMR (600 MHz, DMSO-d_6, VT 100 °C) δ: 7.85 (1H, s), 7.75 (1H, s), 7.36-7.28 (5H, m), 5.08 (1H, d, J = 12.9 Hz), 5.04 (1H, d, J = 12.9 Hz), 4.36-4.31 (1H, m), 4.28 (1H, dd, J = 8.6, 3.4 Hz), 3.90-3.80 (2H, m), 3.65 (3H, s), 3.49-3.41 (2H, m), 2.16-2.09 (1H, m), 1.95-1.86 (2H, m), 1.85-1.78 (1H, m), 1.28-1.19 (3H, m). ^{13}C NMR (150 MHz, DMSO-d_6, VT 100 °C) δ: 172.5, 171.7, 170.0, 154.3, 137.1, 128.2, 127.6, 127.2, 66.1, 59.8, 51.5, 48.2, 46.9, 40.8, 30.3, 23.4, 17.8. HRMS (EI): *m/z* cald for $C_{19}H_{25}N_3O_6[M^+]$: 391.1743; found: 391.1771. m.p. 124-125 °C; $[\alpha]_D^{22}$ = -85.5 (c = 0.42 in MeOH).



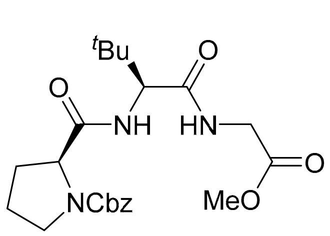
Cbz-Pro-D-Ala-Gly-OMe

85% yield, [1]H NMR (600 MHz, DMSO-d6, VT 100 °C) δ: 7.88 (1H, s), 7.80 (1H, s), 7.39-7.27 (5H, m), 5.07 (2H, s), 4.37-4.32 (1H, m), 4.26 (1H, dd, *J* = 8.2, 3.4 Hz), 3.83 (2H, d, *J* = 5.8 Hz), 3.64 (3H, s), 3.53-3.42 (2H, m), 2.17-2.10 (1H, m), 1.95-1.86 (2H, m), 1.85-1.78 (1H, m), 1.24 (3H, d, *J* = 7.2 Hz). [13]C NMR (150 MHz, DMSO-d6, VT 100 °C) δ: 172.4, 171.7, 169.9, 154.4, 137.1, 128.2, 127.6, 127.2, 66.1, 60.1, 51.5, 48.2, 46.9, 40.8, 30.3, 23.6, 17.9. HRMS (EI): *m/z* cald for $C_{19}H_{25}N_3O_6[M^+]$: 391.1743; found: 391.1718. $[\alpha]_D^{23}$ = 5.1 (c = 0.16 in MeOH).



Cbz-Pro-Val-Gly-OMe

84% yield, [1]H NMR (600 MHz, DMSO-d6, VT 100 °C) δ: 8.03 (1H, s), 7.53 (1H, s), 7.40-7.26 (5H, m), 5.09 (1H, d, *J* = 12.9 Hz), 5.03 (1H, d, *J* = 12.9 Hz), 4.36 (1H, dd, *J* = 8.6, 3.1 Hz), 4.23 (1H, dd, *J* = 8.6, 6.5 Hz), 3.86 (1H, dd, *J* = 17.2, 5.8 Hz), 3.80 (1H, dd, *J* = 17.2, 5.5 Hz), 3.63 (3H, s), 3.55-3.40 (2H, m), 2.19-2.12 (1H, m), 2.10-2.00 (1H, m), 1.92-1.79 (3H, m), 0.89 (3H, d, *J* = 6.5 Hz), 0.85 (3H, d, *J* = 6.9 Hz). [13]C NMR (150 MHz, DMSO-d6, VT 100 °C) δ: 171.8, 171.1, 169.8, 154.3, 137.0, 128.2, 127.5, 127.2, 66.0, 60.0, 57.6, 51.4, 46.9, 40.7, 30.6, 23.5, 19.0, 17.7. HRMS (EI): *m/z* cald for $C_{21}H_{29}N_3O_6[M^+]$: 419.2056; found: 419.2029. m.p. 101-102 °C; $[\alpha]_D^{19}$ = -78.2 (c = 0.20 in MeOH).

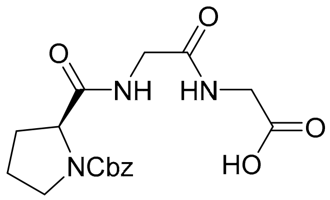


Cbz-Pro-Tle-Gly-OMe

87% yield, [1]H NMR (600 MHz, DMSO-d6, VT 100 °C) δ: 8.10 (1H, s), 7.40 (1H, s), 7.36-7.25 (5H, m), 5.12-4.97 (2H, m), 4.40 (1H, d, *J* = 8.2 Hz), 4.24 (1H, d, *J* = 9.3 Hz), 3.89 (1H, dd, *J* = 17.2, 5.8 Hz), 3.79 (1H, dd, *J* = 17.2, 5.5 Hz), 3.64 (3H, s), 3.48-3.41 (2H, m), 2.20-2.06 (1H, m), 1.91-1.80 (3H, m), 0.92 (9H, s). [13]C NMR (150 MHz, DMSO-d6, 100 °C) δ: 171.4, 170.4, 169.8, 154.3, 137.0, 128.2, 127.5, 127.2, 66.1, 60.0, 59.8, 51.4, 46.9, 40.7, 34.2, 30.1, 26.6, 23.5. HRMS (EI): *m/z* cald for $C_{22}H_{31}N_3O_6[M^+]$: 433.2213; found:

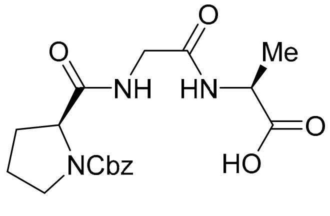
433.2195. m.p. 63-64 °C; $[\alpha]_D^{22}$ = -25.2 (c = 0.12 in $CHCl_3$).

Hydrolysis of Cbz-protected peptide esters: To a solution of Cbz-protected peptide-esters (5.0 mmol) in MeOH (40 mL) and H_2O (20 mL), KOH (7.0 mmol, 39.3 mg) was added at room temperature. The reaction mixture was stirred at room temperature for 15 min and the resulting mixture was concentrated under reduced pressure. The mixture was extracted with ethyl acetate. To the aqueous phase, 1M HCl_{aq} was added until pH = 3. The aqueous phase was extracted with ethyl acetate. The organic phase was washed with brine and was dried over Na_2SO_4. After the removal of solvent under reduced pressure, corresponding Cbz-protected peptide was obtained.



Cbz-Pro-Gly-Gly-OH

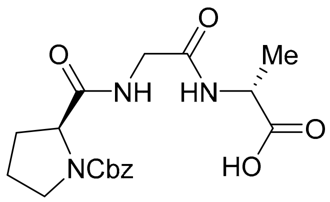
80% yield, ^{1}H NMR (600 MHz, DMSO-d_6, VT 100 °C) δ: 12.18 (1H, br s), 7.91 (1H, s), 7.70 (1H, s), 7.36-7.29 (5H, m), 5.09 (1H, d, J = 12.6 Hz), 5.05 (1H, d, J = 12.6 Hz), 4.28-4.24 (1H, m), 3.82-3.69 (4H, m), 3.51-3.41 (2H, m), 2.18-2.10 (1H, m), 1.97-1.87 (2H, m), 1.85-1.79 (1H, m). ^{13}C NMR (150 MHz, DMSO-d_6, VT 100 °C) δ: 171.7, 170.1, 168.4, 153.8, 136.5, 127.7, 127.0, 126.7, 65.6, 59.6, 46.3, 41.6, 40.3, 29.8, 23.0. HRMS (EI): *m/z* cald for $C_{17}H_{21}N_3O_6[M^+]$: 363.1430; found: 363.1443. m.p. 69-70 °C; $[\alpha]_D^{29}$ = -43.2 (c = 0.17 in MeOH).



Cbz-Pro-Gly-Ala-OH

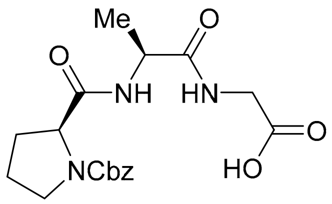
64% yield, ^{1}H NMR (600 MHz, DMSO-d_6, VT 100 °C) δ: 12.12 (1H, br s), 7.92 (1H, s), 7.64 (1H, s), 7.36-7.29 (5H, m), 5.09 (1H, d, J = 12.8 Hz), 5.05 (1H, d, J = 12.8 Hz), 4.30-4.24 (2H, m), 3.75 (1H, dd, J = 16.4, 6.0 Hz), 3.70 (1H, dd, J = 16.4, 5.4 Hz), 3.51-3.41 (2H, m), 2.18-2.10 (1H, m), 2.00-1.88 (2H, m), 1.87-1.79 (1H, m), 1.29 (3H, d, J = 7.3 Hz). ^{13}C NMR (150 MHz, DMSO-d_6, VT 100 °C) δ: 172.9, 171.6, 167.8, 153.7, 136.5, 127.7, 127.0, 126.7, 65.5, 59.6, 47.1, 46.3, 41.6, 29.8, 23.0, 16.9. HRMS (EI): *m/z* cald for

$C_{10}H_{16}N_3O_4$[M^+-Cbz]: 242.1141; found: 242.1127. m.p. 70-72 °C; $[\alpha]_D^{29}$ = -57.5 (c = 0.12 in MeOH).



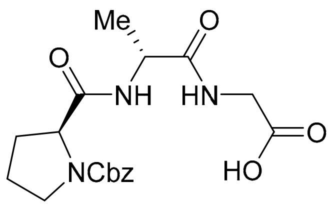
Cbz-Pro-Gly-D-Ala-OH

74% yield, ^{1}H NMR (600 MHz, DMSO-d_6, VT 100 °C) δ: 12.17 (1H, br s), 7.90 (1H, s), 7.66 (1H, s), 7.40-7.25 (5H, m), 5.10 (1H, d, *J* = 12.8 Hz), 5.05 (1H, d, *J* = 12.8 Hz), 4.30-4.23 (2H, m), 3.76-3.69 (2H, m), 3.52-3.47 (1H, m), 3.46-3.42 (1H, m), 2.17-2.11 (1H, m), 1.99-1.87 (2H, m), 1.86-1.78 (1H, m), 1.30 (3H, d, *J* = 6.9 Hz). ^{13}C NMR (150 MHz, DMSO-d_6, VT 100 °C) δ: 173.4, 172.2, 168.3, 154.3, 137.0, 128.2, 127.5, 127.2, 66.1, 60.2, 47.6, 46.8, 42.2, 30.3, 23.5, 17.4. HRMS (EI): *m/z* cald for $C_{18}H_{23}N_3O_6$[M^+]: 377.1587; found: 377.1567. m.p. 74-75 °C; $[\alpha]_D^{29}$ = -34.9 (c = 0.12 in MeOH).



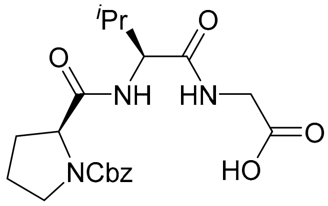
Cbz-Pro-Ala-Gly-OH

82% yield, ^{1}H NMR (600 MHz, DMSO-d_6, VT 100 °C) δ: 12.10 (1H, br s), 7.76 (1H, s), 7.72 (1H, s), 7.36-7.29 (5H, m), 5.08 (1H, d, *J* = 12.4 Hz), 5.04 (1H, d, *J* = 12.4 Hz), 4.36-4.31 (1H, m), 4.28 (1H, d, *J* = 6.4 Hz), 3.80 (1H, dd, *J* = 17.2, 5.5 Hz), 3.75 (1H, dd, *J* = 17.2, 5.5 Hz), 3.49-3.41 (2H, m), 2.20-2.07 (1H, m), 1.98-1.85 (2H, m), 1.83-1.77 (1H, m), 1.21 (3H, s). ^{13}C NMR (150 MHz, DMSO-d_6, VT 100 °C) δ: 172.3, 171.6, 170.6, 154.2, 137.1, 128.2, 127.6, 127.2, 66.0, 59.8, 48.2, 46.9, 40.9, 30.4, 23.4, 17.9. HRMS (EI): *m/z* cald for $C_{18}H_{23}N_3O_6$ [M^+]: 377.1587; found: 377.1579. m.p. 66-67 °C; $[\alpha]_D^{23}$ = -88.7 (c = 0.077 in MeOH).



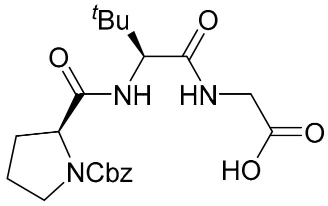
Cbz-Pro-D-Ala-Gly-OH

38% yield, ^{1}H NMR (600 MHz, DMSO-d_6, VT 100 °C) δ: 12.18 (1H, br s), 7.77 (2H, s), 7.40-7.25 (5H, m), 5.07 (2H, s), 4.36-4.31 (1H, m), 4.26 (1H, dd, *J* = 7.9, 2.4 Hz), 3.75 (2H, d, *J* = 6.2 Hz), 3.50-3.41 (2H, m), 2.17-2.08 (1H, m), 1.99-1.86 (2H, m), 1.84-1.78 (1H, m), 1.24 (3H, d, *J* = 6.9 Hz). ^{13}C NMR (150 MHz, DMSO-d_6, VT 100 °C) δ: 172.2, 171.6, 170.5, 154.3, 137.0, 128.2, 127.5, 127.2, 66.1, 60.1, 48.2, 46.9, 40.9, 30.3, 23.6, 17.9. HRMS (EI): *m/z* cald for $C_{18}H_{23}N_3O_6$ [M^+]: 377.1587; found: 377.1587. m.p. 211-212 °C; $[\alpha]_D^{24}$ = -9.4 (c = 0.16 in MeOH).



Cbz-Pro-Val-Gly-OH

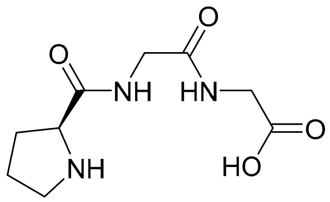
87% yield, ^{1}H NMR (600 MHz, DMSO-d_6, VT 100 °C) δ: 7.91 (1H, s), 7.54 (1H, s), 7.35-7.28 (5H, m), 5.09 (1H, d, *J* = 12.4 Hz), 5.03 (1H, d, *J* = 12.4 Hz), 4.36 (1H, d, *J* = 6.2 Hz), 4.23 (1H, t, *J* = 7.6 Hz), 3.78 (1H, dd, *J* = 17.2, 5.5 Hz), 3.73 (1H, dd, *J* = 17.2, 5.5 Hz), 3.49-3.42 (2H, m), 2.20-2.11 (1H, m), 2.10-2.00 (1H, m), 1.95-1.75 (3H, m), 0.89 (3H, d, *J* = 6.9 Hz), 0.85 (3H, d, *J* = 6.9 Hz). ^{13}C NMR (150MHz, DMSO-d_6, VT 100 °C) δ: 171.8, 171.0, 170.6, 154.3, 137.0, 128.2, 127.5, 127.3, 66.1, 60.1, 57.8, 46.9, 40.8, 30.6, 23.5, 19.1, 17.8. HRMS (EI): *m/z* cald for $C_{20}H_{27}N_3O_6$ [M^+]: 405.1900; found: 405.1878. m.p. 190-191 °C; $[\alpha]_D^{19}$ = -99.4 (c = 0.23 in MeOH).



Cbz-Pro-Tle-Gly-OH

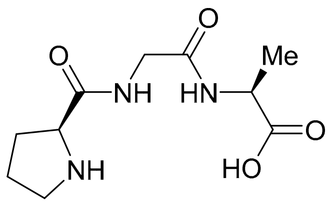
78% yield, ^{1}H NMR (600 MHz, DMSO-d_6, VT 100 °C) δ: 7.99 (1H, s), 7.47 (1H, s), 7.35-7.25 (5H, m), 5.12-4.96 (2H, m), 4.41 (1H, d, *J* = 7.6 Hz), 4.22 (1H, d, *J* = 9.6 Hz), 3.80 (1H, dd, *J* = 17.2, 5.5 Hz), 3.71 (1H, dd, *J* = 17.2, 5.5 Hz), 3.47-3.41 (2H, m), 2.14-2.08 (1H, m), 1.92-1.78 (3H, m), 0.92 (9H, s). ^{13}C NMR (150MHz, DMSO-d_6, VT 100 °C) δ: 171.4, 170.5, 170.3, 154.3, 137.0, 128.2, 127.5, 127.2, 66.0, 60.2, 59.8, 47.0, 40.8, 34.2, 30.3, 26.6, 23.5. HRMS (EI): *m/z* cald for $C_{21}H_{29}N_3O_6$ [M^+]: 419.2056; found: 419.2039. m.p. 199-200 °C; $[\alpha]_D^{21}$ = -172.5 (c = 0.14 in MeOH).

Deprotection of Cbz of Cbz-protected tripeptide: To a solution of Cbz-protected tripeptide (2 mmol) in MeOH (30 mL), 10% Pd/C was added at room temperature. After stirred under hydrogen (1 atm) for 2 h at room temperature, The resulting mixture was filtered. After the removal of solvent under reduced pressure, corresponding tripeptide was obtained.



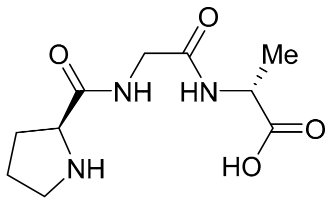
H-Pro-Gly-Gly-OH (3a)

85% yield, ^{1}H NMR (600 MHz, D_2O) δ: 4.46 (1H, dd, *J* = 8.6, 6.9 Hz), 4.07 (1H, d, *J* = 16.8 Hz), 3.99 (1H, d, *J* = 16.8 Hz), 3.81 (1H, d, *J* = 17.2 Hz), 3.77 (1H, d, *J* = 17.2 Hz), 3.47-3.37 (2H, m), 2.50-2.43 (1H, m), 2.15-2.04 (3H, m). ^{13}C NMR (150 MHz, D_2O) δ: 178.8, 173.3, 172.9, 62.5, 49.1, 45.7, 45.2, 32.2, 26.5. HRMS (EI): *m/z* cald for $C_9H_{15}N_3O_4$[M^+]: 229.1063; found: 229.1058. m.p. 114-116 °C; $[\alpha]_D^{28}$ = -16.2 (c = 0.53 in H_2O).



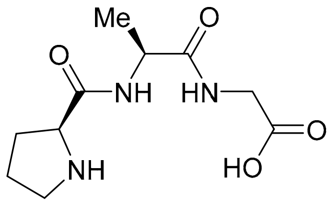
H-Pro-Gly-Ala-OH (3b)

99% yield, ^{1}H NMR (600 MHz, D_2O) δ: 4.45 (1H, dd, *J* = 8.8, 6.7 Hz), 4.15 (1H, q, *J* = 7.4 Hz), 4.02 (1H, d, *J* = 16.5 Hz), 3.98 (1H, d, *J* = 16.5 Hz), 3.48-3.37 (2H, m), 2.50-2.44 (1H, m), 2.15-2.05 (3H, m), 1.33 (3H, d, *J* = 7.4 Hz). ^{13}C NMR (150 MHz, D_2O) δ: 182.6, 172.9, 172.4, 62.5, 53.7, 49.1, 45.2, 32.3, 26.5, 20.1. HRMS (EI): *m/z* cald for $C_{10}H_{18}N_3O_4$[M^++H]: 244.1297; found: 244.1284. m.p. 147-148 °C; $[\alpha]_D^{27}$ = -44.9 (c = 0.21 in H_2O).



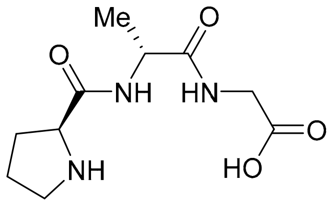
H-Pro-Gly-D-Ala-OH (3c)

93% yield, ^{1}H NMR (600 MHz, D_2O) δ: 4.45 (1H, t, *J* = 7.4 Hz), 4.17 (1H, q, *J* = 7.2 Hz), 4.04 (1H, d, *J* = 17.2 Hz), 3.97 (1H, d, *J* = 17.2 Hz), 3.47-3.37 (2H, m), 2.50-2.43 (1H, m), 2.14-2.05 (3H, m), 1.34 (3H, d, *J* = 7.2 Hz). ^{13}C NMR (150 MHz, D_2O) δ: 182.3, 172.8, 172.5, 62.5, 53.5, 49.1, 45.1, 32.2, 26.5, 20.0. HRMS (EI): *m/z* cald for $C_{10}H_{18}N_3O_4$[M^+]: 243.1220; found: 243.1219. m.p. 126-128 °C; $[\alpha]_D^{27}$ = 6.0 (c = 0.45 in H_2O).



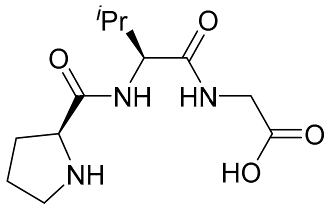
H-Pro-Ala-Gly-OH (3d)

49% yield, ^{1}H NMR (600MHz, D_2O) δ: 4.45-4.37 (2H, m), 3.78 (1H, d, *J* = 17.4 Hz), 3.74 (1H, d, *J* = 17.4 Hz), 3.46-3.34 (2H, m), 2.50-2.41 (1H, m), 2.11-2.04 (3H, m), 1.42 (3H, d, *J* = 7.2 Hz). ^{13}C NMR (150 MHz, D_2O) δ: 178.9, 176.7, 172.0, 62.3, 52.6, 49.2, 46.0, 32.4, 26.5, 19.3. HRMS (EI): *m/z* cald for $C_{10}H_{17}N_3O_4[M^+]$: 243.1219; found: 243.1209. m.p. 237-238 °C; $[\alpha]_D^{25}$ = -66.6 (c = 0.13 in H_2O).



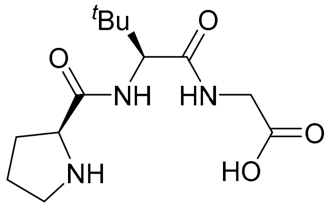
H-Pro-D-Ala-Gly-OH (3e)

99% yield, ^{1}H NMR (600 MHz, D_2O) δ: 4.45-4.37 (2H, m), 3.78 (1H, d, *J* = 17.4 Hz), 3.74 (1H, d, *J* = 17.4 Hz), 3.46-3.34 (2H, m), 2.50-2.41 (1H, m), 2.11-2.04 (3H, m), 1.42 (3H, d, *J* = 7.2 Hz). ^{13}C NMR (150 MHz, D_2O) δ: 179.0, 176.8, 172.1, 62.4, 52.6, 49.2, 46.0, 32.3, 26.5, 19.4. HRMS (EI): *m/z* cald for $C_{10}H_{17}N_3O_4[M^+]$: 243.1219; found: 243.1207. m.p. 241-242 °C; $[\alpha]_D^{25}$ = 13.2 (c = 0.13 in H_2O).



H-Pro-Gly-Val-OH (3f)

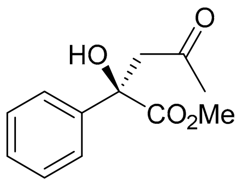
95% yield, ^{1}H NMR (600 MHz, D_2O) δ: 4.47-4.44 (1H, m), 4.25 (1H, d, *J* = 6.5 Hz), 3.80 (1H, d, *J* = 17.2 Hz), 3.73 (1H, d, *J* = 17.2 Hz), 3.50-3.43 (1H, m), 3.41-3.37 (1H, m), 2.54-2.46 (1H, m), 2.19-2.02 (4H, m), 0.94 (6H, dd, *J* = 11.5, 6.7 Hz). ^{13}C NMR (150 MHz, D_2O) δ: 178.8, 175.4, 172.5, 62.5, 62.2, 49.2, 45.9, 32.9, 32.8, 26.5, 21.8, 19.8. HRMS (EI): *m/z* cald for $C_{12}H_{21}N_3O_4[M^+]$: 271.1532; found: 271.1509. m.p. 244-245 °C; $[\alpha]_D^{21}$ = -133.7 (c = 0.17 in MeOH).



H-Pro-Tle-Gly-OH (3g)

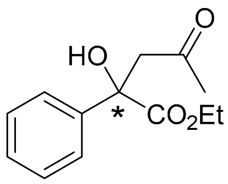
76% yield, ^{1}H NMR (600 MHz, D_2O) δ: 4.50-4.44 (1H, m), 4.21 (1H, s), 3.78 (1H, d, J = 17.2 Hz), 3.73 (1H, d, J = 17.2 Hz), 3.48-3.42 (1H, m), 3.39-3.35 (1H, m), 2.51-2.41 (1H, m), 2.09-1.98 (3H, m), 1.01 (9H, s). ^{13}C NMR (150 MHz, D_2O) δ: 178.8, 174.2, 172.1, 65.2, 62.2, 49.2, 45.8, 36.3, 32.6, 28.6, 26.4. HRMS (EI): *m/z* cald for $C_{13}H_{23}N_3O_4[M^+]$: 285.1689; found: 285.1704. m.p. 255-256 °C; $[\alpha]_D^{21}$ = -79.0 (c = 0.10 in MeOH).

4. General procedure for tripeptide-catalyzed asymmetric aldol reaction of α-Ketoesters: A mixture of H-Pro-Tle-Gly-OH **3g** (20 µmol, 5.7 mg), acetone (10 mmol, 0.74 mL) and THF (1.0 mL) was stirred at 0 °C for 10 min. To the resulting mixture, α-Ketoesters (0.1 mmol) was added. The mixture was stirred at 0 °C for 6 days and then was filtrated to remove catalyst. the mixture was concentrated under reduced pressure. Preparative thin layer chromatography on silica gel using hexane/ethyl acetate as eluent gave the aldol adduct. The enantiomeric excess of aldol adduct was determined by chiral HPLC.



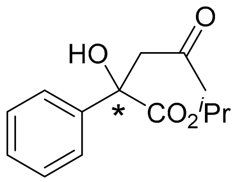
(*R*)-methyl 2-hydroxy-4-oxo-2-phenylpentanoate (4a).

76% yield, ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.57 (2H, d, J = 7.6 Hz), 7.37-7.35 (2H, m), 7.33-7.28 (1H, m), 4.48 (1H, s), 3.75 (3H, s), 3.56 (1H, d, J = 17.7 Hz), 3.03 (1H, d, J = 17.7 Hz), 2.20 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 208.1, 174.5, 140.4, 128.7, 128.3, 125.1, 76.6, 53.4, 53.2, 30.9. HRMS (EI): *m/z* cald for $C_{12}H_{14}O_4[M^+]$: 222.0892; found: 222.0862. m.p. 71-72 °C; $[\alpha]_D^{27}$ = 353.8 (c = 0.14 in $CHCl_3$), HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane /^{i}PrOH = 97/3, 1.0 mL/min, 254 nm, 35 °C) minor enantiomer t = 26.7 min, major enantiomer t = 21.7 min.



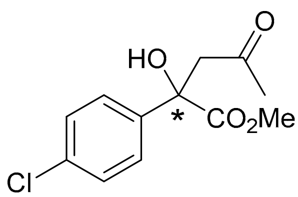
Ethyl 2-hydroxy-4-oxo-2-phenylpentanoate (4b).

63% yield, ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.57 (2H, d, J = 7.2 Hz), 7.35 (2H, t, J = 7.2 Hz), 7.29 (1H, t, J = 7.2 Hz), 4.38 (1H, s), 4.22 (2H, q, J = 7.2 Hz), 3.54 (1H, d, J = 17.7 Hz), 3.01 (1H, d, J = 17.7 Hz), 2.20 (3H, s), 1.25 (3H, t, J = 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 207.7, 174.0, 140.5, 128.6, 128.2, 125.1, 76.4, 62.4, 53.2, 30.8, 14.1. HRMS (EI): *m/z* cald for $C_{13}H_{16}O_4[M^+]$: 236.1049; found: 236.1026. $[\alpha]_D^{26}$ = 160.5 (c = 0.11 in $CHCl_3$), HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane /^{i}PrOH = 97/3, 1.0 mL/min, 254 nm, 35 °C) minor enantiomer t = 25.9 min, major enantiomer t = 20.2 min.



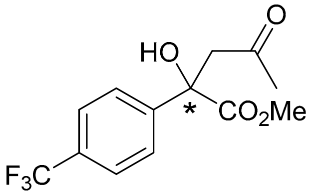
Isopropyl 2-hydroxy-4-oxo-2-phenylpentanoate (4c).

33% yield, ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.58-7.56 (2H, m), 7.36-7.33 (2H, m), 7.29 (1H, tt, J = 7.4, 1.5 Hz), 5.06 (1H, sep, 6.4 Hz), 4.33 (1H, s), 3.51 (1H, d, J = 17.5 Hz), 3.01 (1H, d, J = 17.5 Hz), 2.19 (3H, s), 1.23 (6H, t, J = 6.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 207.4, 173.5, 140.7, 128.5, 128.1, 125.1, 76.3, 70.3, 53.2, 30.8, 21.7, 21.7. HRMS (EI): *m/z* cald for $C_{14}H_{18}O_4[M^+]$: 250.1205; found: 250.1180. $[\alpha]_D^{27}$ = 313.3 (c = 0.26 in $CHCl_3$), HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane /^{i}PrOH = 97/3, 1.0 mL/min, 254 nm, 35 °C) minor enantiomer t = 24.2 min, major enantiomer t = 18.3 min.



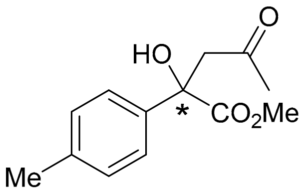
Methyl 2-hydroxy-4-oxo-2-(4-chlorophenyl)pentanoate (4d)

84% Yield, ^{1}H NMR ($CDCl_3$) δ: 7.53-7.48 (2H, m), 7.35-7.30 (2H, m), 4.43 (1H, s), 3.76 (3H, s), 3.52 (1H, d, J = 17.7 Hz), 2.97 (1H, d, J = 17.7 Hz), 2.21 (3H, s). ^{13}C NMR ($CDCl_3$) δ: 208.8, 175.2, 139.9, 135.3, 129.8, 127.6, 77.2, 54.5, 54.1, 31.8. HRMS (EI): *m/z* cald for $C_{12}H_{13}Cl_1O_4[M^+]$: 256.0480; found: 256.0502. $[\alpha]_D^{28}$ = 276.8 (c = 0.23 in $CHCl_3$), HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane /^{i}PrOH = 97/,3 1.0 mL/min, 254 nm, 35 °C) minor enantiomer t = 26.8 min, major enantiomer t = 20.4 min.



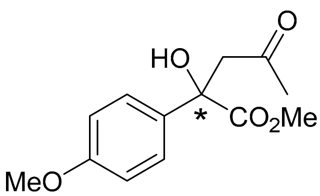
Methyl 2-hydroxy-4-oxo-2-(4-(trifluoromethyl)phenyl)pentanoate (4e)

95% Yield, ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.71 (2H, d, J = 8.2 Hz), 7.62 (2H, d, J = 8.2 Hz), 4.49 (1H, s), 3.78 (3H, s), 3.55 (1H, d, J = 17.5 Hz), 2.99 (1H, d, J = 17.5 Hz), 2.23 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 207.6, 173.9, 144.3, 130.6 (q, J = 32.3 Hz), 125.7, 124.1 (q, J = 272.0 Hz), 76.4, 53.6, 53.1, 30.8. HRMS (EI): *m/z* cald for $C_{13}H_{13}F_3O_4[M^+]$: 290.0766; found: 290.0750. $[\alpha]_D^{27}$ = 363.8 (c = 0.22 in $CHCl_3$), HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane /^{i}PrOH = 97/3, 1.0 mL/min, 254 nm, 35 °C) minor enantiomer t = 19.0 min, major enantiomer t = 15.9 min.



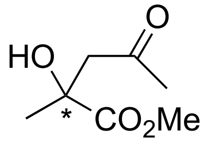
Methyl 2-hydroxy-4-oxo-2-(p-tolyl)pentanoate (4f)

25% yield, ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.45-7.42 (2H, m), 7.17 (2H, d, J = 8.2 Hz), 4.39 (1H, s), 3.75 (3H, s), 3.54 (1H, d, J = 17.9 Hz), 3.00 (1H, d, J = 17.9 Hz), 2.34 (3H, s), 2.21 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 208.1, 174.7, 138.1, 137.5, 129.4, 125.0, 76.5, 53.3, 53.2, 30.9, 21.2. HRMS (EI): *m/z* cald $C_{13}H_{16}O_4[M^+]$: 236.1049; found: 236.1066. $[\alpha]_D^{26}$ = 137.2 (c = 0.16 in $CHCl_3$), HPLC (DAICEL CHIRALPAK OD-H, *n*-hexane /^{i}PrOH = 90/10, 1.0 mL/min, 254 nm, 35 °C) minor enantiomer t = 28.4 min, major enantiomer t = 20.8 min.



Methyl 2-hydroxy-2-(4-methoxyphenyl)-4-oxopentanoate (4g)

10% yield, ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.49-7.45 (2H, m), 6.90-6.86 (2H, m), 4.38 (1H, s), 3.80 (3H, s), 3.75 (3H, s), 3.53 (1H, d, J = 17.7 Hz), 3.00 (1H, d, J = 17.7 Hz), 2.20 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 208.1, 174.7, 159.6, 132.5, 126.3, 114.0, 76.2, 55.5, 53.3, 53.2, 30.9. HRMS (EI): *m/z* cald for $C_{13}H_{16}O_5$ $[M^+]$: 252.0998; found: 252.0974. $[\alpha]_D^{26}$ = 54.2 (c = 0.07 in $CHCl_3$), HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane /^{i}PrOH = 97/3, 1.0 mL/min, 254 nm, 35 °C) minor enantiomer t = 49.2 min, major enantiomer t = 35.6 min.



Methyl 2-hydroxy-2-methyl-4-oxopentanoate (4h)

92% yield, ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.70 (3H, S), 3.06 (1H, d, J = 17.7 Hz), 2.73 (1H, d, J = 17.7 Hz), 2.10 (3H, s), 1.32 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 207.8, 176.2, 72.6, 52.8, 52.3, 30.5, 26.2. HRMS (EI): *m/z* cald for $C_7H_{12}O_4$ [M^+]: 160.0736; found: 160.0739. $[\alpha]_D^{28}$ = 38.2 (c = 0.20 in $CHCl_3$), HPLC (DAICEL CHIRALPAK OD-H, *n*-hexane /^{i}PrOH = 90/10, 1.0 mL/min, 234 nm, 35 °C) minor enantiomer t = 10.5 min, major enantiomer t = 9.6 min.

5. Computational Details

All calculations were performed using Gaussian 03 and 09 program suite.[5] [6] Geometries were fully optimized at the B3LYP/6-31G(d',p') level. Frequency calculations were performed with structures characterized as transition states based on the observed number of imaginary frequencies, and thermodynamic corrections at 298 K and 1 atm were also calculated at the same level of theory. The electronic energies were then improved by the B3LYP/6-31G(d',p') single-point calculations, which took the solvent effects of acetone into account by using the CPCM solvation model. Gibbs energies in solution can be obtained from adding the gas-phase Gibbs energy corrections of the solute (the B3LYP/6-31G(d',p') to the single-point energies (the B3LYP/6-31G(d',p'). we confirmed that all transition states were connected by the minimum energy path to the corresponding prereaction complexes and products.

6. Reference

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5. Gaussian 03, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.
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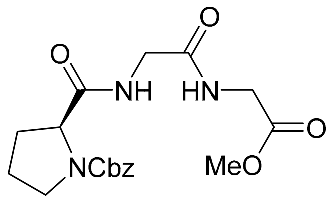
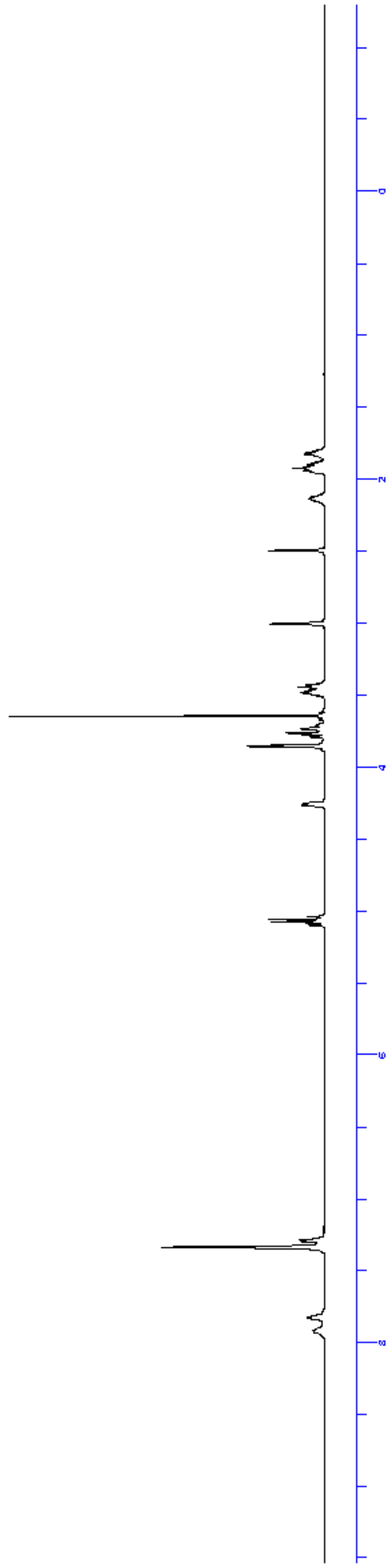
E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

7. Copy of NMR spectra

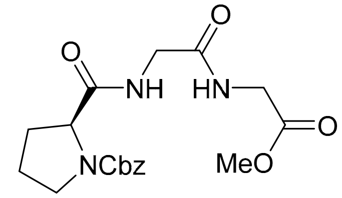
^{1}H NMR (600 MHZ, DMSO-d_6, VT 100 °C)



Cbz-Pro-Gly-Gly-OMe



^{13}C NMR (150 MHz, DMSO-d₆, VT 100 °C)



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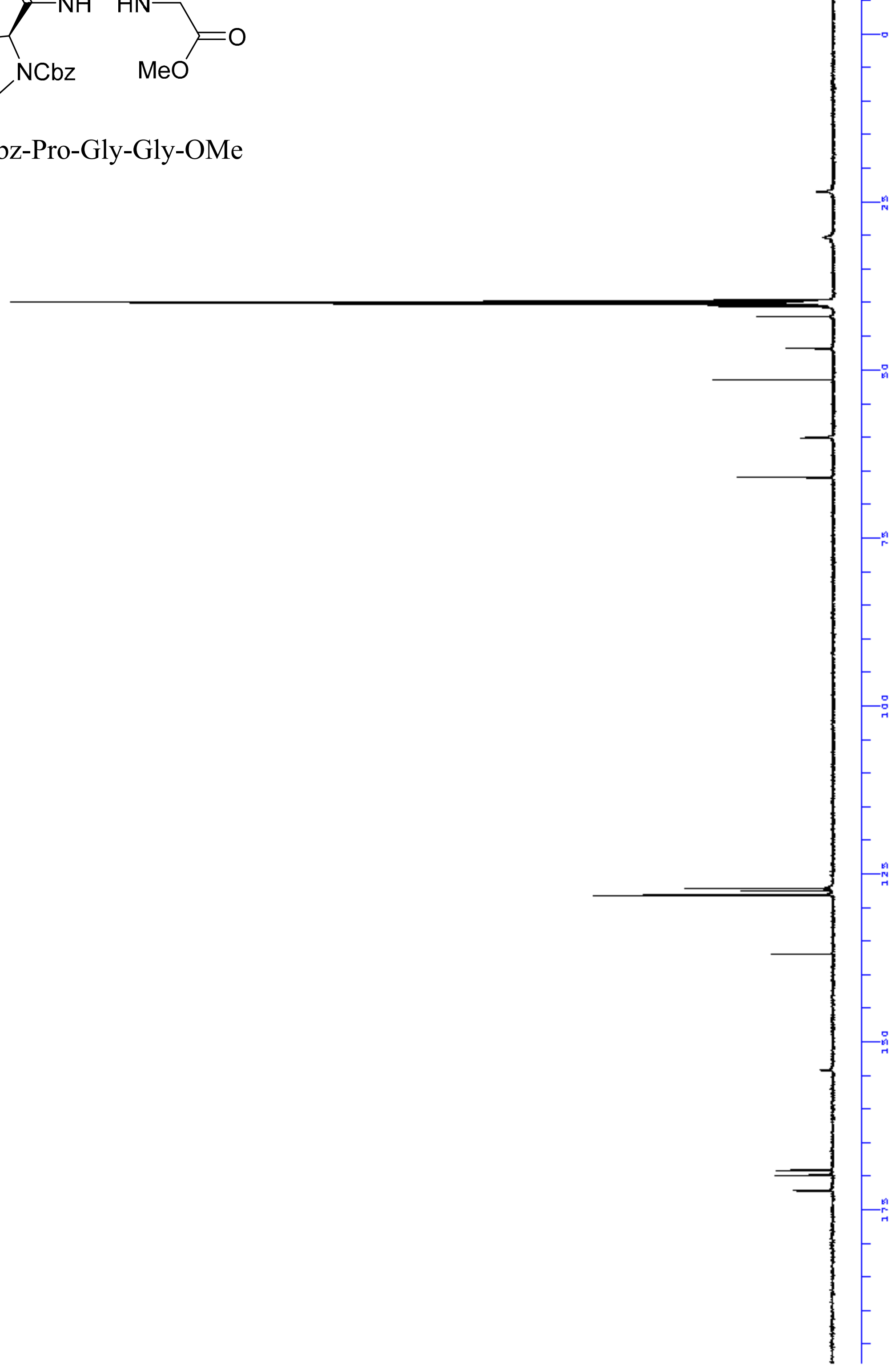
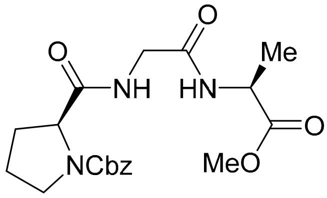


^{1}H NMR (600 MHZ, DMSO-d_6, VT 100 °C)



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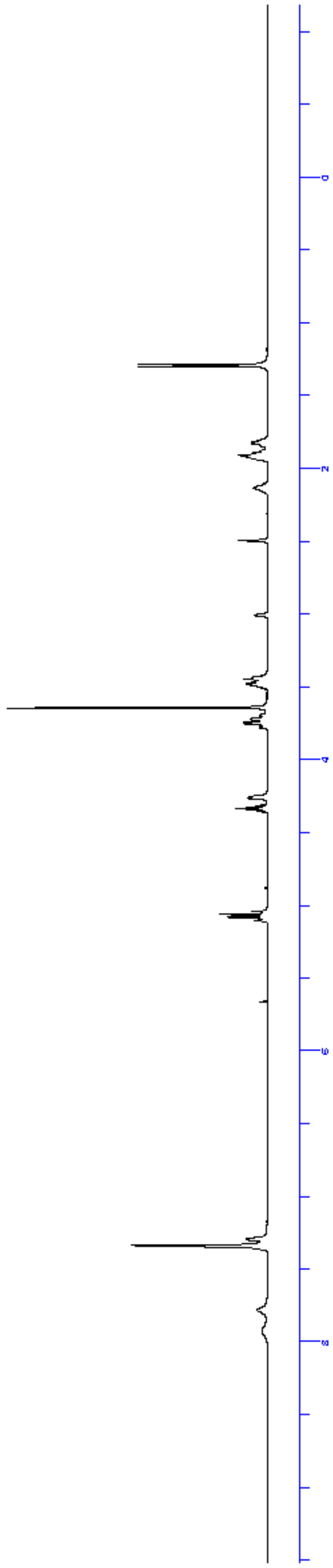
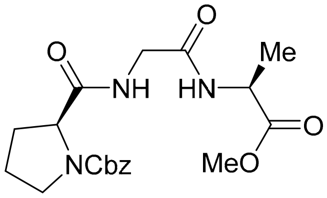


^{13}C NMR (150 MHZ, DMSO-d$_6$, VT 100 °C)



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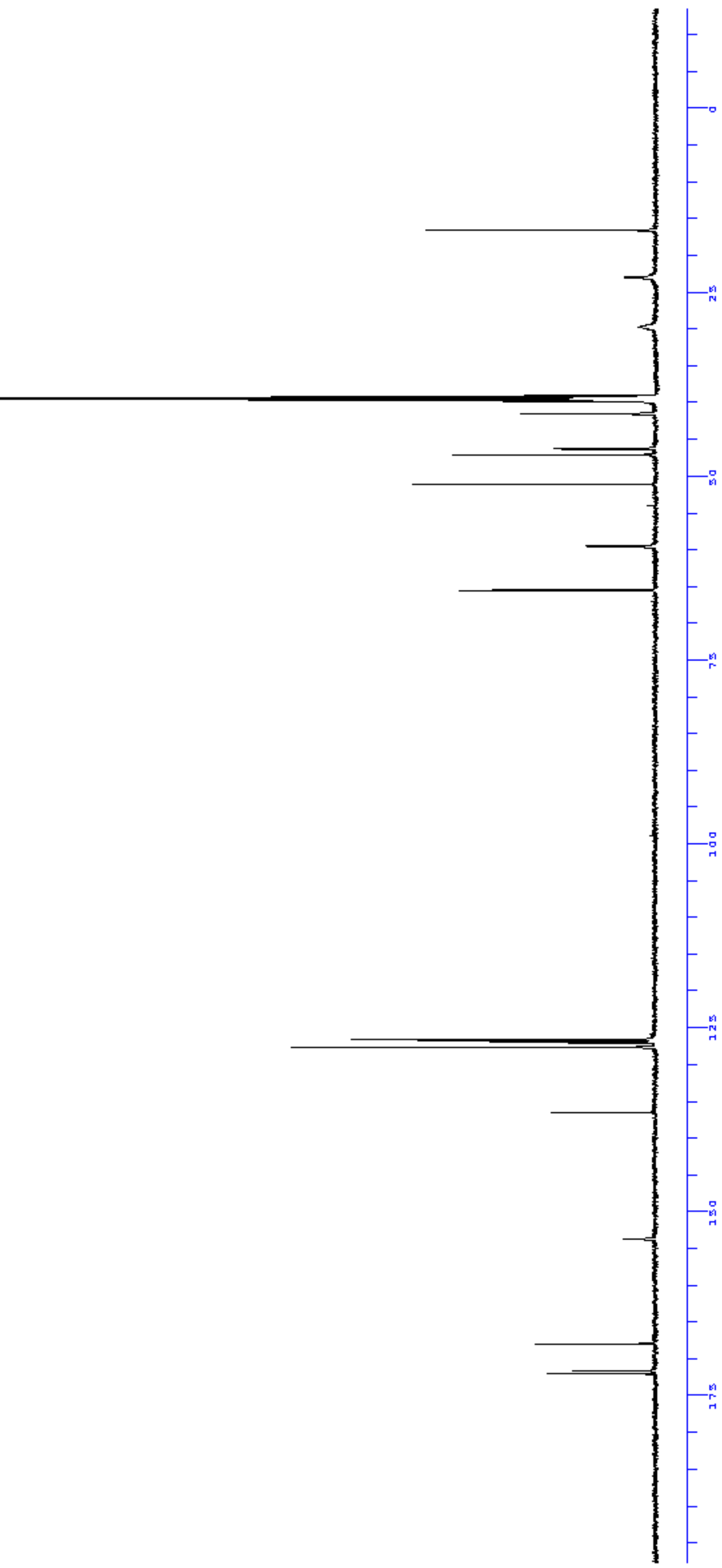

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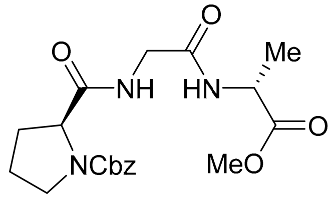
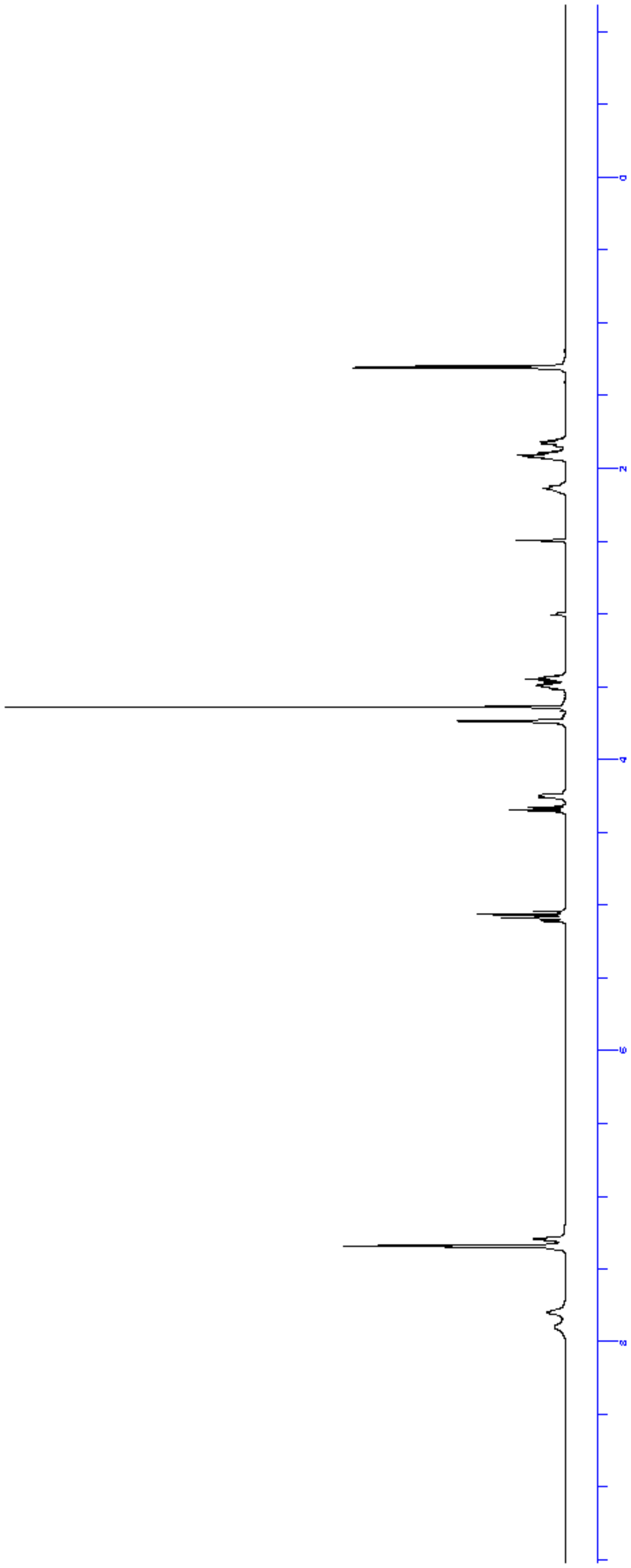
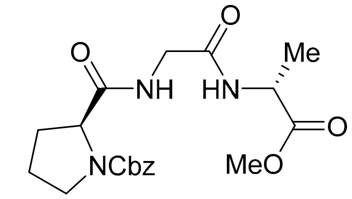


Cbz-Pro-Gly-D-Ala-OMe



^{13}C NMR (150 MHZ, DMSO-d$_6$, VT 100 °C)



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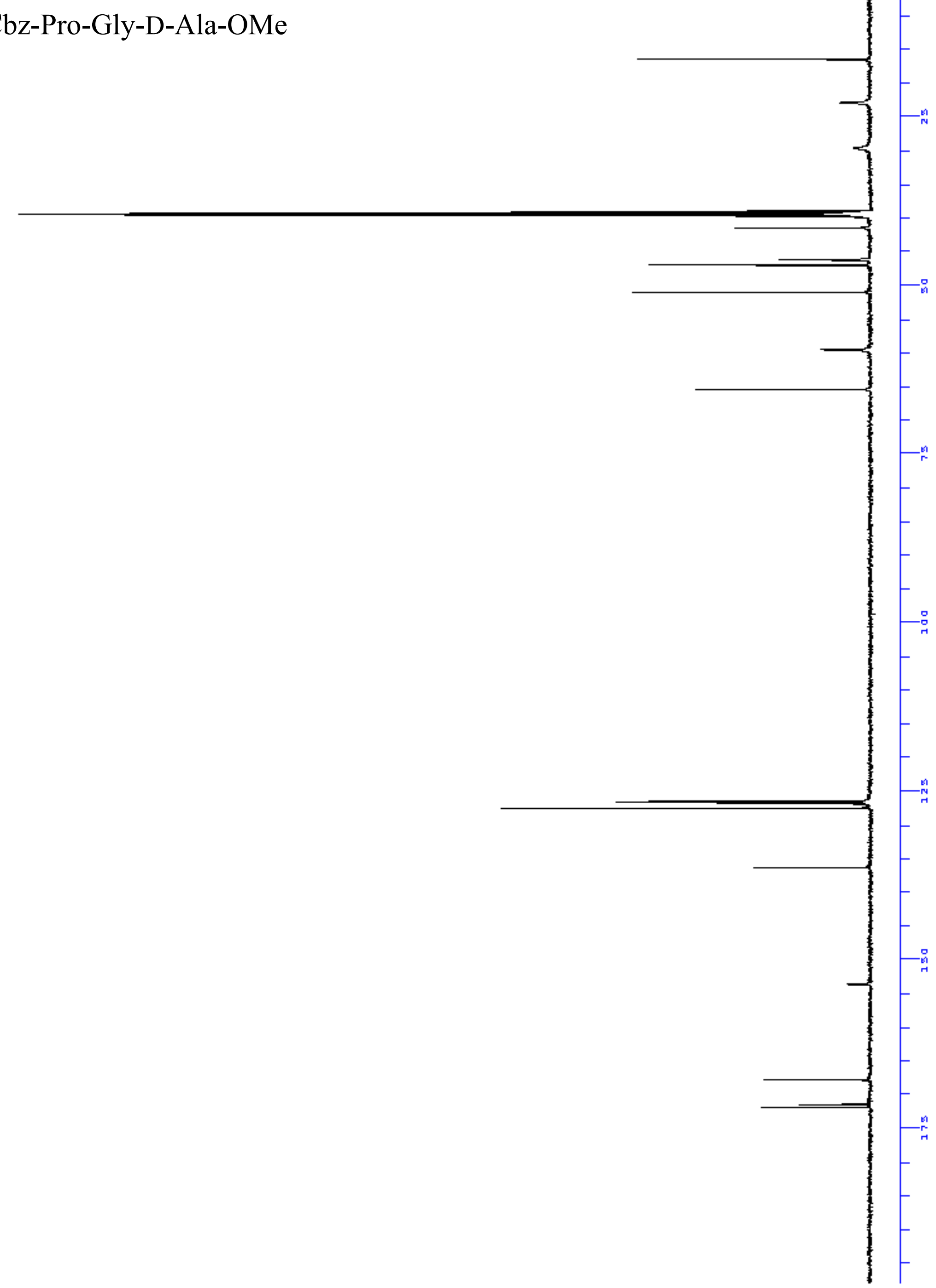

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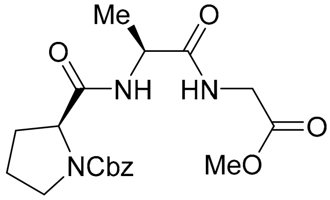

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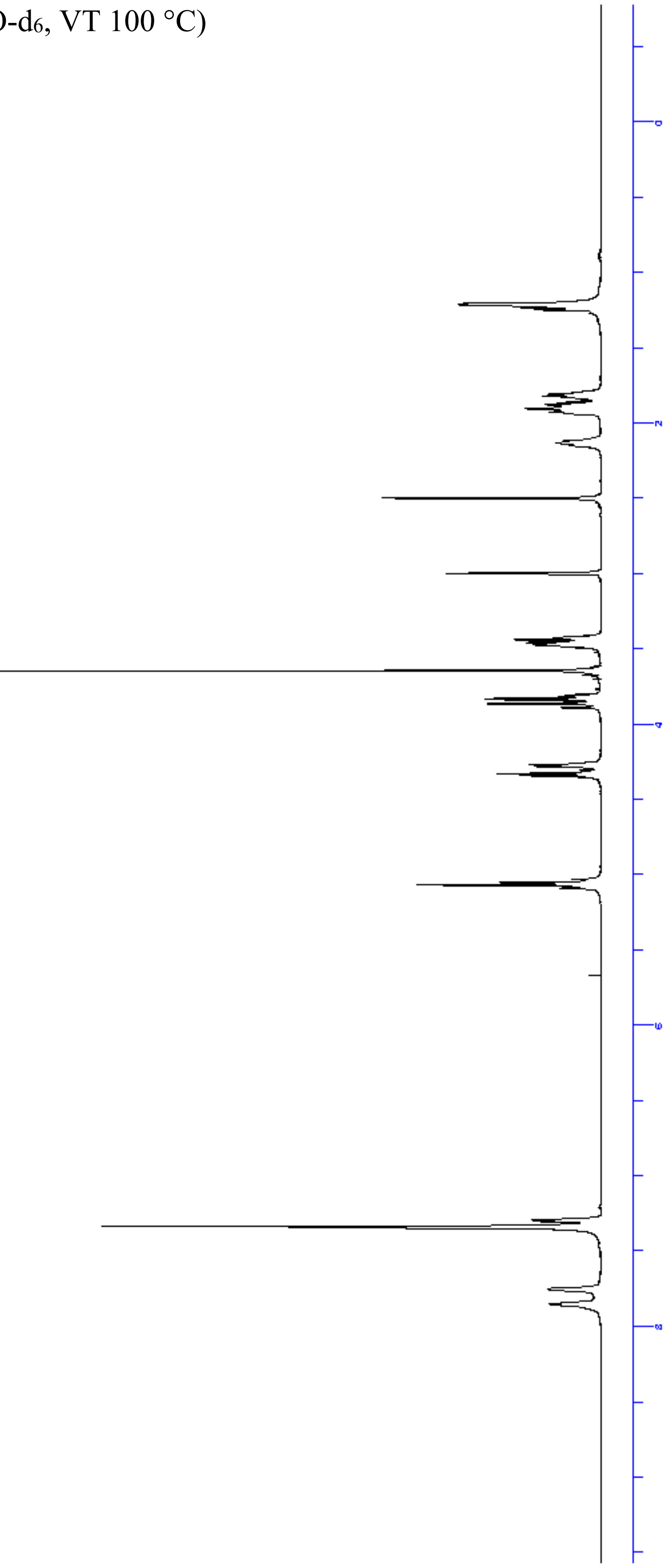

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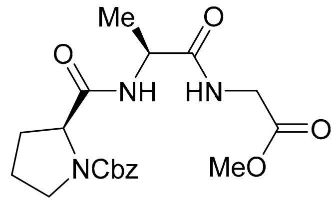

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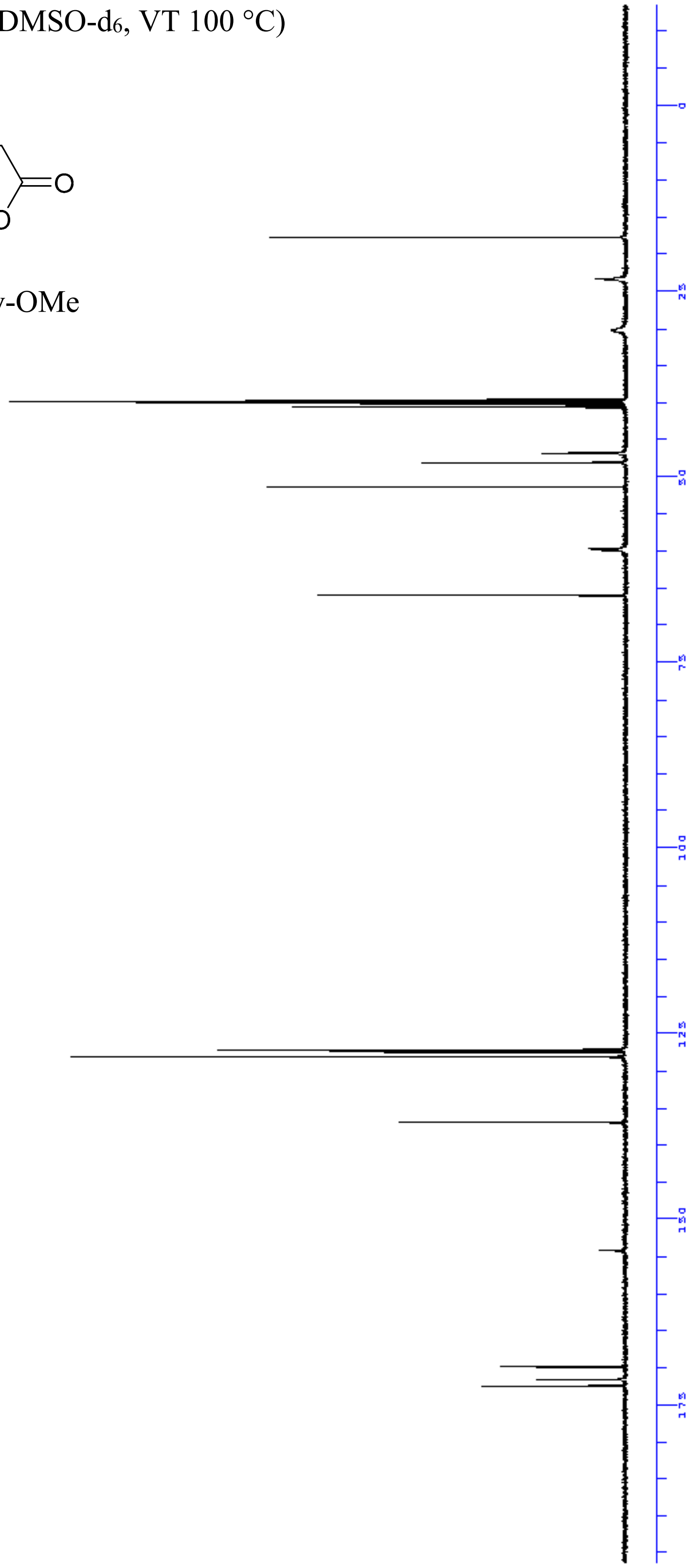

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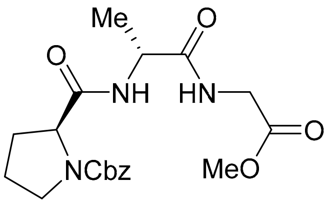

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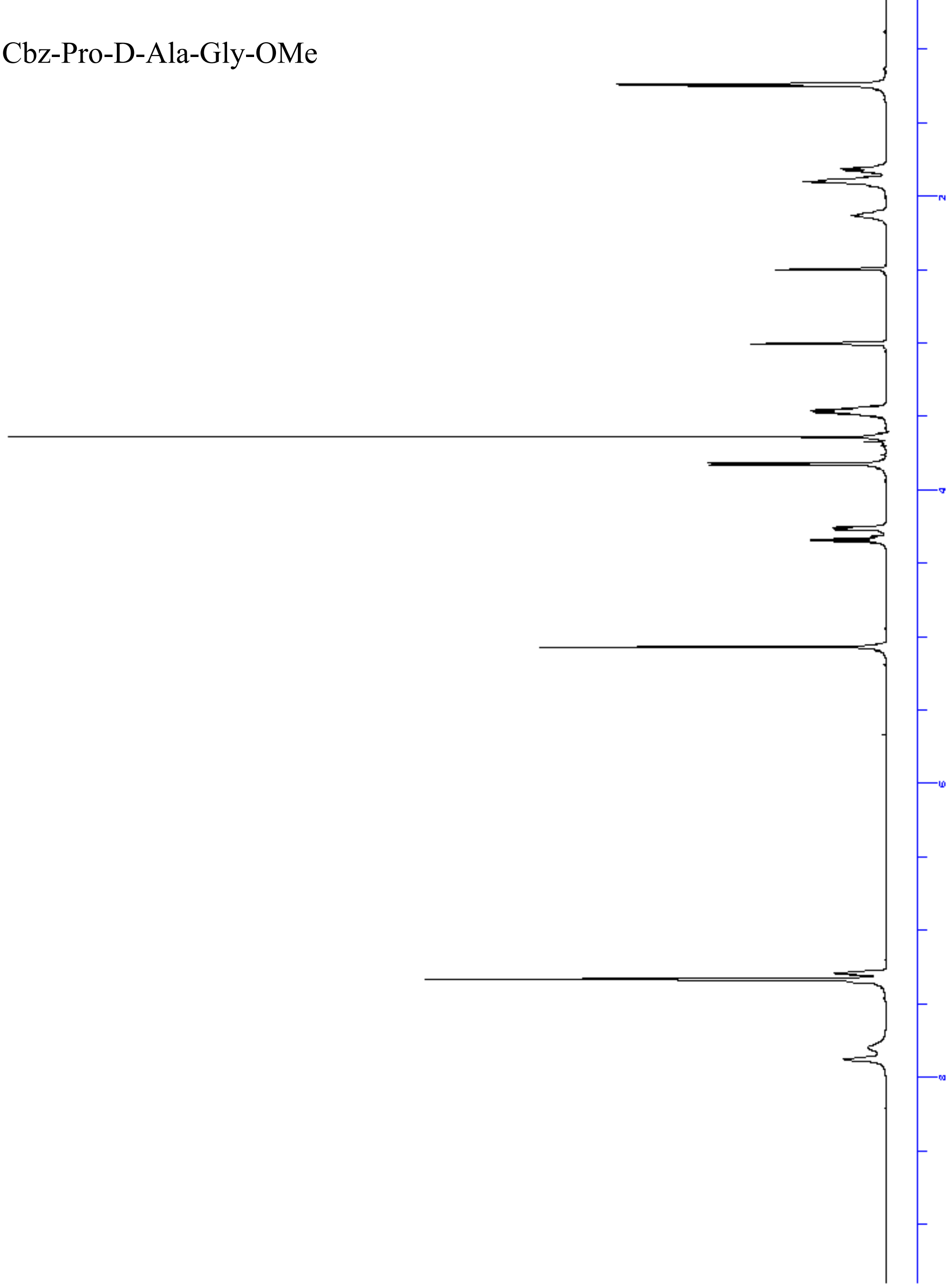

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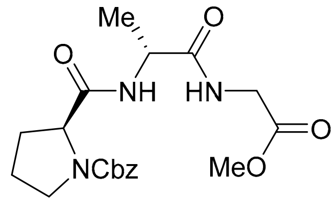

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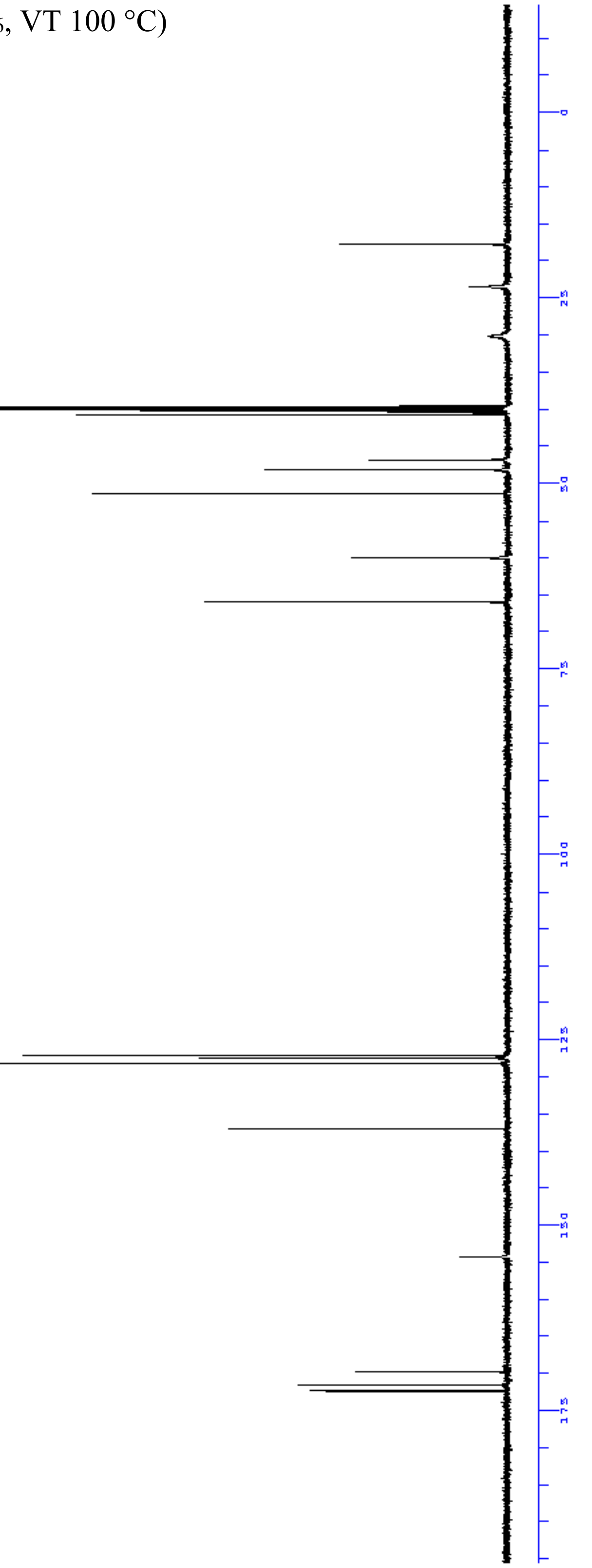

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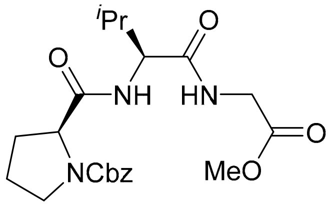

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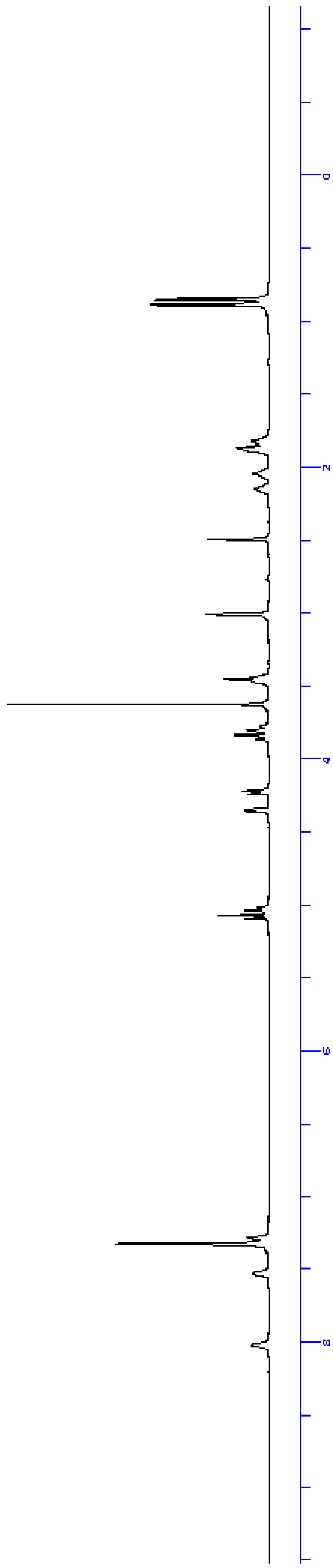

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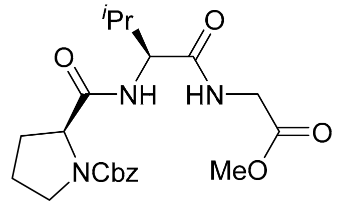

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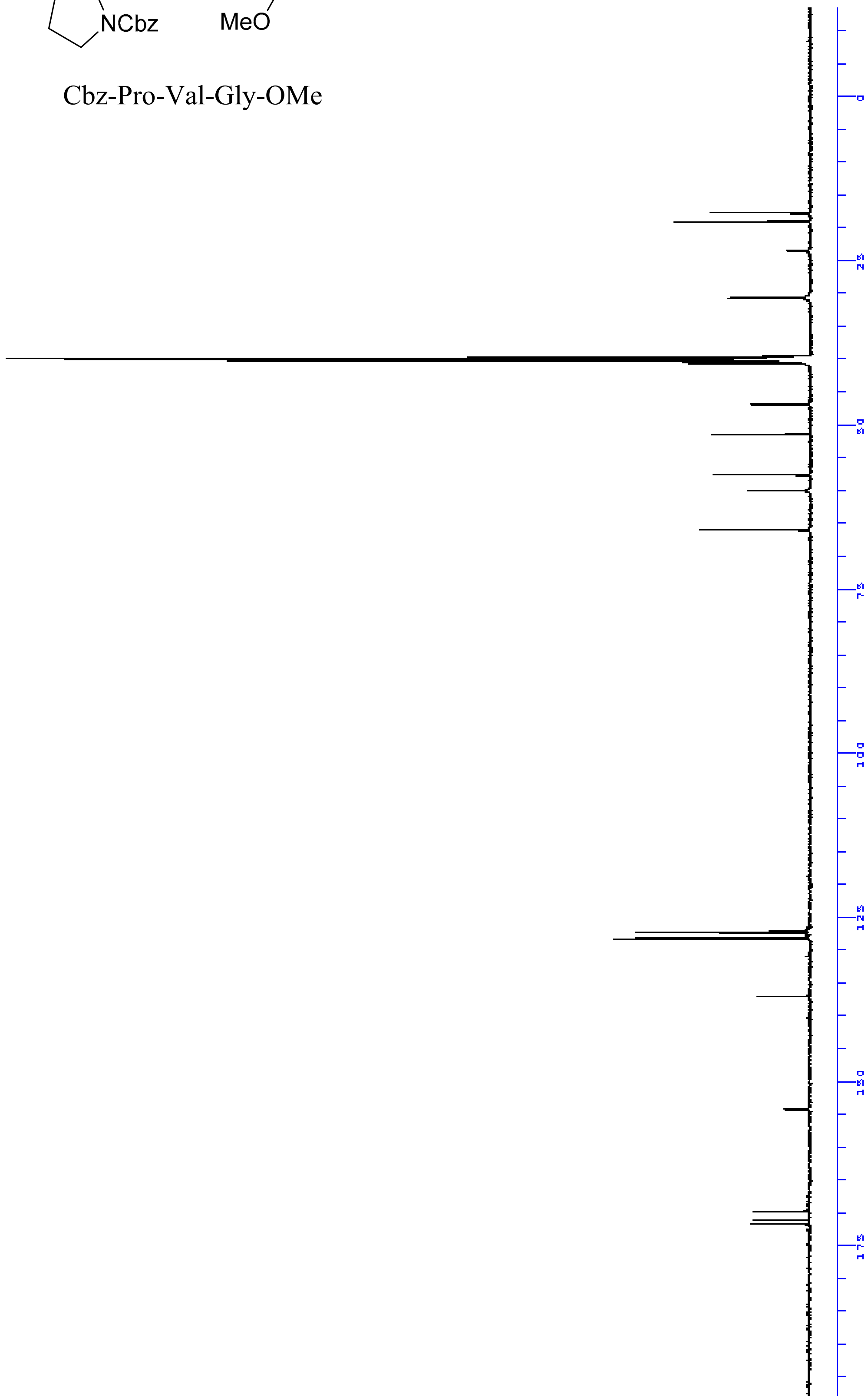

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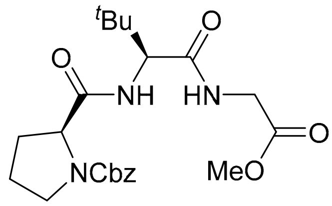

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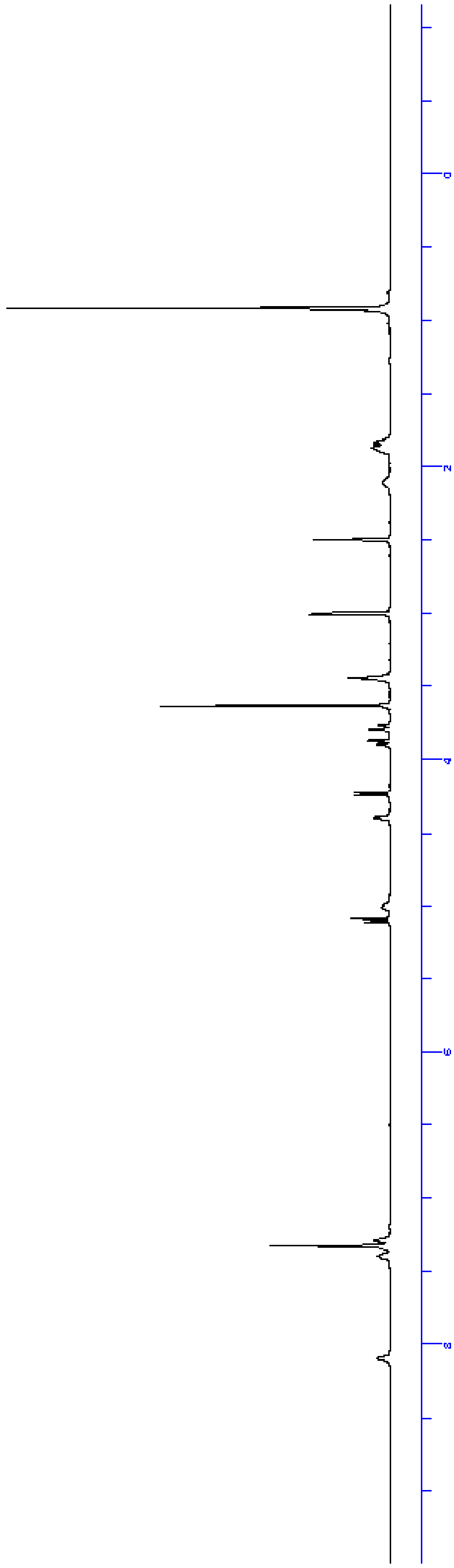

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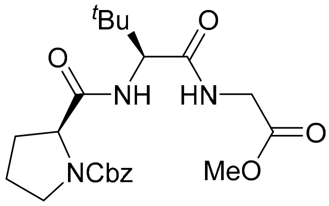

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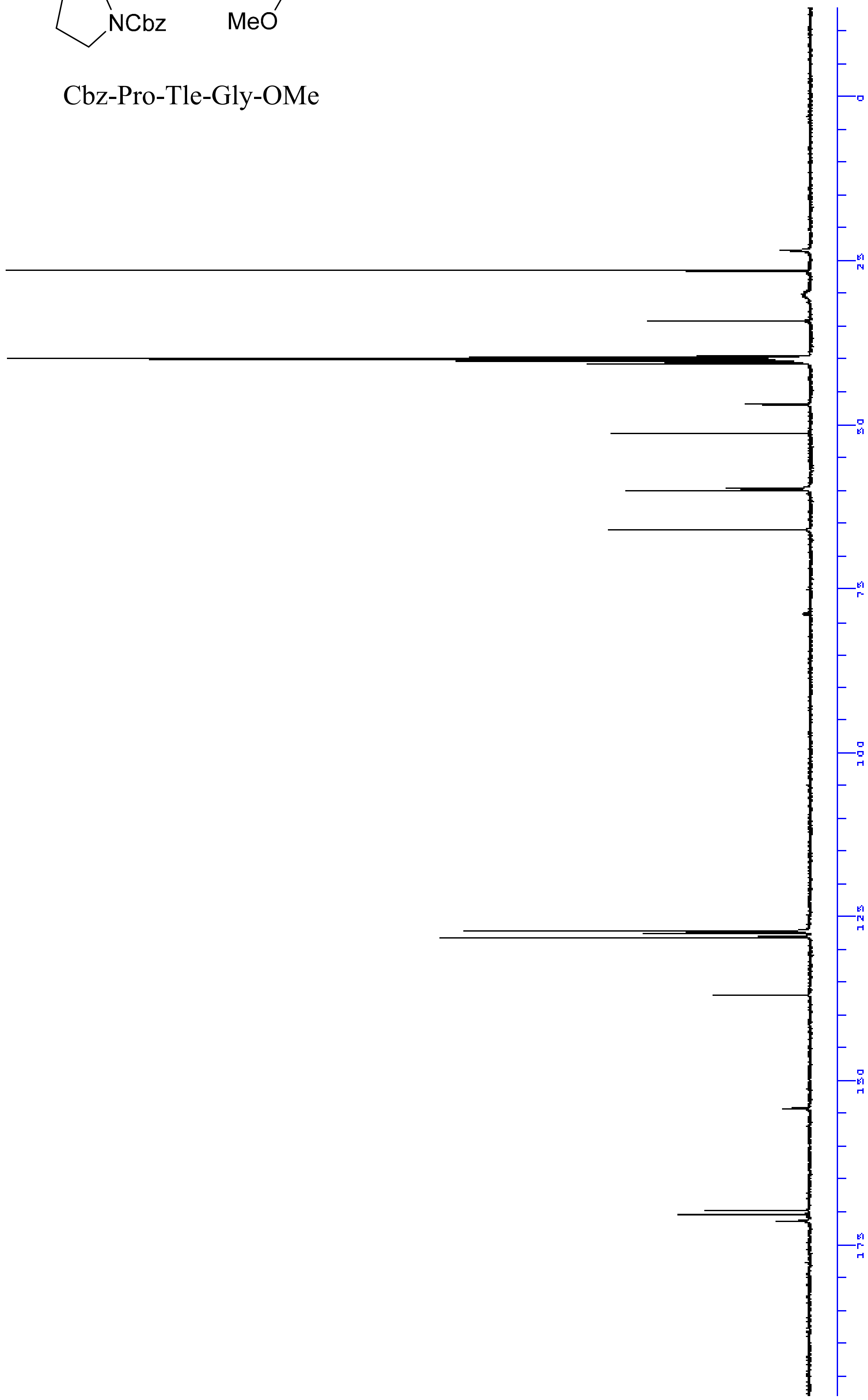

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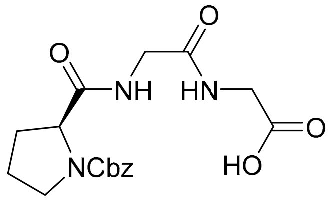

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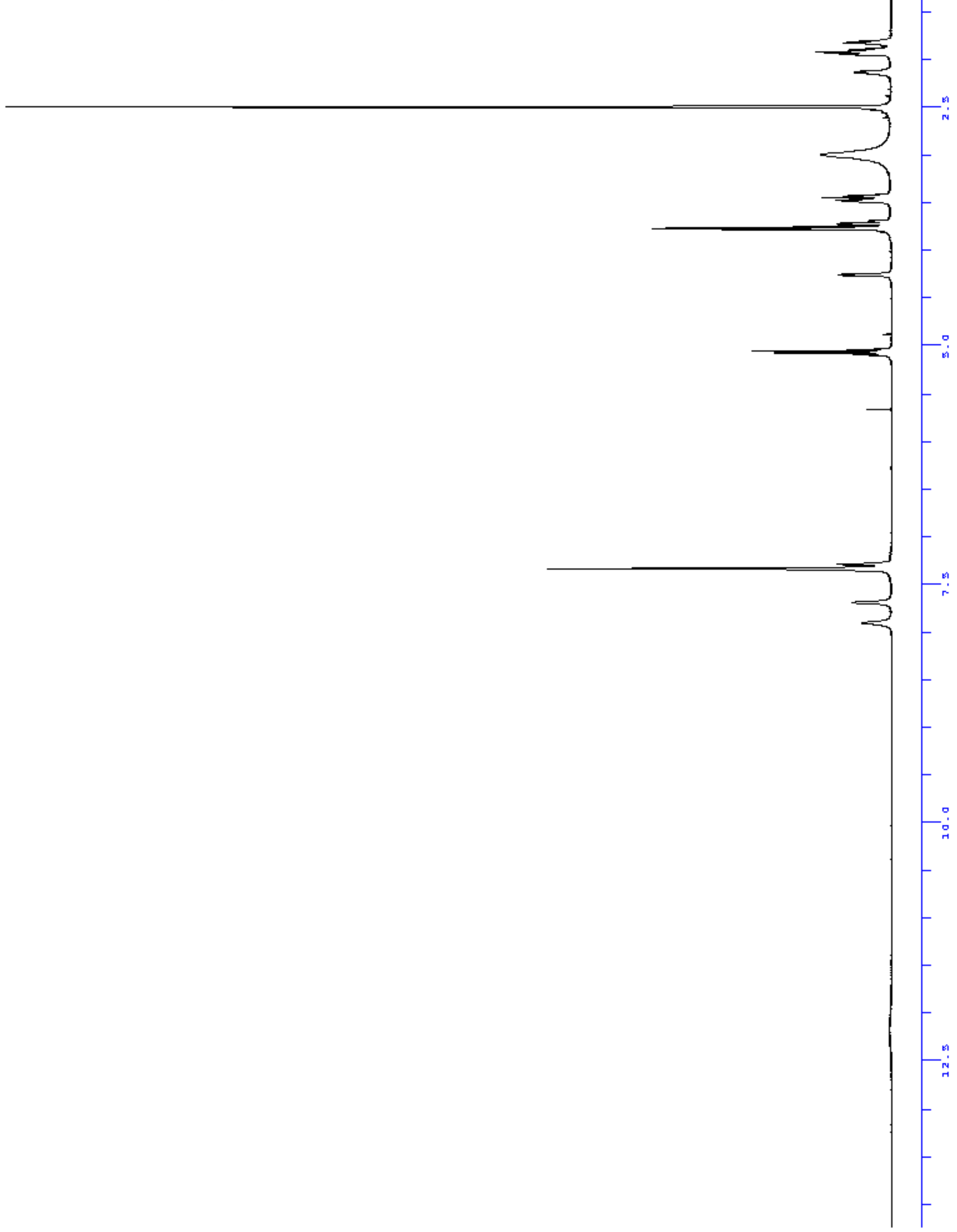
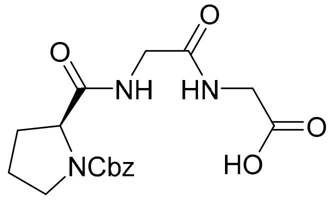


^{13}C NMR (150 MHZ, DMSO-d_6, VT 100 °C)



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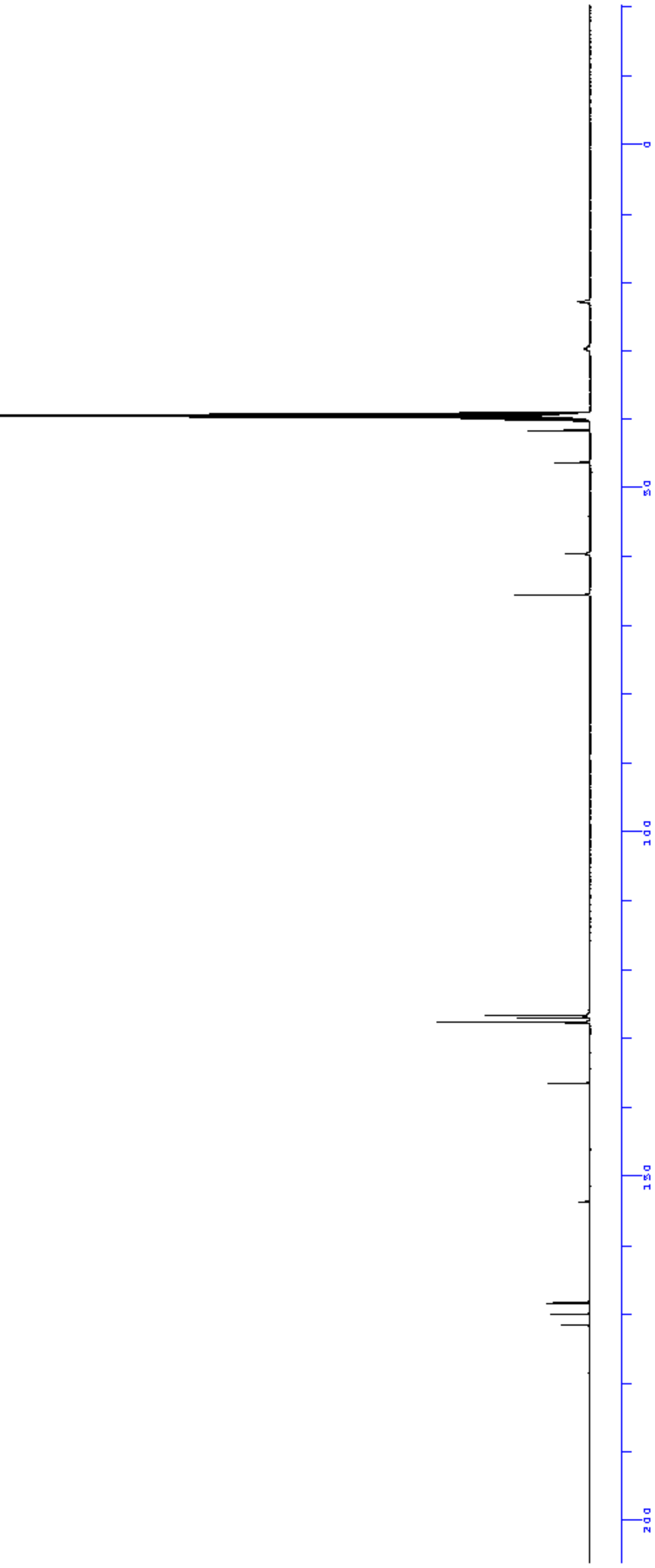

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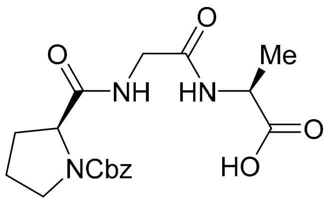

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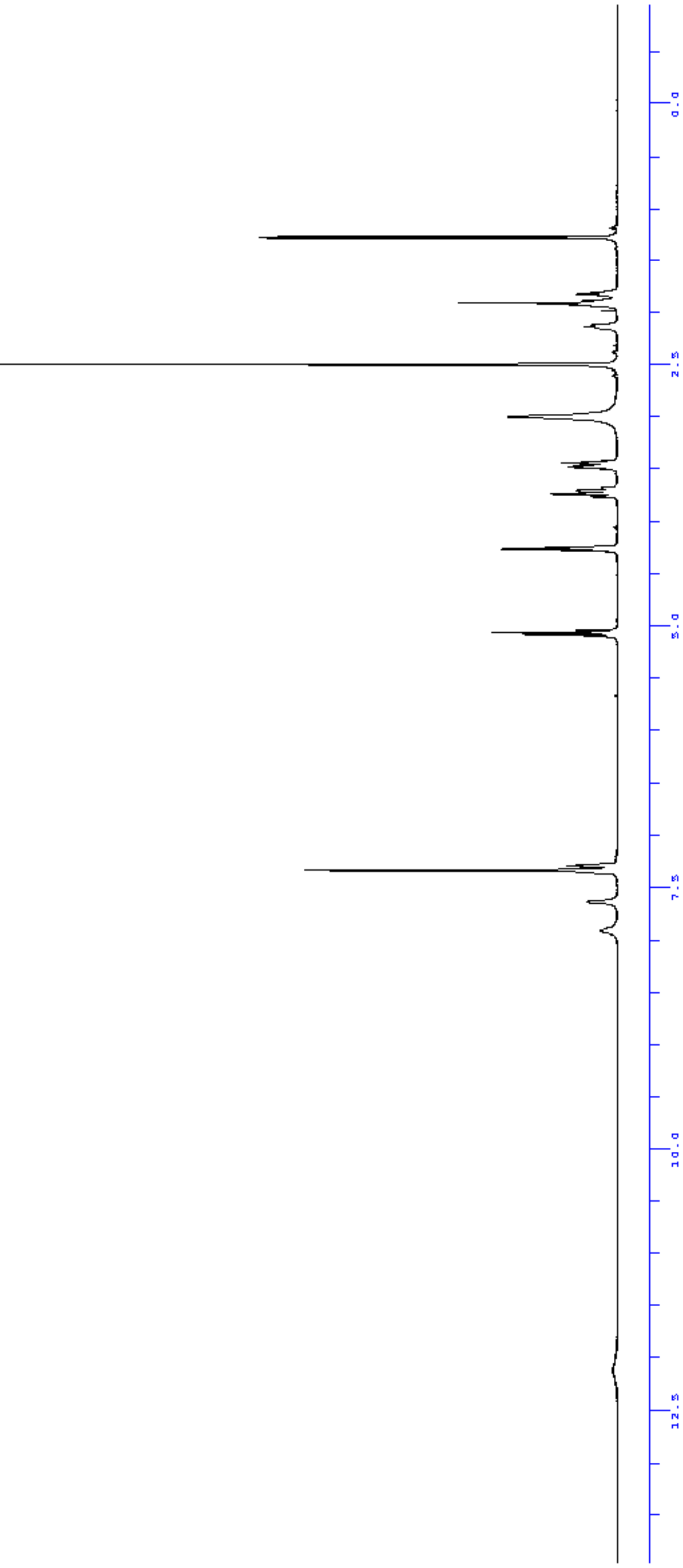
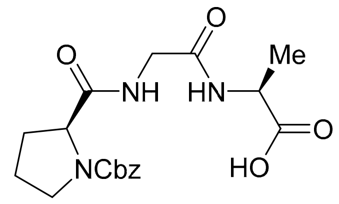


^{13}C NMR (150 MHZ, DMSO-d$_6$, VT 100 °C)



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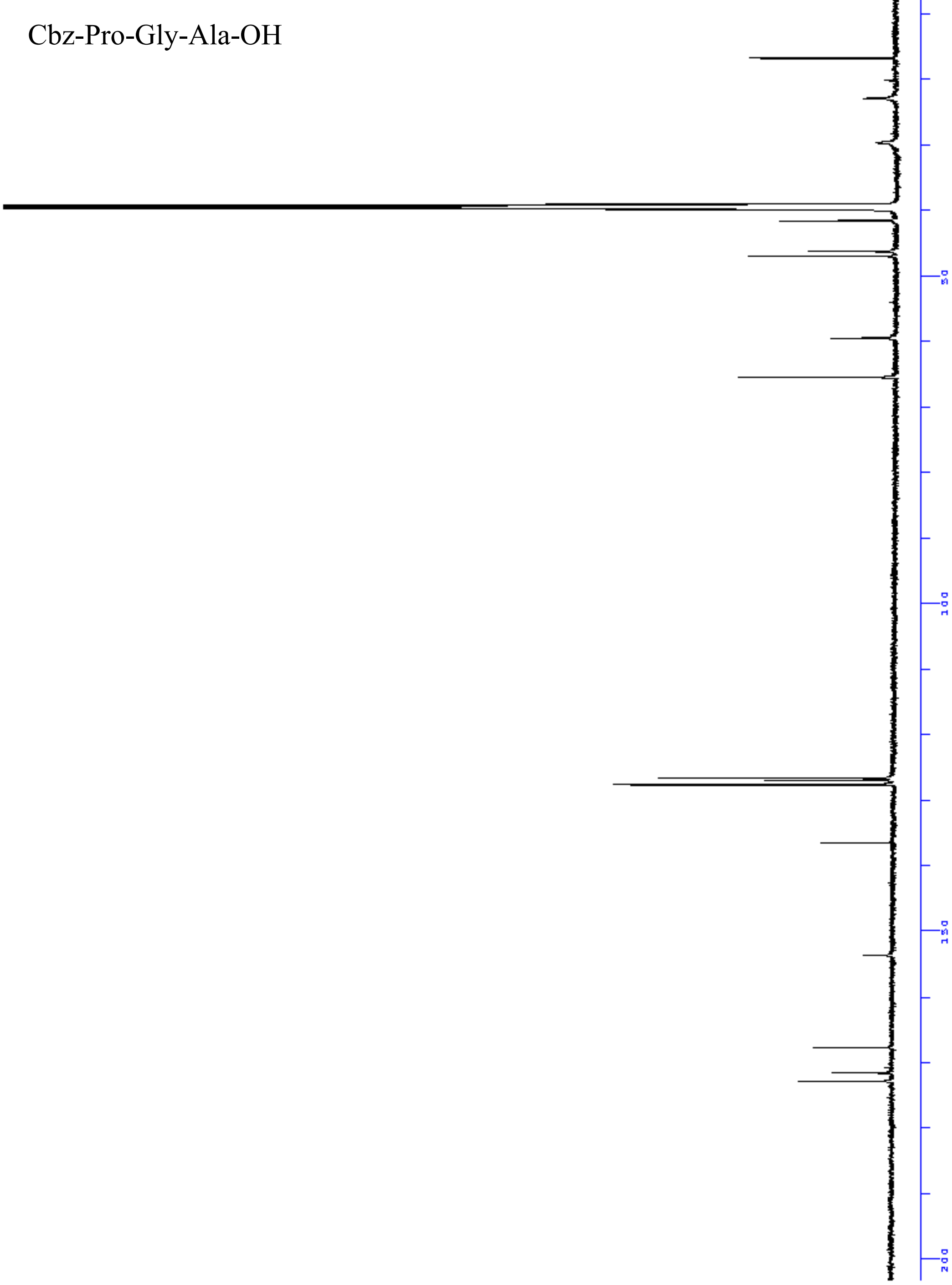

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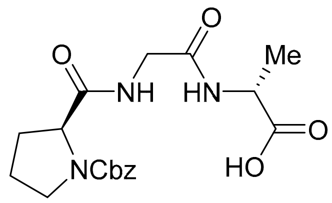
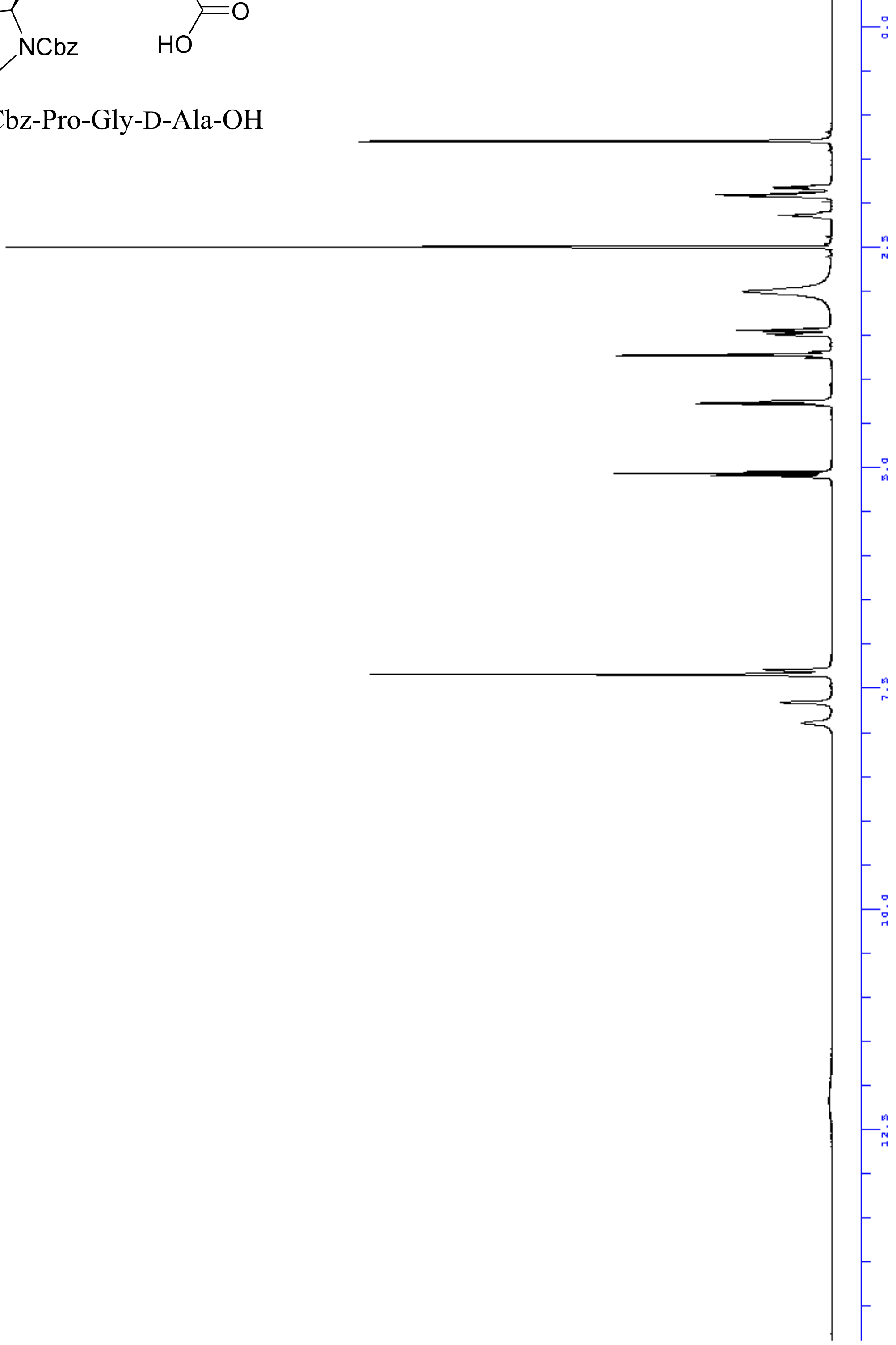


Cbz-Pro-Gly-D-Ala-OH



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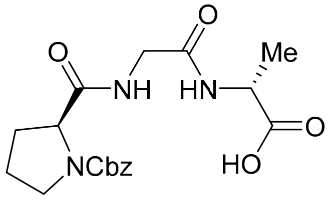

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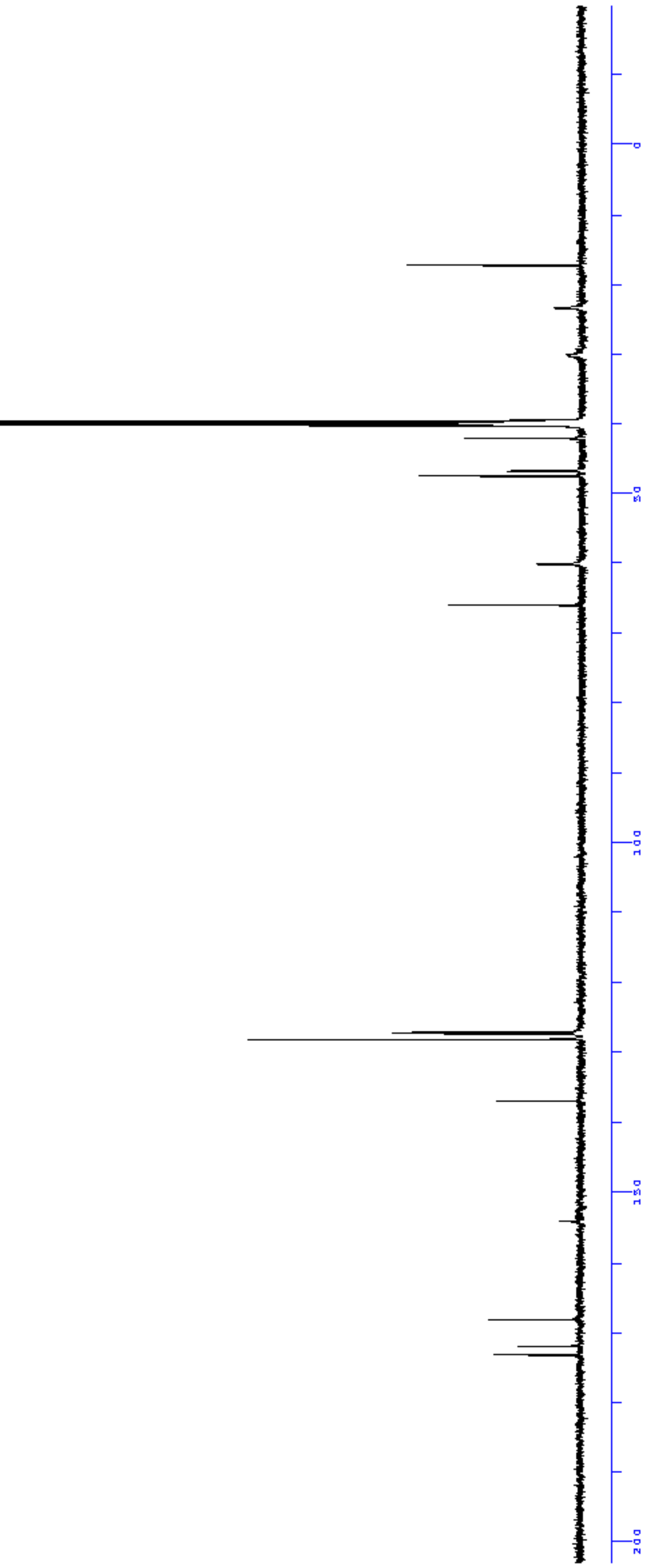

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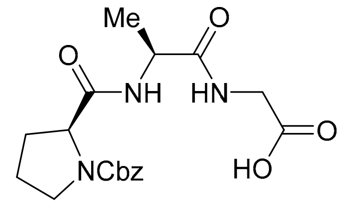

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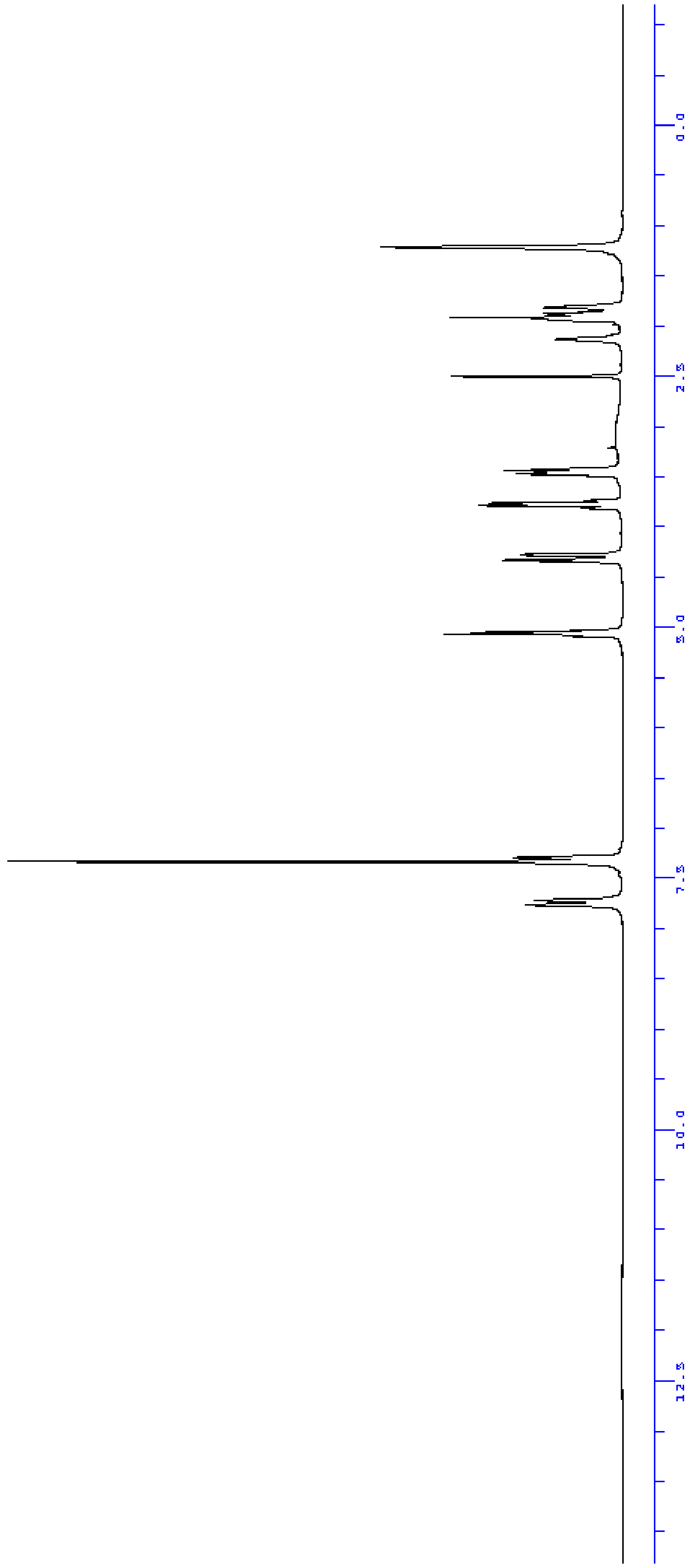

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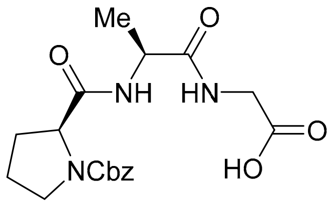

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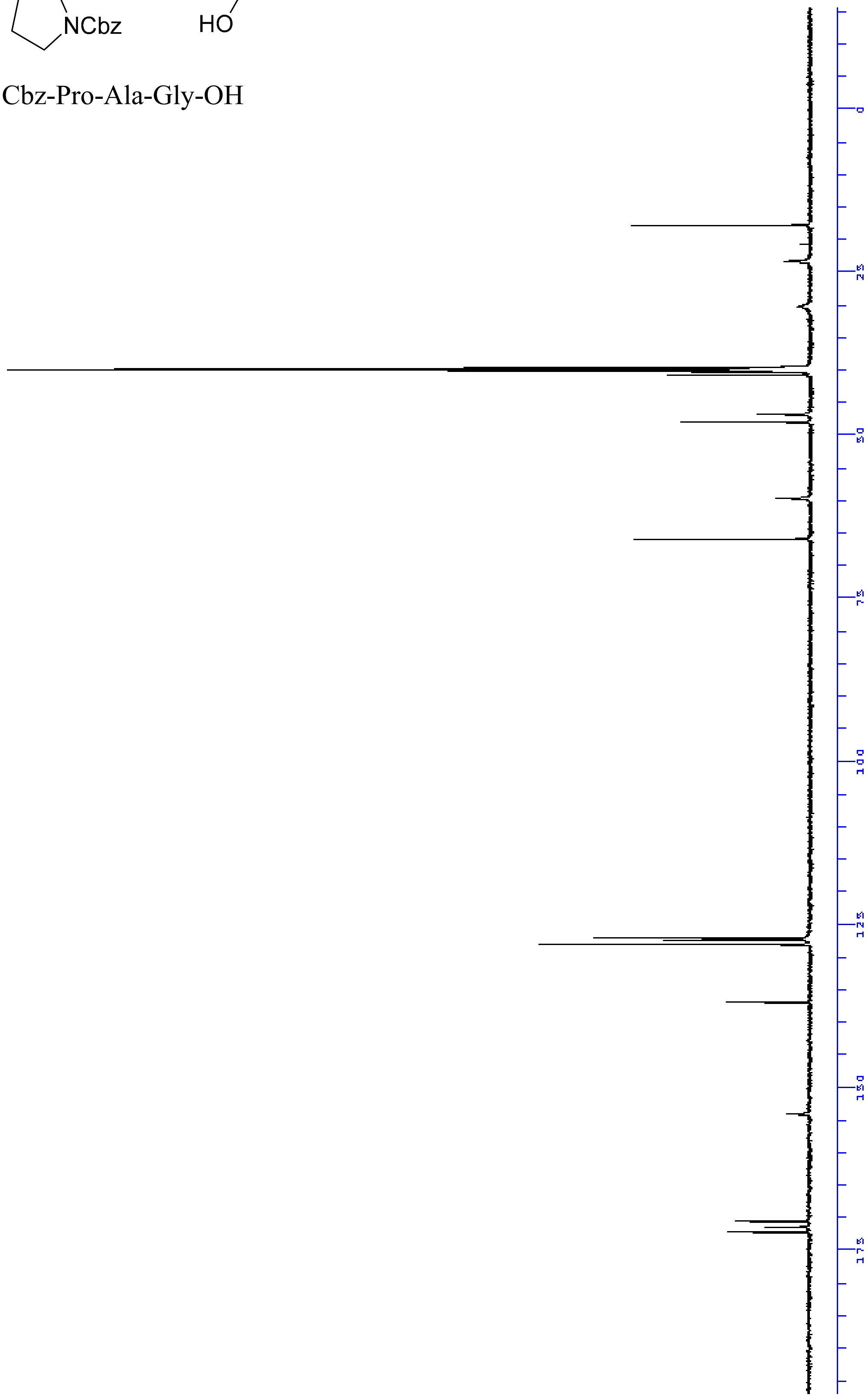

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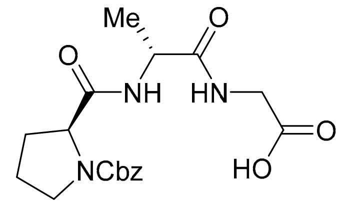

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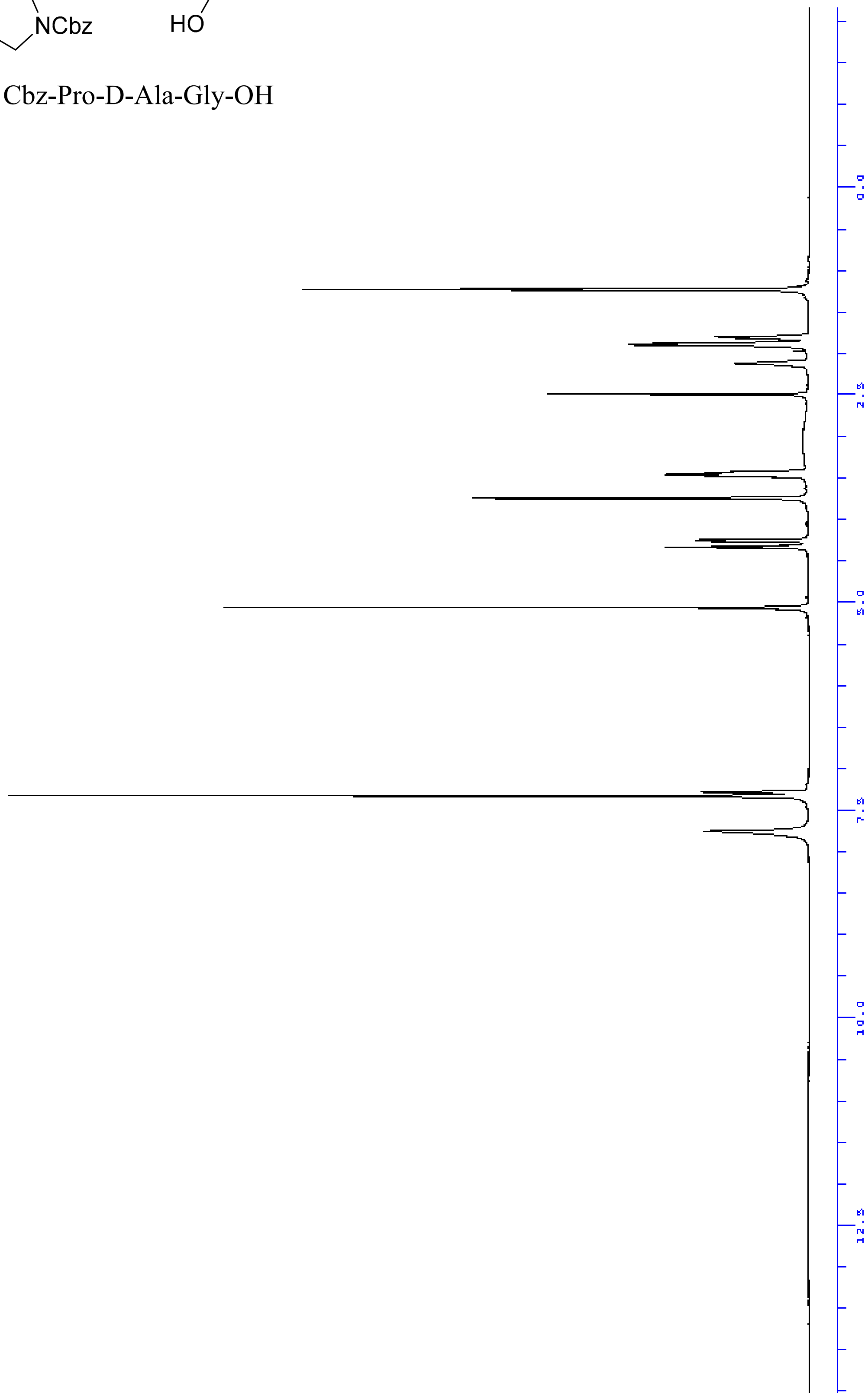

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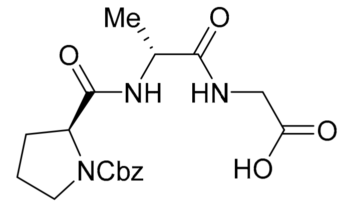

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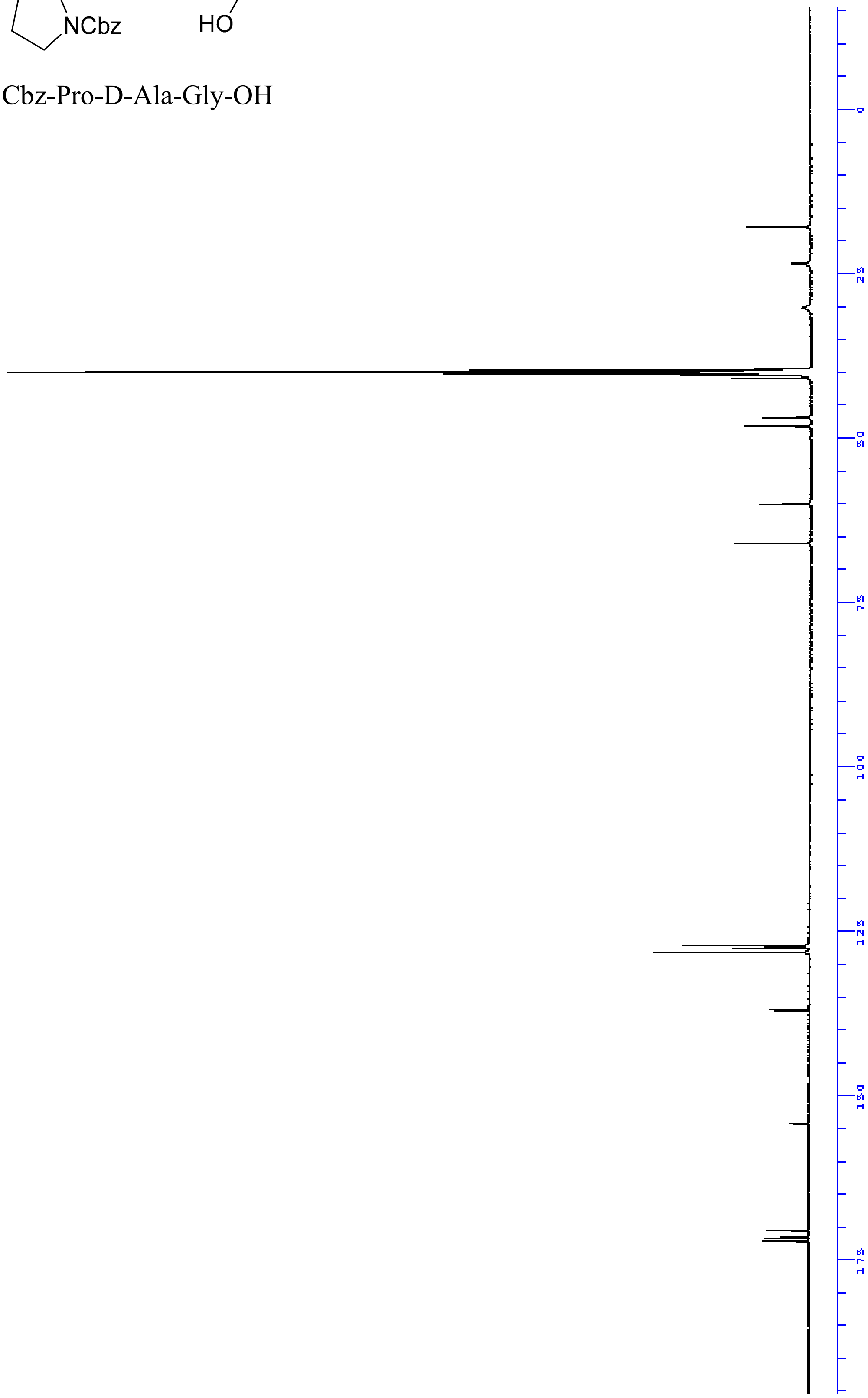

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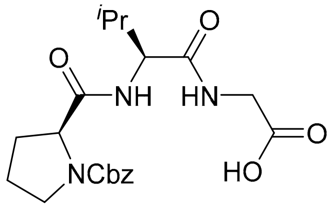

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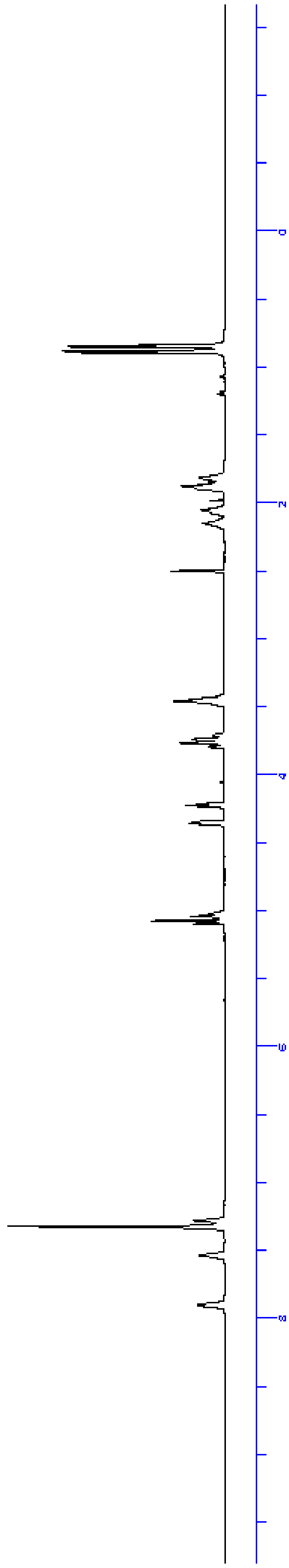

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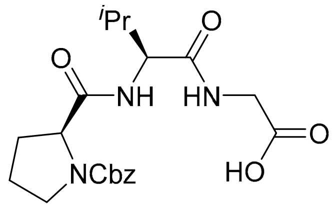

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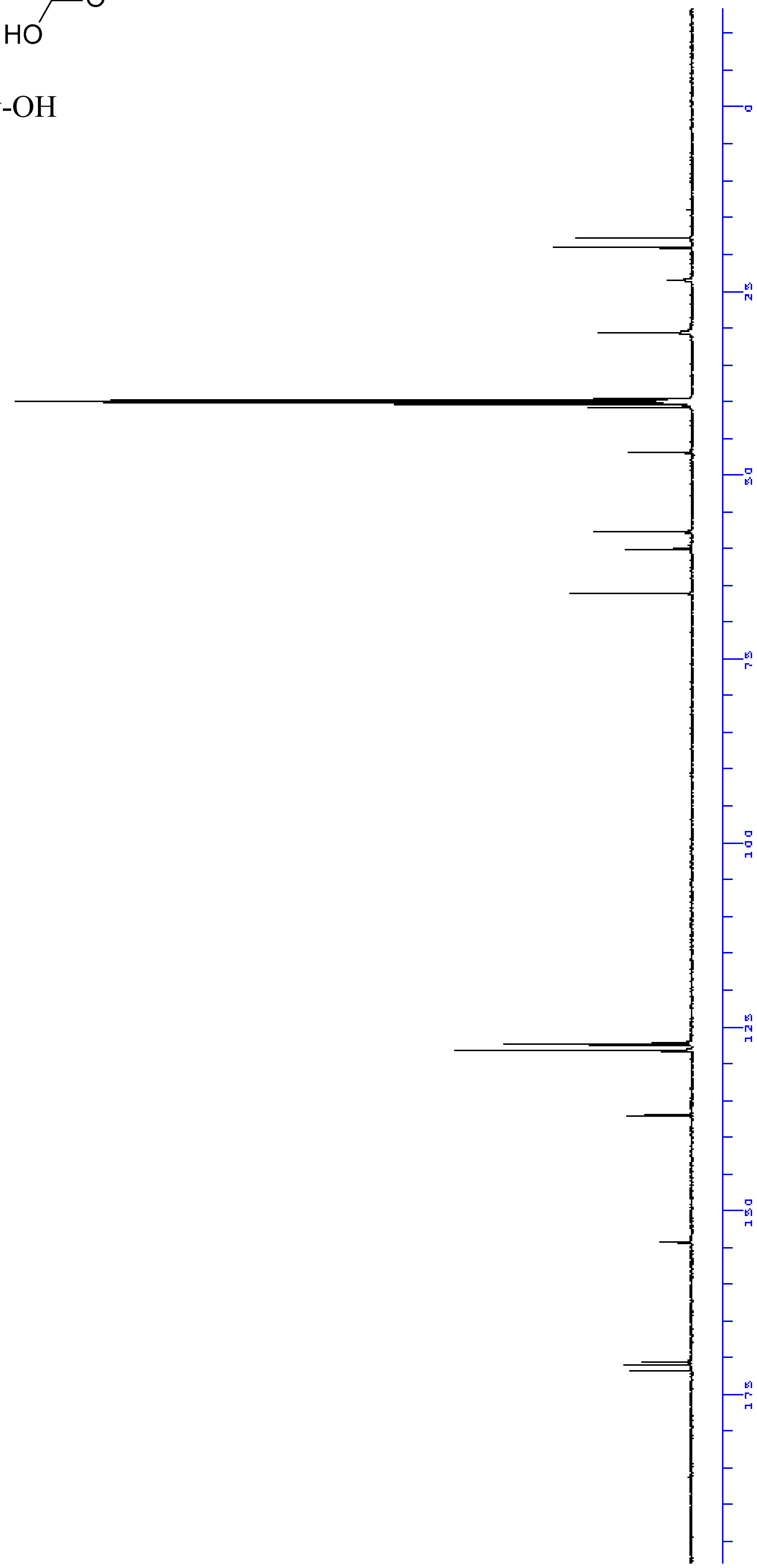

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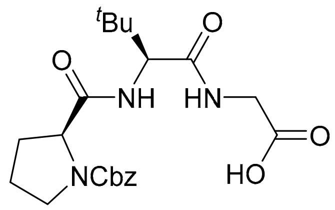

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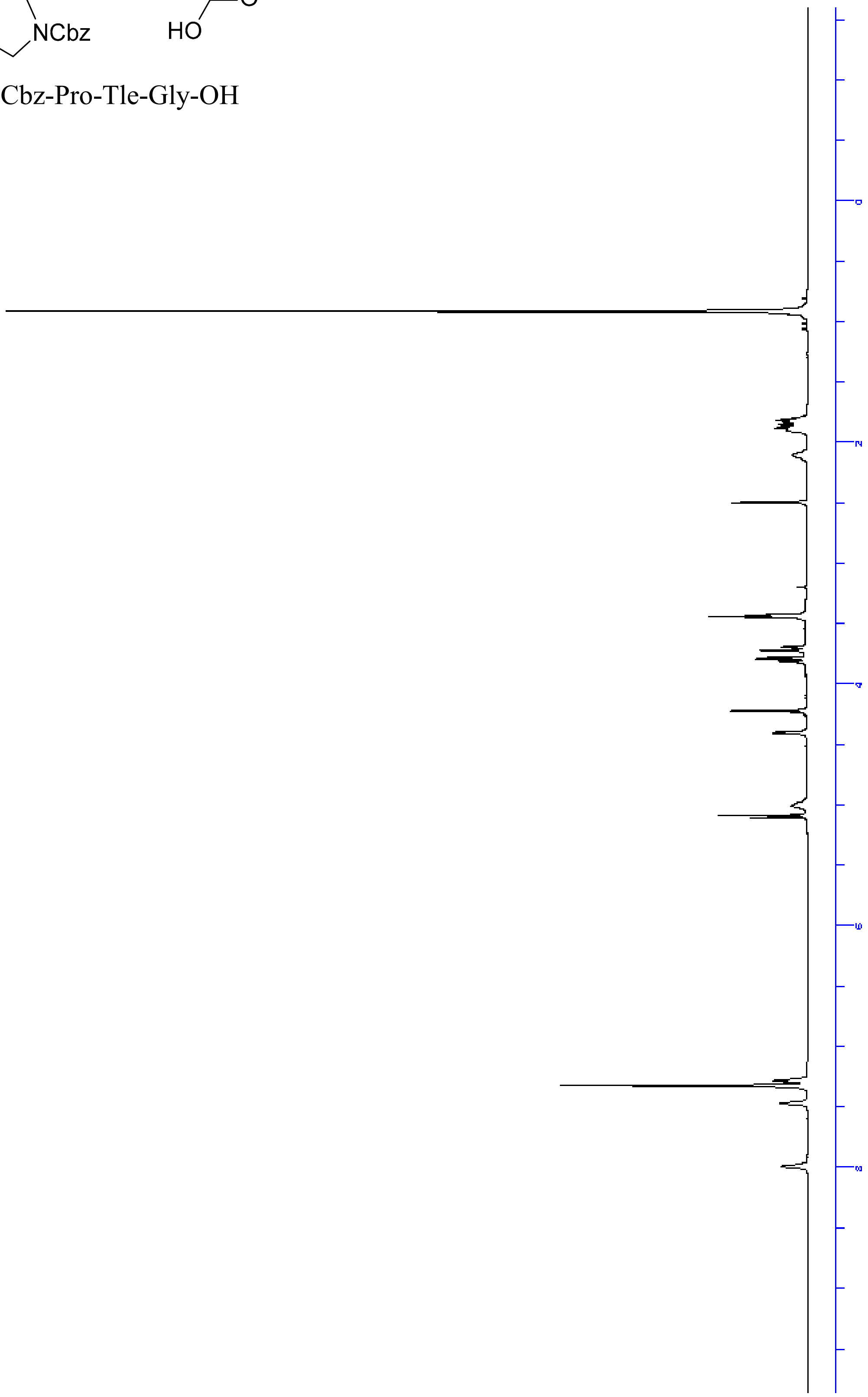

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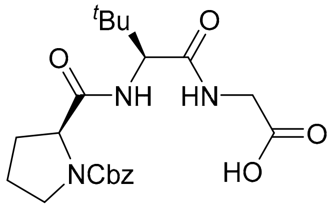

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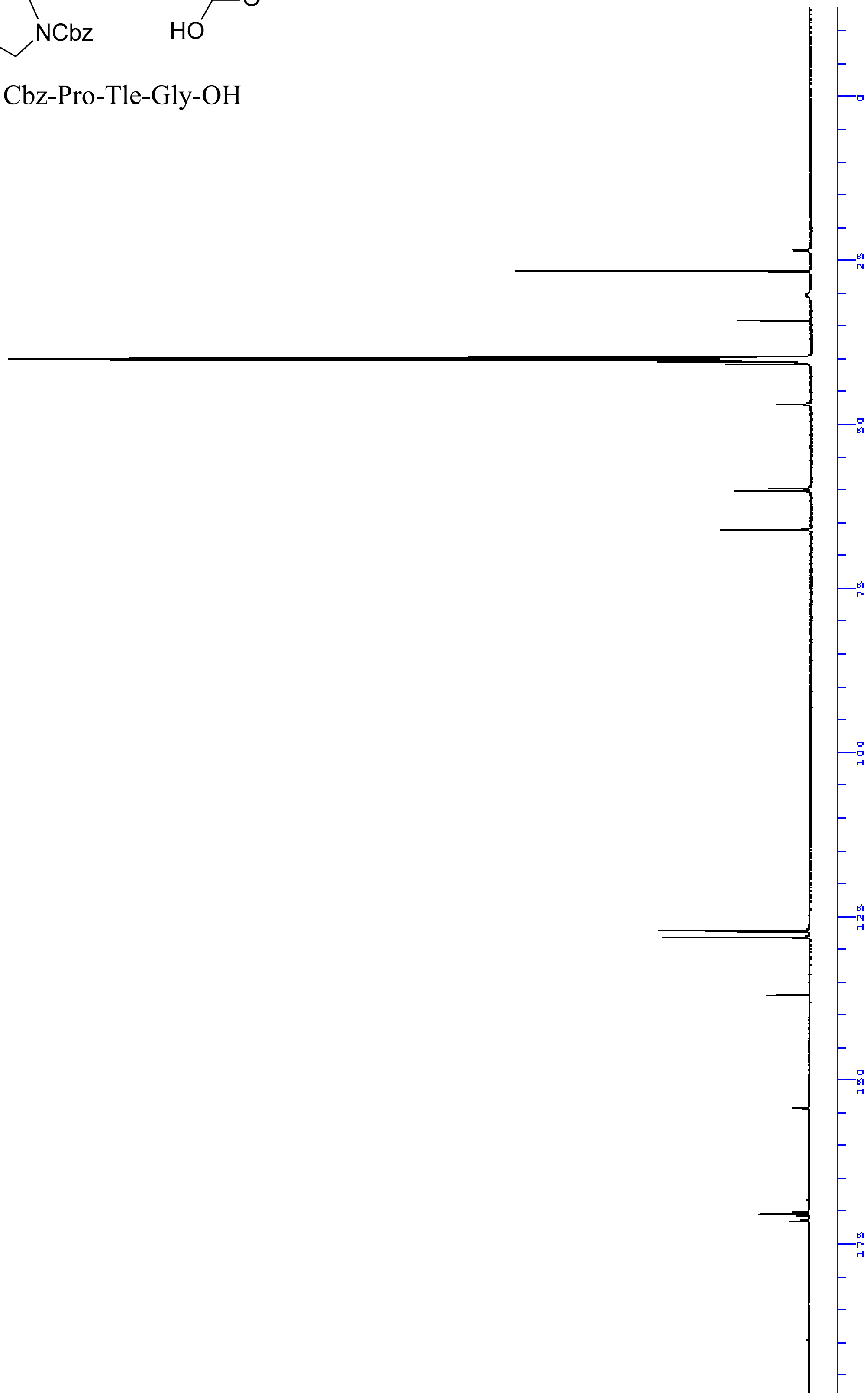
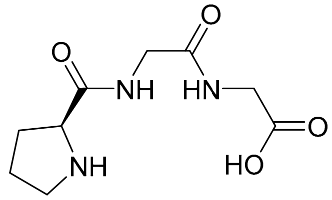
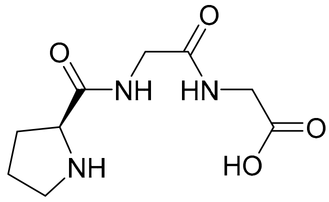


^{1}H NMR (600 MHz, D_2O)

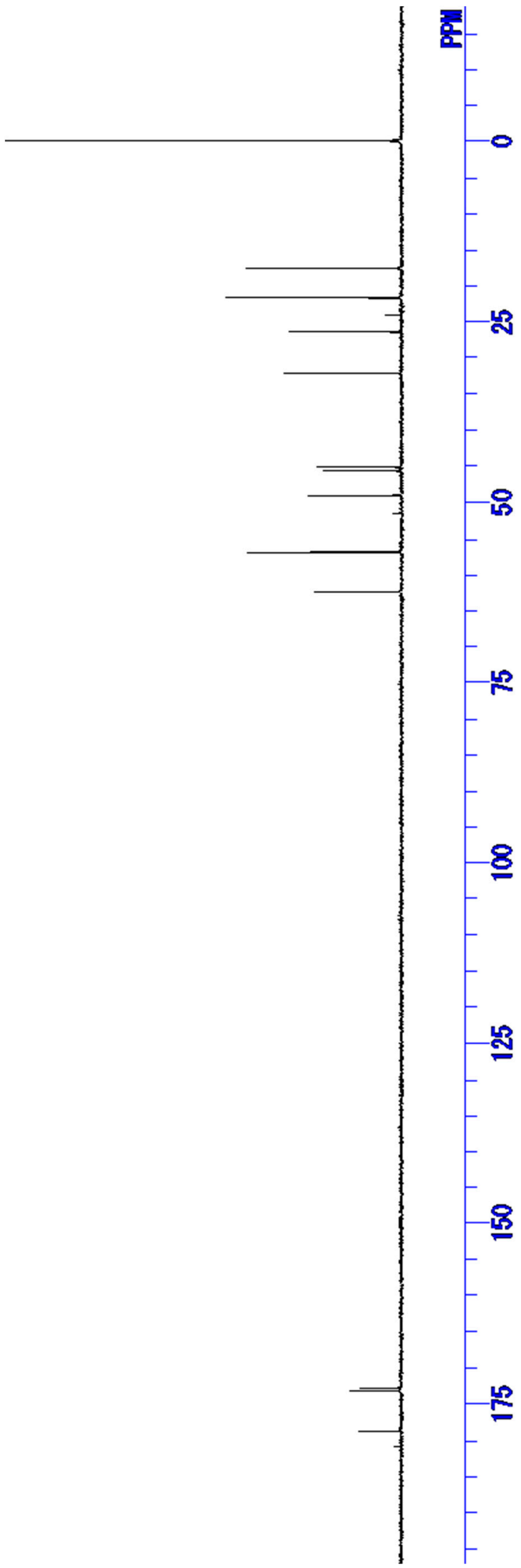


H-Pro-Gly-Gly-OH **3a**

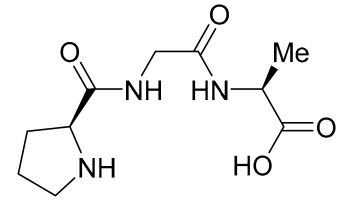
^{13}C NMR (150 MHz, D_2O)



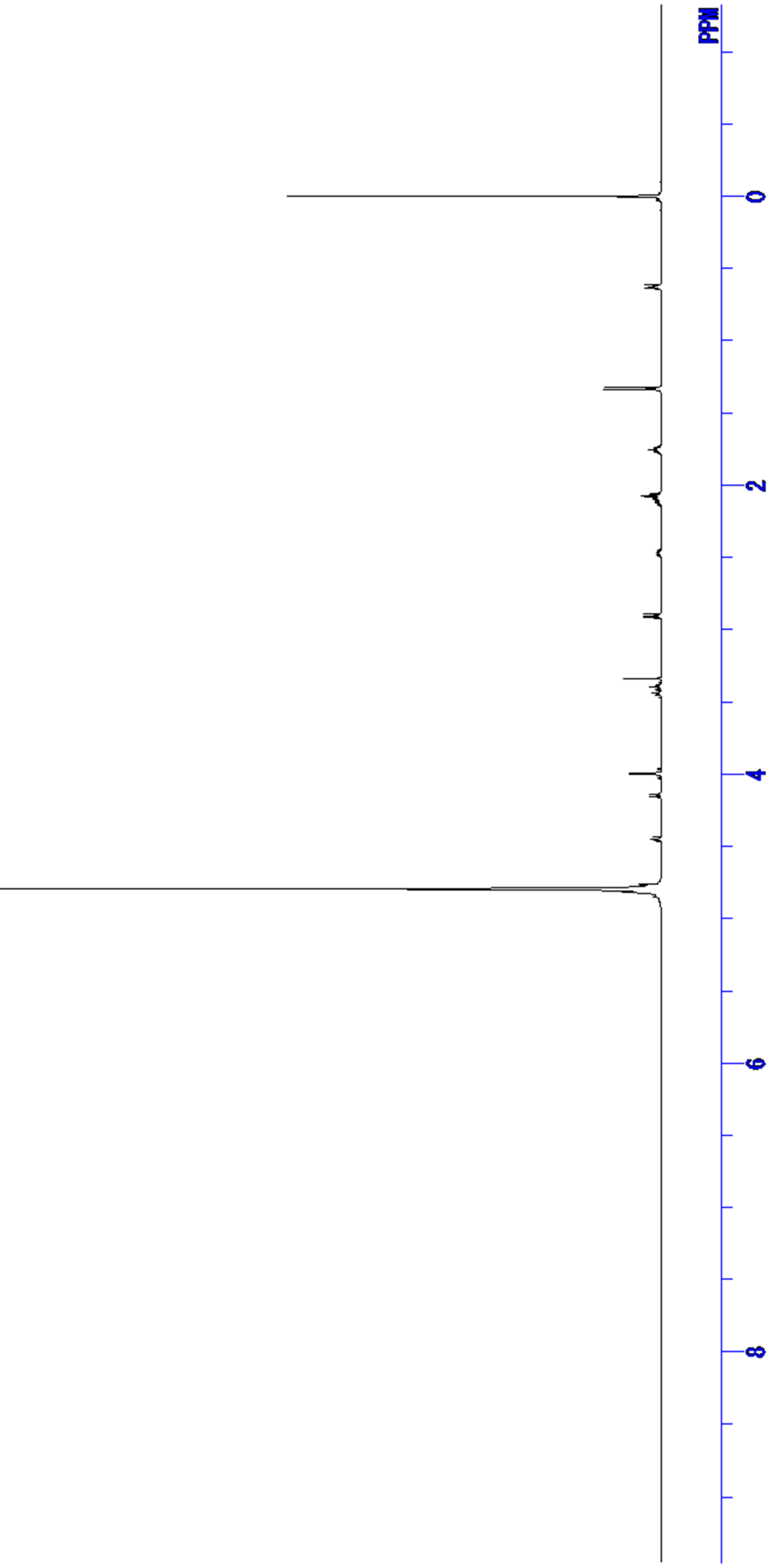
H-Pro-Gly-Gly-OH **3a**



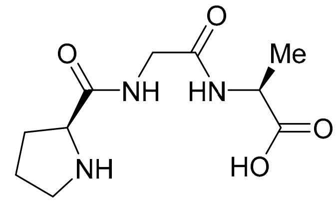
^1H NMR (600 MHz, D_2O)



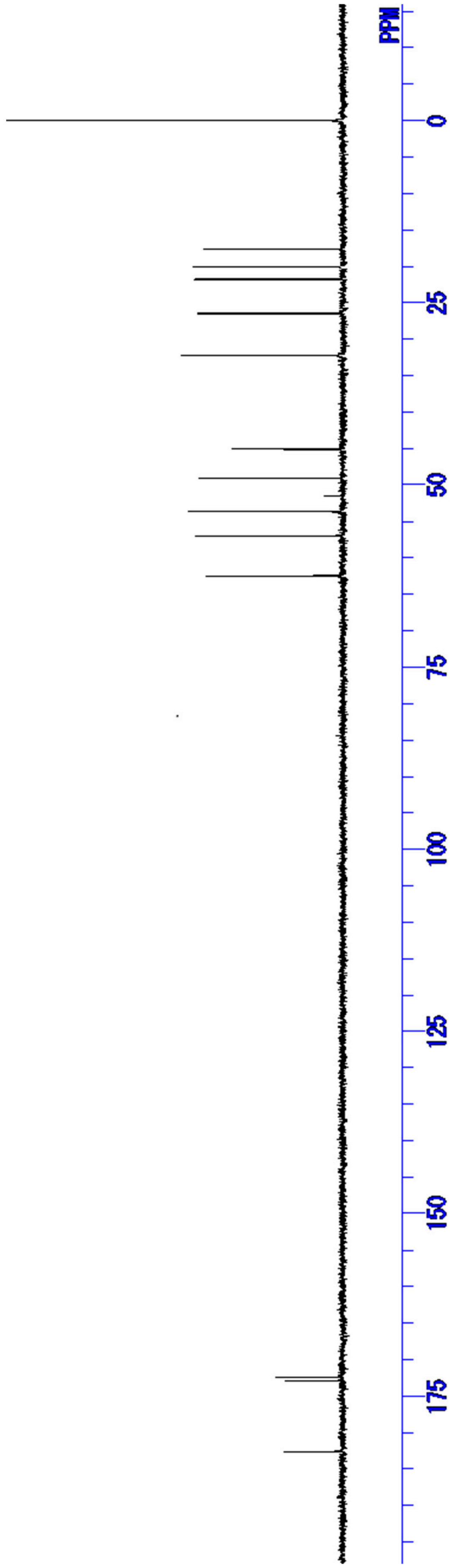
H-Pro-Gly-Ala-OH **3b**



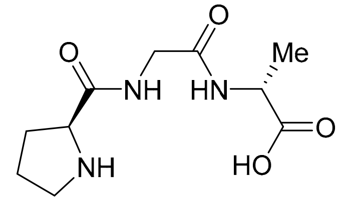
^{13}C NMR (150 MHz, D_2O)



H-Pro-Gly-Ala-OH **3b**

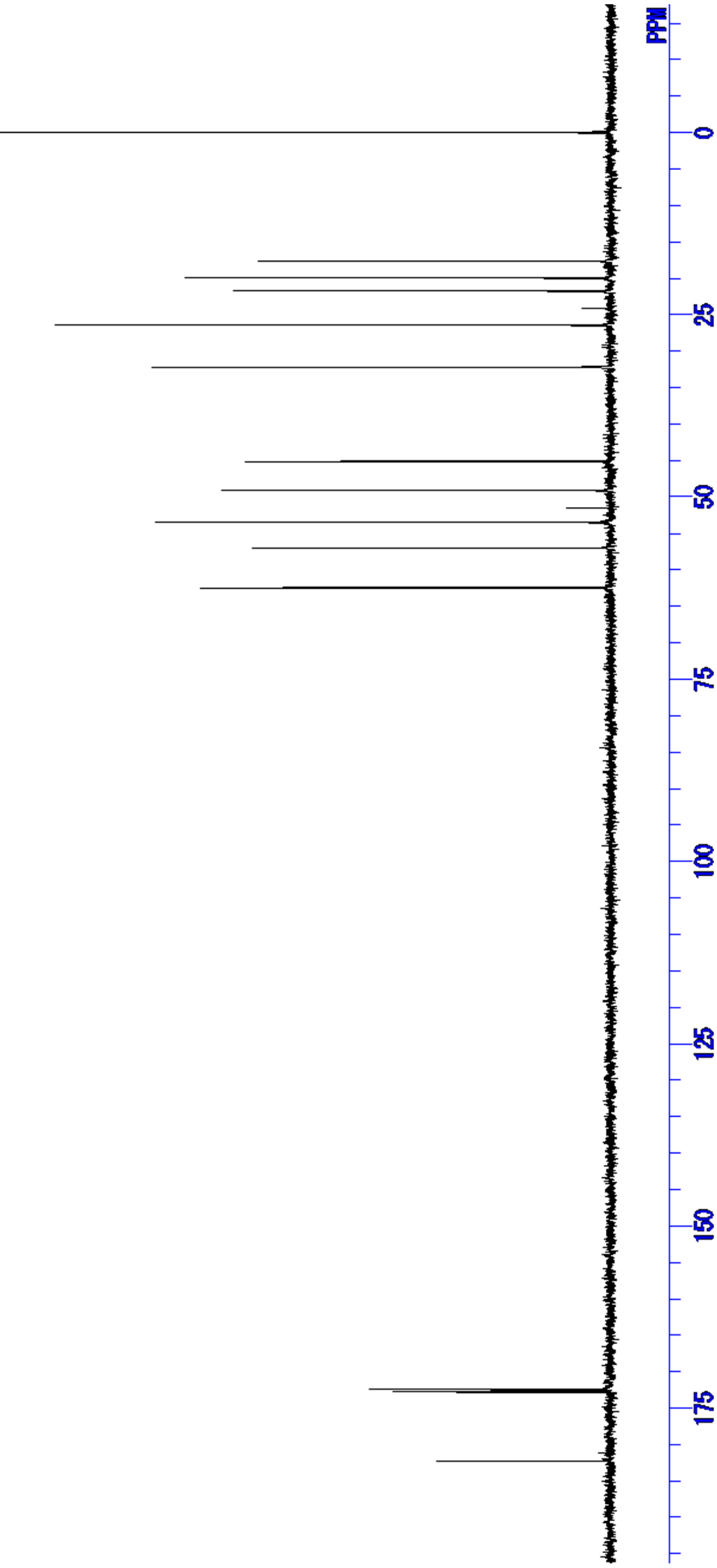


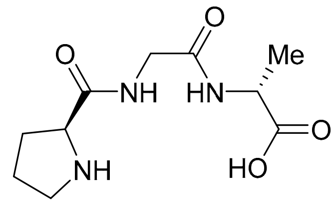
^{1}H NMR (600 MHz, D_2O)



H-Pro-Gly-D-Ala-OH **3c**

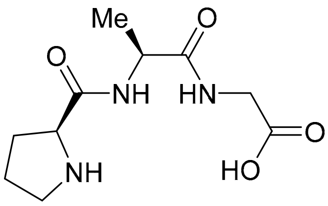
^{13}C NMR (150 MHz, D_2O)



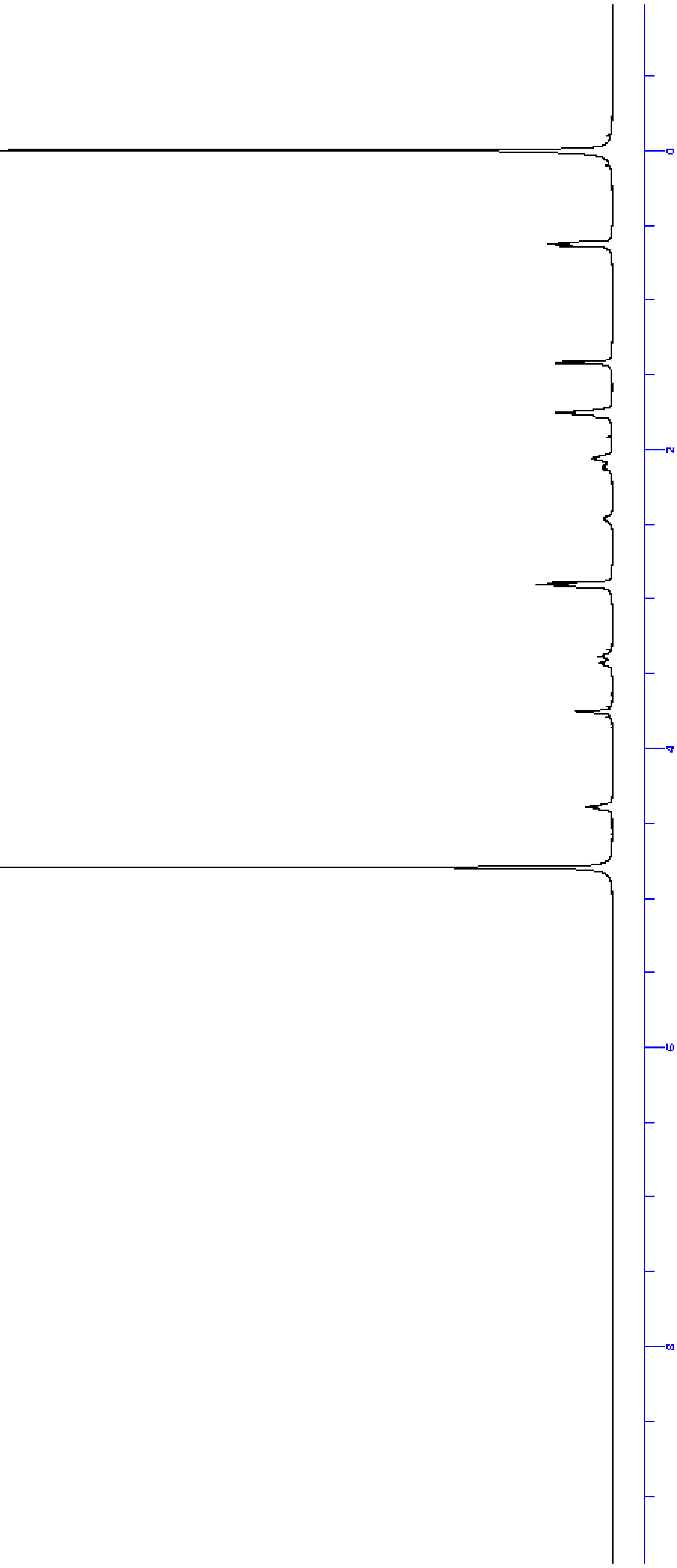


H-Pro-Gly-D-Ala-OH **3c**

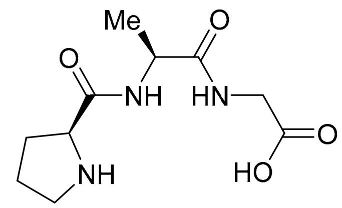
^{1}H NMR (600 MHz, D_2O)



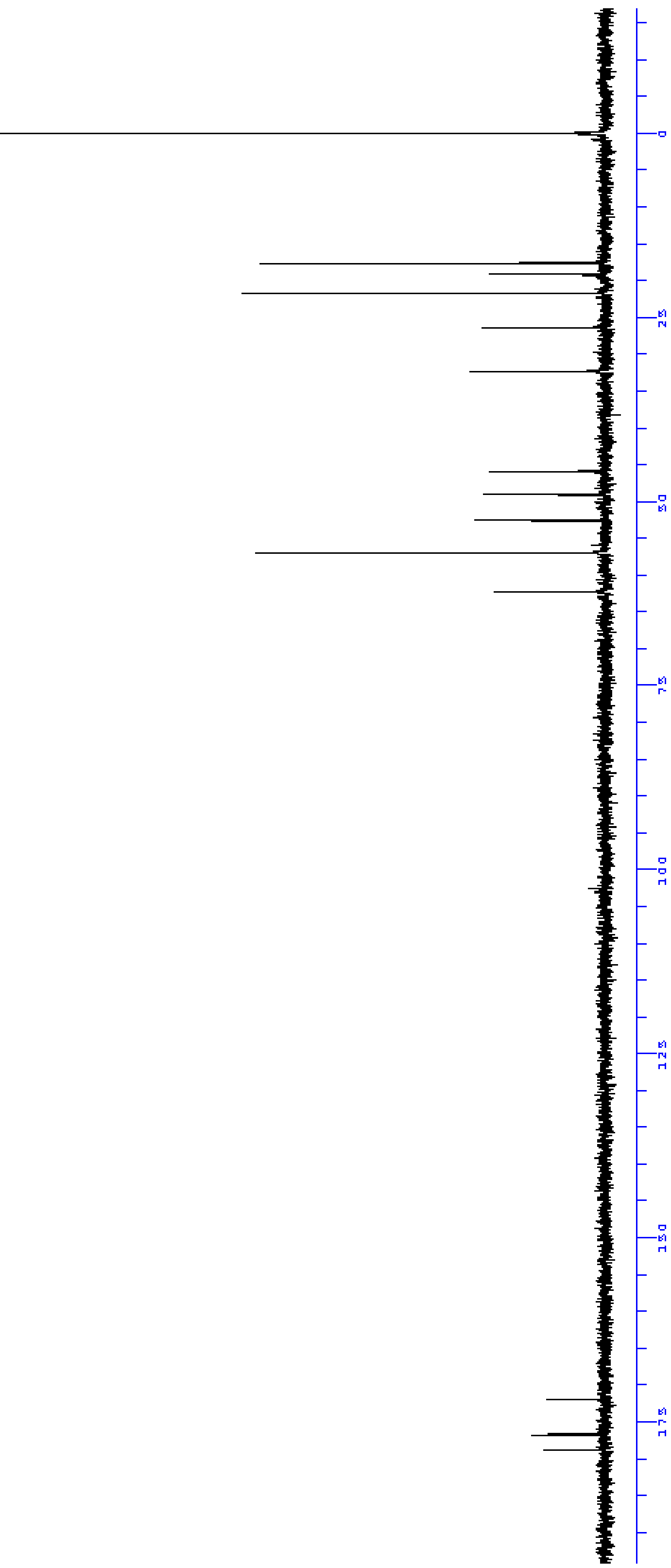
H-Pro-Ala-Gly-OH **3d**



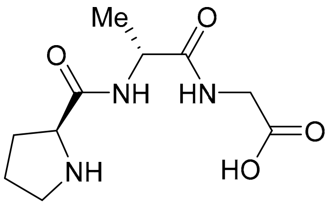
^{13}C NMR (150 MHz, D_2O)



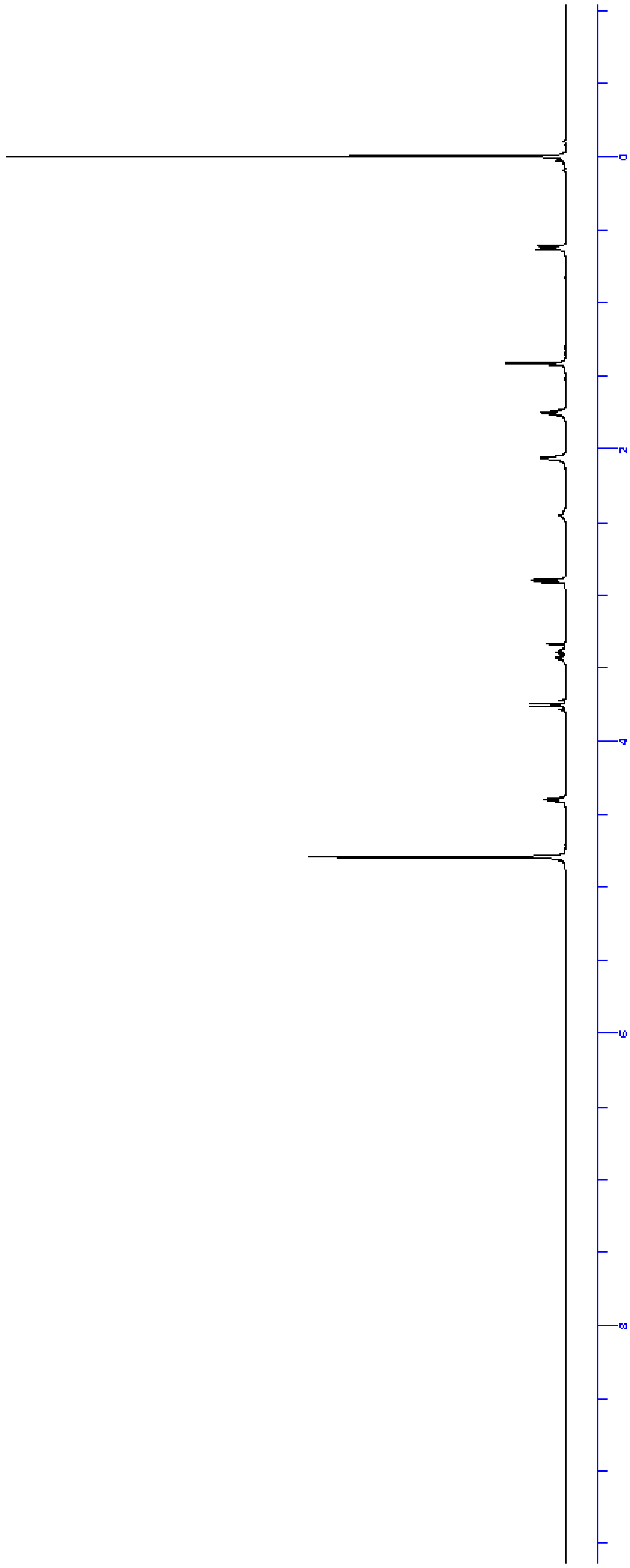
H-Pro-Ala-Gly-OH **3d**



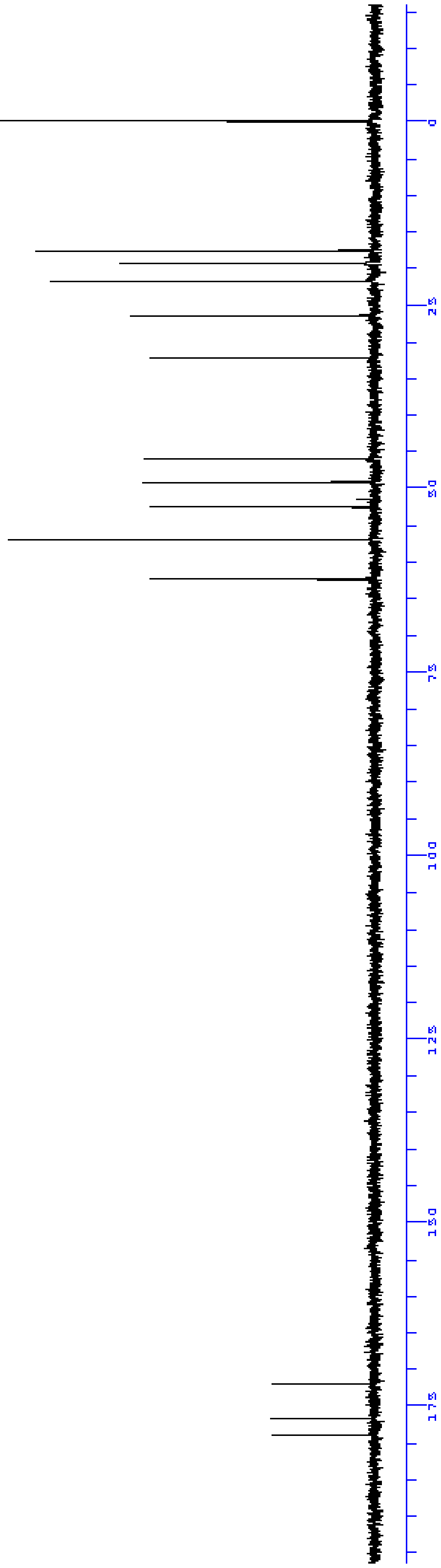
^{1}H NMR (600 MHz, D_2O)

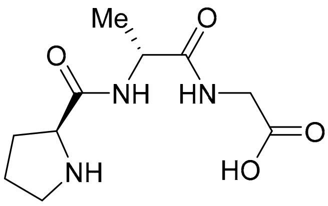


H-Pro-D-Ala-Gly-OH **3e**



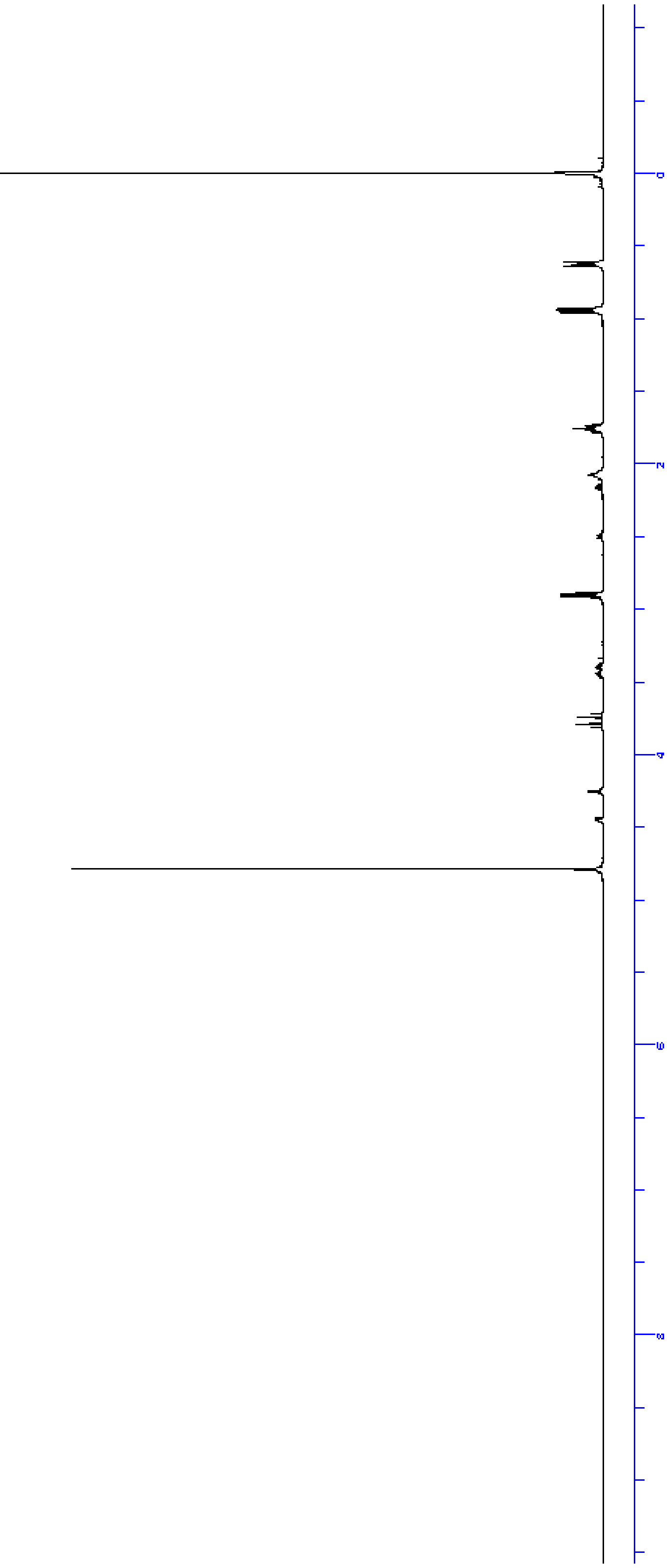
^{13}C NMR (150 MHz, D_2O)

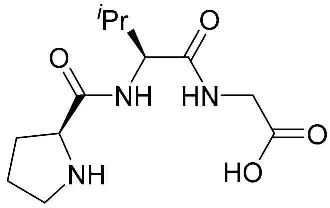




H-Pro-D-Ala-Gly-OH **3e**

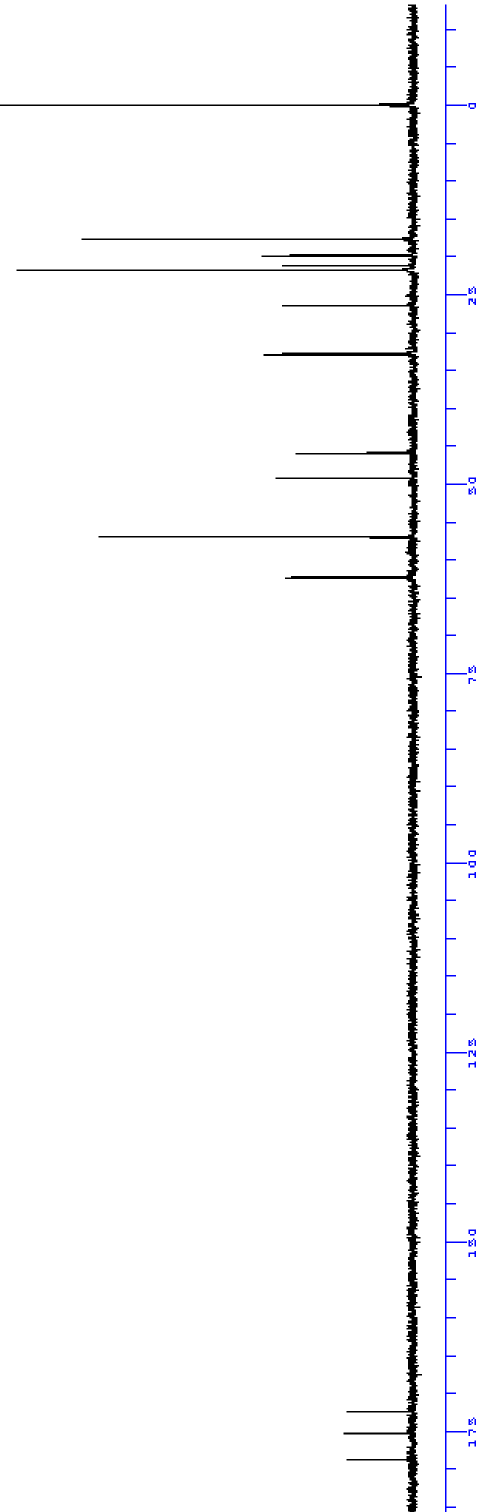
^{1}H NMR (600 MHz, D_2O)

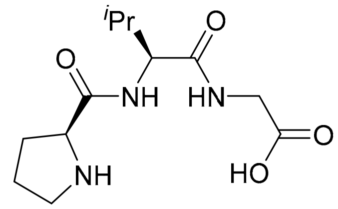




H-Pro-Val-Gly-OH **3f**

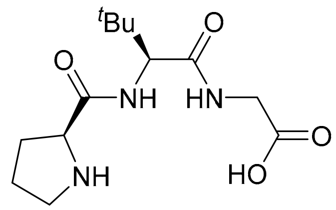
^{13}C NMR (150 MHz, D_2O)



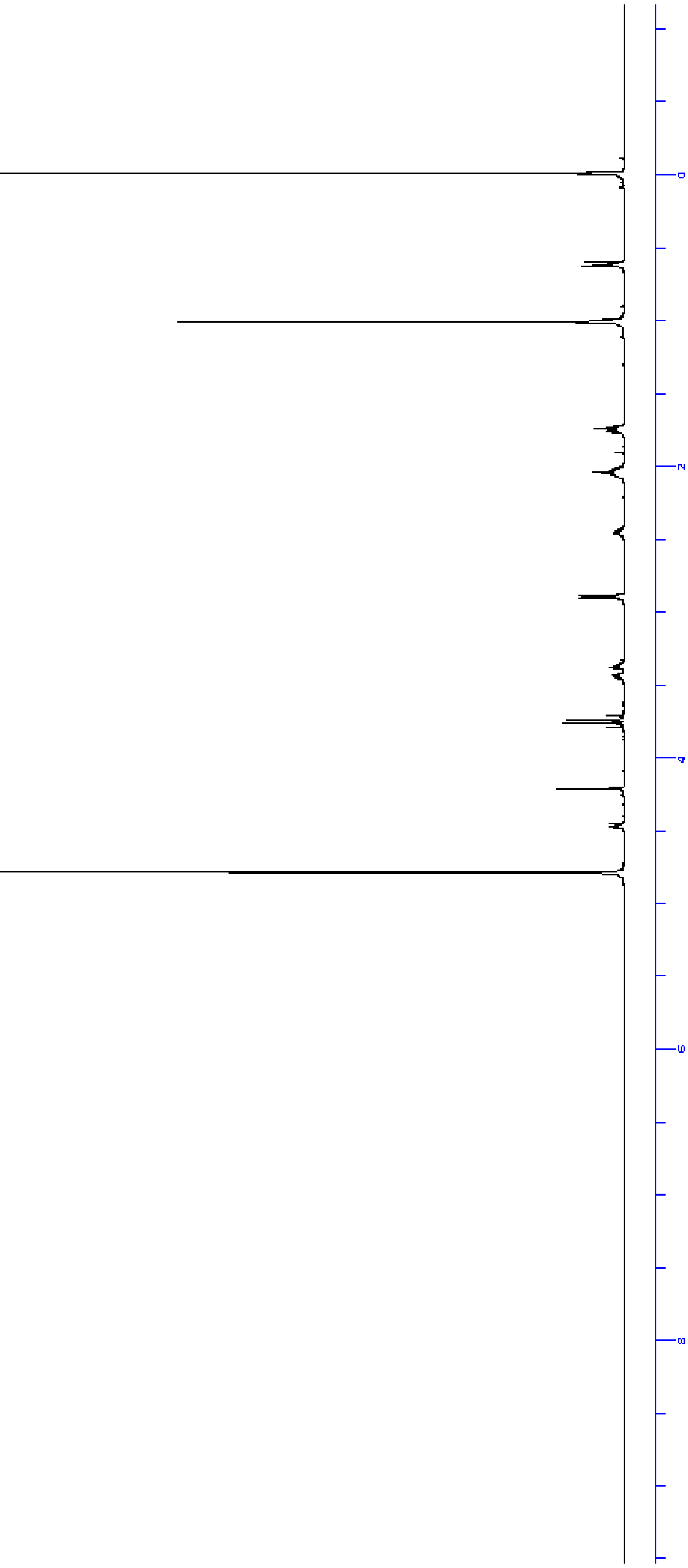


H-Pro-Val-Gly-OH **3f**

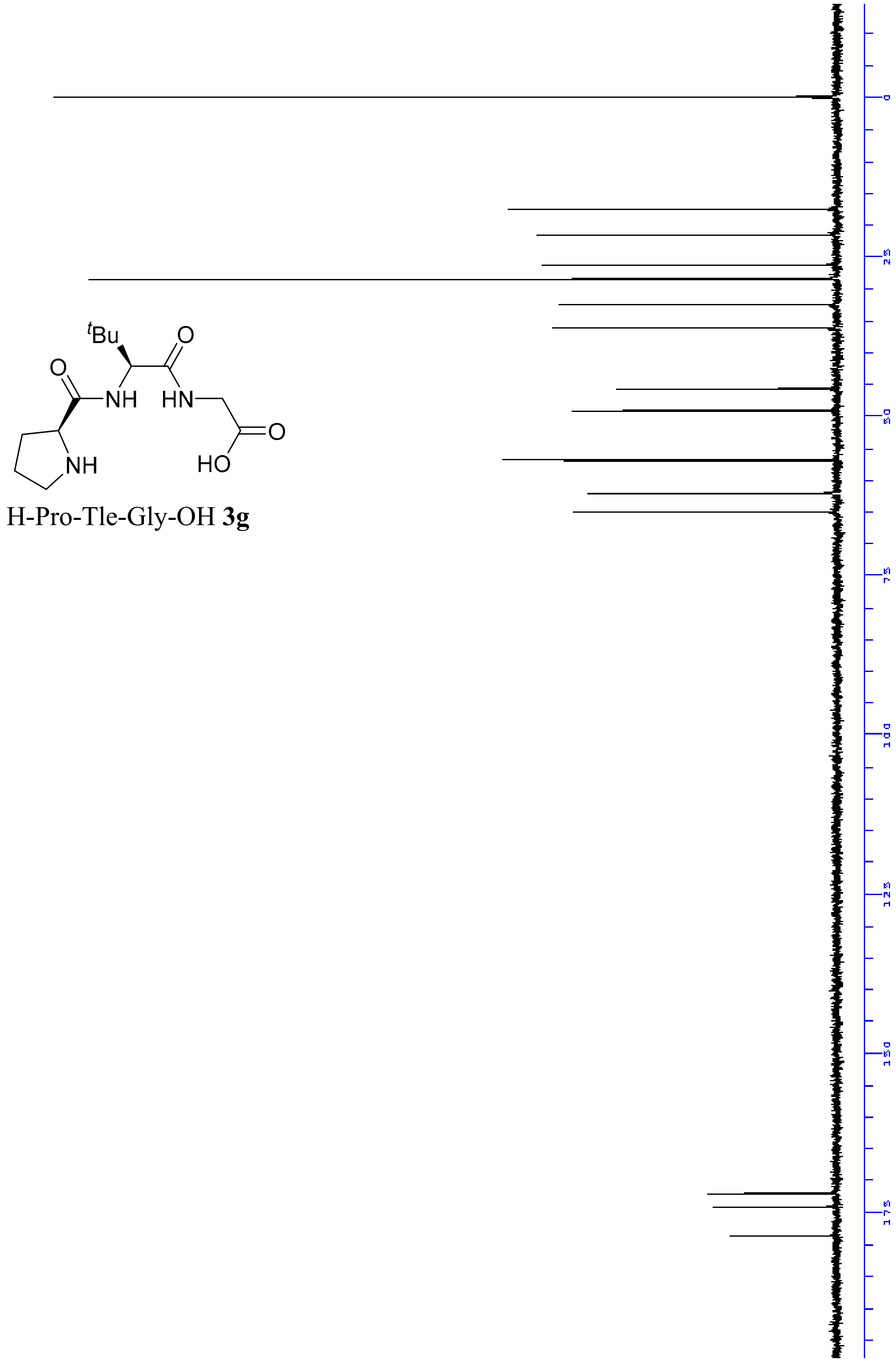
^{1}H NMR (600 MHz, D_2O)



H-Pro-Tle-Gly-OH **3g**

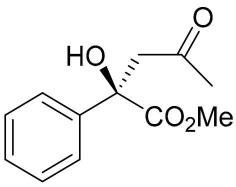


^{13}C NMR (150 MHz, D_2O)

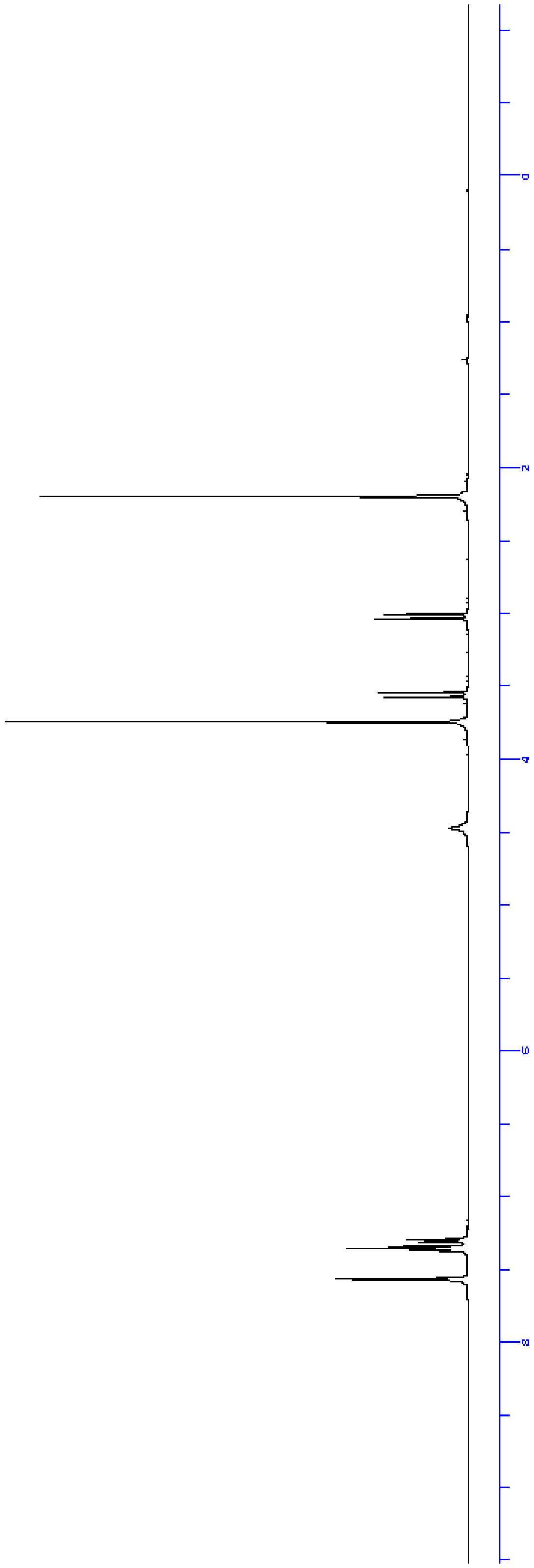


H-Pro-Tle-Gly-OH **3g**

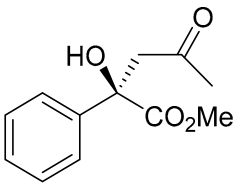
^{1}H NMR (600 MHz, $CDCl_3$)



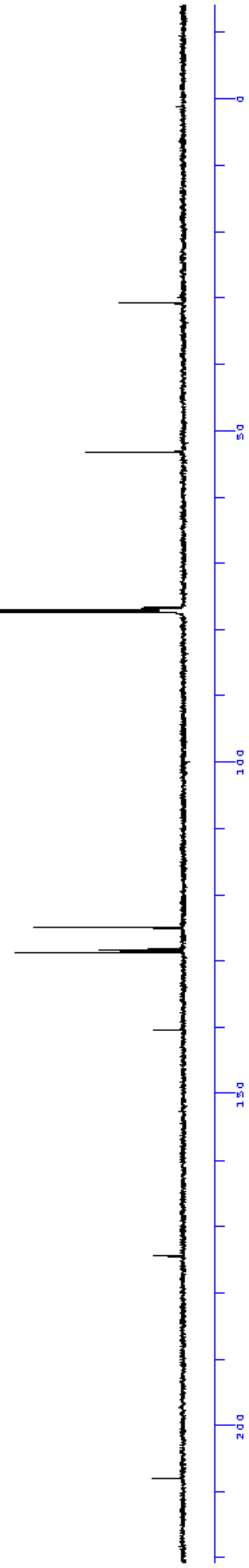
4a



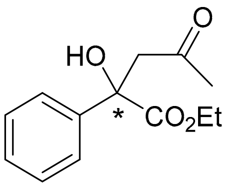
^{13}C NMR (150 MHz, $CDCl_3$)



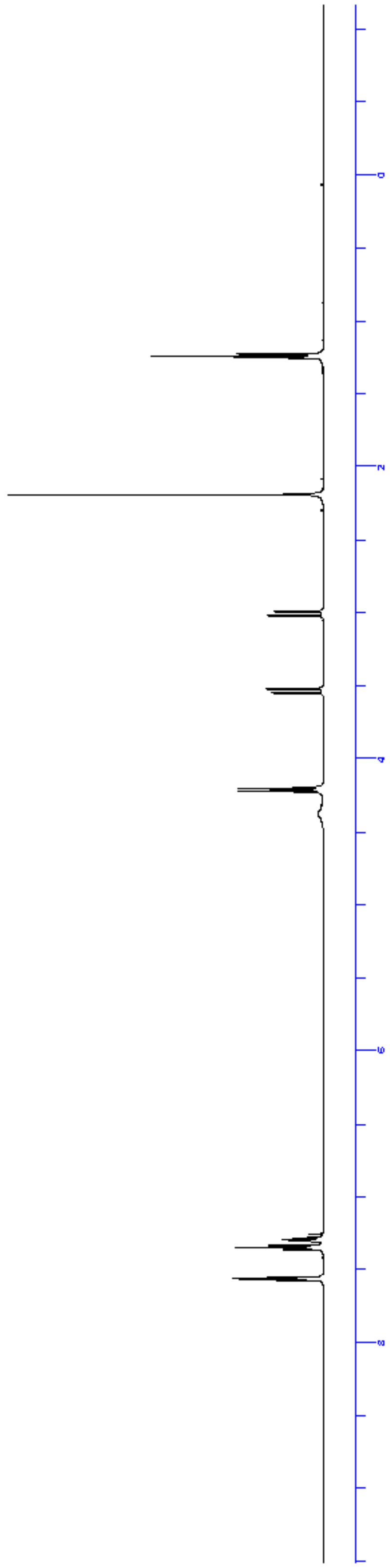
4a



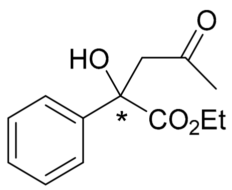
^{1}H NMR (600 MHz, $CDCl_3$)



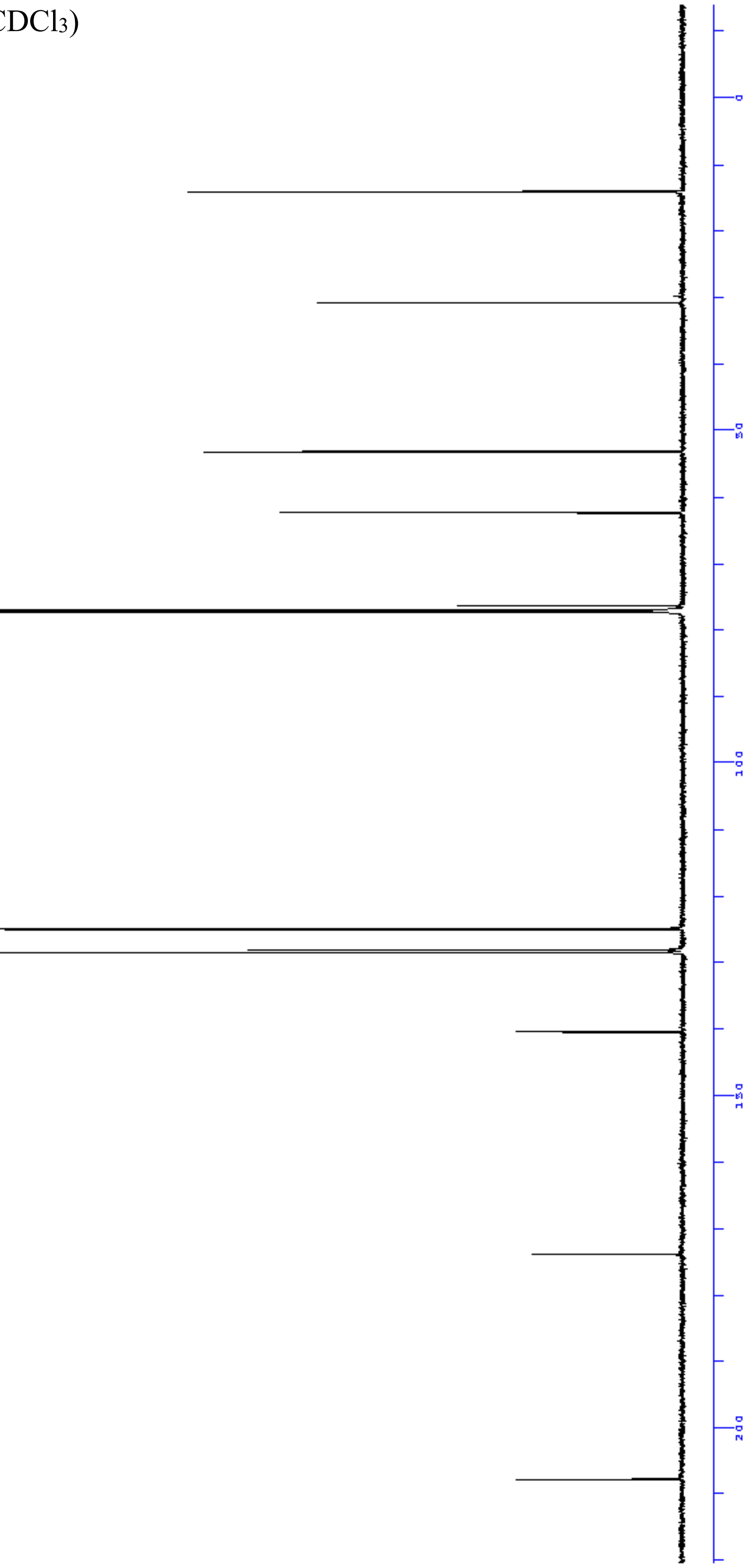
4b



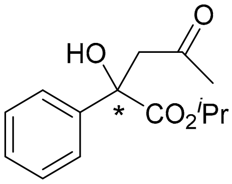
^{13}C NMR (150 MHz, $CDCl_3$)



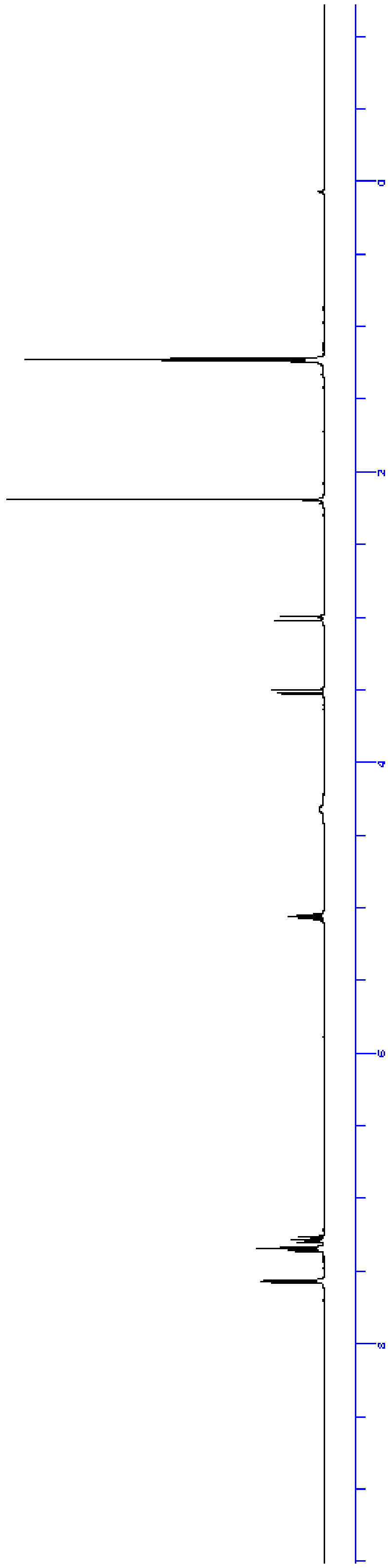
4b



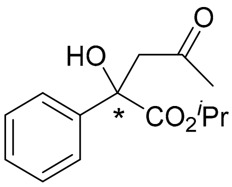
^{1}H NMR (600 MHz, $CDCl_3$)



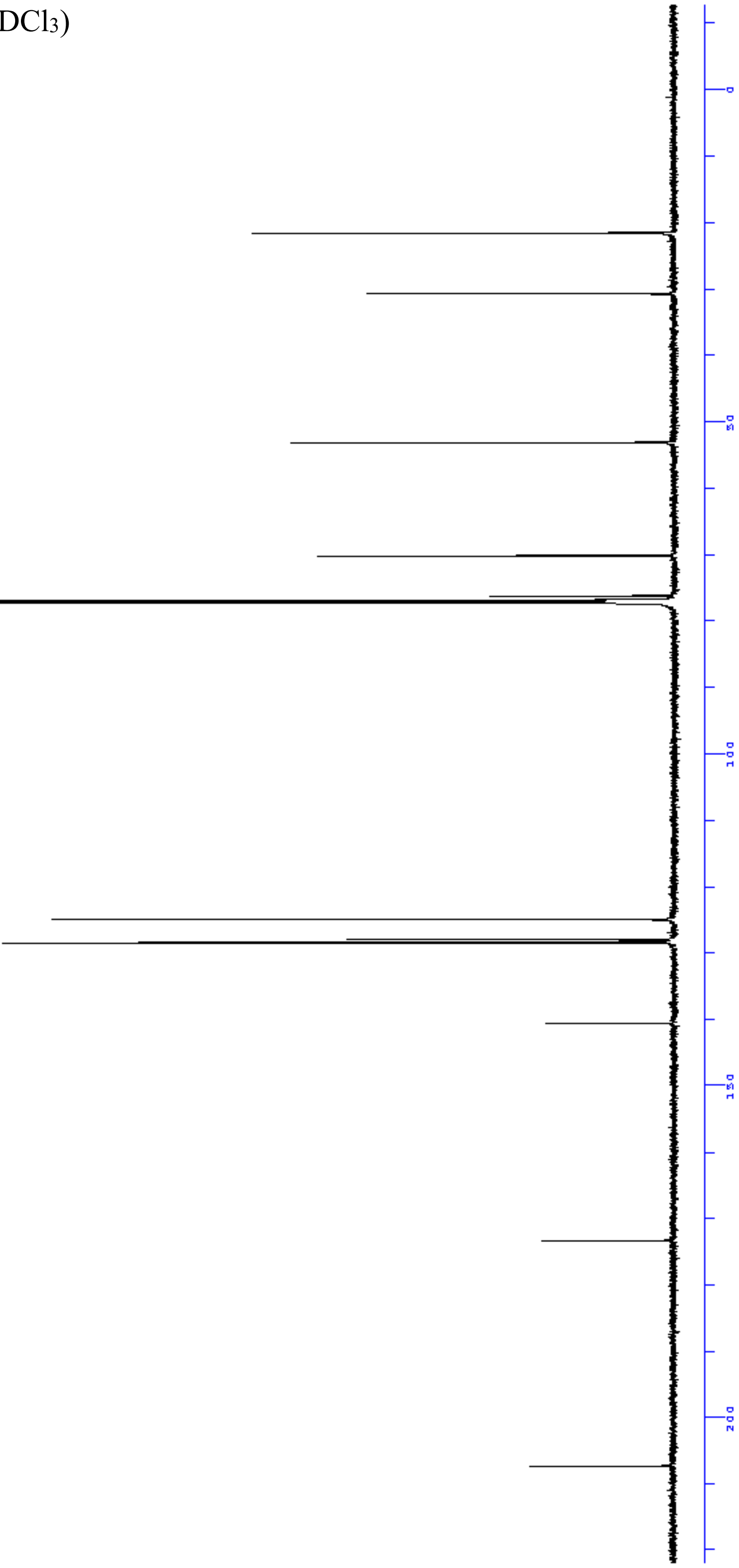
4c



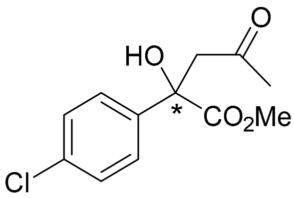
[13]C NMR (150 MHz, CDCl3)



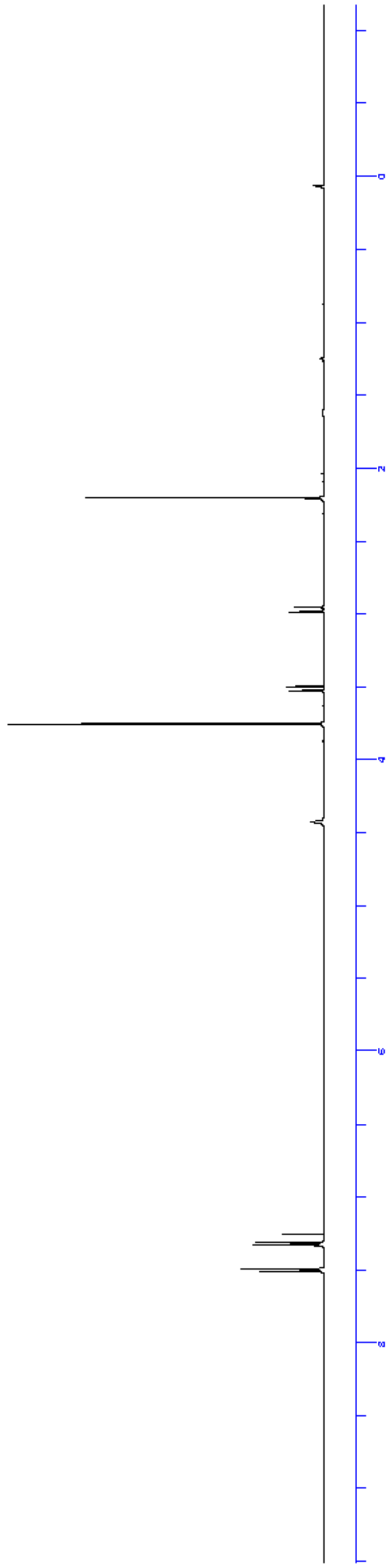
4c



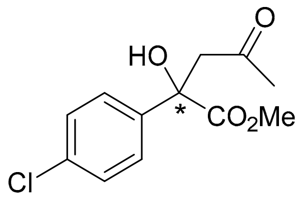
^{1}H NMR (600 MHz, $CDCl_3$)



4d



^{13}C NMR (150 MHz, $CDCl_3$)



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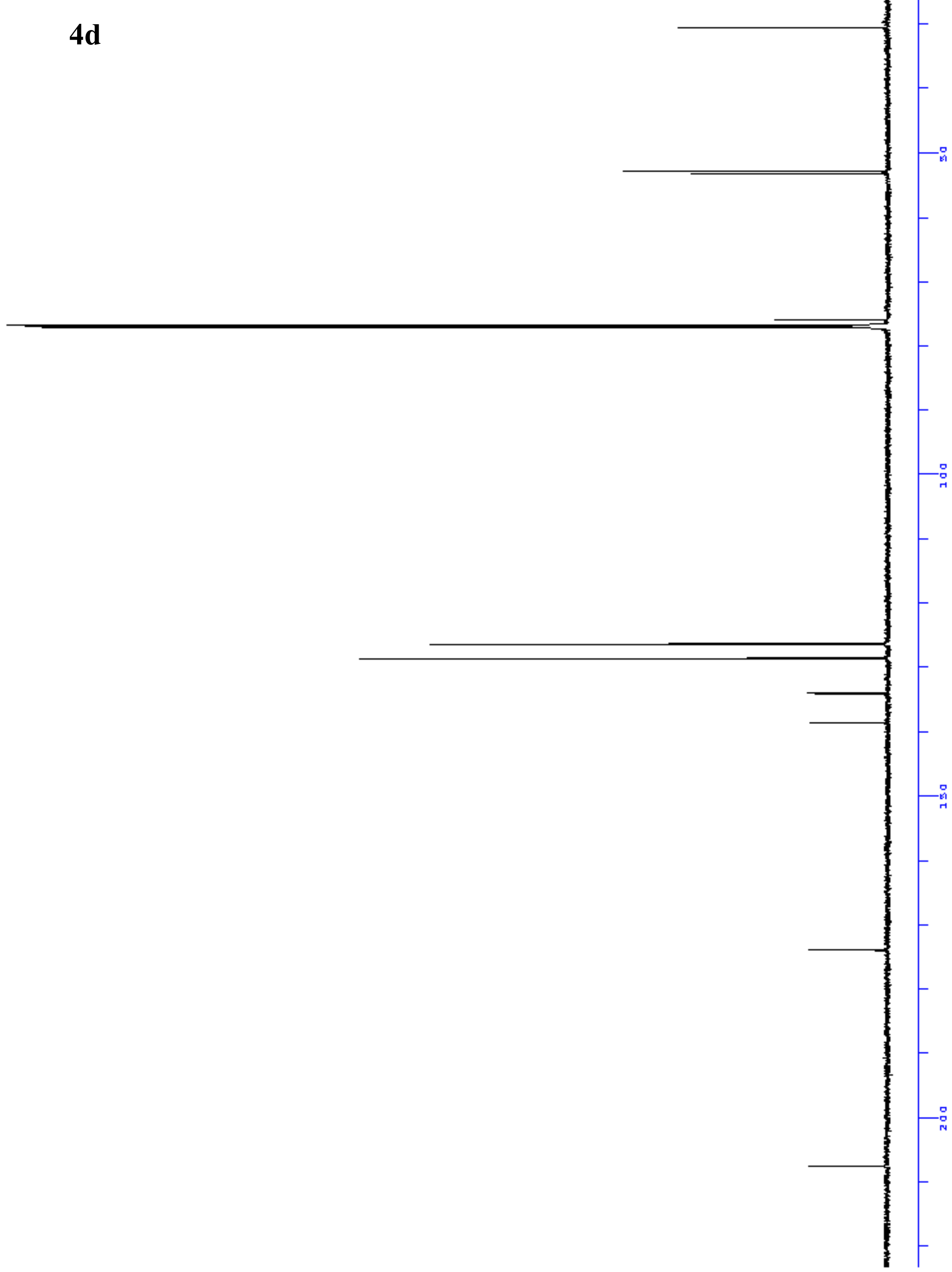
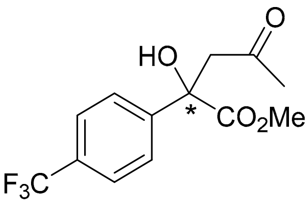
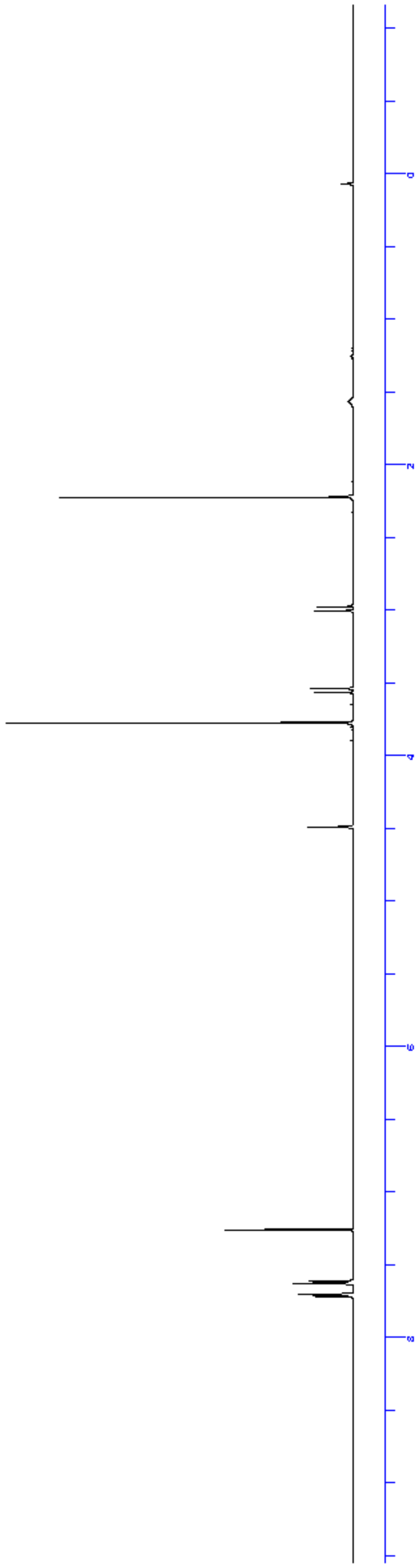


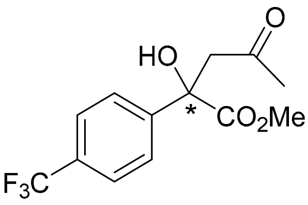
[1]H NMR (600 MHz, $CDCl_3$)



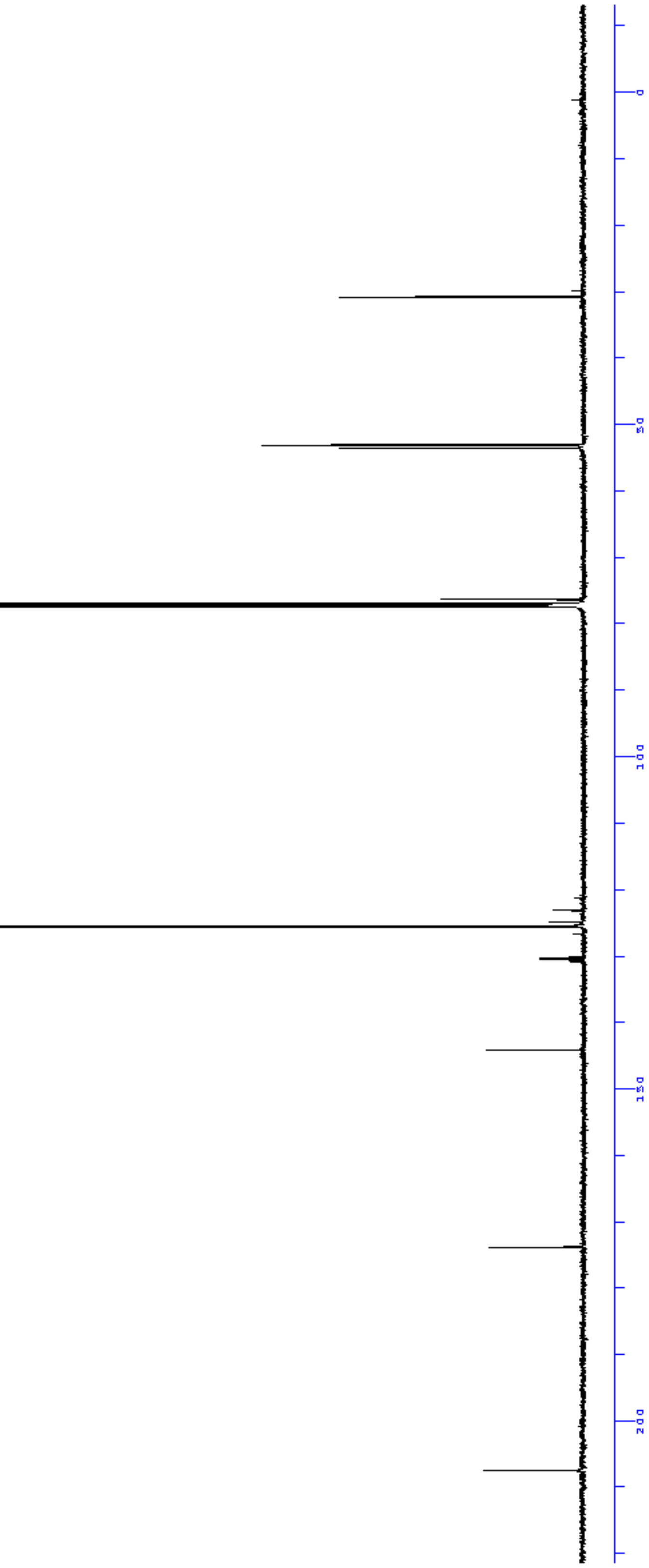
4e



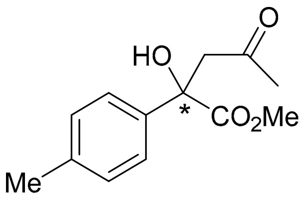
^{13}C NMR (150 MHz, $CDCl_3$)



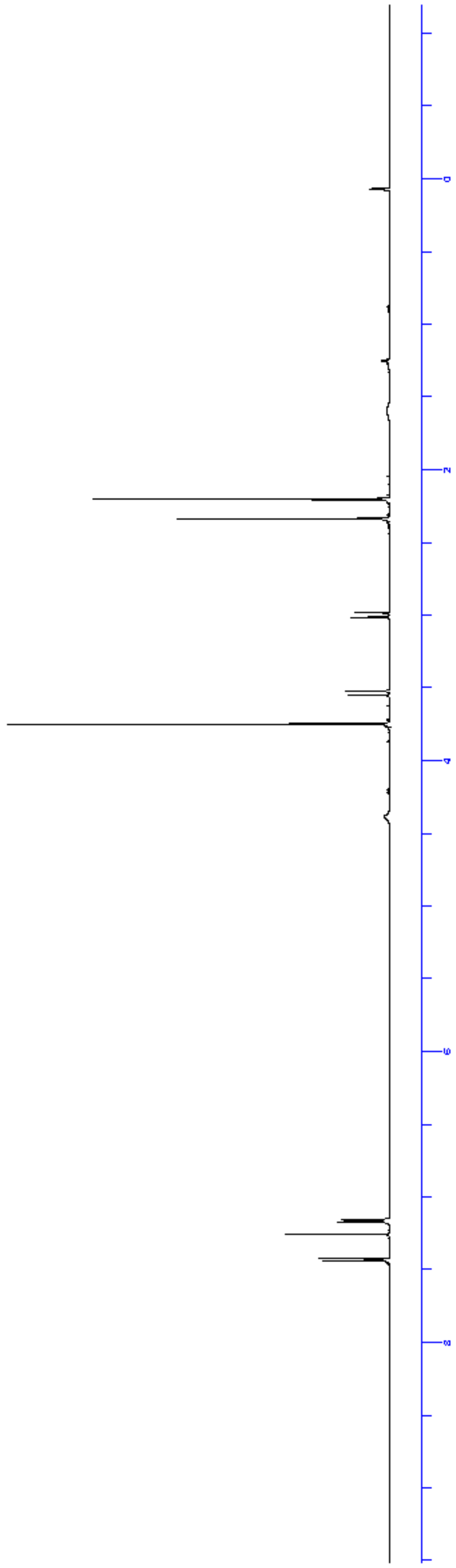
4e



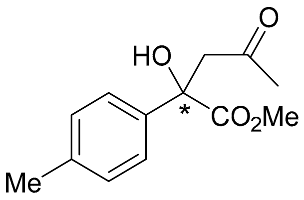
[1]H NMR (600 MHz, $CDCl_3$)



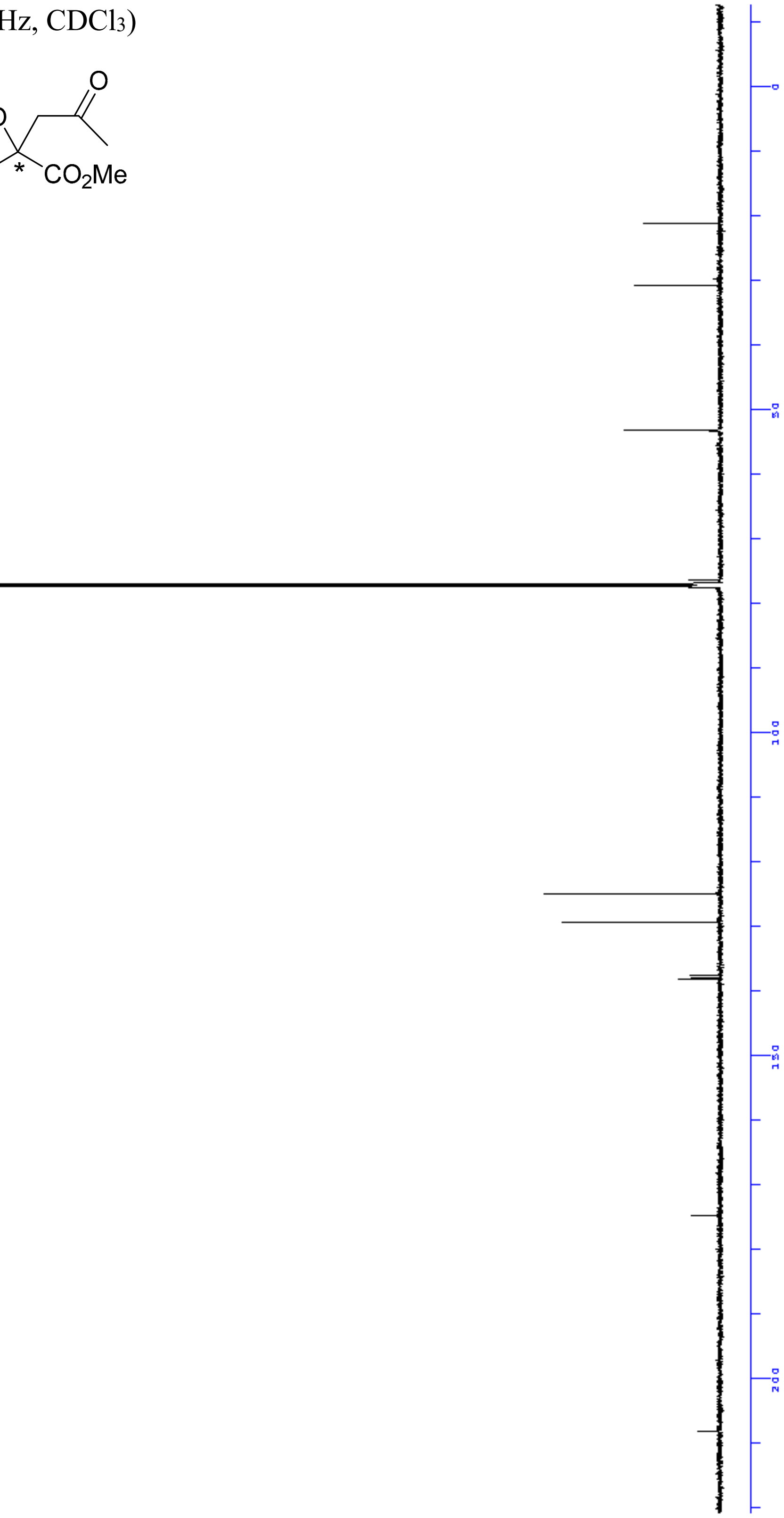
4f



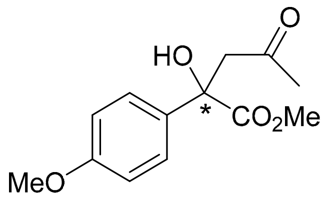
^{13}C NMR (150 MHz, $CDCl_3$)



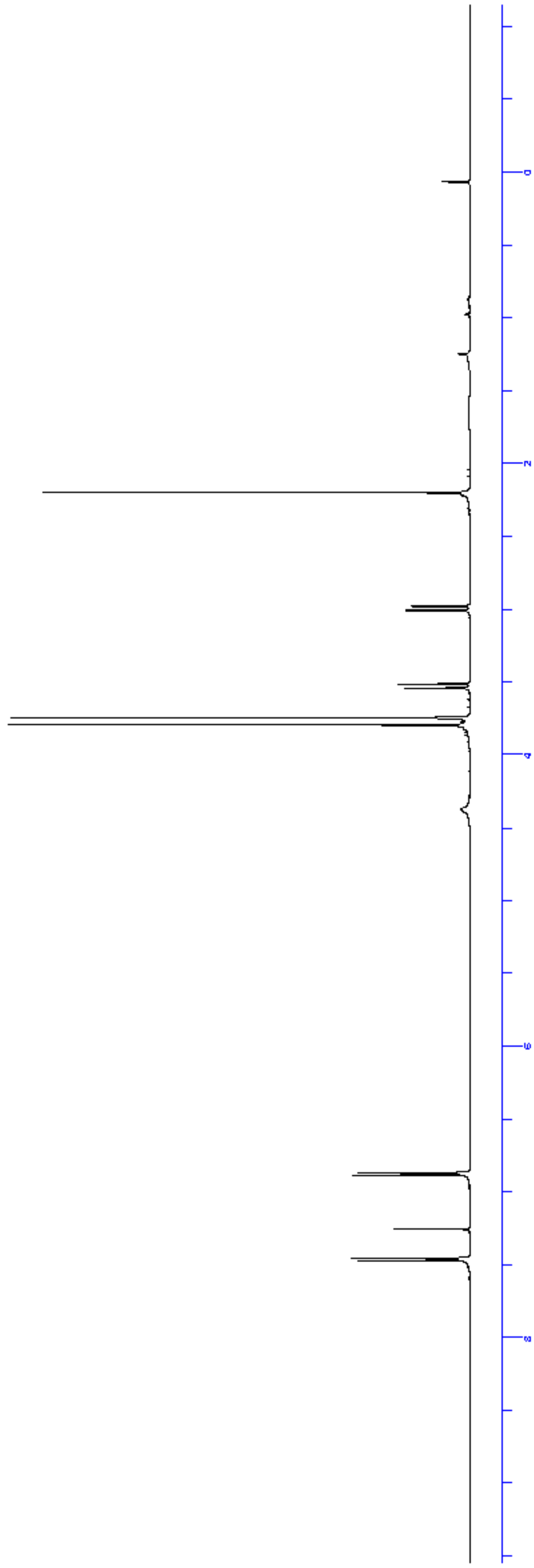
4f



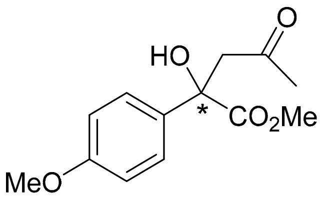
^{1}H NMR (600 MHz, $CDCl_3$)



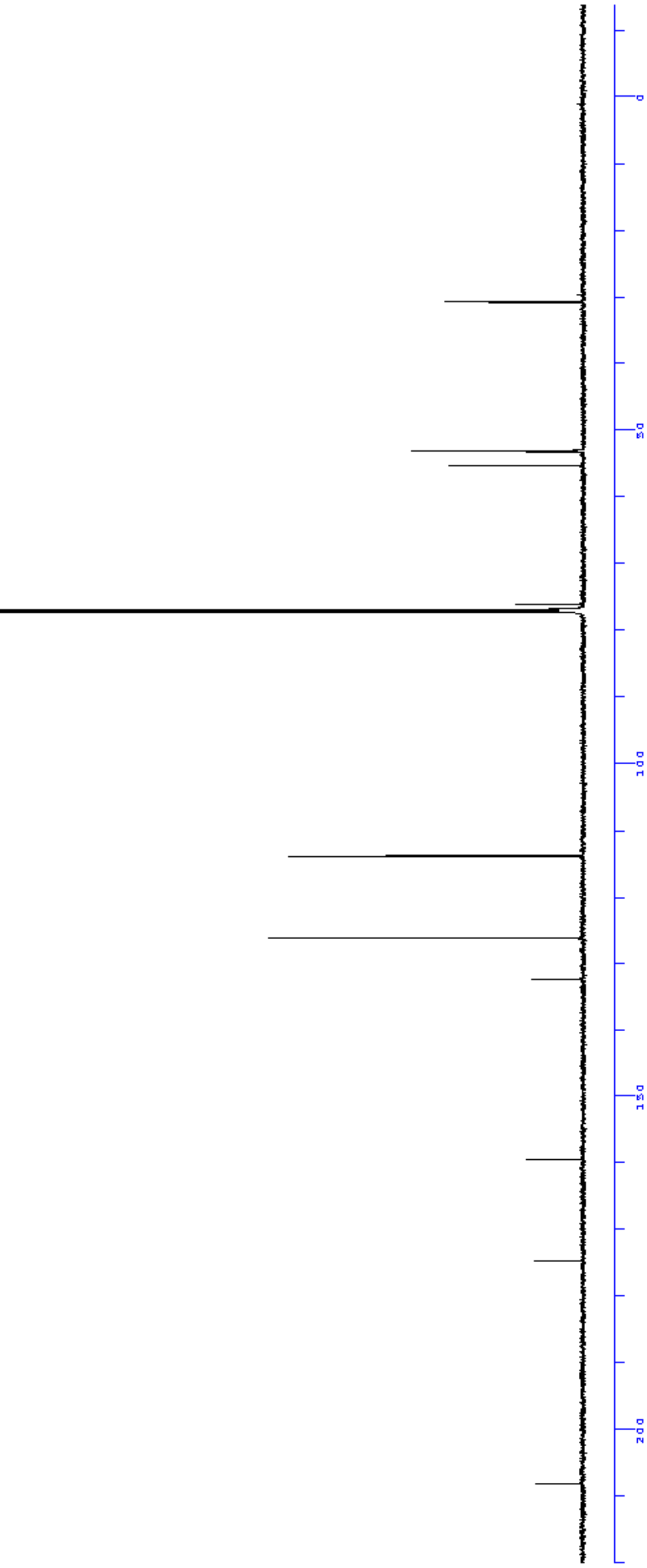
4g



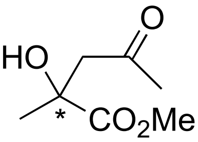
^{13}C NMR (150 MHz, $CDCl_3$)



4g



^{1}H NMR (600 MHz, $CDCl_3$)



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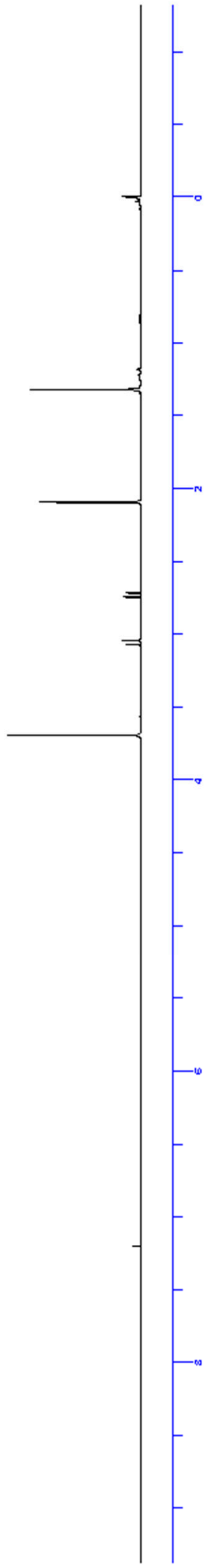
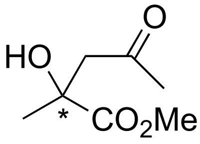


^{13}C NMR (150 MHz, $CDCl_3$)



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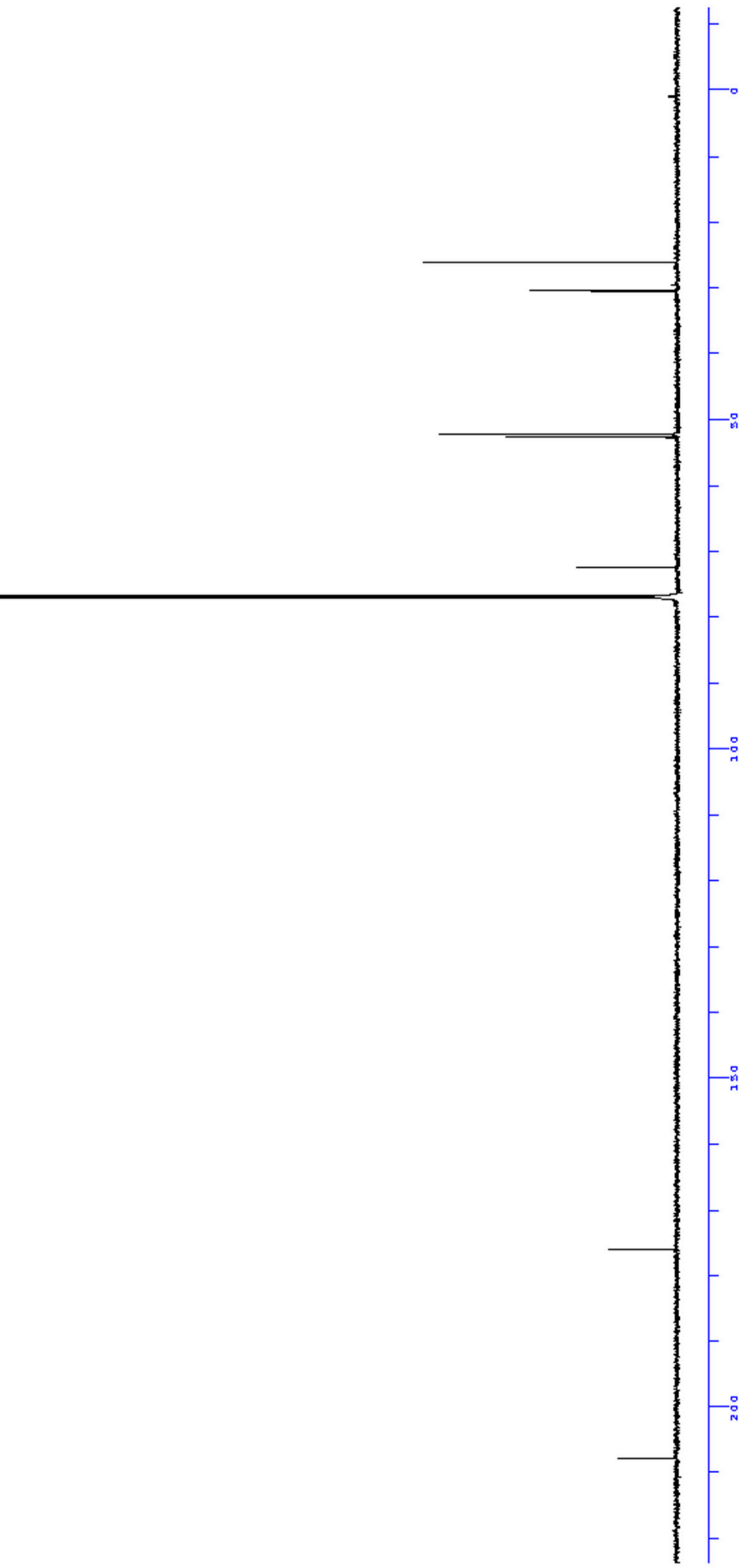
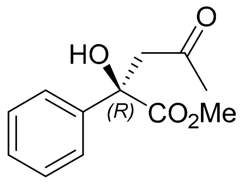
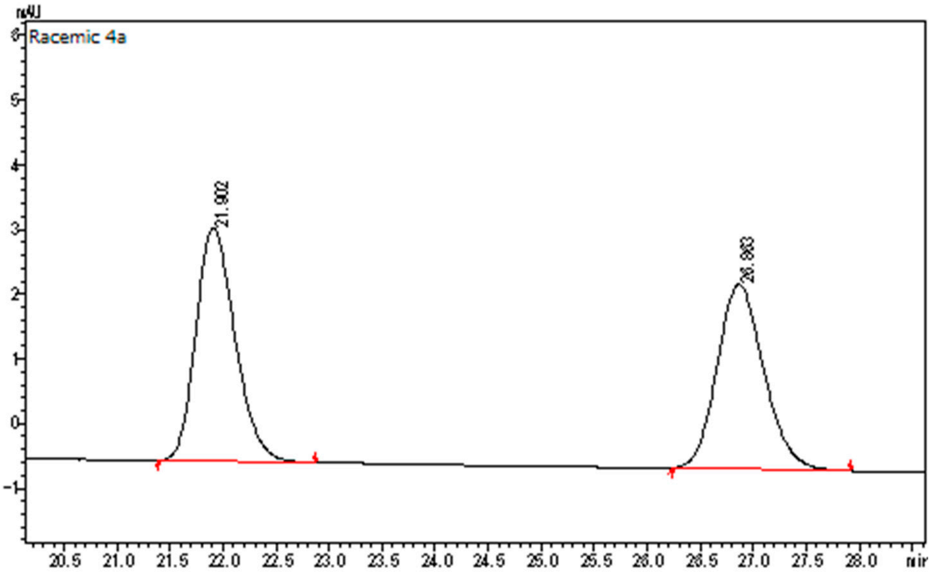


8. Copy of HPLC spectra

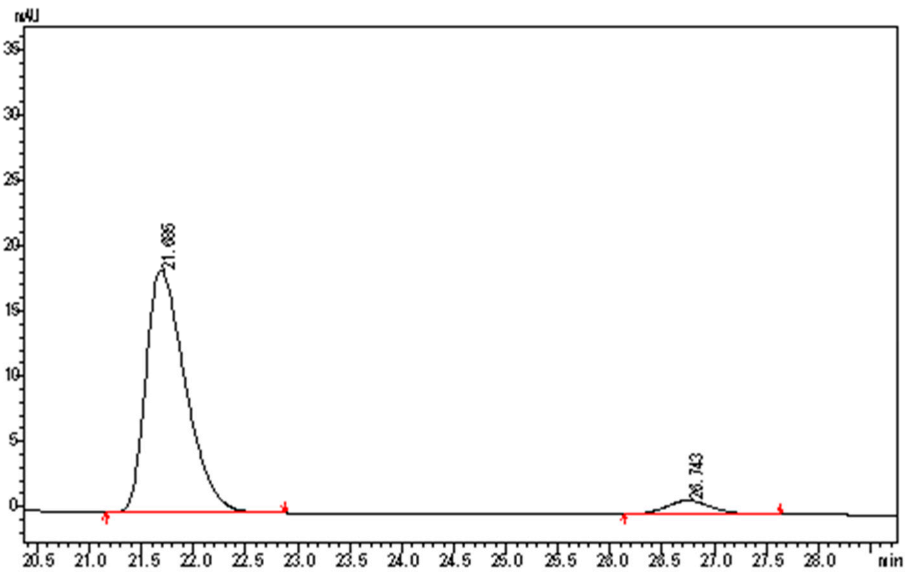


4a, 88% *ee*

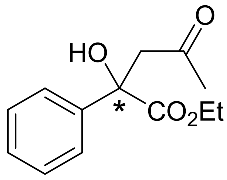
DAICEL CHIRALPAK AD-H, *n*-hexane /^{i}PrOH = 97/3, 1.0 mL/min, 254 nm, 35 °C.



Rt/min	Area/%
21.902	51.397
26.863	48.603

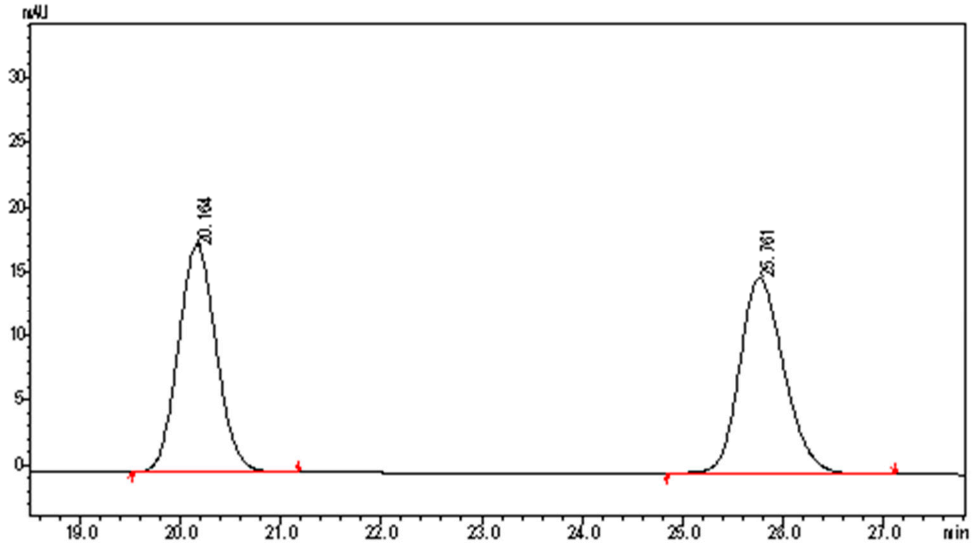


Rt/min	Area/%
21.685	93.889
26.743	6.111

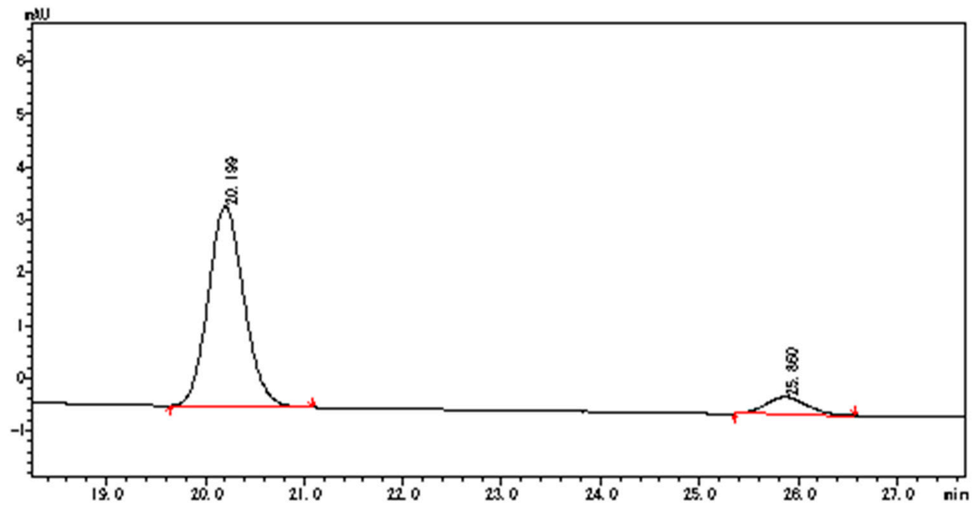


4b, 82% *ee*

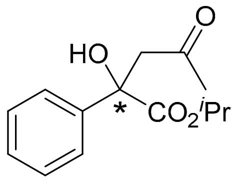
DAICEL CHIRALPAK AD-H, *n*-hexane /^{i}PrOH = 97/3, 1.0 mL/min, 254 nm, 35 °C.



Rt/min	Area/%
20.164	49.617
25.761	50.383

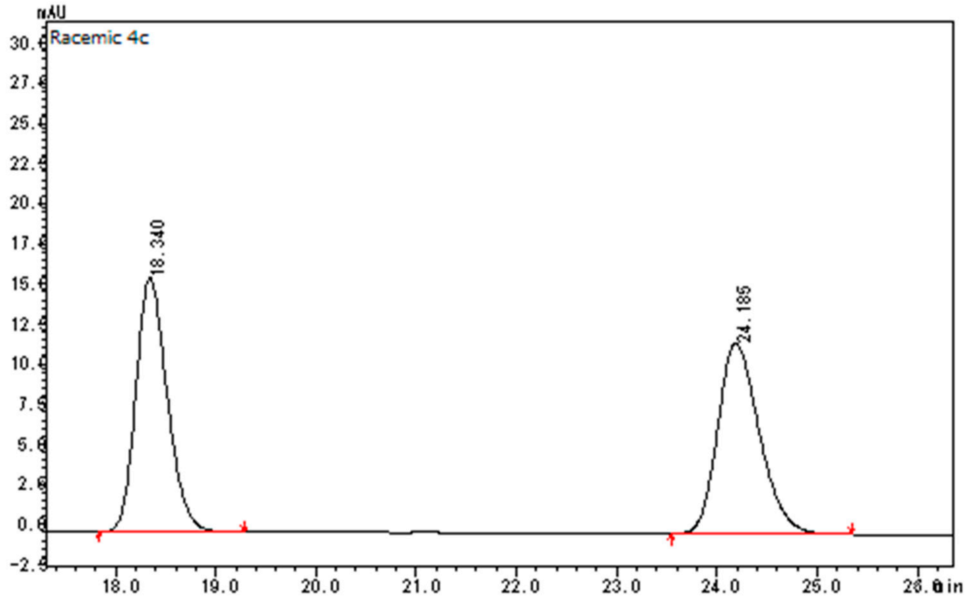


Rt/min	Area/%
20.199	91.012
25.860	8.988

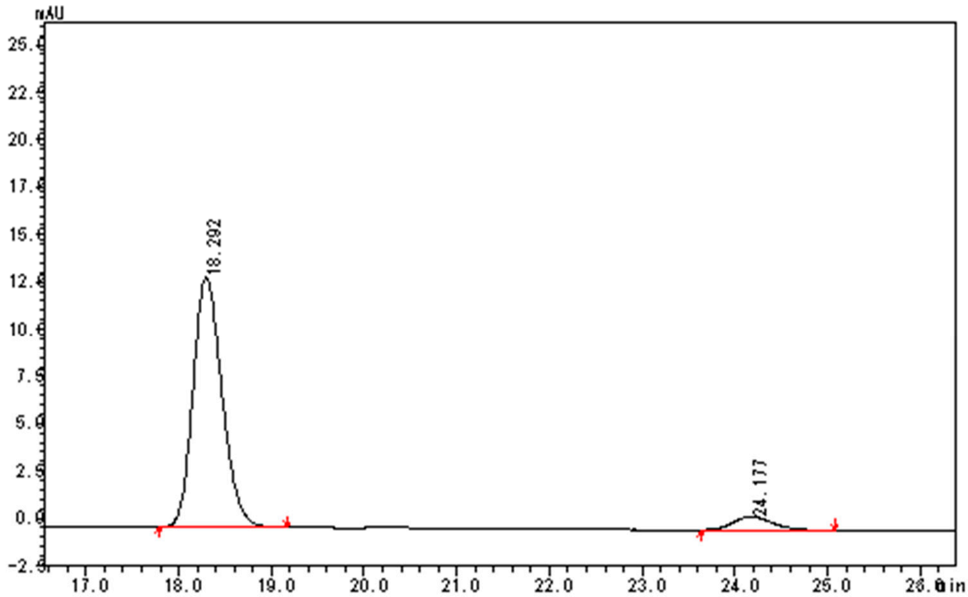


4c, 86% *ee*

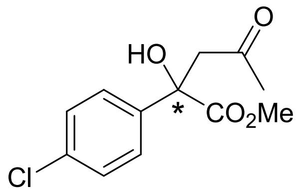
DAICEL CHIRALPAK AD-H, *n*-hexane /^{i}PrOH = 97/3, 1.0 mL/min, 254 nm, 35 °C.



Rt/min	Area/%
18.340	49.905
24.185	50.095

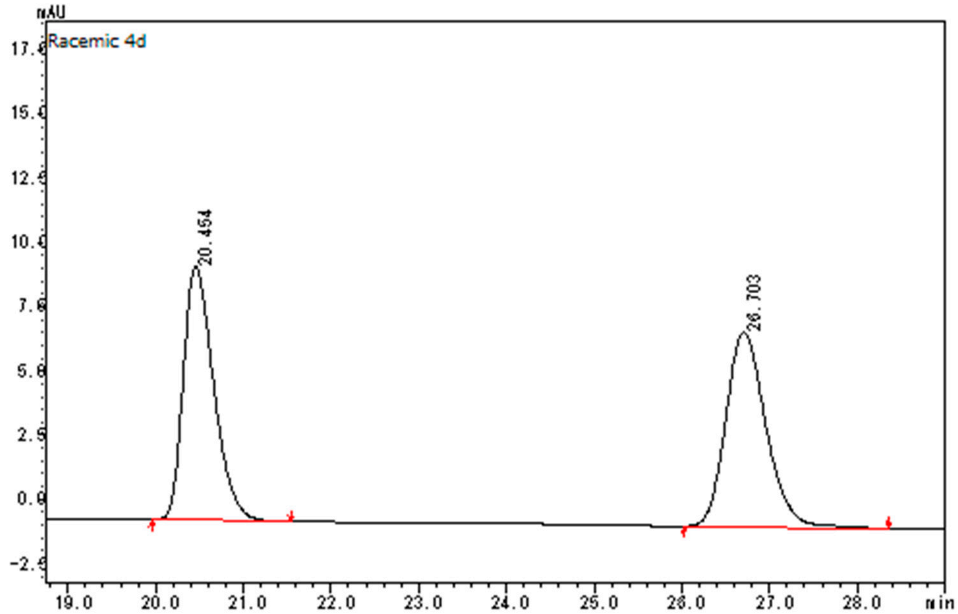


Rt/min	Area/%
18.292	93.106
24.177	6.894

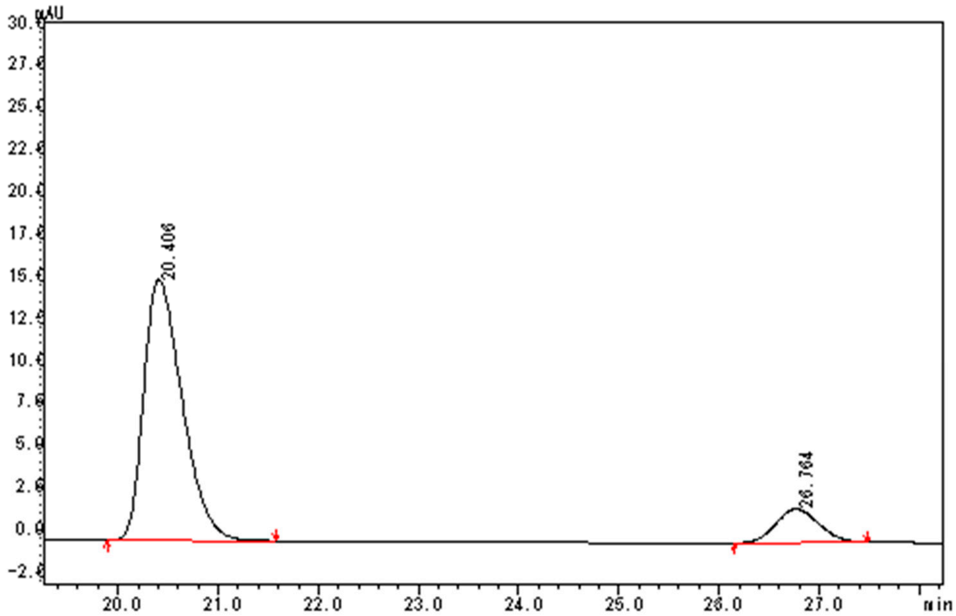


4d, 75% *ee*

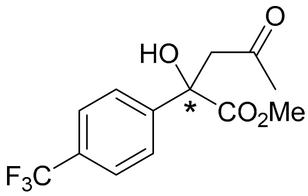
DAICEL CHIRALPAK AD-H, *n*-hexane /^{i}PrOH = 97/3, 1.0 mL/min, 254 nm, 35 °C.



Rt/min	Area/%
20.454	49.693
26.703	50.307

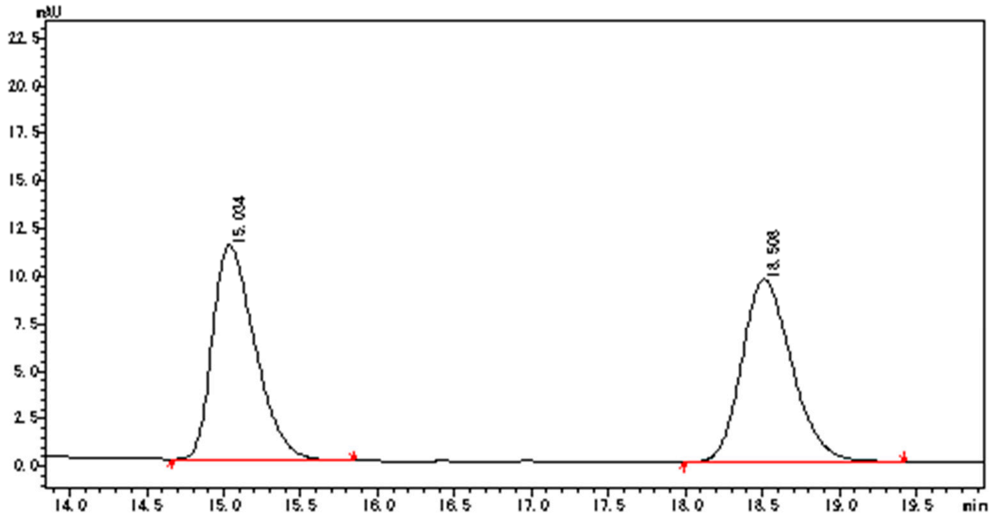


Rt/min	Area/%
20.406	87.381
26.764	12.620

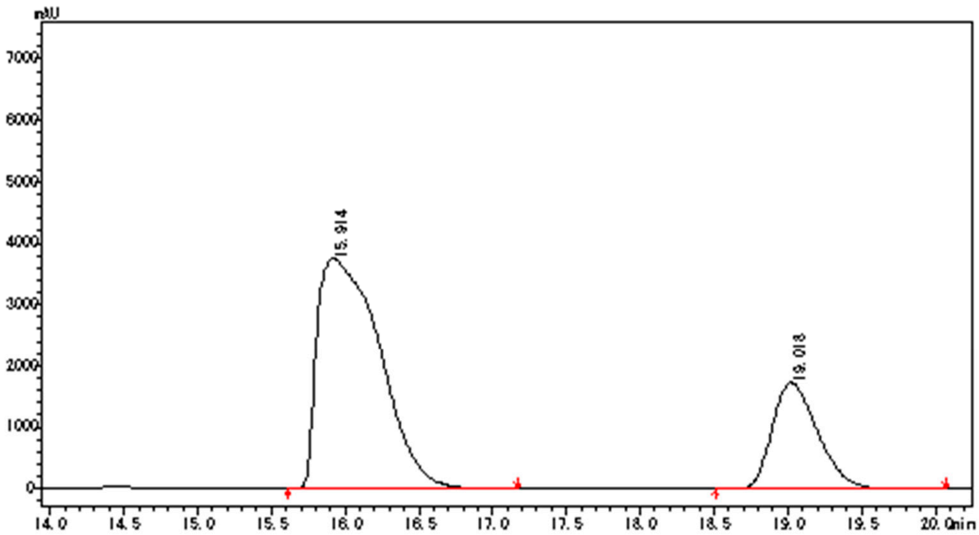


4e, 50% *ee*

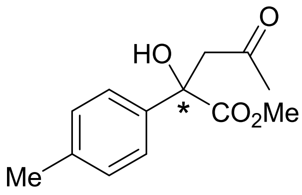
DAICEL CHIRALPAK AD-H, *n*-hexane /^{i}PrOH = 97/3, 1.0 mL/min, 254 nm, 35 °C



Rt/min	Area/%
15.034	49.954
18.508	50.046

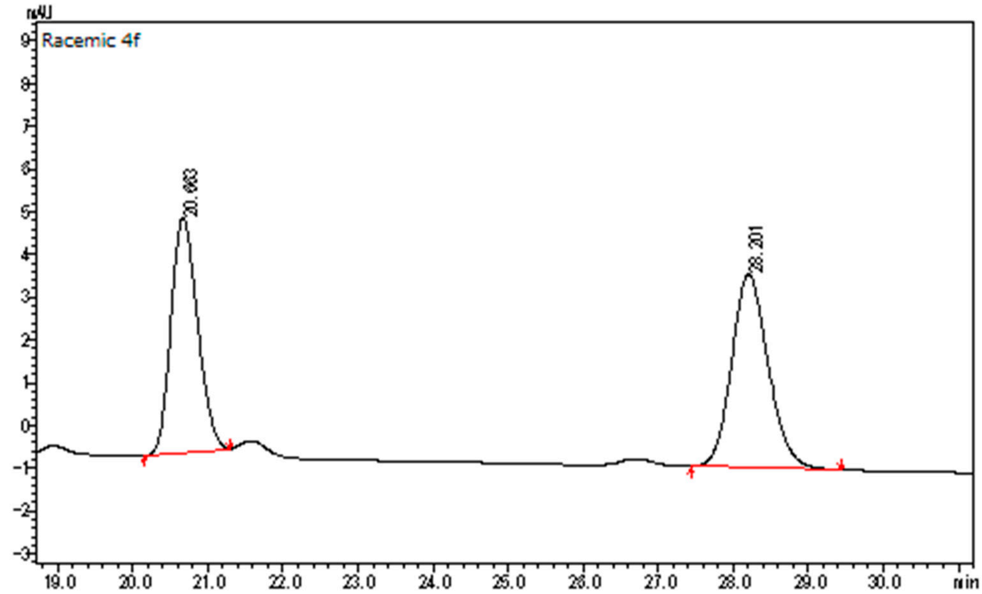


Rt/min	Area/%
15.914	74.939
19,018	25.061

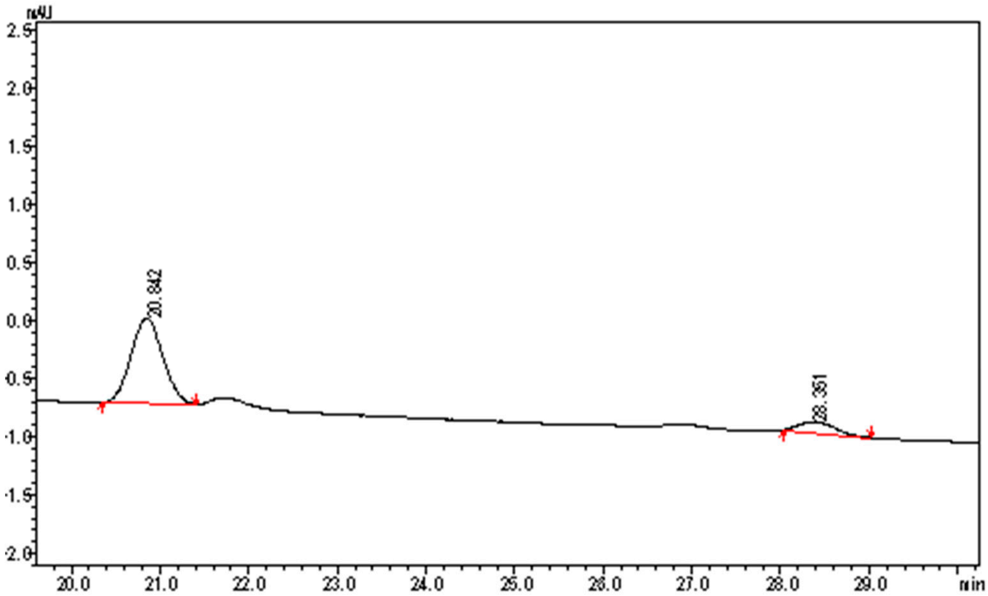


4f, 75% *ee*

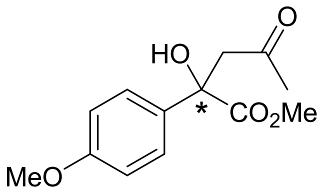
DAICEL CHIRALPAK OD-H, *n*-hexane /^{i}PrOH = 90/10, 1.0 mL/min, 254 nm, 35 °C.



Rt/min	Area/%
20.663	46.835
28.201	53.166

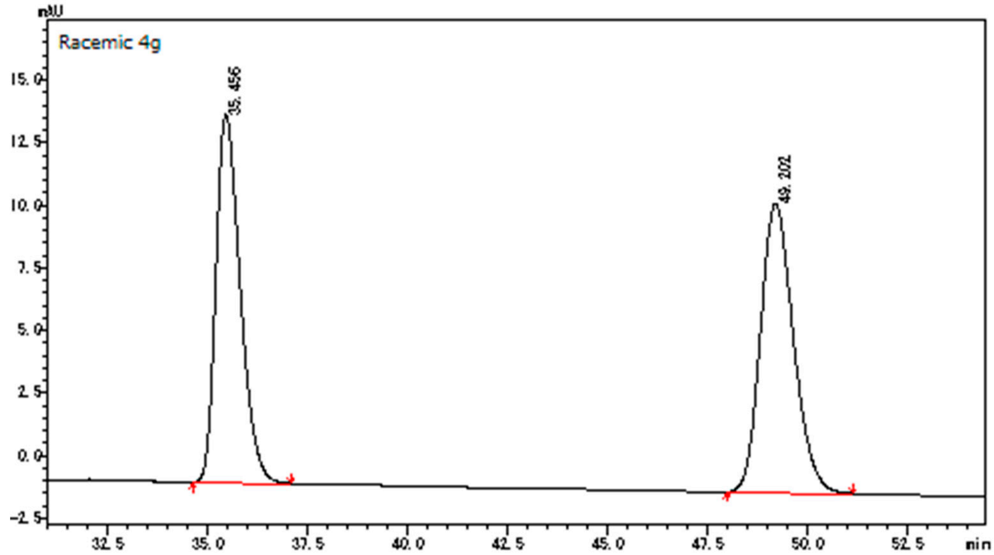


Rt/min	Area/%
20.842	87.742
28.351	12.258

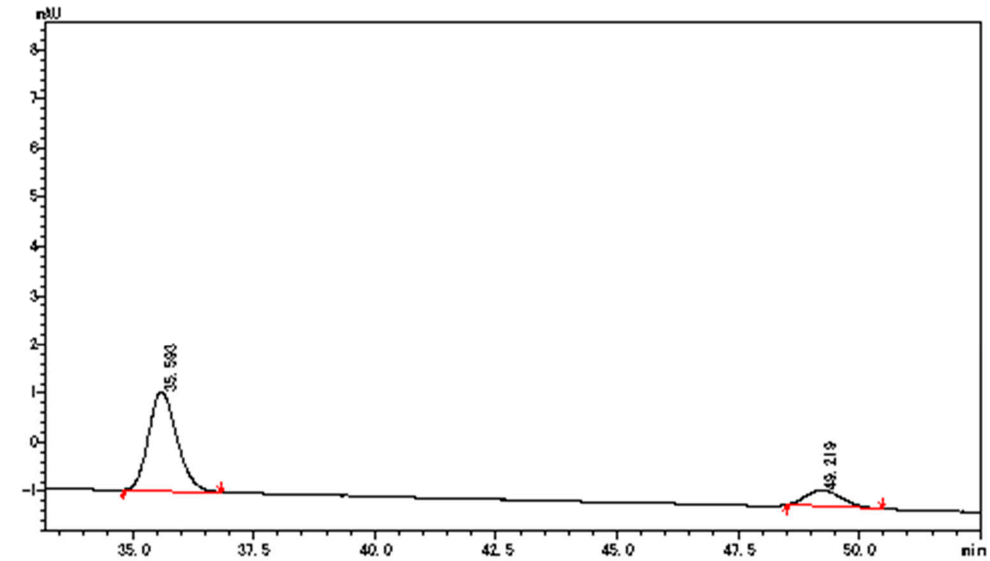


4g, 65% *ee*

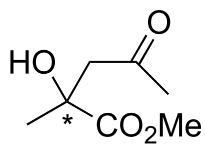
DAICEL CHIRALPAK AD-H, *n*-hexane /^{i}PrOH = 97/3, 1.0 mL/min, 254 nm, 35 °C.



Rt/min	Area/%
35.456	48.464
49.202	51.536

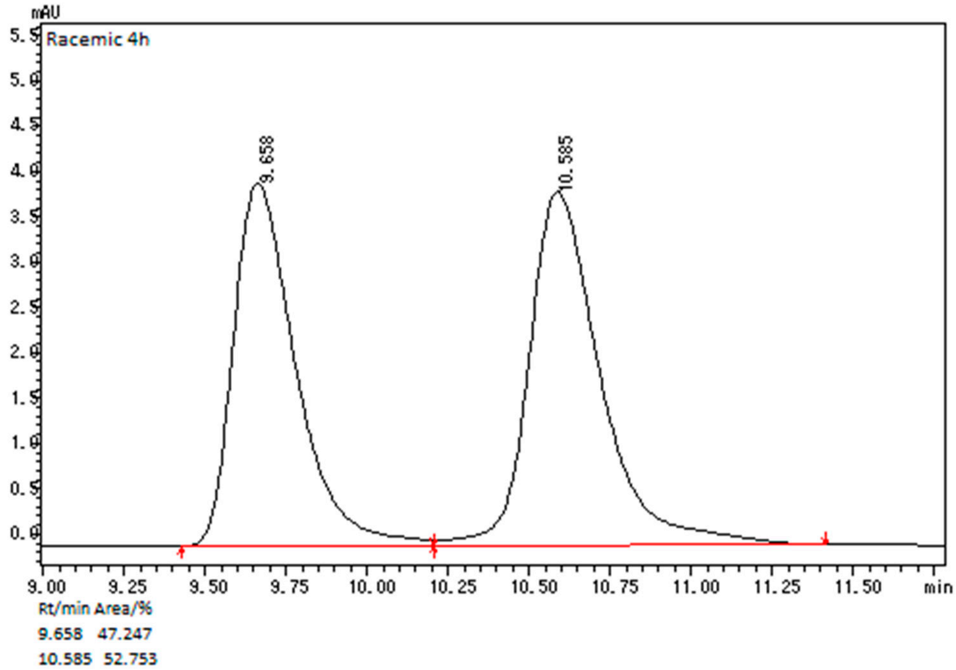


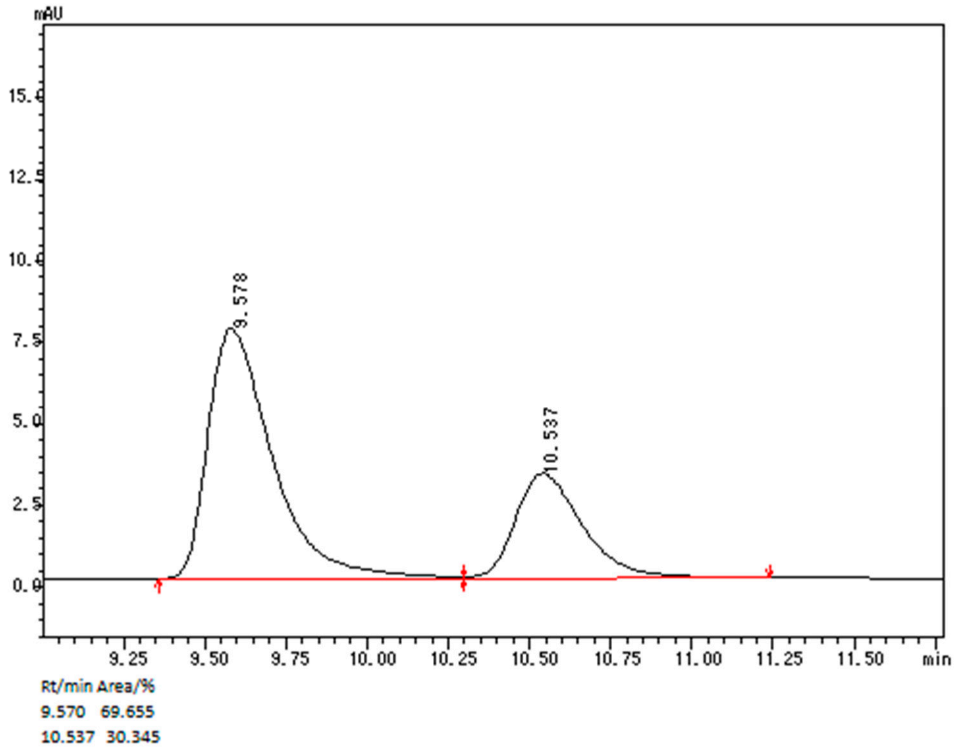
Rt/min	Area/%
35.593	82.650
49.219	17.350



4h, 39% *ee*

DAICEL CHIRALPAK OD-H, *n*-hexane /^{i}PrOH = 90/10, 1.0 mL/min, 234 nm, 35 °C.





9. Geometries and Cartesian Coordinates

3a-TS-(*R*)

E = -1507.37468331 a.u.

(B3LYP/6-31G(d',p'))

227.30 i cm^{-1}

E = -1507.39991319 a.u.

(CPCM/B3LYP/6-31G(d',p'))

H	-2.373004	-0.210450	0.000000
N	-1.412538	-0.408382	0.291295
C	-0.605568	-1.177153	-0.480110
C	-0.900409	0.331682	1.440120
O	0.568136	-1.426277	-0.248611
C	-1.234079	-1.784653	-1.764097
N	-2.674370	-1.511637	-1.966298
C	-0.575573	-1.175502	-3.017803
C	-2.885642	-0.504204	-3.044582
C	-1.478625	0.023543	-3.338551
H	-1.052919	-2.861597	-1.700979
H	0.466083	-0.915386	-2.818658
H	-0.599141	-1.905654	-3.836167
H	-1.257221	0.869899	-2.679232
H	-3.568720	0.276536	-2.713598
H	-3.321027	-1.017660	-3.913786
H	-1.384509	0.371627	-4.370886
C	-3.669369	-2.182755	-1.376738
C	-5.009083	-1.776114	-1.522374
C	-3.318284	-3.305185	-0.434439
H	-5.282503	-1.184871	-2.388808
H	-5.769628	-2.464457	-1.171767
H	-2.580777	-2.990553	0.312133
H	-4.212857	-3.655672	0.081597
H	-2.884517	-4.146164	-0.991239
H	0.157650	0.094233	1.556048
C	-1.029819	1.848452	1.215006
H	-1.444797	0.037308	2.347849
N	-2.324945	2.303348	1.172028
O	-0.060333	2.573297	1.076619
H	-3.079194	1.624656	1.189785
C	-2.621019	3.643383	0.705888
C	-2.778358	3.815098	-0.818631
O	-3.172876	2.735999	-1.529237
O	-2.584408	4.875070	-1.353534
H	-3.438755	1.973298	-0.967029
C	-5.137591	-0.220420	-0.142738
O	-4.091449	0.502058	-0.275929
C	-5.199013	-1.075544	1.149186
O	-5.861837	-2.072882	1.335663
O	-4.403467	-0.539640	2.094994
H	-3.546128	4.000372	1.175755
H	-1.809597	4.308663	1.006863
C	-6.480808	0.328300	-0.587657
C	-7.698650	-0.320759	-0.319747
C	-6.501395	1.548912	-1.281740
C	-7.709819	2.105286	-1.699393
C	-8.903919	0.241664	-0.738799
C	-8.915803	1.454738	-1.430652
H	-5.570694	2.066617	-1.487839
H	-7.706584	3.053244	-2.232195
H	-7.701229	-1.263207	0.217411
H	-9.837777	-0.271769	-0.521891
H	-9.857496	1.890365	-1.756121
C	-4.423125	-1.214696	3.368787
H	-5.438568	-1.231956	3.775018
H	-4.065966	-2.243334	3.263067
H	-3.758643	-0.639880	4.014992

3a-TS-(*S*)

E = -1507.371746151 a.u.

(B3LYP/6-31G(d',p'))

225.96 i cm^{-1}

E = -1507.39749766 a.u.

(CPCM/B3LYP/6-31G(d',p'))

C	-1.052250	-0.166909	0.000000
O	0.139822	-0.168924	0.473539
C	-1.509203	1.131232	-0.718620
O	-0.650035	2.124294	-0.455359
H	1.280998	-1.615612	0.777766
N	1.935557	-2.274533	1.204663
C	2.450394	-3.293185	0.475422
C	2.434684	-1.952414	2.538287
O	3.251124	-4.121778	0.881696
C	1.987098	-3.399015	-1.005460
N	1.065312	-2.336446	-1.467327
C	3.201063	-3.237815	-1.938512
C	1.798653	-1.302337	-2.254913
C	3.269856	-1.718483	-2.146455
H	1.521870	-4.382607	-1.111327
H	4.094361	-3.670786	-1.484313
H	3.006426	-3.751778	-2.887948
H	3.730881	-1.229147	-1.281487
H	1.617400	-0.302938	-1.859179
H	1.435962	-1.346615	-3.290915
H	3.837442	-1.428098	-3.034771
C	-0.265385	-2.379866	-1.378120
C	-1.055763	-1.273156	-1.751669
C	-0.905542	-3.574958	-0.725580
H	-0.628052	-0.549663	-2.438033
H	-2.114103	-1.454176	-1.898811
H	-1.981936	-3.425516	-0.637302
H	-0.726594	-4.481061	-1.318631
H	-0.498199	-3.746251	0.277339
H	3.188719	-2.692977	2.807421
C	3.100453	-0.563568	2.544767
H	1.616009	-1.987977	3.271047
N	2.228969	0.481523	2.359190
O	4.301374	-0.419443	2.690944
H	1.269258	0.271349	2.106465
C	2.721819	1.809112	2.043809
C	2.963079	2.097292	0.548343
O	2.202867	1.432808	-0.341386
O	3.785327	2.901914	0.190470
H	1.446793	0.937571	0.059490
O	-2.488877	1.256962	-1.419789
H	2.016225	2.560778	2.420104
H	3.678510	1.957363	2.547466
C	-2.143365	-0.847428	0.810165
C	-1.775548	-1.479834	2.007256
C	-3.499541	-0.850516	0.437267
C	-4.450415	-1.480064	1.239815
C	-2.728995	-2.109692	2.807751
C	-4.071195	-2.114411	2.425878
H	-3.805842	-0.347488	-0.473586
H	-5.495179	-1.470330	0.937746
H	-0.733149	-1.466865	2.307017
H	-2.422175	-2.591202	3.733420
H	-4.816863	-2.602835	3.048615
C	-0.925687	3.381728	-1.101448
H	-1.021148	3.242427	-2.182039
H	-1.854505	3.812235	-0.714640
H	-0.073419	4.020500	-0.868424

3g-TS-(*R*)-1

E = -1664.62808242 a.u.

(B3LYP/6-31G(d',p'))

229.47 i cm^{-1}

E = -1664.65137075 a.u.

(CPCM/B3LYP/6-31G(d',p'))

H	1.748912	0.079826	0.000000
N	0.738927	-0.074065	-0.044190
C	0.116757	-0.311332	1.133544
C	0.232938	0.387416	-1.356171
O	-1.080149	-0.450911	1.340266
C	1.054142	-0.481564	2.370777
N	2.502550	-0.312948	2.119527
C	0.744978	0.605618	3.417258

C	2.987127	0.997906	2.640650
C	1.704783	1.738644	3.029938
H	0.847340	-1.483098	2.758828
H	-0.311258	0.879806	3.386850
H	0.976918	0.226549	4.420430
H	1.321319	2.296576	2.168637
H	3.565758	1.527924	1.886255
H	3.628078	0.802129	3.512132
H	1.881233	2.453123	3.838752
C	3.310963	-1.263921	1.639263
C	4.648601	-0.980459	1.299411
C	2.722507	-2.617271	1.334065
H	5.131860	-0.131167	1.769409
H	5.291429	-1.832559	1.109469
H	1.829249	-2.535424	0.704817
H	3.456995	-3.237950	0.820332
H	2.425981	-3.119561	2.264238
C	-1.154322	-0.095238	-1.886013
C	0.430748	1.922494	-1.362984
H	0.964197	-0.036334	-2.055005
N	1.529252	2.341816	-2.073298
O	-0.286004	2.702452	-0.756663
H	2.224954	1.646203	-2.311492
C	1.941374	3.729902	-1.996878
C	2.530188	4.203825	-0.653540
O	3.090923	3.273590	0.144108
O	2.521487	5.367387	-0.347744
H	3.145464	2.370806	-0.253165
C	4.466930	-0.132367	-0.578901
O	3.498546	0.701995	-0.548928
C	4.210928	-1.420688	-1.406353
O	4.723896	-2.507761	-1.249968
O	3.330197	-1.166770	-2.394224
H	2.690569	3.919220	-2.774406
H	1.084260	4.378585	-2.190420
C	5.895290	0.376939	-0.699350
C	6.984976	-0.472632	-0.957523
C	6.128892	1.754428	-0.564675
C	7.419262	2.269412	-0.685163
C	8.272890	0.048186	-1.080183
C	8.496674	1.419816	-0.944309
H	5.299446	2.423959	-0.365670
H	7.580162	3.339732	-0.579335
H	6.825025	-1.540756	-1.062018
H	9.104409	-0.622936	-1.282777
H	9.502093	1.822979	-1.039699
C	3.064980	-2.275288	-3.277073
H	3.987191	-2.600830	-3.767405
H	2.643464	-3.117615	-2.720776
H	2.349504	-1.901017	-4.010301
C	-1.261720	-1.620718	-1.687641
C	-2.381137	0.600038	-1.261154
C	-1.149490	0.207389	-3.403567
H	-2.416280	0.444808	-0.182418
H	-2.374366	1.675076	-1.455674
H	-3.290347	0.173627	-1.705290
H	-1.026388	1.278142	-3.605676
H	-0.346336	-0.329866	-3.925906
H	-2.101262	-0.103905	-3.848585
H	-0.381590	-2.143582	-2.086661
H	-1.372253	-1.872721	-0.629477
H	-2.141854	-2.002767	-2.219153

3g-TS-(*R*)-2

E =-1664.63230560 a.u.

(B3LYP/6-31G(d',p'))

198.29 i cm^{-1}

E = -1664.65803403 a.u.

(CPCM/B3LYP/6-31G(d',p'))

H	-0.703919	0.065312	0.000000
N	-1.695890	0.158770	-0.243128
C	-2.296664	-0.787893	-1.001626
C	-2.460466	1.298826	0.275928

O	-3.479283	-0.805028	-1.316543
C	-1.429472	-1.972829	-1.512027
N	0.004851	-1.918613	-1.161319
C	-1.889435	-3.293342	-0.872163
C	0.286573	-2.750132	0.046302
C	-1.075376	-3.349414	0.430173
H	-1.553784	-1.982979	-2.597134
H	-2.971049	-3.292894	-0.723479
H	-1.628561	-4.131122	-1.530236
H	-1.554502	-2.740824	1.203360
H	0.729995	-2.123614	0.822032
H	1.005557	-3.528959	-0.237256
H	-0.969244	-4.363882	0.824616
C	0.946084	-1.339139	-1.886306
C	2.289354	-1.284559	-1.385877
C	0.558924	-0.639602	-3.158189
H	2.585983	-2.122768	-0.761881
H	3.030179	-1.074426	-2.156043
H	-0.265331	0.061489	-2.993195
H	1.403135	-0.076863	-3.553003
H	0.233273	-1.374883	-3.906882
C	-2.696315	1.221221	1.834544
C	-1.865629	2.659579	-0.145506
H	-3.440839	1.239019	-0.206688
N	-0.594809	2.658761	-0.644925
O	-2.517023	3.686565	-0.003129
H	-0.079126	1.793803	-0.768143
C	0.110279	3.892600	-0.915113
C	1.371346	4.118817	-0.072721
O	1.690401	3.201546	0.859735
O	2.063956	5.092476	-0.245410
H	1.156146	2.385669	0.780282
C	2.319032	0.131000	-0.157739
O	1.125409	0.389699	0.303759
C	2.804629	1.248037	-1.129183
O	2.061717	1.747517	-1.952557
O	4.071425	1.620707	-0.956996
H	0.427294	3.950857	-1.961804
H	-0.577372	4.721097	-0.720725
C	3.345006	-0.347174	0.875647
C	4.629280	-0.804217	0.540088
C	2.967029	-0.341564	2.223224
C	3.848349	-0.779248	3.214462
C	5.508344	-1.244999	1.527480
C	5.120755	-1.235078	2.870606
H	1.976518	0.020515	2.478736
H	3.538994	-0.759169	4.257148
H	4.953056	-0.804940	-0.497239
H	6.500363	-1.593616	1.248886
H	5.808511	-1.577106	3.640529
C	4.510660	2.765361	-1.726440
H	4.314568	2.608569	-2.790901
H	3.989045	3.662497	-1.381208
H	5.581268	2.845340	-1.534605
C	-3.164239	-0.201729	2.199794
C	-1.401091	1.546280	2.603414
C	-3.810255	2.206567	2.243222
H	-4.010338	-0.518886	1.579086
H	-2.359423	-0.935642	2.084082
H	-3.482992	-0.228887	3.248553
H	-3.555573	3.237105	1.990675
H	-4.753452	1.961529	1.738580
H	-3.982300	2.136551	3.324740
H	-0.576905	0.885837	2.307115
H	-1.081653	2.581493	2.437386
H	-1.559001	1.420400	3.681500

3g-TS-(*S*)-1

E = -1664.62602184 a.u.

(B3LYP/6-31G(d',p'))

229.57 i cm^{-1}

E = -1664.64883060 a.u.

(CPCM/B3LYP/6-31G(d',p'))

C	-1.124627	-1.109635	-0.043784
O	-2.343794	-0.854355	-0.337370
C	-0.127903	0.080769	-0.111549
O	-0.524892	0.938658	-1.063848
H	-3.850528	-1.844746	0.324314
N	-4.771563	-2.275660	0.225099
C	-5.385913	-2.631804	1.378154
C	-5.319019	-1.918907	-1.099042
O	-6.490666	-3.137700	1.513049
C	-4.557828	-2.403218	2.684318
N	-3.301585	-1.640018	2.520080
C	-5.374971	-1.520204	3.644471
C	-3.507334	-0.204867	2.878583
C	-5.007308	-0.103181	3.182402
H	-4.356821	-3.391141	3.106706
H	-6.438223	-1.754678	3.571566
H	-5.043365	-1.694345	4.675851
H	-5.560325	0.156808	2.272059
H	-3.196450	0.456545	2.069464
H	-2.893979	0.009435	3.764383
H	-5.213280	0.664391	3.933750
C	-2.095751	-2.170520	2.291911
C	-0.978915	-1.356168	2.023918
C	-1.979135	-3.667613	2.180880
H	-1.012220	-0.315063	2.325658
H	-0.002674	-1.816333	2.120084
H	-0.959813	-3.947867	1.913960
H	-2.234668	-4.146857	3.134736
H	-2.655655	-4.065839	1.415844
C	-6.517839	-2.718101	-1.704547
C	-5.526330	-0.385470	-1.054403
H	-4.479812	-2.116483	-1.778029
N	-4.683924	0.330947	-1.864645
O	-6.343461	0.154526	-0.323064
H	-3.874079	-0.144545	-2.237535
C	-4.658926	1.778802	-1.793994
C	-3.976308	2.411644	-0.564347
O	-3.123003	1.661261	0.144105
O	-4.192625	3.562822	-0.279092
H	-2.931360	0.755306	-0.219703
O	0.876947	0.225145	0.547389
H	-4.158225	2.169422	-2.687012
H	-5.683610	2.156914	-1.792731
C	-0.514473	-2.406605	-0.548109
C	-1.333081	-3.295664	-1.258812
C	0.840638	-2.733065	-0.366198
C	1.352634	-3.927474	-0.871744
C	-0.818861	-4.491388	-1.761765
C	0.525568	-4.813111	-1.568405
H	1.491497	-2.046478	0.166926
H	2.403426	-4.165653	-0.723510
H	-2.374826	-3.035273	-1.413842
H	-1.468713	-5.169168	-2.310776
H	0.928289	-5.743554	-1.961533
C	0.289818	2.117826	-1.211321
H	0.256667	2.714806	-0.295500
H	1.326604	1.843628	-1.426792
H	-0.146056	2.672367	-2.043172
C	-6.256414	-4.226458	-1.523114
C	-7.900476	-2.349915	-1.129815
C	-6.521638	-2.395000	-3.217845
H	-5.262603	-4.510974	-1.894598
H	-6.336199	-4.514990	-0.471881
H	-6.998256	-4.801087	-2.091227
H	-6.647109	-1.322191	-3.406776
H	-5.592922	-2.718895	-3.706389
H	-7.352494	-2.915352	-3.707324
H	-7.948599	-2.540260	-0.057171
H	-8.142327	-1.298118	-1.305868
H	-8.662785	-2.964060	-1.626735

3g-TS-(*S*)-2

E =-1664.62521409 a.u.

(B3LYP/6-31G(d',p'))

252.01 i cm^{-1}

E = -1664.65222544 a.u.

(CPCM/B3LYP/6-31G(d',p'))

H	5.566038	-3.243832	0.000000
N	4.658903	-2.997706	-0.395530
C	3.970778	-3.899402	-1.139961
C	4.090358	-1.676343	-0.106685
O	2.874971	-3.698841	-1.645713
C	4.605240	-5.299410	-1.376369
N	5.840302	-5.589493	-0.621891
C	3.646104	-6.400076	-0.892656
C	5.530768	-6.339742	0.628498
C	4.007087	-6.535214	0.594709
H	4.789929	-5.368096	-2.451351
H	2.609289	-6.113874	-1.077748
H	3.856560	-7.332015	-1.431369
H	3.507624	-5.753179	1.176502
H	5.898206	-5.785769	1.495850
H	6.065697	-7.297092	0.585816
H	3.716749	-7.500166	1.019979
C	7.079601	-5.385376	-1.059416
C	8.211944	-5.593885	-0.235891
C	7.269573	-4.760180	-2.413642
H	8.086812	-6.196803	0.657116
H	9.135474	-5.770009	-0.776312
H	6.708014	-3.822503	-2.490125
H	8.325339	-4.543926	-2.582772
H	6.918212	-5.429354	-3.209459
C	3.805864	-1.468058	1.430145
C	4.909612	-0.515461	-0.710178
H	3.128347	-1.654321	-0.627234
N	6.187950	-0.795986	-1.109765
O	4.419522	0.600887	-0.805921
H	6.580192	-1.713250	-0.933115
C	7.107357	0.271985	-1.445671
C	8.087062	0.691070	-0.331929
O	8.320504	-0.181751	0.665251
O	8.640647	1.760186	-0.368829
H	7.922806	-1.063725	0.508548
H	7.707928	-0.000538	-2.324116
H	6.524544	1.158209	-1.704198
C	3.043084	-2.697919	1.962980
C	5.116399	-1.299925	2.223697
C	2.912337	-0.227406	1.632022
H	2.150620	-2.908516	1.361027
H	3.671916	-3.594735	1.971031
H	2.718767	-2.515140	2.994272
H	3.390358	0.684744	1.270792
H	1.960308	-0.337851	1.097979
H	2.685948	-0.110300	2.699294
H	5.777615	-2.167938	2.113156
H	5.675418	-0.411129	1.910452
H	4.893961	-1.188664	3.292026
C	8.541354	-3.729760	0.502944
O	7.594337	-2.913104	0.175304
C	8.442139	-4.051584	2.020394
O	7.599645	-4.746567	2.547302
O	9.325302	-3.317410	2.708801
C	9.930337	-3.495292	-0.054591
C	11.050623	-4.197386	0.417661
C	10.103596	-2.568598	-1.088598
C	11.365871	-2.343545	-1.640628
C	12.311117	-3.972667	-0.129781
C	12.473539	-3.044299	-1.163152
H	9.240864	-2.018722	-1.448509
H	11.483976	-1.612642	-2.437014
H	10.938652	-4.919886	1.223011
H	13.170489	-4.518823	0.252139
H	13.458580	-2.866660	-1.587757
C	9.183448	-3.342103	4.143482
H	9.295739	-4.362534	4.521859
H	8.200475	-2.959123	4.432546
H	9.975485	-2.696548	4.523950