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Organocatalytic Enantio- and Diastereoselective Synthesis of 3,5-Disubstituted Prolines

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General Methods.[1] NMR spectra were acquired on a 300 spectrometer, running at 300 or 500 MHz and 75.4 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR; $CDCl_3$, 77.0 ppm for ^{13}C NMR). The following abbreviations are used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; d, doublet; t, triplet; m, multiplet; bs, broad signal. ^{13}C NMR spectra were acquired on a broad band decoupled mode. For infrared (IR) spectra only characteristic bands are given in cm^{-1}. Mass spectra (MS) were recorded on a GC-MS spectrometer using electronic impact (EI) techniques (70 eV). High resolution mass spectrometry (HRMS) were recorded under chemical ionization (CI) TOF conditions using GC when necessary. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates and visualized by ultraviolet irradiation, phosphomolybdic acid or potassium permanganate reagent. Melting points (M.p.) are given in ºC. Optical rotations (α value) were measured in the specified solvent at given concentration in g/100 mL. The enantiomeric excess (e.e.) of the products were determined by chiral stationary phase HPLC using photodiode array detector and using the indicated chiral column in each case. Standards for the optimization of the HPLC conditions for the separation of the two enantiomers were synthesized using either a equimolar mixture of **3a** with the corresponding quinidine-based primary amine as catalyst or, alternatively, using benzydrylamine as catalyst.

Materials. Analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC) silica gel was used.

[1] SGIker technical support (MEC, GV/EJ and European Social Fund) is gratefully acknowledged (NMR, Elementary analysis, HRMS analysis and allocation of computational resources).

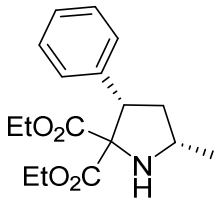
Synthesis of pyrrolidines (4a-q)

General procedure for the Michael addition/imine formation step.

The aminomalonate **1** (0.56 mmol) was added to a solution of 9-*epi*-9-amino-9-deoxycinchonidine **3a** (0.08 mmol), methanesulfonic acid (0.16 mmol), and the corresponding α,β-unsaturated ketone **2** (0.40 mmol) in THF (2 mL). The reaction was stirred at room temperature, following its evolution by ^{1}H-NMR. After consumption of the starting material, the solvent was removed obtaining the corresponding cyclic imine, which was reduced without further purification as follows.

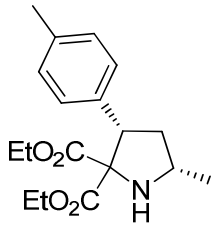
General procedure for the reduction step.

$NaBH_3CN$ (0.8 mmol) was added to a solution of the crude cyclic imine in dried EtOH (15 mL) under inert atmosphere. The mixture was stirred at room temperature for 2 hours, HCl (1 M) was added till reaching an acidic pH and it was stirred for another 10 minutes. The solvent was removed under reduced pressure and a saturated solution of NaCl (10 mL) was added, followed by the addition of NaOH (4 M), till a basic pH was observed, and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The pyrrolidines **1a-q** were obtained following this procedure, and purified by flash column chromatography with the indicated eluent.



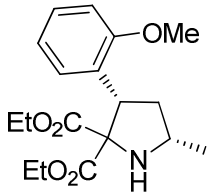
(3*S*,5*S*)-Diethyl 5-methyl-3-phenylpyrrolidine-2,2-dicarboxylate, (4a).

The pyrrolidine **4a** (110 mg, 0.36 mmol, 89%) was obtained after 42 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate **1a** (98 mg, 0.56 mmol) and (*E*)-4-phenylbut-3-en-2-one **2a** (59 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.46-7.03 (m, 5H), 4.41-4.25 (m, 2H), 4.14 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.78 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.42 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.32-3.17 (m, 1H), 2.79 (bs, 1H), 2.29 (ddd, *J* = 12.3, 7.0, 5.4 Hz, 1H), 1.82-1.67 (m, 1H), 1.35 (d, *J* = 6.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.72 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 171.3, 170.3, 140.1, 128.6, 128.0, 126.9, 77.9, 61.8, 61.5, 53.6, 50.9, 41.6, 19.9, 14.0, 13.3. FTIR (ATR, cm^{-1}): 1723 (C=O st). MS (70 eV) *m/z* (%): 232 (M^+ - CO_2Et, 100), 204 (8), 186 (2), 170 (1), 159 (11), 144 (9), 127 (11), 116 (43), 103 (3), 91 (8), 77 (3), 65 (1), 55 (4), 44 (1), 29 (6). HRMS: calculated for $[C_{17}H_{24}NO_4]^+$: 306.1705 [$(M + H)^+$]; found: 306.1706. The ee was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 10.28 min, τ_{minor} = 9.42 min (89% ee). $[\alpha]_D^{20}$: -20.8 (*c* = 1.00, CH_2Cl_2).



(3*S*,5*S*)-Diethyl 5-methyl-3-(*p*-tolyl)pyrrolidine-2,2-dicarboxylate, (4b).

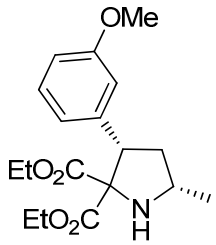
The pyrrolidine **4b** (89 mg, 0.28 mmol, 70%) was obtained after 41 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate **1a** (98 mg, 0.56 mmol) and (*E*)-4-(*p*-tolyl)but-3-en-2-one **2b** (64 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.15 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 4.35-4.17 (m, 2H), 4.09 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.74 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.41 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.27-3.11 (m, 1H), 2.74 (bs, 1H), 2.29-2.14 (m, 4H), 1.75-1.60 (m, 1H), 1.29 (d, *J* = 6.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.70 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 171.2, 170.4, 136.8, 136.3, 128.6, 128.4, 77.8, 61.6, 61.3, 53.5, 50.5, 41.6, 20.9, 19.9, 13.9, 13.2. FTIR (ATR, cm^{-1}): 1724 (C=O st). MS (70 eV) *m/z* (%): 246 (M^+ - CO_2Et, 100), 218 (4), 201 (6), 184 (1), 173 (13), 155 (13), 145 (5), 130 (38), 115 (55), 103 (4), 91 (5), 77 (3), 65 (1), 55 (4), 45 (1), 29 (5). HRMS: calculated for $[C_{18}H_{26}NO_4]^+$: 320.1862 [$(M + H)^+$]; found: 320.1862. The ee was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 14.02 min, τ_{minor} = 12.50 min (90% ee). $[\alpha]_D^{20}$: -26.8 (*c* = 1.03, CH_2Cl_2).



(3*S*,5*S*)-Diethyl 3-(2-methoxyphenyl)-5-methylpyrrolidine-2,2-dicarboxylate, (4c).

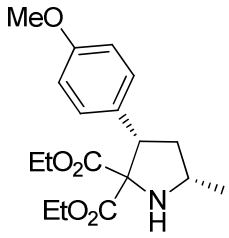
The pyrrolidine **4c** (90 mg, 0.27 mmol, 67%) was obtained after 119 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc 8:2) according to the general procedure using diethyl 2-aminomalonate **1a** (98 mg, 0.56 mmol) and (*E*)-4-(2-methoxyphenyl)but-3-en-2-one **2c** (71 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.24 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.14 (ddd, *J* = 8.2, 7.6, 1.7 Hz, 1H), 6.87-6.81 (m, 1H), 6.78 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.72 (dd, *J* = 9.8, 8.0 Hz, 1H), 4.30 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.14 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.86-3.71 (m, 4H), 3.48 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.30-3.13 (m, 1H), 2.86 (bs, 1H), 2.29 (ddd, *J* = 12.3, 8.0, 5.9 Hz, 1H), 1.76-1.62 (m, 1H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.75 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 171.1, 169.8, 157.7, 129.8, 129.1, 127.8, 120.4, 110.3, 77.6, 61.7, 61.1, 55.3, 53.5, 44.4, 41.3,

19.9, 14.0, 13.4. FTIR (ATR, cm^{-1}): 1731 (C=O st). MS (70 eV) *m/z* (%): 262 (M^+ - CO_2Et, 100), 234 (1), 216 (32), 201 (30), 186 (5), 174 (5), 155 (11), 146 (13), 127 (14), 117 (5), 107 (3), 91 (9), 77 (4), 65 (1), 55 (4), 44 (1), 29 (4). HRMS: calculated for $[C_{18}H_{26}NO_5]^+$: 336.1811 [$(M + H)^+$]; found: 336.1800. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 4.90 min, τ_{minor} = 7.39 min (89% ee). $[\alpha]_D^{20}$: +1.0 (*c* = 1.03, CH_2Cl_2).



(3*S*,5*S*)-Diethyl 3-(3-methoxyphenyl)-5-methylpyrrolidine-2,2-dicarboxylate, (4d).

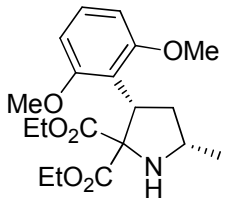
The pyrrolidine **4d** (104 mg, 0.31 mmol, 77%) was obtained after 68 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate **1a** (98 mg, 0.56 mmol) and (*E*)-4-(3-methoxyphenyl)but-3-en-2-one **2d** (71 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.30-7.21 (m, 1H), 7.15 (ddd, *J* = 8.1, 7.5, 1.7 Hz, 1H), 6.90-6.75 (m, 2H), 4.73 (dd, *J* = 9.8, 8.0 Hz, 1H), 4.31 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.15 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.86-3.72 (m, 4H), 3.49 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.31-3.14 (m, 1H), 2.87 (bs, 1H), 2.30 (ddd, *J* = 12.3, 8.0, 5.9 Hz, 1H), 1.78-1.62 (m, 1H), 1.32 (d, *J* = 6.2 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.76 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 169.6, 168.7, 157.7, 140.1, 127.3, 119.2, 112.6, 111.0, 76.2, 60.2, 59.9, 53.5, 51.9, 49.3, 40.1, 18.3, 12.4, 11.7. FTIR (ATR, cm^{-1}): 1724 (C=O st). MS (70 eV) *m/z* (%): 262 (M^+ - CO_2Et, 100), 234 (4), 216 (2), 201 (3), 188 (8), 174 (6), 161 (5), 146 (30), 127 (9), 117 (6), 103 (2), 91 (5), 77 (3), 65 (1), 55 (3), 41 (1), 29 (4). HRMS: calculated for $[C_{18}H_{26}NO_5]^+$: 336.1811 [$(M + H)^+$]; found: 336.1794. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 4.96 min, τ_{minor} = 6.91 min (89% ee). $[\alpha]_D^{20}$: -26.8 (*c* = 0.98, CH_2Cl_2).



(3*S*,5*S*)-Diethyl 3-(4-methoxyphenyl)-5-methylpyrrolidine-2,2-dicarboxylate, (4e).

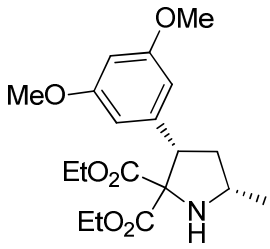
The pyrrolidine **4e** (106 mg, 0.32 mmol, 79%) was obtained after 41 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate **1a** (98 mg, 0.56 mmol) and (*E*)-4-(4-methoxyphenyl)but-3-en-2-one **2e** (71 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23

mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.19 (d, *J* = 8.7 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 4.36-4.16 (m, 2H), 4.09 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.83-3.68 (m, 4H), 3.43 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.25-3.11 (m, 1H), 2.67 (bs, 1H), 2.21 (ddd, *J* = 12.3, 7.0, 5.4 Hz, 1H), 1.74-1.59 (m, 1H), 1.29 (d, *J* = 6.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.74 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 171.3, 170.4, 158.6, 131.9, 129.5, 113.3, 77.7, 61.7, 61.4, 55.2, 53.4, 50.1, 41.6, 19.9, 13.9, 13.4. FTIR (ATR, cm^{-1}): 1722 (C=O st). MS (70 eV) *m/z* (%): 262 (M^+ - CO_2Et, 100), 234 (1), 216 (1), 201 (10), 189 (15), 174 (9), 155 (17), 146 (23), 127 (19), 115 (3), 103 (2), 91 (5), 77 (3), 65 (1), 55 (5), 42 (1), 19 (4). HRMS: calculated for $[C_{18}H_{26}NO_5]^+$: 336.1811 [$(M + H)^+$]; found: 336.1797. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 5.14 min, τ_{minor} = 7.47 min (89% ee). $[\alpha]_D^{20}$: -28.6 (*c* = 0.99, CH_2Cl_2).



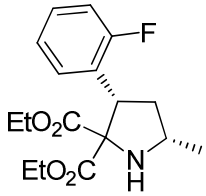
(3*S*,5*S*)-Diethyl 3-(2,6-dimethoxyphenyl)-5-methylpyrrolidine-2,2-dicarboxylate, (4f).

The pyrrolidine **4f** (92 mg, 0.25 mmol, 63%) was obtained after 97 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc 1:1) according to the general procedure using diethyl 2-aminomalonate **1a** (98 mg, 0.56 mmol) and (*E*)-4-(2,6-dimethoxyphenyl)but-3-en-2-one **2f** (82 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.07 (t, *J* = 8.3 Hz, 1H), 6.46 (d, *J* = 8.3 Hz, 2H), 5.12 (t, *J* = 9.0 Hz, 1H), 4.29 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.11 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.83-3.70 (m, 7H), 3.59 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.24-3.07 (m, 1H), 2.93 (bs, 1H), 2.17 (ddd, *J* = 12.0, 9.2, 6.7 Hz, 1H), 1.87 (ddd, *J* = 12.0, 10.3, 8.7 Hz, 1H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.74 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 171.1, 169.1, 158.6, 127.6, 118.7, 104.1, 78.7, 61.8, 60.8, 56.0, 54.7, 40.5, 40.3, 19.5, 14.0, 13.4. FTIR (ATR, cm^{-1}): 1731 (C=O st). MS (70 eV) *m/z* (%): 292 (M^+ - CO_2Et, 100), 264 (11), 246 (13), 231 (23), 215 (7), 201 (5), 191 (3), 176 (10), 155 (10), 146 (4), 127 (11), 102 (2), 91 (4), 77 (2), 55 (3), 41 (1), 29 (3). HRMS: calculated for $[C_{19}H_{28}NO_6]^+$: 366.1917 [$(M + H)^+$]; found: 366.1901. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 6.36 min, τ_{minor} = 5.27 min (77% ee). $[\alpha]_D^{20}$: -20.8 (*c* = 0.99, CH_2Cl_2).



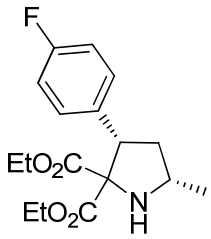
(3*S*,5*S*)-Diethyl 3-(3,5-dimethoxyphenyl)-5-methylpyrrolidine-2,2-dicarboxylate, (4g).

The pyrrolidine **4g** (98 mg, 0.27 mmol, 67%) was obtained after 29 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate **1a** (98 mg, 0.56 mmol) and (*E*)-4-(3,5-dimethoxyphenyl)but-3-en-2-one **2g** (82 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.47 (d, *J* = 2.3 Hz, 2H), 6.29 (t, *J* = 2.3 Hz, 1H), 4.32 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.22 (dd, *J* = 11.2, 7.0 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.88-3.72 (m, 7H), 3.54 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.29-3.13 (m, 1H), 2.68 (bs, 1H), 2.25 (ddd, *J* = 12.3, 7.0, 5.3 Hz, 1H), 1.76-1.59 (m, 1H), 1.32 (d, *J* = 6.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.79 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 171.2, 170.4, 160.4, 142.5, 106.6, 99.2, 77.7, 61.8, 61.5, 55.3, 53.6, 51.1, 41.7, 19.9, 14.0, 13.4. FTIR (ATR, cm^{-1}): 1724 (C=O st). MS (70 eV) *m/z* (%): 292 (M^+ - CO_2Et, 100), 246 (2), 218 (6), 204 (3), 191 (4), 176 (17), 155 (5), 127 (5), 109 (2), 91 (2), 77 (1), 55 (2), 41 (1), 29 (3). HRMS: calculated for $[C_{19}H_{28}NO_6]^+$: 366.1917 [$(M + H)^+$]; found: 366.1903. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 5.91 min, τ_{minor} = 8.39 min (87% ee). $[\alpha]_D^{20}$: -27.4 (*c* = 1.01, CH_2Cl_2).



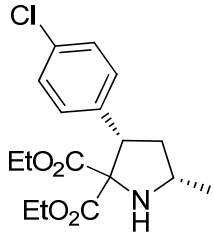
(3*S*,5*S*)-Diethyl 3-(2-fluorophenyl)-5-methylpyrrolidine-2,2-dicarboxylate, (4h).

The pyrrolidine **4h** (100 mg, 0.31 mmol, 78%) was obtained after 42 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate **1a** (98 mg, 0.56 mmol) and (*E*)-4-(2-fluorophenyl)but-3-en-2-one **2h** (66 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.32 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.22-7.09 (m, 1H), 7.09-6.89 (m, 2H), 4.62 (dd, *J* = 9.6, 7.9 Hz, 1H), 4.30 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.14 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.82 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.54 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.32-3.15 (m, 1H), 2.84 (bs, 1H), 2.35 (ddd, *J* = 12.8, 7.9, 6.0 Hz, 1H), 1.76-1.54 (m, 1H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.80 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 170.7, 169.6, 161.1 (d, $^{1}J_{CF}$ = 247.1 Hz), 129.8 (d, $^{3}J_{CF}$ = 4.1 Hz), 128.3 (d, $^{3}J_{CF}$ = 8.4 Hz), 128.1 (d, $^{2}J_{CF}$ = 13.9 Hz), 123.8 (d, $^{4}J_{CF}$ = 3.5 Hz), 115.0 (d, $^{2}J_{CF}$ = 23.1 Hz), 77.6, 61.9, 61.4, 53.3, 43.0, 41.7, 19.9, 14.0, 13.3. FTIR (ATR, cm^{-1}): 1724 (C=O st). MS (70 eV) *m/z* (%): 250 (M^+ - CO_2Et, 100), 222 (11), 201 (2), 190 (1), 176 (15), 162 (6), 149 (11), 134 (43), 109 (8), 96 (1), 81 (1), 68 (1), 55 (3), 29 (5). HRMS: calculated for $[C_{17}H_{23}FNO_4]^+$: 324.1611 [$(M + H)^+$]; found: 324.1601. The ee was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 15.79 min, τ_{minor} = 13.19 min (89% ee). $[\alpha]_D^{20}$: -31.6 (*c* = 1.03, CH_2Cl_2).



(3*S*,5*S*)-Diethyl 3-(4-fluorophenyl)-5-methylpyrrolidine-2,2-dicarboxylate, (4i).

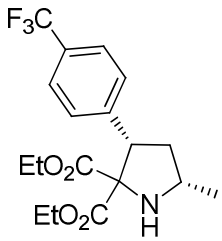
The pyrrolidine **4i** (95 mg, 0.29 mmol, 74%) was obtained after 26 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate **1a** (98 mg, 0.56 mmol) and (*E*)-4-(4-fluorophenyl)but-3-en-2-one **2i** (66 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.35-7.23 (m, 2H), 7.00-6.86 (m, 2H), 4.41-4.21 (m, 2H), 4.14 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.81 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.48 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.31-3.15 (m, 1H), 2.76 (bs, 1H), 2.27 (ddd, *J* = 12.3, 7.0, 5.4 Hz, 1H), 1.77-1.54 (m, 1H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.78 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 171.1, 170.2, 161.9 (d, $^{1}J_{CF}$ = 245.4 Hz), 135.8 (d, $^{4}J_{CF}$ = 3.2 Hz), 130.1 (d, $^{3}J_{CF}$ = 7.9 Hz), 114.7 (d, $^{2}J_{CF}$ = 21.1 Hz), 77.7, 61.8, 61.5, 53.4, 50.0, 41.7, 19.9, 13.9, 13.4. FTIR (ATR, cm^{-1}): 1724 (C=O st). MS (70 eV) *m/z* (%): 250 (M^+ - CO_2Et, 100), 222 (7), 201 (3), 188 (1), 177 (12), 155 (8), 134 (21), 127 (11), 109 (9), 88 (1), 55 (5), 44 (1), 29 (5). HRMS: calculated for $[C_{17}H_{23}FNO_4]^+$: 324.1611 [$(M + H)^+$]; found: 324.1599. The ee was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (99:1)]; flow rate 1.0 mL/min; τ_{major} = 14.52 min, τ_{minor} = 13.65 min (89% ee). $[\alpha]_D^{20}$: -26.7 (*c* = 0.99, CH_2Cl_2).



(3*S*,5*S*)-Diethyl 3-(4-chlorophenyl)-5-methylpyrrolidine-2,2-dicarboxylate, (4j).

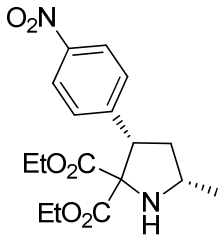
The pyrrolidine **4j** (104 mg, 0.31 mmol, 78%) was obtained after 27 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate **1a** (98 mg, 0.56 mmol) and (*E*)-4-(4-chlorophenyl)but-3-en-2-one **2j** (72 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.27-7.10 (m, 4H), 4.35-4.16 (m, 2H), 4.09 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.77 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.46 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.27-3.12 (m, 1H), 2.73 (bs, 1H), 2.23 (ddd, *J* = 12.3, 7.0, 5.4 Hz, 1H), 1.72-1.55 (m, 1H), 1.29 (d, *J* = 6.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.74 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 171.0, 170.1, 138.6, 132.6, 129.9, 128.0, 77.6, 61.8, 61.5, 53.4, 50.1, 41.4, 19.9, 14.0, 13.3. FTIR (ATR, cm^{-1}): 1724

(C=O st). MS (70 eV) *m/z* (%): 266 (M^+ - CO_2Et, 100), 238 (5), 220 (1), 193 (8), 178 (5), 165 (3), 150 (27), 138 (1), 127 (11), 115 (6), 103 (2), 89 (4), 78 (1), 55 (4), 29 (5). HRMS: calculated for $[C_{17}H_{23}ClNO_4]^+$: 340.1316 [$(M + H)^+$]; found: 340.1313. The ee was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 13.42 min, τ_{minor} = 12.14 min (89% ee). $[\alpha]_D^{20}$: -34.0 (*c* = 0.99, CH_2Cl_2).



(3*S*,5*S*)-Diethyl 5-methyl-3-(4-(trifluoromethyl)phenyl)pyrrolidine-2,2-dicarboxylate, (4k).

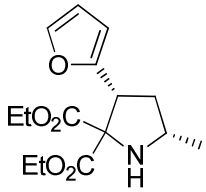
The pyrrolidine **4k** (79 mg, 0.21 mmol, 53%) was obtained after 23 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate **1a** (98 mg, 0.56 mmol) and (*E*)-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one **2k** (86 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.64-7.36 (m, 4H), 4.40-4.26 (m, 2H), 4.14 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.77 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.45 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.34-3.19 (m, 1H), 2.82 (bs, 1H), 2.30 (ddd, *J* = 12.4, 7.1, 5.4 Hz, 1H), 1.79-1.65 (m, 1H), 1.34 (d, *J* = 6.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.70 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 171.0, 170.0, 144.4, 129.3 (q, $^2J_{CF}$ = 32.5 Hz), 129.0, 124.8 (q, $^3J_{CF}$ = 3.7 Hz), 124.2 (q, $^1J_{CF}$ = 271.8 Hz), 77.7, 62.0, 61.6, 53.5, 50.4, 41.3, 19.9, 13.9, 13.2. FTIR (ATR, cm^{-1}): 1727 (C=O st). MS (70 eV) *m/z* (%): 300 (M^+ - CO_2Et, 100), 272 (13), 254 (1), 240 (1), 226 (14), 199 (15), 184 (35), 159 (5), 127 (6), 103 (1), 89 (1), 55 (4), 29 (5). HRMS: calculated for $[C_{18}H_{23}F_3NO_4]^+$: 374.1579 [$(M + H)^+$]; found: 374.1569. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 5.58 min, τ_{minor} = 6.97 min (87% ee). $[\alpha]_D^{20}$: -23.4 (*c* = 1.03, CH_2Cl_2).



(3*S*,5*S*)-Diethyl 5-methyl-3-(4-nitrophenyl)pyrrolidine-2,2-dicarboxylate, (4l).

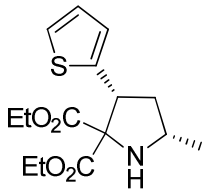
The pyrrolidine **4l** (98 mg, 0.28 mmol, 70%) was obtained after 20 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate **1a** (98 mg, 0.56 mmol) and (*E*)-4-(4-nitrophenyl)but-3-en-2-one **2l** (77 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium

cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.14-8.07 (m, 2H), 7.54-7.48 (m, 2H), 4.39-4.26 (m, 2H), 4.16 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.82 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.49 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.35-3.21 (m, 1H), 2.81 (bs, 1H), 2.35 (ddd, *J* = 12.6, 7.2, 5.5 Hz, 1H), 1.77-1.63 (m, 1H), 1.34 (d, *J* = 6.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.76 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 170.8, 169.6, 148.3, 146.9, 129.5, 128.1, 77.7, 62.1, 61.7, 53.4, 50.2, 41.4, 20.0, 14.0, 13.5. FTIR (ATR, cm^{-1}): 1724 (C=O st), 1522 (NO_2 st as), 1343 (NO_2 st sym). MS (70 eV) *m/z* (%): 277 (M^+ - CO_2Et, 100), 261 (1), 249 (8), 231 (3), 203 (6), 189 (2), 172 (1), 157 (11), 142 (5), 130 (5), 115 (8), 103 (2), 89 (3), 77 (2), 55 (2), 41 (1), 29 (4). HRMS: calculated for $[C_{17}H_{23}N_2O_6]^+$: 351.1556 [$(M + H)^+$]; found: 351.1542. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 15.16 min, τ_{minor} = 19.05 min (86% ee). $[\alpha]_D^{20}$: -29.5 (*c* = 0.98, CH_2Cl_2).



(3*S*,5*S*)-Diethyl 3-(furan-2-yl)-5-methylpyrrolidine-2,2-dicarboxylate, (4m).

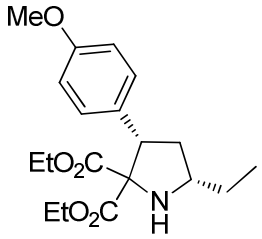
The pyrrolidine **4m** (94 mg, 0.32 mmol, 80%) was obtained after 120 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate **1a** (98 mg, 0.56 mmol) and (*E*)-4-(furan-2-yl)but-3-en-2-one **2m** (54 mg, 0.40 mmol) in the presence of trifluoroacetic acid (18 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23 mg, 0.08 mmol) and using $CHCl_3$ (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.29 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.25 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.14 (d, *J* = 3.2 Hz, 1H), 4.41-4.28 (m, 2H), 4.13 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.99 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.71 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.29-3.16 (m, 1H), 2.80 (bs, 1H), 2.24 (ddd, *J* = 12.3, 7.0, 5.4 Hz, 1H), 1.78-1.69 (m, 1H), 1.32 (d, *J* = 6.2 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 170.7, 170.3, 153.2, 141.5, 110.2, 107.1, 76.6, 62.0, 61.9, 53.8, 45.1, 39.8, 19.9, 13.9, 13.6. FTIR (ATR, cm^{-1}): 1727 (C=O st). MS (70 eV) *m/z* (%): 222 (M^+ - CO_2Et, 100), 201 (7), 176 (3), 149 (20), 127 (24), 106 (25), 91 (3), 79 (6), 67 (1), 55 (8), 41 (1), 29 (6). HRMS: calculated for $[C_{15}H_{22}NO_5]^+$: 296.1498 [$(M + H)^+$]; found: 296.1498. The ee was determined by HPLC using a Chiralcel OZ3 column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 8.99 min, τ_{minor} = 11.09 min (86% ee). $[\alpha]_D^{20}$: -26.4 (*c* = 1.01, CH_2Cl_2).



(3*S*,5*S*)-Diethyl 5-methyl-3-(thiophen-2-yl)pyrrolidine-2,2-dicarboxylate, (4n).

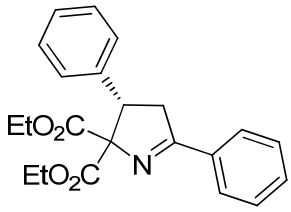
The pyrrolidine **4n** (101 mg, 0.32 mmol, 81%) was obtained after 120 hours as a yellow oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3)

according to the general procedure using diethyl 2-aminomalonate **1a** (98 mg, 0.56 mmol) and (*E*)-4-(thiophen-2-yl)but-3-en-2-one **2n** (62 mg, 0.40 mmol) in the presence of trifluoroacetic acid (18 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23 mg, 0.08 mmol) and using $CHCl_3$ (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.13 (dd, *J* = 5.0, 1.2 Hz, 1H), 6.97-6.88 (m, 2H), 4.51 (dd, *J* = 11.4, 6.7 Hz, 1H), 4.35 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.17 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.89 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.62 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.36-3.18 (m, 1H), 2.56 (bs, 1H), 2.38 (ddd, *J* = 12.1, 6.7, 5.4 Hz, 1H), 1.84-1.71 (m, 1H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 168.9, 168.2, 140.5, 124.3, 123.5, 121.9, 75.4, 59.8, 59.7, 51.4, 44.3, 40.3, 17.9, 11.9, 11.4. FTIR (ATR, cm^{-1}): 1724 (C=O st). MS (70 eV) *m/z* (%): 238 (M^+ - CO_2Et, 100), 201 (8), 190 (1), 176 (1), 165 (18), 155 (20), 137 (4), 127 (24), 110 (4), 97 (7), 82 (3), 68 (2), 55 (8), 45 (4), 29 (6). HRMS: calculated for $[C_{15}H_{22}NO_4S]^+$: 312.1270 [$(M + H)^+$]; found: 312.1269. The ee was determined by HPLC using a Chiralcel OZ3 column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 8.11 min, τ_{minor} = 10.00 min (87% ee). $[\alpha]_D^{20}$: -22.4 (*c* = 0.97, CH_2Cl_2).



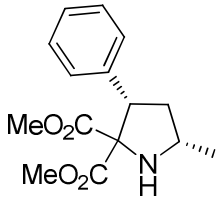
(3*S*,5*S*)-Diethyl 5-ethyl-3-(4-methoxyphenyl)pyrrolidine-2,2-dicarboxylate, (4o).

The pyrrolidine **4o** (92 mg, 0.26 mmol, 65%) was obtained after 168 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc 8:2) according to the general procedure using diethyl 2-aminomalonate **1a** (98 mg, 0.56 mmol) and (*E*)-4-(4-methoxyphenyl)pent-3-en-2-one **2o** (76 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.28-7.20 (m, 2H), 6.81-6.74 (m, 2H), 4.31 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.23-4.08 (m, 2H), 3.86-3.73 (m, 4H), 3.50 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.08-2.98 (m, 1H), 2.75 (bs, 1H), 2.28 (ddd, *J* = 12.6, 7.3, 5.6 Hz, 1H), 1.87-1.72 (m, 1H), 1.70-1.66 (m, 1H), 1.64-1.48 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.78 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 171.4, 170.4, 158.6, 132.3, 129.6, 113.3, 77.4, 61.7, 61.4, 59.5, 55.3, 49.4, 39.3, 28.2, 14.0, 13.4, 11.4. FTIR (ATR, cm^{-1}): 1722 (C=O st). MS (70 eV) *m/z* (%): 276 (M^+ - CO_2Et, 100), 246 (1), 230 (1), 216 (1), 203 (7), 186 (2), 169 (16), 141 (13), 121 (3), 104 (1), 91 (3), 69 (3), 54 (1), 29 (4). HRMS: calculated for $[C_{19}H_{28}NO_5]^+$: 350.1967 [$(M + H)^+$]; found: 350.1948. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 4.66 min, τ_{minor} = 6.86 min (89% ee). $[\alpha]_D^{20}$: -24.1 (*c* = 1.02, CH_2Cl_2).



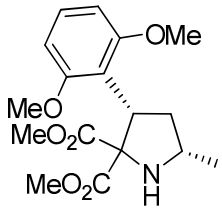
(3*S*)-Diethyl 3,5-diphenyl-3,4-dihydro-2*H*-pyrrole-2,2-dicarboxylate, (4p).

The pyrroline **4p** (34 mg, 0.09 mmol, 31%) was obtained after 192 hours as a yellow oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate **1a** (74 mg, 0.42 mmol) and (*E*)-1,3-diphenyl-2-propen-1-one **2p** (62 mg, 0.30 mmol) in the presence of methanesulfonic acid (12 mg, 0.12 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (18 mg, 0.06 mmol) and using THF (1.5 mL) as solvent. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.02-7.96 (m, 2H), 7.52-7.40 (m, 3H), 7.27-7.17 (m, 5H), 4.54 (dd, *J* = 9.0, 5.6 Hz, 1H), 4.40 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.21 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.81 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.71-3.54 (m, 2H), 3.40 (dd, *J* = 17.4, 5.6 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.84 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 177.6, 168.9, 167.5, 139.5, 133.1, 131.5, 128.4, 128.3, 128.2, 128.1, 127.2, 91.5, 62.1, 61.1, 48.3, 43.6, 13.9, 13.4. FTIR (ATR, cm^{-1}): 1729 (C=O st). MS (70 eV) *m/z* (%): 365 (1), 292 (M^+ - CO_2Et, 100), 246 (12), 233 (15), 219 (37), 191 (11), 187 (90), 165 (4), 140 (4), 115 (24), 105 (62), 91 (7), 77 (17), 65 (2). HRMS: calculated for $[C_{22}H_{24}NO_4]^+$: 366.1705 [$(M + H)^+$]; found: 366.1701. The ee was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (97:3)]; flow rate 1.0 mL/min; τ_{major} = 33.56 min, τ_{minor} = 24.49 min (58% ee).



(3*S*,5*S*)-Dimethyl 5-methyl-3-phenylpyrrolidine-2,2-dicarboxylate, (4r).

The pyrrolidine **4r** (101 mg, 0.37 mmol, 91%) was obtained after 41 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc 8:2) according to the general procedure using dimethyl 2-aminomalonate **1b** (82 mg, 0.56 mmol) and (*E*)-4-phenylbut-3-en-2-one **2a** (59 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.33-7.07 (m, 5H), 4.30 (dd, *J* = 11.3, 7.1 Hz, 1H), 3.75 (s, 3H), 3.30-3.17 (m, 1H), 3.12 (s, 3H), 2.80 (bs, 1H), 2.35-2.21 (m, 1H), 1.80-1.69 (m, 1H), 1.34 (d, *J* = 6.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 171.8, 170.7, 139.7, 128.4, 128.1, 127.0, 78.1, 53.9, 53.1, 52.3, 51.3, 41.5, 19.8. FTIR (ATR, cm^{-1}): 1727 (C=O st). MS (70 eV) *m/z* (%): 218 (M^+ - CO_2Me, 100), 184 (2), 173 (6), 158 (11), 141 (18), 131 (9), 116 (47), 103 (3), 91 (8), 77 (4), 68 (3), 59 (4), 42 (3), 28 (2). HRMS: calculated for $[C_{15}H_{20}NO_4]^+$: 278.1392 [$(M + H)^+$]; found: 278.1380. The ee was determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 11.86 min, τ_{minor} = 10.17 min (90% ee). $[\alpha]_D^{20}$: -28.0 (*c* = 1.00, CH_2Cl_2).

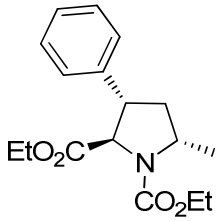


(3*S*,5*S*)-Dimethyl 3-(2,6-dimethoxyphenyl)-5-methylpyrrolidine-2,2-dicarboxylate, (4s).

The pyrrolidine **4s** (91 mg, 0.27 mmol, 67%) was obtained after 72 hours as a white solid, after isolation by flash column chromatography (hexanes/EtOAc gradient from 6:4 to 4:6) according to the general procedure using dimethyl 2-aminomalonate **1b** (82 mg, 0.56 mmol) and (*E*)-4-(2,6-dimethoxyphenyl)but-3-en-2-one **2f** (82 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine **3a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). M.p.: 118-120°C (hexanes/EtOAc 6:4). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.11 (t, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 2H), 5.18-5.12 (m, 1H), 3.78 (s, 6H), 3.76 (s, 3H), 3.25-3.14 (m, 4H), 2.18 (ddd, *J* = 12.0, 9.1, 6.6 Hz, 1H), 1.93 (ddd, *J* = 12.0, 10.4, 9.1 Hz, 1H), 1.33 (d, *J* = 6.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 171.6, 169.7, 158.5, 127.7, 118.2, 104.1, 78.7, 55.6, 54.8, 53.2, 51.8, 40.9, 40.0, 19.5. FTIR (ATR, cm^{-1}): 1727 (C=O st). MS (70 eV) *m/z* (%): 278 (M^+ - CO_2Me, 100), 246 (11), 231 (22), 216 (8), 204 (3), 191 (4), 176 (11), 161 (3), 141 (25), 113 (20), 91 (16), 77 (3), 59 (3), 42 (2), 28 (1). HRMS: calculated for $[C_{17}H_{24}NO_6]^+$: 338.1604 [$(M + H)^+$]; found: 338.1595. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 7.71 min, τ_{minor} = 6.47 min (80% ee). $[\alpha]_D^{20}$: -17.5 (*c* = 0.66, CH_2Cl_2). M.p.: 118-120ºC (hexanes/EtOAc).

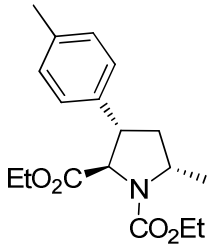
General procedure for the Synthesis of Prolines (5a-o, 5r and 5s).

MeLi (1.00 mmol) was added dropwise to a solution of the corresponding pyrrolidine **4** (1.00 mmol) in THF (10 mL) at -78ºC under inert atmosphere. The reaction was stirred at -78ºC during 1 hour and then the reaction was quenched with the dropwise addition of water (1 mL) at -78ºC. The reaction mixture was warmed to room temperature, then brine (5 mL) was added and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) yielding the desired product **5**.



(2*R*,3*S*,5*S*)-Diethyl 5-methyl-3-phenylpyrrolidine-1,2-dicarboxylate, (5a).

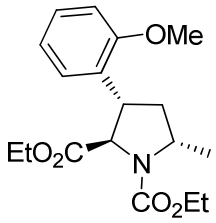
The pyrrolidine **5a** (44 mg, 0.14 mmol, 84%, dr: 7:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4a** (52 mg, 0.17 mmol), methyllithium (0.12 mL of a 1.46 M solution in diethyl ether, 0.17 mmol) and THF (1.7 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamer ratio 1.4:1, *denotes minor rotamer signals), δ 7.36-7.23 (m, 5H), 4.51* (d, *J* = 6.2 Hz, 1H), 4.43 (d, *J* = 6.6 Hz, 1H), 4.25-4.03 (m, 5H), 3.48-3.31 (m, 1H), 2.66-2.43 (m, 1H), 1.90-1.74 (m, 1H), 1.40-1.14 (m, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.6, 172.2*, 155.4*, 154.5, 140.7, 140.6*, 128.7, 127.1, 127.1, 66.7, 66.4*, 61.4*, 61.0, 60.9, 55.1, 54.2*, 47.9, 47.1*, 41.7*, 41.4, 21.5*, 20.3, 14.6*, 14.5, 14.2, 14.1*. FTIR (ATR, cm^{-1}): 1742 (C=O st), 1708 (NC=O st). MS (70 eV) *m/z* (%): 305 (1), 260 (1), 232 (M^+ - CO_2Et, 100), 216 (2), 204 (10), 188 (12), 172 (1), 160 (29), 144 (4), 129 (7), 117 (16), 104 (3), 91 (9), 77 (2), 55 (2). HRMS: calculated for $[C_{17}H_{24}NO_4]^+$: 306.1705 [$(M + H)^+$]; found: 306.1699. $[\alpha]_D^{20}$: -51.2 (*c* = 0.44, CH_2Cl_2).



(2*R*,3*S*,5*S*)-Diethyl 5-methyl-3-*p*-tolylpyrrolidine-1,2-dicarboxylate, (5b).

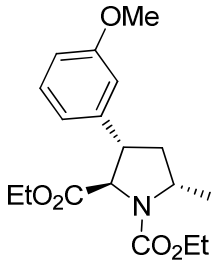
The pyrrolidine **5b** (26 mg, 0.08 mmol, 80%, dr: 10:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4b** (32 mg, 0.10 mmol), methyllithium (0.07 mL of a 1.48 M solution in diethyl ether, 0.10 mmol) and THF (1.0 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamer ratio 1.4:1, *denotes minor rotamer signals), δ 7.19-7.09 (m, 4H), 4.47* (d, *J* = 6.7 Hz, 1H), 4.40 (d, *J* = 6.9 Hz, 1H), 4.26-4.00

(m, 5H), 3.41-3.30 (m, 1H), 2.63-2.42 (m, 1H), 2.33 (s, 3H), 1.90-1.69 (m, 1H), 1.42-1.13 (m, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.6, 172.3*, 155.4*, 154.5, 137.6, 137.5*, 136.8, 136.7*, 129.3, 127.0, 66.8, 66.5*, 61.3*, 61.0, 60.9, 55.1, 54.2*, 47.6, 46.7*, 41.8*, 41.5, 21.5*, 21.0, 20.3, 14.6*, 14.5, 14.2, 14.1*. FTIR (ATR, cm^{-1}): 1743 (C=O st), 1710 (NC=O st). MS (70 eV) *m/z* (%): 319 (2), 246 (M^+ - CO_2Et, 100), 230 (4), 218 (11), 202 (12), 186 (1), 174 (29), 158 (5), 145 (5), 131 (20), 117 (7), 105 (6), 91 (7), 77 (2), 55 (2). HRMS: calculated for $[C_{18}H_{26}NO_4]^+$: 320.1862 [$(M + H)^+$]; found: 320.1852. $[\alpha]_D^{20}$: -63.2 (*c* = 0.61, CH_2Cl_2).



(2*R*,3*S*,5*S*)-Diethyl 3-(2-methoxyphenyl)-5-methylpyrrolidine-1,2-dicarboxylate, (5c).

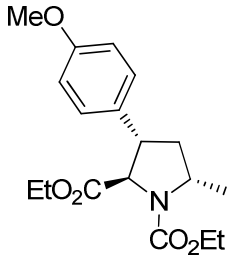
The pyrrolidine **5c** (30 mg, 0.09 mmol, 78%, dr: >20:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4c** (38 mg, 0.12 mmol), methyllithium (0.08 mL of a 1.40 M solution in diethyl ether, 0.12 mmol) and THF (1.2 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamer ratio 1.4:1, *denotes minor rotamer signals), δ 7.29-7.19 (m, 2H), 6.95-6.90 (m, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 4.63* (d, *J* = 5.4 Hz, 1H), 4.51 (d, *J* = 5.9 Hz, 1H), 4.27-4.01 (m, 5H), 3.82 (s, 3H), 3.77-3.65 (m, 1H), 2.62-2.41 (m, 1H), 1.86-1.72 (m, 1H), 1.35-1.14 (m, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.8, 172.5*, 157.0, 155.6*, 154.7, 129.3*, 129.1, 128.1, 128.0*, 127.1, 120.5, 120.4*, 110.5, 110.4*, 65.2, 65.0*, 61.3*, 60.9, 60.8, 55.2, 55.0, 54.1*, 41.8, 41.1*, 39.7*, 39.3, 21.7*, 20.6, 14.6*, 14.5, 14.2, 14.1*. FTIR (ATR, cm^{-1}): 1743 (C=O st), 1705 (NC=O st). MS (70 eV) *m/z* (%): 335 (7), 289 (4), 262 (M^+ - CO_2Et, 100), 246 (3), 233 (5), 218 (8), 203 (1), 190 (34), 174 (5), 161 (5), 147 (11), 131 (8), 115 (5), 91 (14), 77 (3), 55 (2). HRMS: calculated for $[C_{18}H_{26}NO_5]^+$: 336.1811 [$(M + H)^+$]; found: 336.1808. $[\alpha]_D^{20}$: -54.0 (*c* = 1.20, CH_2Cl_2).



(2*R*,3*S*,5*S*)-Diethyl 3-(3-methoxyphenyl)-5-methylpyrrolidine-1,2-dicarboxylate, (5d).

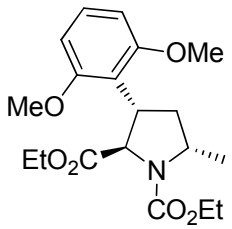
The pyrrolidine **5d** (14 mg, 0.04 mmol, 77%, dr: >20:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4d** (18 mg, 0.05 mmol), methyllithium (0.04 mL, 1.53 M solution in diethyl ether, 0.05 mmol) and THF (0.5 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamer ratio 1.4:1, *denotes minor rotamer signals), δ 7.28-7.20 (m, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 6.82-6.75 (m, 2H), 4.49* (d, *J* = 6.6 Hz, 1H),

4.43 (d, *J* = 6.8 Hz, 1H), 4.26-4.01 (m, 5H), 3.80 (s, 3H), 3.41-3.32 (m, 1H), 2.62-2.47 (m, 1H), 1.90-1.71 (m, 1H), 1.45-1.11 (m, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.6, 172.2*, 159.8, 155.4*, 154.5, 142.4, 142.3*, 129.6, 119.4, 113.3, 113.2*, 112.1, 66.6, 66.4*, 61.4*, 61.1, 61.0, 60.9*, 55.2, 55.0, 54.2*, 47.8, 47.0*, 41.7*, 41.3, 21.5*, 20.4, 14.6*, 14.5, 14.2, 14.1*. FTIR (ATR, cm^{-1}): 1742 (C=O st), 1705 (NC=O st). MS (70 eV) *m/z* (%): 335 (1), 262 (M^+ - CO_2Et, 100), 246 (4), 234 (5), 218 (7), 206 (2), 190 (18), 174 (2), 162 (3), 147 (6), 134 (3), 121 (3), 103 (1), 91 (4), 78 (1), 65 (1). HRMS: calculated for $[C_{18}H_{26}NO_5]^+$: 336.1811 [$(M + H)^+$]; found: 336.1798. $[\alpha]_D^{20}$: -47.5 (*c* = 0.99, CH_2Cl_2).



(2*R*,3*S*,5*S*)-Diethyl 3-(4-methoxyphenyl)-5-methylpyrrolidine-1,2-dicarboxylate, (5e).

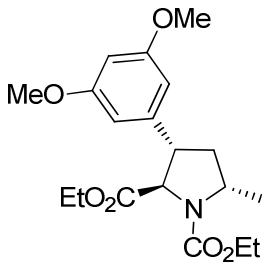
The pyrrolidine **5e** (52 mg, 0.16 mmol, 73%, dr: 6:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4e** (71 mg, 0.21 mmol), methyllithium (0.16 mL of a 1.35 M solution in diethyl ether, 0.21 mmol) and THF (2.1 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamer ratio 1.4:1, *denotes minor rotamer signals), δ 7.17 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.43* (d, *J* = 6.8 Hz, 1H), 4.35 (d, *J* = 6.9 Hz, 1H), 4.26-4.01 (m, 5H), 3.79 (s, 3H), 3.39-3.29 (m, 1H), 2.60-2.41 (m, 1H), 1.87-1.69 (m, 1H), 1.43-1.13 (m, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.6, 172.2*, 158.7, 155.4*, 154.4, 132.5, 132.4*, 128.1, 114.0, 67.0, 66.7*, 61.3*, 61.0, 60.9, 55.3, 55.0, 54.1*, 47.2, 46.4*, 41.9*, 41.6, 21.5*, 20.3, 14.6*, 14.5, 14.2, 14.1*. FTIR (ATR, cm^{-1}): 1742 (C=O st), 1705 (NC=O st). MS (70 eV) *m/z* (%): 335 (5), 262 (M^+ - CO_2Et, 100), 246 (2), 233 (9), 218 (6), 206 (5), 190 (17), 174 (3), 161 (5), 147 (15), 134 (5), 116 (9), 103 (2), 91 (7), 77 (2), 55 (2). HRMS: calculated for $[C_{18}H_{26}NO_5]^+$: 336.1811 [$(M + H)^+$]; found: 336.1795. $[\alpha]_D^{20}$: -57.4 (*c* = 1.04, CH_2Cl_2).



(2*R*,3*S*,5*S*)-Diethyl 3-(2,6-dimethoxyphenyl)-5-methylpyrrolidine-1,2-dicarboxylate, (5f).

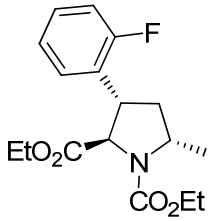
The pyrrolidine **5f** (32 mg, 0.09 mmol, 73%, dr: 3:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4f** (44 mg, 0.12 mmol), methyllithium (0.09 mL of a 1.31 M solution in diethyl ether, 0.12 mmol) and THF (1.2 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamer ratio 1.3:1, *denotes minor rotamer

signals), δ 7.16 (t, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 2H), 4.62* (d, *J* = 8.5 Hz, 1H), 4.48 (d, *J* = 8.6 Hz, 1H), 4.29-3.78 (m, 6H), 3.75 (s, 6H), 2.96-2.72 (m, 1H), 2.21-1.96 (m, 1H), 1.55-1.50 (m, 3H), 1.29* (t; *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 7.1 Hz, 3H), 0.91* (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 171.4*, 171.3, 159.6, 155.6*, 154.7, 128.3, 128.2*, 112.7*, 112.6, 103.8, 62.8*, 62.5, 61.0*, 60.8, 60.2, 55.4, 54.5, 54.0*, 38.0, 37.8*, 35.8*, 35.1, 21.2*, 20.1, 14.6, 13.8, 13.7*. FTIR (ATR, cm^{-1}): 1744 (C=O st), 1698 (NC=O st). MS (70 eV) *m/z* (%): 292 (M^+ - CO_2Et, 100), 263 (1), 246 (1), 220 (11), 204 (2), 191 (2), 177 (3), 161 (4), 147 (3), 132 (1), 121 (3), 103 (1), 91 (5), 79 (1), 68 (1), 56 (1). HRMS: calculated for $[C_{19}H_{28}NO_6]^+$: 366.1917 [(M + H)$^+$]; found: 366.1907. $[\alpha]_D^{20}$: 54.6 (*c* = 1.01, CH_2Cl_2).



(2*R*,3*S*,5*S*)-Diethyl 3-(3,5-dimethoxyphenyl)-5-methylpyrrolidine-1,2-dicarboxylate, (5g).

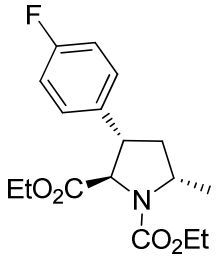
The pyrrolidine **5g** (52 mg, 0.14 mmol, 84%, dr: 10:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4g** (61 mg, 0.17 mmol), methyllithium (0.11 mL of a 1.48 M solution in diethyl ether, 0.17 mmol) and THF (1.7 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamer ratio 1.5:1, *denotes minor rotamer signals), δ 6.42 (d, *J* = 2.0 Hz, 2H), 6.35 (t, *J* = 2.0 Hz, 1H), 4.47* (d, *J* = 6.7 Hz, 1H), 4.41 (d, *J* = 6.6 Hz, 1H), 4.27-3.99 (m, 5H), 3.78 (s, 6H), 3.40-3.25 (m, 1H), 2.63-2.42 (m, 1H), 1.89-1.69 (m, 1H), 1.46-1.12 (m, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.6, 172.2*, 161.0, 155.4*, 154.5, 143.2, 143.0*, 105.4, 98.8*, 98.7, 66.5, 66.4*, 61.4*, 61.1, 61.0, 60.9*, 55.3, 55.0, 54.1*, 48.0, 47.2*, 41.6*, 41.2, 21.5*, 20.4, 14.6*, 14.4, 14.2, 14.1*. FTIR (ATR, cm^{-1}): 1742 (C=O st), 1703 (NC=O st). MS (70 eV) *m/z* (%): 365 (8), 319 (2), 292 (M^+ - CO_2Et, 100), 264 (2), 248 (5), 220 (11), 203 (2), 177 (4), 161 (2), 145 (1), 119 (1), 91 (1), 77 (1), 55 (1). HRMS: calculated for $[C_{19}H_{28}NO_6]^+$: 366.1917 [(M + H)$^+$]; found: 366.1394. $[\alpha]_D^{20}$: -47.7 (c = 0.65, CH_2Cl_2).



(2*R*,3*S*,5*S*)-Diethyl 3-(2-fluorophenyl)-5-methylpyrrolidine-1,2-dicarboxylate, (5h).

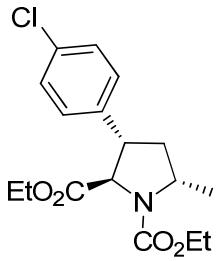
The pyrrolidine **5h** (50 mg, 0.15 mmol, 85%, dr: 17:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4h** (59 mg, 0.18 mmol), methyllithium (0.13 mL of a 1.40 M solution in diethyl ether, 0.18 mmol) and

THF (1.8 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamer ratio 1.4:1, *denotes minor rotamer signals), δ 7.34-7.29 (m, 1H), 7.26-7.19 (m, 1H), 7.14-7.09 (m, 1H), 7.07-6.98 (m, 1H), 4.59* (d, *J* = 6.0 Hz, 1H), 4.47 (d, *J* = 6.4 Hz, 1H), 4.29-4.01 (m, 5H), 3.68-3.60 (m, 1H), 2.66-2.44 (m, 1H), 1.91-1.74 (m, 1H), 1.41-1.12 (m, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.3, 171.9*, 160.8 (d, $^{1}J_{CF}$ = 246.2 Hz), 155.5*, 154.5, 128.8 (d, $^{3}J_{CF}$ = 8.2 Hz), 128.7* (d, $^{3}J_{CF}$ = 8.3 Hz), 127.9 (d, $^{3}J_{CF}$ = 3.6 Hz), 127.8 (d, $^{2}J_{CF}$ = 26.7 Hz), 124.3 (d, $^{4}J_{CF}$ = 3.4 Hz), 115.6 (d, $^{2}J_{CF}$ = 22.2 Hz), 115.5* (d, $^{2}J_{CF}$ = 22.2 Hz), 65.4, 65.1*, 61.4*, 61.2, 61.1, 61.0*, 55.0, 54.0*, 41.2, 40.4*, 40.2*, 39.8, 21.5*, 20.4, 14.6*, 14.5, 14.1, 14.0*. FTIR (ATR, cm^{-1}): 1746 (C=O st), 1709 (NC=O st). MS (70 eV) *m/z* (%): 323 (4), 250 (M^+ - CO_2Et, 100), 234 (1), 222 (10), 206 (17), 190 (1), 178 (42), 162 (5), 150 (4), 135 (14), 122 (3), 109 (11), 96 (1), 83 (1), 56 (1). HRMS: calculated for $[C_{17}H_{23}FNO_4]^+$: 324.1611 [$(M + H)^+$]; found: 324.1603. $[\alpha]_D^{20}$: -46.8 (*c* = 1.36, CH_2Cl_2).



(2*R*,3*S*,5*S*)-Diethyl 3-(4-fluorophenyl)-5-methylpyrrolidine-1,2-dicarboxylate, (5i).

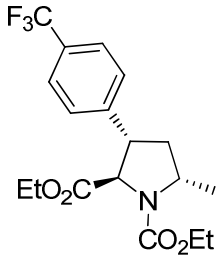
The pyrrolidine **5i** (41 mg, 0.13 mmol, 71%, dr: 6:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4i** (58 mg, 0.18 mmol), methyllithium (0.13 mL of a 1.35 M solution in diethyl ether, 0.18 mmol) and THF (1.8 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamer ratio 1.3:1, *denotes minor rotamer signals), δ 7.25-7.19 (m, 2H), 7.07-6.95 (m, 2H), 4.43* (d, *J* = 6.7 Hz, 1H), 4.36 (d, *J* = 6.9 Hz, 1H), 4.26-4.02 (m, 5H), 3.41-3.31 (m, 1H), 2.60-2.46 (m, 1H), 1.85-1.68 (m, 1H), 1.43-1.11 (m, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.4, 172.0*, 161.9 (d, $^{1}J_{CF}$ = 245.6 Hz), 155.3*, 154.4, 136.2, 128.7 (d, $^{3}J_{CF}$ = 8.0 Hz), 115.5 (d, $^{2}J_{CF}$ = 21.4 Hz), 66.9, 66.7*, 61.4*, 61.1, 61.0, 55.0, 54.1*, 47.2, 46.4*, 41.9*, 41.6, 21.4*, 20.3, 14.6*, 14.4, 14.2, 14.1*. FTIR (ATR, cm^{-1}): 1742 (C=O st), 1706 (NC=O st). MS (70 eV) *m/z* (%): 323 (1), 250 (M^+ - CO_2Et, 100), 234 (1), 222 (6), 206 (9), 178 (29), 162 (4), 150 (4), 135 (19), 122 (3), 109 (12), 95 (1), 82 (2), 68 (1), 55 (2). HRMS: calculated for $[C_{17}H_{23}FNO_4]^+$: 324.1611 [$(M + H)^+$]; found: 324.1593. $[\alpha]_D^{20}$: -47.9 (*c* = 1.01, CH_2Cl_2).



(2*R*,3*S*,5*S*)-Diethyl 3-(4-chlorophenyl)-5-methylpyrrolidine-1,2-dicarboxylate, (5j).

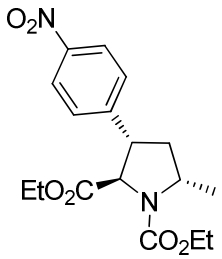
The pyrrolidine **5j** (73 mg, 0.21 mmol, 86%, dr: 7:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4j** (85 mg,

0.25 mmol), methyllithium (0.19 mL of a 1.31 M solution in diethyl ether, 0.25 mmol) and THF (2.5 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamers ratio 1.3:1, *denotes minor rotamer signals), δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 4.45* (d, *J* = 6.4 Hz, 1H), 4.38 (d, *J* = 6.8 Hz, 1H), 4.27-3.97 (m, 5H), 3.43-3.28 (m, 1H), 2.64-2.44 (m, 1H), 1.87-1.66 (m, 1H), 1.45-1.11 (m, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.3, 172.0*, 155.3*, 154.4, 139.2, 139.1*, 132.9, 128.8, 128.5, 66.6, 66.4*, 61.5*, 61.2, 61.1, 61.0*, 55.0, 54.1*, 47.3, 46.4*, 41.7*, 41.4, 21.5*, 20.3, 14.6*, 14.5, 14.2, 14.1*. FTIR (ATR, cm^{-1}): 1742 (C=O st), 1704 (NC=O st). MS (70 eV) *m/z* (%): 339 (1), 266 (M^+ - CO_2Et, 100), 252 (1), 238 (6), 222 (9), 194 (30), 181 (2), 166 (4), 151 (9), 129 (13), 115 (13), 101 (2), 82 (4), 77 (2), 55 (4). HRMS: calculated for $[C_{17}H_{23}ClNO_4]^+$: 340.1316 [(M + H)$^+$]; found: 340.1302. $[\alpha]_D^{20}$: -78.5 (*c* = 1.00, CH_2Cl_2).



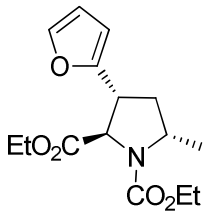
(2*R*,3*S*,5*S*)-Diethyl 5-methyl-3-(4-(trifluoromethyl)phenyl)pyrrolidine-1,2-dicarboxylate, (5k).

The pyrrolidine **5k** (39 mg, 0.10 mmol, 80%, dr: 5:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4k** (49 mg, 0.13 mmol), methyllithium (0.10 mL of a 1.31 M solution in diethyl ether, 0.13 mmol) and THF (1.3 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamer ratio 1.3:1, *denotes minor rotamer signals), δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 4.53* (d, *J* = 5.8 Hz, 1H), 4.45 (d, *J* = 6.4 Hz, 1H), 4.28-4.01 (m, 5H), 3.53-3.36 (m, 1H), 2.70-2.48 (m, 1H), 1.90-1.71 (m, 1H), 1.44-1.13 (m, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.2, 171.8*, 155.4*, 154.4, 144.9, 129.5 (q, $^{2}J_{CF}$ = 32.7 Hz), 127.6, 125.6 (q, $^{3}J_{CF}$ = 3.6 Hz), 124.0 (q, $^{1}J_{CF}$ = 272.0 Hz), 66.5, 66.2*, 61.5*, 61.2, 61.1, 61.0*, 55.0, 54.1*, 47.5, 46.7*, 41.6*, 41.2, 21.5*, 20.4, 14.6*, 14.4, 14.2, 14.1*. FTIR (ATR, cm^{-1}): 1743 (C=O st), 1706 (NC=O st). MS (70 eV) *m/z* (%): 373 (1), 300 (M^+ - CO_2Et, 100), 286 (1), 272 (4), 256 (12), 228 (28), 200 (2), 185 (4), 159 (3), 145 (1), 129 (4), 115 (1), 82 (1), 55 (1). HRMS: calculated for $[C_{18}H_{23}F_3NO_4]^+$: 374.1579 [(M + H)$^+$]; found: 374.1565. $[\alpha]_D^{20}$: -55.1 (*c* = 1.00, CH_2Cl_2).



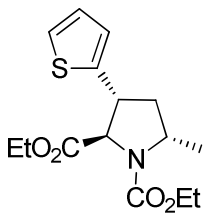
(2*R*,3*S*,5*S*)-Diethyl 5-methyl-3-(4-nitrophenyl)pyrrolidine-1,2-dicarboxylate, (5l).

The pyrrolidine **5l** (13 mg, 0.04 mmol, 60%[2], dr: 7:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4l** (54 mg, 0.15 mmol), methyllithium (0.10 mL of a 1.53 M solution in diethyl ether, 0.15 mmol) and THF (1.5 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamer ratio 1.1:1, *denotes minor rotamer signals), δ 8.20 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 4.55* (d, *J* = 6.5 Hz, 1H), 4.47 (d, *J* = 6.3 Hz, 1H), 4.27-4.08 (m, 5H), 3.58-3.41 (m, 1H), 2.71-2.51 (m, 1H), 1.89-1.75 (m, 1H), 1.40-1.19 (m, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 171.9, 171.6*, 155.4*, 154.3, 148.4, 147.1, 128.1, 124.0, 66.3, 66.1*, 61.6*, 61.3, 61.3, 61.2*, 55.0, 54.1*, 47.5, 46.6*, 41.6*, 41.2, 21.5*, 20.4, 14.6*, 14.5, 14.2, 14.2*. FTIR (ATR, cm^{-1}): 1742 (C=O st), 1705 (NC=O st), 1521 (NO_2 st as), 1346 (NO_2 st sym). MS (70 eV) *m/z* (%): 277 (M^+ - CO_2Et, 100), 261 (2), 249 (4), 233 (13), 205 (39), 187 (10), 177 (2), 159 (8), 143 (2), 129 (12), 115 (10), 103 (2), 91 (4), 77 (2), 55 (2). HRMS: calculated for $[C_{17}H_{23}N_2O_6]^+$: 351.1556 [$(M + H)^+$]; found: 351.1540. $[\alpha]_D^{20}$: -72.7 (*c* = 0.61, CH_2Cl_2).



(2*R*,3*S*,5*S*)-Diethyl 3-(furan-2-yl)-5-methylpyrrolidine-1,2-dicarboxylate, (5m).

The pyrrolidine **5m** (29 mg, 0.10 mmol, 78%, dr: 9:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4m** (37 mg, 0.13 mmol), methyllithium (0.10 mL of a 1.31 M solution in diethyl ether, 0.13 mmol) and THF (1.3 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamer ratio 1.3:1, *denotes minor rotamer signals), δ 7.36-7.31 (m, 1H), 6.36-6.25 (m, 1H), 6.20-6.12 (m, 1H), 4.60* (d, *J* = 4.4 Hz, 1H), 4.53 (d, *J* = 4.7 Hz, 1H), 4.26-4.00 (m, 5H), 3.53-3.40 (m, 1H), 2.60-2.40 (m, 1H), 2.04-1.87 (m, 1H), 1.32-1.12 (m, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.2, 171.9*, 155.4*, 154.4, 154.2*, 154.1, 141.8, 110.3, 105.7, 105.6*, 64.5, 61.4*, 61.3, 61.2, 61.0*, 54.6, 53.7*, 41.5, 40.6*, 37.3*, 36.9, 21.4*, 20.4, 14.6*, 14.5, 14.2, 14.1*. FTIR (ATR, cm^{-1}): 1735 (C=O st), 1703 (NC=O st). MS (70 eV) *m/z* (%): 295 (16), 250 (1), 222 (M^+ - CO_2Et, 100), 206 (4), 194 (9), 178 (12), 162 (1), 150 (32), 134 (4), 122 (7), 107 (12), 94 (5), 79 (8), 68 (2), 55 (3). HRMS: calculated for $[C_{15}H_{22}NO_5]^+$: 296.1498 [$(M + H)^+$]; found: 296.1489. $[\alpha]_D^{20}$: -47.3 (*c* = 1.01, CH_2Cl_2).

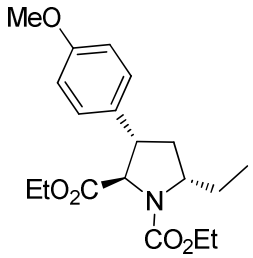


(2*R*,3*S*,5*S*)-Diethyl 5-methyl-3-(thiophen-2-yl)pyrrolidine-1,2-dicarboxylate, (5n).

The pyrrolidine **5n** (52 mg, 0.17 mmol, 84%, dr: 13:1) was obtained after 1 hour as a

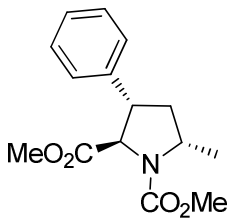
[2] Calculated yield over a conversion of 40%.

colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4n** (62 mg, 0.20 mmol), methyllithium (0.14 mL of a 1.48 M solution in diethyl ether, 0.20 mmol) and THF (2.0 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamer ratio 1.4:1, *denotes minor rotamer signals), δ 7.22-7.16 (m, 1H), 6.96-6.90 (m, 2H), 4.50* (d, *J* = 6.1 Hz, 1H), 4.43 (d, *J* = 6.3 Hz, 1H), 4.26-3.99 (m, 5H), 3.69-3.62 (m, 1H), 2.71-2.52 (m, 1H), 1.98-1.79 (m, 1H), 1.42-1.13 (m, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.1, 171.8*, 155.2*, 154.3, 144.3, 126.9, 124.3, 124.2*, 124.0, 67.3, 67.2*, 61.4*, 61.2, 61.1, 61.0*, 54.9, 54.0*, 43.3, 42.6*, 42.1*, 41.7, 21.4*, 20.3, 14.6*, 14.5, 14.2, 14.1*. FTIR (ATR, cm^{-1}): 1742 (C=O st), 1705 (NC=O st). MS (70 eV) *m/z* (%): 311 (6), 238 (M^+ - CO_2Et, 100), 222 (4), 210 (5), 194 (5), 182 (1), 166 (15), 150 (3), 137 (3), 123 (12), 110 (3), 97 (7), 79 (2), 65 (1), 53 (1). HRMS: calculated for $[C_{15}H_{22}NO_4S]^+$: 312.1270 $[(M + H)^+]$; found: 312.1255. $[\alpha]_D^{20}$: -51.1 (*c* = 1.01, CH_2Cl_2).



(2*R*,3*S*,5*S*)-Diethyl 5-ethyl-3-(4-methoxyphenyl)pyrrolidine-1,2-dicarboxylate, (5o).

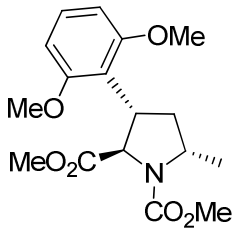
The pyrrolidine **5o** (49 mg, 0.14 mmol, 89%, dr: 6:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4o** (55 mg, 0.16 mmol), methyllithium (0.10 mL of a 1.53 M solution in diethyl ether, 0.16 mmol) and THF (1.6 mL), quenching the reaction with the dropwise addition of ^{t}BuOH (0.06 mL) in THF (1 mL) at -78ºC. ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamer ratio 1.3:1, *denotes minor rotamer signals), δ 7.17 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.38* (d, *J* = 7.1 Hz, 1H), 4.33 (d, *J* = 7.1 Hz, 1H), 4.26-4.02 (m, 4H), 4.00-3.87 (m, 1H), 3.80 (s, 3H), 3.42-3.26 (m, 1H), 2.54-2.37 (m, 1H), 2.33-2.17 (m, 1H), 2.07-1.93* (m, 1H), 1.93-1.74 (m, 1H), 1.52-1.36 (m, 1H), 1.32-1.12 (m, 6H), 0.90-0.78 (m, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.5, 172.1*, 158.7, 155.3*, 154.4, 132.5, 132.3*, 128.1, 114.0, 67.1, 66.9*, 61.3*, 61.0, 60.9, 60.5, 59.6*, 55.3, 47.3, 46.5*, 38.6*, 38.3, 27.1*, 26.1, 14.6*, 14.4, 14.2, 14.1*, 9.8, 9.6*. FTIR (ATR, cm^{-1}): 1742 (C=O st), 1706 (NC=O st). MS (70 eV) *m/z* (%): 349 (3), 320 (4), 276 (M^+ - CO_2Et, 100), 248 (7), 232 (3), 218 (1), 204 (11), 187 (1), 174 (11), 160 (2), 147 (13), 130 (12), 115 (3), 91 (5), 77 (2), 58 (1). HRMS: calculated for $[C_{19}H_{28}NO_5]^+$: 350.1967 $[(M + H)^+]$; found: 350.1949. $[\alpha]_D^{20}$: -52.2 (c = 1.00, CH_2Cl_2).



(2*R*,3*S*,5*S*)-Dimethyl 5-methyl-3-phenylpyrrolidine-1,2-dicarboxylate, (5r).

The pyrrolidine **5r** (61 mg, 0.22 mmol, 80%, dr: 10:1) was obtained after 1 hour as a

colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4r** (76 mg, 0.27 mmol), methyllithium (0.19 mL of a 1.48 M solution in diethyl ether, 0.27 mmol) and THF (2.7 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamer ratio 1.2:1, *denotes minor rotamer signals), δ 7.37-7.19 (m, 5H), 4.54* (d, *J* = 6.4 Hz, 1H), 4.47 (d, *J* = 6.4 Hz, 1H), 4.22-4.00 (m, 1H), 3.79-3.60 (m, 6H), 3.50-3.33 (m, 1H), 2.66-2.44 (m, 1H), 1.93-1.75 (m, 1H), 1.37 (d, *J* = 6.0 Hz, 3H), 1.26* (d, *J* = 6.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 173.0, 172.7*, 155.8*, 154.8, 140.6, 140.4*, 128.7, 127.2, 127.0, 66.5, 66.4*, 55.2, 54.2*, 52.6, 52.2, 47.8, 47.0*, 41.7*, 41.3, 21.4*, 20.3. FTIR (ATR, cm^{-1}): 1747 (C=O st), 1699 (NC=O st). MS (70 eV) *m/z* (%): 277 (1), 262 (1), 218 (M^+ - CO_2Et, 100), 202 (10), 186 (3), 170 (1), 158 (5), 143 (18), 128 (8), 117 (27), 103 (4), 91 (15), 77 (4), 59 (11). HRMS: calculated for $[C_{15}H_{20}NO_4]^+$: 278.1392 [$(M + H)^+$]; found: 278.1381. $[\alpha]_D^{20}$: -58.9 (*c* = 1.19, CH_2Cl_2).

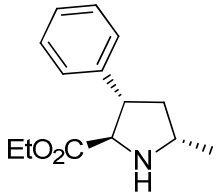


(2*R*,3*S*,5*S*)-Dimethyl 3-(2,6-dimethoxyphenyl)-5-methylpyrrolidine-1,2-dicarboxylate, (5s).

The pyrrolidine **5s** (10 mg, 0.03 mmol, 75%, dr: 3:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine **4s** (14 mg, 0.04 mmol), methyllithium (0.03 mL of a 1.53 M solution in diethyl ether, 0.04 mmol) and THF (0.4 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) (rotamer ratio 1.4:1, *denotes minor rotamer signals), δ 7.17 (t, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 8.3 Hz, 2H), 4.60* (d, *J* = 8.4 Hz, 1H), 4.48 (d, *J* = 8.5 Hz, 1H), 4.11-4.02 (m, 1H), 4.01-3.84 (m, 1H), 3.80-3.63 (m, 9H), 3.46 (s, 3H), 2.92-2.70 (m, 1H), 2.17-1.98 (m, 1H), 1.55-1.49 (m, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) (*denotes minor rotamer signals), δ 171.8, 159.5, 156.0*, 155.1, 128.4, 112.5*, 112.4, 103.8, 62.8*, 62.4, 55.5, 54.7, 54.0*, 52.3*, 52.2, 51.3, 38.0, 37.5*, 35.7*, 34.9, 21.2*, 20.1. FTIR (ATR, cm^{-1}): 1746 (C=O st), 1698 (NC=O st). MS (70 eV) *m/z* (%): 337 (2), 305 (1), 278 (M^+ - CO_2Me, 100), 262 (1), 246 (2), 219 (1), 204 (2), 188 (4), 175 (1), 161 (6), 147 (3), 134 (1), 121 (4), 105 (1), 91 (6), 77 (2), 59 (6). HRMS: calculated for $[C_{17}H_{24}NO_6]^+$: 338.1604 [$(M + H)^+$]; found: 338.1596. $[\alpha]_D^{20}$: 60.7 (*c* = 0.99, CH_2Cl_2).

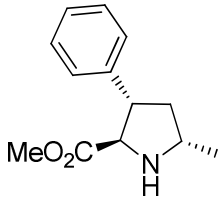
General procedure for the Synthesis of Prolines (6a-b).

Trimethylsilyl iodide (10 mmol) was added dropwise to a solution of **5a,p** (1 mmol) in dry $CHCl_3$ under inert atmosphere. The reaction mixture was refluxed for 24 h, then MeOH was added and the mixture was refluxed for 3 h more and the mixture was allowed to reach room temperature. After this time, the solvent was removed under reduced pressure, Et_2O (5 mL) and a few drops of HCl conc. were added and the solution was stirred for 10-15 min. The mixture was washed with Et_2O (3 × 20 mL). The liquid phase was basified by the addition of NH_3 (aq.), and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure, yielding the desired product **6a,b** without further purification.



(2*R*,3*S*,5*S*)-Ethyl 5-methyl-3-phenylpyrrolidine-2-carboxylate, (6a).

The pyrrolidine **6a** (36 mg, 0.15 mmol, 80%) was obtained as a colourless oil according to the general procedure starting from pyrrolidine **5a** (59 mg, 0.19 mmol), trimethylsilyl iodide (0.27 mL, 1.9 mmol) and $CHCl_3$ (10.0 mL), followed by the addition of MeOH (5.6 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.33-7.16 (m, 5H), 4.26-4.01 (m, 2H), 3.84 (d, *J* = 7.4 Hz, 1H), 3.58-3.42 (m, 1H), 3.42-3.28 (m, 1H), 2.47-2.25 (m, 2H), 1.67-1.56 (m, 1H), 1.25 (d, *J* = 6.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 175.2, 143.0, 128.5, 127.4, 126.6, 67.2, 60.9, 54.6, 50.8, 44.0, 21.2, 14.2. FTIR (ATR, cm^{-1}): 1730 (C=O st). MS (70 eV) *m/z* (%): 161 (13), 160 (M^+ - CO_2Et, 100), 144 (4), 129 (4), 117 (10), 100 (2), 91 (9), 83 (4), 73 (3), 63 (1), 55 (4). HRMS: calculated for $[C_{14}H_{20}NO_2]^+$: 234.1494 [$(M + H)^+$]; found: 234.1484. $[\alpha]_D^{20}$: -60.5 (*c* = 1.00, CH_2Cl_2).



(2*R*,3*S*,5*S*)-Methyl 5-methyl-3-phenylpyrrolidine-2-carboxylate, (6b).

The pyrrolidine **6b** (33 mg, 0.15 mmol, 70%) was obtained as a colourless oil according to the general procedure starting from pyrrolidine **5p** (61 mg, 0.22 mmol), trimethylsilyl iodide (0.30 mL, 2.2 mmol) and $CHCl_3$ (11.0 mL), followed by the addition of MeOH (6.4 mL). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.38-7.21 (m, 5H), 3.88 (d, *J* = 7.3 Hz, 1H), 3.68 (s, 3H), 3.55-3.44 (m, 1H), 3.43-3.35 (m, 1H), 2.42 (bs, 1H), 2.32 (ddd, *J* = 12.4, 7.4, 5.2 Hz, 1H), 1.66-1.55 (m, 1H), 1.25 (d, *J* = 6.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 175.8, 143.0, 128.6, 127.3, 126.7, 67.1, 54.6, 52.1, 50.6, 44.1, 21.0. FTIR (ATR, cm^{-1}): 1731 (C=O st). MS (70 eV) *m/z* (%): 204 (1), 183 (1), 160 (M^+ - CO_2Me, 100), 144 (5), 128 (5), 115 (21), 103 (3), 91 (15), 83 (12), 72 (4), 65 (3), 55 (11). HRMS: calculated for $[C_{13}H_{18}NO_2]^+$: 220.1338 [$(M + H)^+$]; found: 220.1323. $[\alpha]_D^{20}$: -66.3 (*c* = 1.01, CH_2Cl_2).

NMR spectra

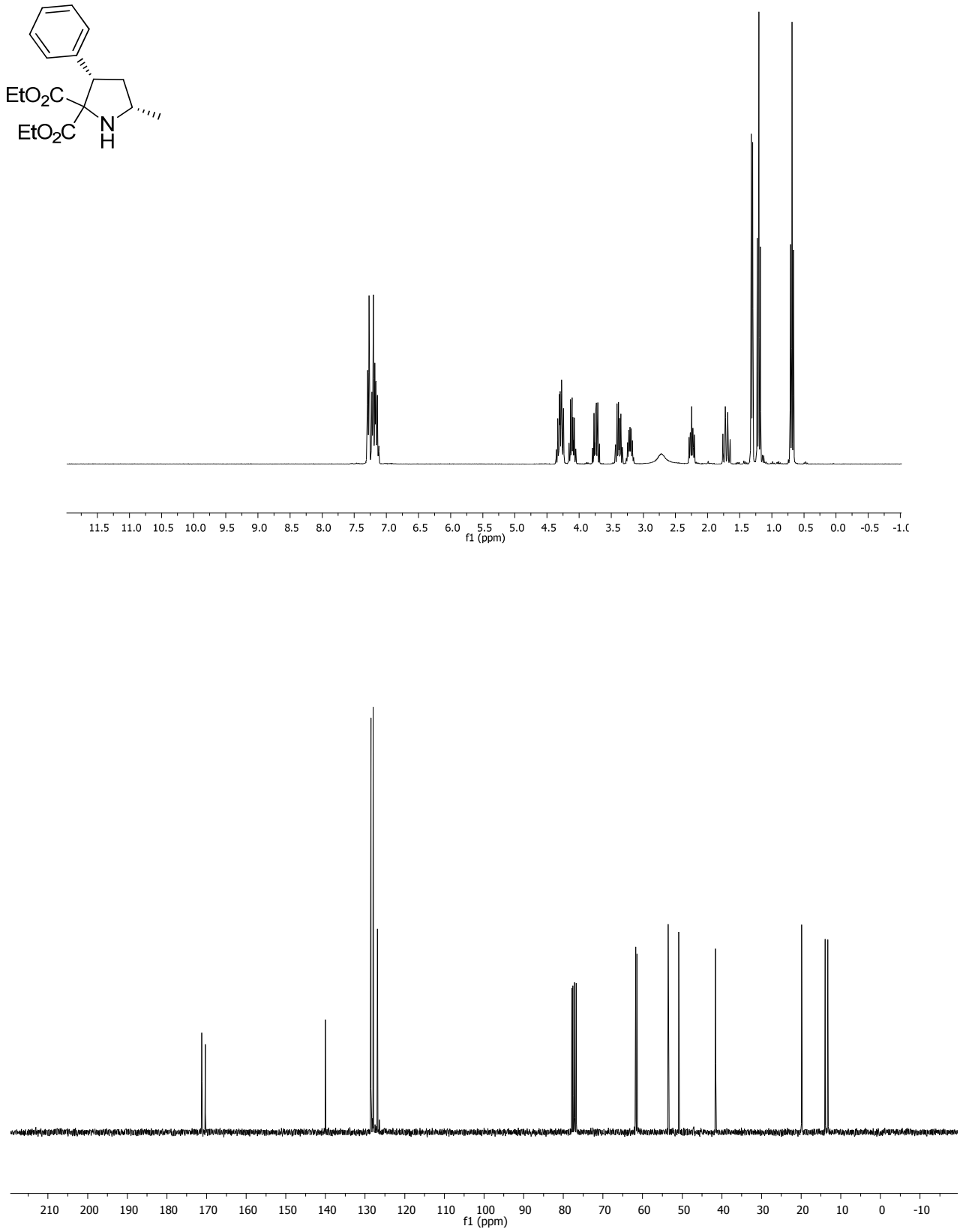


Figure 1: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4a**.

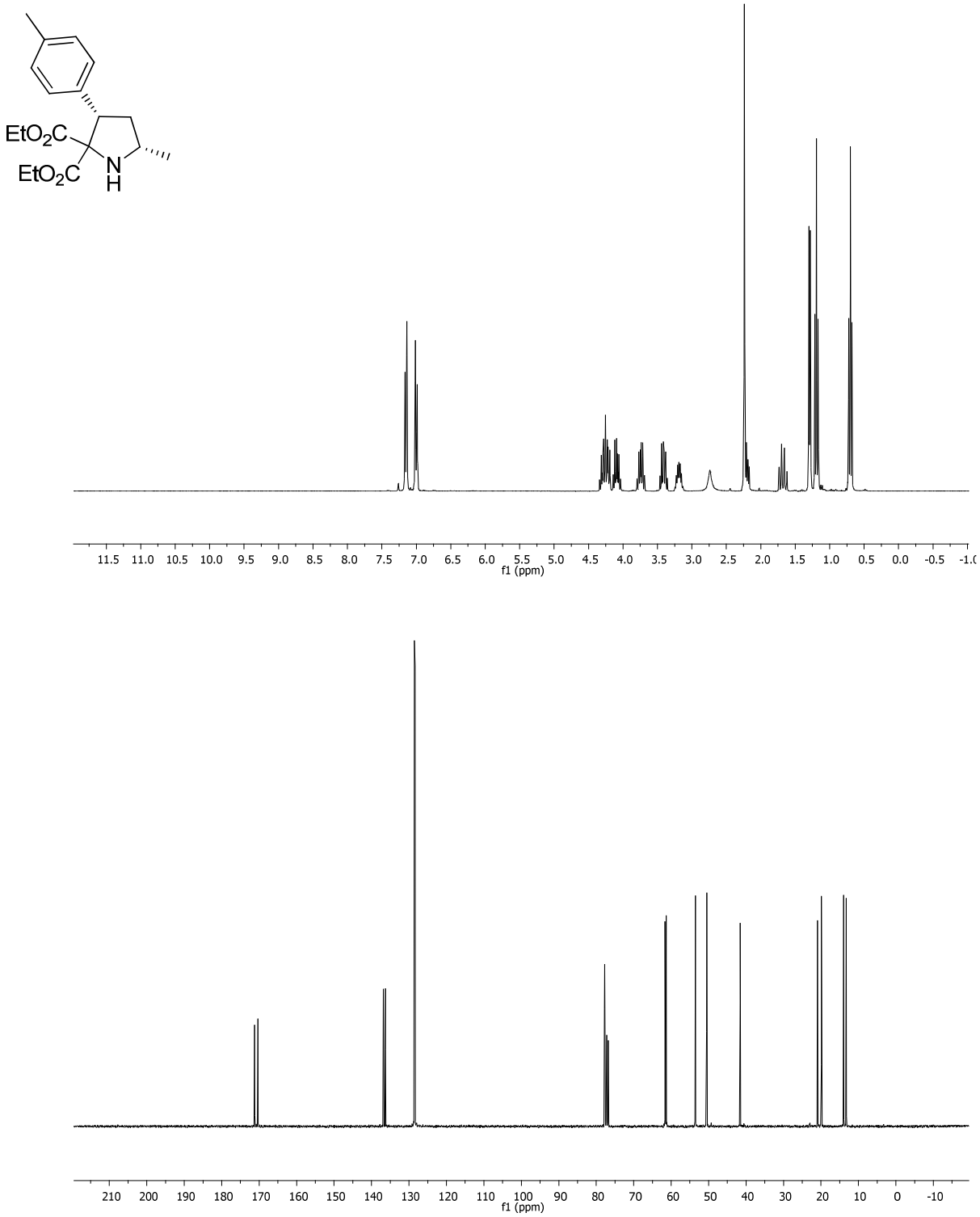


Figure 2: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4b**.

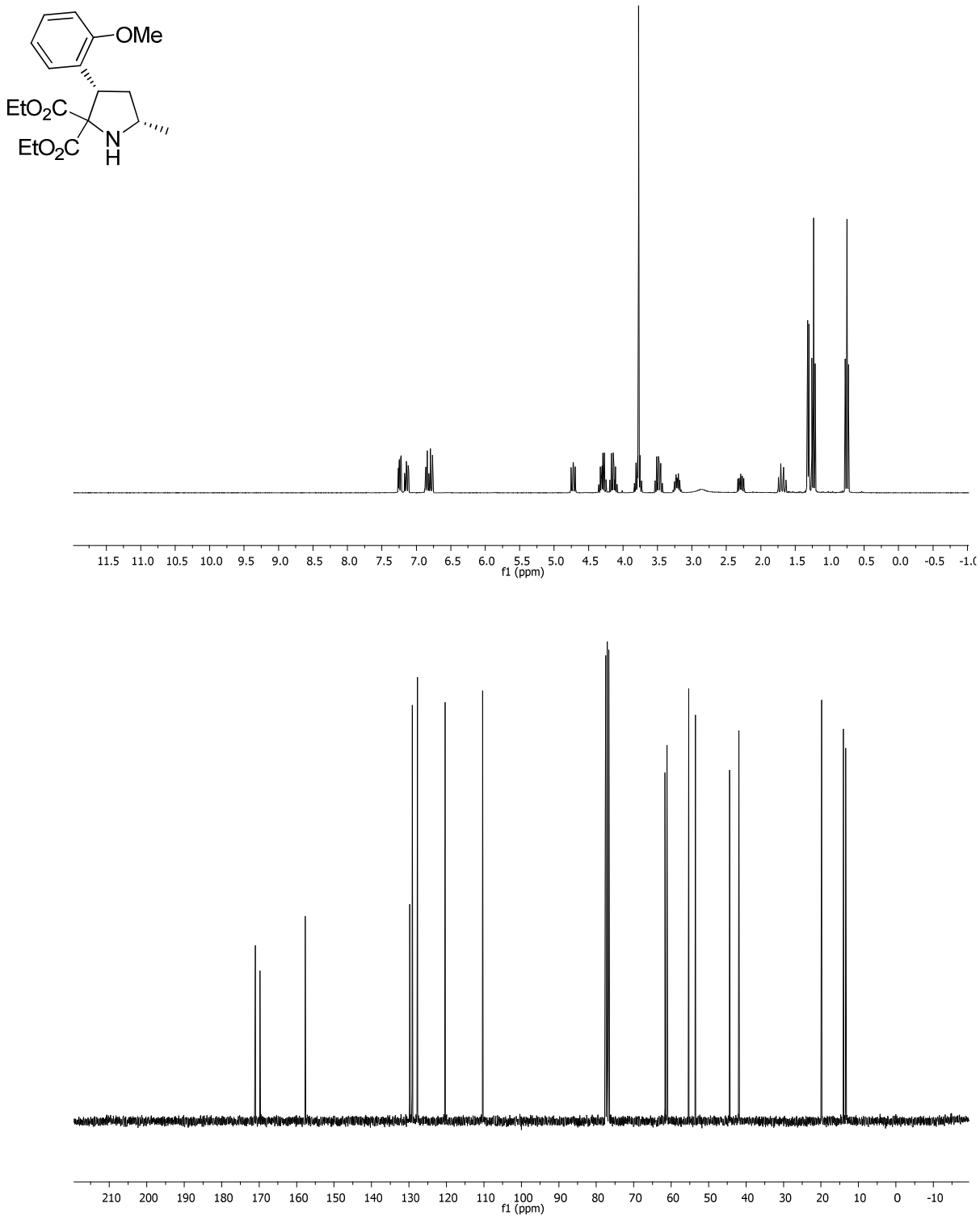


Figure 3: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4c**.

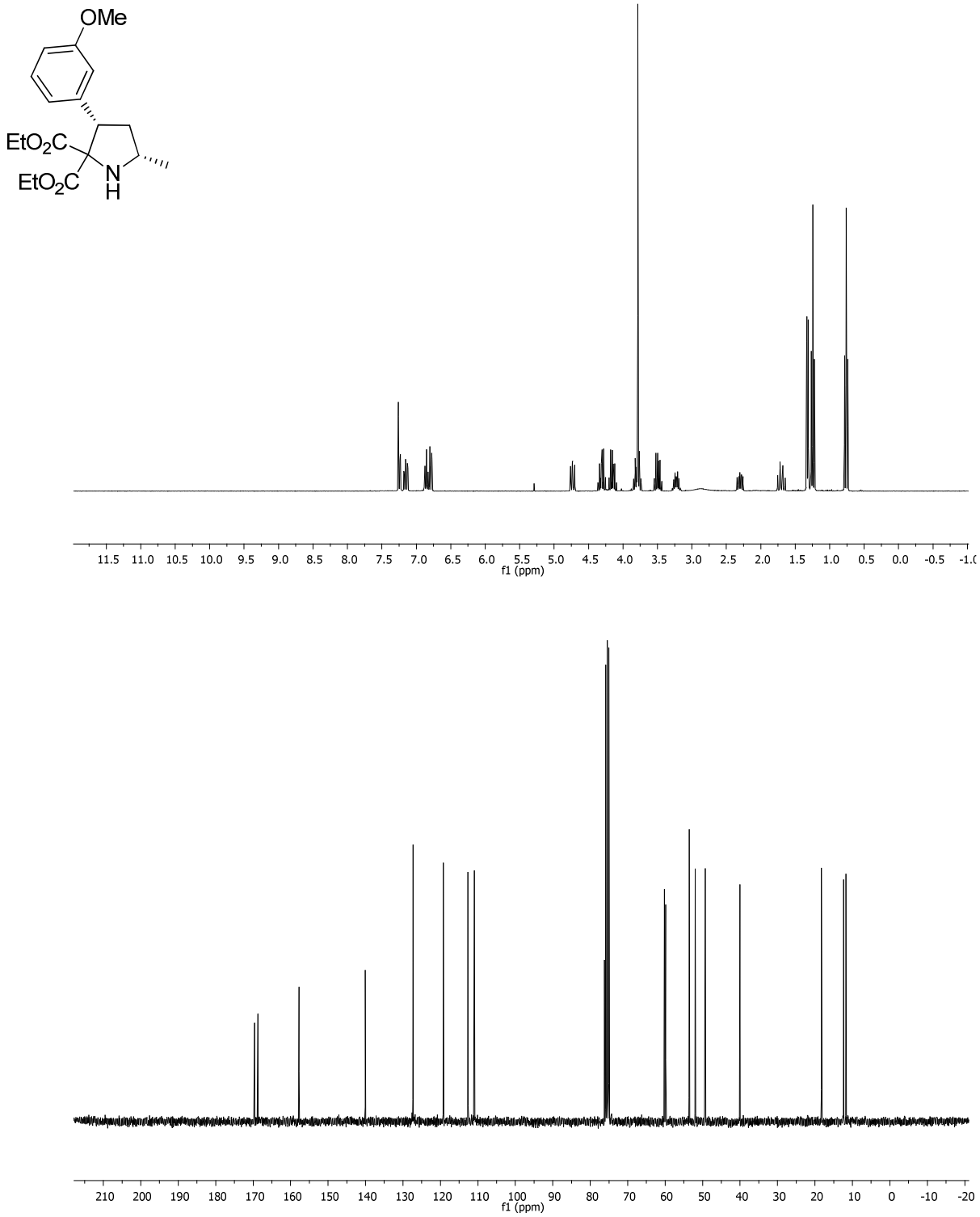


Figure 4: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4d**.

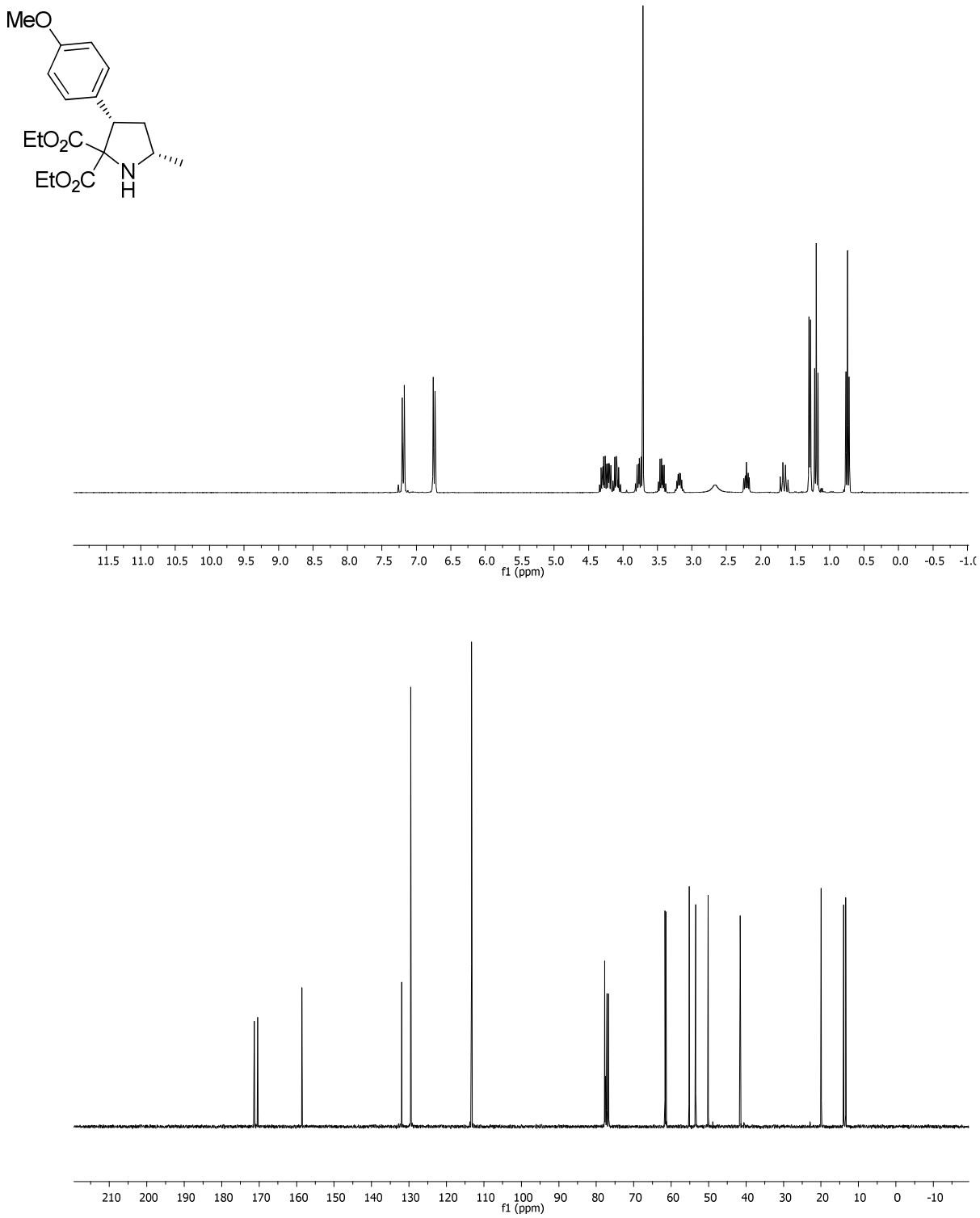


Figure 5: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4e**.

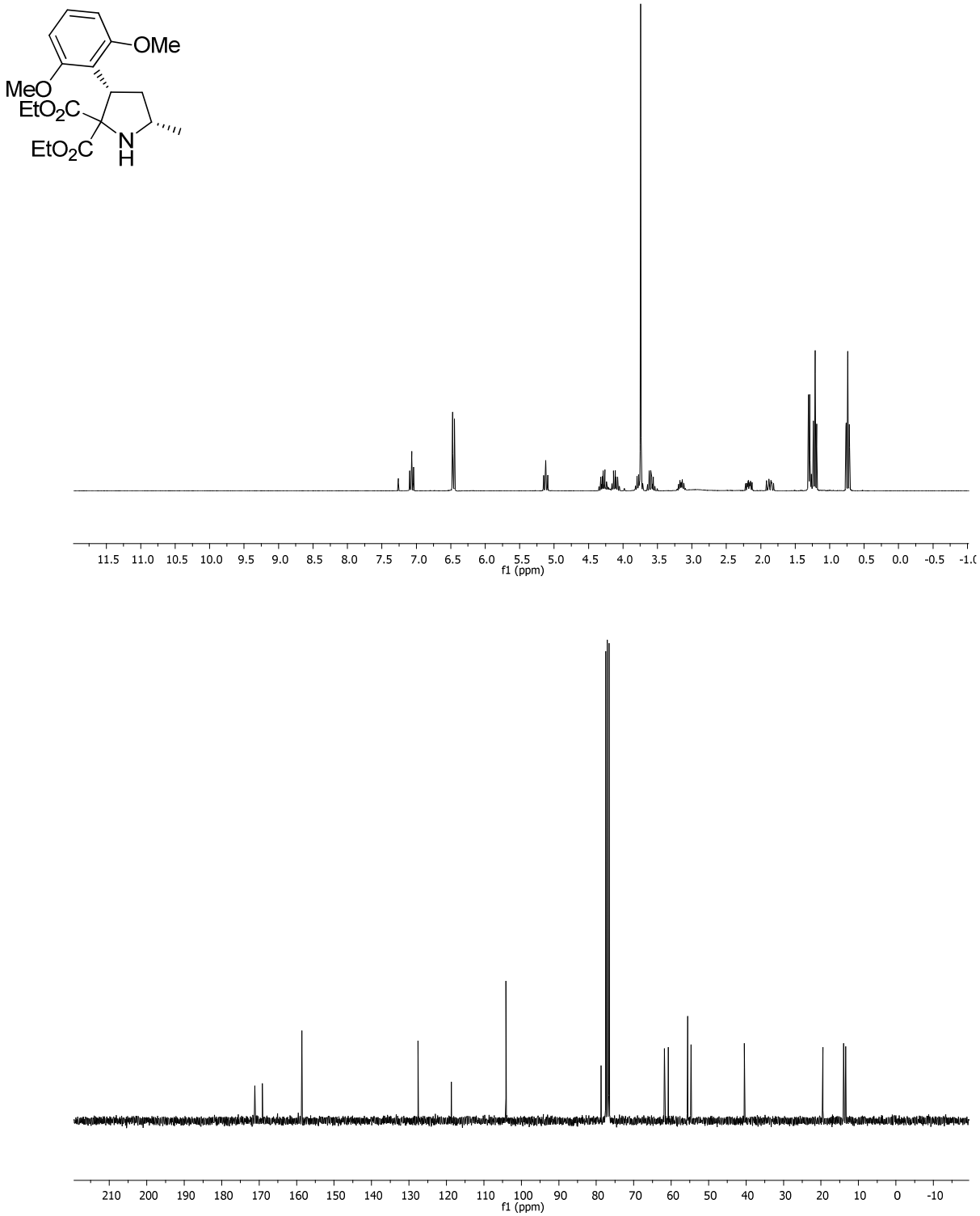


Figure 6: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4f**.

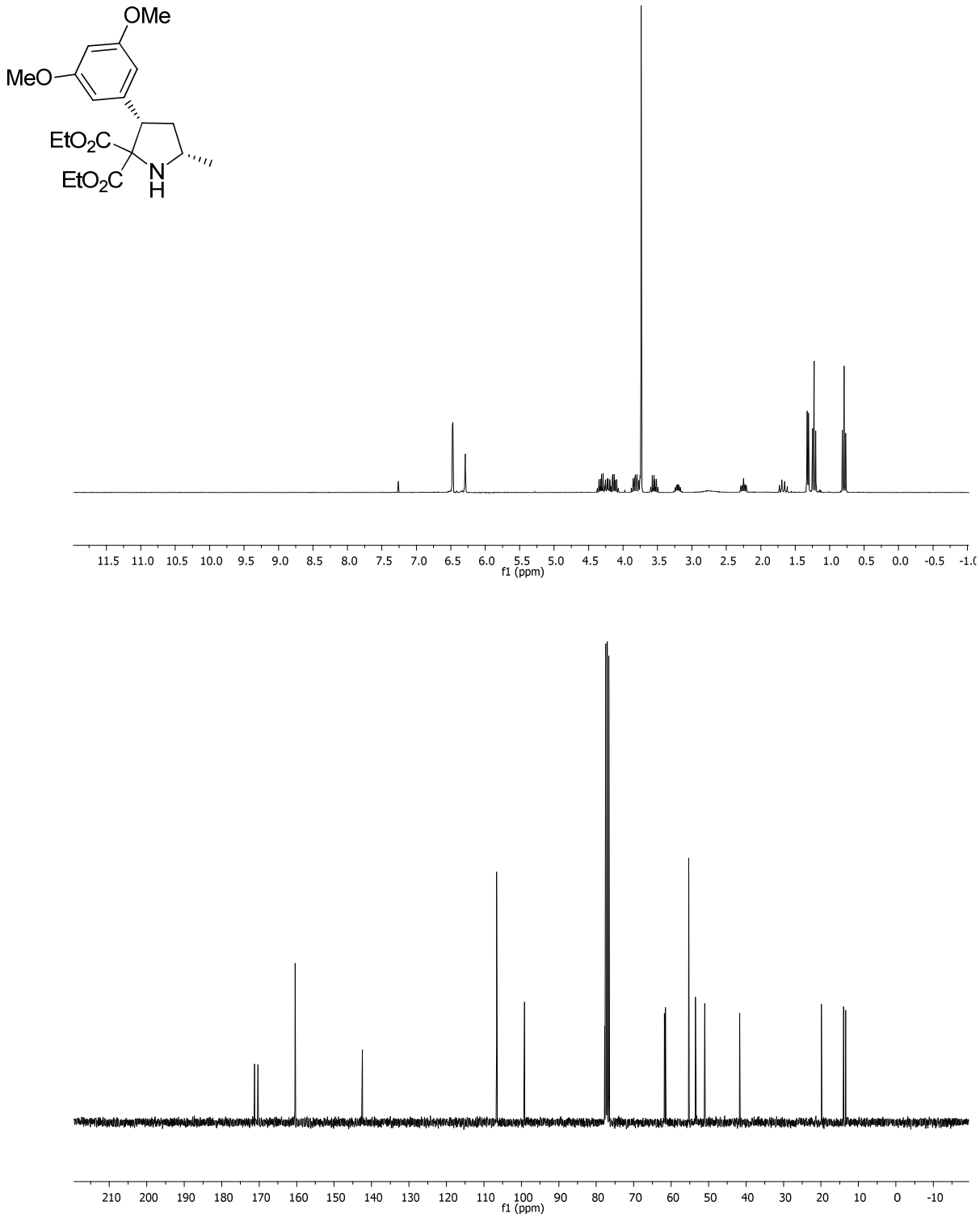


Figure 7: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4g**.

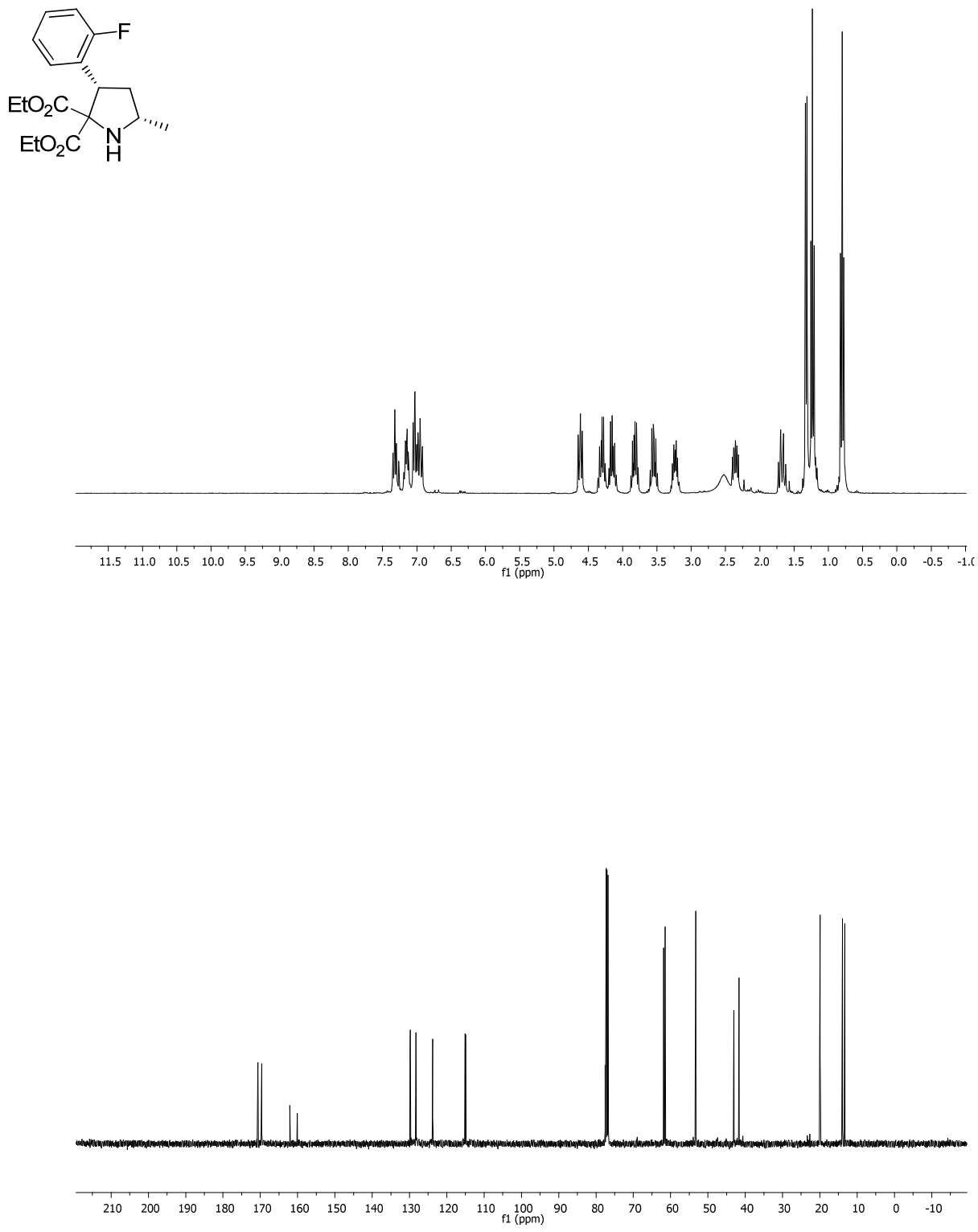


Figure 8: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4h**.

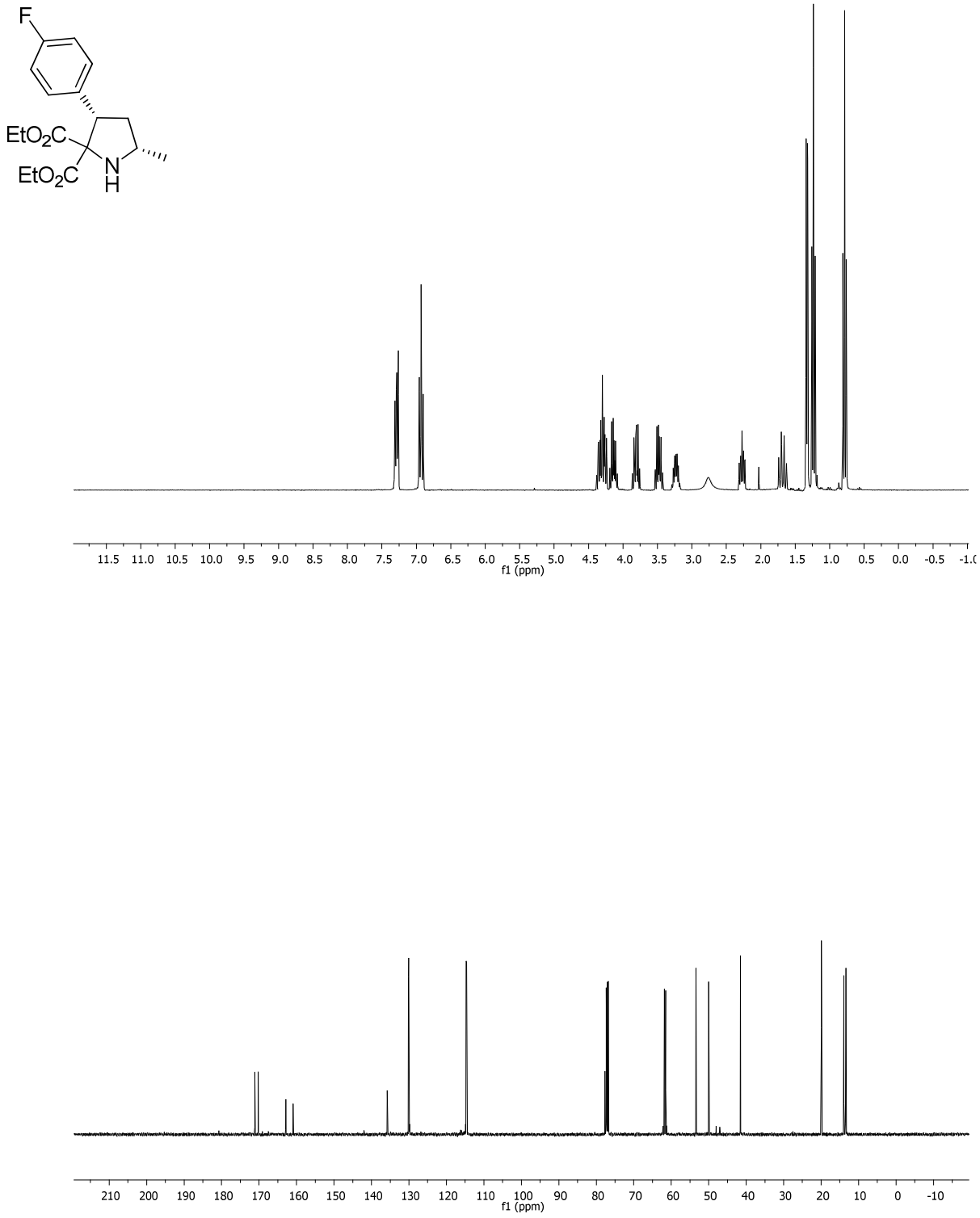


Figure 9: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4i**.

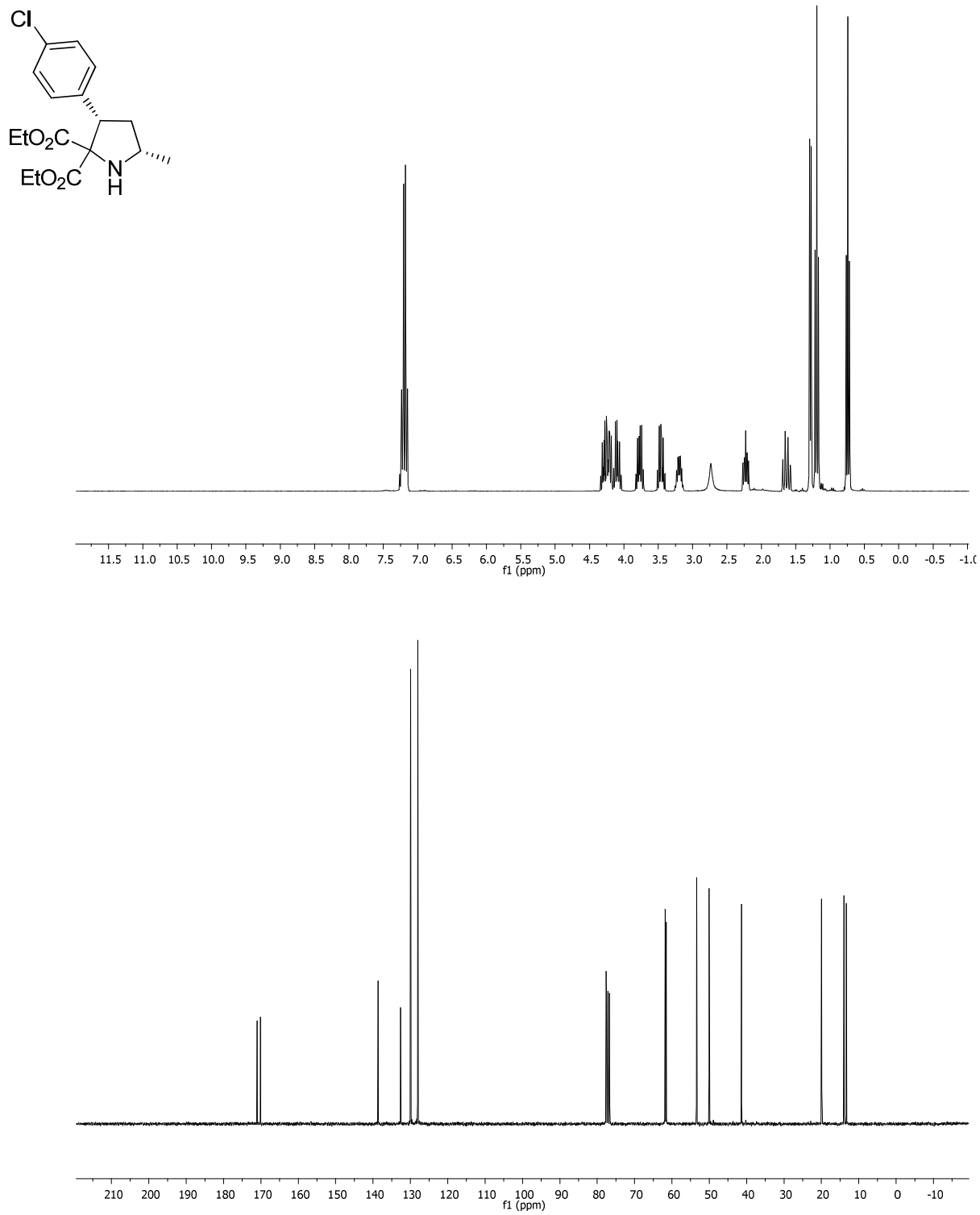


Figure 10: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4j**.

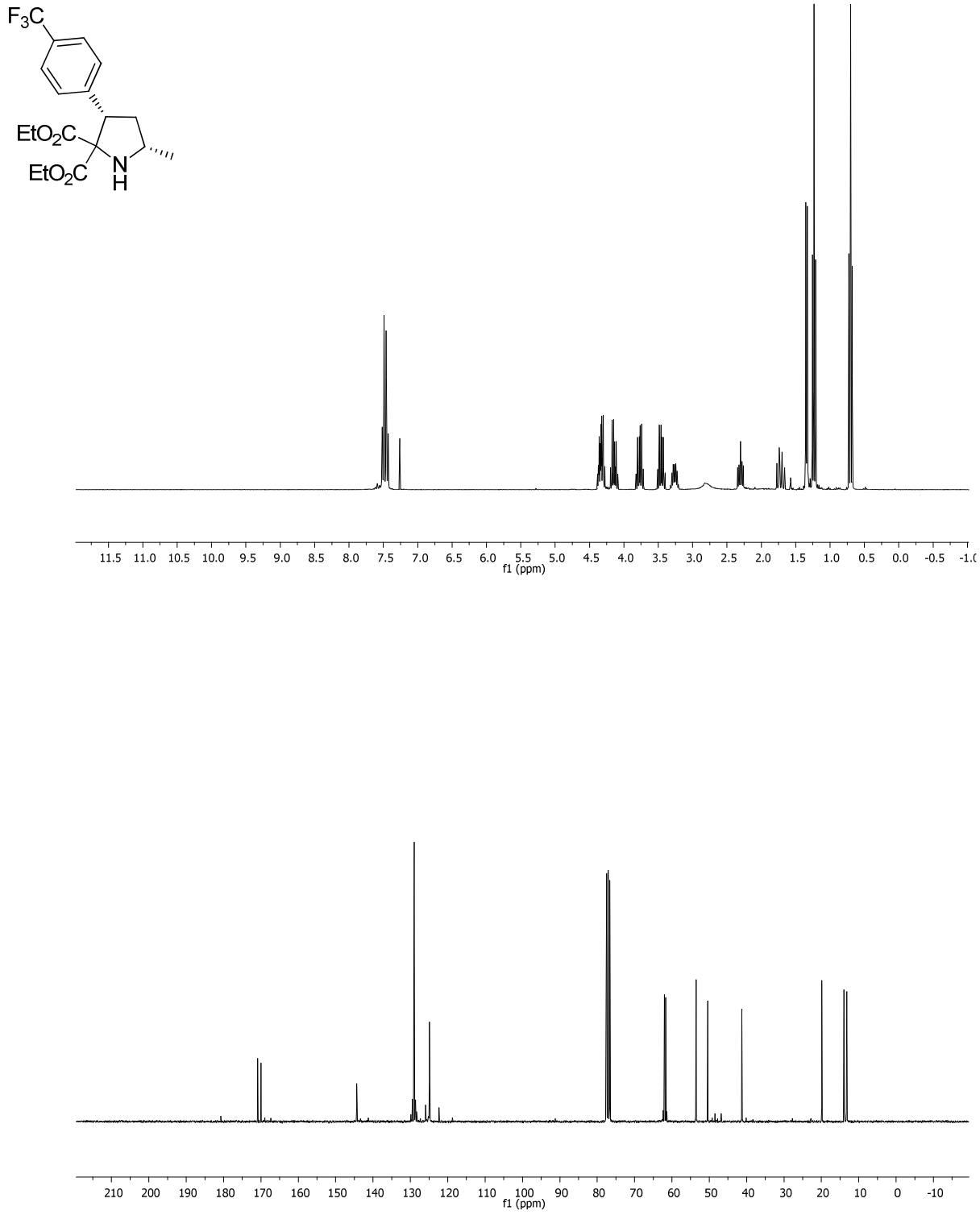


Figure 11: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4k**.

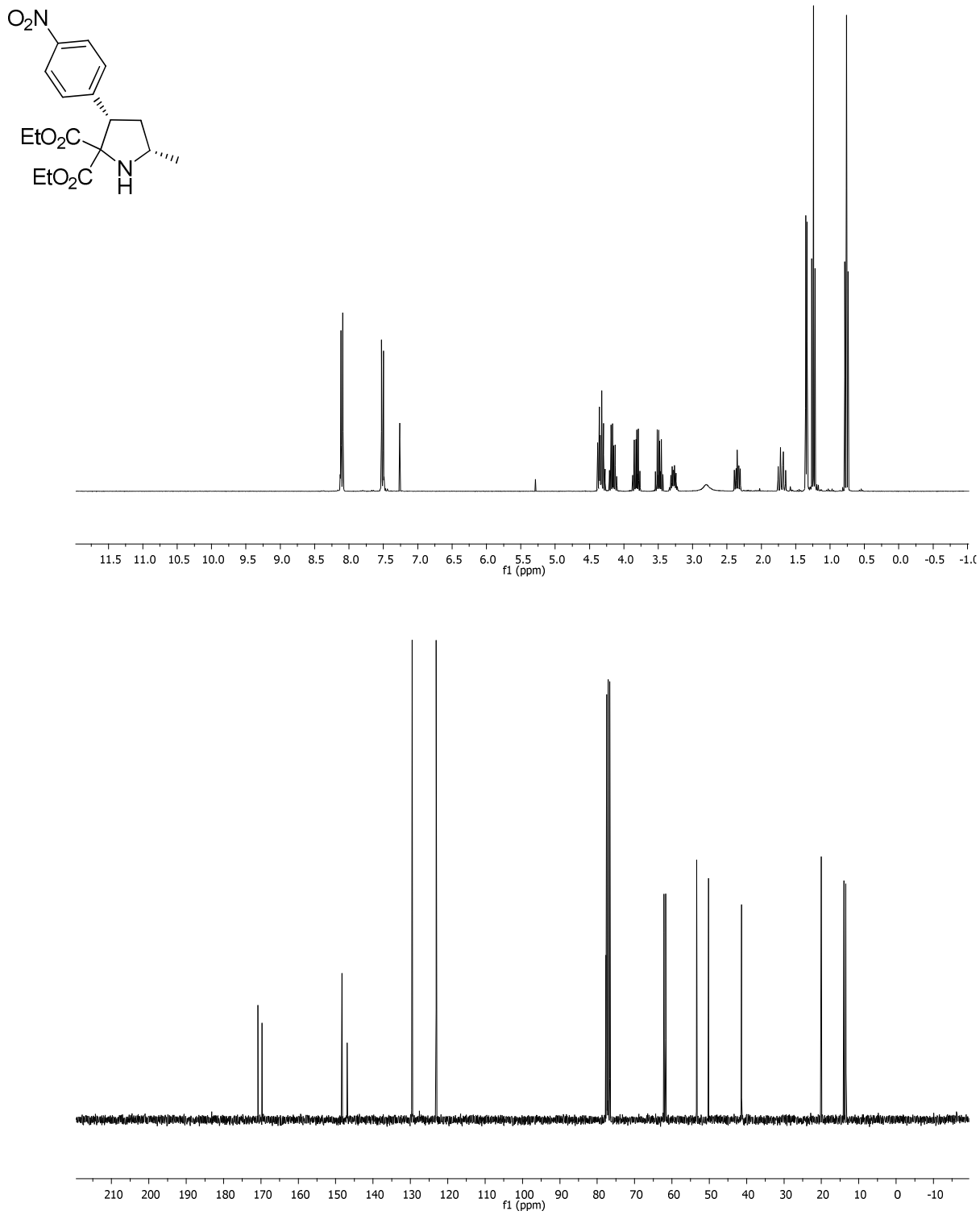


Figure 12: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4l**.

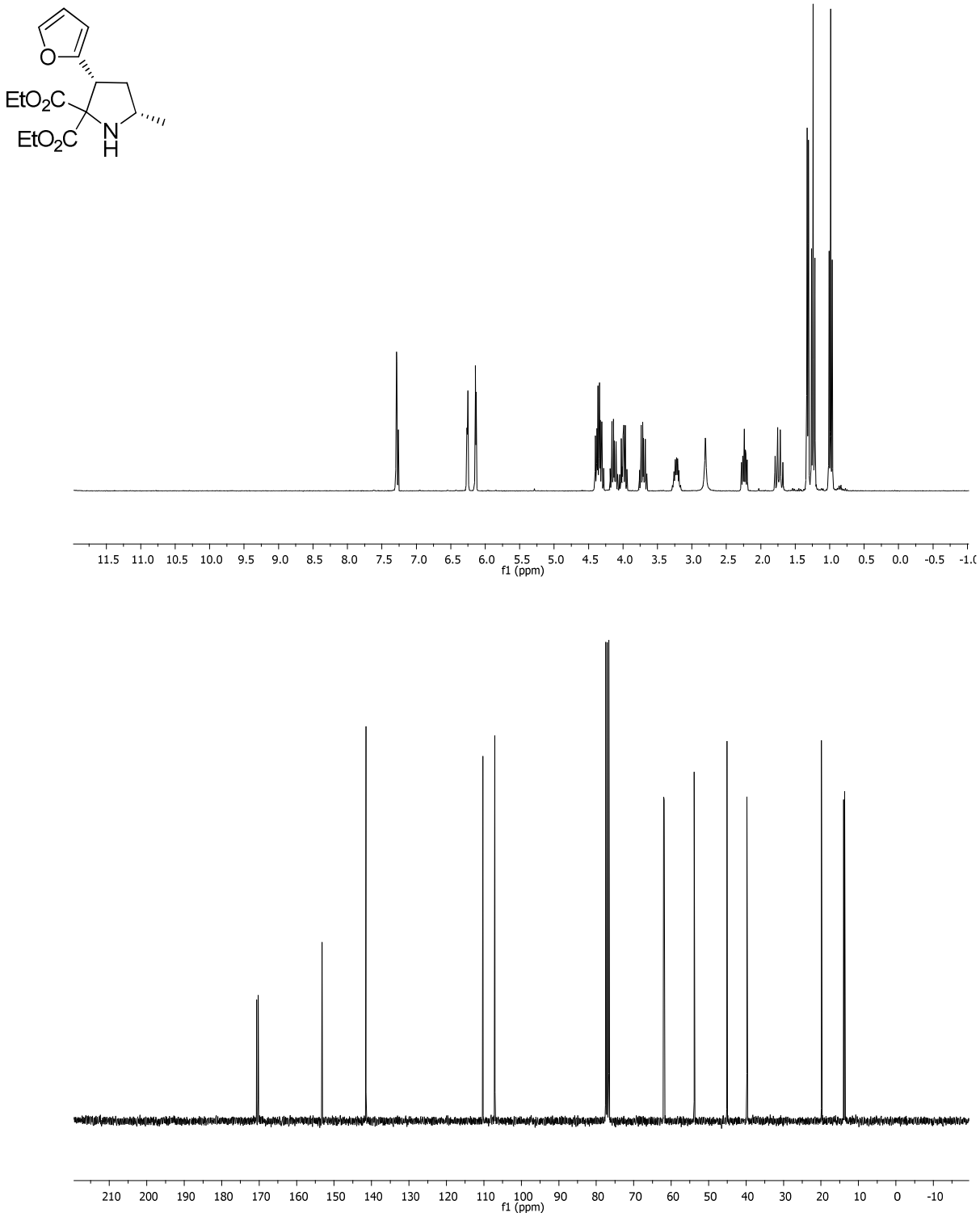


Figure 13: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4m**.

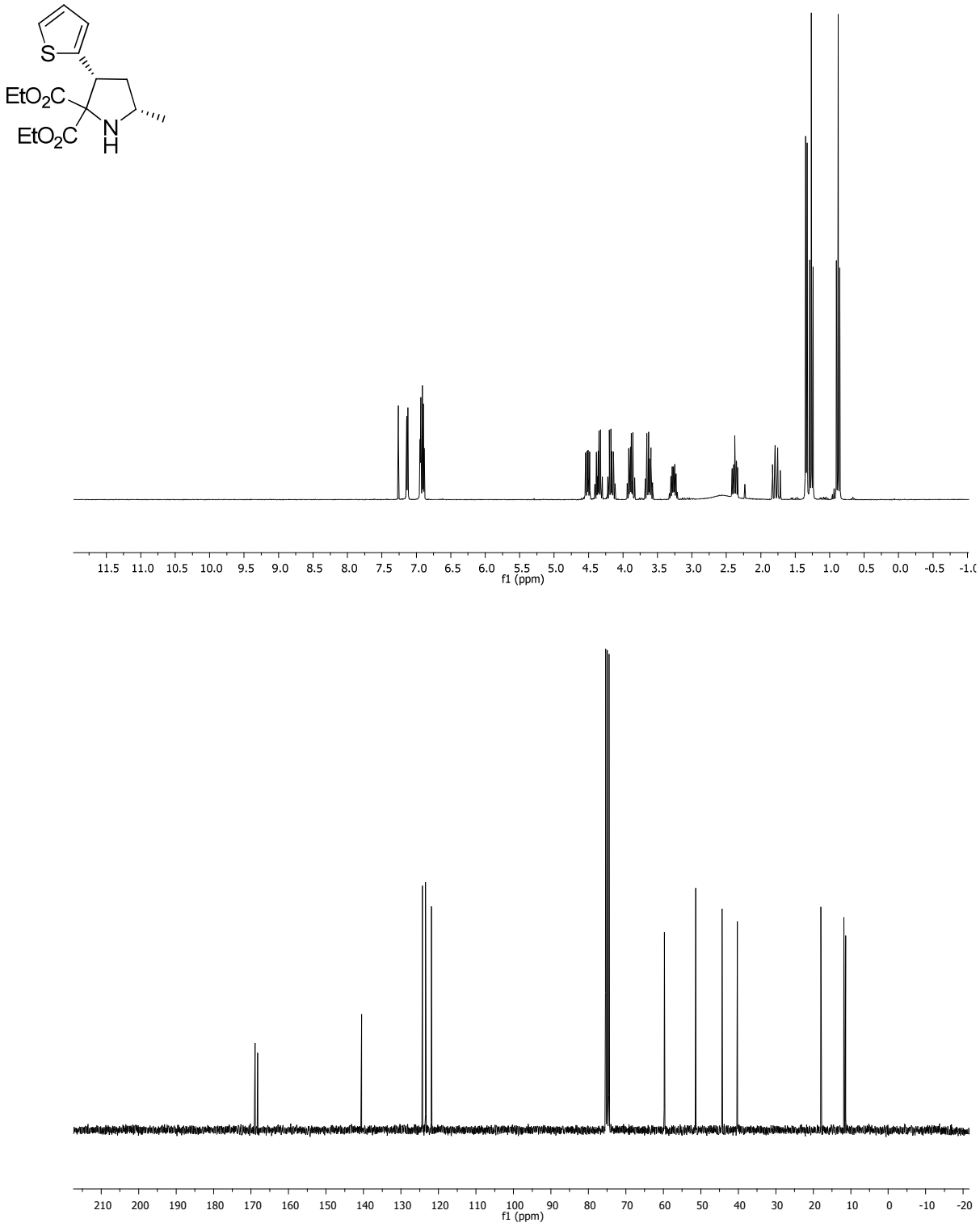


Figure 14: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4n**.

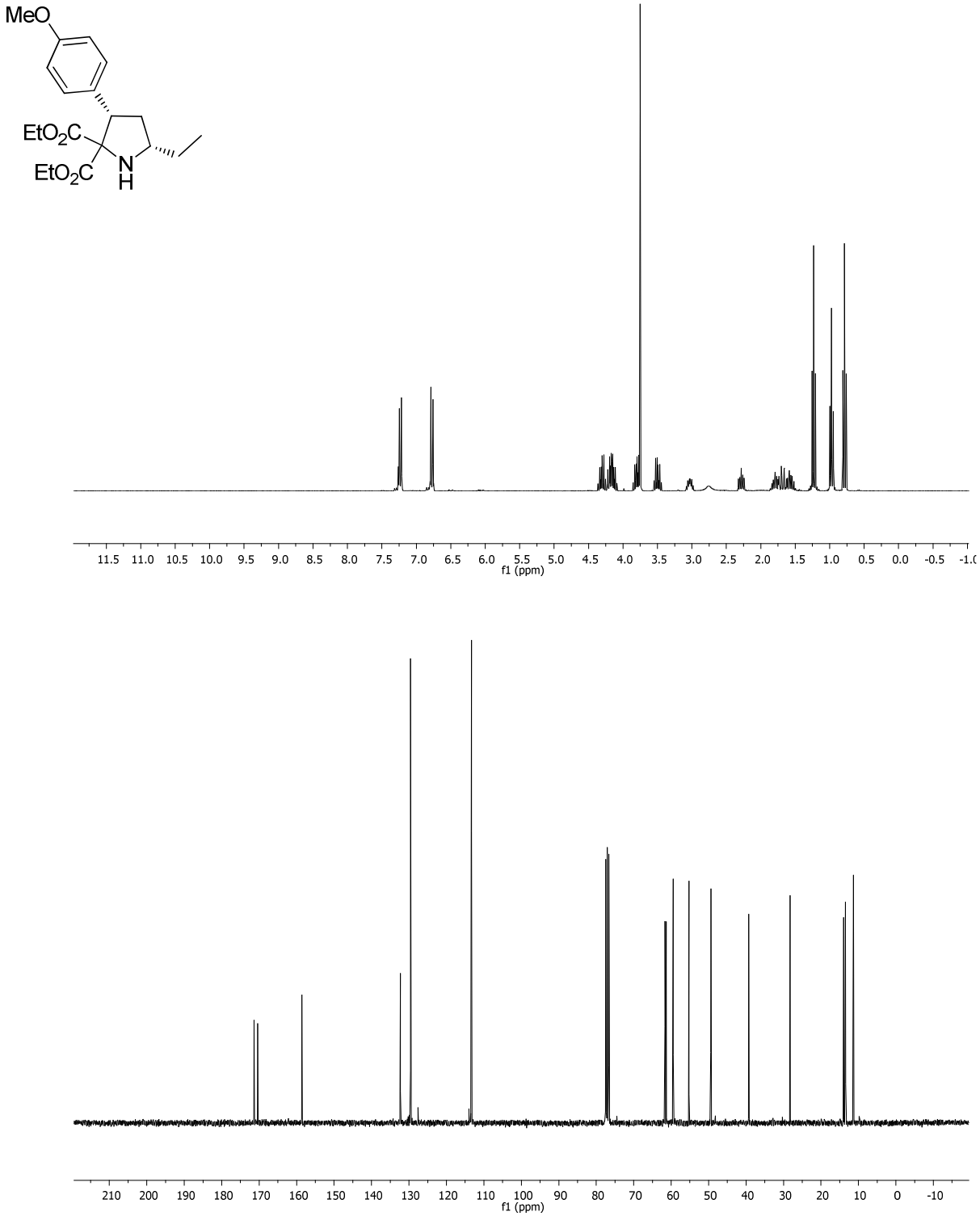


Figure 15: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4o**.

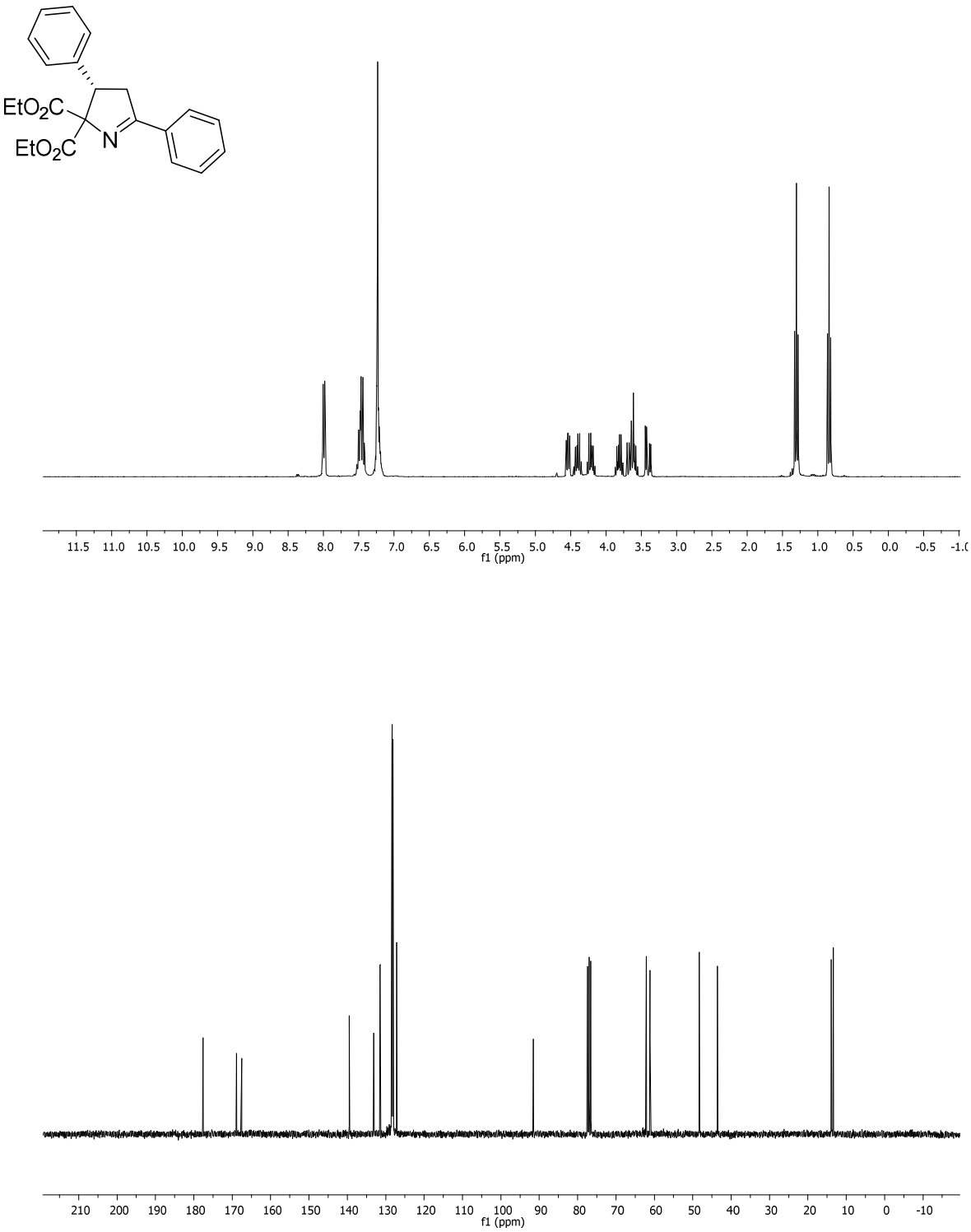


Figure 16: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4p**.

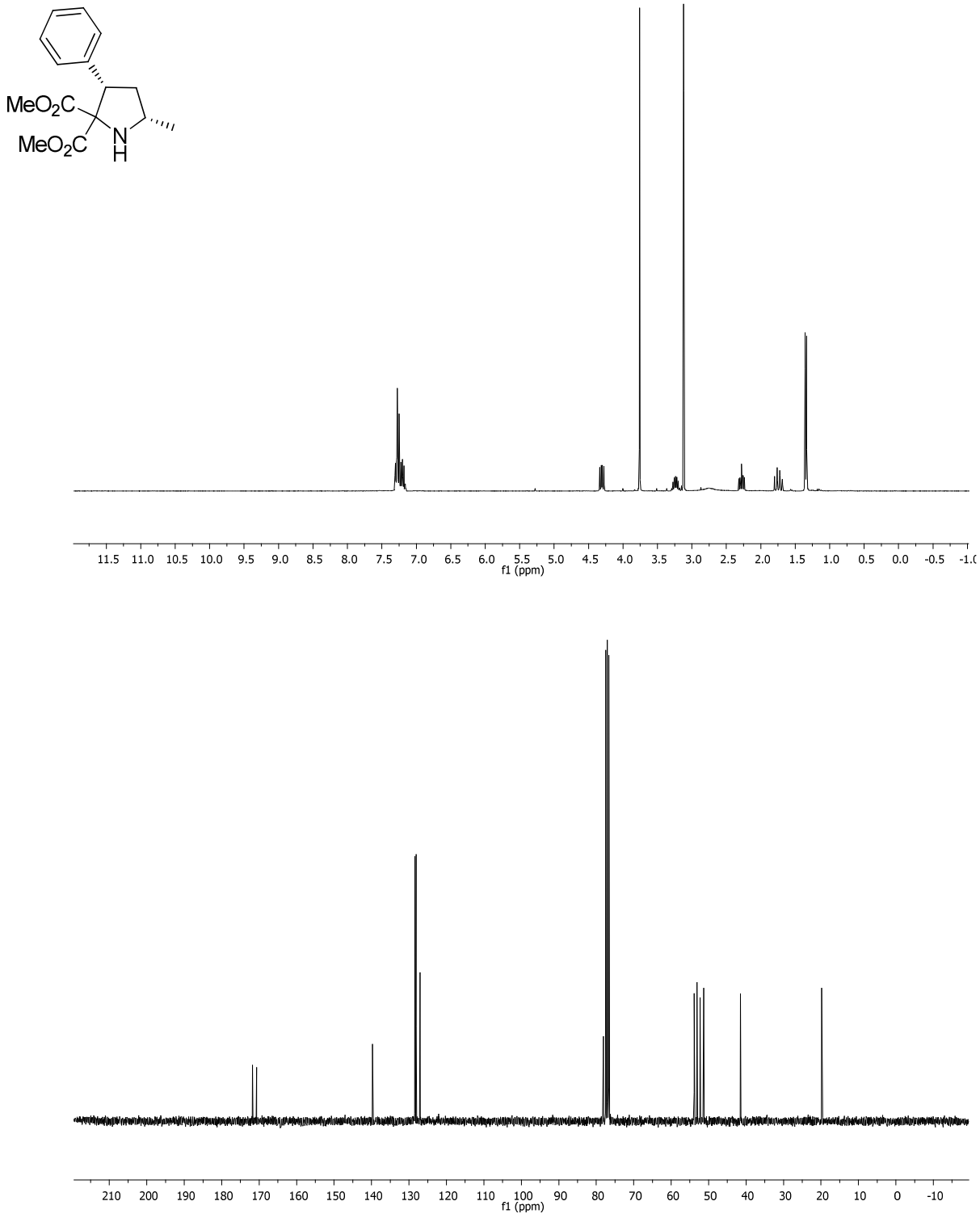


Figure 17: ^{1}H-NMR and ^{13}C-NMR spectra for **4r**.

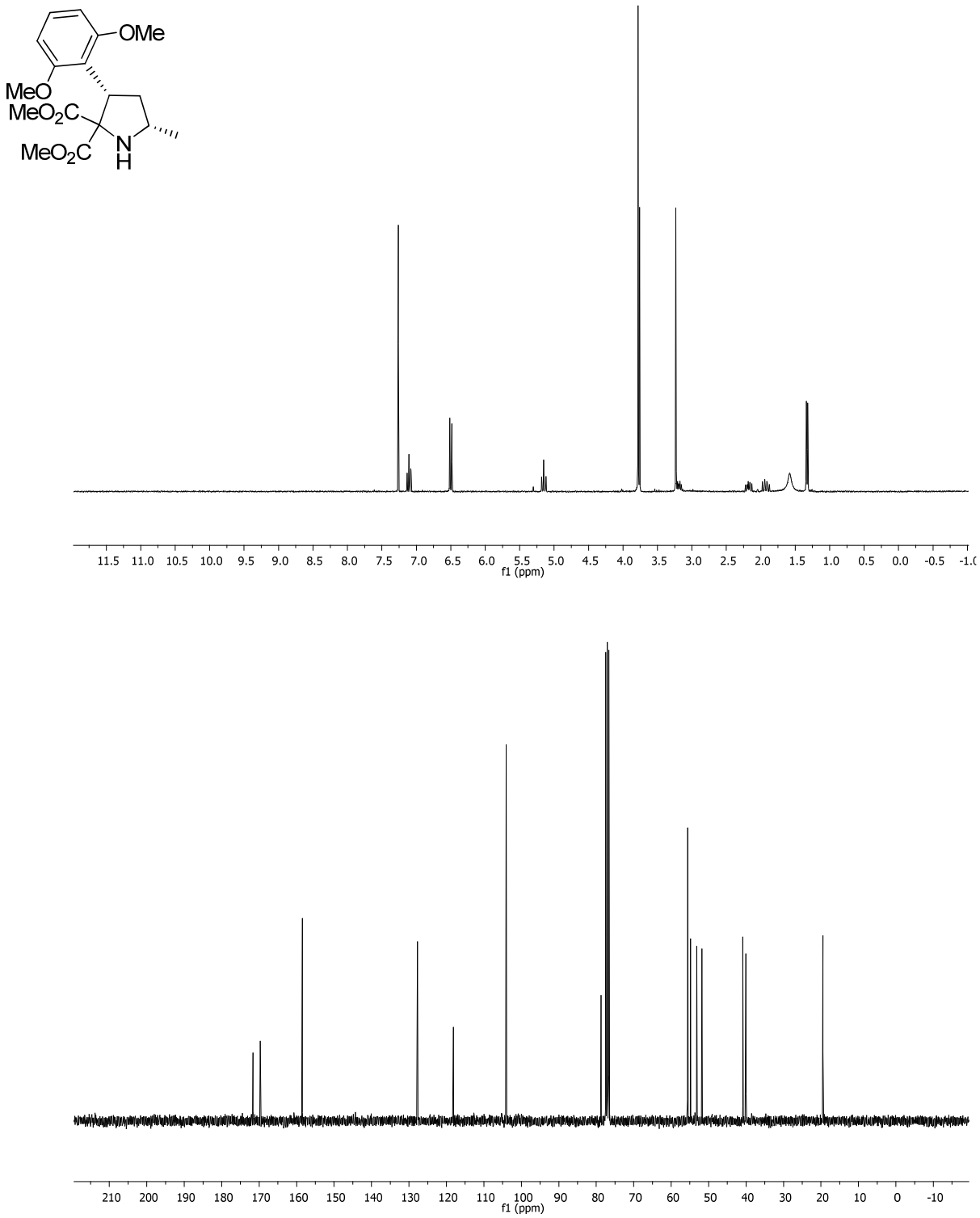


Figure 18: ^{1}H-NMR and ^{13}C-NMR spectra for compound **4s**.

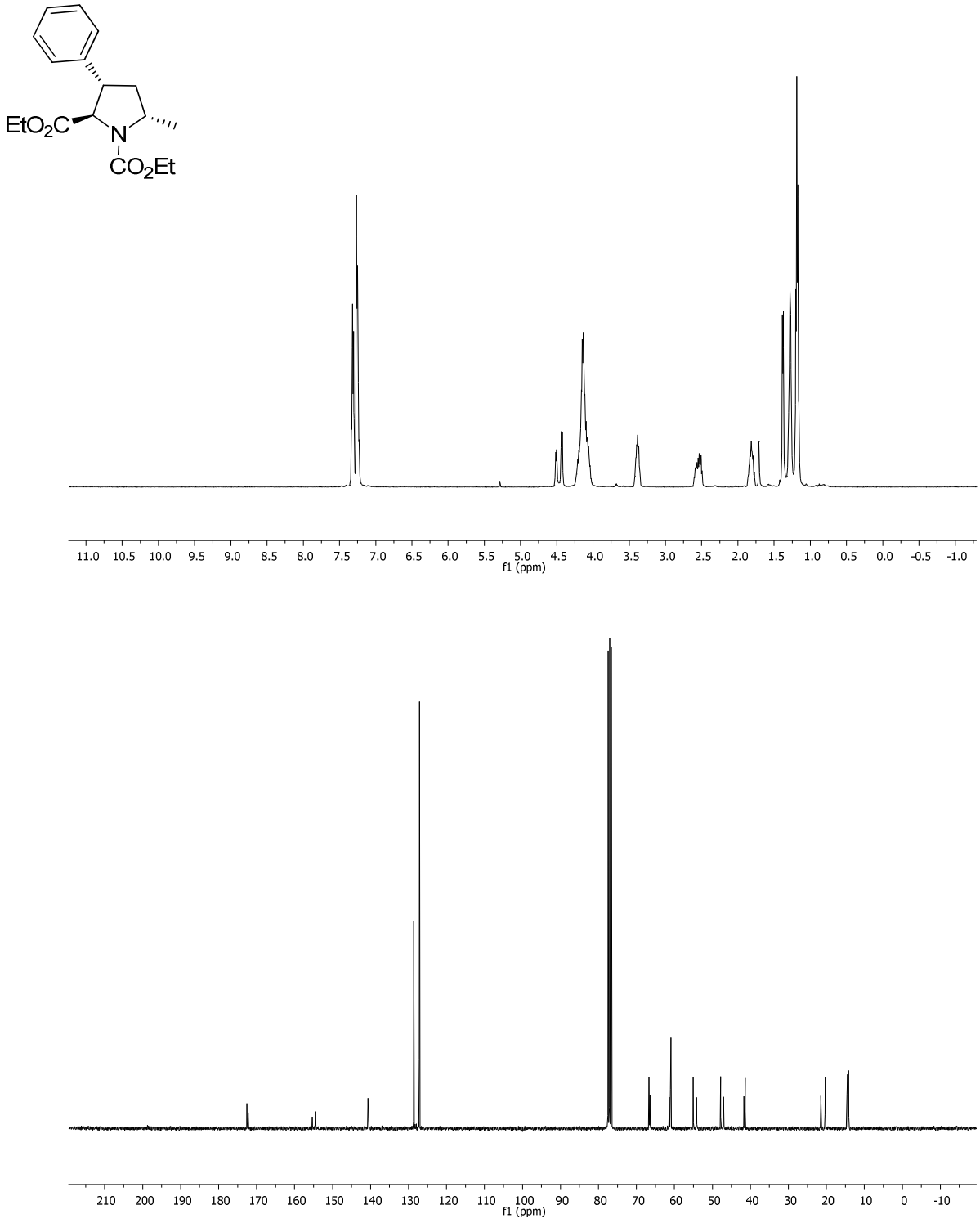


Figure 19: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5a**.

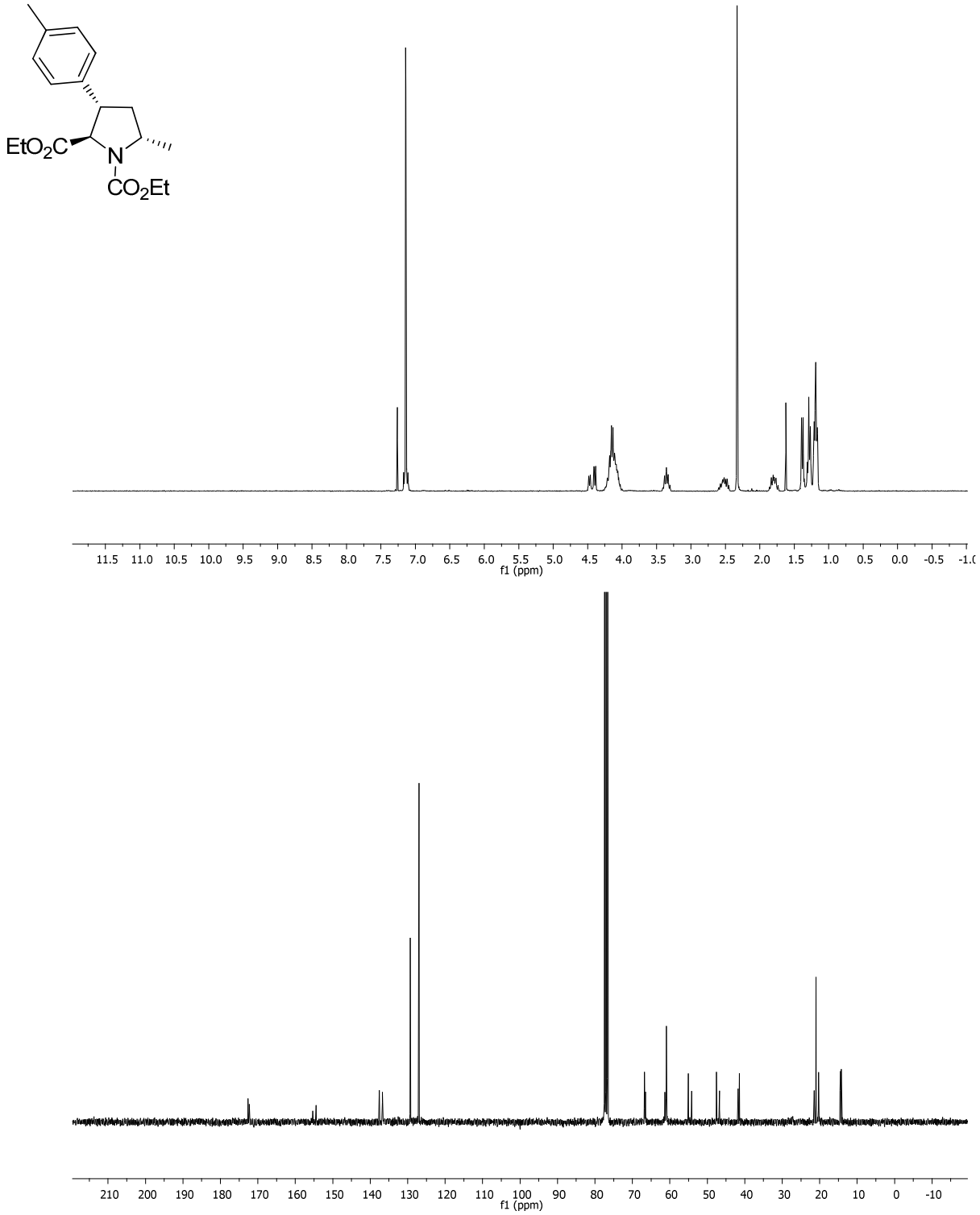


Figure 20: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5b**.

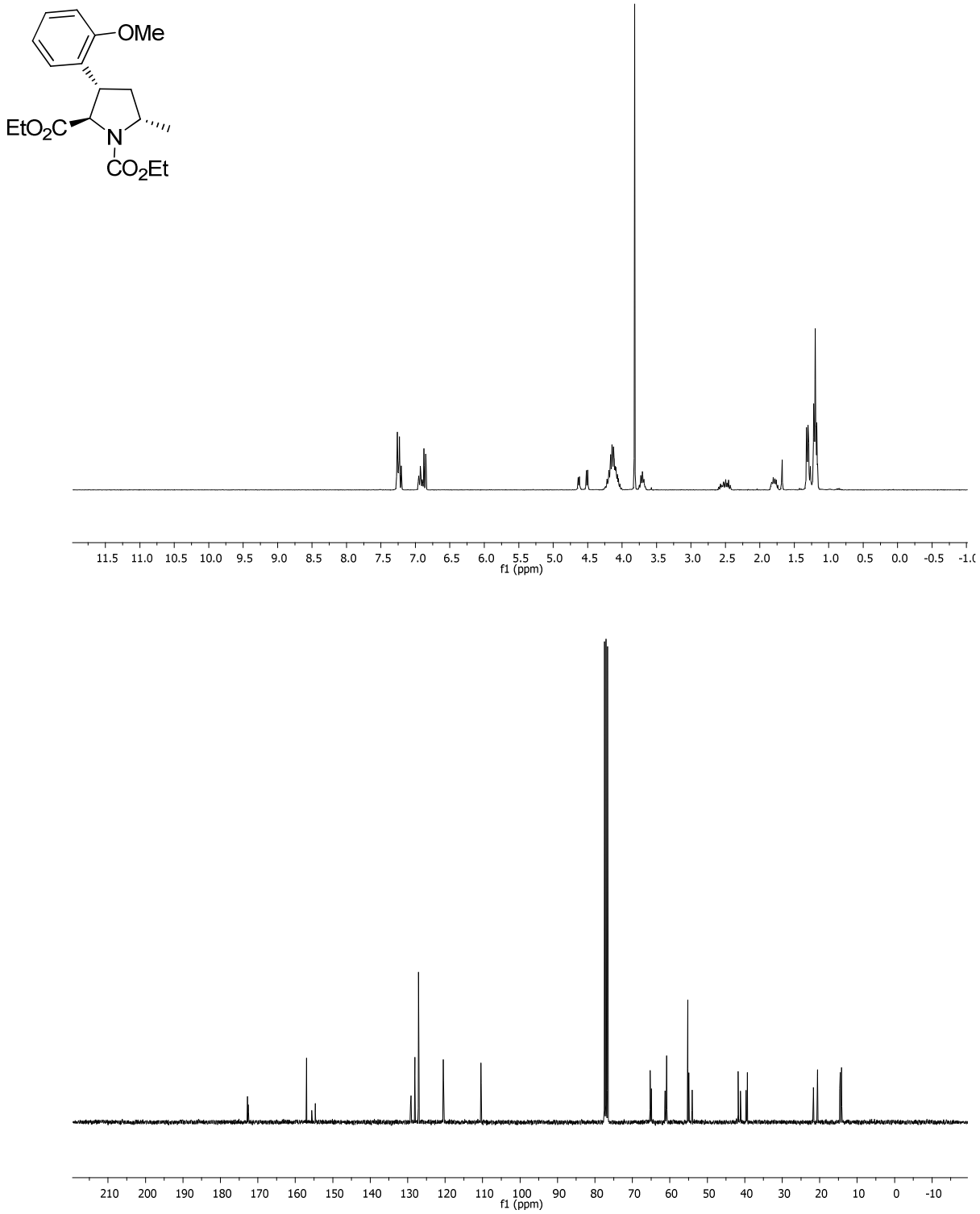


Figure 21: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5c**.

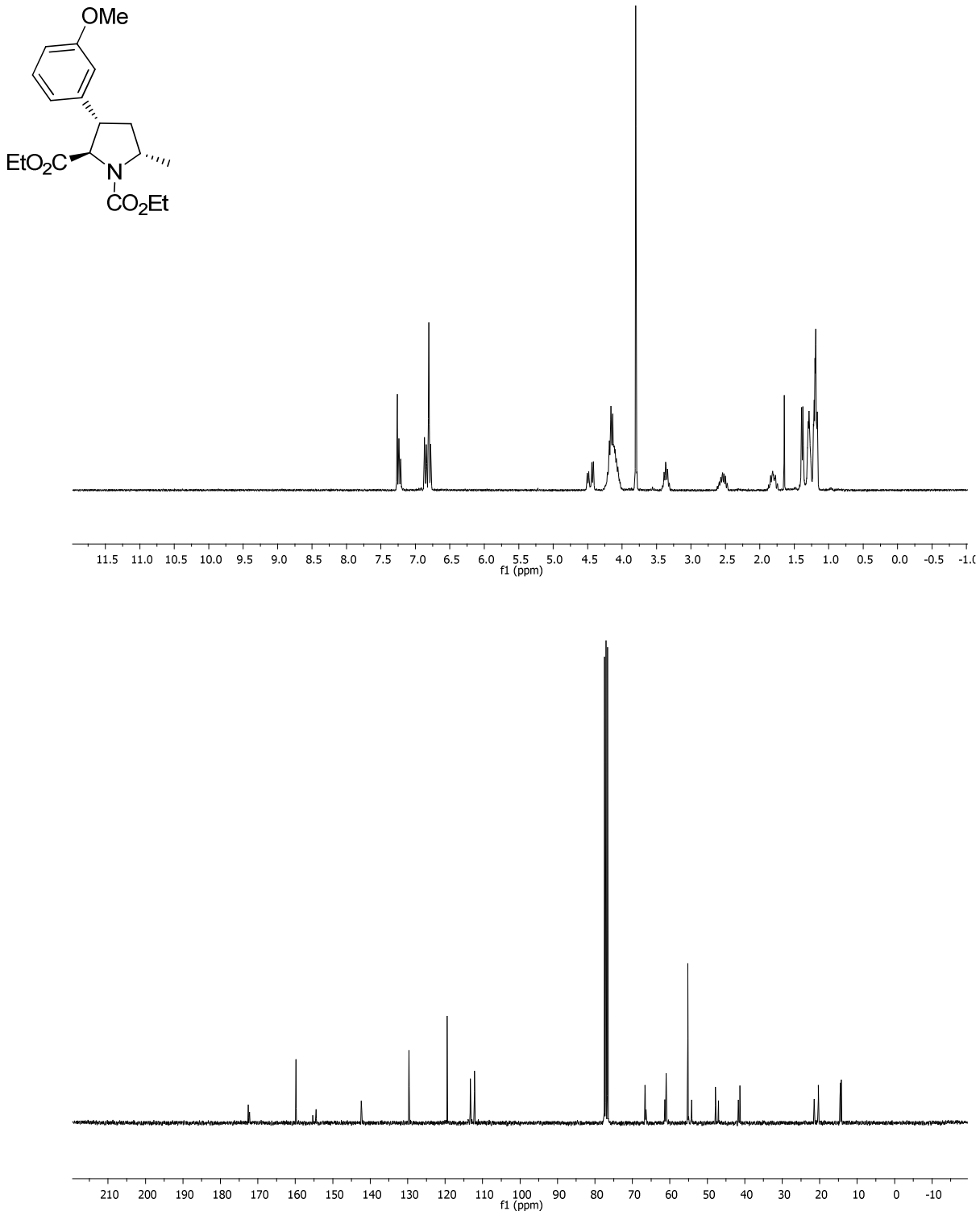


Figure 22: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5d**.

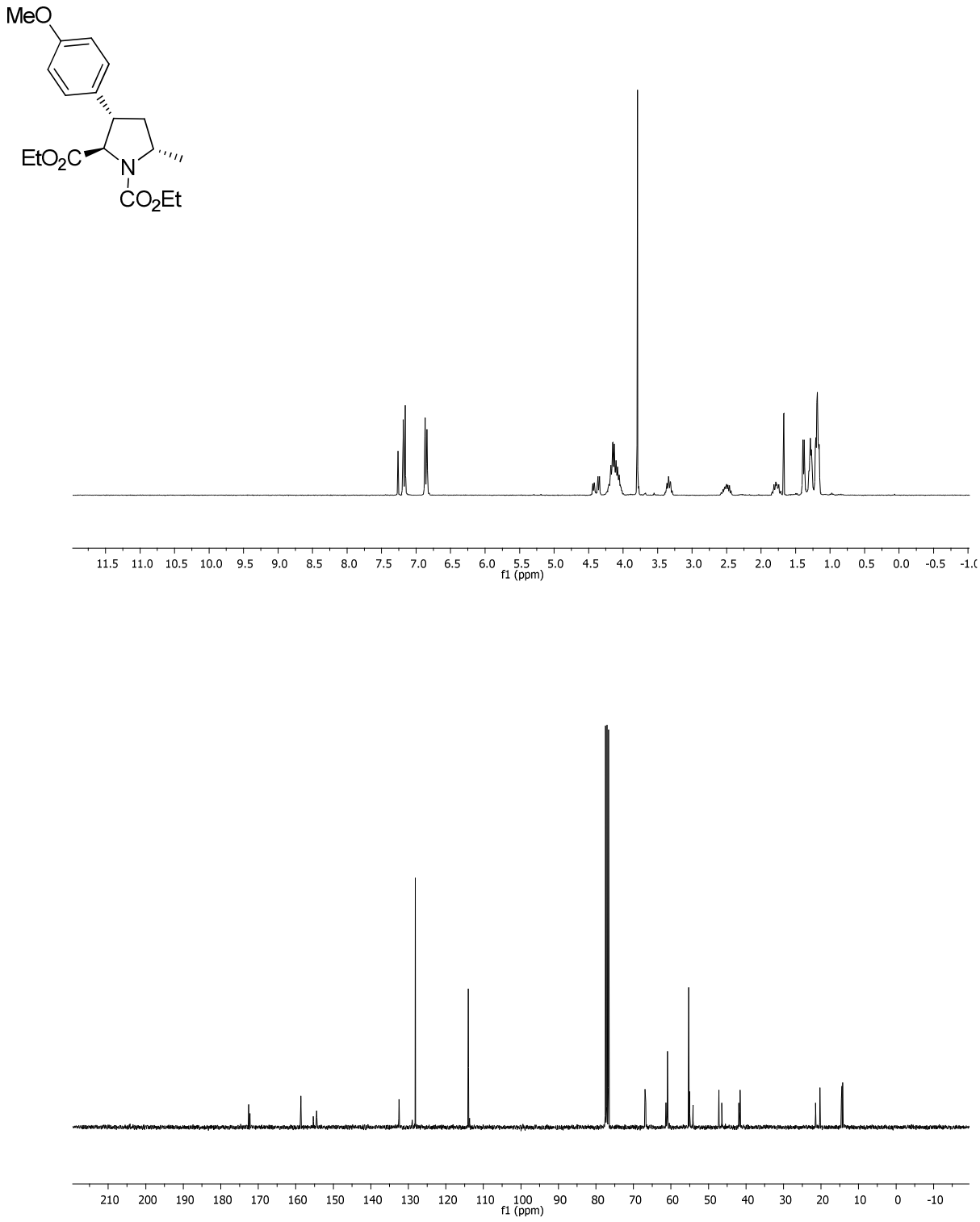


Figure 23: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5e**.

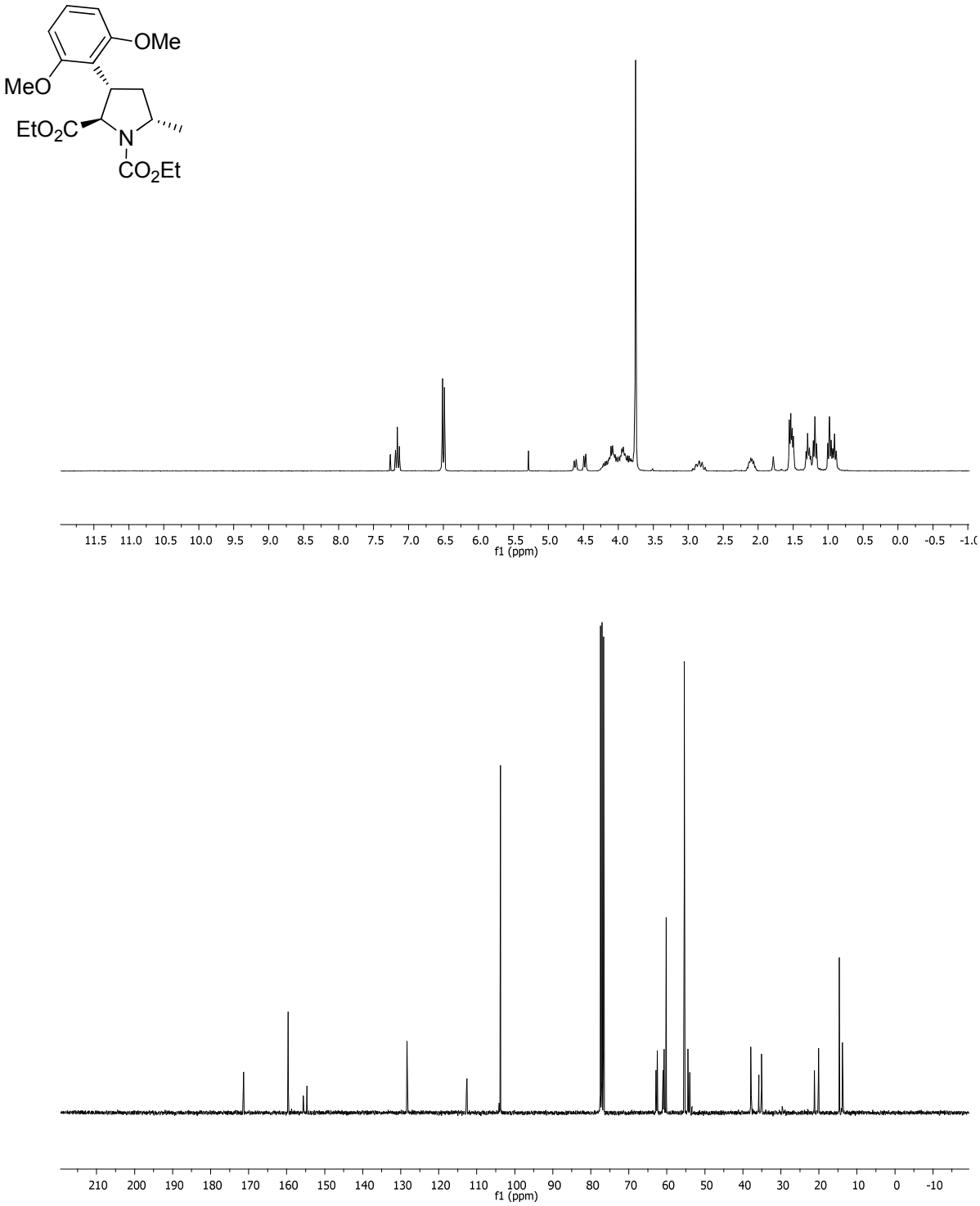


Figure 24: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5f**.

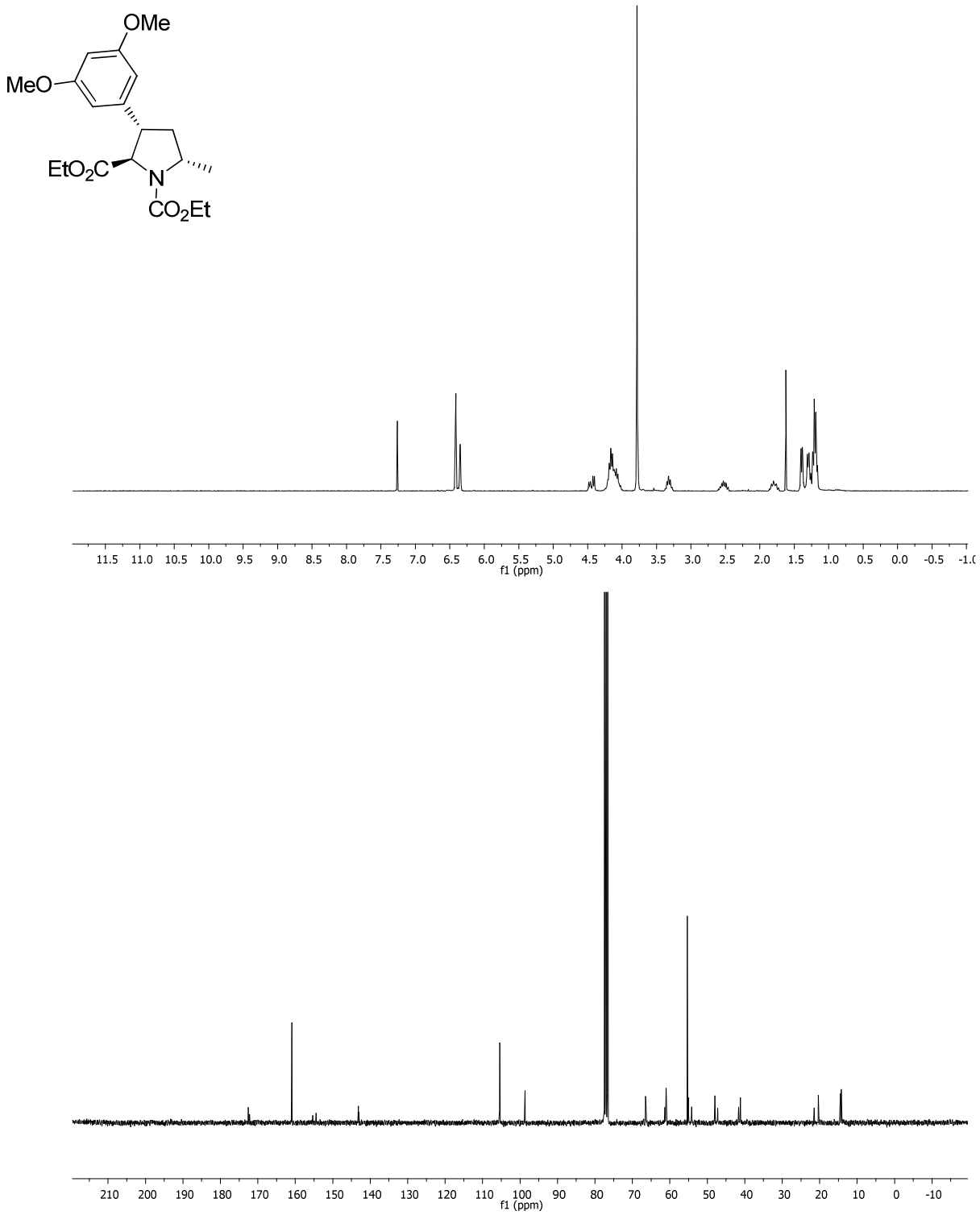


Figure 25: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5g**.

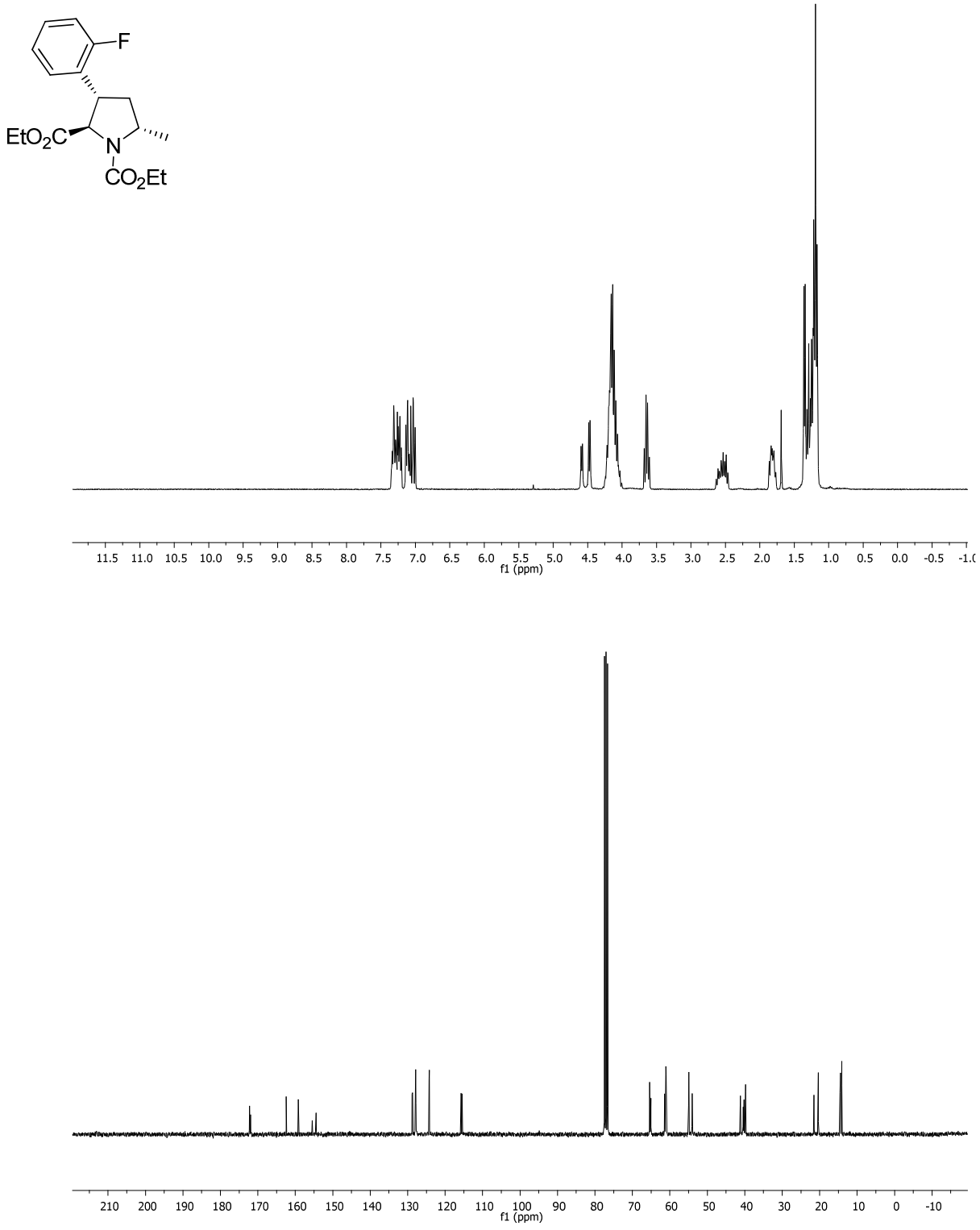


Figure 26: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5h**.

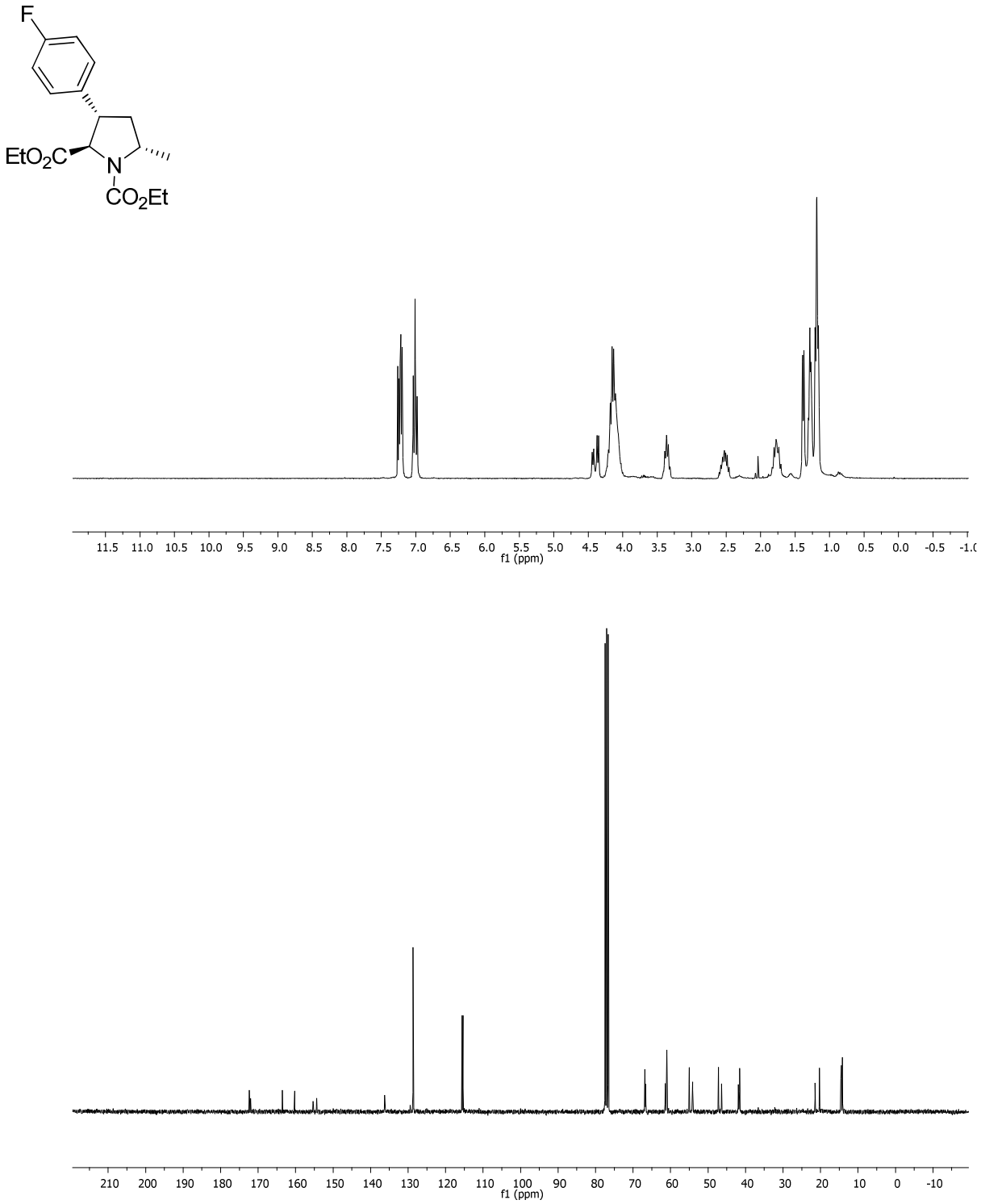


Figure 27: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5i**.

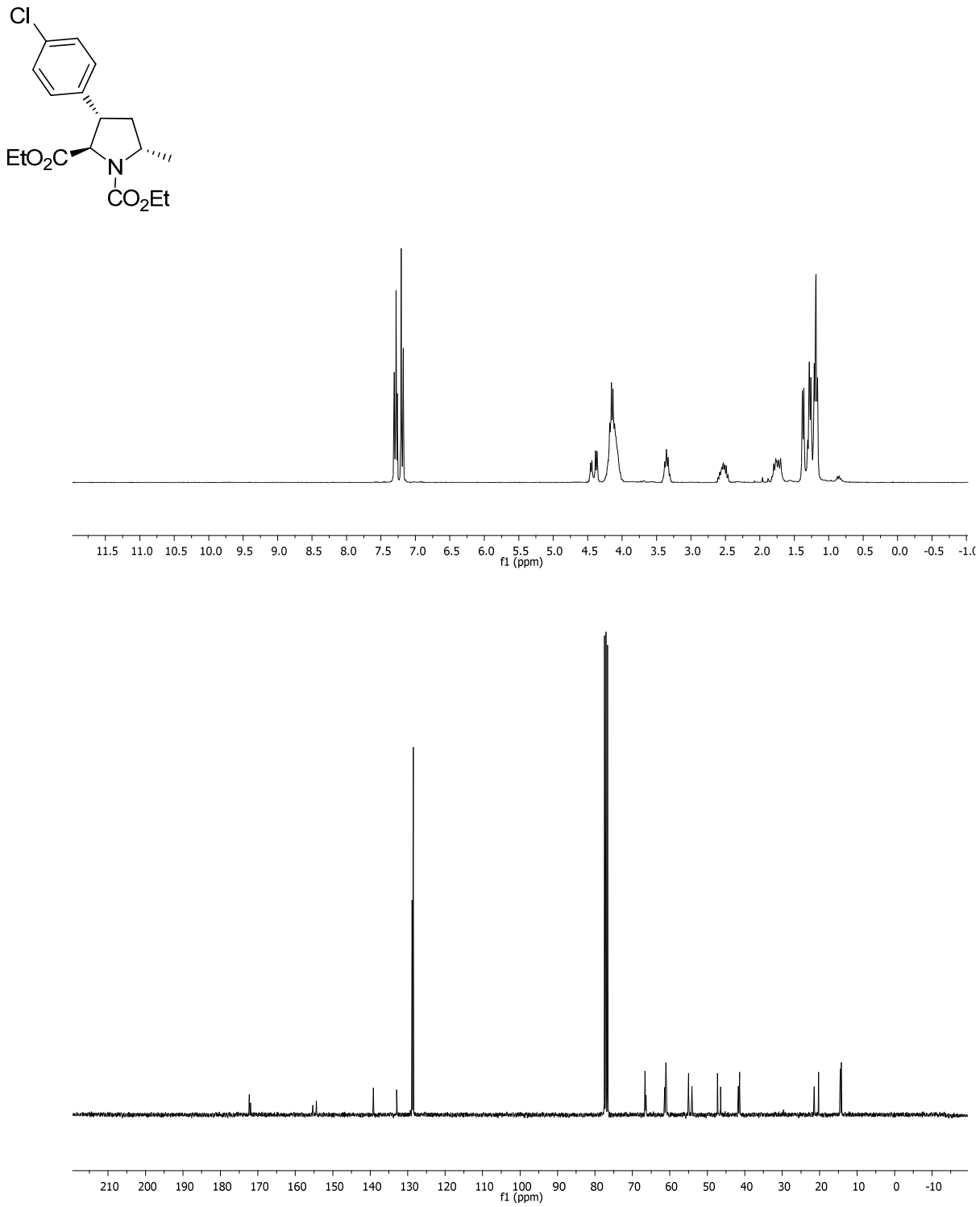


Figure 28: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5j**.

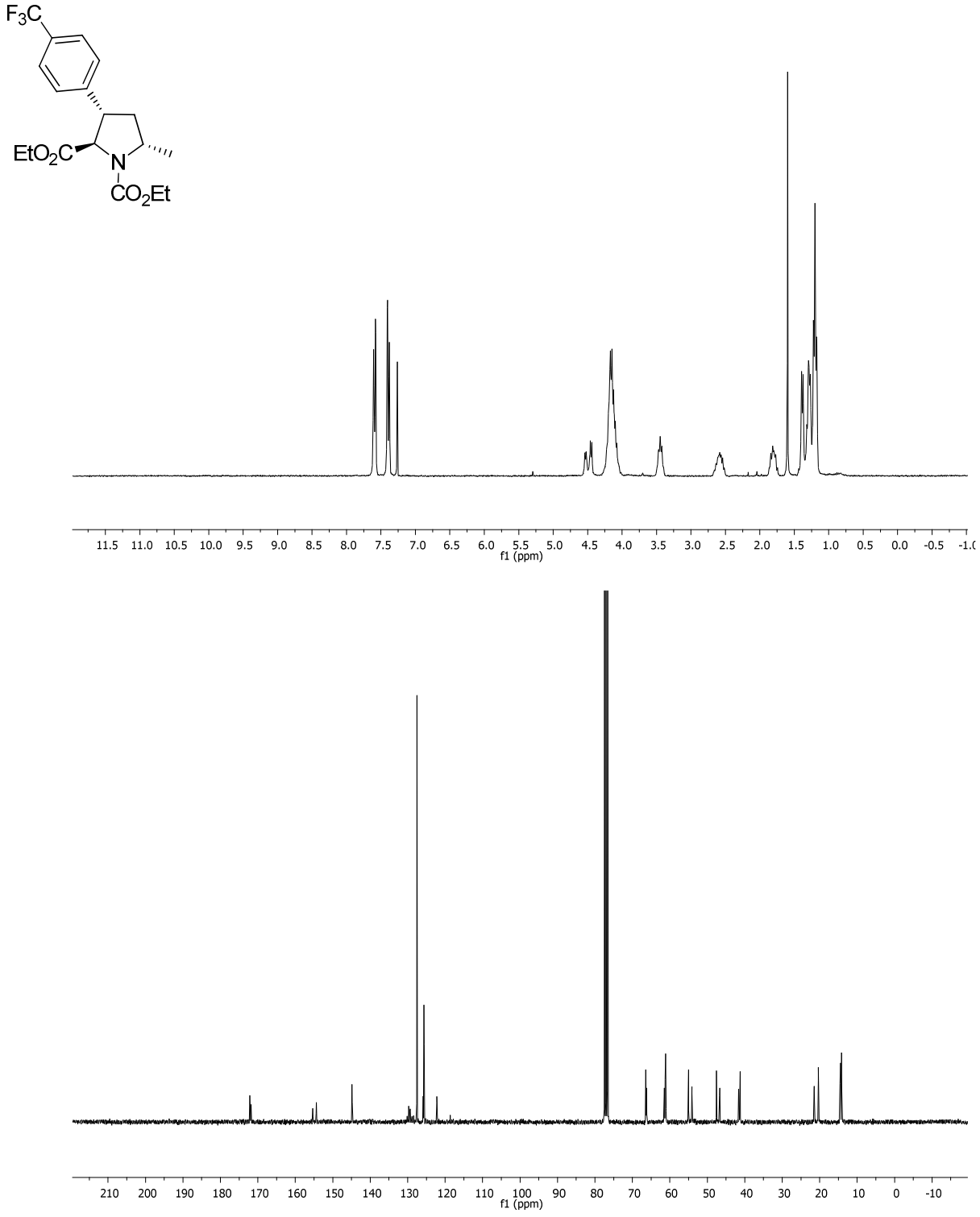


Figure 29: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5k**.

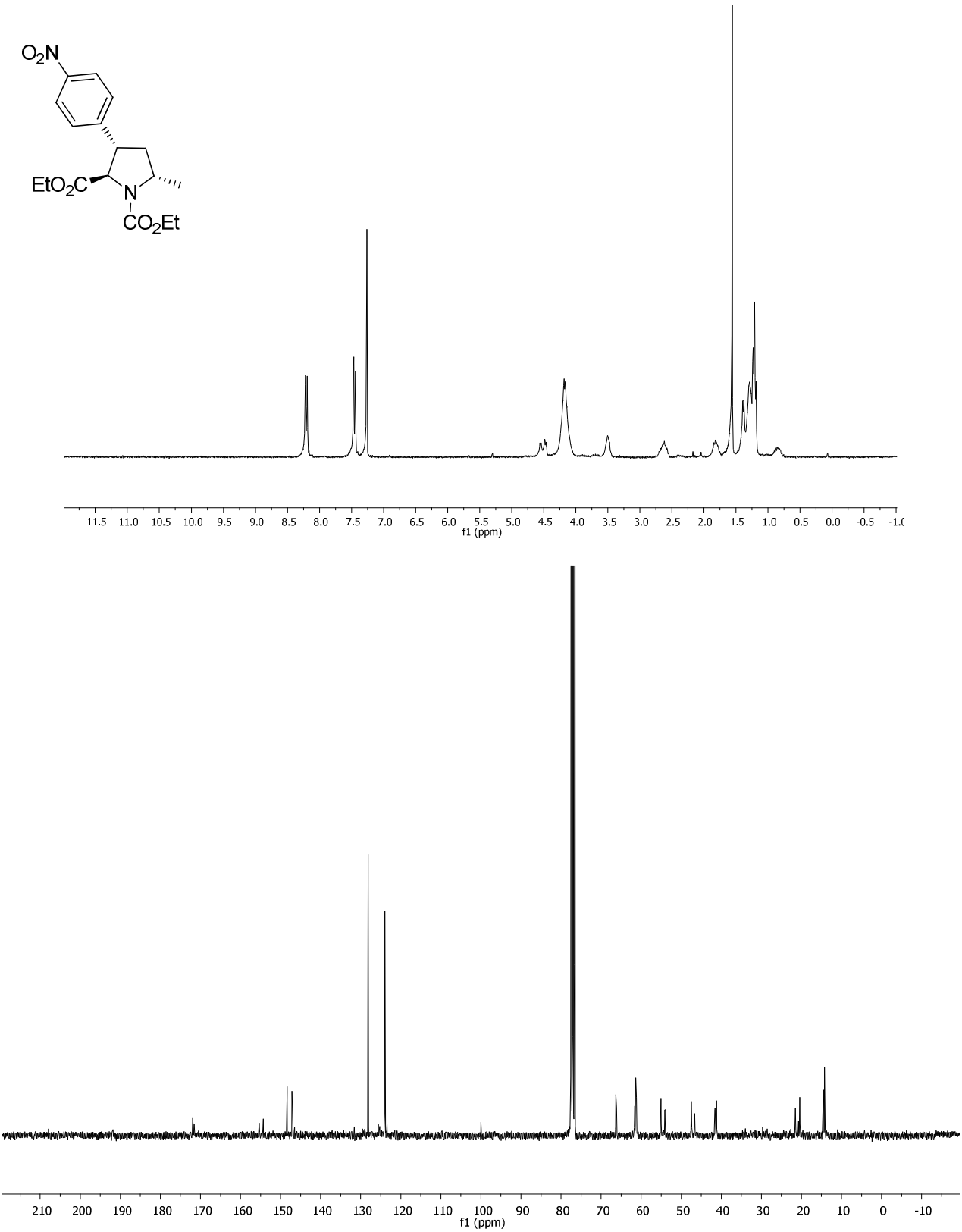


Figure 30: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5l**.

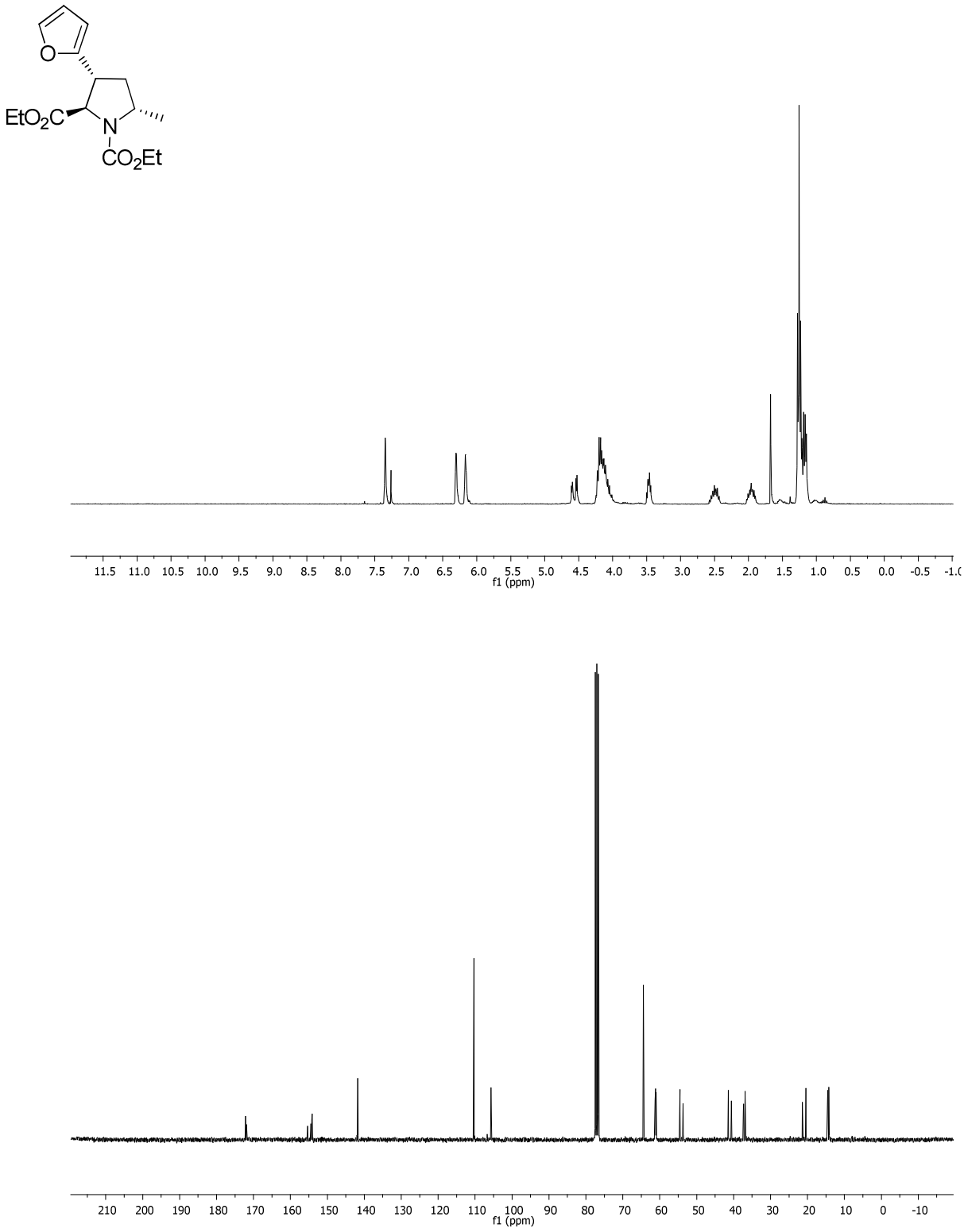
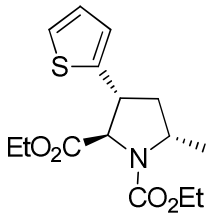
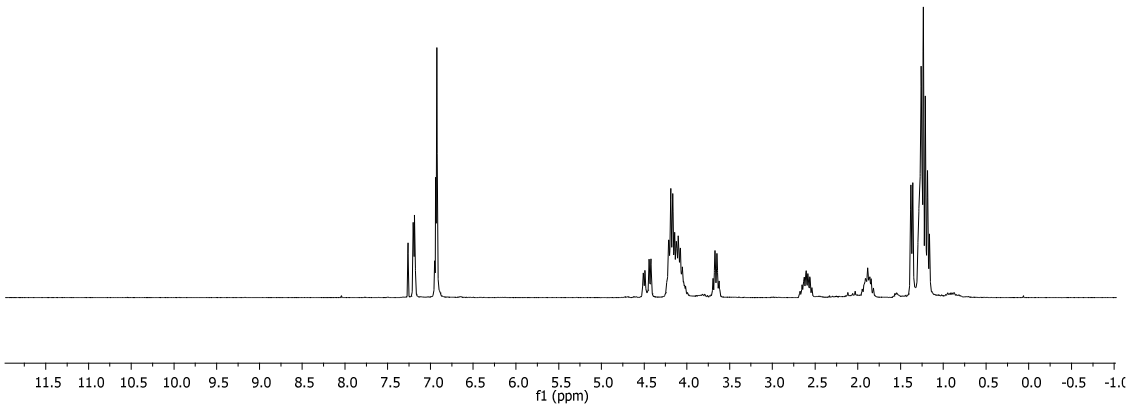


Figure 31: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5m**.





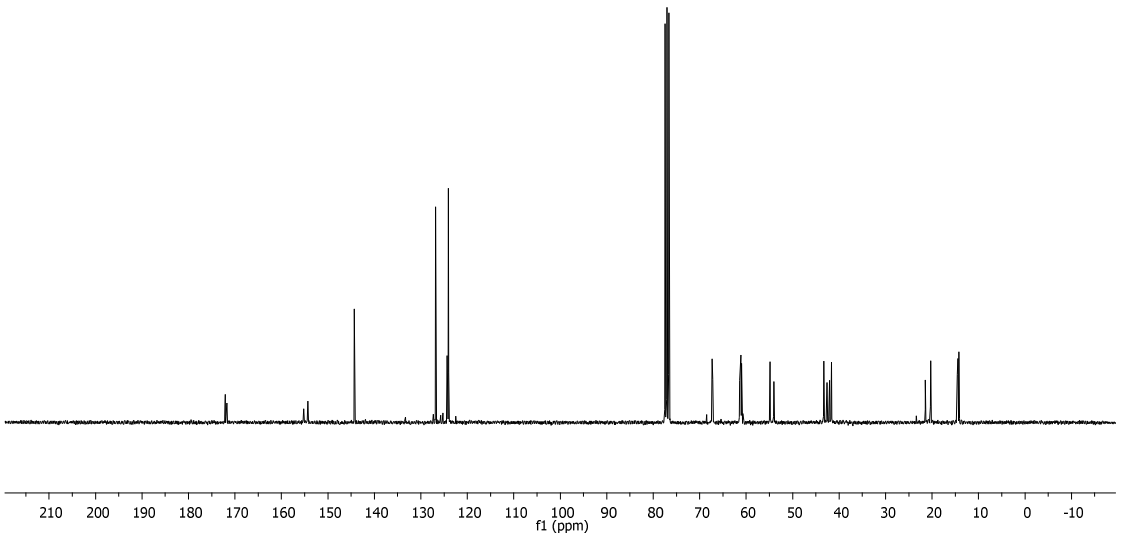


Figure 32: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5n**.

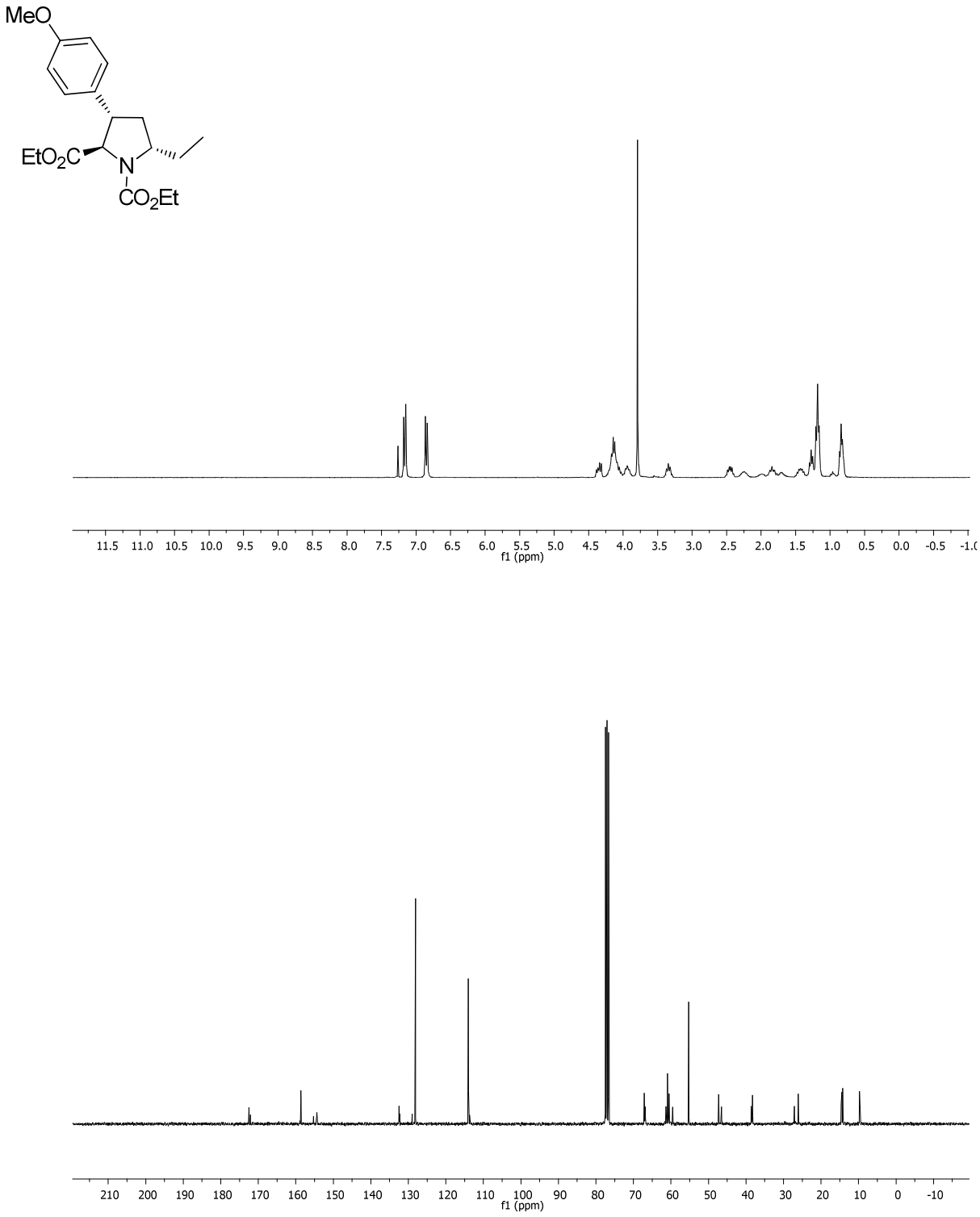


Figure 33: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5o**.

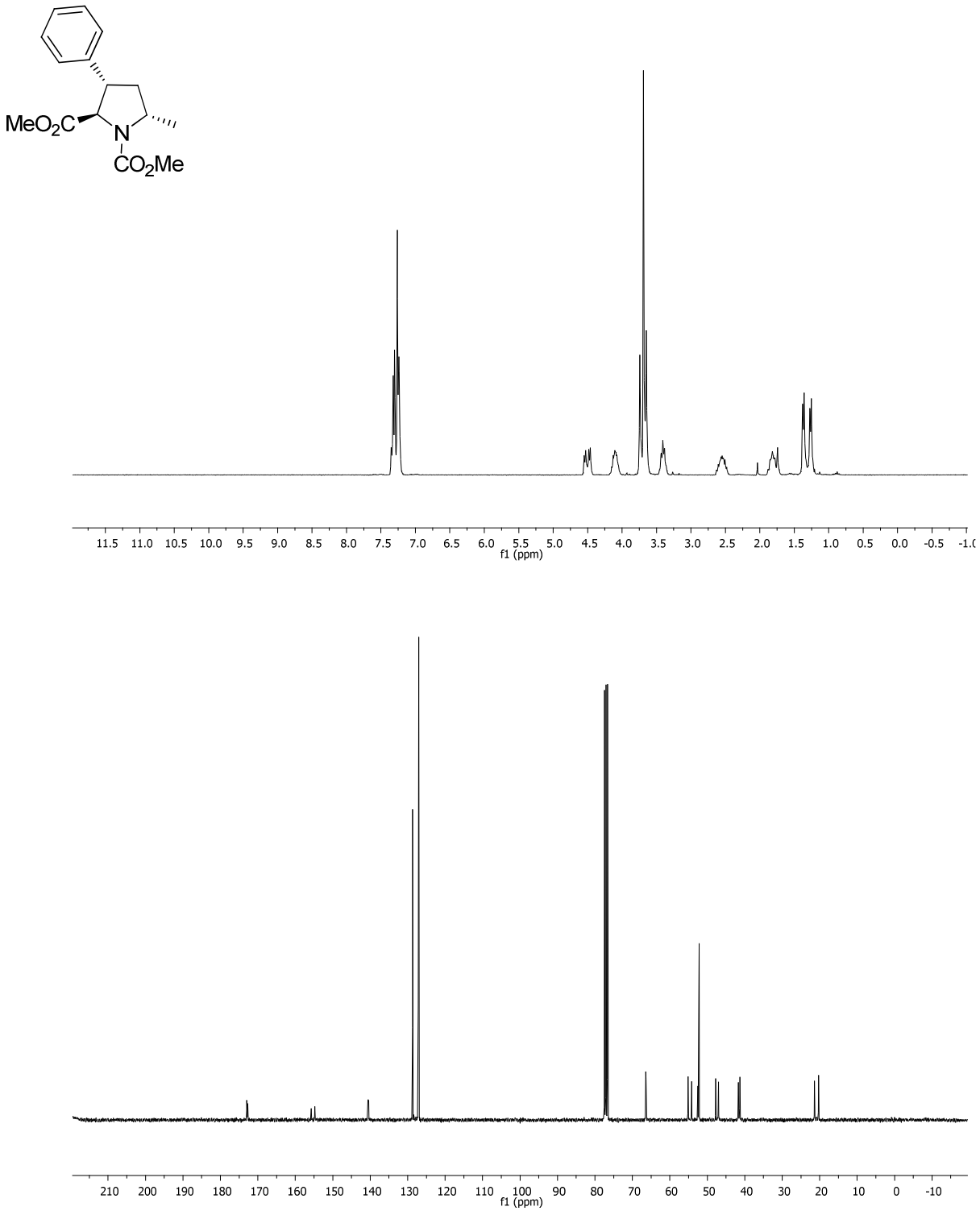


Figure 34: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5r**.

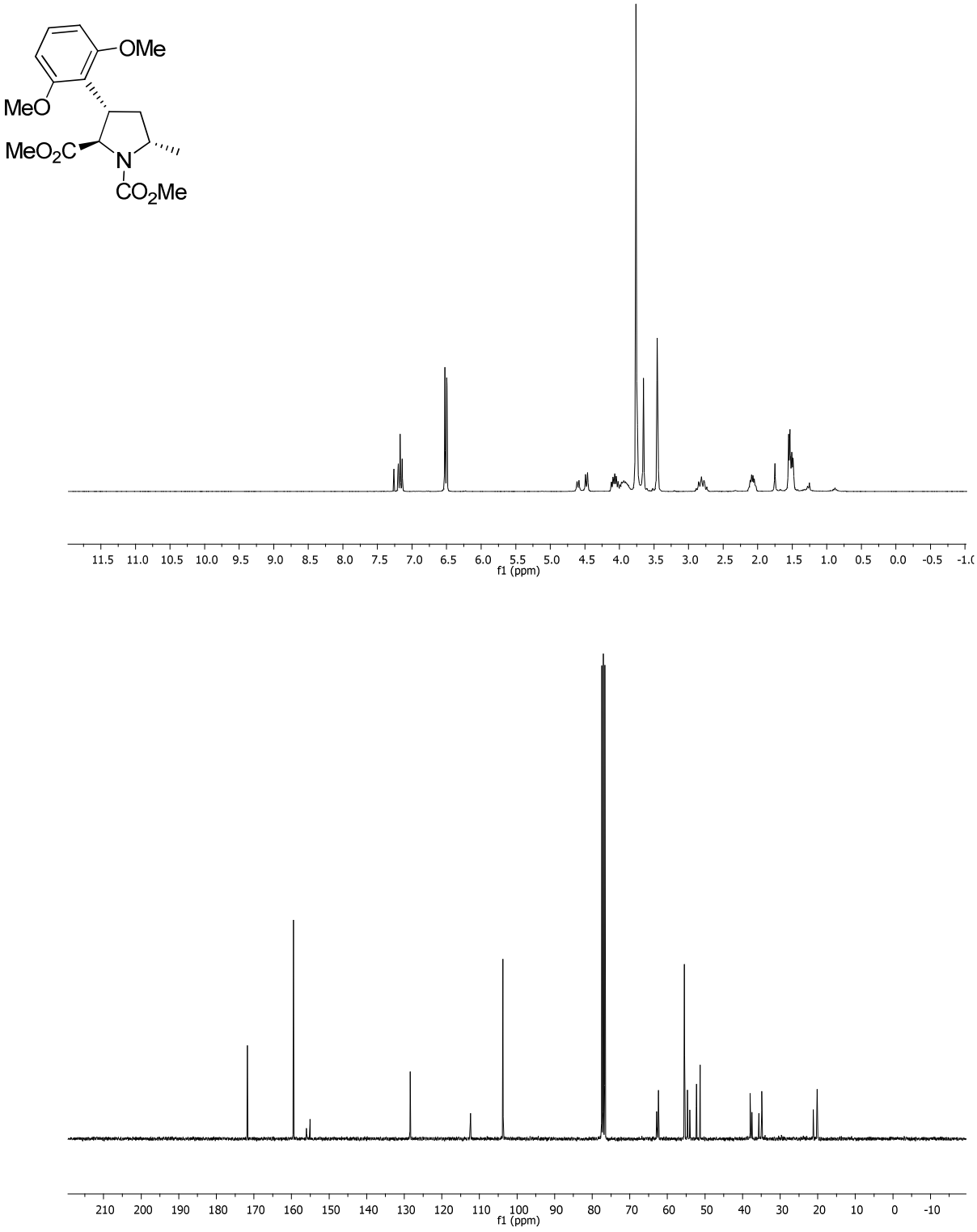


Figure 35: ^{1}H-NMR and ^{13}C-NMR spectra for compound **5s**.

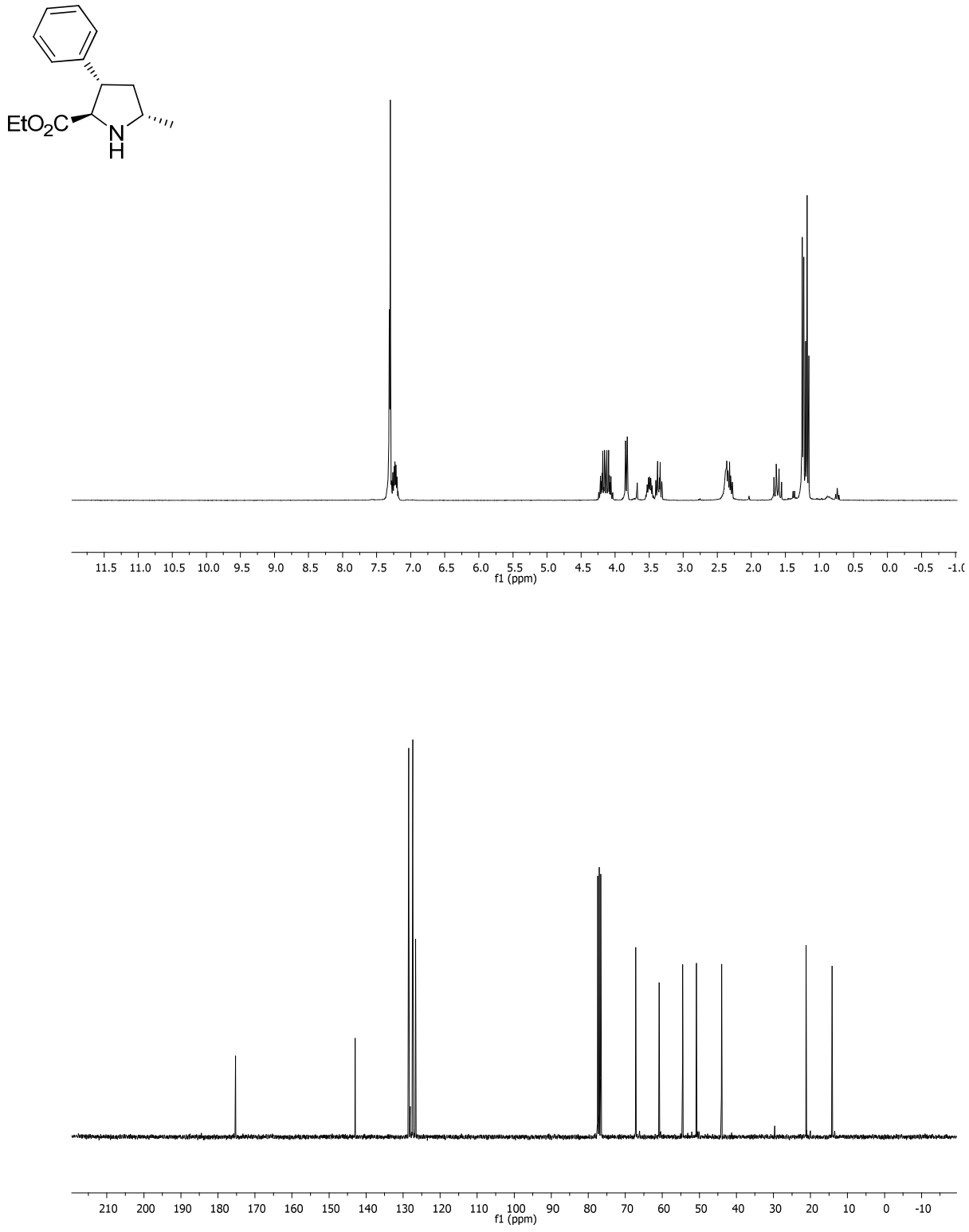


Figure 36: ^{1}H-NMR and ^{13}C-NMR spectra for compound **6a**.

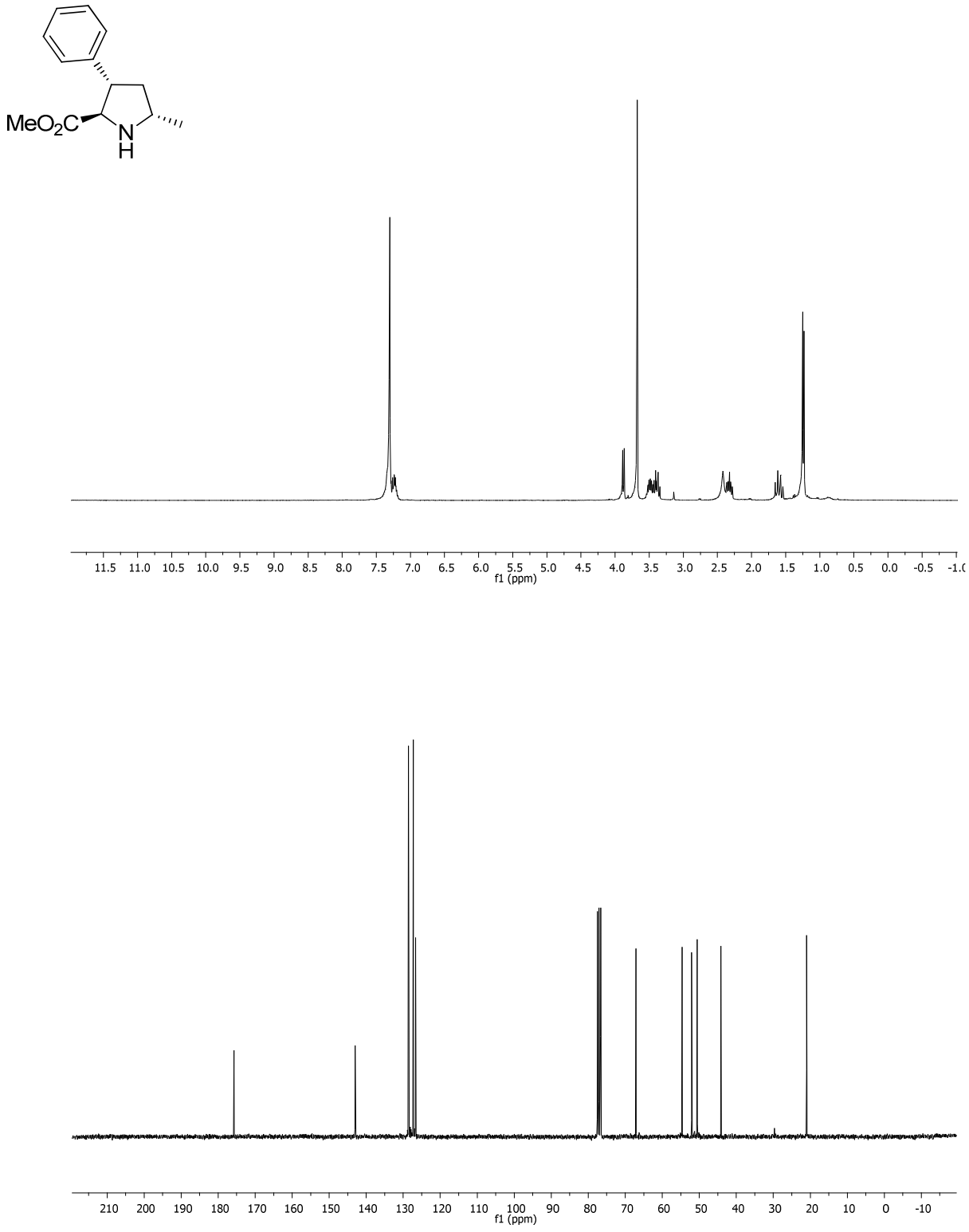
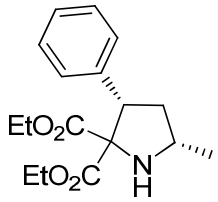
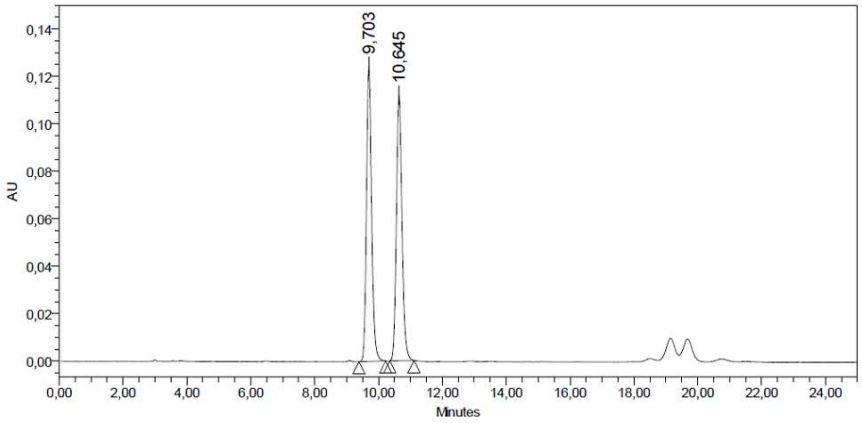


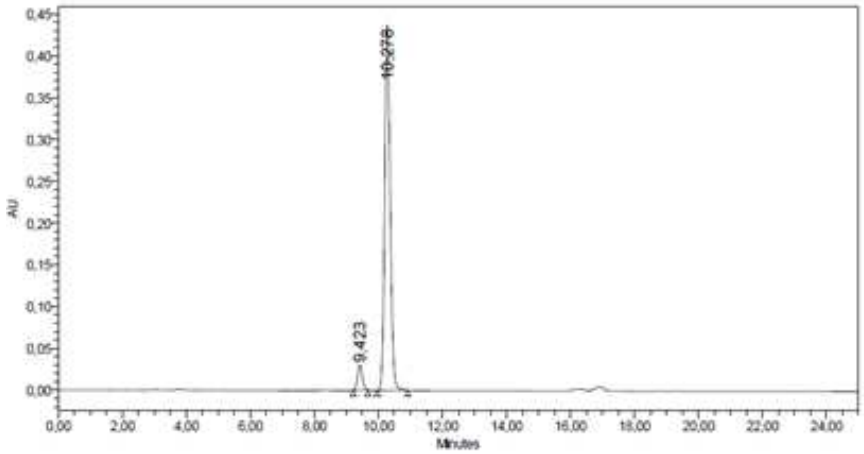
Figure 37: ^{1}H-NMR and ^{13}C-NMR spectra for compound **6r**.

HPLC Chromatograms



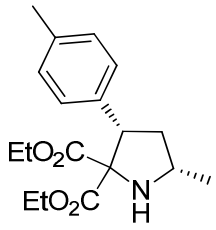


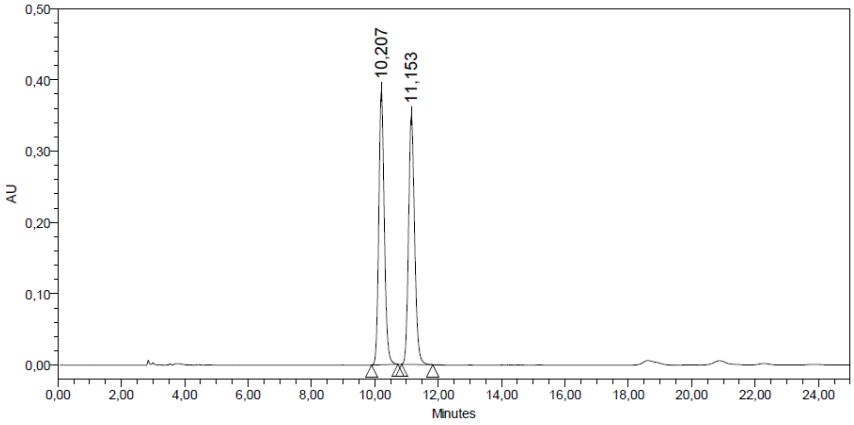
	RT	% Area
1	9,703	50,20
2	10,645	49,80



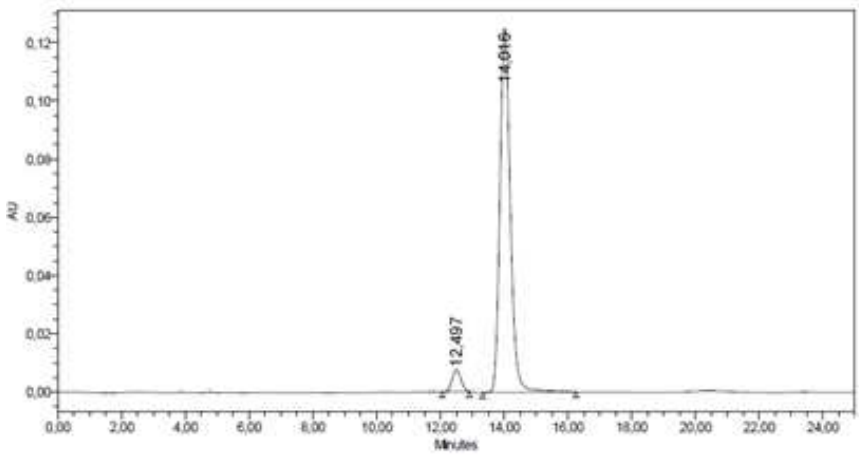
	RT	% Area
1	9,423	5,61
2	10,278	94,39

Figure 38: HPLC chromatogram for compounds ***rac*-4a** and **4a**.



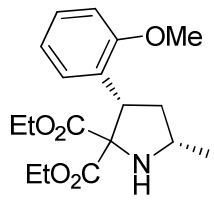


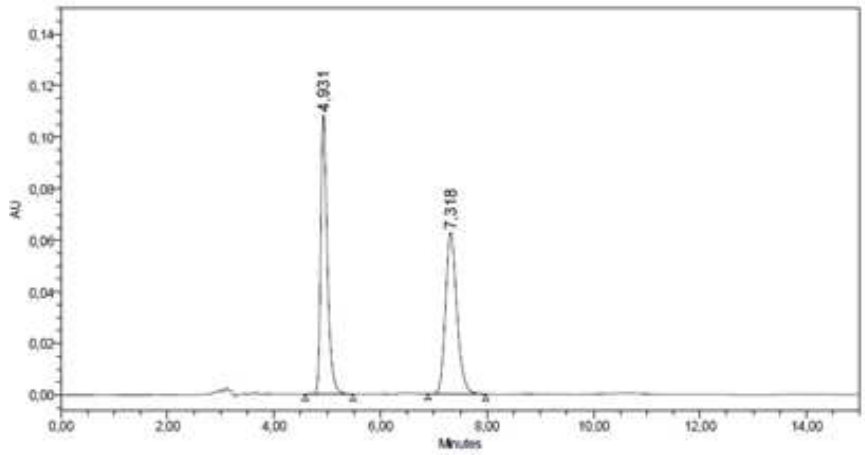
	RT	% Area
1	10,207	50,02
2	11,153	49,98



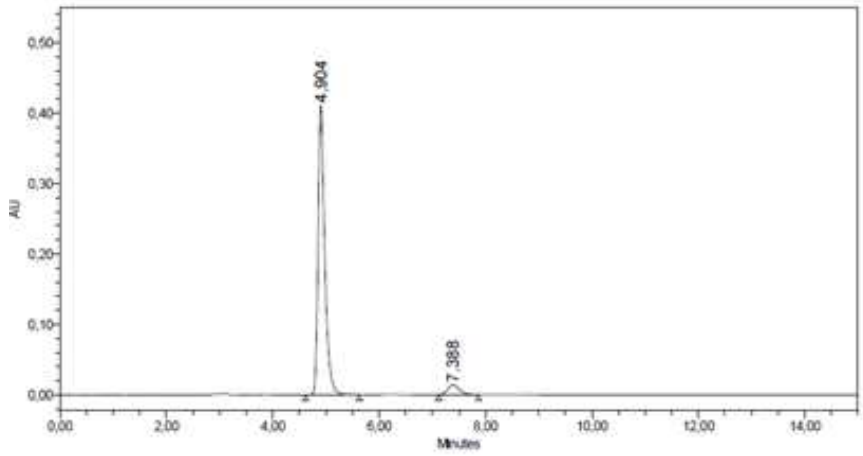
	RT	% Area
1	12,497	4,79
2	14,016	95,21

Figure 39: HPLC chromatogram for compounds ***rac*-4b** and **4b**.



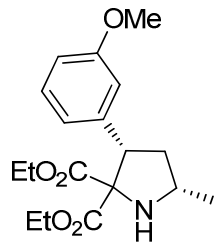


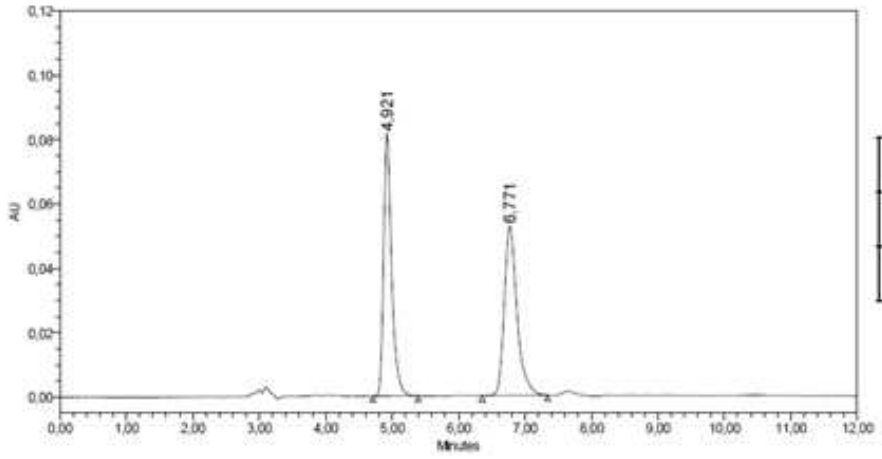
	RT	% Area
1	4,931	50,06
2	7,318	49,94



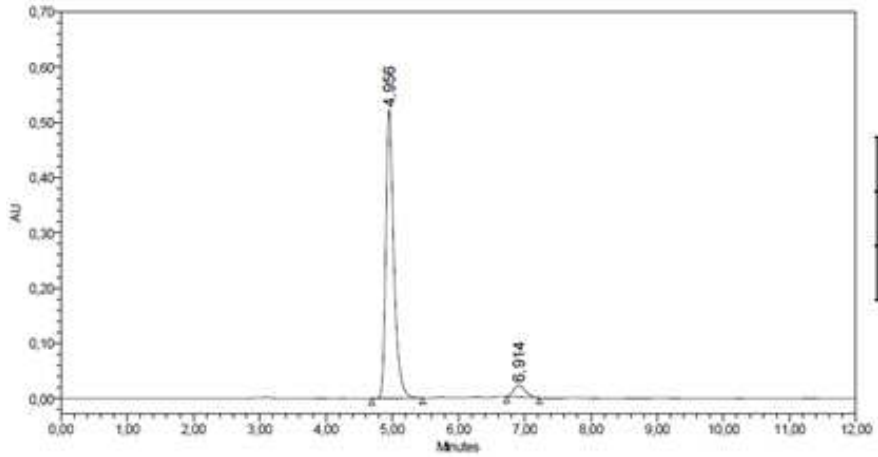
	RT	% Area
1	4,904	94,40
2	7,388	5,60

Figure 40: HPLC chromatogram for compounds ***rac*-4c** and **4c**.



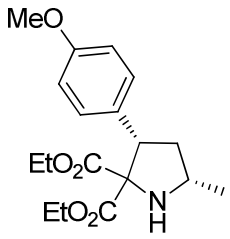


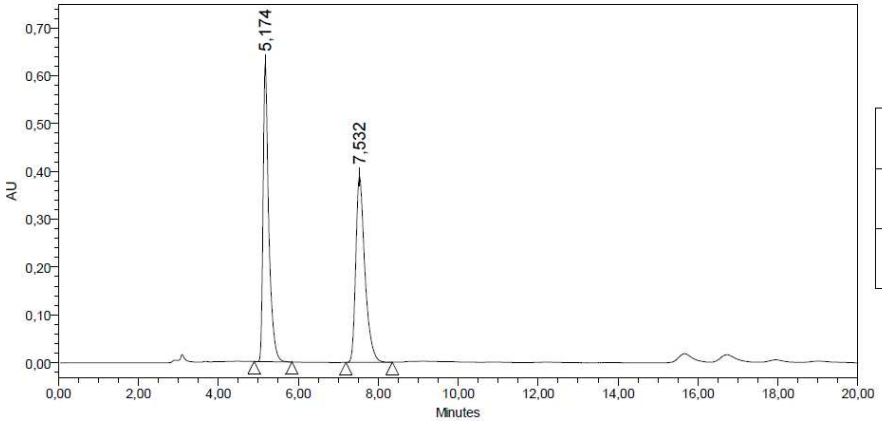
	RT	% Area
1	4,921	49,22
2	6,771	50,78



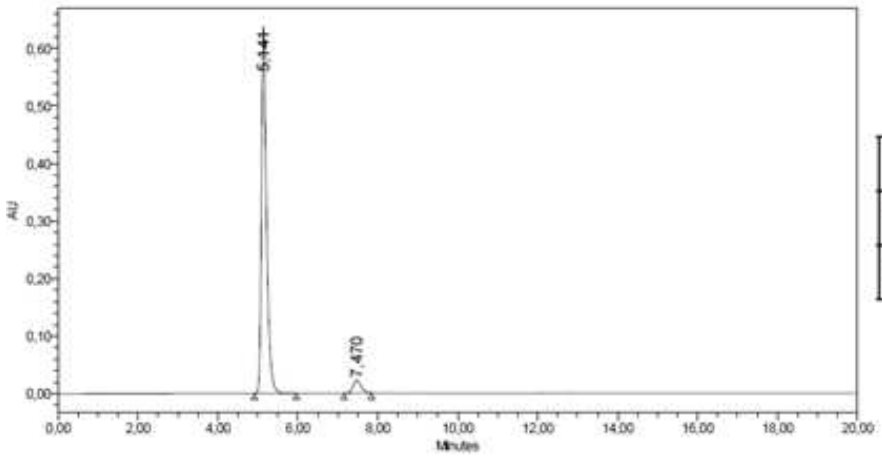
	RT	% Area
1	4,956	94,39
2	6,914	5,61

Figure 41: HPLC chromatogram for compounds ***rac*-4d** and **4d**.



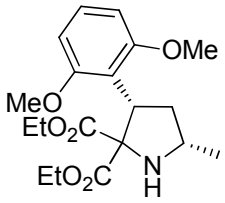


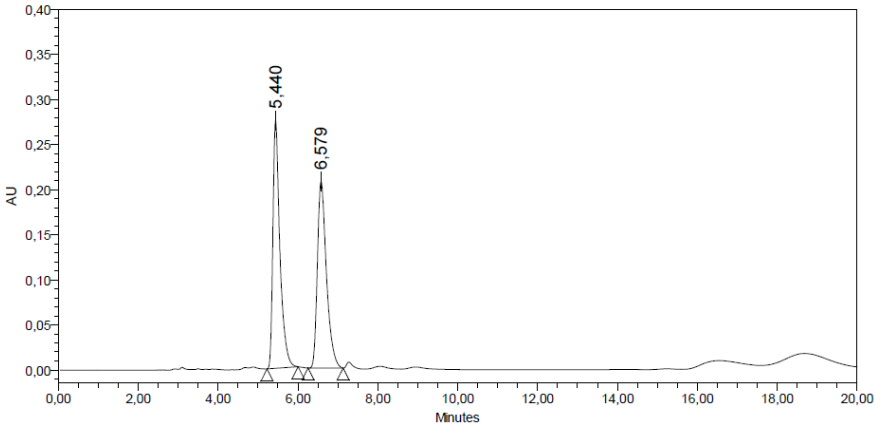
	RT	% Area
1	5,174	50,04
2	7,532	49,96



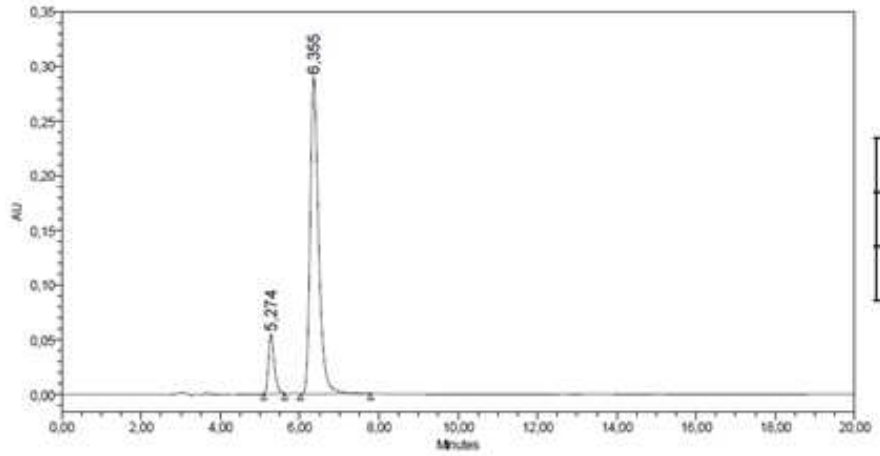
	RT	% Area
1	5,141	94,74
2	7,470	5,26

Figure 42: HPLC chromatogram for compounds ***rac*-4e** and **4e**.



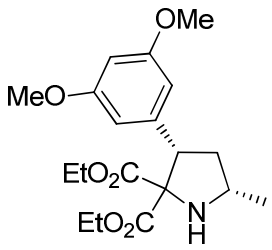


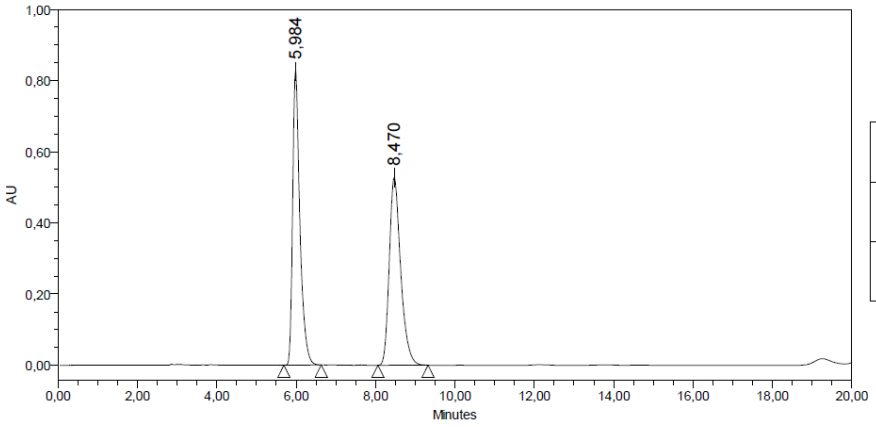
	RT	% Area
1	5,440	50,61
2	6,579	49,39



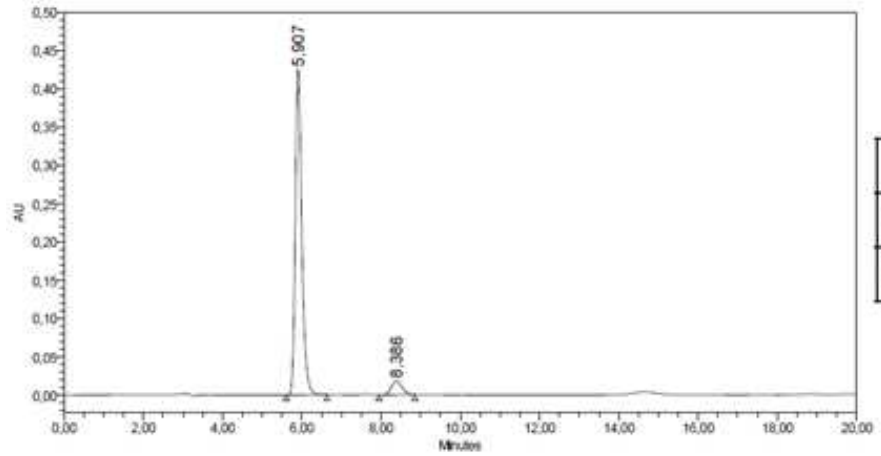
	RT	% Area
1	5,274	11,64
2	6,355	88,36

Figure 43: HPLC chromatogram for compounds ***rac*-4f** and **4f**.



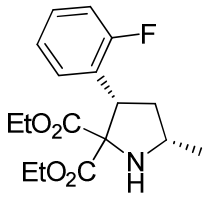


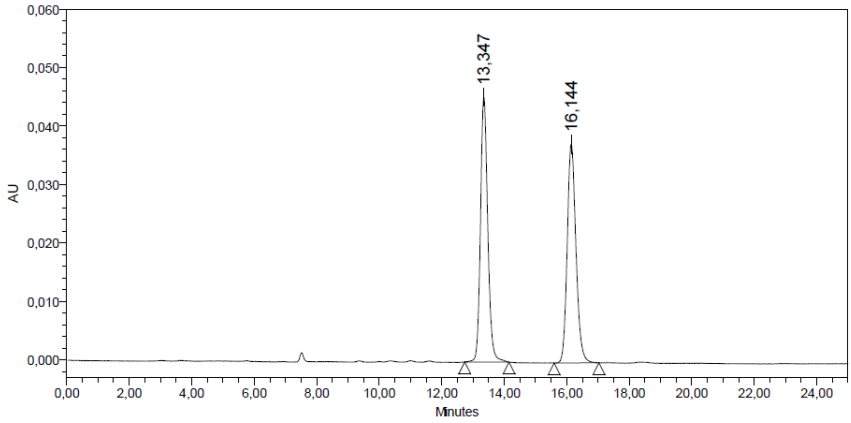
	RT	% Area
1	5,984	49,90
2	8,470	50,10



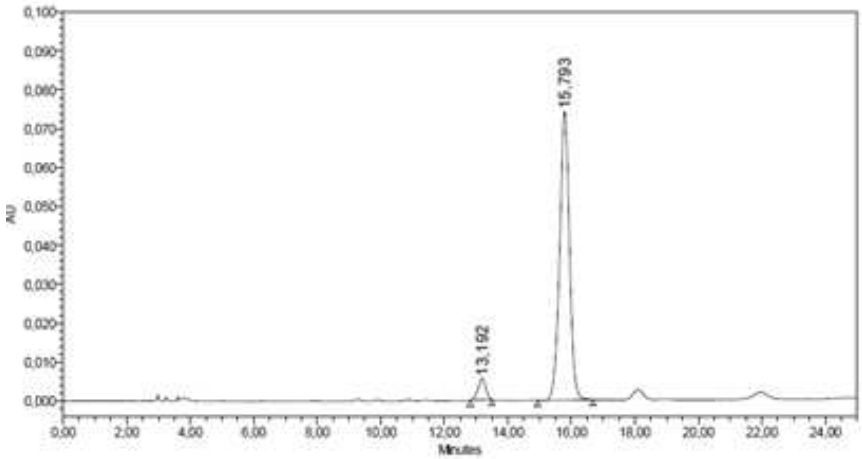
	RT	% Area
1	5,907	93,58
2	8,386	6,42

Figure 44: HPLC chromatogram for compounds ***rac*-4g** and **4g**.



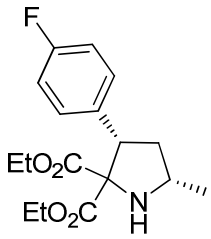


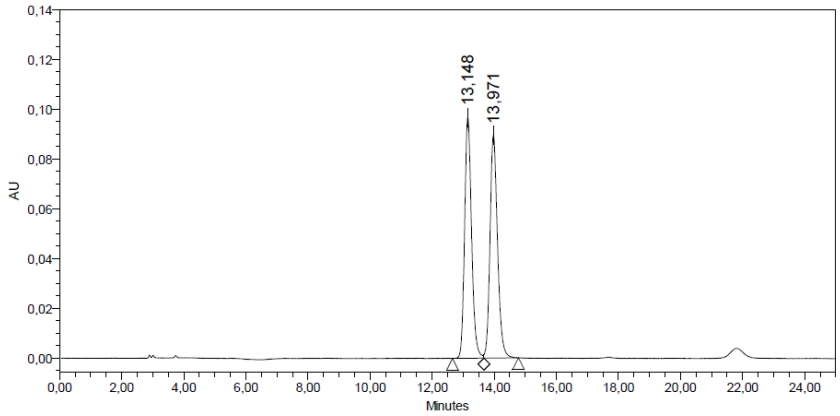
	RT	% Area
1	13,347	50,18
2	16,144	49,82



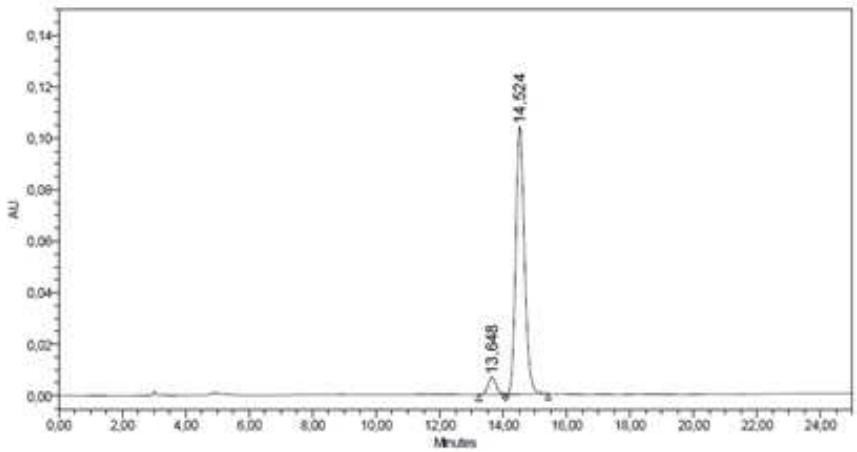
	RT	% Area
1	13,192	5,40
2	15,793	94,60

Figure 45: HPLC chromatogram for compounds ***rac*-4h** and **4h**.



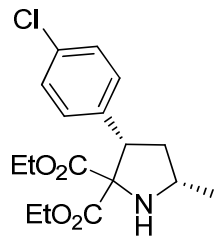


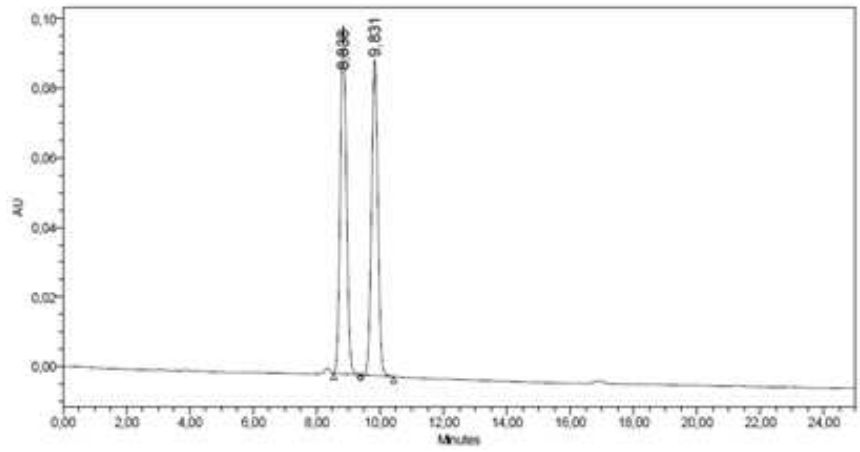
	RT	% Area
1	13,148	49,95
2	13,971	50,05



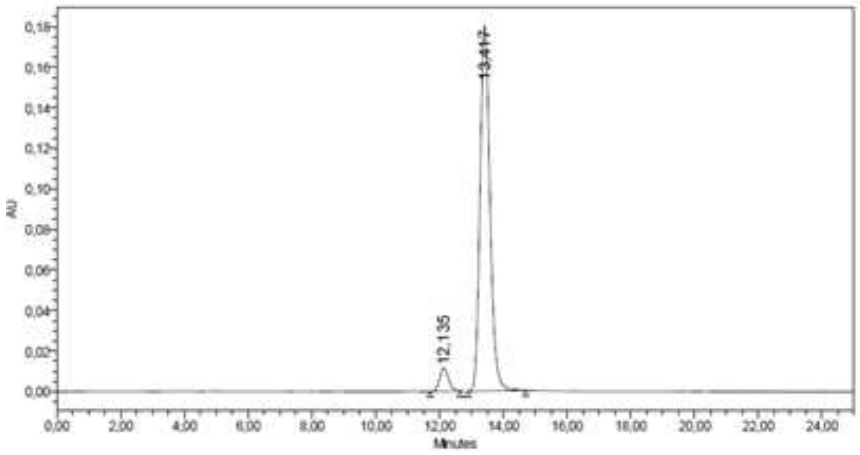
	RT	% Area
1	13,648	5,71
2	14,524	94,29

Figure 46: HPLC chromatogram for compounds ***rac*-4i** and **4i**.



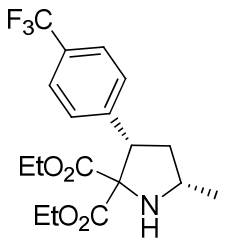


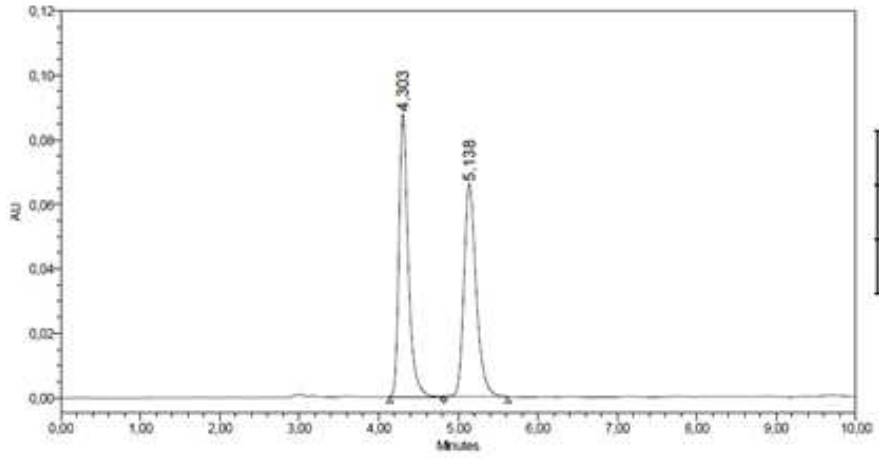
	RT	% Area
1	8,838	51,86
2	9,831	48,14



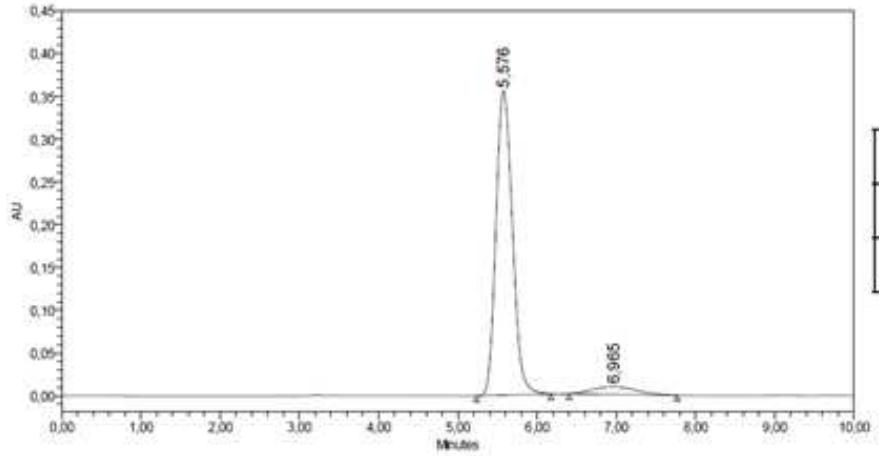
	RT	% Area
1	12,135	5,48
2	13,417	94,52

Figure 47: HPLC chromatogram for compounds ***rac*-4j** and **4j**.



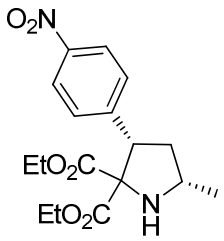


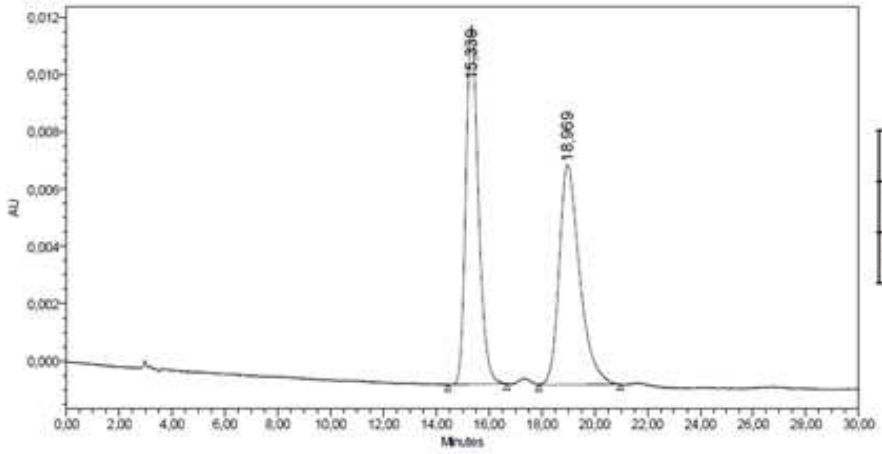
	RT	% Area
1	4,303	50,09
2	5,138	49,91



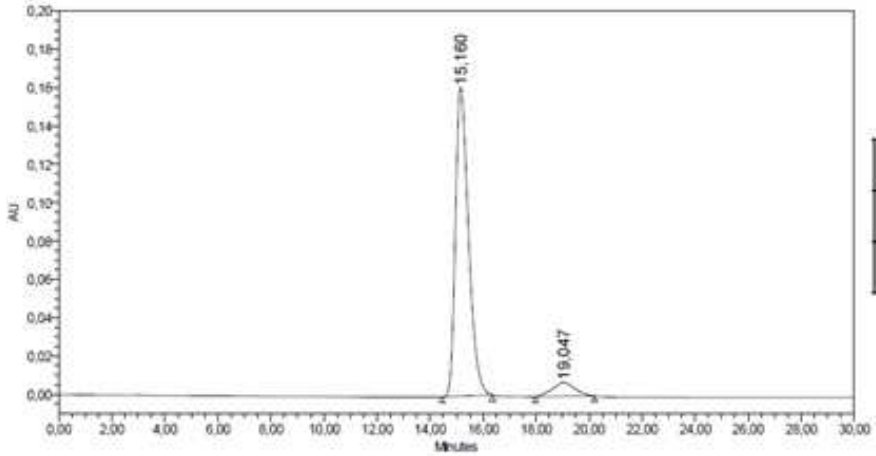
	RT	% Area
1	5,576	93,61
2	6,965	6,39

Figure 48: HPLC chromatogram for compounds ***rac*-4k** and **4k**.



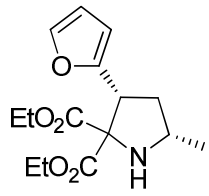


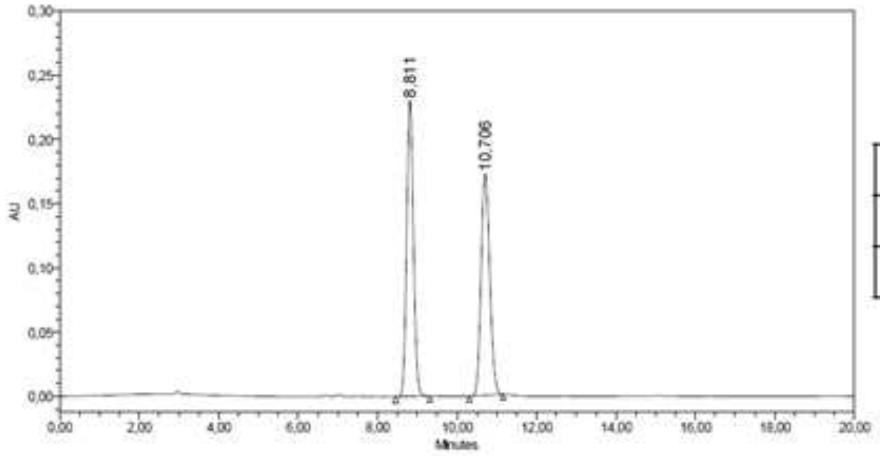
	RT	% Area
1	15,339	50,07
2	18,969	49,93



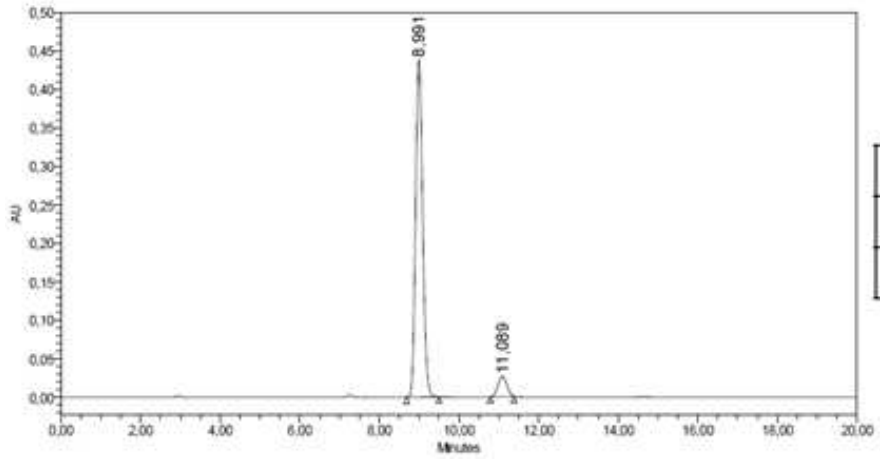
	RT	% Area
1	15,160	92,78
2	19,047	7,22

Figure 49: HPLC chromatogram for compounds ***rac*-4l** and **4l**.



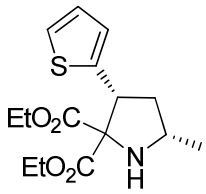


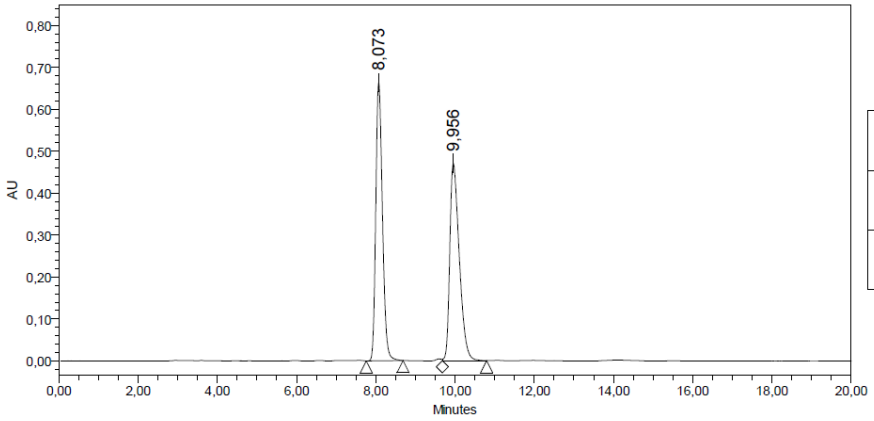
	RT	% Area
1	8,811	51,05
2	10,706	48,95



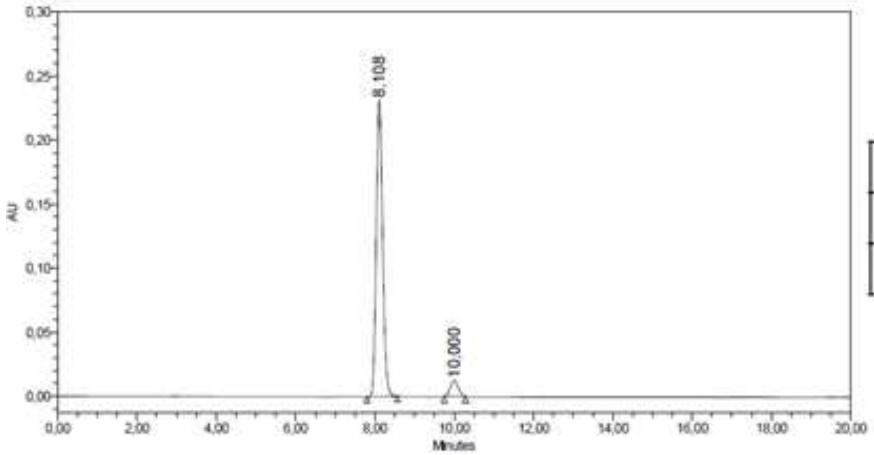
	RT	% Area
1	8,991	93,04
2	11,089	6,96

Figure 50: HPLC chromatogram for compounds ***rac*-4m** and **4m**.



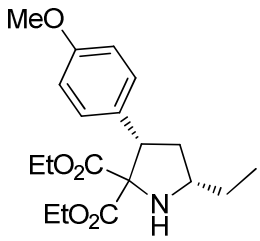


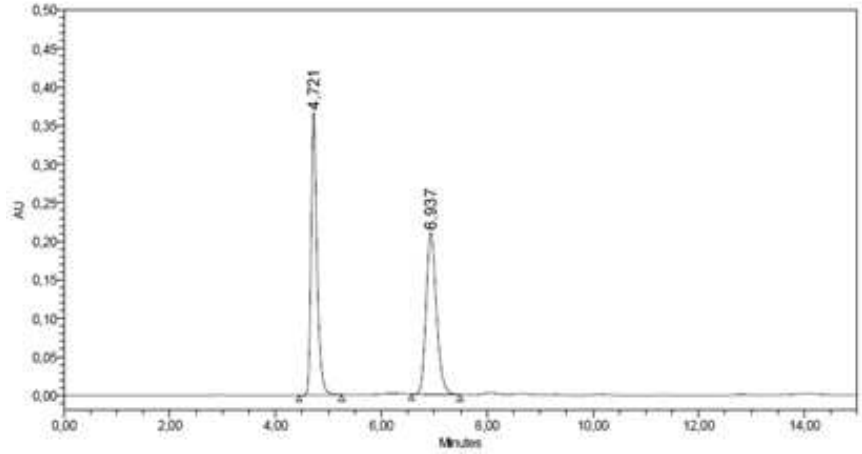
	RT	% Area
1	8,073	49,83
2	9,956	50,17



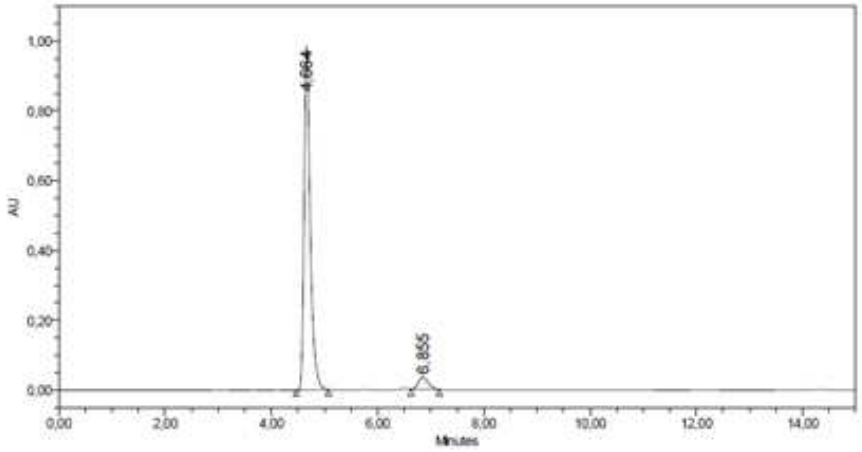
	RT	% Area
1	8,108	93,72
2	10,000	6,28

Figure 51: HPLC chromatogram for compounds ***rac*-4n** and **4n**.



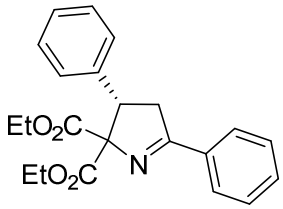


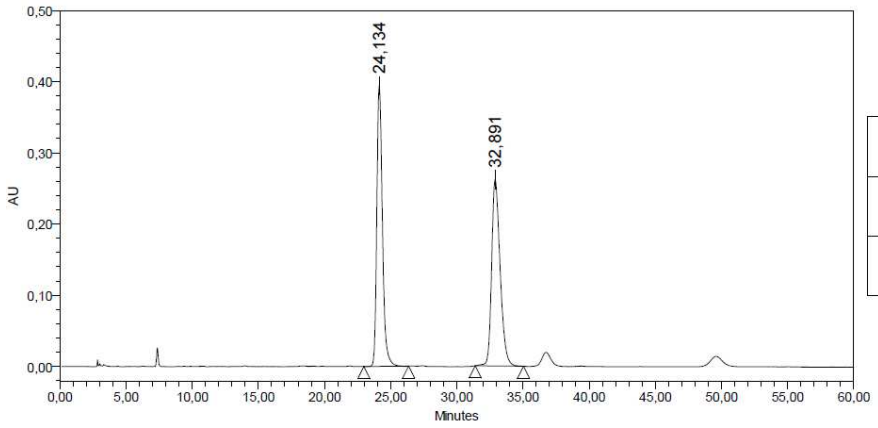
	RT	% Area
1	4,721	50,03
2	6,937	49,97



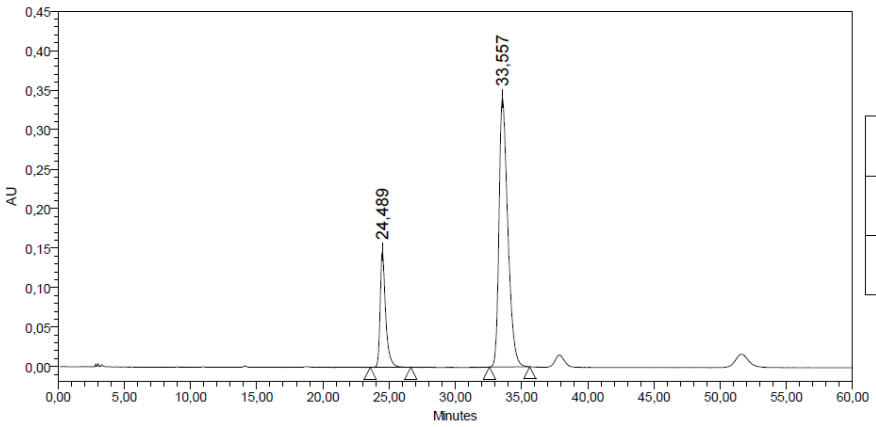
	RT	% Area
1	4,664	94,56
2	6,855	5,44

Figure 52: HPLC chromatogram for compounds ***rac*-4o** and **4o**.



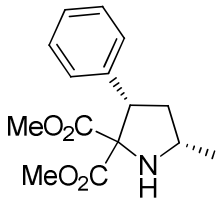


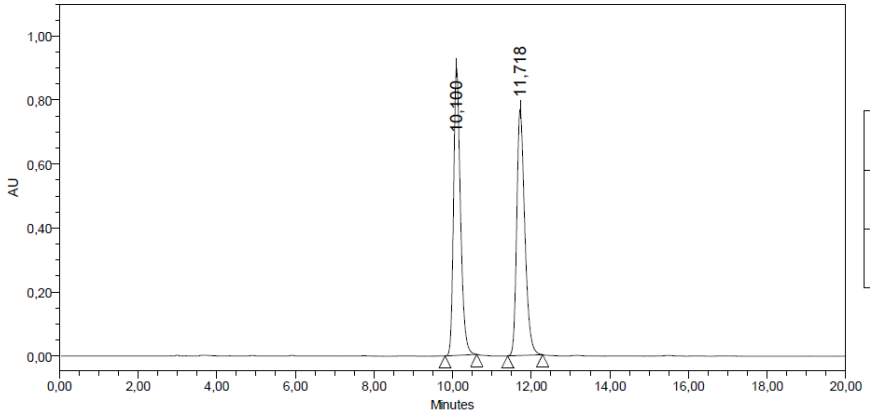
	RT	% Area
1	24,134	50,01
2	32,891	49,99



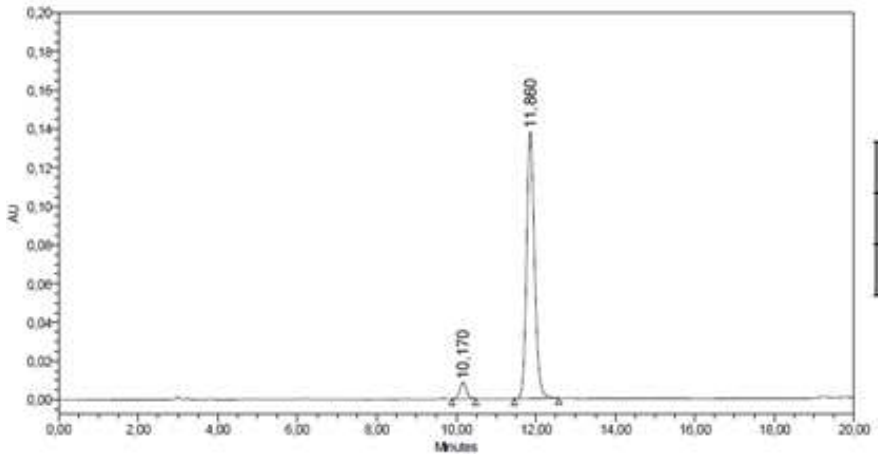
	RT	% Area
1	24,489	21,00
2	33,557	79,00

Figure 53: HPLC chromatogram for compounds ***rac*-4p** and **4p**.



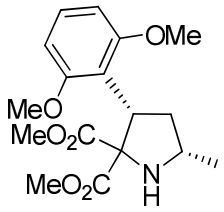


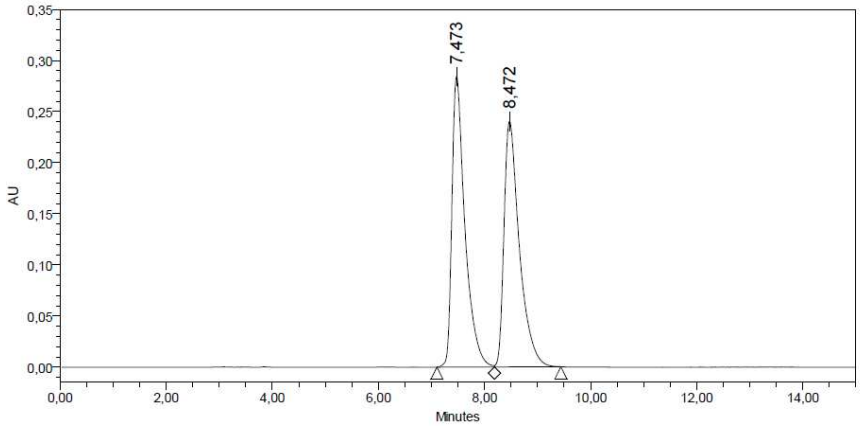
	RT	% Area
1	10,100	49,94
2	11,718	50,06



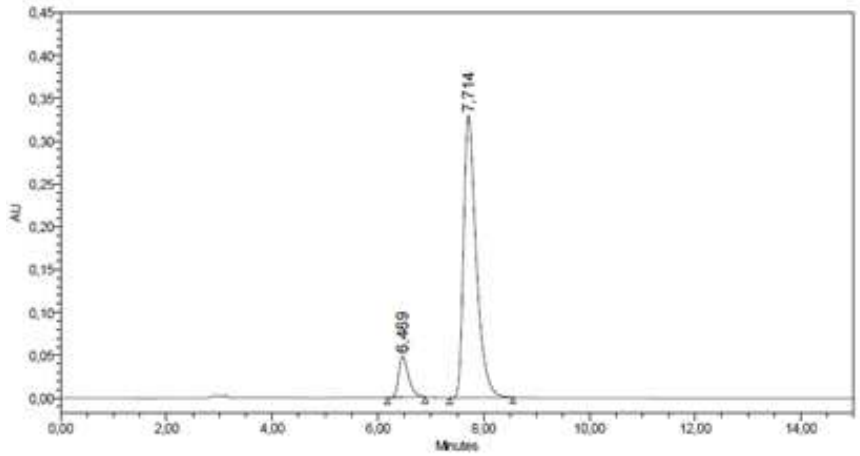
	RT	% Area
1	10,170	4,94
2	11,860	95,06

Figure 54: HPLC chromatogram for compounds ***rac*-4r** and **4r**.





	RT	% Area
1	7,473	50,15
2	8,472	49,85



	RT	% Area
1	6,469	10,09
2	7,714	89,91

Figure 55: HPLC chromatogram for compounds ***rac*-4s** and **4s**.