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Supporting Information

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Organocatalytic Enantioselective [3+2] Cycloaddition of Azomethine Ylides and α,β-Unsaturated Aldehydes

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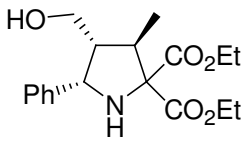
1. General methods:

Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or $CHCl_3$ solution (oils) and were taken on a Perkin-Elmer FT-IR 600 and only characteristic signals are reported. NMR spectra were recorded in a Bruker AC-300 or Bruker AC-500 at 20ºC, running at 300 MHz or 500 MHz for ^1H and 75 MHz or 125.7 MHz for ^{13}C in $CDCl_3$ solution. Resonances are reported in ppm relative to tetramethylsilane unless otherwise stated and the coupling constants *J* are given in Hz. Mass spectra were recorded under electron impact at 70 eV in a Waters Micromass GCT or in a Hewlett Packard 5989B mass spectrometer. Optical rotations were recorded on a Perkin Elemer 241 Polarimeter (λ = 589 nm, 1 dm cell). Microanalyses were obtained with a LECO CHNS-932 element analyser. TLC was carried out with 0.2 mm thick silica gel plates (Merck Kiesegel GF_{254}) and visualization was accomplished by UV light or by spraying with phosphomolybdic acid. Flash column chromatography on silica gel was performed with Merck Kiesegel 60 (230-400 mesh). All solvents used in reactions were purified according to standard procedures.[1] α,α-Diphenylprolinol and the α,β-unsaturated aldehydes employed as starting materials were used as purchased. Imines **1** were prepared using literature procedures.[2] Enantiomeric excesses were determined by HPLC in a Waters600 chromatograph equipped with a photodiode array UV detector Waters996 and using a Chiracel OD or Chiracel OJ column under conditions specified in each case. The racemic standards needed for the optimization of the conditions for the separation of both enantiomers were prepared using DL-proline as catalyst for each case.

2. Organocatalytic [3+2] cycloaddition of α,β-unsaturated aldehydes and azomethine ylides

General Procedure: α,β-Unsaturated aldehyde (1.00 mmol) was added over a cooled (0 ºC) solution of α,α-diphenylprolinol **8** (0.20 mmol) in THF (4 mL). After stirring for 30 min at this temperature, imine **1** (1.3 mmol) and water (4.0 mmol) were added at once. The reaction was stirred at 4 ºC for 72 h, after which the crude reaction mixture was flash column chromatographed (hexanes/AcOEt 8:2), affording the corresponding cycloaddition product **2** which showed to be somewhat unstable and, for that reason and for better characterization purposes, it was reduced to the corresponding primary alcohol. Therefore, $NaBH_4$ (4.00 mmol) was added over a cooled (0 ºC) solution of the corresponding adduct **2** in MeOH (3 mL). After stirring for 15 min. at this temperature, sat. NH_4Cl (3 mL) and CH_2Cl_2 (5 mL) were added and the mixture was stirred for further 30 min at rt. The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Pure alcohols **11** were isolated after flash column chromatography purification (hexanes/AcOEt 1:1).

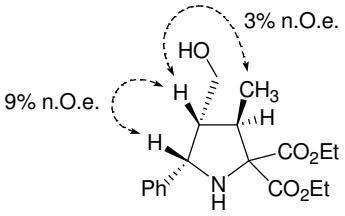
Diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-methyl-5-phenylpyrrolidine-2,2-dicarboxylate (11a)



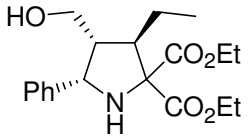
11a

Pyrrolidine **2a** (208 mg, 0.62 mmol) was prepared according to the general procedure using crotonaldehyde (58 µl, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1a** (197 mg, 0.75 mmol). Yield: 89%. *endo*/*exo*: >95:<5 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.12 (d, 3H, *J*=6.8 Hz); 1.29 (m, 6H); 2.92 (dt, 1H, *J*=2.8, 9.1 Hz); 3.06 (bs, 1H); 3.30 (m, 1H); 4.24 (m, 4H); 5.11 (d, 1H, *J*=9.2 Hz); 7.23 (m, 5H); 9.00 (d, 1H, *J*=2.9 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.2; 15.1; 38.7; 60.9; 61.2; 61.7; 61.8; 77.1; 127.1; 127.7; 128.7; 140.0; 169.6; 171.7; 201.4. IR ($CHCl_3$, cm^{-1}): 3357 (NH); 1730 (CO). MS (70eV) *m*/*z* (%): 333 (M^+, 1), 260 (100), 214 (14), 186 (13), 158 (9), 143 (7), 91 (7). HRMS: Calcd for $C_{18}H_{23}NO_5$: 333.1576. Found: 333.1570. Reduction of **2a** (183 mg, 0.55 mmol) afforded diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-methyl-5-phenylpyrrolidine-2,2-dicarboxylate **11a** (171 mg, 0.51 mmol). Yield: 93%. e.e.: 98% (Chiracel OD, hexane/2-propanol 95:5, flow rate 1.00 mL/min t_R for the major (3*R*,4*R*,5*S*) isomer: 12.97 min; t_R for the minor (3*S*,4*S*,5*R*) isomer: 15.17 min). $[\alpha]_D^{20}$= −46.2 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.15 (d, 3H, *J*=7.1 Hz); 1.28 (m, 6H); 2.16 (m, 1H); 2.94 (m, 1H); 3.00 (bs, 1H); 3.19 (dd, 1H, *J*=7.3, 11.3 Hz); 3.35 (dd, 1H, *J*=5.3, 11.3 Hz); 4.26 (m, 4H); 4.86 (d, 1H, *J*=8.1 Hz); 7.26 (m, 5H). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.1; 14.2; 15.7;

39.5; 51.6; 61.5; 61.7; 61.9; 75.0; 127.2; 127.3; 128.4; 141.5; 170.7; 172.1. IR ($CHCl_3$, cm^{-1}): 3366 (NH+OH); 1728 (CO). MS (70eV) *m/z* (%): 335 (M^+, 1), 289 (5), 262 (12), 245 (46), 216 (67), 172 (62), 156 (52), 143 (27), 129 (85), 117 (100), 106 (17), 91 (48), 77 (14), 55 (10). Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.42; H, 7.49; N, 4.23.



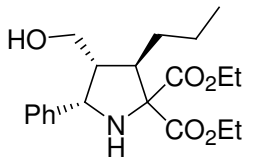
Diethyl (3*R*,4*R*,5*S*)-3-ethyl-4-hydroxymethyl-5-phenylpyrrolidine-2,2-dicarboxylate (11b)



11b

Pyrrolidine **2b** (221 mg, 0.64 mmol) was prepared according to the general procedure using *E*-2-pentenal (69 µl, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1a** (197 mg, 0.75 mmol). Yield: 91%. *endo*/*exo*: >95:<5 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 0.93 (t, 3H, *J*=7.4 Hz); 1.32 (m, 7H); 1.83 (m, 1H); 2.92 (m, 1H); 3.02 (bs, 1H); 3.25 (m, 1H); 4.29 (m, 4H); 5.15 (d, 1H, *J*=8.6 Hz); 7.21 (m, 5H); 9.06 (d, 1H, *J*=4.3 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 12.9; 14.0; 14.2; 23.8; 45.7; 59.2; 61.7; 61.8; 62.0; 75.1; 127.2; 127.7; 128.6; 139.0; 169.6; 171.8; 202.2. IR ($CHCl_3$, cm^{-1}): 3348 (NH); 1731 (CO). MS (70eV) *m/z* (%): 347 (M^+, 1), 274 (100), 228 (11), 200 (12), 172 (6), 143 (7), 117 (11); 91 (7). HRMS: Calcd for $C_{19}H_{25}NO_5$: 347.1733. Found: 347.1727. Reduction of **2b** (203 mg, 0.58 mmol) afforded diethyl (3*R*,4*R*,5*S*)-3-ethyl-4-hydroxymethyl-5-phenylpyrrolidine-2,2-dicarboxylate **11b** (186 mg, 0.53 mmol). Yield: 91%. e.e.: 97% (Chiracel OD, hexane/2-propanol 95:5, flow rate 1.00 mL/min t_R for the major (3*R*,4*R*,5*S*) isomer: 11.52 min; t_R for the minor (3*S*,4*S*,5*R*) isomer: 13.87 min). $[\alpha]_D^{20}$= −69.4 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.06 (t, 3H, *J*=7.3 Hz); 1.31 (m, 6H); 1.43 (m, 1H); 1.67 (m, 1H); 2.30 (m, 1H); 2.87 (m, 1H); 3.06 (bs, 1H); 3.31 (m, 2H); 4.26 (m, 4H); 4.88 (d, 1H, *J*=7.0 Hz); 7.29 (m, 5H). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 13.0; 14.0; 14.2; 23.5; 46.9; 49.3; 61.6; 61.7; 62.2; 62.5; 74.7; 126.9; 127.3; 128.5; 140.4; 170.9; 172.2. IR ($CHCl_3$, cm^{-1}): 3357 (NH+OH); 1730 (CO). MS (70eV) *m/z* (%): 349 (M^+, 3), 259 (16), 230 (100), 216 (14), 186 (29), 156 (35), 143 (37), 117 (46), 106 (7), 91 (22), 77 (6). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.38; H, 7.86; N, 3.94.

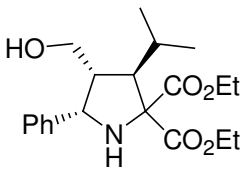
Diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-5-phenyl-3-propylpyrrolidine-2,2-dicarboxylate (11c)



11c

Pyrrolidine **2c** (220 mg, 0.61 mmol) was prepared according to the general procedure using *E*-2-hexenal (81 µl, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1a** (197 mg, 0.75 mmol). Yield: 87%. *endo*/*exo*: >95:<5 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 0.90 (t, 3H, *J*=7.3 Hz); 1.22 (m, 9H); 1.69 (m, 1H); 2.84 (m, 1H); 3.05 (bs, 1H); 3.31 (m, 1H); 4.25 (m, 4H); 5.14 (d, 1H, *J*=9.2 Hz); 7.32 (m, 5H); 9.02 (d, 1H, *J*=4.2 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 13.9; 14.0; 14.2; 21.4; 33.0; 43.8; 59.6; 61.6; 61.7; 62.0; 75.1; 127.2; 127.7; 128.6; 139.0; 169.6; 171.8; 202.1. IR ($CHCl_3$, cm^{-1}): 3345 (NH); 1729 (CO). MS (70eV) *m*/*z* (%): 332 (M^+-29, 3), 288 (100), 242 (10), 214 (11), 189 (8), 144 (8), 117 (14); 91 (10). HRMS: Calcd for $C_{20}H_{27}NO_5$: 361.1889. Found: 361.1894. Reduction of **2c** (200 mg, 0.55 mmol) afforded diethyl (3*R*,4*R*,5*S*)-4-Hydroxymethyl-5-phenyl-3-propylpyrrolidine-2,2-dicarboxylate **11c** (191 mg, 0.53 mmol). Yield: 95%. e.e.: 97% (Chiracel OD, hexane/2-propanol 98:2, flow rate 1.00 mL/min t_R for the major (3*R*,4*R*,5*S*) isomer: 11.64 min; t_R for the minor (3*S*,4*S*,5*R*) isomer: 13.55 min). $[\alpha]_D^{20}$= −57.2 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 0.92 (t, 3H, *J*=6.3 Hz); 1.28 (m, 6H); 1.35 (m, 2H); 1.52 (m, 2H); 2.25 (m, 1H); 2.95 (bs+m, 2H); 3.25 (m, 2H); 4.23 (m, 4H); 4.84 (d, 1H, *J*=7.1 Hz); 7.25 (m, 5H). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.2; 14.4; 21.5; 32.9; 44.9; 49.7; 61.6; 61.7; 62.2; 62.4; 74.8; 126.9; 127.2; 128.4; 140.5; 170.9; 172.2. IR ($CHCl_3$, cm^{-1}): 3360 (NH+OH); 1728 (CO). MS (70eV) *m*/*z* (%): 363 (M^+, 2), 317 (3), 273 (19), 244 (53), 230 (100), 216 (21), 200 (56), 156 (47), 143 (25), 128 (22), 117 (68), 91 (29). Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 66.12; H, 8.11; N, 3.77.

Diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-*iso*-propyl-5-phenylpyrrolidine-2,2-dicarboxylate (11d)



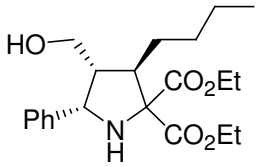
11d

Pyrrolidine **2d** (215 mg, 0.60 mmol) was prepared according to the general procedure using *E*-4-methyl-2-pentenal (83 µl, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1a** (197 mg, 0.75 mmol). Yield: 85%. *endo*/*exo*: >95:<5 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 0.80 (d, 3H, *J*=6.7Hz); 1.00 (d, 3H, *J*=6.8Hz); 1.30 (m, 6H); 2.11 (m, 1H); 2.89 (bs, 1H); 3.03 (m, 1H); 3.35 (m, 1H); 4.21 (m, 2H); 4.31 (m, 2H); 5.07 (d, 1H, *J*=9.1Hz); 7.24 (m, 5H); 9.05 (d, 1H, *J*=4.5Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.1; 19.3; 23.5; 27.7; 50.0; 55.8; 61.8; 62.0; 62.7; 74.8; 127.3; 127.8; 128.6; 138.9; 169.7; 172.2; 202.5. IR ($CHCl_3$, cm^{-1}): 3365 (NH); 1728 (CO). MS (70eV) *m*/*z* (%): 361 (M^+, 1), 288 (100), 214 (7), 189 (7), 144 (9), 117 (10), 91

(7). HRMS: Calcd for $C_{20}H_{27}NO_5$: 361.1889. Found: 361.1890. Reduction of **2d** (207 mg, 0.57 mmol) afforded diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-*iso*-propyl-5-phenylpyrrolidine-2,2-dicarboxylate **11d** (185 mg, 0.51 mmol). Yield: 89%. e.e.: 95% (Chiracel OD, hexane/2-propanol 95:5, flow rate 1.00 mL/min t_R for the major (3*R*,4*R*,5*S*) isomer: 8.50 min; t_R for the minor (3*S*,4*S*,5*R*) isomer: 10.32 min). $[\alpha]_D^{20}$= −74.7 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 0.90 (d, 3H, *J*=6.7 Hz); 1.05 (d, 3H, *J*=6.9 Hz); 1.28 (m, 6H); 1.61 (bs, 1H); 2.26 (m, 1H); 2.40 (m, 1H); 2.99 (m+bs, 2H); 3.32 (d, 2H, *J*=5.4 Hz); 4.51 (m, 4H); 4.79 (d, 1H, *J*=7.1 Hz); 7.27 (m, 5H). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.1; 17.7; 23.7; 27.1; 45.3; 51.0; 61.7; 62.0; 63.5; 63.6; 74.0; 126.8; 127.4; 128.6; 140.2; 170.6; 172.6. IR ($CHCl_3$, cm^{-1}): 3437 (NH+OH); 1726 (CO). MS (70eV) *m*/*z* (%): 363 (M^+, 1), 272 (7), 230 (100), 216 (11), 200 (11), 156 (32), 143 (16), 117 (26), 91 (12). Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 65.97; H, 8.11; N, 3.91.

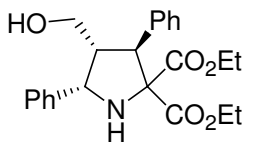
Diethyl (3*R*,4*R*,5*S*)-3-Butyl-4-hydroxymethyl-5-phenylpyrrolidine-2,2-dicarboxylate (11e)

Pyrrolidine **2e** (231 mg, 0.62 mmol) was prepared according to the general procedure using *E*-2-heptenal (92 µl, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1a** (197 mg, 0.75 mmol). Yield: 88%. *endo*/*exo*: >95:<5 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 0.78 (t, 3H, *J*=6.4Hz); 1.32 (m, 10H); 1.68 (m, 1H); 1.76 (m, 1H); 2.75 (m, 1H); 2.91 (bs, 1H); 3.42 (m, 1H); 4.46 (m, 4H); 5.15 (d, 1H, *J*=9.1Hz); 7.28 (m, 5H); 9.08 (d, 1H, *J*=4.5Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.1; 14.3; 22.4; 27.8; 30.7; 31.8; 44.0; 59.6; 61.7; 62.0; 75.1; 127.2; 127.7; 128.6; 139.0; 169.7; 171.9; 202.2. IR ($CHCl_3$, cm^{-1}): 3362 (NH); 1725 (CO). MS (70eV) *m*/*z* (%): 346 (M^+-29, 6), 218 (100), 191 (5), 136 (7), 115 (12), 91 (6). HRMS: Calcd for $C_{21}H_{29}NO_5$: 375.2046. Found: 375.2053. Reduction of **2e** (223 mg, 0.59 mmol) afforded diethyl (3*R*,4*R*,5*S*)-3-butyl-4-hydroxymethyl-5-phenylpyrrolidine-2,2-dicarboxylate **11e** (208 mg, 0.55 mmol). Yield: 93%. e.e.: 99% (Chiracel OD, hexane/2-propanol 98:2, flow rate 1.00 mL/min t_R for the major (3*R*,4*R*,5*S*) isomer: 11.21 min; t_R for the minor (3*S*,4*S*,5*R*) isomer: 12.46 min). $[\alpha]_D^{20}$= −62.5 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 0.90 (t, 3H, *J*=6.4 Hz); 1.29 (m, 6H); 1.51 (m, 3H); 2.27 (m, 1H); 2.94 (m, 2H); 3.28 (m, 2H); 4.27 (m, 4H); 4.86 (d, 1H, *J*=7.0 Hz); 7.31 (m, 5H). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.1; 14.2; 22.6; 28.1; 30.7; 32.0; 45.2; 49.8; 61.6; 62.2; 62.4; 74.8; 126.9; 127.3; 128.5; 140.5; 170.9; 172.2. IR ($CHCl_3$, cm^{-1}): 3440 (NH+OH); 1729 (CO). MS (70eV) *m*/*z* (%): 359(M^+-18, 1), 206 (100), 189 (15), 147 (33), 117 (12), 91 (21). Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.77; H, 8.34; N, 3.65.



11e

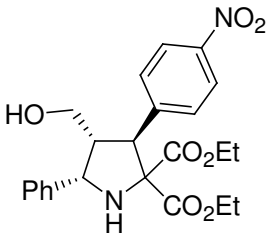
Diethyl (3*S*,4*R*,5*S*)-4-hydroxymethyl-3,5-diphenylpyrrolidine-2,2-dicarboxylate (11f)



11f

Pyrrolidine **2f** (227 mg, 0.57 mmol) was prepared according to the general procedure using cinnamaldehyde (88 µl, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1a** (197 mg, 0.75 mmol). Yield: 82%. *endo*/*exo*: >95:<5 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 0.79 (t, 3H, *J*=7.1 Hz); 1.26 (t, 3H, *J*=7.1 Hz); 3.30 (bs, 1H); 3.51 (m, 1H); 3.84 (m, 1H); 4.19 (m, 2H); 4.31 (m, 2H); 4.84 (d, 1H, *J*=7.9 Hz); 7.34 (m, 10H); 9.07 (d, 1H, *J*=3.2 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 13.4; 14.0; 48.3; 60.0; 61.6; 61.8; 62.9; 76.9; 127.1; 127.6; 128.4; 128.6; 128.7; 128.9; 131.3; 137.5; 169.5; 171.6; 200.6. IR ($CHCl_3$, cm^{-1}): 3345 (NH); 1729 (CO). MS (70eV) *m*/*z* (%): 395 (6), 350 (11), 249 (6), 189 (8), 144 (12), 115 (9), 91 (7), 77 (100). HRMS: Calcd for $C_{23}H_{25}NO_5$: 395.1733. Found: 395.1735. Reduction of **2f** (205 mg, 0.52 mmol) afforded diethyl (3*S*,4*R*,5*S*)-4-hydroxymethyl-3,5-diphenylpyrrolidine-2,2-dicarboxylate **11f** (181 mg, 0.46 mmol). Yield: 88%. e.e.: >99% (Chiracel OD, hexane/2-propanol 98:2, flow rate 1.00 mL/min t_R for the major (3*S*,4*R*,5*S*) isomer: 21.18 min; t_R for the minor (3*R*,4*S*,5*R*) isomer: 24.38 min). $[\alpha]_D^{20}$= −37.6 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 0.77 (t, 3H, *J*=7.1 Hz); 1.24 (t, 3H, *J*=7.1 Hz); 1.25 (bs, 1H); 2.98 (m, 1H); 3.25 (m, 2H); 3.49 (m, 1H); 3.89 (m, 1H); 4.27 (m, 4H); 5.17 (d, 1H, *J*=8.1 Hz); 7.32 (m, 10H). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 13.3; 19.8; 50.5; 61.5; 61.6; 62.0; 63.0; 76.6; 127.1; 127.2; 127.4; 128.2; 128.5; 128.6; 138.7; 141.1; 170.2; 171.9. IR ($CHCl_3$, cm^{-1}): 3368 (NH+OH); 1726 (CO). MS (70eV) *m*/*z* (%): 351 (M^+-46, 5), 307 (18), 278 (19), 234 (41), 218 (16), 191 (36), 129 (23), 117 (100), 91 (21). Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.43; H, 6.83; N, 3.44.

Diethyl (3*S*,4*R*,5*S*)-4-hydroxymethyl-3-(*p*-nitrophenyl)-5-phenylpyrrolidine-2,2-dicarboxylate (11g)

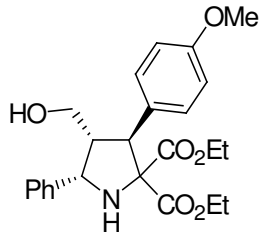


11g

Pyrrolidine **2g** (247 mg, 0.56 mmol) was prepared according to the general procedure using *p*-nitrocinnamaldehyde (124 mg, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1a** (197 mg, 0.75 mmol). Yield: 80%. *endo*/*exo*: >95:<5 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 0.81 (t, 3H, *J*=7.1 Hz); 1.24 (t, 3H, *J*=7.0 Hz); 3.28 (d, 1H, *J*=3.6 Hz); 3.61 (m, 2H); 3.93 (m, 2H); 4.27 (m, 2H); 4.87 (d, 1H, *J*=8.6 Hz); 5.47 (bs, 1H); 7.32 (m, 5H); 7.55 (d, 2H, *J*=8.5 Hz); 8.13 (d, 2H, *J*=8.5 Hz); 9.04 (d, 1H, *J*=1.8 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 13.5; 14.0; 47.7; 59.4; 61.9; 62.2; 62.3; 76.5; 123.4; 127.1; 128.2; 128.9; 129.9; 138.9; 145.0; 147.3; 169.0; 171.1; 199.3. IR ($CHCl_3$, cm^{-1}): 3350 (NH); 1730 (CO). MS

(70eV) *m*/*z* (%): 440 (15), 355 (41), 281 (93), 267 (71), 221 (52), 207 (100), 147 (47), 115 (48), 101 (24), 85 (36), 71 (42). HRMS: Calcd for $C_{23}H_{24}N_2O_7$: 440.1584. Found: 440.1596. Reduction of **2g** (231 mg, 0.53 mmol) afforded diethyl (3*S*,4*R*,5*S*)-4-hydroxymethyl-3-(*p*-nitrophenyl)-5-phenylpyrrolidine-2,2-dicarboxylate **11g** (202 mg, 0.46 mmol). Yield: 87%. e.e.: 94% (Chiracel OD, hexane/2-propanol 95:5, flow rate 1.00 mL/min t_R for the minor (3*R*,4*S*,5*R*) isomer: 24.75 min; t_R for the major (3*S*,4*R*,5*S*) isomer: 27.52 min). $[\alpha]_D^{20}$= −27.7 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 0.79 (t, 3H, *J*=8.0 Hz); 1.27 (t, 3H, *J*=8.2 Hz); 2.96 (m, 1H); 3.15 (m, 1H); 3.27 (bs, 2H); 3.54 (m, 1H); 3.94 (m, 1H); 4.27 (m, 4H); 5.15 (d, 1H, *J*=8.0 Hz); 7.33 (m, 5H); 7.55 (d, 2H, *J*=7.2 Hz); 8.14 (d, 2H, *J*=7.2 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 13.5; 14.0; 50.2; 50.4; 61.5; 61.8; 62.0; 62.7; 76.5; 123.3; 127.2; 128.6; 129.9; 140.8; 146.5; 147.1; 169.8; 171.4. IR ($CHCl_3$, cm^{-1}): 3364 (NH+OH); 1728 (CO). MS (70eV) *m*/*z* (%): 442 (M^+, 1), 400 (15), 355 (40), 341 (24), 281 (79), 267 (29), 219 (100), 207 (92), 191 (25), 155 (20), 149 (42), 127 (29); 115 (38); 97 (23), 88 (28), 73 (62). Anal. Calcd for $C_{23}H_{26}N_2O_7$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.41; H, 6.04; N, 6.28.

Diethyl (3*S*,4*R*,5*S*)-4-Hydroxymethyl-3-(*p*-methoxyphenyl)-5-phenylpyrrolidine-2,2-dicarboxylate (11h)

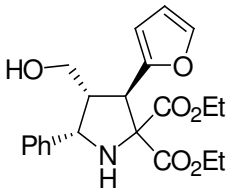


11h

Pyrrolidine **2h** (271 mg, 0.64 mmol) was prepared according to the general procedure using *p*-methoxycinnamaldehyde (113 mg, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1a** (197 mg, 0.75 mmol). Yield: 91%. *endo*/*exo*: 92:8 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 0.81 (t, 3H, *J*=7.0 Hz); 1.26 (t, 3H, *J*=7.0 Hz); 3.26 (m, 1H); 3.55 (m, 2H); 3.74 (s, 3H); 3.90 (m, 2H); 4.28 (m, 2H); 4.73 (d, 1H, *J*=8.3 Hz); 6.81 (d, 2H, *J*=8.6 Hz); 7.31 (m, 7H); 9.03 (d, 1H, *J*=3.3 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 13.5; 14.0; 47.7; 55.3; 59.9; 61.6; 61.8; 52.6; 76.7; 113.7; 127.1; 127.8; 128.7; 129.8; 130.4; 139.2; 159.0; 169.6; 171.7; 200.8. IR ($CHCl_3$, cm^{-1}): 3355 (NH); 1728 (CO). MS (70eV) *m*/*z* (%): 394 (M^+-29, 7), 274 (53), 223 (38), 201 (100), 139 (26), 112 (11), 91 (31), 77 (10), 69 (36). HRMS: Calcd for $C_{24}H_{27}NO_6$: 425.1838. Found: 425.1846. Reduction of **2h** (177 mg, 0.42 mmol) afforded diethyl (3*S*,4*R*,5*S*)-4-hydroxymethyl-3-(*p*-methoxyphenyl)-5-phenylpyrrolidine-2,2-dicarboxylate **11h** (160 mg, 0.37 mmol). Yield: 90%. e.e.: >99% (Chiracel OD, hexane/2-propanol 98:2, flow rate 1.00 mL/min t_R for the minor (3*R*,4*S*,5*R*) isomer: 34.91 min; t_R for the major (3*S*,4*R*,5*S*) isomer: 39.76 min). $[\alpha]_D^{20}$= −45.8 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 0.83 (t, 3H, *J*=7.1 Hz); 1.25 (t, 3H, *J*=7.1 Hz); 2.94 (m, 1H); 3.23 (m, 3H); 3.56 (m, 1H); 3.79 (s, 3H); 3.92 (m, 1H); 4.22 (m, 4H); 5.14 (d, 1H, *J*=8.2 Hz); 6.82 (d, 2H, *J*=8.7 Hz); 7.33 (m, 7H). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 13.5; 14.0; 49.7; 50.4; 55.3; 61.5; 61.6; 62.0; 62.8; 76.6; 113.7; 127.2; 127.4; 128.5; 129.8; 130.4; 141.4; 158.8; 170.3; 172.1. IR ($CHCl_3$, cm^{-1}): 3364

(NH+OH); 1728 (CO). MS (70eV) *m/z* (%): 427 (M^+, 20), 400 (17), 354 (85), 341 (31), 281 (97), 266 (35), 263 (61), 221 (46), 207 (100), 189 (39), 155 (30), 147 (63); 141 (30); 117 (43), 111 (37), 91 (22), 71 (46). Anal. Calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.55; H, 6.86; N, 3.36.

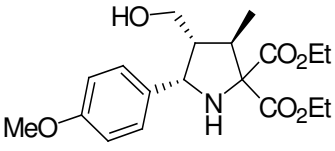
Diethyl (3*R*,4*R*,5*S*)-3-furyl-4-hydroxymethyl-5-phenylpyrrolidine-2,2-dicarboxylate (11i)



11i

Pyrrolidine **2i** (242 mg, 0.63 mmol) was prepared according to the general procedure using *E*-3-(2-furyl)acroleine (85 mg, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1a** (197 mg, 0.75 mmol). Yield: 90%. *endo*/*exo*: >95:<5 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 0.98 (t, 3H, *J*=7.1 Hz); 1.25 (t, 3H, *J*=7.1 Hz); 3.25 (m, 1H); 3.54 (m, 2H); 3.76 (m, 1H); 4.03 (m, 2H); 4.86 (d, 1H, *J*=7.5 Hz); 5.33 (bs, 1H); 6.27 (m, 2H); 7.38 (m, 6H); 9.06 (d, 1H, *J*=2.6 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 13.7; 14.0; 42.4; 57.9; 61.9; 62.2; 62.5; 75.0; 108.7; 110.6; 127.1; 127.9; 128.0; 142.0; 145.9; 150.8; 168.9; 171.1; 200.0. IR ($CHCl_3$, cm^{-1}): 3348 (NH); 1731 (CO). MS (70eV) *m/z* (%): 385 (M^+, 1), 318 (38), 211 (26), 147 (100), 126 (8), 91 (10), 71 (5), 65 (43). HRMS: Calcd for $C_{21}H_{23}NO_6$: 385.1525. Found: 385.1519. Reduction of **2i** (225 mg, 0.58 mmol) afforded diethyl (3*R*,4*R*,5*S*)-3-furyl-4-hydroxymethyl-5-phenylpyrrolidine-2,2-dicarboxylate **11i** (201 mg, 0.52 mmol). Yield: 89%. e.e.: 99% (Chiracel OD, hexane/2-propanol 95:5, flow rate 1.00 mL/min t_R for the major (3*R*,4*R*,5*S*) isomer: 14.53 min; t_R for the minor (3*S*,4*S*,5*R*) isomer: 17.34 min). $[\alpha]_D^{20}$= −7.9 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 0.98 (t, 3H, *J*=7.1 Hz); 1.27 (t, 3H, *J*=7.1 Hz); 1.71 (bs, 1H); 2.92 (m, 1H); 3.26 (m, 2H); 3.79 (m, 1H); 4.02 (m, 1H); 4.28 (m, 4H); 5.11 (d, 1H, *J*=8.0 Hz); 6.29 (m, 2H); 7.33 (m, 6H). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 13.7; 14.0; 44.7; 49.0; 61.7; 61.8; 62.1; 62.5; 74.9; 108.3; 110.5; 127.1; 127.4; 128.5; 140.8; 141.7; 152.3; 169.9; 171.5. IR ($CHCl_3$, cm^{-1}): 3368 (NH+OH); 1729 (CO). MS (70eV) *m/z* (%): 341 (M^+-46, 21), 297 (42), 268 (12), 224 (19), 209 (10), 181 (20), 157 (25), 153 (11), 117 (100), 107 (24), 91 (14), 77 (12). Anal. Calcd for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.04; H, 6.63; N, 3.57.

Diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-5-(*p*-methoxyphenyl)-3-methylpyrrolidine-2,2-dicarboxylate (11j)

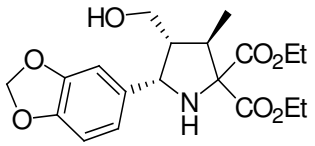


11j

Pyrrolidine **2j** (225 mg, 0.62 mmol) was prepared according to the general procedure using crotonaldehyde (58 µl, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1b** (220 mg, 0.75 mmol). Yield: 88%. *endo*/*exo*: 93:7 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC,

TMS): 1.11 (d, 3H, *J*=7.0 Hz); 1.26 (m, 6H); 2.88 (dt, 1H, *J*= 3.4, 9.4 Hz); 3.02 (bs, 1H); 2.28 (m, 1H); 3.76 (s, 3H); 4.25 (m, 4H); 5.07 (d, 1H, *J*=9.4 Hz); 6.78 (d, 2H, *J*=8.7 Hz); 7.23 (d, 2H, *J*=8.7 Hz); 9.02 (d, 1H, *J*=3.4 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.2; 15.1; 38.6; 55.2; 60.6; 60.9; 61.6; 61.8; 75.0; 114.0; 128.2; 131.9; 159.1; 169.6; 171.7; 201.6. IR ($CHCl_3$, cm^{-1}): 3350 (NH); 1726 (CO). MS (70eV) *m/z* (%): 363 (M^+, 1), 290 (100), 218 (47), 135 (13), 91 (6), 77 (7), 63 (9). HRMS: Calcd for $C_{19}H_{25}NO_6$: 363.1682. Found: 363.1679. Reduction of **2j** (198 mg, 0.53 mmol) afforded diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-5-(*p*-methoxyphenyl)-3-methylpyrrolidine-2,2-dicarboxylate **11j** (182 mg, 0.50 mmol). Yield: 95%. e.e.: 84% (Chiracel OJ, hexane/2-propanol 80:20, flow rate 1.00 mL/min t_R for the minor (3*S*,4*S*,5*R*) isomer: 8.80 min; t_R for the major (3*R*,4*R*,5*S*) isomer: 10.94 min). $[\alpha]_D^{20}$= −38.2 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.13 (d, 3H, *J*=7.1 Hz); 1.28 (m, 6H); 2.23 (m, 1H); 2.88 (m, 1H); 3.00 (bs, 1H); 3.21 (m, 1H); 3.36 (m, 1H); 3.78 (s, 3H); 4.25 (m, 4H); 4.81 (d, 1H, *J*=8.1 Hz); 6.87 (d, 2H, *J*=8.3 Hz); 7.21 (d, 2H, *J*=8.4 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.2; 15.6; 39.5; 51.4; 55.2; 61.3; 61.5; 61.6; 61.7; 74.9; 113.8; 128.2; 133.4; 158.8; 170.7; 172.2. IR ($CHCl_3$, cm^{-1}): 3355 (NH+OH); 1727 (CO). MS (70eV) *m/z* (%): 319 (M^+-78, 13), 275 (39), 260 (23), 246 (22), 201 (40), 186 (30), 161 (17), 154 (16), 146 (100), 135 (34), 121 (30), 91 (19), 77 (11). Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.41; H, 7.37; N, 3.88.

Diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-methyl-5-(3,4-methylenedioxyphenyl)pyrrolidine-2,2-dicarboxylate (11k)

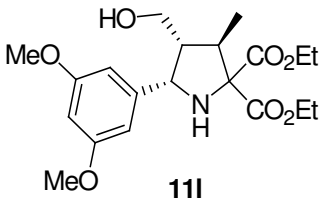


11k

Pyrrolidine **2k** (247 mg, 0.65 mmol) was prepared according to the general procedure using crotonaldehyde (58 µl, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1c** (230 mg, 0.75 mmol). Yield: 93%. *endo*/*exo*: >95:<5 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.09 (d, 3H, *J*=7.0 Hz); 1.26 (m, 6H); 2.84 (dt, 1H, *J*= 3.4, 9.5 Hz); 3.00 (bs, 1H); 3.24 (m, 1H); 4.24 (m, 4H); 5.03 (d, 1H, *J*=9.3 Hz); 5.89 (s, 2H); 7.55 (m, 3H); 9.04 (d, 1H, *J*=3.4 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.2; 15.0; 38.5; 60.7; 60.9; 61.6; 61.7; 74.0; 101.1; 107.5; 108.2; 120.2; 134.0; 147.0; 148.0; 169.5; 171.7; 201.4. IR ($CHCl_3$, cm^{-1}): 3342 (NH); 1727 (CO). MS (70eV) *m/z* (%): 377 (M^+, 14), 307 (21), 304 (100), 258 (13), 233 (37), 202 (17), 191 (18), 114 (9); 77 (10). HRMS: Calcd for $C_{19}H_{23}NO_7$: 377.1475. Found: 377.1478. Reduction of **2k** (215 mg, 0.57 mmol) afforded diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-methyl-5-(3,4-methylenedioxyphenyl)pyrrolidine-2,2-dicarboxylate **11k** (199 mg, 0.52 mmol). Yield: 92%. e.e.: >99% (Chiracel OJ, hexane/2-propanol 95:5, flow rate 1.00 mL/min t_R for the major (3*R*,4*R*,5*S*) isomer: 31.96 min; t_R for the minor (3*S*,4*S*,5*R*) isomer: 37.47 min). $[\alpha]_D^{20}$= −25.9

(*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.10 (d, 3H, *J*=7.0 Hz); 1.22 (m, 6H); 1.45 (bs, 1H); 2.18 (m, 1H); 2.85 (m, 1H); 2.97 (bs, 1H); 3.18 (dd, 1H, *J*=7.1, 11.3); 3.33 (dd, 1H, *J*=5.4, 11.3); 4.21 (m, 4H); 4.75 (d, 1H, *J*=8.1 Hz); 5.89 (s, 2H); 6.77 (m, 3H). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.2; 15.6; 39.5; 51.4; 61.4; 61.6; 61.7; 74.9; 101.0; 107.8; 108.0; 120.1; 135.6; 146.6; 147.7; 170.6; 172.1. IR ($CHCl_3$, cm^{-1}): 3350 (NH+OH); 1728 (CO). MS (70eV) *m*/*z* (%): 379 (M^+, 3), 306 (100), 242 (14), 233 (26), 214 (12), 201 (10), 193 (37), 187 (13), 159 (26), 148 (10), 134 (16), 130 (6). Anal. Calcd for $C_{19}H_{25}NO_7$: C, 60.15; H, 6.64; N, 3.69. Found: C, 60.05; H, 6.71; N, 3.62.

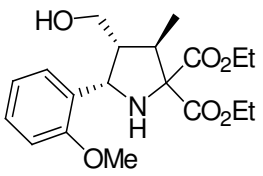
Diethyl (3*R*,4*R*,5*S*)-5-(3,5-dimethoxyphenyl)-4-hydroxymethyl-3-methylpyrrolidine-2,2-dicarboxylate (11l)



11l

Pyrrolidine **2l** (252 mg, 0.64 mmol) was prepared according to the general procedure using crotonaldehyde (58 µl, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1d** (242 mg, 0.75 mmol). Yield: 91%. *endo*/*exo*: >95:<5 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.09 (d, 3H, *J*=7.0 Hz); 1.25 (m, 6H); 2.84 (dt, 1H, *J*= 3.6, 9.4 Hz); 3.03 (bs, 1H); 3.24 (m, 1H); 3.70 (s, 6H); 4.23 (m, 4H); 4.98 (d, 1H, *J*=9.9 Hz); 6.27 (t, 1H, *J*=2.2 Hz); 6.45 (d, 2H, *J*=2.2 Hz); 8.99 (d, 1H, *J*=3.6 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.1; 14.9; 38.6; 55.3; 60.6; 61.1; 61.6; 61.8; 75.0; 99.3; 104.9; 142.6; 161.0; 169.5; 171.7; 201.2. IR ($CHCl_3$, cm^{-1}): 3355 (NH); 1727 (CO). MS (70eV) *m*/*z* (%): 393 (M^+, 18), 320 (100), 302 (9), 292 (8), 281 (8), 250 (12), 218 (11), 207 (19), 191 (7), 146 (21), 101 (17), 91 (32). HRMS: Calcd for $C_{20}H_{27}NO_7$: 393.1788. Found: 393.1792. Reduction of **2l** (200 mg, 0.51 mmol) afforded diethyl (3*R*,4*R*,5*S*)-5-(3,5-dimethoxyphenyl)-4-hydroxymethyl-3-methylpyrrolidine-2,2-dicarboxylate **11l** (187 mg, 0.47 mmol). Yield: 93%. e.e.: 94% (Chiracel OJ, hexane/2-propanol 98:2, flow rate 1.00 mL/min t_R for the minor (3*S*,4*R*,5*R*) isomer: 46.07 min; t_R for the major (3*R*,4*R*,5*S*) isomer: 54.39 min). $[\alpha]_D^{20}$= −33.4 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.10 (d, 3H, *J*=7.1 Hz); 1.24 (m, 6H); 1.46 (bs, 1H); 2.18 (m, 1H); 2.89 (m, 1H); 3.00 (bs, 1H); 3.21 (dd, 1H, *J*=6.9, 11.6); 3.55 (dd, 1H, *J*=5.3, 11.6); 3.76 (s, 6H); 4.21 (m, 4H); 4.76 (d, 1H, *J*=8.0 Hz); 6.31 (t, 1H, *J*=1.9 Hz); 6.48 (d, 2H, *J*=1.9 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.2; 15.6; 39.4; 51.5; 55.2; 61.4; 61.5; 61.6; 62.0; 74.9; 99.0; 105.0; 144.3; 160.8; 170.6; 172.1. IR ($CHCl_3$, cm^{-1}): 3348 (NH+OH); 1726 (CO). MS (70eV) *m*/*z* (%): 349 (M^+-46, 9), 302 (7), 276 (9), 232 (14), 216 (9), 203 (7), 176 (100), 164 (7), 151 (6), 91 (7), 77 (9). Anal. Calcd for $C_{20}H_{29}NO_7$: C, 60.74; H, 7.39; N, 3.54. Found: C, 60.79; H, 7.32; N, 3.61.

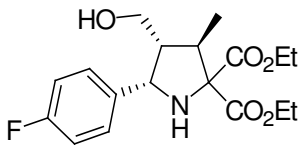
Diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-5-(*o*-methoxyphenyl)-3-methylpyrrolidine-2,2-dicarboxylate (11m)



11m

Pyrrolidine **2m** (218 mg, 0.60 mmol) was prepared according to the general procedure crotonaldehyde (58 µl, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1e** (205 mg, 0.75 mmol). Yield: 86%. *endo*/*exo*: 91:9 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.10 (d, 3H, *J*=7.0 Hz); 1.29 (m, 6H); 2.96 (m, 2H); 3.15 (m, 1H); 3.74 (s, 3H); 4.29 (m, 4H); 5.30 (d, 1H, *J*=9.0 Hz); 6.80 (d, 1H, *J*=6.8 Hz); 6.97 (t, 2H, *J*=6.8 Hz); 7.54 (dd, 1H, *J*=4.6, 10.3 Hz); 8.96 (d, 1H, *J*=4.6 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.1; 14.2; 14.8; 38.8; 55.0; 55.6; 59.4; 61.6; 61.8; 74.9; 109.7; 120.7; 127.5; 128.2; 128.6; 155.8; 169.8; 171.7; 201.7. IR ($CHCl_3$, cm^{-1}): 3350 (NH); 1726 (CO). MS (70eV) *m*/*z* (%): 363 (M^+, 1), 290 (100), 219 (15), 206 (15), 188 (12), 172 (12), 149 (12), 132 (15), 91 (12). HRMS: Calcd for $C_{19}H_{25}NO_6$: 363.1682. Found: 363.1671. Reduction of **2m** (195 mg, 0.54 mmol) afforded diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-5-(*o*-methoxyphenyl)-3-methylpyrrolidine-2,2-dicarboxylate **11m** (176 mg, 0.48 mmol). Yield: 90%. e.e.: 93% (Chiracel OJ, hexane/2-propanol 95:5, flow rate 1.00 mL/min t_R for the major (3*R*,4*R*,5*S*) isomer: 11.79 min; t_R for the minor (3*S*,4*S*,5*R*) isomer: 13.57 min). $[\alpha]_D^{20}$= −33.7 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.13 (d, 3H, *J*=7.0 Hz); 1.28 (m, 6H); 2.13 (bs, 1H); 2.42 (m, 1H); 2.85 (m, 1H); 3.03 (bs, 1H); 3.11 (m, 1H); 3.30 (m, 1H); 3.82 (s, 3H); 4.25 (m, 4H); 5.17 (d, 1H, *J*=8.0 Hz); 6.87 (d, 1H, *J*=6.8 Hz); 6.97 (t, 1H, *J*=6.9 Hz); 7.23 (m, 1H); 7.48 (d, 1H, *J*=7.5 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.1; 14.2; 15.5; 39.1; 50.8; 55.5; 55.7; 61.5; 61.7; 62.1; 74.9; 110.2; 121.1; 128.0; 128.2; 130.2; 156.0; 170.8; 172.2. IR ($CHCl_3$, cm^{-1}): 3350 (NH+OH); 1728 (CO). MS (70eV) *m*/*z* (%): 319 (M^+-46, 15), 275 (99), 260 (85), 246 (49), 202 (67), 186 (41), 172 (20), 147 (100), 134 (20), 121 (26), 91 (49). Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.37; H, 7.38; N, 3.79.

Diethyl (3*R*,4*R*,5*S*)-5-(*p*-fluorophenyl)-4-hydroxymethyl-3-methylpyrrolidine-2,2-dicarboxylate (11n)

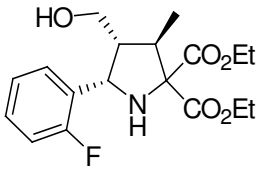


11n

Pyrrolidine **2n** (182 mg, 0.52 mmol) was prepared according to the general procedure using crotonaldehyde (58 µl, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1f** (211 mg, 0.75 mmol). Yield: 74%. *endo*/*exo*: >95:<5 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.11 (d, 3H, *J*=7.1 Hz); 1.28 (m, 6H); 2.89 (dt, 1H, *J*=3.5, 9.4 Hz); 3.05 (bs, 1H); 3.29 (m, 1H); 4.28 (m, 4H); 5.11 (d, 1H, *J*=9.4 Hz); 6.98 (m, 2H); 7.30 (m, 2H); 9.01 (d, 1H, *J*=3.5 Hz). ^{13}C-

NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.2; 15.1; 38.5; 53.6; 60.4; 60.7; 61.8; 75.0; 115.6 (d, $J_{C\text{-}F}$=21.4 Hz); 128.7 (d, $J_{C\text{-}F}$=8.0 Hz); 135.7; 162.5 (d, $J_{C\text{-}F}$=247.4 Hz); 169.5; 171.7; 201.2. IR ($CHCl_3$, cm^{-1}): 3342 (NH); 1727 (CO). MS (70eV) *m/z* (%): 351 (M^+, 1), 281 (5), 278 (100), 232 (15), 207 (11), 204 (22), 176 (15), 161 (10), 134 (11), 108 (13). HRMS: Calcd for $C_{18}H_{22}FNO_5$: 351.1482. Found: 351.1491. Reduction of **2n** (147 mg, 0.42 mmol) afforded diethyl (3*R*,4*R*,5*S*)-5-(*p*-fluorophenyl)-4-hydroxymethyl-3-methylpyrrolidine-2,2-dicarboxylate **11n** (132 mg, 0.37 mmol). Yield: 89%. e.e.: 98% (Chiracel OJ, hexane/2-propanol 95:5, flow rate 1.00 mL/min t_R for the major (3*R*,4*R*,5*S*) isomer: 17.53 min; t_R for the minor (3*S*,4*S*,5*R*) isomer: 22.95 min). $[\alpha]_D^{20}$= −51.3 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.12 (d, 3H, *J*=7.2 Hz); 1.29 (m, 6H); 2.23 (m, 1H); 2.89 (m, 1H); 3.05 (bs, 1H); 3.11 (dd, 1H, *J*=6.5, 11.5 Hz); 3.33 (dd, 1H, *J*=5.7, 11.5 Hz); 4.24 (m, 4H); 4.84 (d, 1H, *J*=8.0 Hz); 6.98 (t, 2H, *J*=8.6 Hz); 7.30 (m, 2H). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.2; 15.7; 39.5; 51.4; 61.2; 61.5; 61.6; 61.8; 74.9; 115.2 (d, $J_{C\text{-}F}$=21.2 Hz); 128.8 (d, $J_{C\text{-}F}$=7.9 Hz); 137.1; 161.8 (d, $J_{C\text{-}F}$=247.4 Hz); 170.6; 172.1. IR ($CHCl_3$, cm^{-1}): 3350 (NH+OH); 1726 (CO). MS (70eV) *m/z* (%): 307 (M^+-46, 5), 280 (28), 263 (63), 248 (38), 234 (58), 217 (10), 189 (50), 174 (43), 161 (23), 154 (16), 135 (100), 129 (29), 108 (54), 55 (13). Anal. Calcd for $C_{18}H_{24}FNO_5$: C, 61.18; H, 6.85; N, 3.96. Found: C, 61.23; H, 6.77; N, 4.04.

Diethyl (3*R*,4*R*,5*S*)-5-(*o*-fluorophenyl)-4-hydroxymethyl-3-methylpyrrolidine-2,2-dicarboxylate (11o)

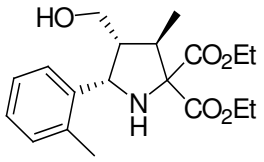


11o

Pyrrolidine **2o** (177 mg, 0.50 mmol) was prepared according to the general procedure using crotonaldehyde (58 µl, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1g** (211 mg, 0.75 mmol). Yield: 72%. *endo*/*exo*: >95:<5 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.12 (d, 3H, *J*=7.1 Hz); 1.29 (m, 6H); 3.00 (dt, 1H, *J*=3.1, 8.7 Hz); 3.81 (m, 1H); 4.26 (m, 4H); 5.37 (d, 1H, *J*=8.8 Hz); 6.98 (t, 1H, *J*=3.3 Hz); 7.12 (t, 1H, *J*=4.2 Hz); 7.25 (m, 1H); 7.52 (t, 1H, *J*=4.2 Hz); 9.14 (d, 1H, *J*=3.3 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.2; 15.1; 38.6; 54.2; 61.7; 61.9; 62.4; 62.9; 74.8; 114.9; (d, $J_{C\text{-}F}$=21.4 Hz); 124.3 (d, $J_{C\text{-}F}$=2.0 Hz); 124.8 (d, $J_{C\text{-}F}$=8.0 Hz); 128.1 (d, $J_{C\text{-}F}$=10.4 Hz); 131.2 (d, $J_{C\text{-}F}$=34.0 Hz); 160.2 (d, $J_{C\text{-}F}$=249.7 Hz); 168.0; 168.7; 201.7. IR ($CHCl_3$, cm^{-1}): 3345 (NH); 1731 (CO). MS (70eV) *m/z* (%): 351 (M^+, 1), 278 (100), 232 (19), 207 (23), 204 (19), 176 (14), 149 (15), 135 (10), 109 (15). HRMS: Calcd for $C_{18}H_{22}FNO_5$: 351.1482. Found: 351.1475. Reduction of **2o** (151 mg, 0.43 mmol) afforded diethyl (3*R*,4*R*,5*S*)-5-(*o*-fluorophenyl)-4-hydroxymethyl-3-methylpyrrolidine-2,2-dicarboxylate **11o** (134 mg, 0.38 mmol). Yield: 88%. e.e.: 93% (Chiracel OJ, hexane/2-propanol 98:2, flow rate 1.00 mL/min t_R for the major (3*R*,4*R*,5*S*) isomer: 24.38

min; t_R for the minor (3*S*,4*S*,5*R*) isomer: 29.18 min). $[\alpha]_D^{20}$= −34.9 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.17 (d, 3H, *J*=7.1 Hz); 1.29 (m, 6H); 1.48 (bs, 1H); 2.37 (m, 1H); 2.93 (bs, 1H); 3.06 (m, 1H); 3.21 (m, 1H); 3.32 (m, 1H); 4.27 (m, 4H); 5.13 (d, 1H, *J*=7.7 Hz); 7.00 (t, 1H, *J*=4.1 Hz); 7.11 (t, 1H, *J*=1.9 Hz); 7.22 (m, 1H); 7.56 (t, 1H, *J*=1.8 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.3; 16.1; 39.6; 50.5; 55.2; 61.6; 61.8; 62.0; 74.7; 114.8; (d, $J_{C\text{-}F}$=21.8 Hz); 124.1 (d, $J_{C\text{-}F}$=3.2 Hz); 124.2 (d, $J_{C\text{-}F}$=9.7 Hz); 128.5 (d, $J_{C\text{-}F}$=7.9 Hz); 131.6 (d, $J_{C\text{-}F}$=37.5 Hz); 159.4 (d, $J_{C\text{-}F}$=237.2 Hz); 170.7; 171.9. IR ($CHCl_3$, cm^{-1}): 3348 (NH+OH); 1728 (CO). MS (70eV) *m*/*z* (%): 307 (M^+-46, 5), 246 (13), 263 (92), 248 (66), 234 (93), 206 (10), 190 (90), 174 (59), 161 (31), 154 (34), 149 (28), 135 (100), 124 (25), 109 (68), 83 (11), 55 (15). Anal. Calcd for $C_{18}H_{24}FNO_5$: C, 61.18; H, 6.85; N, 3.96. Found: C, 61.13; H, 6.91; N, 4.92.

Diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-methyl-5-(*o*-tolyl)pyrrolidine-2,2-dicarboxylate (11p)

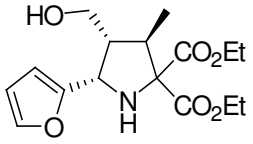


11p

Pyrrolidine **2p** (221 mg, 0.64 mmol) was prepared according to the general procedure using crotonaldehyde (58 µl, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1h** (208 mg, 0.75 mmol). Yield: 91%. *endo*/*exo*: >95:<5 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.12 (d, 3H, *J*=7.0 Hz); 1.27 (m, 6H); 2.21 (s, 3H); 2.86 (m, 2H); 3.25 (m, 1H); 4.25 (m, 4H); 5.27 (d, 1H, *J*=9.3 Hz); 7.65 (m, 3H); 7.65 (d, 1H, *J*=7.1 Hz); 8.86 (d, 1H, *J*=4.4 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.2; 15.0; 19.4; 38.9; 57.5; 59.3; 61.6; 61.7; 75.0; 126.2; 126.5; 127.4; 130.4; 134.6; 137.5; 169.4; 171.7; 201.2. IR ($CHCl_3$, cm^{-1}): 3350 (NH); 1728 (CO). MS (70eV) *m*/*z* (%): 347 (M^+, 6), 274 (100), 228 (9), 200 (13), 172 (8), 157 (9), 131 (10), 105 (7), 91 (4). HRMS: Calcd for $C_{19}H_{25}NO_5$: 347.1733. Found: 347.1729. Reduction of **2p** (207 mg, 0.60 mmol) afforded diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-methyl-5-(*o*-tolyl)pyrrolidine-2,2-dicarboxylate **11p** (189 mg, 0.54 mmol). Yield: 91%. e.e.: 99% (Chiracel OD, hexane/2-propanol 98:2, flow rate 1.00 mL/min t_R for the major (3*R*,4*R*,5*S*) isomer: 16.64 min; t_R for the minor (3*S*,4*S*,5*R*) isomer: 19.14 min). $[\alpha]_D^{20}$= −71.7 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.17 (d, 3H, *J*=7.2 Hz); 1.26 (m, 6H); 1.48 (bs, 1H); 2.27 (m, 4H); 2.84 (bs, 1H); 3.02 (m, 1H); 3.20 (m, 2H); 4.25 (m, 4H); 5.05 (d, 1H, *J*=7.5 Hz); 7.14 (m, 3H); 7.66 (d, 1H, *J*=7.2 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.1; 14.2; 16.7; 19.4; 40.2; 49.7; 58.2; 61.5; 61.6; 62.3; 74.4; 126.0; 126.4; 126.9; 130.2; 135.2; 138.8; 170.7; 172.1. IR ($CHCl_3$, cm^{-1}): 3355 (NH+OH); 1729 (CO). MS (70eV) *m*/*z* (%): 349 (M^+, 2), 276 (100), 230 (7), 203 (12), 184 (10), 170 (5), 157 (9),

131 (14), 105 (9), 91 (6). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.23; H, 7.75; N, 3.96.

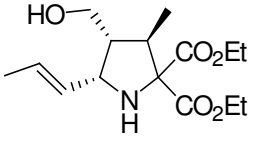
Diethyl (3*R*,4*R*,5*S*)-5-(2-furyl)-4-hydroxymethyl-3-methylpyrrolidine-2,2-dicarboxylate (11q)



11q

Pyrrolidine **2q** (190 mg, 0.59 mmol) was prepared according to the general procedure using crotonaldehyde (58 µl, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1i** (190 mg, 0.75 mmol). Yield: 84%. *endo*/*exo*: >95:<5 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.14 (d, 3H, *J*=6.9 Hz); 1.27 (m, 6H); 2.99 (m, 1H); 3.14 (bs, 1H); 3.29 (m, 1H); 4.24 (m, 4H); 5.01 (d, 1H, *J*=8.7 Hz); 6.25 (m, 2H); 7.28 (d, 1H, *J*=11.7 Hz); 9.24 (d, 1H, *J*=3.1 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.2; 14.6; 39.0; 55.4; 60.6; 61.8; 61.9; 62.1; 74.7; 107.9; 110.3; 142.4; 153.6; 169.9; 171.3; 200.3. IR ($CHCl_3$, cm^{-1}): 3342 (NH); 1727 (CO). MS (70eV) *m*/*z* (%): 323 (M^+, 1), 250 (100), 204 (7), 176 (15), 148 (8), 105 (4), 91 (7). HRMS: Calcd for $C_{16}H_{21}NO_6$: 323.1369. Found: 323.1377. Reduction of **2q** (173 mg, 0.54 mmol) afforded diethyl (3*R*,4*R*,5*S*)-5-(2-furyl)-4-hydroxymethyl-3-methylpyrrolidine-2,2-dicarboxylate **11q** (157 mg, 0.48 mmol). Yield: 90%. e.e.: 98% (Chiracel OD, hexane/2-propanol 85:15, flow rate 1.00 mL/min t_R for the major (3*R*,4*R*,5*S*) isomer: 7.50 min; t_R for the minor (3*S*,4*S*,5*R*) isomer: 11.93 min). $[\alpha]_D^{20}$= −11.2 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.09 (d, 3H, *J*=8.1 Hz); 1.26 (m, 6H); 1.78 (bs, 1H); 2.40 (m, 1H); 2.72 (m, 1H); 3.10 (bs, 1H); 3.20 (dd, 1H, *J*=8.8, 11.6 Hz); 3.53 (dd, 1H, *J*=3.9, 11.6 Hz); 4.23 (m, 4H); 4.77 (d, 1H, *J*=7.8 Hz); 6.20 (d, 1H, *J*=3.1 Hz); 6.29 (dd, 1H, *J*=1.9, 3.0 Hz); 7.33 (d, 1H, *J*=1.9 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.0; 14.2; 14.6; 39.5; 51.3; 56.7; 61.6; 61.7; 61.9; 75.0; 107.3; 110.4; 141.9; 156.0; 170.8; 171.8. IR ($CHCl_3$, cm^{-1}): 3350 (NH+OH); 1727 (CO). MS (70eV) *m*/*z* (%): 325 (M^+, 2), 252 (100), 206 (8), 188 (36), 161 (29), 139 (30), 107 (16), 81 (12). Anal. Calcd for $C_{16}H_{23}NO_6$: C, 59.06; H, 7.13; N, 4.31. Found: C, 58.97; H, 7.08; N, 4.26.

Diethyl (3*R*,4*R*,5*R*,1'*E*)-4-hydroxymethyl-3-methyl-5-(1-propenyl)pyrrolidine-2,2-dicarboxylate (11r)



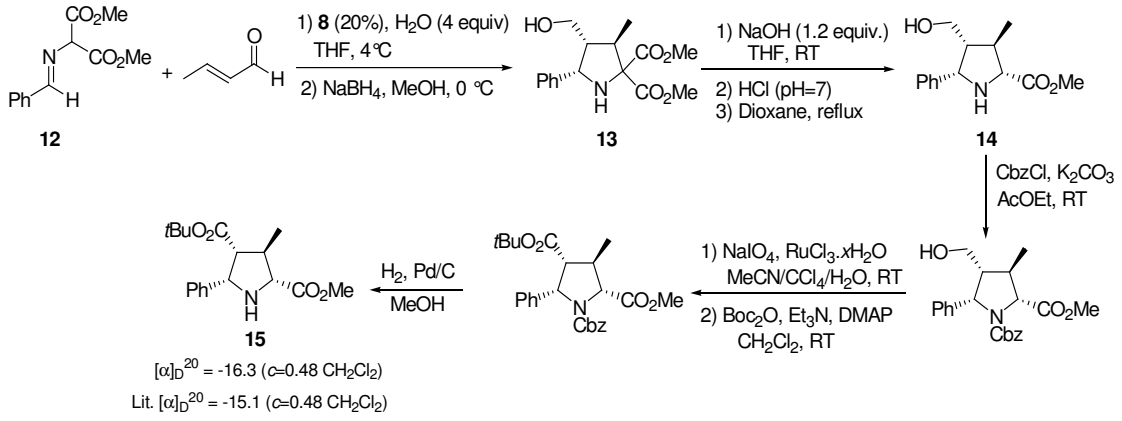
11r

Pyrrolidine **2r** (119 mg, 0.40 mmol) was prepared according to the general procedure using crotonaldehyde (58 µl, 0.70 mmol), (*S*)-α,α-diphenylprolinol (35 mg, 0.14 mmol) and imine **1j** (171 mg, 0.75 mmol). Yield: 57%. *endo*/*exo*: 91:9 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.10 (d, 3H, *J*=6.8 Hz); 1.26 (t, 6H, *J*=7.1 Hz); 1.64 (d, 3H, *J*=6.8 Hz); 2.81 (m, 2H); 3.14 (m,

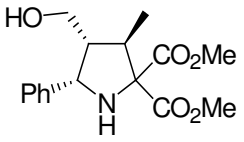
1H); 4.27 (m, 4H); 4.34 (m, 1H); 5.33 (m, 1H); 5.67 (m, 1H); 9.58 (d, 1H, *J*=2.7 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 13.9; 14.1; 15.0; 17.6; 38.9; 60.3; 60.8; 61.6; 61.7; 61.8; 74.7; 128.9; 129.6; 170.2; 171.3; 201.7. IR ($CHCl_3$, cm^{-1}): 3339 (NH); 1725 (CO). MS (70eV) *m/z* (%):297 (M^+, 4), 224 (100), 178 (9), 150 (16), 122 (12), 107 (8), 95 (8), 80 (11), 55 (7). HRMS: Calcd for $C_{15}H_{23}NO_5$: 297.1576. Found: 297.1574. Reduction of **2r** (97 mg, 0.33 mmol) afforded diethyl (3*R*,4*R*,5*R*,1'*E*)-4-hydroxymethyl-3-methyl-5-(1-propenyl)pyrrolidine-2,2-dicarboxylate **11r** (86 mg, 0.29 mmol). Yield: 88%. e.e.: 97% (Chiracel OD, hexane/2-propanol 95:5, flow rate 1.00 mL/min t_R for the major (3*R*,4*R*,5*R*,1'*E*) isomer: 9.18 min; t_R for the minor (3*S*,4*S*,5*S*,1'*E*) isomer: 11.06 min). $[\alpha]_D^{20}$= −12.5 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.11 (d, 3H, *J*=6.9 Hz); 1.26 (m, 6H); 1.69 (d, 3H, *J*=6.1 Hz); 1.87 (bs, 1H); 2.10 (m, 1H); 2.74 (m+bs, 2H); 3.67 (m, 2H); 4.11 (m, 1H); 4.20 (m, 4H); 5.50 (m, 1H); 5.68 (m, 1H). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 13.9; 14.2; 15.5; 17.8; 40.1; 51.0; 61.0; 61.5; 61.6; 61.9; 74.9; 128.1; 130.7; 171.0; 171.7. IR ($CHCl_3$, cm^{-1}): 3353 (NH+OH); 1724 (CO). MS (70eV) *m/z* (%): 299 (M^+, 2), 253 (4), 226 (100), 194 (7), 180 (14), 154 (11), 134 (14), 120 (10), 95 (9), 55 (6). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 60.23; H, 8.47; N, 4.59.

3. Determination of the absolute configuration.

The absolute configuration of the pyrrolidines **2a-r** obtained in the organocatalytic asymmetric [3+2] cycloaddition of azomethine ylides derived from imines **1a-j** and α,β-unsaturated aldehydes was determined by chemical correlation. Thus, known compound[3] **15** was prepared following the synthetic scheme depicted bellow.



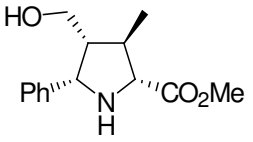
Dimethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-methyl-5-phenylpyrrolidine-2,2-dicarboxylate (13).



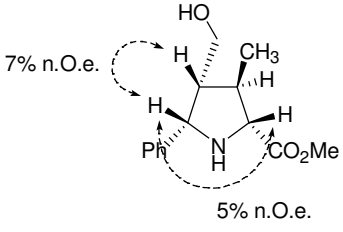
13

The [3+2] cycloaddition reaction was carried out according to the general procedure using crotonaldehyde (116 µl, 1.40 mmol), (*S*)-α,α-diphenylprolinol (70 mg, 0.28 mmol) and imine **12** (352 mg, 0.75 mmol), furnishing the corresponding pyrrolidine (338 mg, 1.10 mmol). Yield: 79%. *endo*/*exo*: >95:<5 (^{1}H-NMR analysis). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.12 (d, 3H, *J*=7.4 Hz); 2.92 (dt, 1H, *J*=3.4, 9.4 Hz); 3.31 (m, 1H); 3.78 (s, 3H); 3.81 (s, 3H); 5.12 (d, 1H, *J*=9.5 Hz); 7.28 (m, 5H); 9.00 (d, 1H, *J*=3.4 Hz). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.9; 38.7; 52.5; 52.7; 60.6; 61.0; 75.0; 127.2; 128.6; 128.9; 139.7; 169.9; 172.0; 201.1. IR ($CHCl_3$, cm^{-1}): 3340 (NH); 1730 (CO). MS (70eV) *m*/*z* (%): 305 (M^+, 3), 246 (100), 214 (14), 186 (20), 175 (18), 158 (13), 143 (19), 91 (11). HRMS: Calcd for $C_{16}H_{19}NO_5$: 305.1263. Found: 305.1255. Reduction of the pyrrolidine (333 mg, 1.08 mmol) afforded dimethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-methyl-5-phenylpyrrolidine-2,2-dicarboxylate **13** (320 mg, 1.04 mmol). Yield: 96%. e.e.: 99% (Chiracel OD, hexane/2-propanol 98:2, flow rate 1.00 mL/min t_R for the major (3*R*,4*R*,5*S*) isomer: 40.80 min; t_R for the minor (3*S*,4*S*,5*R*) isomer: 45.39 min). $[\alpha]_D^{20}$= −21.2 (*c*=1.0, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.12 (d, 3H, *J*=6.8 Hz); 2.27 (bs, 1H); 2.91 (m, 1H); 3.20 (bs, 1H); 3.39 (m, 1H); 3.79 (s, 3H); 3.80 (s, 3H); 4.85 (d, 1H, *J*=9.5 Hz); 7.35 (m, 5H). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 15.6; 39.8; 51.4; 52.5; 52.8; 61.6; 61.9; 75.1; 127.2; 127.4; 128.5; 141.4; 171.1; 172.6. IR ($CHCl_3$, cm^{-1}): 3353 (NH+OH); 1724 (CO). MS (70eV) *m*/*z* (%): 289 (M^+-18, 2), 248 (100), 216 (14), 175 (16), 170 (15), 149 (15), 117 (10), 91 (13). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.49; H, 6.91; N, 4.50.

Methyl (2*R*,3*R*,4*R*,5*S*)-4-hydroxymethyl-3-methyl-5-phenylpyrrolidine-2-carboxylate (14).

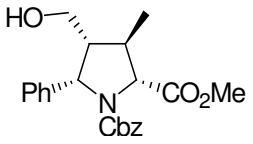


6M NaOH (0.20 mL, 1.22 mmol) was added over a solution of **13** (312 mg, 1.02 mmol) in MeOH (15 mL) and the reaction was stirred for 5h. The mixture was carefully driven to pH=7 with 4M HCl and the volatiles were removed under reduced pressure. Next, dioxane (5 mL) was added and the mixture was refluxed for 1h. The solvent was removed and pyrrolidine **14** (185 mg, 0.74 mmol) was isolated after flash column chromatography purification. Yield:



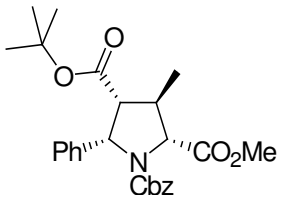
73%. ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.12 (d, 3H, *J*=6.8 Hz); 2.25 (m, 1H); 2.92 (m, 1H); 3.19 (m, 1H); 3.38 (m, 1H); 3.58 (d, 1H, *J*=9.3 Hz); 3.82 (s, 3H); 4.91 (d, 1H, *J*=9.5 Hz); 7.38 (m, 5H). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 15.6; 39.7; 51.3; 52.6; 61.4; 62.0; 64.5; 127.1; 127.5; 128.7; 141.2; 172.4. HRMS: Calcd for $C_{14}H_{19}NO_3$: 249.1365. Found: 249.1359.

Methyl (2*R*,3*R*,4*R*,5*S*)-1-benzyloxycarbonyl-4-hydroxymethyl-3-methyl-5-phenyl-pyrrolidine-2-carboxylate.



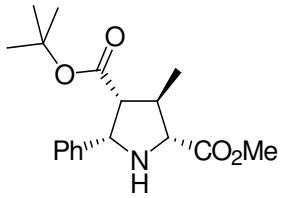
CbzCl (116 μL, 0.80 mmol) was added over a suspension of K_2CO_3 (302 mg, 2.20 mmol) and **14** (182 mg, 0.73 mmol) in AcOEt (25 mL) and the reaction was stirred for 3h. Saturated NH_4Cl was added (15 mL) and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Pure *N*-protected pyrrolidine (243 mg, 0.63 mmol) was isolated after flash column chromatography purification (hexanes/AcOEt 1:1). Yield: 87%. ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.12 (m, 3H); 2.23 (m, 1H); 2.78 (m, 1H); 3.12 (m, 1H); 3.41 (m, 1H); 3.68 (d, 1H, *J*=9.3 Hz); 3.89 (s, 3H); 4.86 (d, 1H, *J*=9.3 Hz); 5.07 (s, 2H); 7.62 (m, 10H). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 15.5; 39.6; 51.5; 52.9; 61.0; 61.8; 64.3; 68.2; 127.1; 127.3; 127.5; 127.9; 128.0; 128.7; 140.6; 141.2; 160.7; 172.8. HRMS: Calcd for $C_{22}H_{25}NO_5$: 383.1733. Found: 383.1728.

(2*R*,3*R*,4*R*,5*S*)-1-benzyloxycarbonyl-4-*tert*-butoxycarbonyl-2-methoxycarbonyl-3-methyl-5-phenylpyrrolidine.



According to a reported procedure,[4] $NaIO_4$ (248 mg, 1.16 mmol) and $RuCl_3.xH_2O$ (60 mg) were added over a solution of the *N*-protected pyrrolidine (224 mg, 0.58 mmol) in CH_3CN (10 mL), CCl_4 (10 mL) and H_2O (16 mL). The mixture was vigorously stirred at RT for 4 hours after which the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Next, esterification was performed following another reported procedure[5] and, therefore, crude acid was dissolved in CH_2Cl_2 (8 mL), cooled to 0ºC and DMAP (25 mg), Et_3N (0.40 mL, 2.90 mmol) and Boc_2O (520 mg, 2.44 mmol) were sequentially added to the reaction mixture. The mixture was stirred for 24 hours at RT after which the reaction was quenched with sat. NH_4Cl (45 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Pure product (97 mg, 0.21 mmol) was isolated after flash column chromatography purification (hexanes/AcOEt 1:1). Yield: 37%. ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 1.06 (s, 9H); 1.21 (m, 3H); 2.60 (m, 1H); 3.07 (m, 1H); 3.49 (m, 1H); 3.75 (s, 3H); 4.69 (d, 1H, *J*=7.6 Hz); 5.13 (s, 2H); 7.43 (m, 10H). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.1; 25.7; 40.3; 52.1; 55.3; 62.0; 64.4; 70.1; 80.7; 126.8; 127.2; 127.3; 127.9; 128.4; 128.7; 139.8; 141.3; 170.2; 172.7.

(2*R*,3*R*,4*R*,5*S*)-4-*tert*-butoxycarbonyl-2-methoxycarbonyl-3-methyl-5-phenylpyrrolidine (15).



A solution of the Cbz-protected pyrrolidine (76 mg, 0.17 mmol) in MeOH (15 mL) was stirred under a H_2 atmosphere (balloon) for 24 hours in the presence of Pd/C (35 mg), after which the mixture was stirred through a short celite path and the solvent was removed under reduced pressure. Saturated NH_4Cl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Pure pyrrolidine **15** (36 mg, 0.11 mmol) was isolated after flash column chromatography purification (hexanes/AcOEt 2:8). Yield: 68%. $[\alpha]_D^{20}= -16.3$ (c=0.5, CH_2Cl_2). Lit.[3] ($[\alpha]_D^{20}= -15.1$ (c=0.48, CH_2Cl_2)). ^{1}H-NMR (300MHz, $CDCl_3$, 25ºC, TMS): 0.98 (s, 9H); 1.17 (d, 3H, J=6.8 Hz); 2.57 (m, 1H); 2.80 (bs, 1H); 2.97 (m, 1H); 3.42 (d, 1H, J=9.1 Hz); 3.79 (s, 3H); 4.72 (d, 1H, J=9.1 Hz); 7.36 (m, 5H). ^{13}C-NMR (75MHz, $CDCl_3$, 25ºC, TMS): 14.2; 25.3; 40.3; 51.7; 55.4; 62.7; 63.8; 79.5; 127.1; 127.4; 128.2; 141.5; 170.7; 173.9. The other spectroscopic and analytical data matched with those reported in the literature.

References and notes

1.- Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, 1997.

2.- Cabrera, S.; Arrayas, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394

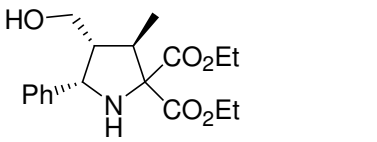
3.- Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174.

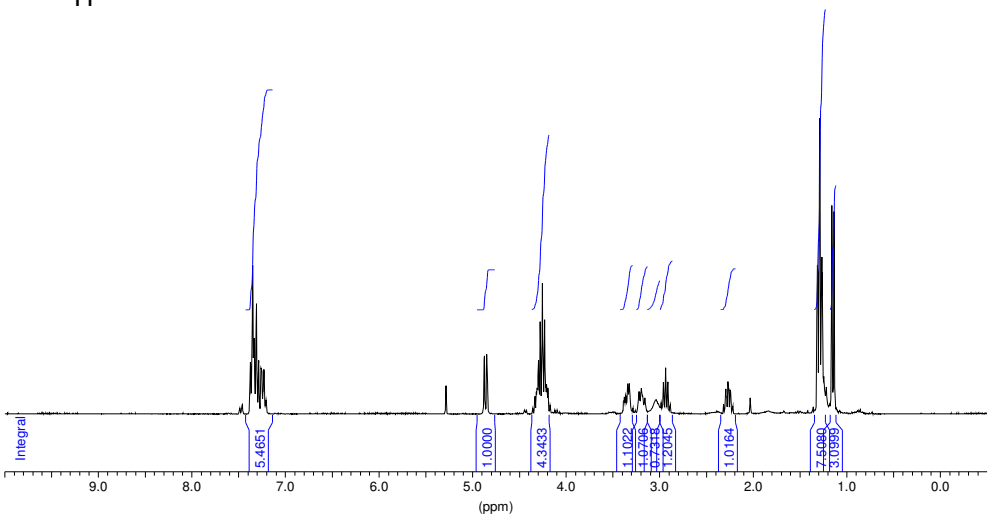
4.- Hart, B. P.; Verma, S. K.; Rapoport, H. *J. Org. Chem.* **2003**, *68*, 187.

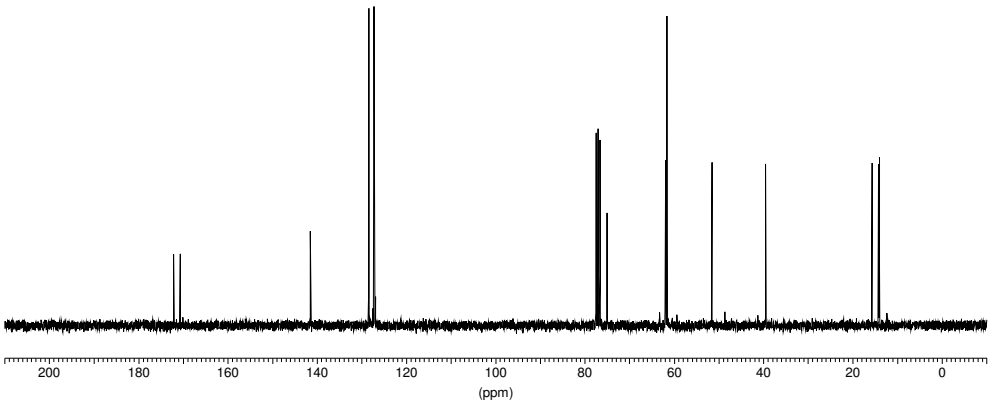
5.- Qiu, X.-L.; Qing, F.-L. *J. Org. Chem.* **2003**, *68*, 3614.

4. ^{1}H-NMR and ^{13}C-NMR spectra of pyrrolidines 11a-r

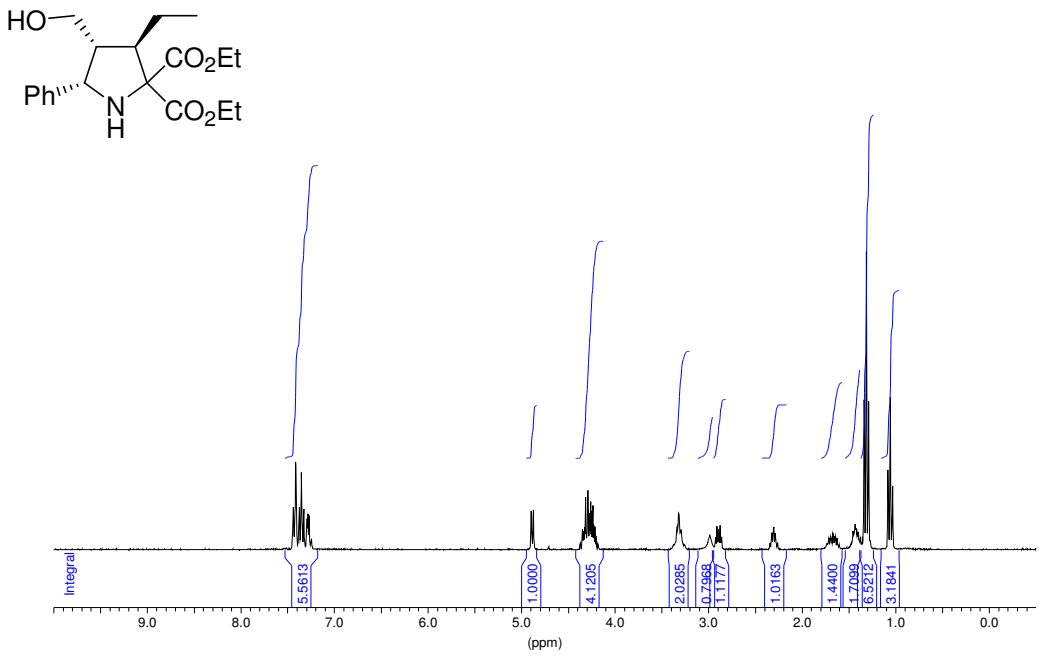
4.1.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-methyl-5-phenylpyrrolidine-2,2-dicarboxylate (**11a**)

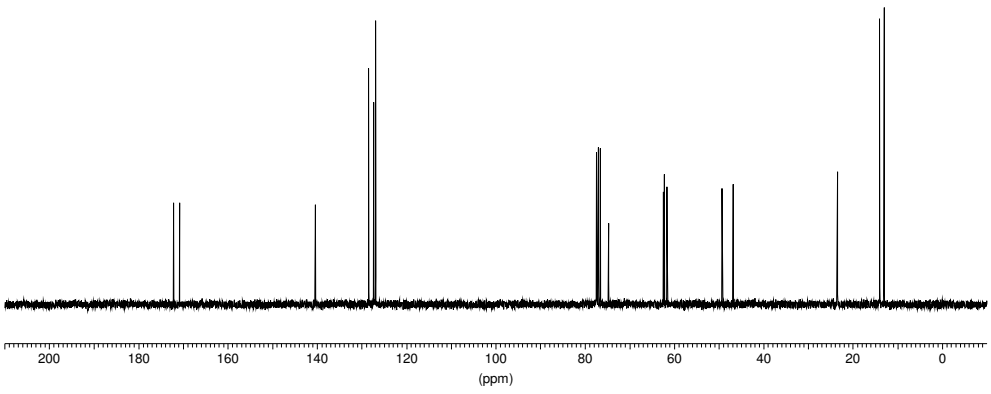




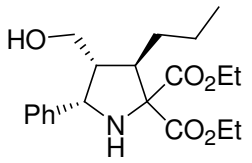


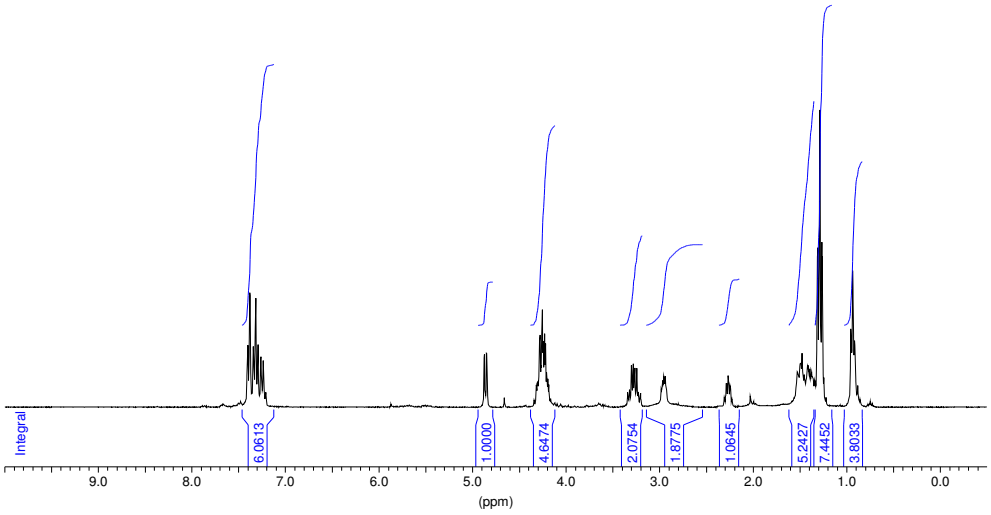
4.2.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*R*,4*R*,5*S*)-3-ethyl-4-hydroxymethyl-5-phenylpyrrolidine-2,2-dicarboxylate (**11b**)

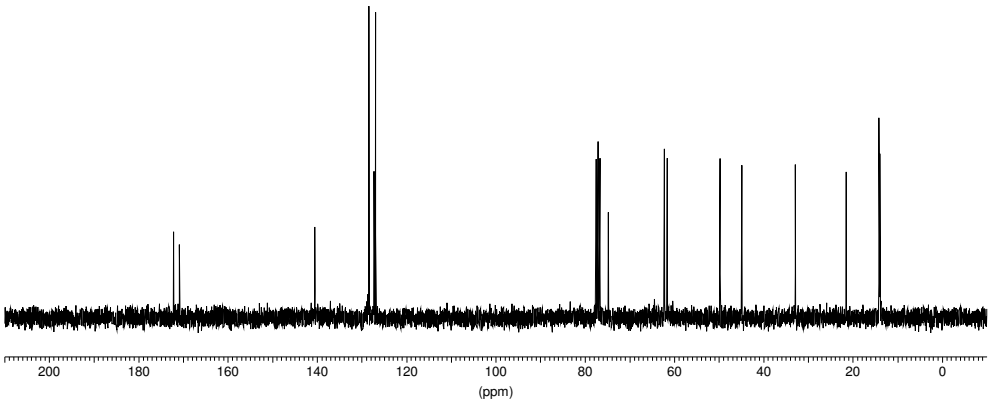




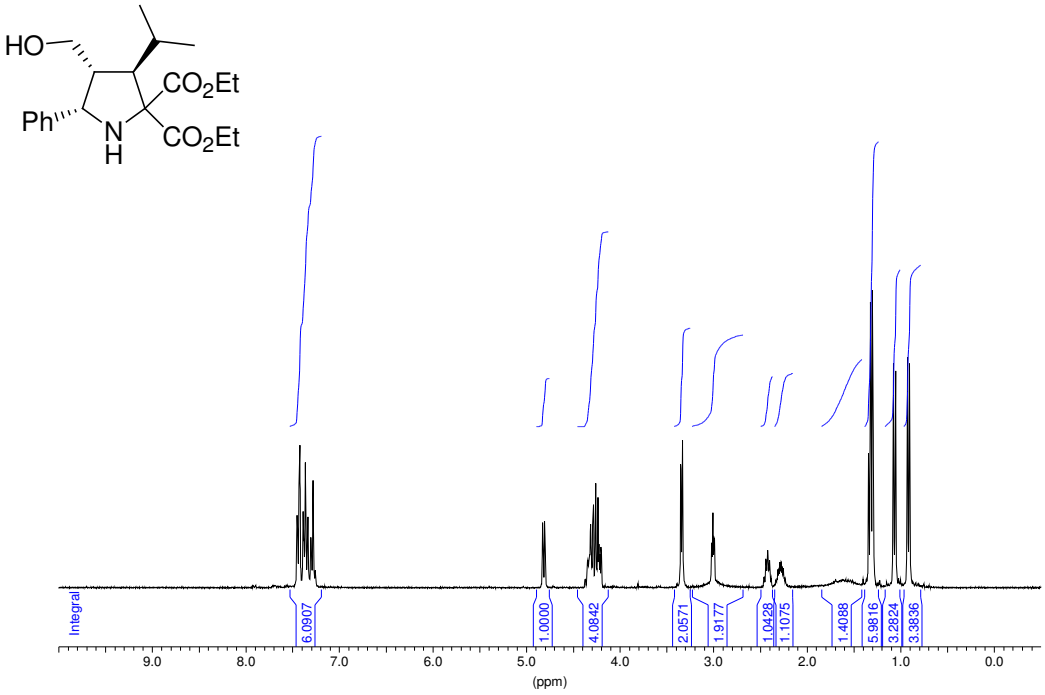
4.3.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3R,4R,5S)-4-hydroxymethyl-5-phenyl-3-propylpyrrolidine-2,2-dicarboxylate (**11c**)

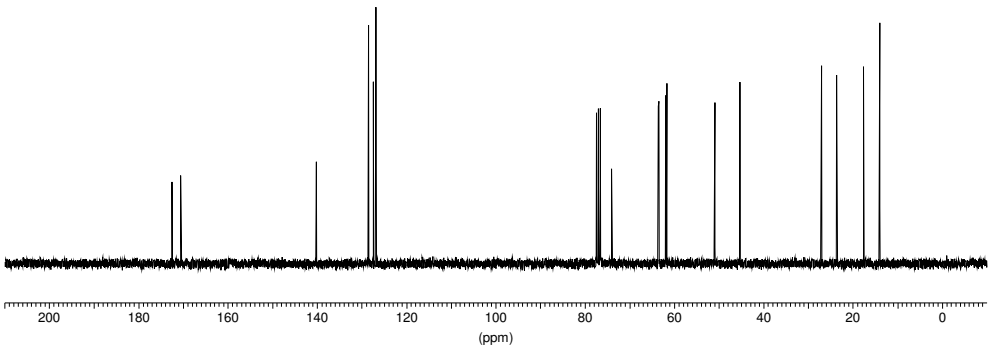




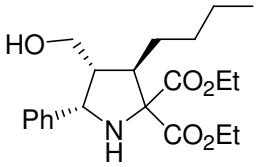


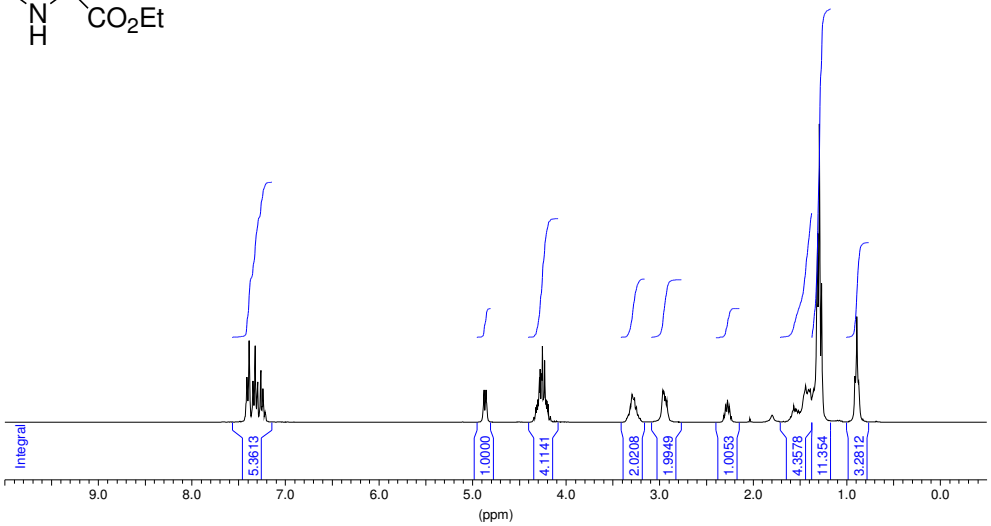
4.4.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-*iso*-propyl-5-phenylpyrrolidine-2,2-dicarboxylate (**11d**)

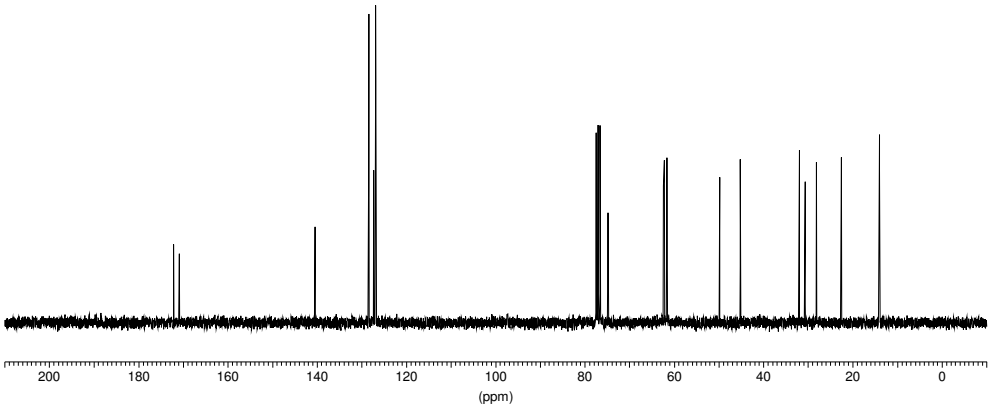




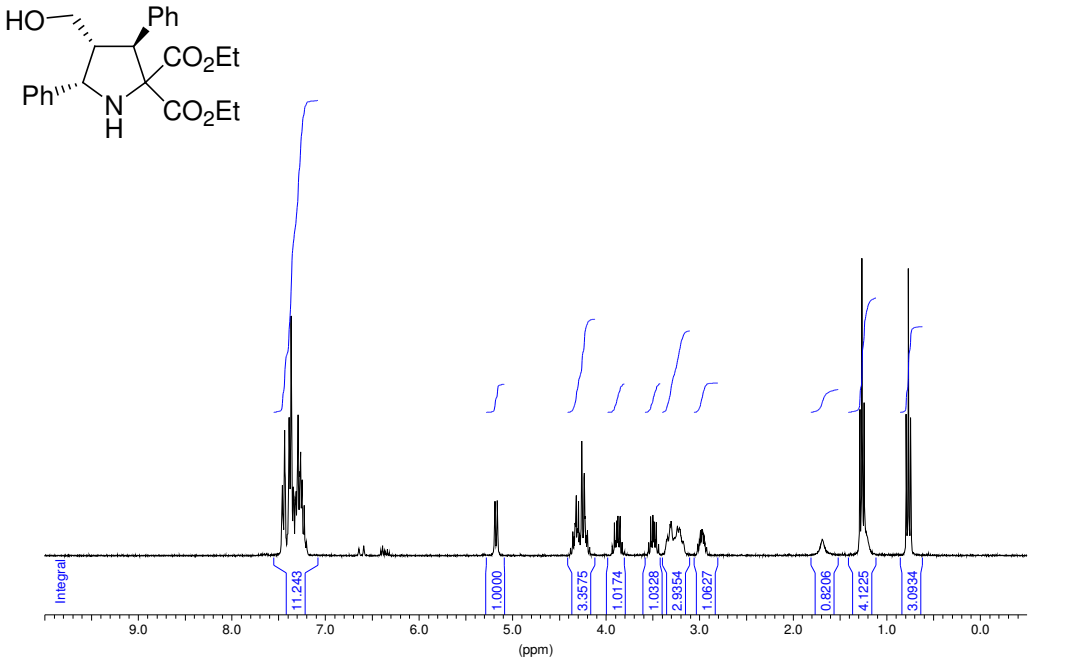
4.5.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*R*,4*R*,5*S*)-3-butyl-4-hydroxymethyl-5-phenylpyrrolidine-2,2-dicarboxylate (**11e**)

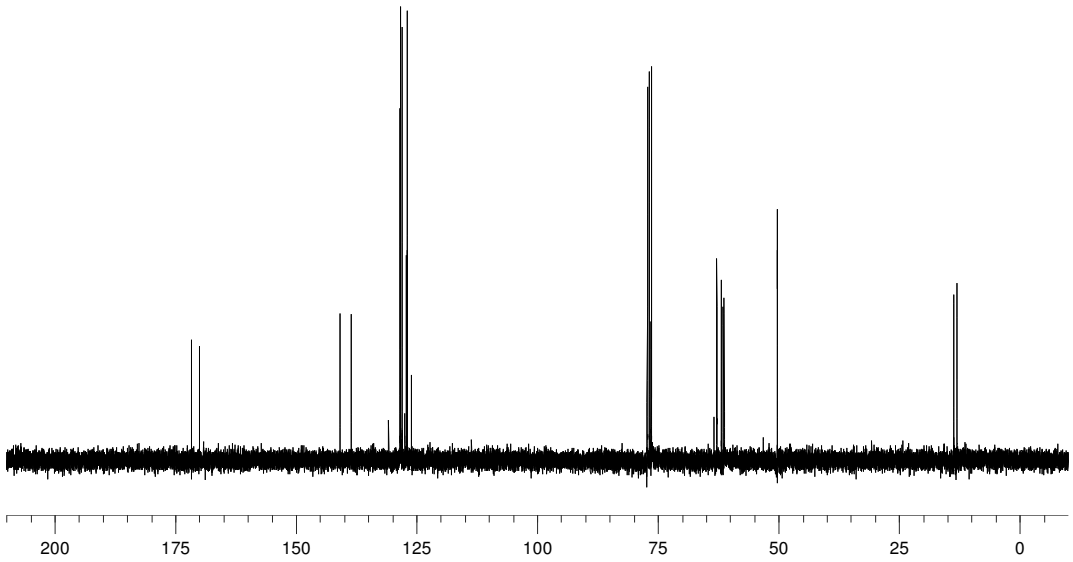




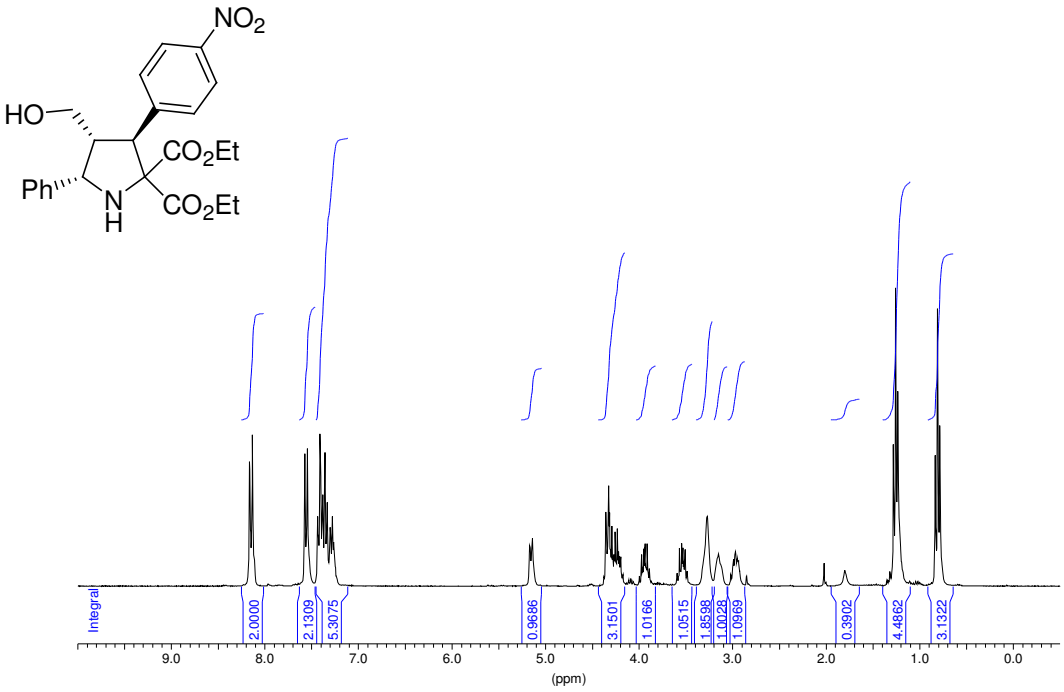


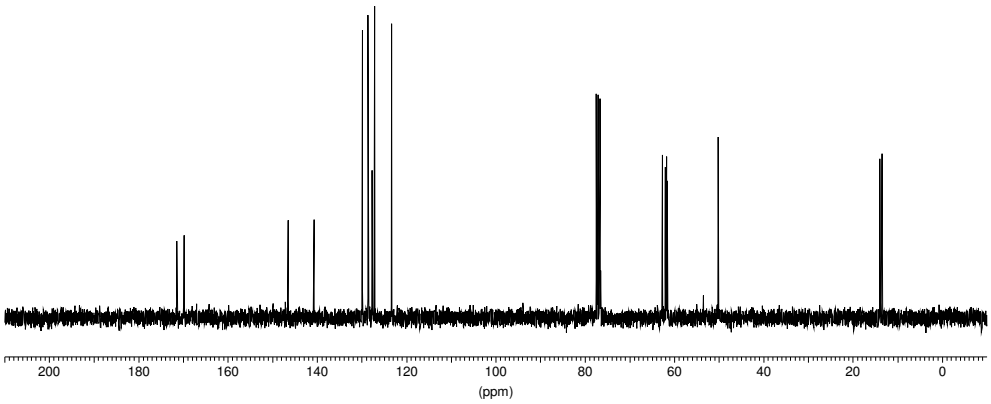
4.6.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*S*,4*R*,5*S*)-4-hydroxymethyl-3,5-diphenylpyrrolidine-2,2-dicarboxylate (**11f**)



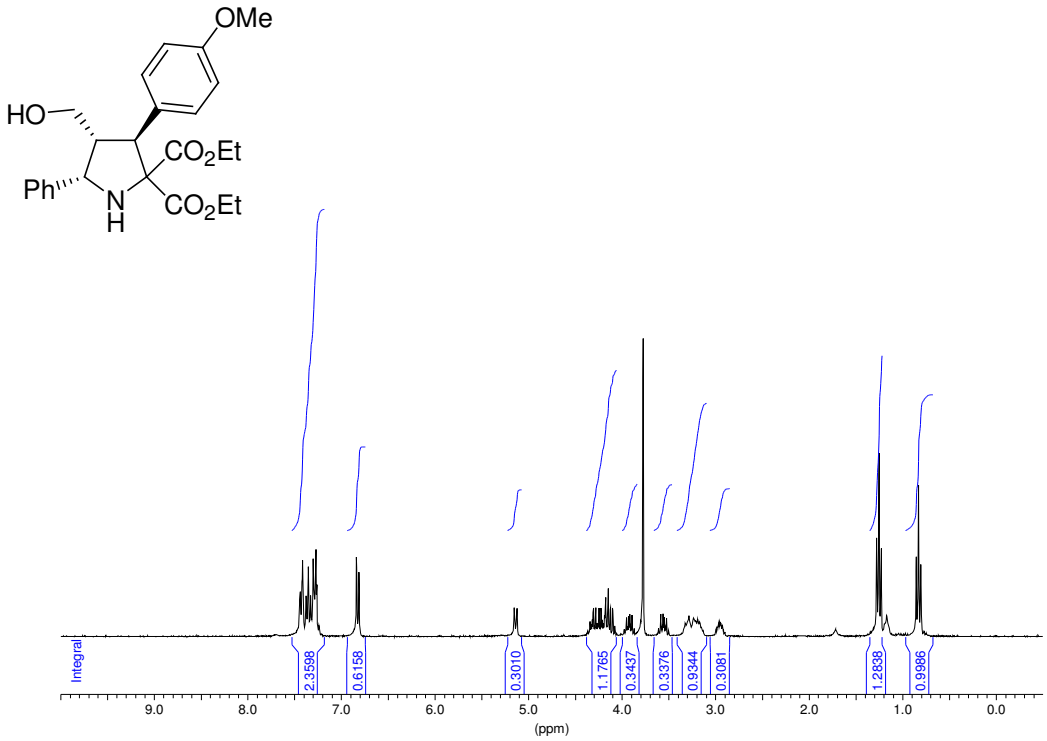


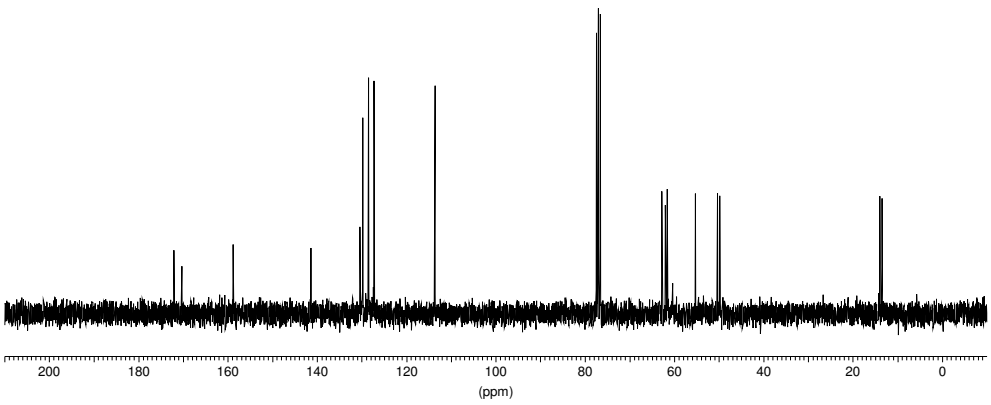
4.7.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*S*,4*R*,5*S*)-4-hydroxymethyl-3-(*p*-nitrophenyl)-5-phenylpyrrolidine-2,2-dicarboxylate (**11g**)



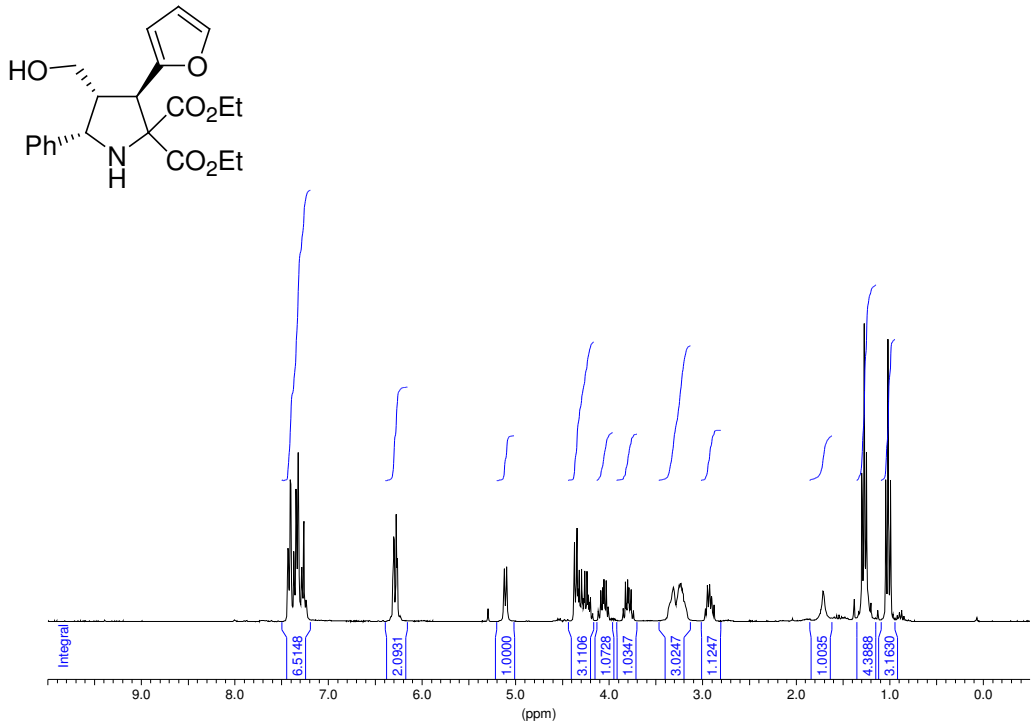


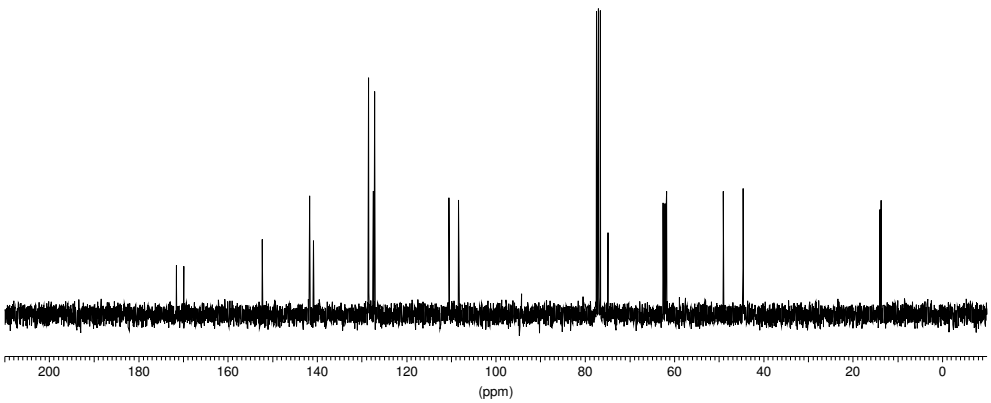
4.8.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*S*,4*R*,5*S*)-4-hydroxymethyl-3-(*p*-methoxyphenyl)-5-phenylpyrrolidine-2,2-dicarboxylate (**11h**)



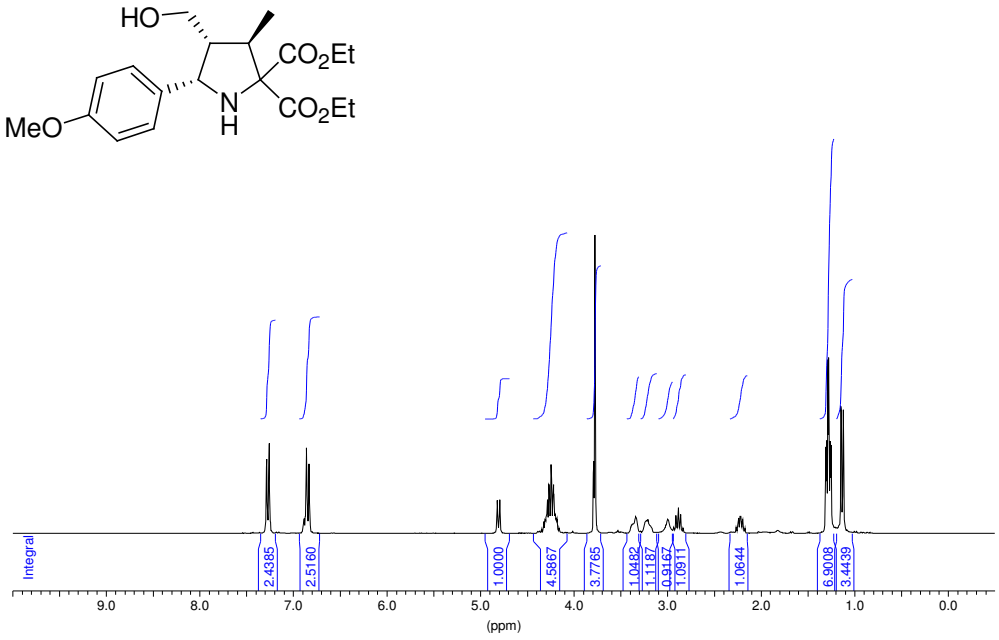


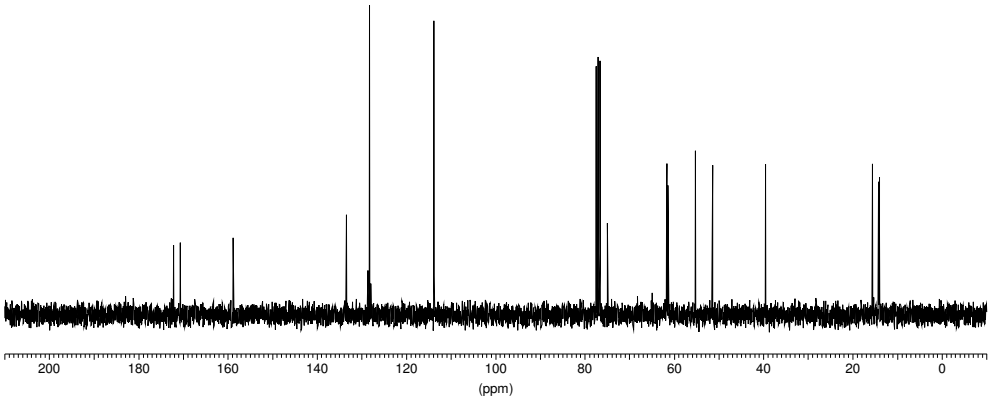
4.9.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*R*,4*R*,5*S*)-3-furyl-4-hydroxymethyl-5-phenylpyrrolidine-2,2-dicarboxylate (**11i**)



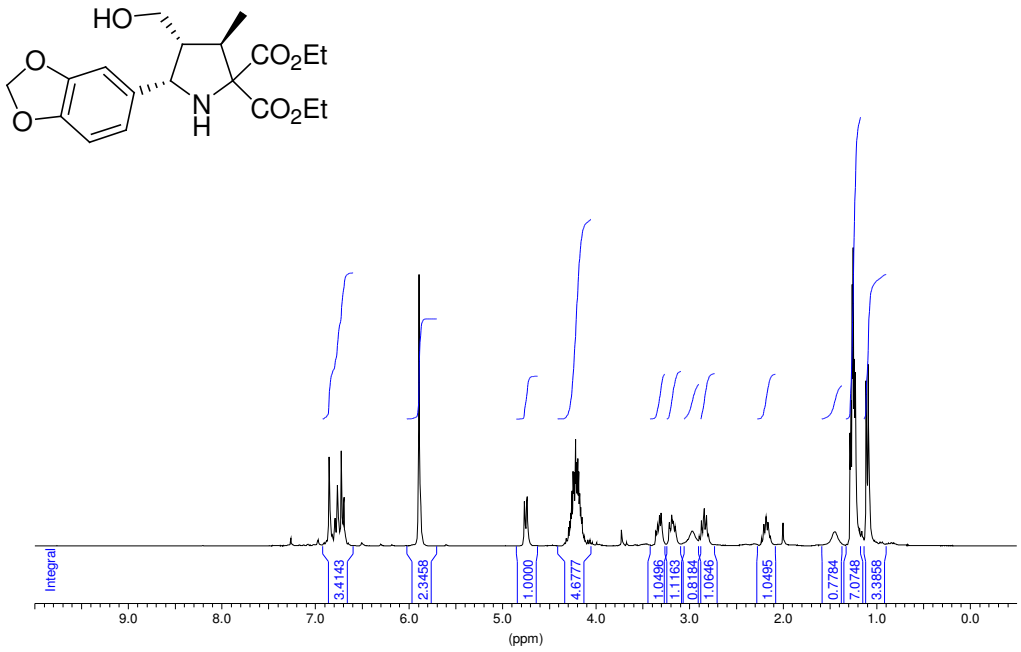


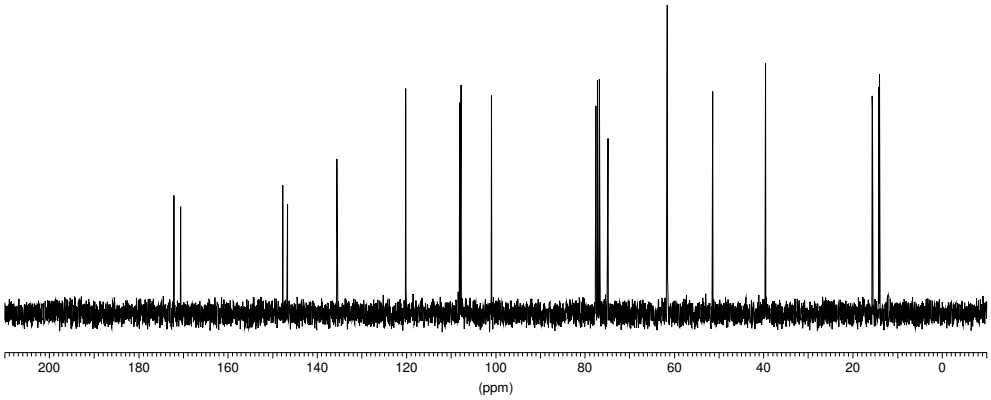
4.10.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-5-(*p*-methoxyphenyl)-3-methylpyrrolidine-2,2-dicarboxylate (**11j**)



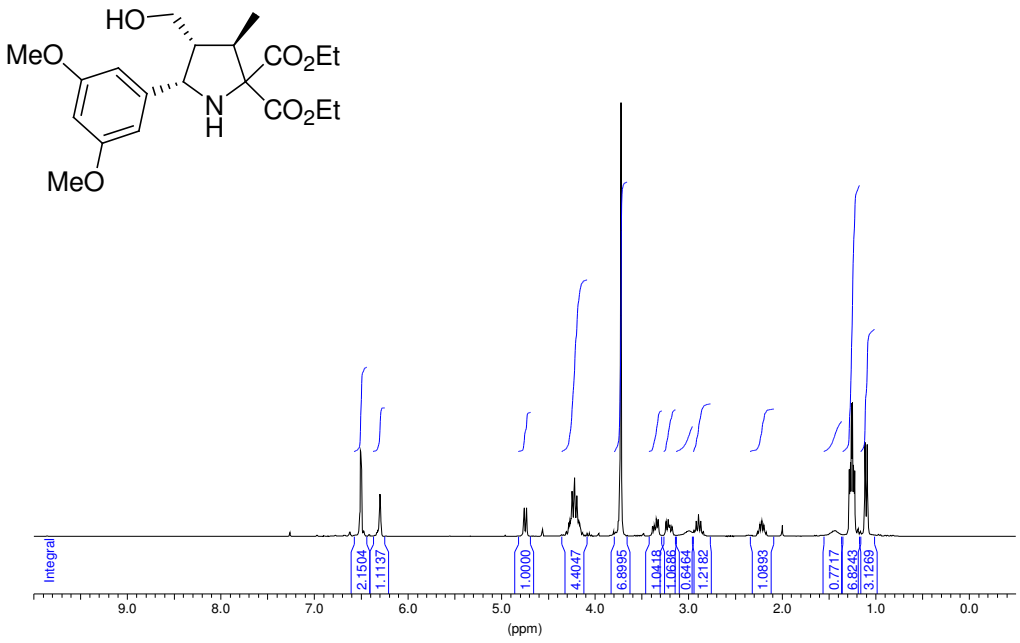


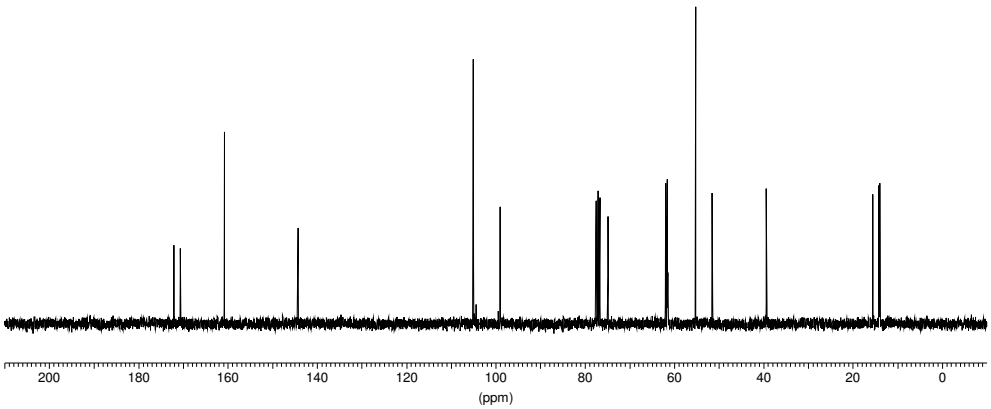
4.11.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-methyl-5-(3,4-methylenedioxyphenyl)pyrrolidine-2,2-dicarboxylate (**11k**)



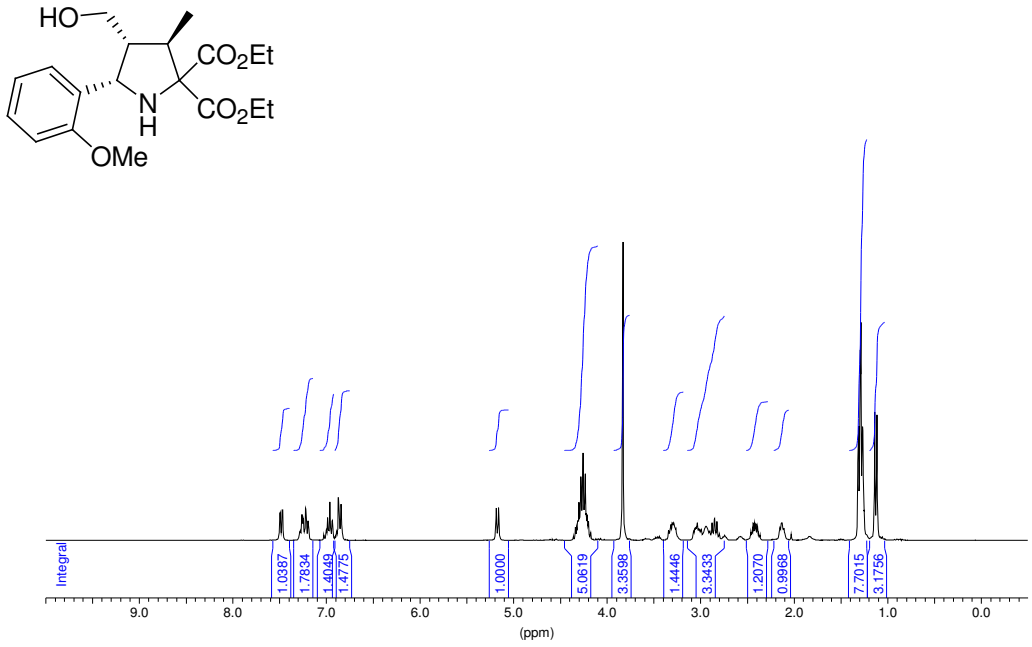


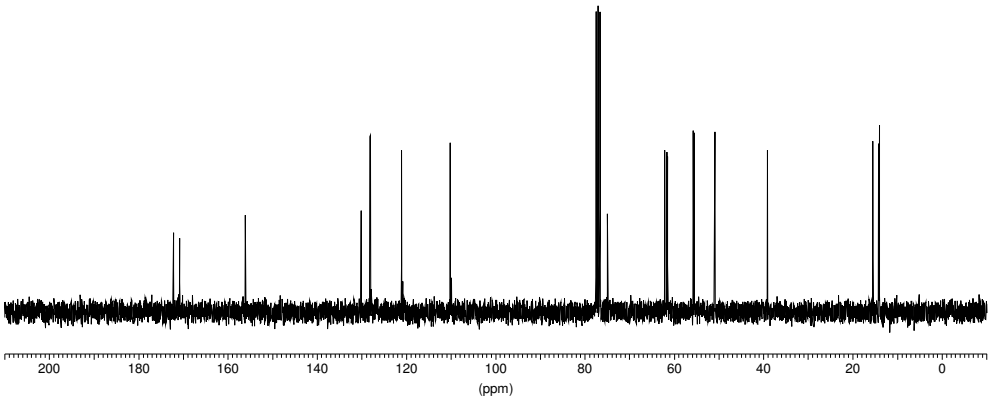
4.12.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*R*,4*R*,5*S*)-5-(3,5-dimethoxyphenyl)-4-hydroxymethyl-3-methylpyrrolidine-2,2-dicarboxylate (**11l**)



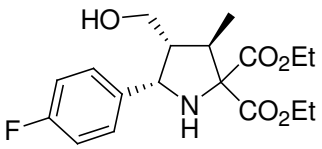


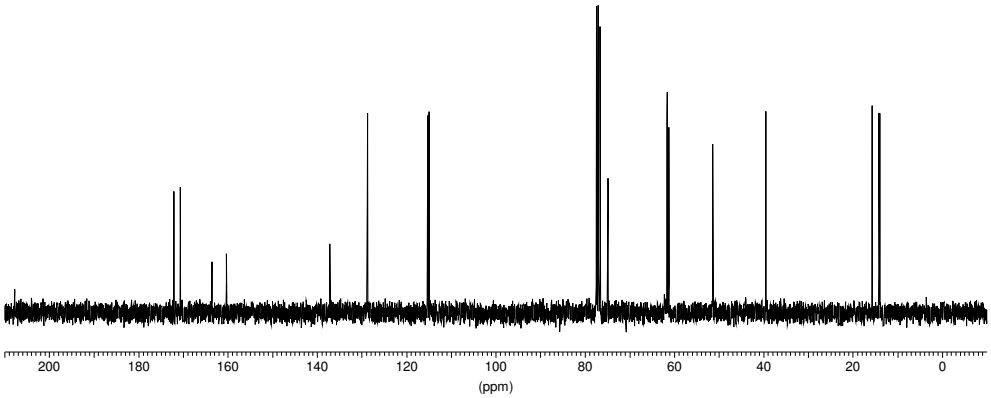
4.13.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-5-(*o*-methoxyphenyl)-3-methylpyrrolidine-2,2-dicarboxylate (**11m)**



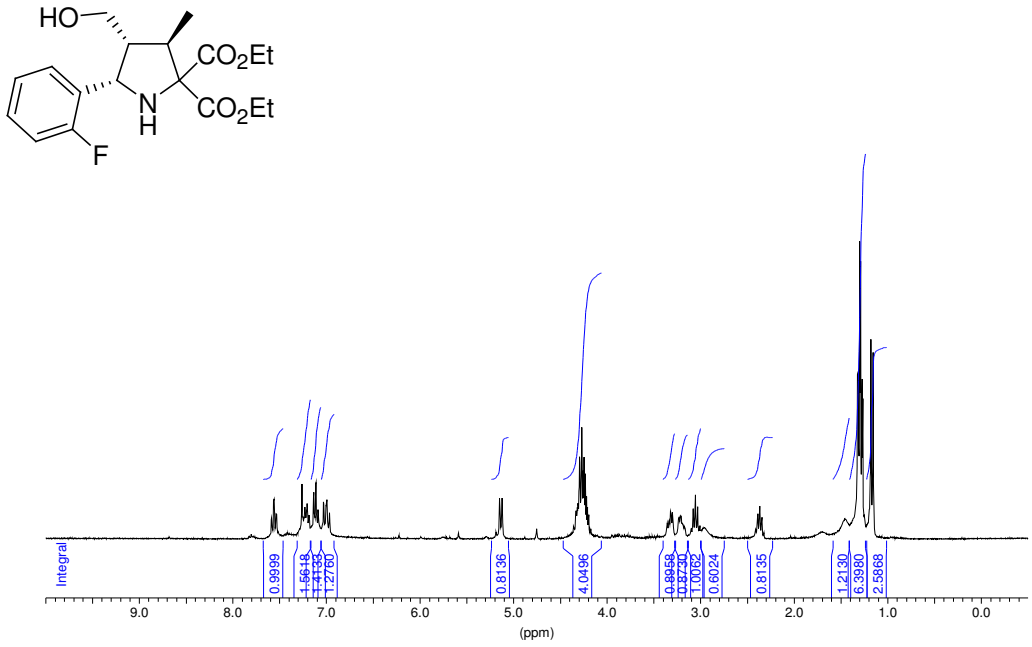


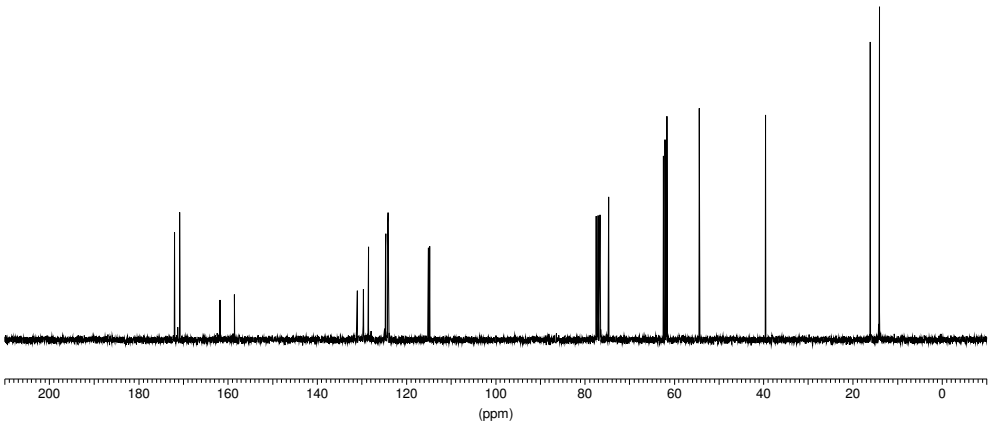
4.14.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*R*,4*R*,5*S*)-5-(*p*-fluorophenyl)-4-hydroxymethyl-3-methylpyrrolidine-2,2-dicarboxylate (**11n**)



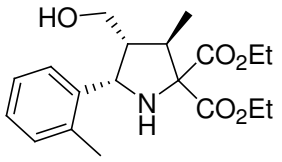


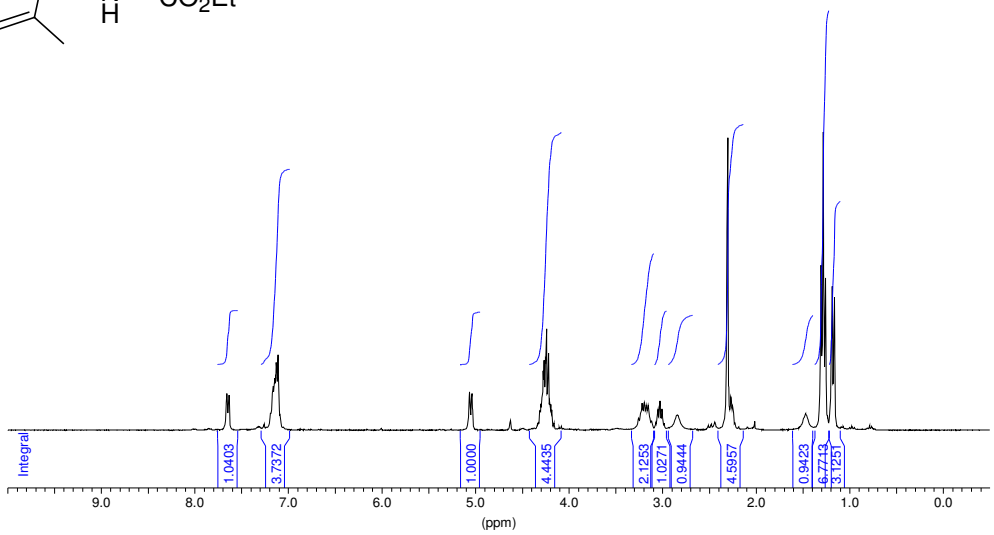
4.15.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*R*,4*R*,5*S*)-5-(*o*-fluorophenyl)-4-hydroxymethyl-3-methylpyrrolidine-2,2-dicarboxylate (**11o**)

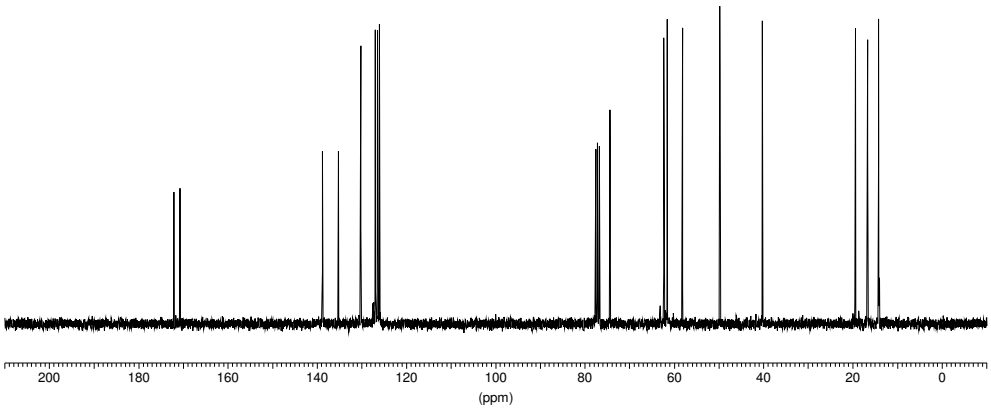




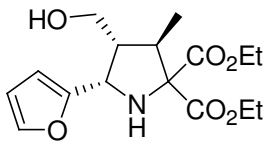
4.16.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-methyl-5-(*o*-tolyl)pyrrolidine-2,2-dicarboxylate (**11p**)

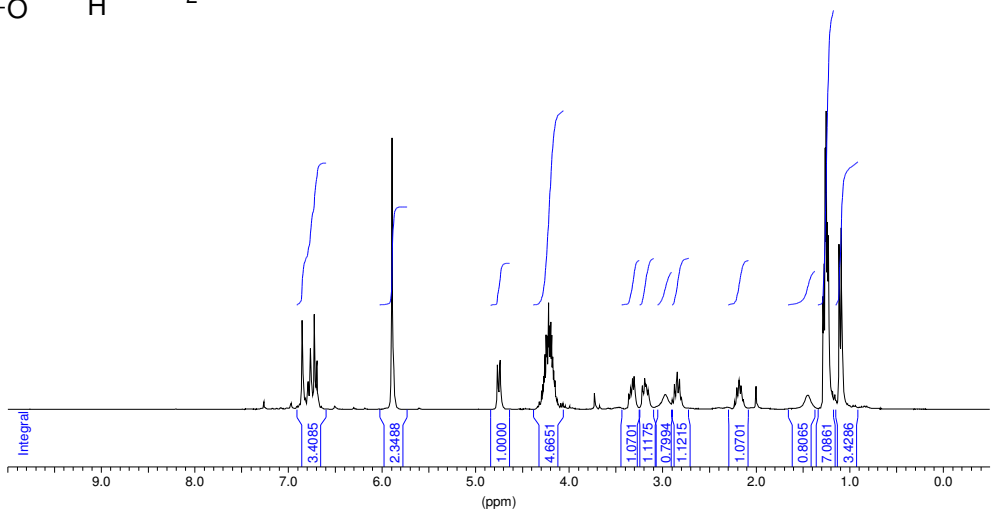


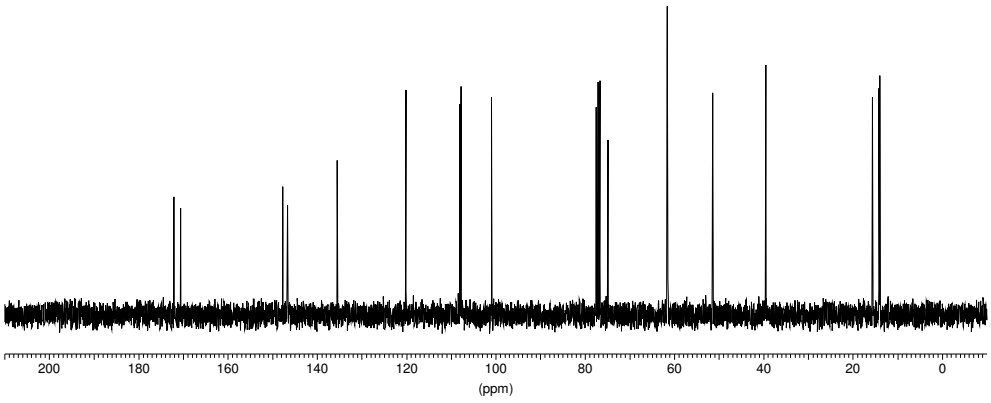




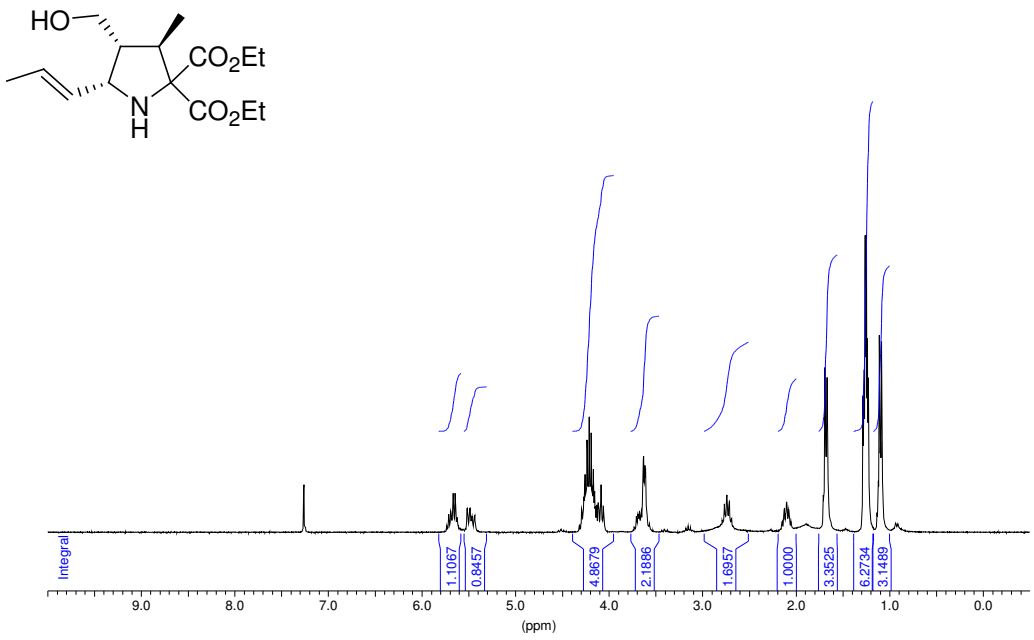
4.17.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*R*,4*R*,5*S*)-5-(2-furyl)-4-hydroxymethyl-3-methylpyrrolidine-2,2-dicarboxylate (**11q**)

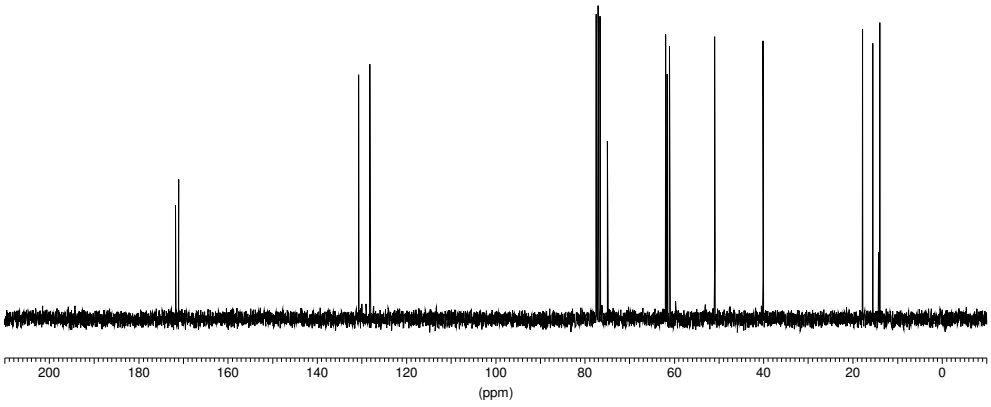






4.18.- ^{1}H-NMR and ^{13}C-NMR spectra of diethyl (3*R*,4*R*,5*R*,1'*E*)-4-hydroxymethyl-3-methyl-5-(1-propenyl)pyrrolidine-2,2-dicarboxylate (**11r**)



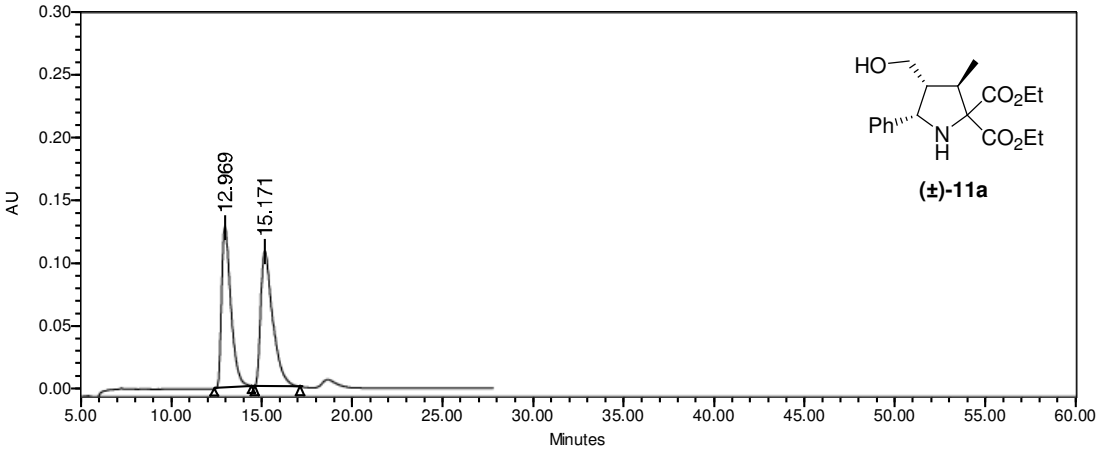


5. HPLC chromatograms of racemic and enantioenriched pyrrolidines 11a-r

5.1.- HPLC chromatograms of diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-methyl-5-phenylpyrrolidine-2,2-dicarboxylate (**11a**)

SampleName	pyrrolidine Ph, Me rac	Sample Type	Unknown
Vial	1	Date Acquired	11/04/06 11:47:33 AM
Injection	1	Acq Method Set	od 100 95 5
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 11:49:45 AM
Run Time	40.0 Minutes		

Auto-Scaled Chromatogram

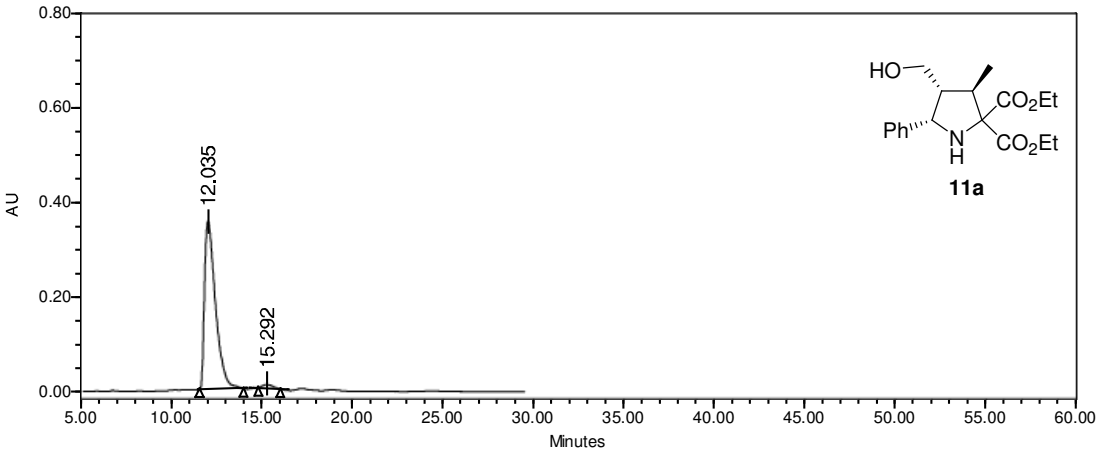


Peak Results

	RT	Area	Height	% Area
1	12.969	4578388	127252	48.14
2	15.171	4932230	106814	51.86

SampleName	Pyrrolidine Me, Ph, Ph2ProOH	Sample Type	Unknown
Vial	1	Date Acquired	30/01/07 4:45:31 PM
Injection	1	Acq Method Set	od 100 95 05
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 11:54:39 AM
Run Time	60.0 Minutes		

Auto-Scaled Chromatogram



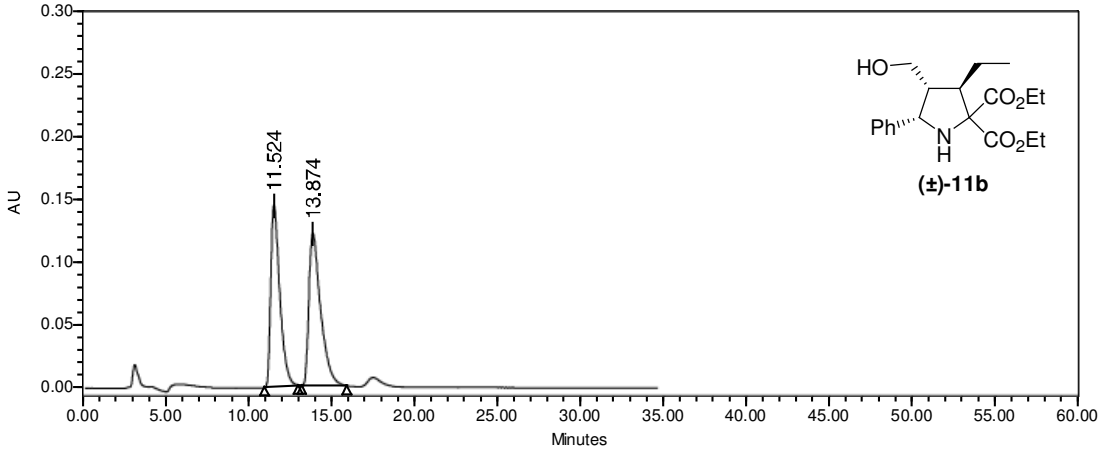
Peak Results

	RT	Area	Height	% Area
1	12.035	15110414	353717	99.17
2	15.292	126466	10878	0.83

5.2.- HPLC chromatograms of diethyl (3*R*,4*R*,5*S*)-3-ethyl-4-hydroxymethyl-5-phenylpyrrolidine-2,2-dicarboxylate (**11b**)

SampleName	pyrrolidine Ph, Et rac	Sample Type	Unknown
Vial	1	Date Acquired	11/04/06 12:21:57 PM
Injection	1	Acq Method Set	od 100 95 5
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 11:57:34 AM
Run Time	40.0 Minutes		

Auto-Scaled Chromatogram

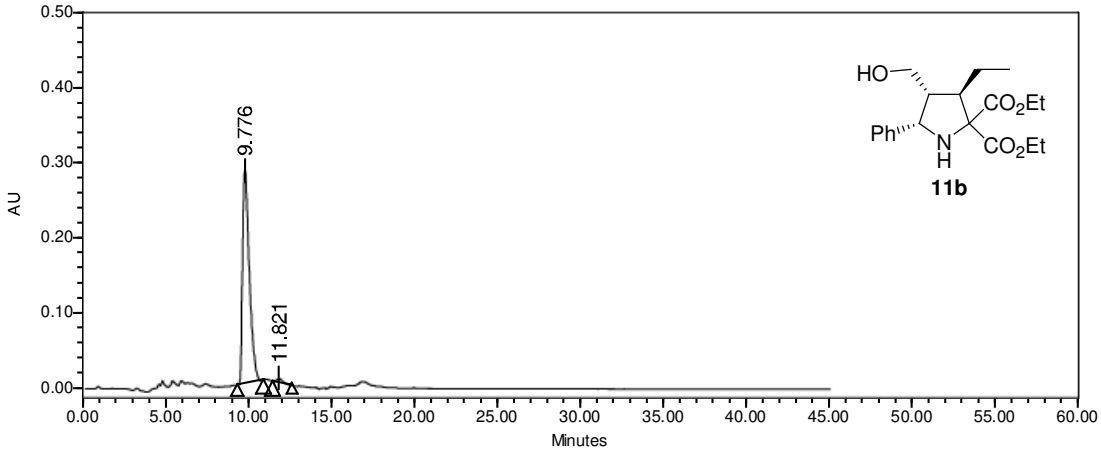


Peak Results

	RT	Area	Height	% Area
1	11.524	5486979	143988	48.07
2	13.874	5926843	120621	51.93

SampleName	Pyrrolidine Et, Ph, Ph2ProOH	Sample Type	Unknown
Vial	1	Date Acquired	30/01/07 5:51:50 PM
Injection	1	Acq Method Set	od 100 95 05
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 12:00:31 PM
Run Time	60.0 Minutes		

Auto-Scaled Chromatogram



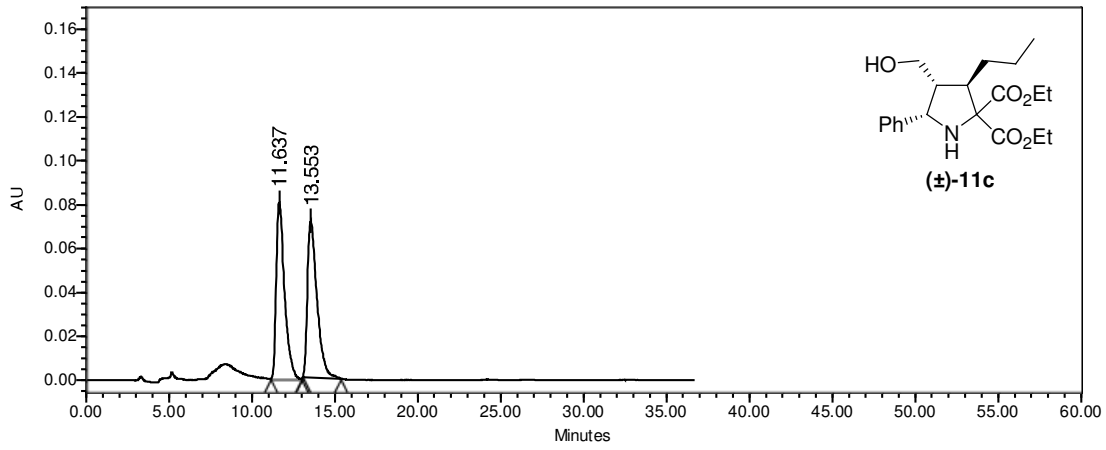
Peak Results

	RT	Area	Height	% Area
1	9.776	8029804	282792	98.32
2	11.821	137127	5369	1.68

5.3.- HPLC chromatograms of diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-5-phenyl-3-propyl-pyrrolidine-2,2-dicarboxylate (**11c**)

SampleName	pyrrolidine Ph, n-Pr rac	Sample Type	Unknown
Vial	1	Date Acquired	17/07/06 2:08:24 PM
Injection	1	Acq Method Set	od 100 98 02
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 12:07:03 PM
Run Time	50.0 Minutes		

Auto-Scaled Chromatogram

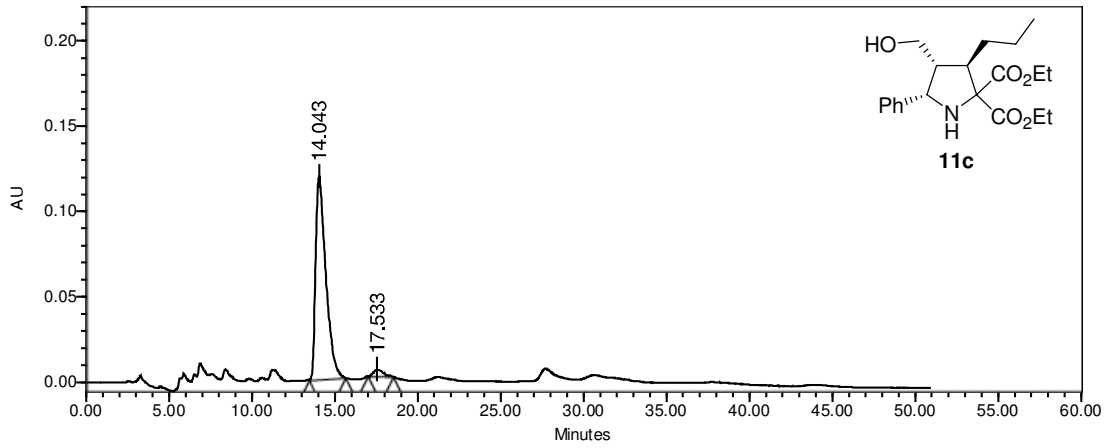


Peak Results

	RT	Area	Height	% Area
1	11.637	2803281	80384	49.63
2	13.553	2844619	71395	50.37

SampleName	Pyrrolidine nPr, Ph Ph2ProOH	Sample Type	Unknown
Vial	1	Date Acquired	29/01/07 3:33:15 PM
Injection	1	Acq Method Set	od 100 98 02
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 12:10:30 PM
Run Time	60.0 Minutes		

Auto-Scaled Chromatogram



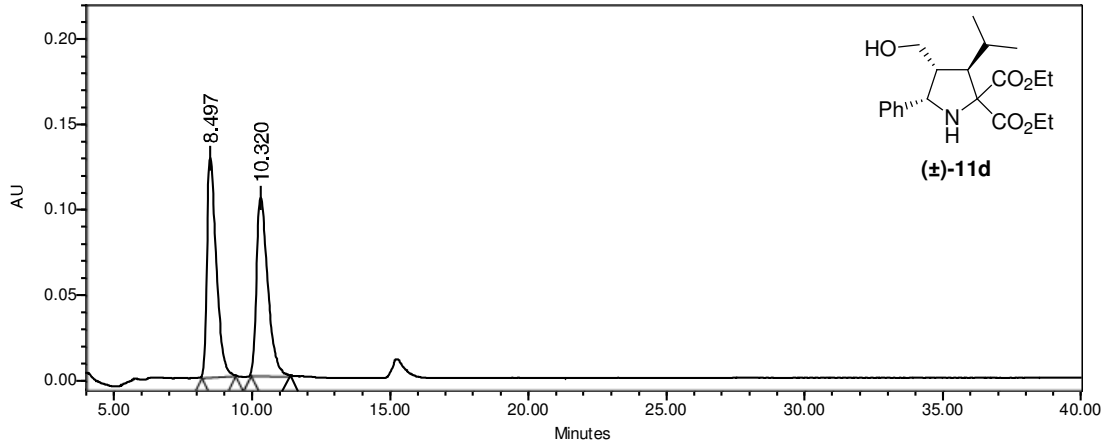
Peak Results

	RT	Area	Height	% Area
1	14.043	5094200	119108	98.75
2	17.533	116070	4425	2.25

5.4.- HPLC chromatograms of diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-*iso*-propyl-5-phenylpyrrolidine-2,2-dicarboxylate (**11d**)

SampleName	pyrrolidine Ph, iPr rac	Sample Type	Unknown
Vial	1	Date Acquired	11/04/06 10:57:22 AM
Injection	1	Acq Method Set	od 100 95 5
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 12:15:23 PM
Run Time	40.0 Minutes		

Auto-Scaled Chromatogram

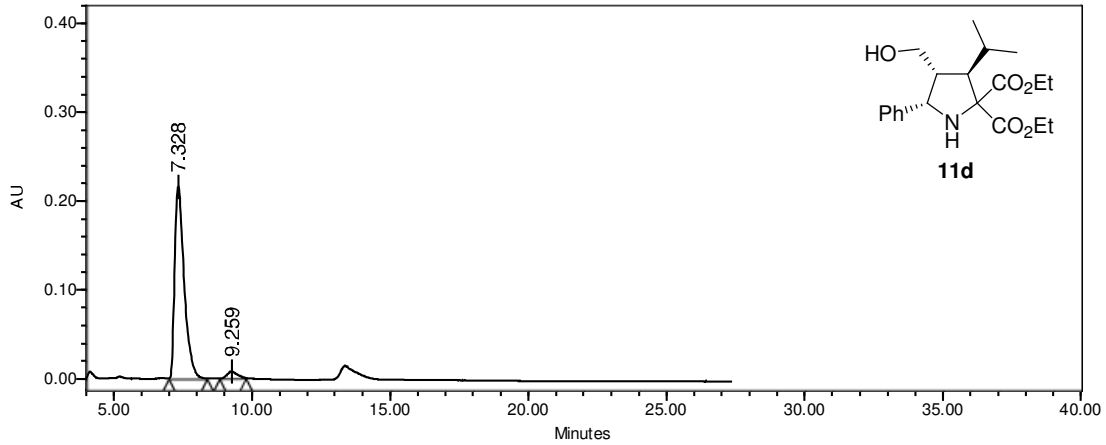


Peak Results

	RT	Area	Height	% Area
1	8.497	3013272	128116	50.85
2	10.320	2912337	103798	49.15

SampleName	Pyrrolidine iPr, Ph, Ph2ProOH	Sample Type	Unknown
Vial	1	Date Acquired	30/01/07 4:14:08 PM
Injection	1	Acq Method Set	od 100 95 05
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 12:18:19 PM
Run Time	60.0 Minutes		

Auto-Scaled Chromatogram



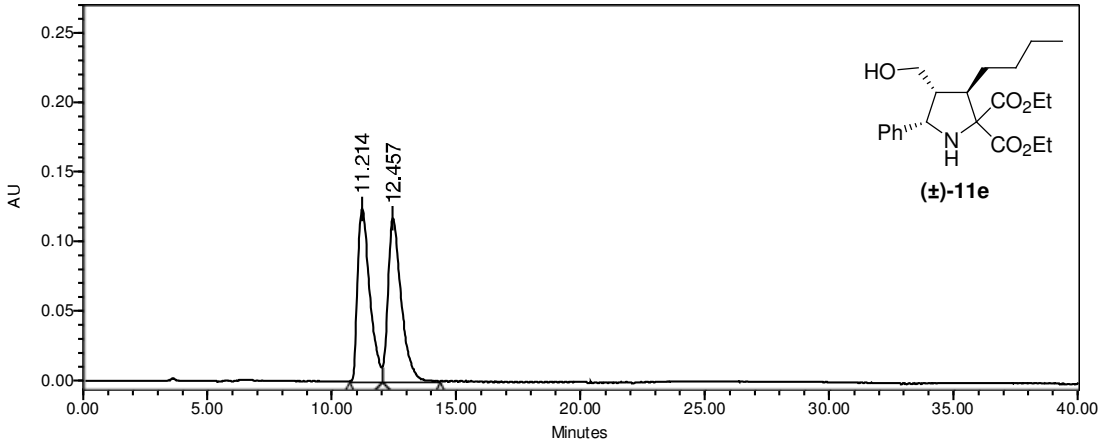
Peak Results

	RT	Area	Height	% Area
1	7.328	5065856	215511	97.56
2	9.259	126698	7277	2.44

5.5.- HPLC chromatograms of diethyl (3*R*,4*R*,5*S*)-3-butyl-4-hydroxymethyl-5-phenylpyrrolidine-2,2-dicarboxylate (**11e**)

SampleName	pyrrolidine nBu, Ph rac	Sample Type	Unknown
Vial	1	Date Acquired	28/07/06 10:37:38 AM
Injection	1	Acq Method Set	od 100 98 02
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	28/07/06 11:27:37 AM
Run Time	40.0 Minutes		

Auto-Scaled Chromatogram

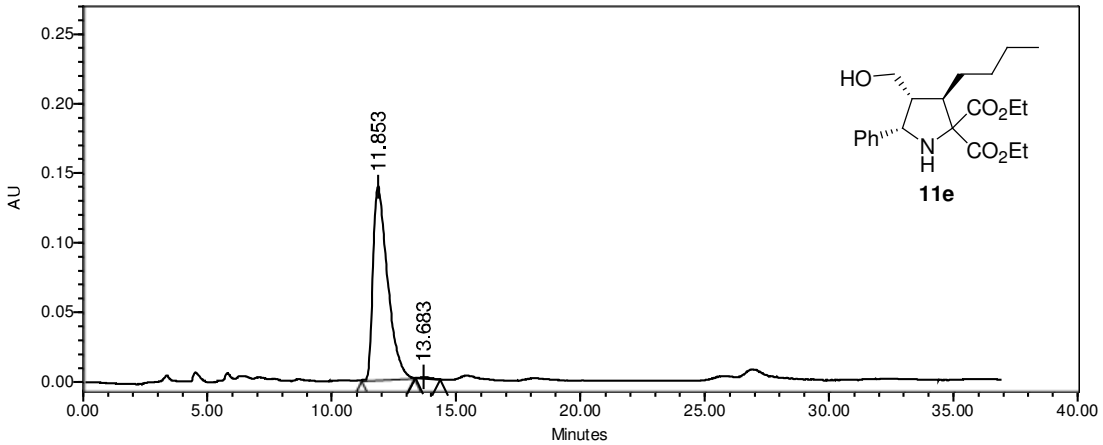


Peak Results

	RT	Area	Height	% Area
1	11.214	4189445	123930	48.92
2	12.457	4374853	117375	51.08

SampleName	Pyrrolidine nBu, Ph, Ph2Pro-OH	Sample Type	Unknown
Vial	1	Date Acquired	31/01/07 11:25:13 AM
Injection	1	Acq Method Set	od 100 98 02
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 12:24:27 PM
Run Time	60.0 Minutes		

Auto-Scaled Chromatogram



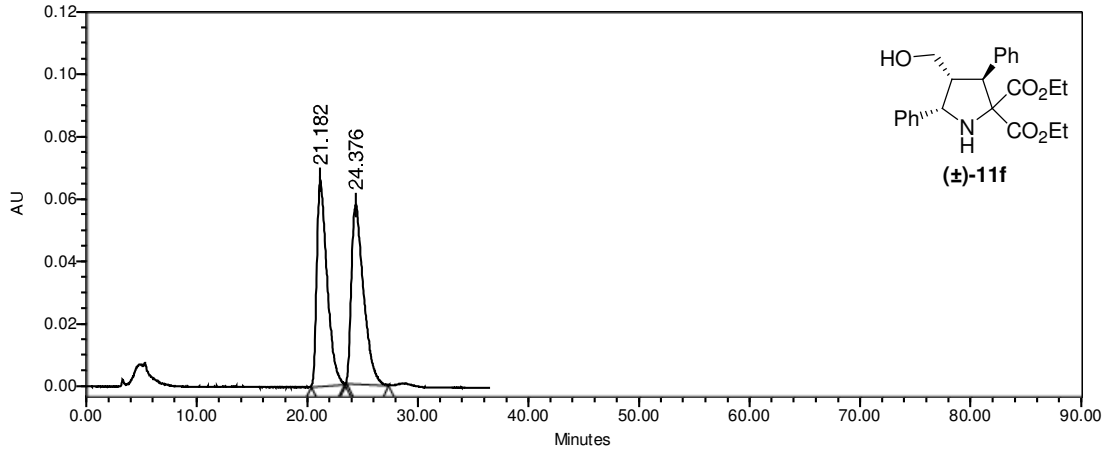
Peak Results

	RT	Area	Height	% Area
1	11.853	5614666	138395	99.37
2	13.683	35812	1177	0.63

5.6.- HPLC chromatograms of diethyl (3*S*,4*R*,5*S*)-4-hydroxymethyl-3,5-diphenylpyrrolidine-2,2-dicarboxylate (**11f**)

SampleName	pyrrolidine Ph, Ph rac	Sample Type	Unknown
Vial	1	Date Acquired	17/07/06 1:23:36 PM
Injection	1	Acq Method Set	od 100 98 02
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 12:32:08 PM
Run Time	50.0 Minutes		

Auto-Scaled Chromatogram

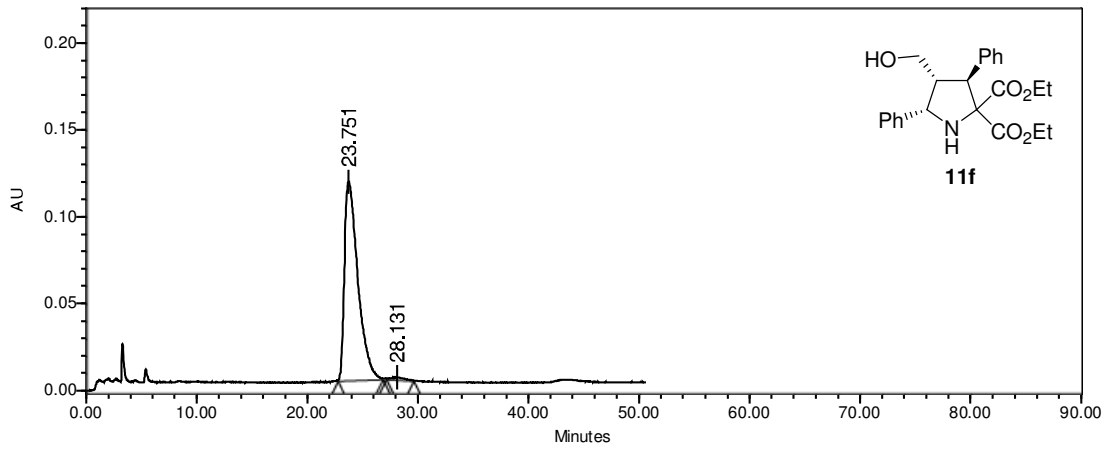


Peak Results

	RT	Area	Height	% Area
1	21.182	4291084	66113	49.42
2	24.376	4392473	57326	50.58

SampleName	pyrrolidine Ph, Ph, Ph2ProOH	Sample Type	Unknown
Vial	1	Date Acquired	1/02/07 6:30:20 PM
Injection	1	Acq Method Set	od 100 98 02
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 12:38:36 PM
Run Time	60.0 Minutes		

Auto-Scaled Chromatogram



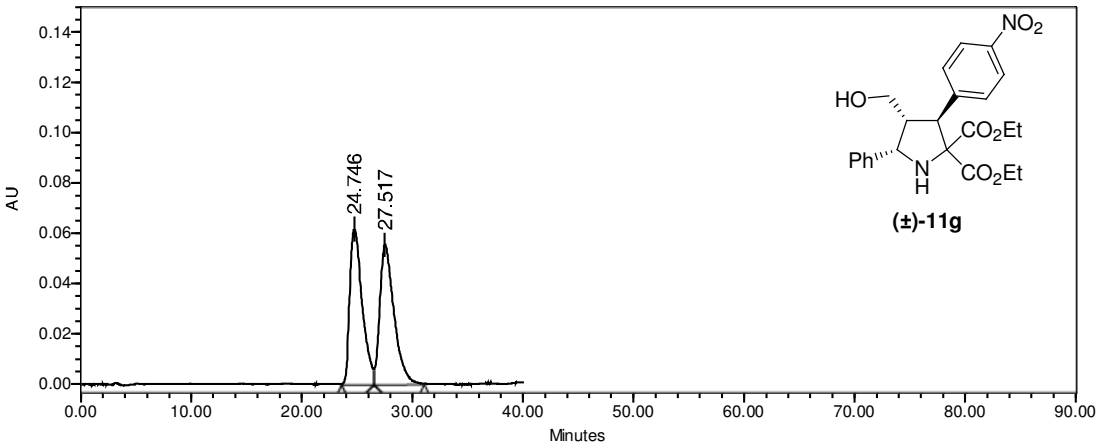
Peak Results

	RT	Area	Height	% Area
1	23.751	9555170	114031	99.84
2	28.131	15312	1130	0.16

5.7.- HPLC chromatograms of diethyl (3*S*,4*R*,5*S*)-4-hydroxymethyl-3-(*p*-nitrophenyl)-5-phenylpyrrolidine-2,2-dicarboxylate (**11g**)

SampleName	pyrrolidine NO2Ph,Ph, Pro	Sample Type	Unknown
Vial	1	Date Acquired	17/07/06 5:13:59 PM
Injection	1	Acq Method Set	od 100 95 05
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 3:17:38 PM
Run Time	40.0 Minutes		

Auto-Scaled Chromatogram

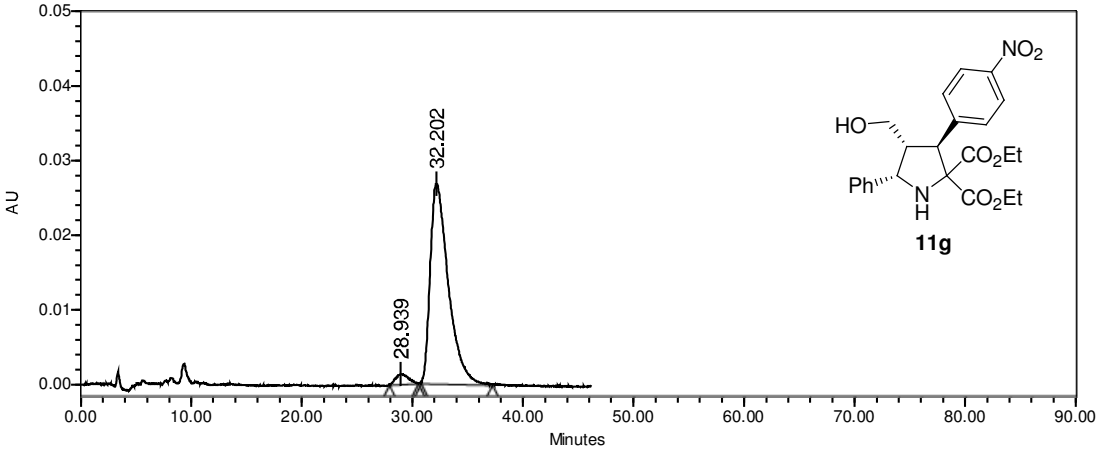


Peak Results

	RT	Area	Height	% Area
1	24.746	4769725	61611	49.15
2	27.517	4933858	55303	50.85

SampleName	pyrrolidine p-NO2, Ph, Ph2ProOH	Sample Type	Unknown
Vial	1	Date Acquired	1/02/07 5:26:56 PM
Injection	1	Acq Method Set	od 100 95 05
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 3:29:46 PM
Run Time	60.0 Minutes		

Auto-Scaled Chromatogram



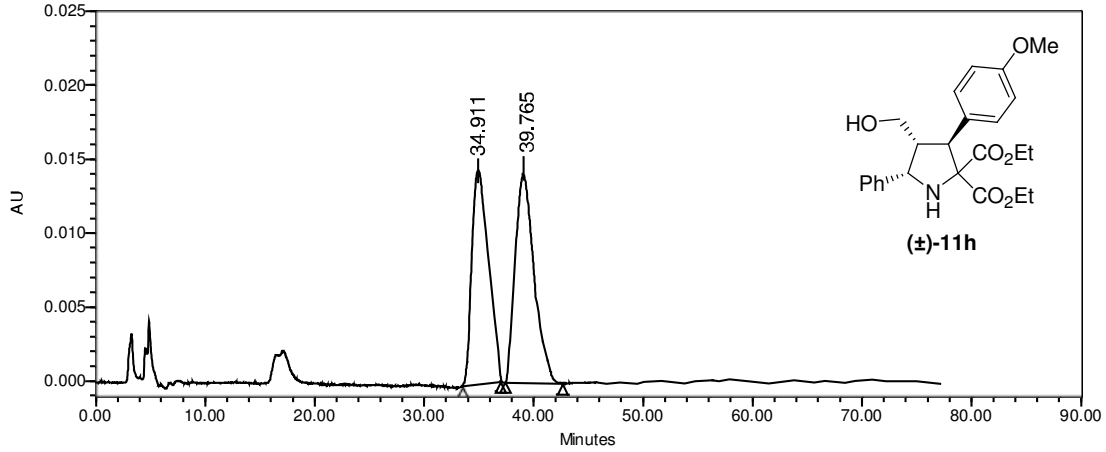
Peak Results

	RT	Area	Height	% Area
1	28.939	101142	1327	3.23
2	32.202	3025447	26729	96.77

5.8.- HPLC chromatograms of diethyl (3*S*,4*R*,5*S*)-4-hydroxymethyl-3-(*p*-methoxyphenyl)-5-phenylpyrrolidine-2,2-dicarboxylate (**11h**)

SampleName	pyrrolidine pOMePh, Ph rac	Sample Type	Unknown
Vial	1	Date Acquired	18/07/06 12:48:55 PM
Injection	1	Acq Method Set	od 100 98 02
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 1:10:42 PM
Run Time	60.0 Minutes		

Auto-Scaled Chromatogram

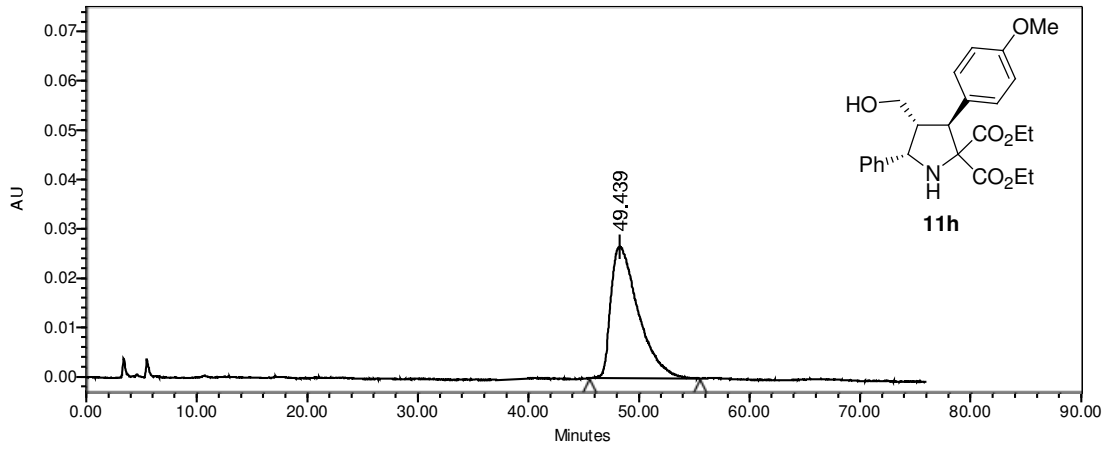


Peak Results

	RT	Area	Height	% Area
1	34.911	1064729	13215	45.66
2	39.765	1360409	12888	58.34

SampleName	pyrrolidine, pOMe, Ph, Ph2ProOH	Sample Type	Unknown
Vial	1	Date Acquired	2/02/07 9:19:08 AM
Injection	1	Acq Method Set	od 100 98 02
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 1:21:24 PM
Run Time	80.0 Minutes		

Auto-Scaled Chromatogram



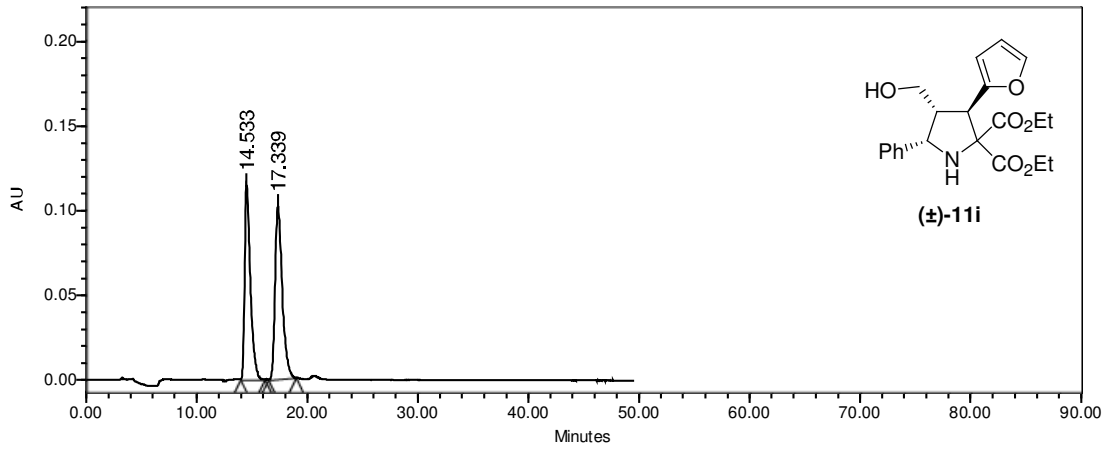
Peak Results

	RT	Area	Height	% Area
1	49.439	4656873	26796	100.00

5.9.- HPLC chromatograms of diethyl (3*R*,4*R*,5*S*)-3-furyl-4-hydroxymethyl-5-phenylpyrrolidine-2,2-dicarboxylate (**11i**)

SampleName	pyrrolidine furil, Ph rac	Sample Type	Unknown
Vial	1	Date Acquired	18/07/06 2:08:28 PM
Injection	1	Acq Method Set	od 100 95 05
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 12:43:01 PM
Run Time	60.0 Minutes		

Auto-Scaled Chromatogram

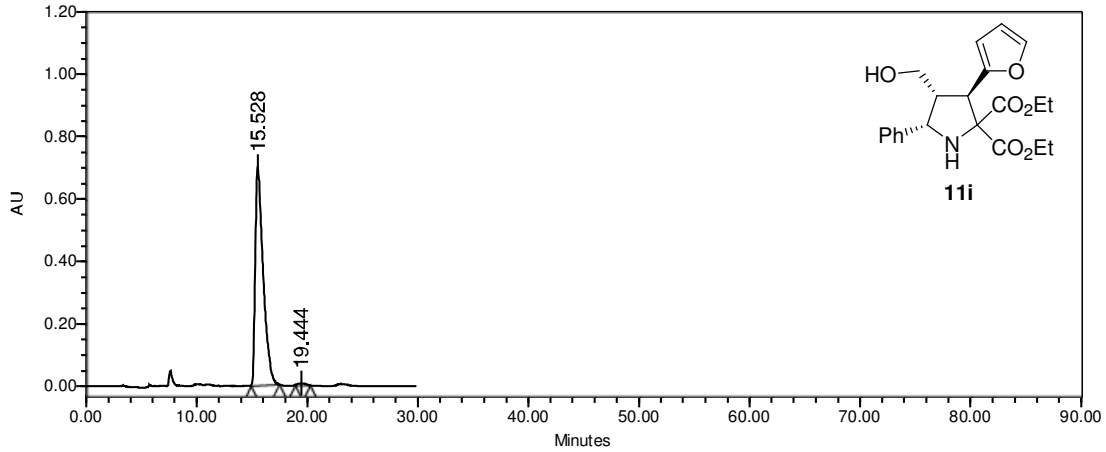


Peak Results

	RT	Area	Height	% Area
1	14.533	4184637	114880	47.69
2	17.339	4589827	101951	52.31

SampleName	pyrrolidine, furyl, Ph, Ph2ProOH	Sample Type	Unknown
Vial	1	Date Acquired	2/02/07 10:47:22 AM
Injection	1	Acq Method Set	od 100 95 5
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 12:47:50 PM
Run Time	80.0 Minutes		

Auto-Scaled Chromatogram



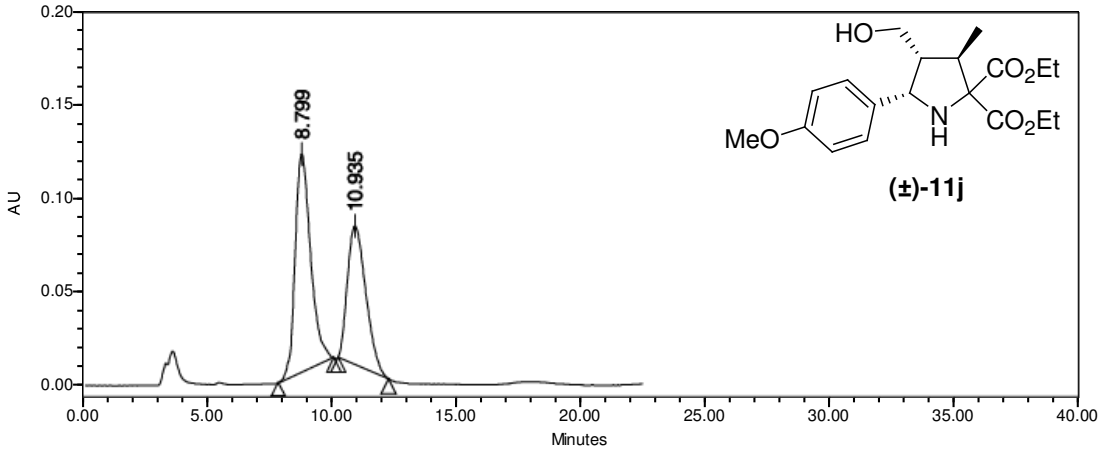
Peak Results

	RT	Area	Height	% Area
1	15.528	35438287	702140	99.87
2	19.444	46129	6916	0.13

5.10.- HPLC chromatograms of diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-5-(*p*-methoxyphenyl)-3-methylpyrrolidine-2,2-dicarboxylate (**11j**)

SampleName	pyrrolidine Me, pOMePh, rac	Sample Type	Unknown
Vial	1	Date Acquired	1/02/07 12:42:13 PM
Injection	1	Acq Method Set	oj 100 80 20
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 5:36:07 PM
Run Time	60.0 Minutes		

Auto-Scaled Chromatogram

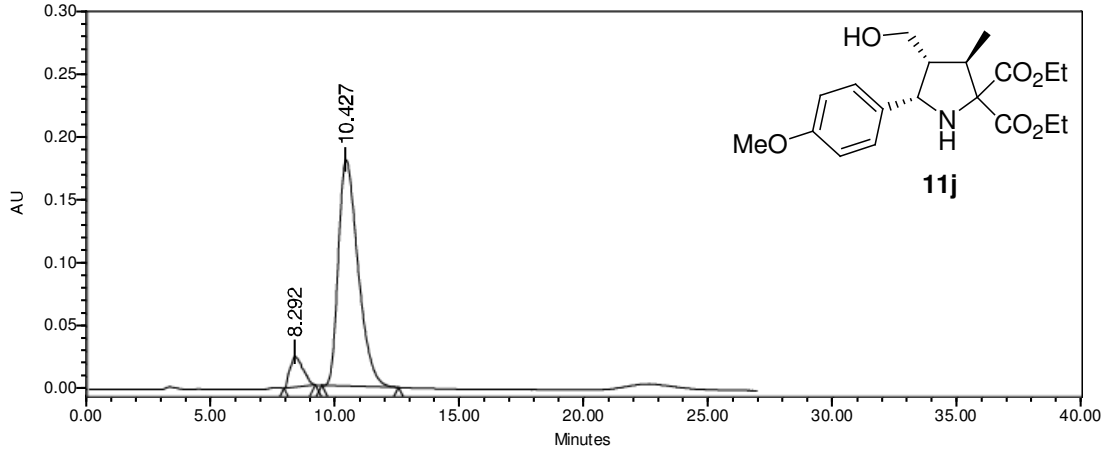


Peak Results

	RT	Area	Height	% Area
1	8.799	4503203	109888	54.25
2	10.935	3797650	73742	45.75

SampleName	pyrrolidine Me, pOMe, Ph2ProOH	Sample Type	Unknown
Vial	1	Date Acquired	9/02/07 9:11:51 AM
Injection	1	Acq Method Set	oj 100 80 20
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 5:39:12 PM
Run Time	120.0 Minutes		

Auto-Scaled Chromatogram



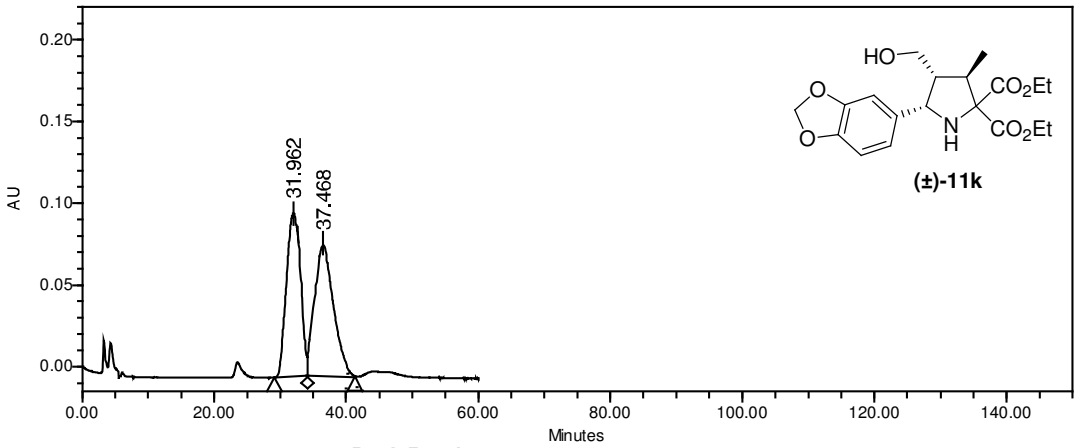
Peak Results

	RT	Area	Height	% Area
1	8.292	888234	13770	7.33
2	10.427	9881471	179590	92.67

5.11.- HPLC chromatograms of diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-methyl-5-(3,4-methylenedioxyphenyl)pyrrolidine-2,2-dicarboxylate (**11k**)

SampleName	pyrrolidine Me, piperonal rac	Sample Type	Unknown
Vial	1	Date Acquired	7/02/07 1:45:03 PM
Injection	1	Acq Method Set	oj 100 95 05
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 4:05:05 PM
Run Time	90.0 Minutes		

Auto-Scaled Chromatogram

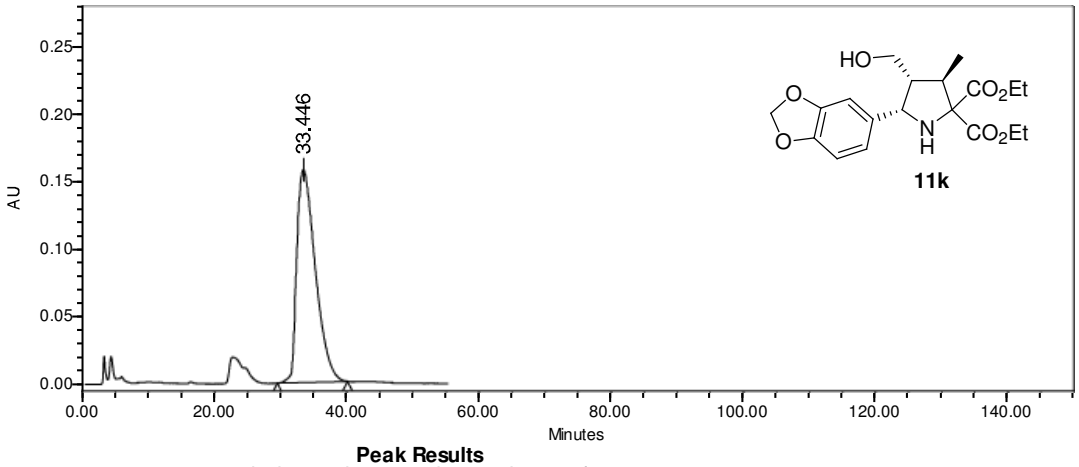


Peak Results

	RT	Area	Height	% Area
1	31.962	14907981	99774	47.38
2	37.468	16557900	82339	52.62

SampleName	pyrrolidine Me, pip, pH2pROoh	Sample Type	Unknown
Vial	1	Date Acquired	7/02/07 6:01:53 PM
Injection	1	Acq Method Set	oj 100 95 05
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 4:08:28 PM
Run Time	120.0 Minutes		

Auto-Scaled Chromatogram



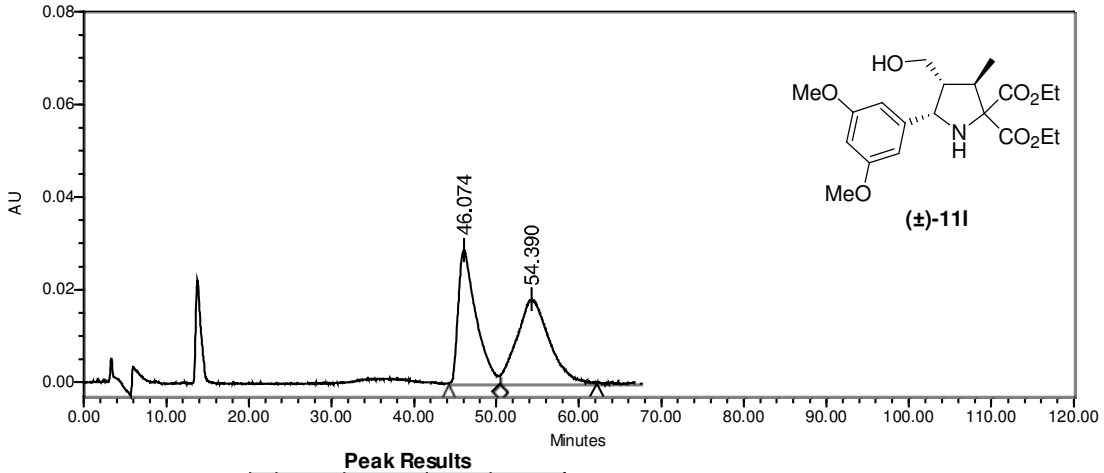
Peak Results

	RT	Area	Height	% Area
1	33.446	31001253	157974	100.00

5.12.- HPLC chromatograms of diethyl (3*R*,4*R*,5*S*)-5-(3,5-dimethoxyphenyl)-4-hydroxymethyl-3-methylpyrrolidine-2,2-dicarboxylate (**11l**)

SampleName	pyrrolidine Me, MeO2Ph, rac	Sample Type	Unknown
Vial	1	Date Acquired	8/02/07 12:14:22 PM
Injection	1	Acq Method Set	OJ 100 98 02
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 5:22:34 PM
Run Time	120.0 Minutes		

Auto-Scaled Chromatogram

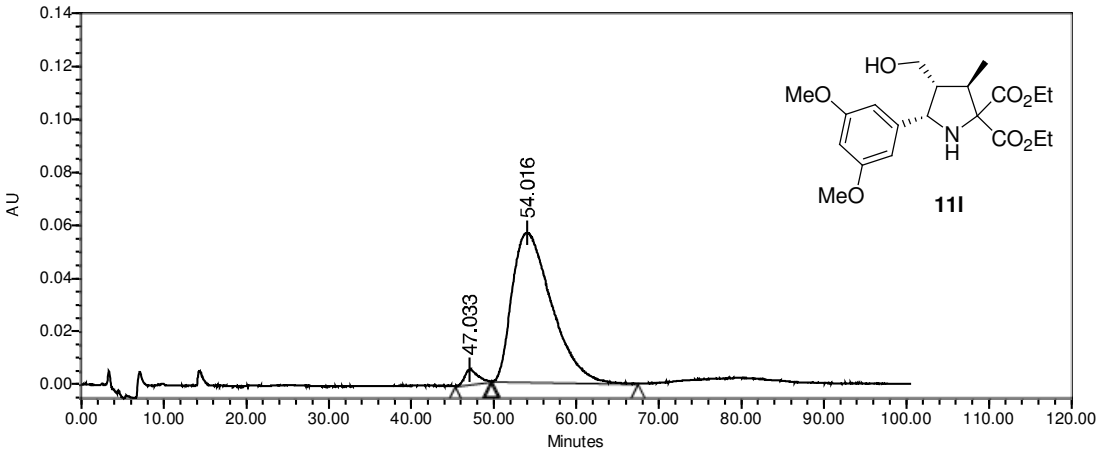


Peak Results

	RT	Area	Height	% Area
1	46.074	4319544	28855	44.95
2	54.390	5290120	18156	55.05

SampleName	pyrrolidine Me, MeO2Ph, Ph2ProOH	Sample Type	Unknown
Vial	1	Date Acquired	8/02/07 4:26:28 PM
Injection	1	Acq Method Set	OJ 100 98 02
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 5:25:48 PM
Run Time	120.0 Minutes		

Auto-Scaled Chromatogram



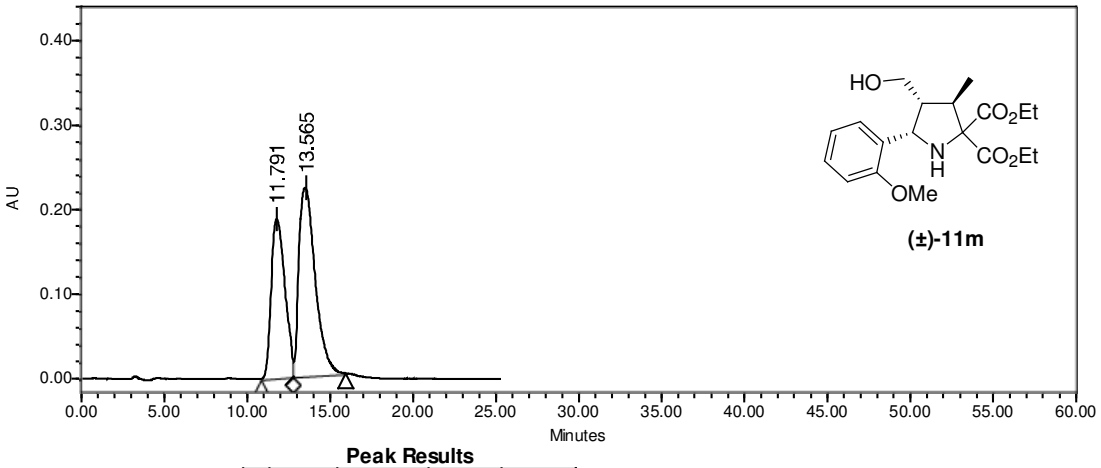
Peak Results

	RT	Area	Height	% Area
1	47.033	581041	5375	3.01
2	54.016	18739412	56167	96.99

5.13.- HPLC chromatograms of diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-5-(*o*-methoxyphenyl)-3-methylpyrrolidine-2,2-dicarboxylate (**11m**)

SampleName	pyrrolidine Me, o-MeOPh, rac	Sample Type	Unknown
Vial	1	Date Acquired	8/02/07 2:45:03 PM
Injection	1	Acq Method Set	oj 100 95 05
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 5:28:29 PM
Run Time	120.0 Minutes		

Auto-Scaled Chromatogram

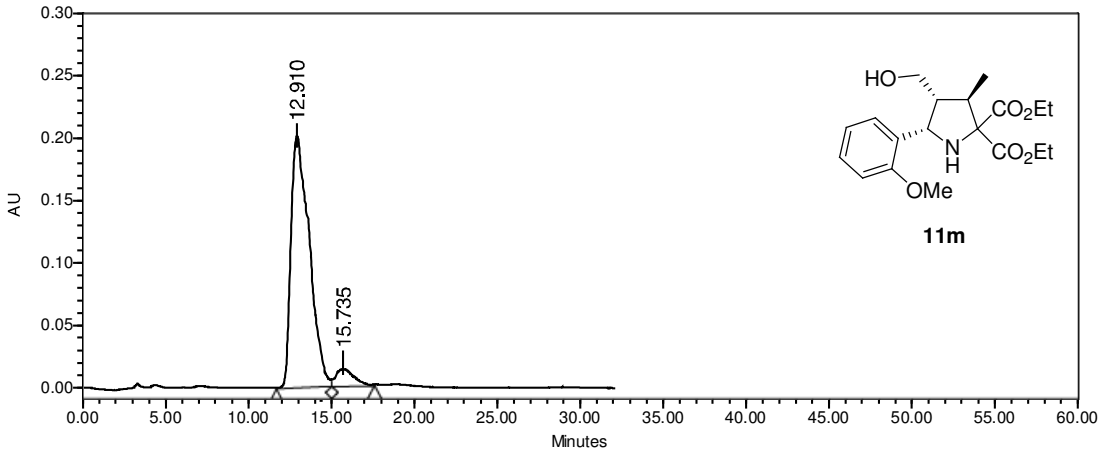


Peak Results

	RT	Area	Height	% Area
1	11.791	10906575	188220	47.22
2	13.565	12190788	222415	52.78

SampleName	pyrrolidine Me, o-OMe, Ph2ProOH	Sample Type	Unknown
Vial	1	Date Acquired	9/02/07 10:12:10 AM
Injection	1	Acq Method Set	oj 100 95 05
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 5:32:12 PM
Run Time	120.0 Minutes		

Auto-Scaled Chromatogram



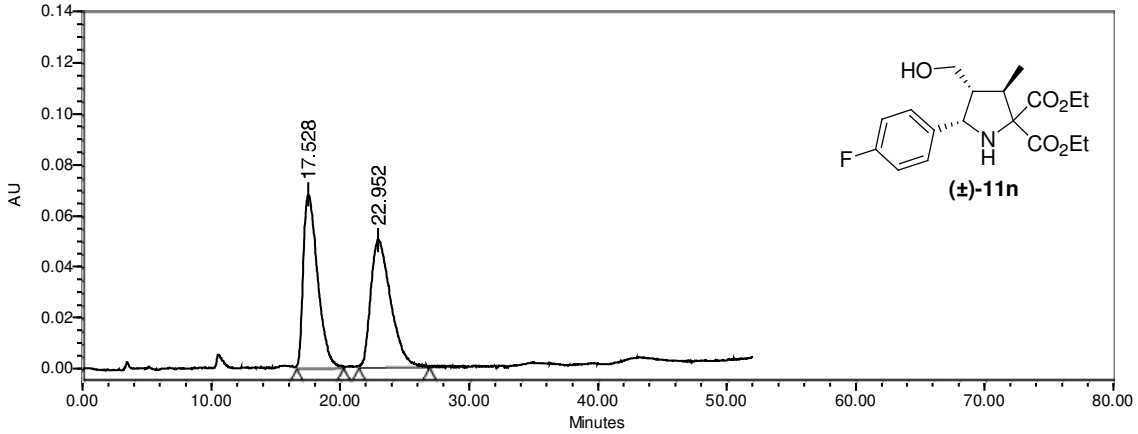
Peak Results

	RT	Area	Height	% Area
1	12.910	14893680	201221	96.69
2	15.735	509857	10521	3.31

5.14.- HPLC chromatograms of diethyl (3*R*,4*R*,5*S*)-5-(*p*-fluorophenyl)-4-hydroxymethyl-3-methylpyrrolidine-2,2-dicarboxylate (**11n**)

SampleName	s151A(4F)	Sample Type	Unknown
Vial	1	Date Acquired	2/02/07 6:00:02 PM
Injection	1	Acq Method Set	OJ 100 95 05
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 3:54:22 PM
Run Time	80.0 Minutes		

Auto-Scaled Chromatogram

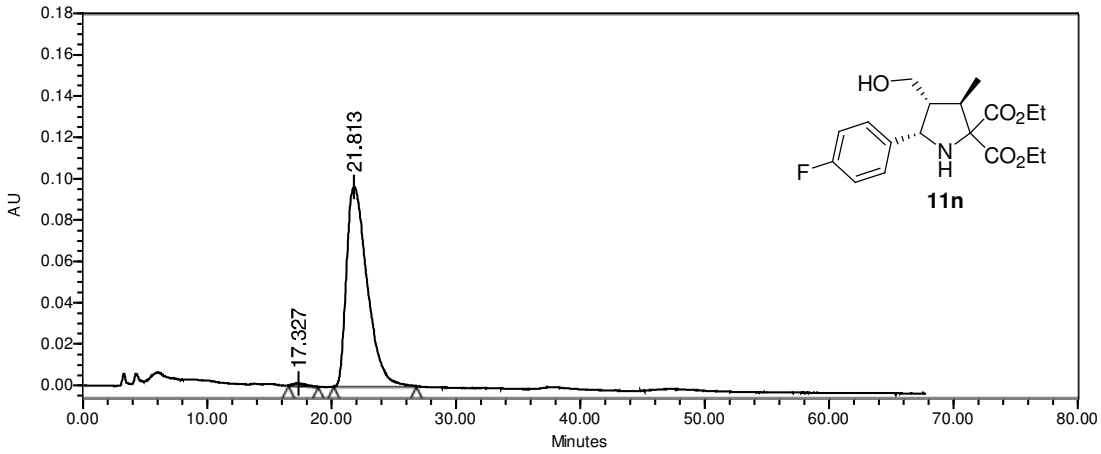


Peak Results

	Name	RT	Area	Height	Amount	Units
1		17.528	5163062	67622		
2		22.952	5247358	49450		

SampleName	pyrrolidine Me, pFPh, Ph2ProOH	Sample Type	Unknown
Vial	1	Date Acquired	8/02/07 8:12:48 AM
Injection	1	Acq Method Set	oj 100 95 05
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 4:00:52 PM
Run Time	90.0 Minutes		

Auto-Scaled Chromatogram



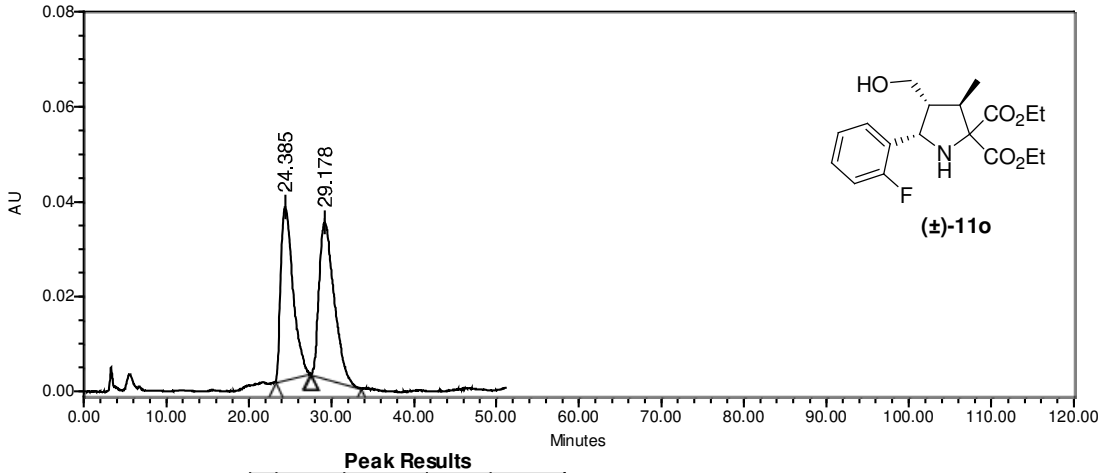
Peak Results

	RT	Area	Height	% Area
1	17.327	81675	1169	0.73
2	21.813	11179953	96552	99.27

5.15.- HPLC chromatograms of diethyl (3*R*,4*R*,5*S*)-5-(*o*-fluorophenyl)-4-hydroxymethyl-3-methylpyrrolidine-2,2-dicarboxylate (**11o**)

SampleName	pyrrolidine Me, oFPh, rac	Sample Type	Unknown
Vial	1	Date Acquired	8/02/07 10:07:29 AM
Injection	1	Acq Method Set	OJ 100 98 02
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 5:13:58 PM
Run Time	90.0 Minutes		

Auto-Scaled Chromatogram

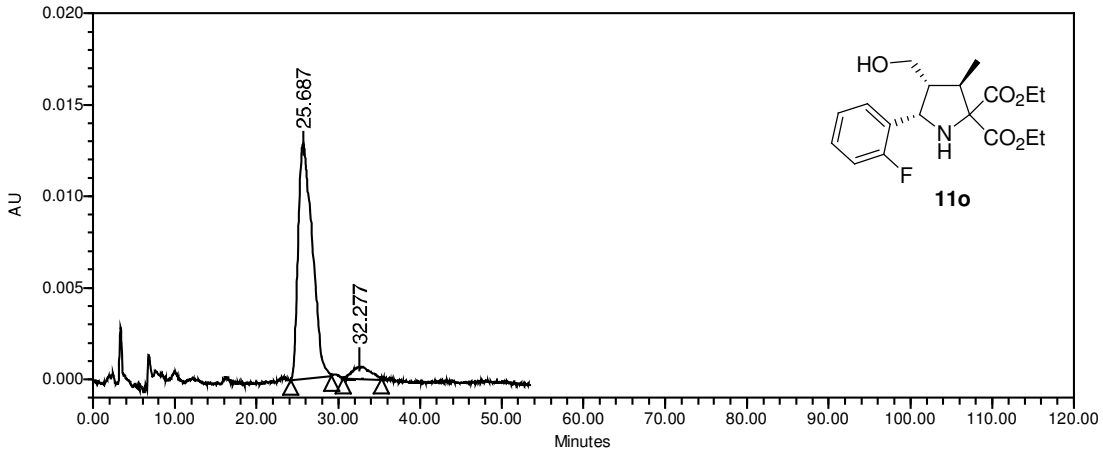


Peak Results

	RT	Area	Height	% Area
1	24.385	3717985	36305	47.17
2	29.178	4163575	32797	52.83

SampleName	pyrrolidine Me, oFPh, Ph2ProOH	Sample Type	Unknown
Vial	1	Date Acquired	8/02/07 10:58:31 AM
Injection	1	Acq Method Set	OJ 100 98 02
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 5:19:46 PM
Run Time	90.0 Minutes		

Auto-Scaled Chromatogram



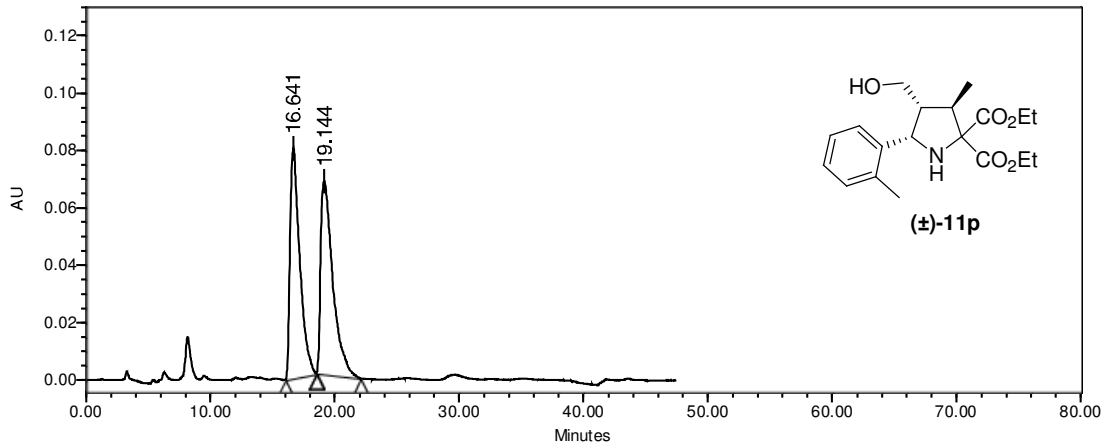
Peak Results

	RT	Area	Height	% Area
1	25.687	1458617	12928	96.41
2	32.277	54314	704	3.59

5.16.- HPLC chromatograms of diethyl (3*R*,4*R*,5*S*)-4-hydroxymethyl-3-methyl-5-(*o*-tolyl)pyrrolidine-2,2-dicarboxylate (**11p**)

SampleName	pyrrolidine Me, o-Tol, rac	Sample Type	Unknown
Vial	1	Date Acquired	9/02/07 11:00:49 AM
Injection	1	Acq Method Set	od 100 98 02
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 6:12:26 PM
Run Time	120.0 Minutes		

Auto-Scaled Chromatogram

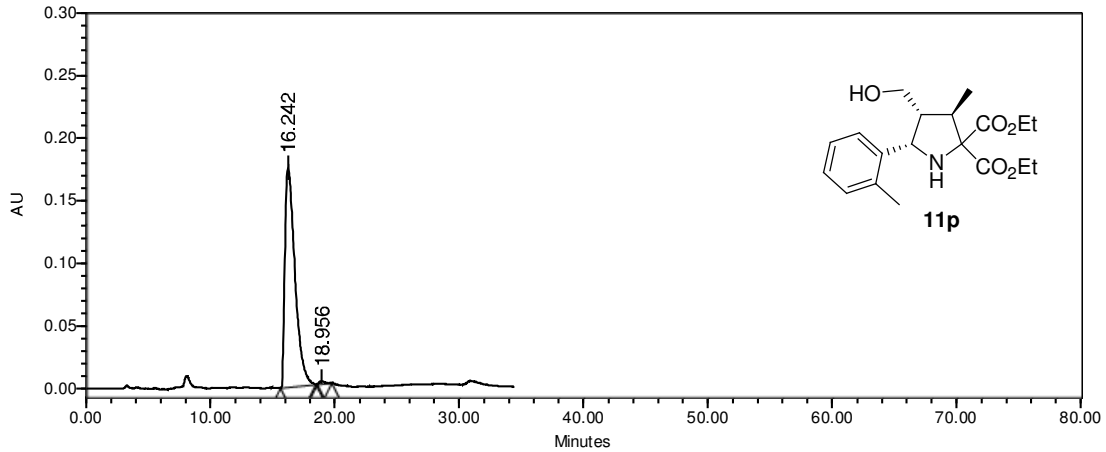


Peak Results

	RT	Area	Height	% Area
1	16.641	4364864	80183	49.02
2	19.144	4538560	67189	50.98

SampleName	pyrrolidine Me, o-Tol, Ph2ProOH	Sample Type	Unknown
Vial	1	Date Acquired	9/02/07 11:49:54 AM
Injection	1	Acq Method Set	od 100 98 02
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 6:16:01 PM
Run Time	120.0 Minutes		

Auto-Scaled Chromatogram



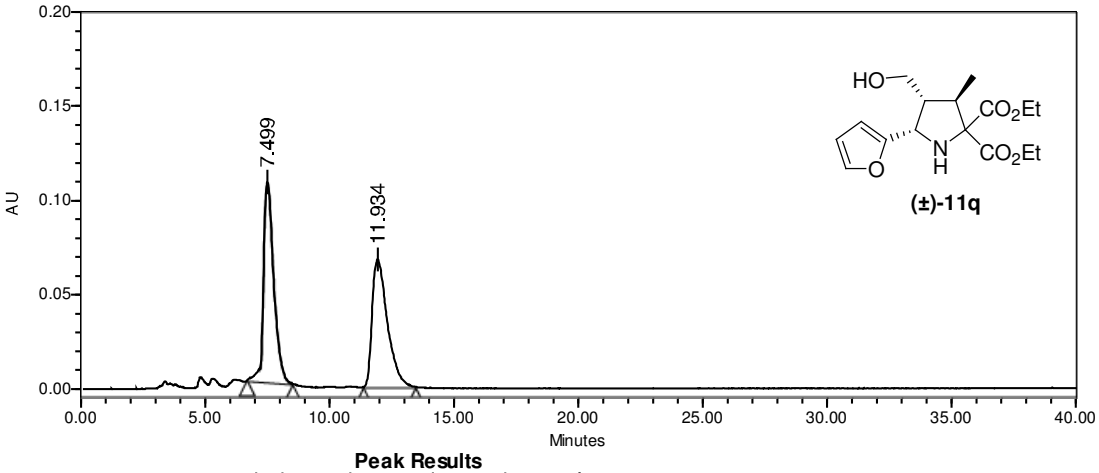
Peak Results

	RT	Area	Height	% Area
1	16.242	9611289	174884	99.49
2	18.956	49462	1757	0.51

5.17.- HPLC chromatograms of diethyl (3*R*,4*R*,5*S*)-5-(2-furyl)-4-hydroxymethyl-3-methylpyrrolidine-2,2-dicarboxylate (**11q**)

SampleName	Pyrrolidine Me, furyl, rac	Sample Type	Unknown
Vial	1	Date Acquired	31/01/07 1:29:04 PM
Injection	1	Acq Method Set	od 100 85 15
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 3:38:48 PM
Run Time	60.0 Minutes		

Auto-Scaled Chromatogram

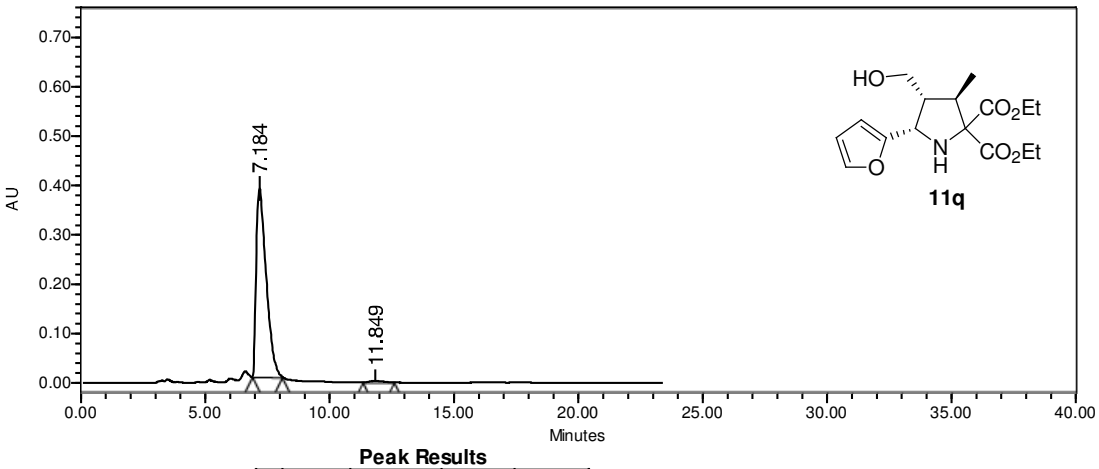


Peak Results

	RT	Area	Height	% Area
1	7.499	2669487	101167	48.04
2	11.934	2886798	67682	51.96

SampleName	pyrrolidine, Me,furyl,Ph2ProOH	Sample Type	Unknown
Vial	1	Date Acquired	7/02/07 10:20:15 AM
Injection	1	Acq Method Set	od 100 85 15
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	12/02/07 3:46:56 PM
Run Time	50.0 Minutes		

Auto-Scaled Chromatogram



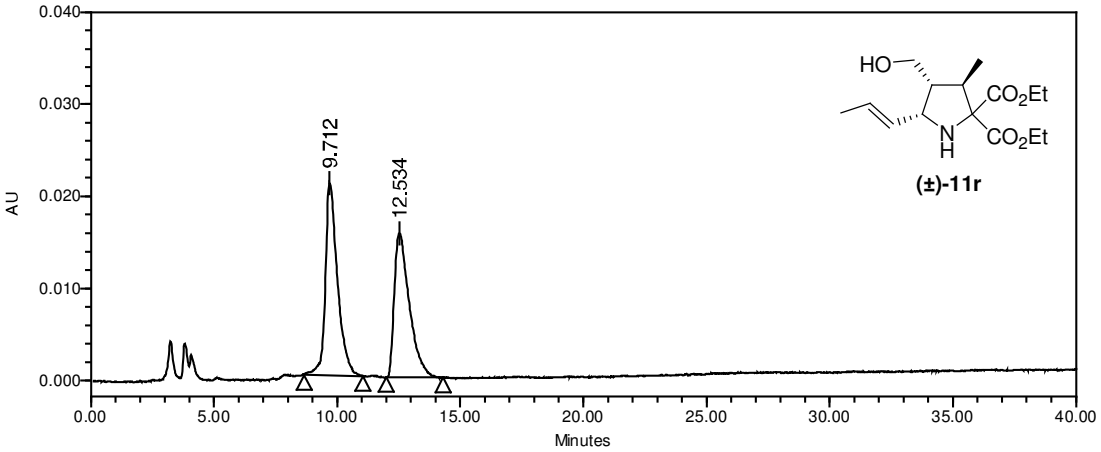
Peak Results

	RT	Area	Height	% Area
1	7.184	10723966	382304	98.91
2	11.849	118536	3335	1.09

5.18.- HPLC chromatograms of diethyl (3*R*,4*R*,5*R*,1'*E*)-4-hydroxymethyl-3-methyl-5-(1-propenyl)pyrrolidine-2,2-dicarboxylate (**11r**)

SampleName	pyrrolidine Me, crotyl rac	Sample Type	Unknown
Vial	1	Date Acquired	13/02/07 4:27:32 PM
Injection	1	Acq Method Set	od 100 95 05
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	20/02/07 1:10:13 PM
Run Time	90.0 Minutes		

Auto-Scaled Chromatogram

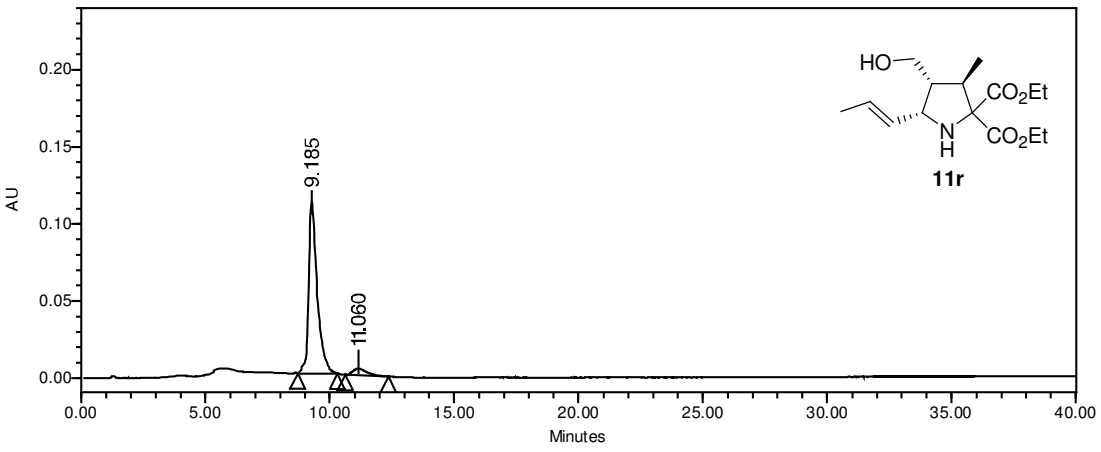


Peak Results

	RT	Area	Height	% Area
1	9.712	640661	20004	49.21
2	12.534	661299	15627	50.79

SampleName	pyrrolidine Me, crotyl, Ph2ProOH	Sample Type	Unknown
Vial	1	Date Acquired	13/02/07 5:15:06 PM
Injection	1	Acq Method Set	od 100 95 05
Injection Volume	10.00 ul	Processing Method	LC Default Processing
Channel	996	Date Processed	20/02/07 1:14:06 PM
Run Time	90.0 Minutes		

Auto-Scaled Chromatogram



Peak Results

	RT	Area	Height	% Area
1	9.185	2254230	103974	98.63
2	11.060	31312	2575	1.37