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

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General Methods. NMR spectra were acquired on a 300 spectrometer, running at 300 or 500 MHz and 75.4 MHz for $^1$H and $^{13}$C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals (CHCl$_3$, 7.26 ppm for $^1$H NMR; CDCl$_3$, 77.0 ppm for $^{13}$C NMR). The following abbreviations are used to indicate the multiplicity in $^1$H NMR spectra: s, singlet; d, doublet; t, triplet; m, multiplet; bs, broad signal. $^{13}$C NMR spectra were acquired on a broad band decoupled mode. For infrared (IR) spectra only characteristic bands are given in cm$^{-1}$. Mass spectra (MS) were recorded on a GC-MS spectrometer using electronic impact (EI) techniques (70 eV). High resolution mass spectrometry (HRMS) were recorded under chemical ionization (CI) TOF conditions using GC when necessary. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates and visualized by ultraviolet irradiation, phosphomolybdic acid or potassium permanganate reagent. Melting points (M.p.) are given in ºC. Optical rotations ($\alpha$ value) were measured in the specified solvent at given concentration in g/100 mL. The enantiomeric excess (e.e.) of the products were determined by chiral stationary phase HPLC using photodiode array detector and using the indicated chiral column in each case. Standards for the optimization of the HPLC conditions for the separation of the two enantiomers were synthesized using either a equimolar mixture of 3a with the corresponding quinidine-based primary amine as catalyst or, alternatively, using benzydrylamine as catalyst.

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

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Synthesis of pyrrolidines (4a-q)

General procedure for the Michael addition/imine formation step.

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

General procedure for the reduction step.

NaBH₃CN (0.8 mmol) was added to a solution of the crude cyclic imine in dried EtOH (15 mL) under inert atmosphere. The mixture was stirred at room temperature for 2 hours, HCl (1 M) was added till reaching an acidic pH and it was stirred for another 10 minutes. The solvent was removed under reduced pressure and a saturated solution of NaCl (10 mL) was added, followed by the addition of NaOH (4 M), till a basic pH was observed, and the mixture was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried with anhydrous Na₂SO₄, filtered and the solvent was removed under reduced pressure. The pyrrolidines 1a-q were obtained following this procedure, and purified by flash column chromatography with the indicated eluent.

![Diethyl 5-methyl-3-phenylpyrrolidine-2,2-dicarboxylate, (4a).](image)

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

The pyrrolidine 4a (110 mg, 0.36 mmol, 89%) was obtained after 42 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate 1a (98 mg, 0.56 mmol) and (E)-4-phenylbut-3-en-2-one 2a (59 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ¹H-NMR (CDCl₃, 300 MHz) δ 7.46-7.03 (m, 5H), 4.41-4.25 (m, 2H), 4.14 (dq, J = 10.7, 7.1 Hz, 1H), 3.78 (dq, J = 10.6, 7.1 Hz, 1H), 3.42 (dq, J = 10.6, 7.1 Hz, 1H), 3.32-3.17 (m, 1H), 2.79 (bs, 1H), 2.29 (ddd, J = 12.3, 7.0, 5.4 Hz, 1H), 1.82-1.67 (m, 1H), 1.35 (d, J = 6.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 0.72 (t, J = 7.1 Hz, 3H). ¹³C-NMR (CDCl₃, 75 MHz) δ 171.3, 170.3, 140.1, 128.6, 128.0, 126.9, 77.9, 61.8, 61.5, 53.6, 50.9, 41.6, 19.9, 14.0, 13.3. FTIR (ATR, cm⁻¹): 1723 (C=O st). MS (70 eV) m/z (%): 232 (M⁺ - CO₂Et, 100), 204 (8), 186 (2), 170 (1), 159 (11), 144 (9), 127 (11), 116 (43), 103 (3), 91 (8), 77 (3), 65 (1), 55 (4), 44 (1), 29 (6). HRMS: calculated for [C₁₀H₂₄NO₄]⁺: 306.1705 [(M + H)⁺]; found: 306.1706. The ee was determined by HPLC using a Chiralpak IA column [n-hexane/i-PrOH (98:2)]; flow rate 1.0 mL/min; t_major = 10.28 min, t_minor = 9.42 min (89% ee). [α]D²⁰ = -20.8 (c = 1.00, CH₂Cl₂).
(3S,5S)-Diethyl 5-methyl-3-(p-tolyl)pyrrolidine-2,2-dicarboxylate, (4b).

The pyrrolidine 4b (89 mg, 0.28 mmol, 70%) was obtained after 41 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate 1a (98 mg, 0.56 mmol) and (E)-4-(p-tolyl)but-3-en-2-one 2b (64 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). $^1$H-NMR (CDCl$_3$, 300 MHz) δ 7.15 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.1 Hz, 2H), 4.35-4.17 (m, 2H), 4.09 (dq, J = 10.8, 7.1 Hz, 1H), 3.74 (dq, J = 10.6, 7.1 Hz, 1H), 3.41 (dq, J = 10.6, 7.1 Hz, 1H), 3.27-3.11 (m, 1H), 2.74 (bs, 1H), 2.29-2.14 (m, 4H), 1.75-1.60 (m, 1H), 1.29 (d, J = 6.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H), 0.70 (t, J = 7.1 Hz, 3H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) δ 171.2, 170.4, 136.8, 136.3, 128.6, 128.4, 77.8, 61.6, 61.3, 53.5, 50.5, 41.6, 20.9, 19.9, 13.9, 13.2. FTIR (ATR, cm$^{-1}$): 1724 (C=O st). MS (70 eV) m/z (%): 246 (M$^+$ - CO$_2$Et, 100), 218 (4), 201 (6), 184 (1), 173 (13), 155 (13), 145 (5), 130 (38), 115 (55), 103 (4), 91 (5), 77 (3), 65 (1), 55 (4), 45 (1), 29 (5). HRMS: calculated for [C$_{18}$H$_{26}$NO$_4$]$^+$: 320.1862 [(M + H)$^+$]; found: 320.1862. The ee was determined by HPLC using a Chiralpak IA column [n-hexane/i-PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{\text{major}}$ = 14.02 min, $\tau_{\text{minor}}$ = 12.50 min (90% ee). [$\alpha$]$_D^{20}$: -26.8 (c = 1.03, CH$_2$Cl$_2$).

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

The pyrrolidine 4c (90 mg, 0.27 mmol, 67%) was obtained after 119 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc 8:2) according to the general procedure using diethyl 2-aminomalonate 1a (98 mg, 0.56 mmol) and (E)-4-(2-methoxyphenyl)but-3-en-2-one 2c (71 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). $^1$H-NMR (CDCl$_3$, 300 MHz) δ 7.24 (dd, J = 7.6, 1.7 Hz, 1H), 7.14 (dd, J = 8.2, 7.6, 1.7 Hz, 1H), 6.87-6.81 (m, 1H), 6.78 (dd, J = 8.2, 1.1 Hz, 1H), 4.72 (dd, J = 9.8, 8.0 Hz, 1H), 4.30 (dq, J = 10.7, 7.1 Hz, 1H), 4.14 (dq, J = 10.7, 7.1 Hz, 1H), 3.86-3.71 (m, 4H), 3.48 (dq, J = 10.7, 7.1 Hz, 1H), 3.30-3.13 (m, 1H), 2.86 (bs, 1H), 2.29 (ddd, J = 12.3, 8.0, 5.9 Hz, 1H), 1.76-1.62 (m, 1H), 1.31 (d, J = 6.2 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 0.75 (t, J = 7.1 Hz, 3H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) δ 171.1, 169.8, 157.7, 129.8, 129.1, 127.8, 120.4, 110.3, 77.6, 61.7, 61.1, 55.3, 53.5, 44.4, 41.3,
19.9, 14.0, 13.4. FTIR (ATR, cm\(^{-1}\)): 1731 (C=O st). MS (70 eV) m/z (%): 262 (M\(^+\) - CO\(_2\)Et, 100), 234 (1), 216 (32), 201 (30), 186 (5), 174 (5), 155 (11), 146 (13), 127 (14), 117 (5), 107 (3), 91 (9), 77 (4), 65 (1), 55 (4), 44 (1), 29 (4). HRMS: calculated for [C\(_{18}\)H\(_{26}\)NO\(_5\)]\(^+\): 336.1811 [(M + H)]\(^+\); found: 336.1800. The ee was determined by HPLC using a Chiralpak ASH column [n-hexane/i-PrOH (95:5)]; flow rate 1.0 mL/min; \(t_{\text{major}}\) = 4.90 min, \(t_{\text{minor}}\) = 7.39 min (89% ee). \([\alpha]_{D}^{20}\) = +1.0 (c = 1.03, CH\(_2\)Cl\(_2\)).

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

The pyrrolidine 4d (104 mg, 0.31 mmol, 77%) was obtained after 68 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate 1a (98 mg, 0.56 mmol) and (E)-4-(3-methoxyphenyl)but-3-en-2-one 2d (71 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). \(^1\)H-NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.30-7.21 (m, 1H), 7.15 (ddd, \(J = 8.1, 7.5, 1.7\) Hz, 1H), 6.90-6.75 (m, 2H), 4.73 (dd, \(J = 9.8, 8.0\) Hz, 1H), 4.31 (dq, \(J = 10.8, 7.1\) Hz, 1H), 4.15 (dq, \(J = 10.8, 7.1\) Hz, 1H), 3.86-3.72 (m, 4H), 3.49 (dq, \(J = 10.7, 7.1\) Hz, 1H), 3.31-3.14 (m, 1H), 2.87 (bs, 1H), 2.30 (ddd, \(J = 12.3, 8.0, 5.9\) Hz, 1H), 1.78-1.62 (m, 1H), 1.32 (d, \(J = 6.2\) Hz, 3H), 1.24 (t, \(J = 7.1\) Hz, 3H), 0.76 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz) \(\delta\) 169.6, 168.7, 157.7, 140.1, 127.3, 119.2, 112.6, 111.0, 76.2, 60.2, 59.9, 53.5, 51.9, 49.3, 40.1, 18.3, 12.4, 11.7. FTIR (ATR, cm\(^{-1}\)): 1724 (C=O st). MS (70 eV) m/z (%): 262 (M\(^+\) - CO\(_2\)Et, 100), 234 (4), 216 (2), 201 (3), 188 (8), 174 (6), 161 (5), 146 (30), 127 (9), 117 (6), 103 (2), 91 (5), 77 (3), 65 (1), 55 (3), 41 (1), 29 (4). HRMS: calculated for [C\(_{18}\)H\(_{26}\)NO\(_5\)]\(^+\): 336.1811 [(M + H)]\(^+\); found: 336.1794. The ee was determined by HPLC using a Chiralpak ASH column [n-hexane/i-PrOH (95:5)]; flow rate 1.0 mL/min; \(t_{\text{major}}\) = 4.96 min, \(t_{\text{minor}}\) = 6.91 min (89% ee). \([\alpha]_{D}^{20}\) = -26.8 (c = 0.98, CH\(_2\)Cl\(_2\)).

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

The pyrrolidine 4e (106 mg, 0.32 mmol, 79%) was obtained after 41 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate 1a (98 mg, 0.56 mmol) and (E)-4-(4-methoxyphenyl)but-3-en-2-one 2e (71 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23
mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). \(^1\)H-NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.19 (d, \(J = 8.7\) Hz, 2H), 6.74 (d, \(J = 8.7\) Hz, 2H), 4.36-4.16 (m, 2H), 4.09 (dq, \(J = 10.8, 7.1\) Hz, 1H), 3.83-3.68 (m, 4H), 3.43 (dq, \(J = 10.7, 7.1\) Hz, 1H), 3.25-3.11 (m, 1H), 2.67 (bs, 1H), 2.21 (ddd, \(J = 12.3, 7.0, 5.4\) Hz, 1H), 1.74-1.59 (m, 1H), 1.29 (d, \(J = 6.1\) Hz, 3H), 1.19 (t, \(J = 7.1\) Hz, 3H), 0.74 (t, \(J = 7.1\) Hz, 3H). \(^13\)C-NMR (CDCl\(_3\), 75 MHz) \(\delta\) 171.3, 170.4, 158.6, 131.9, 129.5, 113.3, 77.7, 61.7, 61.4, 55.2, 53.4, 50.1, 41.6, 19.9, 13.9, 13.4. FTIR (ATR, cm\(^{-1}\)) : 1722 (C=O st).

MS (70 eV) \(m/z\) (%): 262 (M\(^+\) - CO\(_2\)Et, 100), 234 (1), 216 (1), 201 (10), 189 (15), 174 (9), 155 (17), 146 (23), 127 (19), 115 (3), 103 (2), 91 (5), 77 (3), 65 (1), 55 (5), 42 (1), 19 (4). HRMS: calculated for [C\(_{18}\)H\(_{26}\)NO\(_5\)]\(^+\): 336.1811 [(M + H)\(^+\)]; found: 336.1797. The ee was determined by HPLC using a Chiralpak ASH column [n-hexane/i-PrOH (95:5)]; flow rate 1.0 mL/min; \(\tau\)\(_{\text{major}}\) = 5.14 min, \(\tau\)\(_{\text{minor}}\) = 7.47 min (89% ee). \([\alpha]_D^{20}\) : -28.6 (c = 0.99, CH\(_2\)Cl\(_2\)).

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

The pyrrolidine 4f (92 mg, 0.25 mmol, 63%) was obtained after 97 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc 1:1) according to the general procedure using diethyl 2-aminomalonate 1a (98 mg, 0.56 mmol) and (E)-4-(2,6-dimethoxyphenyl)but-3-en-2-one 2f (82 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). \(^1\)H-NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.07 (t, \(J = 8.3\) Hz, 1H), 6.46 (d, \(J = 8.3\) Hz, 2H), 5.12 (t, \(J = 9.0\) Hz, 1H), 4.29 (dq, \(J = 10.7, 7.1\) Hz, 1H), 4.11 (dq, \(J = 10.7, 7.1\) Hz, 1H), 3.83-3.70 (m, 7H), 3.59 (dq, \(J = 10.7, 7.1\) Hz, 1H), 3.24-3.07 (m, 1H), 2.93 (bs, 1H), 2.17 (ddd, \(J = 12.0, 9.2, 6.7\) Hz, 1H), 1.87 (ddd, \(J = 12.0, 10.3, 8.7\) Hz, 1H), 1.30 (d, \(J = 6.2\) Hz, 3H), 1.21 (t, \(J = 7.1\) Hz, 3H), 0.74 (t, \(J = 7.1\) Hz, 3H). \(^13\)C-NMR (CDCl\(_3\), 75 MHz) \(\delta\) 171.1, 169.1, 158.6, 127.6, 118.7, 104.1, 78.7, 61.8, 60.8, 56.0, 54.7, 40.5, 40.3, 19.5, 14.0, 13.4. FTIR (ATR, cm\(^{-1}\)) : 1731 (C=O st).

MS (70 eV) \(m/z\) (%): 292 (M\(^+\) - CO\(_2\)Et, 100), 264 (11), 246 (13), 231 (23), 215 (7), 201 (5), 191 (3), 176 (10), 155 (10), 146 (4), 127 (11), 102 (2), 91 (4), 77 (2), 55 (3), 41 (1), 29 (3). HRMS: calculated for [C\(_{19}\)H\(_{26}\)NO\(_6\)]\(^+\): 366.1917 [(M + H)\(^+\)]; found: 366.1901. The ee was determined by HPLC using a Chiralpak ASH column [n-hexane/i-PrOH (95:5)]; flow rate 1.0 mL/min; \(\tau\)\(_{\text{major}}\) = 6.36 min, \(\tau\)\(_{\text{minor}}\) = 5.27 min (77% ee). \([\alpha]_D^{20}\) : -20.8 (c = 0.99, CH\(_2\)Cl\(_2\)).

(3S,5S)-Diethyl 3-(3,5-dimethoxyphenyl)-5-methylpyrroolidine-2,2-dicarboxylate, (4g).
The pyrrolidine 4g (98 mg, 0.27 mmol, 67%) was obtained after 29 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate 1a (98 mg, 0.56 mmol) and (E)-4-(3,5-dimethoxyphenyl)but-3-en-2-one 2g (82 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). \(^1\)H-NMR (CDCl\(_3\), 300 MHz) \(\delta\) 6.47 (d, \(J = 2.3\) Hz, 2H), 6.29 (t, \(J = 2.3\) Hz, 1H), 4.32 (dq, \(J = 10.8, 7.1\) Hz, 1H), 4.22 (dd, \(J = 11.2, 7.0\) Hz, 1H), 4.12 (dq, \(J = 10.8, 7.1\) Hz, 1H), 3.88-3.72 (m, 7H), 3.54 (dq, \(J = 10.6, 7.1\) Hz, 1H), 3.29-3.13 (m, 1H), 2.68 (bs, 1H), 2.25 (ddd, \(J = 12.3, 7.0, 5.3\) Hz, 1H), 1.76-1.59 (m, 1H), 1.32 (d, \(J = 6.1\) Hz, 3H), 1.23 (t, \(J = 7.1\) Hz, 3H), 0.79 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz) \(\delta\) 171.2, 170.4, 160.4, 142.5, 106.6, 99.2, 77.7, 61.8, 61.5, 55.3, 53.6, 51.1, 41.7, 19.9, 14.0, 13.4. FTIR (ATR, cm\(^{-1}\)) : 1724 (C=O st). MS (70 eV) \(m/z\) (%): 292 (M\(^+\) - CO\(_2\)Et, 100), 246 (2), 218 (6), 204 (3), 191 (4), 176 (17), 155 (5), 127 (5), 109 (2), 91 (2), 77 (1), 55 (2), 41 (1), 29 (3). HRMS: calculated for [C\(_{19}\)H\(_{23}\)NO\(_3\)]\(^+\): 366.1917 [(M + H\(^+\)]; found: 366.1903. The ee was determined by HPLC using a Chiralpak ASH column [\(n\)-hexane/i-PrOH (95:5)]; flow rate 1.0 mL/min; \(t_{major} = 5.91\) min, \(t_{minor} = 8.39\) min (87% ee). [\(\alpha\)]\(_D\)\(^{20}\) : -27.4 (c = 1.01, CH\(_2\)Cl\(_2\)).

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

The pyrrolidine 4h (100 mg, 0.31 mmol, 78%) was obtained after 42 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate 1a (98 mg, 0.56 mmol) and (E)-4-(2-fluorophenyl)but-3-en-2-one 2h (66 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). \(^1\)H-NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.32 (dt, \(J = 7.6, 1.6\) Hz, 1H), 7.22-7.09 (m, 1H), 7.09-6.89 (m, 2H), 4.62 (dd, \(J = 9.6, 7.9\) Hz, 1H), 4.30 (dq, \(J = 10.7, 7.1\) Hz, 1H), 4.14 (dq, \(J = 10.7, 7.1\) Hz, 1H), 3.82 (dq, \(J = 10.7, 7.1\) Hz, 1H), 3.54 (dq, \(J = 10.7, 7.2\) Hz, 1H), 3.32-3.15 (m, 1H), 2.84 (bs, 1H), 2.35 (ddd, \(J = 12.8, 7.9, 6.0\) Hz, 1H), 1.76-1.54 (m, 1H), 1.33 (d, \(J = 6.1\) Hz, 3H), 1.23 (t, \(J = 7.1\) Hz, 3H), 0.80 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz) \(\delta\) 170.7, 169.6, 161.1 (d, \(J_{CF} = 247.1\) Hz), 129.8 (d, \(J_{CF} = 4.1\) Hz), 128.3 (d, \(J_{CF} = 8.4\) Hz), 128.1 (d, \(J_{CF} = 13.9\) Hz), 123.8 (d, \(J_{CF} = 3.5\) Hz), 115.0 (d, \(J_{CF} = 23.1\) Hz), 77.6, 61.9, 61.4, 53.3, 43.0, 41.7, 19.9, 14.0, 13.3. FTIR (ATR, cm\(^{-1}\)) : 1724 (C=O st). MS (70 eV) \(m/z\) (%): 250 (M\(^+\) - CO\(_2\)Et, 100), 222 (11), 201 (2), 190 (1), 176 (15), 162 (6), 149 (11), 134 (43), 109 (8), 96 (1), 81 (1), 68 (1), 55 (3), 29 (5). HRMS: calculated for [C\(_{17}\)H\(_{25}\)FNO\(_4\)]\(^+\): 324.1611 [(M + H\(^+\)]; found: 324.1601. The ee was determined by HPLC using a Chiralpak IA column [\(n\)-hexane/i-PrOH (98:2)]; flow rate 1.0 mL/min; \(t_{major} = 15.79\) min, \(t_{minor} = 13.19\) min (89% ee). [\(\alpha\)]\(_D\)\(^{20}\) : -31.6 (c = 1.03, CH\(_2\)Cl\(_2\)).
(3S,5S)-Diethyl 3-(4-fluorophenyl)-5-methylpyrrolidine-2,2-dicarboxylate, (4i).

The pyrrolidine 4i (95 mg, 0.29 mmol, 74%) was obtained after 26 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate 1a (98 mg, 0.56 mmol) and (E)-4-(4-fluorophenyl)but-3-en-2-one 2i (66 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). 1H-NMR (CDCl3, 300 MHz) δ 7.35-7.23 (m, 2H), 7.00-6.86 (m, 2H), 4.41-4.21 (m, 2H), 4.14 (dq, J = 21.1 Hz), 77.7, 61.8, 61.5, 53.4, 50.0, 41.7, 19.9, 13.9, 13.4. FTIR (ATR, cm⁻¹): 1724 (C=O st). MS (70 eV) m/z (%): 250 (M⁺ - CO₂Et, 100), 222 (7), 201 (3), 188 (1), 177 (12), 155 (8), 134 (21), 127 (11), 109 (9), 88 (1), 55 (5), 44 (1), 29 (5). HRMS: calculated for [C₁₁H₂₃FNO₂]⁺: 324.1611 [(M + H)⁺]; found: 324.1599. The ee was determined by HPLC using a Chiralpak IA column [n-hexane/i-PrOH (99:1)]; flow rate 1.0 mL/min; t_major = 14.52 min, t_minor = 13.65 min (89% ee). [α]D²⁰ = -26.7 (c = 0.99, CH₂Cl₂).

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

The pyrrolidine 4j (104 mg, 0.31 mmol, 78%) was obtained after 27 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate 1a (98 mg, 0.56 mmol) and (E)-4-(4-chlorophenyl)but-3-en-2-one 2j (72 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). 1H-NMR (CDCl₃, 300 MHz) δ 7.27-7.10 (m, 4H), 4.35-4.16 (m, 2H), 4.09 (dq, J = 10.7, 7.1 Hz, 1H), 3.77 (dq, J = 10.7, 7.1 Hz, 1H), 3.46 (dq, J = 10.7, 7.1 Hz, 1H), 3.27-3.12 (m, 1H), 2.73 (bs, 1H), 2.23 (ddd, J = 12.3, 7.0, 5.4 Hz, 1H), 1.72-1.55 (m, 1H), 1.29 (d, J = 6.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H), 0.74 (t, J = 7.1 Hz, 3H). 13C-NMR (CDCl₃, 75 MHz) δ 171.0, 170.1, 138.6, 132.6, 129.9, 128.0, 77.6, 61.8, 61.5, 53.4, 50.1, 41.4, 19.9, 14.0, 13.3. FTIR (ATR, cm⁻¹): 1724
(C=O st). MS (70 eV) m/z (%): 266 (M+ - CO₂Et, 100), 238 (5), 220 (1), 193 (8), 178 (5), 165 (3), 150 (27), 138 (1), 127 (11), 115 (6), 103 (2), 89 (4), 78 (1), 55 (4), 29 (5). HRMS: calculated for [C₁₇H₂₃CINO₄]⁺: 340.1316 [(M + H)⁺]; found: 340.1313. The ee was determined by HPLC using a Chiralpak IA column [n-hexane/i-PrOH (98:2)]; flow rate 1.0 mL/min; ŭmajor = 13.42 min, ŭminor = 12.14 min (89% ee). [α]D²⁰: -34.0 (c = 0.99, CH₂Cl₂).

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

The pyrrolidine 4k (79 mg, 0.21 mmol, 53%) was obtained after 23 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate 1a (98 mg, 0.56 mmol) and (E)-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one 2k (86 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ¹H-NMR (CDCl₃, 300 MHz) δ 7.64-7.36 (m, 4H), 4.40-4.26 (m, 2H), 4.14 (dq, J = 10.7, 7.1 Hz, 1H), 3.77 (dq, J = 10.7, 7.1 Hz, 1H), 3.45 (dq, J = 10.7, 7.1 Hz, 1H), 3.34-3.19 (m, 1H), 2.82 (bs, 1H), 2.30 (ddd, J = 12.4, 7.1, 5.4 Hz, 1H), 1.79-1.65 (m, 1H), 1.34 (d, J = 6.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 0.70 (t, J = 7.1 Hz, 3H). ¹³C-NMR (CDCl₃, 75 MHz) δ 171.0, 170.0, 144.4, 129.3 (q, ²JC = 32.5 Hz), 129.0, 124.8 (q, ³JC = 3.7 Hz), 124.2 (q, ¹JC = 271.8 Hz), 77.7, 62.0, 61.6, 53.5, 50.4, 41.3, 19.9, 13.9, 13.2. FTIR (ATR, cm⁻¹): 1727 (C=O st). MS (70 eV) m/z (%): 300 (M⁺ - CO₂Et, 100), 272 (13), 254 (1), 240 (1), 226 (14), 199 (15), 184 (35), 159 (5), 127 (6), 103 (1), 89 (1), 55 (4), 29 (5). HRMS: calculated for [C₁₈H₂₃F₃NO₄]⁺: 374.1579 [(M + H)⁺]; found: 374.1569. The ee was determined by HPLC using a Chiralpak ASH column [n-hexane/i-PrOH (98:2)]; flow rate 1.0 mL/min; ŭmajor = 5.58 min, ŭminor = 6.97 min (87% ee). [α]D²⁰: -23.4 (c = 1.03, CH₂Cl₂).

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

The pyrrolidine 4l (98 mg, 0.28 mmol, 70%) was obtained after 20 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate 1a (98 mg, 0.56 mmol) and (E)-4-(4-nitrophenyl)but-3-en-2-one 2l (77 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium
cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). \(^1\)H-NMR (CDCl\(_3\), 300 MHz) \(\delta\) 8.14-8.07 (m, 2H), 7.54-7.48 (m, 2H), 4.39-4.26 (m, 2H), 4.16 (dq, \(J = 10.7, 7.1\) Hz, 1H), 3.82 (dq, \(J = 10.7, 7.1\) Hz, 1H), 3.49 (dq, \(J = 10.7, 7.2\) Hz, 1H), 3.35-3.21 (m, 1H), 2.81 (bs, 1H), 2.35 (ddd, \(J = 12.6, 7.2, 5.5\) Hz, 1H), 1.77-1.63 (m, 1H), 1.34 (d, \(J = 6.1\) Hz, 3H), 1.24 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz) \(\delta\) 170.8, 169.6, 148.3, 129.5, 128.1, 77.7, 62.1, 61.7, 53.4, 50.2, 41.4, 20.0, 14.0, 13.5. FTIR (ATR, cm\(^{-1}\)) \(=\) 1724 (C=O st), 1522 (NO\(_2\) st as), 1343 (NO\(_2\) sym). MS (70 eV) \(m/z\) (%): 277 (M\(^+\) - CO\(_2\)Et, 100), 261 (1), 249 (8), 231 (3), 203 (6), 189 (2), 172 (1), 157 (11), 142 (5), 130 (5), 115 (8), 103 (2), 89 (3), 77 (2), 55 (2), 41 (1), 29 (4). HRMS: calculated for [C\(_{17}\)H\(_{22}\)N\(_2\)O\(_6\)]\(^+\): 351.1556 [(M + H\(^+\)]; found: 351.1542. The ee was determined by HPLC using a Chiralpak ASH column \([n\text{-hexane/i-PrOH (98:2)}]\); flow rate 1.0 mL/min; \(t_{\text{major}} = 15.16\) min, \(t_{\text{minor}} = 19.05\) min (86% ee). \([\alpha]_{D}^{20} = -29.5\) (c = 0.98, CH\(_2\)Cl\(_2\)).

\[\text{(3S,5S)-Diethyl 3-(furan-2-yl)-5-methylypyrrolidine-2,2-dicarboxylate, (4m).} \]

The pyrrolidine 4m (94 mg, 0.32 mmol, 80%) was obtained after 120 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminalomalate 1a (98 mg, 0.56 mmol) and (E)-4-(furan-2-yl)but-3-en-2-one 2m (54 mg, 0.40 mmol) in the presence of trifluoroacetic acid (18 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23 mg, 0.08 mmol) and using CHCl\(_3\) (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). \(^1\)H-NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.29 (dd, \(J = 1.8, 0.7\) Hz, 1H), 6.25 (dd, \(J = 3.1, 1.9\) Hz, 1H), 6.14 (d, \(J = 3.2\) Hz, 1H), 4.41-4.28 (m, 2H), 4.13 (dq, \(J = 10.7, 7.1\) Hz, 1H), 3.99 (dq, \(J = 10.7, 7.1\) Hz, 1H), 3.71 (dq, \(J = 10.7, 7.1\) Hz, 1H), 3.29-3.16 (m, 1H), 2.80 (bs, 1H), 2.24 (ddd, \(J = 12.3, 7.0, 5.4\) Hz, 1H), 1.78-1.69 (m, 1H), 1.32 (d, \(J = 6.2\) Hz, 3H), 1.24 (t, \(J = 7.1\) Hz, 3H), 0.99 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz) \(\delta\) 170.7, 170.3, 153.2, 141.5, 110.2, 107.1, 76.6, 62.0, 61.9, 53.8, 45.1, 39.8, 19.9, 13.9, 13.6. FTIR (ATR, cm\(^{-1}\)) \(=\) 1727 (C=O st). MS (70 eV) \(m/z\) (%): 222 (M\(^+\) - CO\(_2\)Et, 100), 201 (7), 176 (3), 149 (20), 127 (24), 106 (25), 91 (3), 79 (6), 67 (1), 55 (8), 41 (1), 29 (6). HRMS: calculated for [C\(_{15}\)H\(_{22}\)NO\(_5\)]\(^+\): 296.1498 [(M + H\(^+\)]; found: 296.1498. The ee was determined by HPLC using a Chiralcel OZ3 column \([n\text{-hexane/i-PrOH (95:5)}]\); flow rate 1.0 mL/min; \(t_{\text{major}} = 8.99\) min, \(t_{\text{minor}} = 11.09\) min (86% ee). \([\alpha]_{D}^{20} = -26.4\) (c = 1.01, CH\(_2\)Cl\(_2\)).

\[\text{(3S,5S)-Diethyl 5-methyl-3-(thiophen-2-yl)pyrrolidine-2,2-dicarboxylate, (4n).} \]

The pyrrolidine 4n (101 mg, 0.32 mmol, 81%) was obtained after 120 hours as a yellow oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3)
according to the general procedure using diethyl 2-aminomalonate 1a (98 mg, 0.56 mmol) and (E)-4-(thiophen-2-yl)but-3-en-2-one 2n (62 mg, 0.40 mmol) in the presence of trifluoroacetic acid (18 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23 mg, 0.08 mmol) and using CHCl₃ (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ¹H-NMR (CDCl₃, 300 MHz) δ 7.13 (dd, J = 5.0, 1.2 Hz, 1H), 6.97-6.88 (m, 2H), 4.51 (dd, J = 11.4, 6.7 Hz, 1H), 4.35 (dq, J = 10.7, 7.1 Hz, 1H), 4.17 (dq, J = 10.7, 7.1 Hz, 1H), 3.89 (dq, J = 10.7, 7.1 Hz, 1H), 3.62 (dq, J = 10.7, 7.1 Hz, 1H), 3.36-3.18 (m, 1H), 2.56 (bs, 1H), 2.38 (ddd, J = 12.1, 6.7, 5.4 Hz, 1H), 1.84-1.71 (m, 1H), 1.34 (d, J = 6.2 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H). ¹³C-NMR (CDCl₃, 75 MHz) δ 168.9, 168.2, 140.5, 124.3, 123.5, 121.9, 75.4, 59.8, 59.7, 51.4, 44.3, 40.3, 17.9, 11.9, 11.4. FTIR (ATR, cm⁻¹): 1724 (C=O st). MS (70 eV) m/z (%): 238 (M⁺ - CO₂Et, 100), 201 (8), 190 (1), 176 (1), 165 (18), 155 (20), 137 (4), 127 (24), 110 (4), 97 (7), 82 (3), 68 (2), 55 (8), 45 (4), 29 (6). HRMS: calculated for [C₁₅H₂₅NO₅]+: 312.1270 [(M + H)⁺]; found: 312.1269. The ee was determined by HPLC using a Chiralcel OZ3 column [n-hexane/i-PrOH (95:5)]; flow rate 1.0 mL/min; t_major = 8.11 min, t_minor = 10.00 min (87% ee). [α]D²⁰ = -22.4 (c = 0.97, CH₂Cl₂).

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

The pyrrolidine 4o (92 mg, 0.26 mmol, 65%) was obtained after 168 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc 8:2) according to the general procedure using diethyl 2-aminomalonate 1a (98 mg, 0.56 mmol) and (E)-4-(4-methoxyphenyl)pent-3-en-2-one 2o (76 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). ¹H-NMR (CDCl₃, 300 MHz) δ 7.28-7.20 (m, 2H), 6.81-6.74 (m, 2H), 4.31 (dq, J = 10.8, 7.1 Hz, 1H), 4.23-4.08 (m, 2H), 3.86-3.73 (m, 4H), 3.50 (dq, J = 10.7, 7.2 Hz, 1H), 3.08-2.98 (m, 1H), 2.75 (bs, 1H), 2.28 (ddd, J = 12.6, 7.3, 5.6 Hz, 1H), 1.87-1.72 (m, 1H), 1.70-1.66 (m, 1H), 1.64-1.48 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H), 0.97 (t, J = 7.5 Hz, 3H), 0.78 (t, J = 7.1 Hz, 3H). ¹³C-NMR (CDCl₃, 75 MHz) δ 171.4, 170.4, 158.6, 132.3, 129.6, 113.3, 77.4, 61.7, 61.4, 59.5, 55.3, 49.4, 39.3, 28.2, 14.0, 13.4, 11.4. FTIR (ATR, cm⁻¹): 1722 (C=O st). MS (70 eV) m/z (%): 276 (M⁺ - CO₂Et, 100), 246 (1), 230 (1), 216 (1), 203 (7), 186 (2), 169 (16), 141 (13), 121 (3), 104 (1), 91 (3), 69 (3), 54 (1), 29 (4). HRMS: calculated for [C₁₉H₂₉NO₅]⁺: 350.1967 [(M + H)⁺]; found: 350.1948. The ee was determined by HPLC using a Chiralpak ASH column [n-hexane/i-PrOH (95:5)]; flow rate 1.0 mL/min; t_major = 4.66 min, t_minor = 6.86 min (89% ee). [α]D²⁰ = -24.1 (c = 1.02, CH₂Cl₂).
(3S)-Diethyl 3,5-diphenyl-3,4-dihydro-2H-pyrrole-2,2-dicarboxylate, (4p).

The pyrrolidine 4p (34 mg, 0.09 mmol, 31%) was obtained after 192 hours as a yellow oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) according to the general procedure using diethyl 2-aminomalonate 1a (74 mg, 0.42 mmol) and (E)-1,3-diphenyl-2-propen-1-one 2p (62 mg, 0.30 mmol) in the presence of methanesulfonic acid (12 mg, 0.12 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (18 mg, 0.06 mmol) and using THF (1.5 mL) as solvent. $^1$H-NMR (CDCl$_3$, 300 MHz) δ 8.02-7.96 (m, 2H), 7.52-7.40 (m, 3H), 7.27-7.17 (m, 5H), 4.54 (dd, J = 9.0, 5.6 Hz, 1H), 4.40 (dq, J = 10.7, 7.1 Hz, 1H), 4.21 (dq, J = 10.7, 7.1 Hz, 1H), 3.81 (dq, J = 10.7, 7.1 Hz, 1H), 3.71-3.54 (m, 2H), 3.40 (dd, J = 17.4, 5.6 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H), 0.84 (t, J = 7.1 Hz, 3H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) δ 177.6, 168.9, 167.5, 139.5, 133.1, 131.5, 128.4, 128.3, 128.2, 128.1, 127.2, 91.5, 62.1, 61.1, 48.3, 43.6, 13.9, 13.4. FTIR (ATR, cm$^{-1}$): 1729 (C=O st). MS (70 eV) m/z (%): 365 (1), 292 (M$^+$ - CO$_2$Et, 100), 246 (12), 233 (15), 219 (37), 191 (11), 187 (90), 165 (4), 140 (4), 115 (24), 105 (62), 91 (7), 77 (17), 65 (2). HRMS: calculated for [C$_{22}$H$_{24}$NO$_4$]$^+$: 366.1705 [(M + H)$^+$]; found: 366.1701. The ee was determined by HPLC using a Chiralpak IA column [n-hexane/i-PrOH (97:3)]; flow rate 1.0 mL/min; $\tau_{\text{major}}$ = 33.56 min, $\tau_{\text{minor}}$ = 24.49 min (58% ee).

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

The pyrrolidine 4r (101 mg, 0.37 mmol, 91%) was obtained after 41 hours as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc 8:2) according to the general procedure using dimethyl 2-aminomalonate 1b (82 mg, 0.56 mmol) and (E)-4-phenylbut-3-en-2-one 2a (59 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). $^1$H-NMR (CDCl$_3$, 300 MHz) δ 7.33-7.07 (m, 5H), 4.30 (dd, J = 11.3, 7.1 Hz, 1H), 3.75 (s, 3H), 3.30-3.17 (m, 1H), 3.12 (s, 3H), 2.80 (bs, 1H), 2.35-2.21 (m, 1H), 1.80-1.69 (m, 1H), 1.34 (d, J = 6.1 Hz, 3H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) δ 171.8, 170.7, 139.7, 128.4, 128.1, 127.0, 78.1, 53.9, 53.1, 52.3, 51.3, 41.5, 19.8. FTIR (ATR, cm$^{-1}$): 1727 (C=O st). MS (70 eV) m/z (%): 218 (M$^+$ - CO$_2$Me, 100), 184 (2), 173 (6), 158 (11), 141 (18), 131 (9), 116 (47), 103 (3), 91 (8), 77 (4), 68 (3), 59 (4), 42 (3), 28 (2). HRMS: calculated for [C$_{15}$H$_{20}$NO$_4$]$^+$: 278.1392 [(M + H)$^+$]; found: 278.1380. The ee was determined by HPLC using a Chiralpak IA column [n-hexane/i-PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{\text{major}}$ = 11.86 min, $\tau_{\text{minor}}$ = 10.17 min (90% ee). $[\alpha]_D^{20}$: -28.0 (c = 1.00, CH$_2$Cl$_2$).
The pyrrolidine 4s (91 mg, 0.27 mmol, 67%) was obtained after 72 hours as a white solid, after isolation by flash column chromatography (hexanes/EtOAc gradient from 6:4 to 4:6) according to the general procedure using dimethyl 2-aminomalonate 1b (82 mg, 0.56 mmol) and (E)-4-(2,6-dimethoxyphenyl)but-3-en-2-one 2f (82 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-epi-9-amino-9-deoxycinchonidine 3a (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL). M.p.: 118-120°C (hexanes/EtOAc 6:4). $^1$H-NMR (CDCl$_3$, 300 MHz) δ 7.11 (t, J = 8.3 Hz, 1H), 6.50 (d, J = 8.3 Hz, 2H), 5.18-5.12 (m, 1H), 3.78 (s, 6H), 3.76 (s, 3H), 3.25-3.14 (m, 4H), 2.18 (ddd, J = 12.0, 9.1, 6.6 Hz, 1H), 1.93 (ddd, J = 12.0, 10.4, 9.1 Hz, 1H), 1.33 (d, J = 6.2 Hz, 3H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) δ 171.6, 169.7, 158.5, 127.7, 118.2, 104.1, 78.7, 55.6, 54.8, 53.2, 51.8, 40.9, 40.0, 19.5. FTIR (ATR, cm$^{-1}$): 1727 (C=O st). MS (70 eV) m/z (%): 278 (M+ - CO$_2$Me, 100), 246 (11), 231 (22), 216 (8), 204 (3), 191 (4), 176 (11), 161 (3), 141 (25), 113 (20), 91 (16), 77 (3), 59 (3), 42 (2), 28 (1). HRMS: calculated for [C$_{17}$H$_{24}$NO$_5$]$^+$: 338.1604 [(M + H)$^+$]; found: 338.1595. The ee was determined by HPLC using a Chiralpak ASH column [n-hexane/i-PrOH (95:5)]; flow rate 1.0 mL/min; $\tau_{\text{major}}$ = 7.71 min, $\tau_{\text{minor}}$ = 6.47 min (80% ee). $[\alpha]_D^{20}$: -17.5 (c = 0.66, CH$_2$Cl$_2$). M.p.: 118-120°C (hexanes/EtOAc).
General procedure for the Synthesis of Prolines (5a-o, 5r and 5s).

MeLi (1.00 mmol) was added dropwise to a solution of the corresponding pyrrolidine 4 (1.00 mmol) in THF (10 mL) at -78°C under inert atmosphere. The reaction was stirred at -78°C during 1 hour and then the reaction was quenched with the dropwise addition of water (1 mL) at -78°C. The reaction mixture was warmed to room temperature, then brine (5 mL) was added and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) yielding the desired product 5.

\[(2R,3S,5S)-\text{Diethyl 5-methyl-3-phenylpyrrolidine-1,2-dicarboxylate, (5a).}\]

The pyrrolidine 5a (44 mg, 0.14 mmol, 84%, dr: 7:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4a (52 mg, 0.17 mmol), methylolithium (0.12 mL of a 1.46 M solution in diethyl ether, 0.17 mmol) and THF (1.7 mL). \(^1\)H-NMR (CDCl₃, 300 MHz) (rotamer ratio 1.4:1, *denotes minor rotamer signals), \(\delta\) 7.36-7.23 (m, 5H), 4.51* (d, \(J = 6.2\) Hz, 1H), 4.43 (d, \(J = 6.6\) Hz, 1H), 4.25-4.03 (m, 5H), 3.48-3.31 (m, 1H), 2.66-2.43 (m, 1H), 1.90-1.74 (m, 1H), 1.40-1.14 (m, 9H). \(^{13}\)C-NMR (CDCl₃, 75 MHz) (*denotes minor rotamer signals), \(\delta\) 172.6, 172.2*, 155.4*, 154.5, 140.7, 140.6*, 128.7, 127.1, 127.1, 66.7, 66.4*, 61.4*, 61.0, 60.9, 55.1, 54.2*, 47.9, 47.1*, 41.7*, 41.4, 21.5*, 20.3, 14.6*, 14.5, 14.2, 14.1*. FTIR (ATR, cm\(^{-1}\)): 1742 (C=O st), 1708 (NC=O st). MS (70 eV) m/z (%): 305 (1), 260 (1), 232 (M\(^+\) - CO₂Et, 100), 216 (2), 204 (10), 188 (12), 172 (1), 160 (29), 144 (4), 129 (7), 117 (16), 104 (3), 91 (9), 77 (2), 55 (2). HRMS: calculated for [C\(_{17}\)H\(_{24}\)NO\(_4\)\(^+\)]: 306.1705 [(M + H)\(^+\)]; found: 306.1699. \([\alpha\]\(_D\)\(^{20}\): -51.2 (c = 0.44, CH₂Cl₂).

\[(2R,3S,5S)-\text{Diethyl 5-methyl-3-p-tolylpyrrolidine-1,2-dicarboxylate, (5b).}\]

The pyrrolidine 5b (26 mg, 0.08 mmol, 80%, dr: 10:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4b (32 mg, 0.10 mmol), methylolithium (0.07 mL of a 1.48 M solution in diethyl ether, 0.10 mmol) and THF (1.0 mL). \(^1\)H-NMR (CDCl₃, 300 MHz) (rotamer ratio 1.4:1, *denotes minor rotamer signals), \(\delta\) 7.19-7.09 (m, 4H), 4.47* (d, \(J = 6.7\) Hz, 1H), 4.40 (d, \(J = 6.9\) Hz, 1H), 4.26-4.00
(m, 5H), 3.41-3.30 (m, 1H), 2.63-2.42 (m, 1H), 2.33 (s, 3H), 1.90-1.69 (m, 1H), 1.42-1.13 (m, 9H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.6, 172.3*, 155.4*, 154.5, 137.6, 137.5*, 136.8, 136.7*, 129.3, 127.0, 66.8, 66.5*, 61.3*, 61.0, 60.9, 55.1, 54.2*, 47.6, 46.7*, 41.8*, 41.5, 21.5*, 21.0, 20.3, 14.6*, 14.5, 14.2, 14.1*. FTIR (ATR, cm$^{-1}$): 1743 (C=O st), 1710 (NC=O st). MS (70 eV) m/z (%): 319 (2), 246 (M$^+$ - CO$_2$Et, 100), 230 (4), 218 (11), 202 (12), 186 (1), 174 (29), 158 (5), 145 (5), 131 (20), 117 (7), 105 (6), 91 (7), 77 (2), 55 (2). HRMS: calculated for [C$_{18}$H$_{26}$NO$_4$]$^+$: 320.1862 [(M + H)$^+$]; found: 320.1852. [$\alpha$]$^D_{20}$: -63.2 (c = 0.61, CH$_2$Cl$_2$).

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

The pyrrolidine 5c (30 mg, 0.09 mmol, 78%, dr: >20:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4c (38 mg, 0.12 mmol), methylthium (0.08 mL of a 1.40 M solution in diethyl ether, 0.12 mmol) and THF (1.2 mL). $^1$H-NMR (CDCl$_3$, 300 MHz) (rotamer ratio 1.4:1, *denotes minor rotamer signals), δ 7.29-7.19 (m, 2H), 6.95-6.90 (m, 1H), 6.86 (d, J = 8.1 Hz, 1H), 4.63* (d, J = 5.4 Hz, 1H), 4.51 (d, J = 5.9 Hz, 1H), 4.27-4.01 (m, 5H), 3.82 (s, 3H), 3.77-3.65 (m, 1H), 2.62-2.41 (m, 1H), 1.68-1.72 (m, 1H), 1.35-1.14 (m, 9H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.8, 172.5*, 157.0, 155.6*, 154.7, 129.3*, 129.1, 128.1, 128.0*, 127.1, 120.5, 120.4*, 110.5, 110.4*, 65.2, 65.0*, 61.3*, 60.9, 60.8, 55.2, 55.0, 54.1*, 41.8, 41.1*, 39.7*, 39.3, 21.7*, 20.6, 14.6*, 14.5, 14.2, 14.1*. FTIR (ATR, cm$^{-1}$): 1743 (C=O st), 1705 (NC=O st). MS (70 eV) m/z (%): 335 (7), 289 (4), 262 (M$^+$ - CO$_2$Et, 100), 246 (3), 233 (5), 218 (8), 203 (1), 190 (34), 174 (5), 161 (5), 147 (11), 131 (8), 115 (5), 91 (14), 77 (3), 55 (2). HRMS: calculated for [C$_{18}$H$_{26}$NO$_5$]$^+$: 336.1811 [(M + H)$^+$]; found: 336.1808. [$\alpha$]$^D_{20}$: -54.0 (c = 1.20, CH$_2$Cl$_2$).

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

The pyrrolidine 5d (14 mg, 0.04 mmol, 77%, dr: >20:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/ EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4d (18 mg, 0.05 mmol), methylthium (0.04 mL, 1.53 M solution in diethyl ether, 0.05 mmol) and THF (0.5 mL). $^1$H-NMR (CDCl$_3$, 300 MHz) (rotamer ratio 1.4:1, *denotes minor rotamer signals), δ 7.28-7.20 (m, 1H), 6.85 (d, J = 7.7 Hz, 1H), 6.82-6.75 (m, 2H), 4.49* (d, J = 6.6 Hz, 1H),...
4.43 (d, J = 6.8 Hz, 1H), 4.26-4.01 (m, 5H), 3.80 (s, 3H), 3.41-3.32 (m, 1H), 2.62-2.47 (m, 1H), 1.90-1.71 (m, 1H), 1.45-1.11 (m, 9H). ¹³C-NMR (CDCl₃, 75 MHz) (*denotes minor rotamer signals), δ 172.6, 172.2*, 159.8, 155.4*, 154.5, 142.4, 142.3*, 129.6, 119.4, 113.3, 113.2*, 112.1, 66.6, 66.4*, 61.4*, 61.1, 61.0, 60.9*, 55.2, 55.0, 54.2*, 47.8, 47.0*, 41.7*, 41.3, 21.5*, 20.4, 14.6*, 14.5, 14.2, 14.1*. FTIR (ATR, cm⁻¹): 1742 (C=O st), 1705 (NC=O st). MS (70 eV) m/z (%): 335 (1), 262 (M⁺ - CO₂Et, 100), 246 (4), 234 (5), 218 (7), 206 (2), 190 (18), 174 (2), 162 (3), 147 (6), 134 (3), 121 (3), 103 (1), 91 (4), 78 (1), 65 (1). HRMS: calculated for [C₁₈H₂₆NO₅]⁺: 336.1788. [a]D²⁰: -47.5 (c = 0.99, CH₂Cl₂).

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

The pyrrolidine 5e (52 mg, 0.16 mmol, 73%, dr: 6:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/ EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4e (71 mg, 0.21 mmol), methyllithium (0.16 mL of a 1.35 M solution in diethyl ether, 0.21 mmol) and THF (2.1 mL). ¹H-NMR (CDCl₃, 300 MHz) (rotamer ratio 1.4:1, *denotes minor rotamer signals), δ 7.17 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.43* (d, J = 6.8 Hz, 1H), 4.35 (d, J = 6.9 Hz, 1H), 4.26-4.01 (m, 5H), 3.79 (s, 3H), 3.39-3.29 (m, 1H), 2.60-2.41 (m, 1H), 1.87-1.69 (m, 1H), 1.43-1.13 (m, 9H). ¹³C-NMR (CDCl₃, 75 MHz) (*denotes minor rotamer signals), δ 172.6, 172.2*, 158.7, 155.4*, 154.4, 132.5, 132.4*, 128.1, 114.0, 67.0, 66.7*, 61.3*, 61.0, 60.9, 55.3, 55.0, 54.1*, 47.2, 46.4*, 41.9*, 41.6, 21.5*, 20.3, 14.6*, 14.5, 14.2, 14.1*. FTIR (ATR, cm⁻¹): 1742 (C=O st), 1705 (NC=O st). MS (70 eV) m/z (%): 335 (5), 262 (M⁺ - CO₂Et, 100), 246 (2), 233 (9), 218 (6), 206 (5), 190 (17), 174 (3), 161 (5), 147 (15), 134 (5), 116 (9), 103 (2), 91 (7), 77 (2), 55 (2). HRMS: calculated for [C₁₈H₂₆NO₅]⁺: 336.1811 [(M + H)⁺]; found: 336.1795. [a]D²⁰: -57.4 (c = 1.04, CH₂Cl₂).

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

The pyrrolidine 5f (32 mg, 0.09 mmol, 73%, dr: 3:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4f (44 mg, 0.12 mmol), methyllithium (0.09 mL of a 1.31 M solution in diethyl ether, 0.12 mmol) and THF (1.2 mL). ¹H-NMR (CDCl₃, 300 MHz) (rotamer ratio 1.3:1, *denotes minor rotamer
signals), δ 7.16 (t, J = 8.3 Hz, 1H), 6.50 (d, J = 8.3 Hz, 2H), 4.62* (d, J = 8.5 Hz, 1H), 4.48 (d, J = 8.6 Hz, 1H), 4.29-3.78 (m, 6H), 3.75 (s, 6H), 2.96-2.72 (m, 1H), 2.21-1.96 (m, 1H), 1.55-1.50 (m, 3H), 1.29* (t; J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 7.1 Hz, 3H), 0.91* (t, J = 7.1 Hz, 3H). 13C-NMR (CDCl3, 75 MHz) (*denotes minor rotamer signals), δ 171.4*, 171.3, 159.6, 155.6*, 154.7, 128.3, 128.2*, 112.7*, 112.6, 103.8, 62.8*, 62.5, 61.0*, 60.8, 60.2, 55.4, 54.5, 54.0*, 38.0, 37.8*, 35.8*, 35.1, 21.2*, 20.1, 14.6, 13.8, 13.7*. FTIR (ATR, cm⁻¹): 1744 (C=O st), 1698 (NC=O st).

[α]D0: 54.6 (c = 1.01, CH₂Cl₂).

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

The pyrrolidine 5g (52 mg, 0.14 mmol, 84%, dr: 10:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4g (61 mg, 0.17 mmol), methyllithium (0.11 mL of a 1.48 M solution in diethyl ether, 0.17 mmol) and THF (1.7 mL). 1H-NMR (CDCl3, 300 MHz) (rotamer ratio 1.5:1, *denotes minor rotamer signals), δ 6.42 (d, J = 2.0 Hz, 2H), 6.35 (t, J = 2.0 Hz, 1H), 4.47* (d, J = 6.7 Hz, 1H), 4.41 (d, J = 6.6 Hz, 1H), 4.27-3.99 (m, 5H), 3.78 (s, 6H), 3.40-3.25 (m, 1H), 2.63-2.42 (m, 1H), 1.89-1.69 (m, 1H), 1.46-1.12 (m, 9H). 13C-NMR (CDCl3, 75 MHz) (*denotes minor rotamer signals), δ 172.6, 172.2*, 161.0, 155.4*, 154.5, 143.2, 143.0*, 105.4, 98.8*, 98.7, 66.5, 66.4*, 61.4*, 61.1, 61.0, 60.9*, 55.3, 55.0, 54.1*, 48.0, 47.2*, 41.6*, 41.2, 21.5*, 20.4, 14.6*, 14.4, 14.2, 14.1*. FTIR (ATR, cm⁻¹): 1742 (C=O st), 1703 (NC=O st). MS (70 eV) m/z (%): 365 (8), 319 (2), 292 (M⁺ - CO₂Et, 100), 264 (2), 248 (5), 220 (11), 203 (2), 177 (4), 161 (2), 145 (1), 119 (1), 91 (1), 77 (1), 55 (1). HRMS: calculated for [C₁₉H₂₈NO₆]⁺: 366.1917 [(M + H)⁺]; found: 366.1907. [α]D0: 54.6 (c = 1.01, CH₂Cl₂).

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

The pyrrolidine 5h (50 mg, 0.15 mmol, 85%, dr: 17:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4h (59 mg, 0.18 mmol), methyllithium (0.13 mL of a 1.40 M solution in diethyl ether, 0.18 mmol) and
THF (1.8 mL). $^1$H-NMR (CDCl$_3$, 300 MHz) (rotamer ratio 1.4:1, *denotes minor rotamer signals), $\delta$ 7.34-7.29 (m, 1H), 7.26-7.19 (m, 1H), 7.14-7.09 (m, 1H), 7.07-6.98 (m, 1H), 4.59* (d, $J = 6.0$ Hz, 1H), 4.47 (d, $J = 6.4$ Hz, 1H), 4.29-4.01 (m, 5H), 3.68-3.60 (m, 1H), 2.66-2.44 (m, 1H), 1.91-1.74 (m, 1H), 1.41-1.12 (m, 9H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) (*denotes minor rotamer signals), $\delta$ 172.3, 171.9*, 160.8 (d, $^1J_{CF} = 246.2$ Hz), 155.5*, 154.5, 128.8 (d, $^3J_{CF} = 8.2$ Hz), 128.7* (d, $^3J_{CF} = 8.3$ Hz), 127.9 (d, $^3J_{CF} = 3.6$ Hz), 127.8 (d, $^2J_{CF} = 26.7$ Hz), 124.3 (d, $^4J_{CF} = 3.4$ Hz), 115.6 (d, $^2J_{CF} = 22.2$ Hz), 115.5* (d, $^2J_{CF} = 22.2$ Hz), 65.4, 65.1*, 61.4*, 61.2, 61.1, 61.0*, 55.0, 54.0*, 41.2, 40.4*, 40.2*, 39.8, 21.5*, 20.4, 14.6*, 14.5, 14.1, 14.0*. FTIR (ATR, cm$^{-1}$): 1746 (C=O st), 1709 (NC=O st). \[ \text{HRMS: calculated for } \text{[C}_{17}\text{H}_{23}\text{FNO}]^+ : 324.1611 [(M + H)^+]; \text{found: 324.1603.} \; [\alpha]_D^{20} : -46.8 (c = 1.36, CH}_2\text{Cl}_2). \]

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

The pyrrolidine 5i (41 mg, 0.13 mmol, 71%, dr: 6:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4i (58 mg, 0.18 mmol), methyllithium (0.13 mL of a 1.35 M solution in diethyl ether, 0.18 mmol) and THF (1.8 mL). $^1$H-NMR (CDCl$_3$, 300 MHz) (rotamer ratio 1.3:1, *denotes minor rotamer signals), $\delta$ 7.25-7.19 (m, 2H), 7.07-6.95 (m, 2H), 4.43* (d, $J = 6.7$ Hz, 1H), 4.36 (d, $J = 6.9$ Hz, 1H), 4.26-4.02 (m, 5H), 3.41-3.31 (m, 1H), 2.60-2.46 (m, 1H), 1.85-1.68 (m, 1H), 1.43-1.11 (m, 9H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) (*denotes minor rotamer signals), $\delta$ 172.4, 172.0*, 161.9 (d, $^1J_{CF} = 245.6$ Hz), 155.3*, 154.4, 136.2, 128.7 (d, $^3J_{CF} = 8.0$ Hz), 115.5 (d, $^2J_{CF} = 21.4$ Hz), 66.9, 66.7*, 61.4*, 61.1, 61.0, 55.0, 54.1*, 47.2, 46.4*, 41.9*, 41.6, 21.4*, 20.3, 14.6*, 14.4, 14.2, 14.1*. FTIR (ATR, cm$^{-1}$): 1742 (C=O st), 1706 (NC=O st). MS (70 eV) m/z (%): 323 (4), 250 (M$^+$ - CO$_2$Et, 100), 234 (1), 222 (10), 206 (17), 190 (1), 178 (42), 162 (5), 150 (4), 135 (14), 122 (3), 109 (11), 96 (1), 83 (1), 56 (1). HRMS: calculated for [C$_{17}$H$_{25}$FNO]$: 324.1611 [(M + H)$^+$]; found: 324.1593. $[\alpha]_D^{20}$: -47.9 (c = 1.01, CH$_2$Cl$_2$). 

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

The pyrrolidine 5j (73 mg, 0.21 mmol, 86%, dr: 7:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4j (85 mg,
0.25 mmol), methyllithium (0.19 mL of a 1.31 M solution in diethyl ether, 0.25 mmol) and THF (2.5 mL). $^1$H-NMR (CDCl$_3$, 300 MHz) (rotamers ratio 1.3:1, *denotes minor rotamer signals), δ 7.30 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 4.45* (d, J = 6.4 Hz, 1H), 4.38 (d, J = 6.8 Hz, 1H), 4.27-3.97 (m, 5H), 3.43-3.28 (m, 1H), 2.64-2.44 (m, 1H), 1.87-1.66 (m, 1H), 1.45-1.11 (m, 9H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.3, 172.0*, 155.3*, 154.4, 139.2, 139.1*, 132.9, 128.8, 128.5, 66.6, 66.4*, 61.5*, 61.2, 61.1, 61.0*, 55.0, 54.1*, 47.3, 46.4*, 41.7*, 41.4, 21.5*, 20.3, 14.6*, 14.5, 14.2, 14.1*. FTIR (ATR, cm$^{-1}$): 1742 (C=O st), 1704 (NC=O st).

The pyrrolidine 5k (39 mg, 0.10 mmol, 80%, dr: 5:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4k (49 mg, 0.13 mmol), methyllithium (0.10 mL of a 1.31 M solution in diethyl ether, 0.13 mmol) and THF (1.3 mL). $^1$H-NMR (CDCl$_3$, 300 MHz) (rotamer ratio 1.3:1, *denotes minor rotamer signals), δ 7.59 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 4.53* (d, J = 5.8 Hz, 1H), 4.45 (d, J = 6.4 Hz, 1H), 4.28-4.01 (m, 5H), 3.53-3.36 (m, 1H), 2.70-2.48 (m, 1H), 1.90-1.71 (m, 1H), 1.44-1.13 (m, 9H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) (*denotes minor rotamer signals), δ 172.2, 171.8*, 155.4*, 154.4, 144.9, 129.5 (q, $^2$J$_{CF}$ = 32.7 Hz), 127.6, 125.6 (q, $^3$J$_{CF}$ = 3.6 Hz), 124.0 (q, $^1$J$_{CF}$ = 272.0 Hz), 66.5, 66.2*, 61.5*, 61.2, 61.1, 61.0*, 55.0, 54.1*, 47.5, 46.7*, 41.6*, 41.2, 21.5*, 20.4, 14.6*, 14.4, 14.2, 14.1*. FTIR (ATR, cm$^{-1}$): 1743 (C=O st), 1706 (NC=O st). MS (70 eV) m/z (%): 373 (1), 300 (M$^+$ - CO$_2$Et, 100), 286 (1), 272 (4), 256 (12), 228 (28), 200 (2), 185 (4), 159 (3), 145 (1), 129 (4), 115 (1), 82 (1), 55 (1). HRMS: calculated for [C$_{13}$H$_{23}$ClNO$_4$]: 374.1579 [(M + H)$^+$]; found: 374.1565. [$\alpha$]$_D^{20}$: -55.1 (c = 1.00, CH$_2$Cl$_2$).

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

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

SI-19
The pyrrolidine 5I (13 mg, 0.04 mmol, 60%\(^2\), dr: 7:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4I (54 mg, 0.15 mmol), methyllithium (0.10 mL of a 1.53 M solution in diethyl ether, 0.15 mmol) and THF (1.5 mL). \(^1\)H-NMR (CDCl\(_3\), 300 MHz) (rotamer ratio 1.1:1, *denotes minor rotamer signals), δ 8.20 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 4.55* (d, J = 6.5 Hz, 1H), 4.47 (d, J = 6.3 Hz, 1H), 4.27-4.08 (m, 5H), 3.58-3.41 (m, 1H), 2.71-2.51 (m, 1H), 1.89-1.75 (m, 1H), 1.40-1.19 (m, 9H). \(^13\)C-NMR (CDCl\(_3\), 75 MHz) (*denotes minor rotamer signals), δ 171.9, 171.6*, 155.4*, 154.3, 148.4, 147.1, 128.1, 124.0, 66.3, 66.1*, 61.6*, 61.3, 61.3, 61.2*, 55.0, 54.1*, 47.5, 46.6*, 41.6*, 41.2, 21.5*, 20.4, 14.6*, 14.5, 14.2, 14.2*. FTIR (ATR, cm\(^{-1}\))): 1742 (C=O st), 1705 (NC=O st), 1521 (NO\(_2\) st as), 1346 (NO\(_2\) st sym). MS (70 eV) m/z (%): 277 (M\(^+\) - CO\(_2\)Et, 100), 261 (2), 249 (4), 233 (13), 205 (39), 187 (10), 177 (2), 159 (8), 143 (2), 129 (12), 115 (10), 103 (2), 91 (4), 77 (2), 55 (2). HRMS: calculated for [C\(_{17}\)H\(_{23}\)N\(_2\)O\(_6\)]\(^+\): 351.1556 [(M + H\(^+)\)]; found: 351.1540. \([\alpha]_D^{20}\): -72.7 (c = 0.61, CH\(_2\)Cl\(_2\)).

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

The pyrrolidine 5m (29 mg, 0.10 mmol, 78%, dr: 9:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4m (37 mg, 0.13 mmol), methyllithium (0.10 mL of a 1.31 M solution in diethyl ether, 0.13 mmol) and THF (1.3 mL). \(^1\)H-NMR (CDCl\(_3\), 300 MHz) (rotamer ratio 1.3:1, *denotes minor rotamer signals), δ 7.36-7.31 (m, 1H), 6.36-6.25 (m, 1H), 6.20-6.12 (m, 1H), 4.60* (d, J = 4.4 Hz, 1H), 4.53 (d, J = 4.7 Hz, 1H), 4.26-4.00 (m, 5H), 3.53-3.40 (m, 1H), 2.60-2.40 (m, 1H), 2.04-1.87 (m, 1H), 1.32-1.12 (m, 9H). \(^13\)C-NMR (CDCl\(_3\), 75 MHz) (*denotes minor rotamer signals), δ 172.2, 171.9*, 155.4*, 154.4, 154.2*, 154.1, 141.8, 110.3, 105.7, 105.6*, 64.5, 61.4*, 61.3, 61.2, 61.0*, 54.6, 53.7*, 41.5, 40.6*, 37.3*, 36.9, 21.4*, 20.4, 14.6*, 14.5, 14.2, 14.1*. FTIR (ATR, cm\(^{-1}\))): 1735 (C=O st), 1703 (NC=O st). MS (70 eV) m/z (%): 295 (16), 250 (1), 222 (M\(^+\) - CO\(_2\)Et, 100), 206 (4), 194 (9), 178 (12), 162 (1), 150 (32), 134 (4), 122 (7), 107 (12), 94 (5), 79 (8), 68 (2), 55 (3). HRMS: calculated for [C\(_{15}\)H\(_{20}\)N\(_2\)O\(_3\)]\(^+\): 296.1498 [(M + H\(^+)\)]; found: 296.1489. \([\alpha]_D^{20}\): -47.3 (c = 1.01, CH\(_2\)Cl\(_2\)).

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

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

\(^2\) Calculated yield over a conversion of 40%.
colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4n (62 mg, 0.20 mmol), methyllithium (0.14 mL of a 1.48 M solution in diethyl ether, 0.20 mmol) and THF (2.0 mL). \(^1\)H-NMR (CDCl\(_3\), 300 MHz) (rotamer ratio 1.4:1, \(*\)denotes minor rotamer signals), \(\delta\) 7.22-7.16 (m, 1H), 6.96-6.90 (m, 2H), 4.50* (d, \(J = 6.1\) Hz, 1H), 4.43 (d, \(J = 6.3\) Hz, 1H), 4.26-3.99 (m, 5H), 3.69-3.62 (m, 1H), 2.71-2.52 (m, 1H), 1.98-1.79 (m, 1H), 1.42-1.13 (m, 9H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz) (*denotes minor rotamer signals), \(\delta\) 172.1, 171.8*, 155.2*, 154.3, 144.3, 126.9, 124.3, 124.2*, 124.0, 67.3, 67.2*, 61.4*, 61.2, 61.1, 61.0*, 54.9, 54.0*, 43.3, 42.6*, 42.1*, 41.7, 21.4*, 20.3, 14.6*, 14.5, 14.2, 14.1*. FTIR (ATR, cm\(^{-1}\)): 1742 (C=O st), 1705 (NC=O st).

\[\text{EtO}_2C\]

\[\text{CO}_2\text{Et}\]

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

The pyrrolidine 5o (49 mg, 0.14 mmol, 89%, dr: 6:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4o (55 mg, 0.16 mmol), methyllithium (0.10 mL of a 1.53 M solution in diethyl ether, 0.16 mmol) and THF (1.6 mL), quenching the reaction with the dropwise addition of \(^1\)BuOH (0.06 mL) in THF (1 mL) at -78ºC. \(^1\)H-NMR (CDCl\(_3\), 300 MHz) (rotamer ratio 1.3:1, \(*\)denotes minor rotamer signals), \(\delta\) 7.17 (d, \(J = 8.6\) Hz, 2H), 6.86 (d, \(J = 8.5\) Hz, 2H), 4.38* (d, \(J = 7.1\) Hz, 1H), 4.33 (d, \(J = 7.1\) Hz, 1H), 4.26-4.02 (m, 4H), 4.00-3.87 (m, 1H), 3.80 (s, 3H), 3.42-3.26 (m, 1H), 2.54-2.37 (m, 1H), 2.33-2.17 (m, 1H), 2.07-1.93* (m, 1H), 1.93-1.74 (m, 1H), 1.52-1.36 (m, 1H), 1.32-1.12 (m, 6H), 0.90-0.78 (m, 3H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz) (*denotes minor rotamer signals), \(\delta\) 172.5, 172.1*, 158.7, 155.3*, 154.4, 132.5, 132.3*, 128.1, 114.0, 67.1, 66.9*, 61.3*, 61.0, 60.9, 60.5, 59.6*, 55.3, 47.3, 46.5*, 38.6*, 38.3, 27.1*, 26.1, 14.6*, 14.4, 14.2, 14.1*, 9.8, 9.6*. FTIR (ATR, cm\(^{-1}\)): 1742 (C=O st), 1706 (NC=O st). MS (70 eV) m/z (%): 311 (6), 238 (M+), 222 (4), 210 (5), 194 (5), 182 (1), 166 (15), 150 (3), 137 (3), 123 (12), 110 (3), 97 (7), 79 (2), 65 (1), 53 (1). HRMS: calculated for \([\text{C}_{15}\text{H}_{22}\text{NO}_4\text{S}]^+\)\: 312.1270 \([\text{M} + \text{H}]^+\); found: 312.1255. \([\alpha]_D^{20}\) \(-51.1 \text{ (c = 1.01, CH}_2\text{Cl}_2)\).

\[\text{MeO}\]

\[\text{EtO}_2\text{C}\]

\[\text{CO}_2\text{Et}\]

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

The pyrrolidine 5r (61 mg, 0.22 mmol, 80%, dr: 10:1) was obtained after 1 hour as a
colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4r (76 mg, 0.27 mmol), methyl lithium (0.19 mL of a 1.48 M solution in diethyl ether, 0.27 mmol) and THF (2.7 mL). $^1$H-NMR (CDCl$_3$, 300 MHz) (rotamer ratio 1.2:1, *denotes minor rotamer signals), $\delta$ 7.37-7.19 (m, 5H), 4.54* (d, $J$ = 6.4 Hz, 1H), 4.47 (d, $J$ = 6.4 Hz, 1H), 4.22-4.00 (m, 1H), 3.79-3.60 (m, 6H), 3.50-3.33 (m, 1H), 2.66-2.44 (m, 1H), 1.93-1.75 (m, 1H), 1.37 (d, $J$ = 6.0 Hz, 3H), 1.26* (d, $J$ = 6.1 Hz, 3H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) (*denotes minor rotamer signals), $\delta$ 173.0, 172.7*, 155.8*, 154.8, 140.6, 140.4*, 128.7, 127.2, 127.0, 66.5, 66.4*, 55.2, 54.2*, 52.6, 52.2, 47.8, 47.0*, 41.7*, 41.3, 21.4*, 20.3. FTIR (ATR, cm$^{-1}$): 1747 (C=O st), 1699 (NC=O st). MS (70 eV) m/z (%): 277 (1), 262 (1), 218 (M$^+$ - CO$_2$Et, 100), 202 (10), 186 (3), 170 (1), 158 (5), 143 (18), 128 (8), 117 (27), 103 (4), 91 (15), 77 (4), 59 (11). HRMS: calculated for [C$_{15}$H$_{20}$NO$_4$]$^+$: 278.1392 [(M + H)$^+$]; found: 278.1381. [\alpha]$_D^{20}$: -58.9 (c = 1.19, CH$_2$Cl$_2$).

![Chemical Structure](image:structure.png)

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

The pyrrolidine 5s (10 mg, 0.03 mmol, 75%, dr: 3:1) was obtained after 1 hour as a colourless oil, after isolation by flash column chromatography (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) according to the general procedure starting from pyrrolidine 4s (14 mg, 0.04 mmol), methyl lithium (0.03 mL of a 1.53 M solution in diethyl ether, 0.04 mmol) and THF (0.4 mL). $^1$H-NMR (CDCl$_3$, 300 MHz) (rotamer ratio 1.4:1, *denotes minor rotamer signals), $\delta$ 7.17 (t, $J$ = 8.3 Hz, 1H), 6.51 (d, $J$ = 8.3 Hz, 2H), 4.60* (d, $J$ = 8.4 Hz, 1H), 4.48 (d, $J$ = 8.5 Hz, 1H), 4.11-4.02 (m, 1H), 4.01-3.84 (m, 1H), 3.80-3.63 (m, 9H), 3.46 (s, 3H), 2.92-2.70 (m, 1H), 2.17-1.98 (m, 1H), 1.55-1.49 (m, 3H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) (*denotes minor rotamer signals), $\delta$ 171.8, 159.5, 156.0*, 155.1, 128.4, 112.5*, 112.4, 103.8, 62.8*, 62.4, 55.5, 54.7, 54.0*, 52.3*, 52.2, 51.3, 38.0, 37.5*, 35.7*, 34.9, 21.2*, 20.1. FTIR (ATR, cm$^{-1}$): 1746 (C=O st), 1698 (NC=O st). MS (70 eV) m/z (%): 337 (2), 305 (1), 278 (M$^+$ - CO$_2$Me, 100), 262 (1), 246 (2), 219 (1), 204 (2), 188 (4), 175 (1), 161 (6), 147 (3), 134 (1), 121 (4), 105 (1), 91 (6), 77 (2), 59 (6). HRMS: calculated for [C$_{17}$H$_{24}$NO$_8$]$^+$: 338.1604 [(M + H)$^+$]; found: 338.1596. [\alpha]$_D^{20}$: 60.7 (c = 0.99, CH$_2$Cl$_2$).
Trimethylsilyl iodide (10 mmol) was added dropwise to a solution of 5a,p (1 mmol) in dry CHCl₃ under inert atmosphere. The reaction mixture was refluxed for 24 h, then MeOH was added and the mixture was refluxed for 3 h more and the mixture was allowed to reach room temperature. After this time, the solvent was removed under reduced pressure, Et₂O (5 mL) and a few drops of HCl conc. were added and the solution was stirred for 10-15 min. The mixture was washed with Et₂O (3 x 20 mL). The liquid phase was basified by the addition of NH₃ (aq.), and the mixture was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and the solvent was removed under reduced pressure, yielding the desired product 6a,b without further purification.

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

The pyrrolidine 6a (36 mg, 0.15 mmol, 80%) was obtained as a colourless oil according to the general procedure starting from pyrrolidine 5a (59 mg, 0.19 mmol), trimethylsilyl iodide (0.27 mL, 1.9 mmol) and CHCl₃ (10.0 mL), followed by the addition of MeOH (5.6 mL). ¹H-NMR (CDCl₃, 300 MHz) δ 7.33-7.16 (m, 5H), 4.26-4.01 (m, 2H), 3.84 (d, J = 7.4 Hz, 1H), 3.58-3.42 (m, 1H), 3.42-3.28 (m, 1H), 2.47-2.25 (m, 2H), 1.67-1.56 (m, 1H), 1.25 (d, J = 6.1 Hz, 3H), 1.19 (dt, J = 7.1 Hz, 3H). ¹³C-NMR (CDCl₃, 75 MHz) δ 175.2, 143.0, 128.5, 127.4, 126.6, 67.2, 60.9, 54.6, 50.8, 44.0, 21.2, 14.2. FTIR (ATR, cm⁻¹): 1730 (C=O st). MS (70 eV) m/z (%): 161 (13), 160 (M⁺ - CO₂Et, 100), 144 (4), 129 (4), 117 (10), 100 (2), 91 (9), 83 (4), 73 (3), 63 (1), 55 (4). HRMS: calculated for [C₁₄H₁₀NO₂]⁺: 234.1494 [(M + H)⁺]; found: 234.1484. [α]D²⁰: -60.5 (c = 1.00, CH₂Cl₂).

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

The pyrrolidine 6b (33 mg, 0.15 mmol, 70%) was obtained as a colourless oil according to the general procedure starting from pyrrolidine 5p (61 mg, 0.22 mmol), trimethylsilyl iodide (0.30 mL, 2.2 mmol) and CHCl₃ (11.0 mL), followed by the addition of MeOH (6.4 mL). ¹H-NMR (CDCl₃, 300 MHz) δ 7.38-7.21 (m, 5H), 3.88 (d, J = 7.3 Hz, 1H), 3.68 (s, 3H), 3.55-3.44 (m, 1H), 3.43-3.35 (m, 1H), 2.42 (bs, 1H), 2.32 (ddd, J = 12.4, 7.4, 5.2 Hz, 1H), 1.66-1.55 (m, 1H), 1.25 (d, J = 6.1 Hz, 3H). ¹³C-NMR (CDCl₃, 75 MHz) δ 175.8, 143.0, 128.6, 127.3, 126.7, 67.1, 54.6, 52.1, 50.6, 44.1, 21.0. FTIR (ATR, cm⁻¹): 1731 (C=O st). MS (70 eV) m/z (%): 204 (1), 183 (1), 160 (M⁺ - CO₂Me, 100), 144 (5), 128 (5), 115 (21), 103 (3), 91 (15), 83 (12), 72 (4), 65 (3), 55 (11). HRMS: calculated for [C₁₃H₁₈NO₂]⁺: 220.1338 [(M + H)⁺]; found: 220.1323. [α]D²⁰: -66.3 (c = 1.01, CH₂Cl₂).
NMR spectra

Figure 1: $^1$H-NMR and $^{13}$C-NMR spectra for compound 4a.
Figure 2: $^1$H-NMR and $^{13}$C-NMR spectra for compound 4b.
Figure 3: $^1$H-NMR and $^{13}$C-NMR spectra for compound 4c.
Figure 4: $^1\text{H}$-NMR and $^{13}\text{C}$-NMR spectra for compound 4d.
Figure 5: $^1$H-NMR and $^{13}$C-NMR spectra for compound 4e.
Figure 6: $^1$H-NMR and $^{13}$C-NMR spectra for compound 4f.
Figure 7: $^1$H-NMR and $^{13}$C-NMR spectra for compound 4g.
Figure 8: $^1$H-NMR and $^{13}$C-NMR spectra for compound 4h.
Figure 9: $^1$H-NMR and $^{13}$C-NMR spectra for compound 4i.
Figure 10: $^1$H-NMR and $^{13}$C-NMR spectra for compound 4j.
Figure 11: $^1$H-NMR and $^{13}$C-NMR spectra for compound 4k.
Figure 12: $^1$H-NMR and $^{13}$C-NMR spectra for compound 4I.
Figure 13: $^1$H-NMR and $^{13}$C-NMR spectra for compound 4m.
Figure 14: $^1$H-NMR and $^{13}$C-NMR spectra for compound 4n.
Figure 15: $^1$H-NMR and $^{13}$C-NMR spectra for compound 40.
Figure 16: $^1$H-NMR and $^{13}$C-NMR spectra for compound 4p.
Figure 17: $^1$H-NMR and $^{13}$C-NMR spectra for 4r.
Figure 18: $^1$H-NMR and $^{13}$C-NMR spectra for compound 4s.
Figure 19: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5a.
Figure 20: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5b.
Figure 21: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5c.
Figure 22: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5d.
Figure 23: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5e.
Figure 24: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5f.
Figure 25: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5g.
Figure 26: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5h.
Figure 27: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5i.
Figure 28: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5j.
Figure 29: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5k.
Figure 30: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5I.
Figure 31: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5m.
Figure 32: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5n.
Figure 33: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5o.
Figure 34: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5r.
Figure 35: $^1$H-NMR and $^{13}$C-NMR spectra for compound 5s.
Figure 36: $^1$H-NMR and $^{13}$C-NMR spectra for compound 6a.
Figure 37: $^1$H-NMR and $^{13}$C-NMR spectra for compound 6r.
Figure 38: HPLC chromatogram for compounds *rac-4a* and *4a*. 
Figure 39: HPLC chromatogram for compounds rac-4b and 4b.
Figure 40: HPLC chromatogram for compounds rac-4c and 4c.
Figure 41: HPLC chromatogram for compounds $\textit{rac-4d}$ and $4\text{d}$. 
Figure 42: HPLC chromatogram for compounds \textit{rac-4e} and \textit{4e}. 
Figure 43: HPLC chromatogram for compounds rac-4f and 4f.
Figure 44: HPLC chromatogram for compounds \textit{rac-4g} and 4g.
Figure 45: HPLC chromatogram for compounds \textit{rac-4h} and \textit{4h}.

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Figure 46: HPLC chromatogram for compounds *rac-4i* and *4i*.
Figure 47: HPLC chromatogram for compounds $\text{rac-4j}$ and $4j$. 

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Figure 48: HPLC chromatogram for compounds rac-4k and 4k.
Figure 49: HPLC chromatogram for compounds rac-4I and 4I.
Figure 50: HPLC chromatogram for compounds rac-4m and 4m.
Figure 51: HPLC chromatogram for compounds rac-4n and 4n.
Figure 52: HPLC chromatogram for compounds rac-4o and 4o.
Figure 53: HPLC chromatogram for compounds rac-4p and 4p.
Figure 54: HPLC chromatogram for compounds rac-4r and 4r.
Figure 55: HPLC chromatogram for compounds rac-4s and 4s.