Diastereoselective intramolecular $\alpha$-amidoalkylation reactions of L-DOPA derivatives. Asymmetric synthesis of pyrrolo[2,1-$a$]isoquinolines

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**General experimental methods:** Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or CHCl₃ solution (oils). NMR spectra were recorded at 20-25 °C, running at 250 MHz for $^1$H and 62.8 MHz for $^{13}$C in CDCl₃ solutions. Assignment of individual $^{13}$C resonances are supported by DEPT experiments. $^1$H-$^1$H NOE experiments were carried out in the difference mode by irradiation of all the lines of a multiplet.¹ Mass spectra were recorded under electron impact at 70 eV. GC-MS analyses were performed using a TRB-1 column (methyl polysiloxane, 30 m × 0.25 mm × 0.25 µm). TLC was carried out with 0.2 mm thick silicagel plates. Visualization was accomplished by UV light. Flash column chromatography² on silica gel was performed with Kiesegel 60 (230-400 mesh). CSP HPLC was performed using Chiralcel OD or OJ columns (0.46 cm × 25 cm). All solvents used in reactions were anhydrous and purified according to standard procedures.³ Organolithium reagents were titrated with diphenylacetic acid periodically prior to use. All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 °C) and purged with argon.

**((S)-(−)-2-tert-Butoxycarbonylamino-3-(3,4-dimethoxyphenyl)-propionic acid methyl ester (3).** NEt₃ (4.24 mL, 30.4 mmol) was added to a solution of L-DOPA (1) (5.00 g, 25.3 mmol) in dioxane/water (50%, 80 mL). (Boc)₂O (6.64 g, 30.4 mmol) was added in one portion at 0 ºC, and the resulting mixture was stirred at this temperature for 30 min, and at rt for 18 h. The solvent was removed under vacuum, and H₂O (30 mL) and AcOEt (30 mL) were added. The aqueous phase was acidified with HCl 2M to pH = 1, and was extracted with AcOEt (3 × 20 mL). The combined organic extracts were washed with brine (3 × 20 mL), dried (Na₂SO₄) and concentrated in vacuo to obtain the 2-tert-Butoxycarbonylamino-3-(3,4-dimethoxyphenyl)alanine (2) that was used without further purification. Over a solution of crude 2 in acetone (50 mL), K₂CO₃ (12.25 g, 88.0 mmol) and Me₂SO₄ (8.15 mL, 86.0 mmol) were added, and the mixture was refluxed for 48 h. The solvent was removed under vacuum, and the resulting white solid was dissolved in CH₂Cl₂ (30 mL). The solution was washed with brine (3 × 20 mL), dried (Na₂SO₄) and concentrated in vacuo. Flash column chromatography (silicagel, 60% hexane/ethyl acetate) yielded...
3 as a white solid that was crystallized from pentane (7.9 g, 92%): \([\alpha]_D^{20} +66 \text{ (1, CH}_2\text{Cl}_2); \text{mp (n-pentane) 58-60}^\circ\text{C}; \text{IR (KBr) 3370, 1761, 1690 cm}^{-1}; \text{H NMR (CDCl}_3) 1.32 \text{ (s, 9H), 2.85-2.98 \text{ (m, 2H)}, 3.61 \text{ (s, 3H)}, 3.74 \text{ (s, 3H); 3.75 \text{ (s, 3H), 4.41-4.49 \text{ (m, 1H)}, 5.03 \text{ (d, \(J = 8.3 \text{ Hz, 1H)}, 6.57-6.59 \text{ (m, 2H)}, 6.69 \text{ (d, \(J = 8.3 \text{ Hz); 13C NMR (CDCl}_3) 27.8, 37.2, 51.6, 54.1, 55.2, 55.3, 79.2, 110.7, 111.8, 120.9, 128.1, 147.5, 148.3, 154.6, 171.9; MS (EI) \text{m/z (rel intensity) 339 (M}^+, 6), 283 (33), 266 (4), 222 (21), 151 (100), 57 (24). \text{Anal. Calcd for C}_{17}\text{H}_{25}\text{NO}_6: C, 60.16; H, 7.42; N, 4.13. Found: C, 59.88; H, 7.38; N, 3.99. ee> 99\% (Chiralcel OD, hexane:2-propanol 90:10, 0.8 mL/min, \(t_r \text{(S)} = 16.2 \text{ min > 99\%, } t_r \text{(R) = 14.7 min < 1\%}. \)

\text{(S)-(–)[2-(3,4-Dimethoxyphenyl)-1-hydroxymethyleneethyl]carbamic acid tert-butyl ester (4). A solution of 3 (300 mg, 0.88 mmol) in Et}_2\text{O/THF (50\%, 20 mL) was added dropwise over a suspension of LiAlH}_4 \text{ in dry Et}_2\text{O (15 mL), and the mixture was refluxed for 30 min. The mixture was cooled to \(-10^\circ\text{C, and NaOH 1M (5 mL) was added. The resulting mixture was filtered through a celite pad, washing with AcOEt. The filtrate was acidified with HCl 2M (8 mL) to pH = 5, and extracted with AcOEt (3 \times 20 mL). The organic extracts were washed with brine (3 \times 10 mL), dried (\text{Na}_2\text{SO}_4) and concentrated in vacuo. Flash column chromatography (silicagel, 40% hexane/ethyl acetate) yielded 4 as a white solid that was crystallized from pentane (24 mg, 87%): \([\alpha]_D^{20} -26.7 \text{ (1, CH}_2\text{Cl}_2); \text{mp (n-pentane) 65-67}^\circ\text{C; IR (KBr) 3550, 3450, 1695 cm}^{-1}; \text{H NMR (CDCl}_3) 1.40 \text{ (s, 9H), 2.70 \text{ (bs, 1H), 2.77 \text{ (d, } \(J = 7.1 \text{ Hz, 2H), 3.51-3.59 \text{ (m, 1H), 3.63-3.71 \text{ (m, 1H), 3.82-3.85 \text{ (m, 1H)*, 3.86 \text{ (s, 3H)*, 3.87 \text{ (s, 3H)*, 4.76-4.92 \text{ (bs, 1H), 6.72-6.82 \text{ (m, 3H) (* designates partially overlapped signals); 13C NMR (CDCl}_3) 28.2, 36.8, 53.5, 55.6, 55.7, 63.8, 79.5, 111.0, 112.1, 121.2, 130.2, 147.4, 148.6, 156.1; MS (EI) \text{m/z (rel intensity) 311 (M}^+, 15), 255 (6), 194 (31), 151 (60), 151 (100), 137 (9), 104 (13), 60 (50), 57 (24). \text{Anal. Calcd for C}_{16}\text{H}_{25}\text{NO}_5: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.45; H, 8.22; N, 4.10. \)}

\text{(S)-(–)[1-(tert-Butyldiphenylsilyloxy)methyl]-2-(3,4-dimethoxyphenyl)ethyl]carbamic acid tert-butyl ester (5a). TBDPSiCl (975 mg, 3.5 mmol) was added over a solution of imidazole (242 mg, 3.5 mmol) and phenylalaninol 4 (849 mg, 2.73 mmol) in dry CH}_2\text{Cl}_2 \text{(15 mL) at rt, an the mixture was}
stirred for 18 h. The reaction mixture was quenched with HCl 1M, and the aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried (Na₂SO₄) and concentrated in vacuo. Flash column chromatography (silicagel, 30 % hexane/ethyl acetate) yielded 5a as a yellow oil (1.43 g, 95%): [α]D²⁰ -164 (0.014, CH₂Cl₂); IR (KBr) 3371, 1711 cm⁻¹; ¹H NMR (CDCl₃) 1.12 (s, 9H), 1.44 (s, 9H), 2.88 (d, J = 7.1 Hz, 2H), 3.56-3.68 (m, 2H), 3.80 (s, 3H), 3.86 (s, 3H), 3.87-3.90 (m, 1H), 4.80 (d, J = 9.1 Hz, 1H), 6.74-6.77 (m, 3H), 7.35-7.44 (m, 6H), 7.64-7.76 (m, 4H); ¹³C NMR (CDCl₃) 19.3, 26.9, 28.4, 37.0, 52.9, 55.7, 55.8, 63.9, 79.1, 110.9, 112.2, 121.4, 127.7, 129.7, 130.6, 133.2, 135.5, 147.3, 148.6, 155.3; MS (EI) m/z (rel intensity) 549 (M⁺, 1), 494 (1), 436 (39), 392 (14), 342 (19), 240 (21), 199 (29), 151 (58), 135 (18), 107 (10), 77 (7), 57 (100). Anal. Calcd for C₃₂H₄₃NO₅Si: C, 69.91; H, 7.88; N, 2.55. Found: C, 70.04; H, 8.07; N, 2.43. ee > 99% (Chiralcel OD, hexane:2-propanol 95:5, 1 mL/min, tᵣ (S) = 6.6 min > 99%, tᵣ (R) = 5.1 min < 1%.

(S)-(–)-[1-(Benzyloxymethyl)-2-(3,4-dimethoxyphenyl)ethyl]carbamic acid tert-butyl ester (5b) A solution of phenylalanilol 4 (500 mg, 1.6 mmol) in dry THF (10 mL) was added over a suspension of NaH (78 mg, 3.2 mmol) in dry THF (20 mL) at 0 ºC. Then, BnBr (0.39 mL, 3.2 mmol) was added dropwise, and the reaction mixture allowed to reach rt and stirred for 22 h. Water was added and the aqueous phase was extracted with Et₂O (3 × 15 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried (Na₂SO₄) and concentrated in vacuo. Flash column chromatography (silicagel, 40 % hexane/ethyl acetate) yielded 5b as a yellow oil (400 mg, 60%), together with oxazolidinone 6 as a by-product (162 mg, 30 %). Data for 5b: [α]D²⁰ -17 (0.17, CH₂Cl₂); mp (hexane) 58-59 ºC; IR (KBr) 3361, 1707 cm⁻¹; ¹H NMR (CDCl₃) 1.42 (s, 9H), 2.75-2.85 (m, 2H), 3.39 (d, J = 3.9 Hz, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 3.93 (bs, 1H), 4.42 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.93 (da, J = 8.7 Hz, 1H), 6.68-6.77 (m, 3H), 7.32-7.36 (m, 5H); ¹³C NMR (CDCl₃) 28.3, 37.3, 51.5, 55.6, 55.7, 70.0, 73.1, 79.1, 110.9, 112.2, 127.5, 127.6, 128.3, 130.6, 137.9, 147.3, 148.6, 155.3; MS (EI) m/z (rel intensity) 401 (M⁺, 4), 204 (7), 250 (5), 194 (13), 180 (6), 151 (34), 133 (6), 91 (88), 57 (100). Anal. Calcd for C₂₃H₃₁NO₅: C, 68.80; H, 7.78; N, 3.48. Found: C, 68.80; H, 7.82; N, 3.42. ee > 99%
(S)-(−)-3-Benzyl-4-(3,4-dimethoxyphenylmethyl)-oxazolidin-2-one (6): [α]$_D^{20}$ -13 (2.12, CH$_2$Cl$_2$); IR (KBr) 1749, 1515 cm$^{-1}$; $^1$H NMR (CDCl$_3$) 2.59 (dd, $J = 13.5$, 8.7 Hz, 1H), 3.02 (dd, $J = 13.5$, 5.0 Hz, 1H), 3.78-3.81 (m, 1H)*, 3.79 (s, 3H)*; 3.84 (s, 3H)*, 4.00 (dd, $J = 8.5$, 5.9 Hz, 1H)*, 4.09 (d, $J = 15$ Hz, 1H)*, 4.17 (d, $J = 8.5$ Hz, 1H), 4.85 (d, $J = 15$ Hz, 1H), 6.47 (d, $J = 1.6$ Hz, 1H), 6.58 (dd, $J = 8.3$, 1.6 Hz, 1H), 6.77 (d, $J = 8.3$ Hz, 1H), 7.23-7.39 (m, 5H) (*designates partially overlapped signals); $^{13}$C NMR (CDCl$_3$) 38.0, 46.3, 55.3, 55.7, 55.8, 66.9, 111.2, 111.7, 120.9, 127.8, 127.9, 128.1, 128.7, 135.8, 148.0, 149.0, 158.3; MS (EI) m/z (rel intensity) 327 (M$^+$, 18), 176 (40), 151 (30), 107 (6), 91 (100), 65 (10). Anal. Calcd for C$_{19}$H$_{21}$NO$_4$: C, 69.71; H, 6.46; N, 4.28. Found: C, 69.46; H, 6.58; N, 3.98.

(S)-(–)-[1-(Methoxymethyl)-2-(3,4-dimethoxyphenyl)ethyl]carbamic acid tert-butyl ester (5c). Phenylalanilol 4 (0.70 g, 2.2 mmol) was added over a suspension of KOH (0.14 g, 2.5 mmol) in DMSO (10 mL) at rt. After 5 minutes MeI (0.15 mL, 2.4 mmol) was added and the suspension was stirred for 3 h. Water was added and the aqueous phase was extracted with CH$_2$Cl$_2$(3 × 20 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Flash column chromatography (silicagel, 70 % hexane/ethyl acetate) yielded 5c as a yellow oil (230 mg, 57%), together with dimethylated product 7 (150 mg, 35%), and unreacted starting material. Data for 5c: [α]$_D^{20}$ -73 (1.68, CH$_2$Cl$_2$); IR (KBr) 3357, 1706, 1513 cm$^{-1}$; $^1$H NMR (CDCl$_3$) 1.35 (s, 9H), 2.63-2.80 (m, 2H), 3.20 (d, $J = 4.0$ Hz, 2H), 3.26 (s, 3H), 3.77 (s, 3H)*, 3.79 (s, 3H)*, 3.77-3.80 (m, 1H)*, 4.87 (d, $J = 7.9$ Hz, 1H), 6.65-6.74 (m, 3H) (*designates partially overlapped signals); $^{13}$C NMR (CDCl$_3$) 28.2, 37.1, 51.3, 55.6, 55.7, 58.8, 72.2, 79.1, 110.9, 112.2, 120.8, 130.6, 147.3, 148.6, 155.3; MS (EI) m/z (rel intensity) 325 (M$^+$, 13), 269 (9), 252 (8), 208 (47), 174 (8), 151 (47), 118 (37), 74 (100), 57 (72). Anal. Calcd for C$_{17}$H$_{27}$NO$_5$: C, 62.75; H, 8.36; N, 4.30. Found: C, 62.41; H, 8.35; N, 4.12. ee > 99% (Chiralcel OD, hexane:2-propanol 95:5, 0.8 mL/min, t$_r$ (S) = 9.4 min > 99%, t$_r$ (R) = 10.3 min < 1%.

(S)-(−)-[1-(Methoxymethyl)-2-(3,4-dimethoxyphenyl)ethyl]-N-methyl carbamic acid tert-butyl ester (7): IR (KBr) 1689, 1515 cm$^{-1}$; $^1$H NMR (CDCl$_3$) 1.24 (s, 9H, one rotamer), 1.32 (s, 9H, other
rotamer), 2.61 (s, 3H one rotamer)*, 2.69 (s, 3H other rotamer)*, 2.60-2.70 (m, 2H both rotamers)*, 3.19-3.33 (m, 2H both rotamers)*, 3.25 (s, 3H one rotamer)*, 3.26 (s, 3H other rotamer)*, 3.41 (dd, $J = 10.0, 7.0, \text{Hz}$, 1H both rotamers), 3.76 (s, 3H both rotamers), 3.78 (s, 3H both rotamers), 4.20 (m, 1H one rotamer), 4.43 (m, 1H other rotamer), 6.60-6.72 (m, 3H both rotamers) (*designates partially overlapped signals); $^{13}$C NMR (CDCl$_3$) 28.0 (one rotamer), 28.1 (other rotamer), 34.3 (one rotamer), 34.7 (other rotamer), 55.1, 55.5, 55.6, 55.4 (both rotamers), 72.7 (one rotamer), 72.8(other rotamer), 79.0 (both rotamers), 110.7 (one rotamer), 110.9 (other rotamer), 111.7 (one rotamer), 111.8 (other rotamer), 120.7 (both rotamers), 130.6 (one rotamer), 130.8 (other rotamer), 147.1 (one rotamer), 147.2 (one rotamer) 148.4(other rotamer), 148.5(other rotamer), 155.5 (one rotamer), 155.6(other rotamer); MS (EI) m/z (rel intensity) 325 (M$^+$, 13), 269 (9), 252 (8), 208 (47), 174 (8), 151 (47), 118 (37), 74 (100), 57 (72).

Synthesis of amines 8a-c. General procedure. TFA (6 mL) was added over a solution of 5a-c (1 mmol) in dry CH$_2$Cl$_2$ (15 mL), and the reaction mixture was stirred at rt for 1 h. The reaction was quenched with saturated NaHCO$_3$ (10 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. The amines 8a-c were obtained as yellow oils that were purified by flash column chromatography.

(S)-(−)-1-(tert-Butyldiphenylsilyloxymethyl)-2-(3,4-dimethoxyphenyl)ethylamine (8a). According to the general procedure, 5a (300 mg, 0.54 mmol) was treated with TFA (3 mL). After work-up and column chromatography (silicagel, 5 % ethyl acetate/methanol), amine 8a was obtained as a yellow oil (212 mg, 86%): $[\alpha]_D^{20}$ -38 (0.042, CH$_2$Cl$_2$); IR (KBr) 3425 cm$^{-1}$; $^1$H NMR (CDCl$_3$) 1.19 (bs, 9H), 1.72 (bs, 2H), 2.48 (dd, $J = 13.4, 8.3$ Hz, 1H), 2.74 (dd, $J = 13.4, 5.1$ Hz, 1H), 3.08-3.18 (m, 1H), 3.54 (dd, $J = 10.0, 6.3$ Hz, 1H), 3.64 (dd, $J = 10.0, 4.5$ Hz, 1H), 3.82 (s, 3H), 3.85 (s, 3H), 6.69-6.79 (m, 3H), 7.34-7.46 (m, 6H), 7.65-7.69 (m, 4H); $^{13}$C NMR (CDCl$_3$) 19.2, 26.8, 39.7, 54.3, 55.7, 55.8, 68.1, 111.0,
112.1, 121.0, 127.6, 129.6, 131.3, 133.3, 135.5, 147.3, 148.6; MS (EI) m/z (rel intensity) 450 (M^+1, 3), 392 (24), 298 (100), 220 (74), 198 (66), 178 (89), 151 (97), 135 (51), 107 (22), 74 (33), 57 (24).

(S)-(−)-1-(Benzyloxymethyl)-2-(3,4-dimethoxyphenyl)ethylamine (8b). According to the general procedure, 5b (400 mg, 1.29 mmol) was treated with TFA (3 mL). After work-up and column chromatography (silicagel, 5 % ethyl acetate/methanol), amine 8b was obtained as a yellow oil (310 mg, 80%): [α]_D^{20} -28 (0.062, CH_2Cl_2); IR (CHCl_3) 3300 cm^{-1}; ^1H NMR (CDCl_3) 1.73 (bs, 2H), 2.50 (dd, J = 13.5, 7.9 Hz, 1H), 2.75 (dd, J = 13.5, 5.1 Hz, 1H), 3.24-3.29 (m, 1H), 3.29-3.37 (m, 1H), 3.47 (dd, J = 4.53 (s, 2H), 6.71-6.81 (m, 3H), 7.28-7.35 (m, 5H); ^13C NMR (CDCl_3) 40.0, 52.5, 55.7, 55.8, 73.3, 74.8, 111.1, 112.2, 121.1, 127.6, 128.3, 131.1, 138.1, 147.3, 148.7; MS (EI) m/z (rel intensity) 302 (M^+1, 1), 204 (1), 180 (15), 150 (66), 91 (100), 77 (3), 65 (5).

(S)-(−)-2-(3,4-Dimethoxyphenyl)-1-(methoxymethyl)ethylamine (8c). According to the general procedure, 5b (124 mg, 0.38 mmol) was treated with TFA (1.5 mL). After work-up and column chromatography (silicagel, 5 % ethyl acetate/methanol), amine 8b was obtained as a yellow oil (72 mg, 84%): [α]_D^{20} -15 (1.8, CH_2Cl_2); IR (CHCl_3) 3650 cm^{-1}; ^1H NMR (CDCl_3) 1.83 (bs, 2H), 2.45 (dd, J = 13.5, 7.5 Hz, 1H), 2.69 (dd, J = 13.5, 4.6 Hz, 1H), 3.10-3.21 (m, 2H), 3.25-3.34 (m, 1H)*, 3.33 (s, 3H)*, 3.82 (s, 3H), 3.82 (s, 3H), 6.68-6.78 (m, 3H) (*designates partially overlapped signals); ^13C NMR (CDCl_3) 29.6, 52.2, 55.6, 55.8, 58.8, 76.5, 111.0, 112.1, 121.0, 131.0, 147.3, 148.7; MS (EI) m/z (rel intensity) 225 (M^+, 1), 180 (6), 152 (35), 99 (4), 88 (7), 74 (100), 57 (7).

Synthesis of succinimides 9a-c. General procedure. Succinic anhydride (100 mg, 1 mmol) was added over a solution of amines 8a-c (1 mmol) in dry Et_2O (5 mL), and the mixture was refluxed for 16 h. The amic acid obtained as a white solid was filtered and washed with pentane. Without further purification, the amic acid was treated with anhydrous NaOAc (25 mg, 0.3 mmol) in Ac_2O (0.25 mL, 2.5 mmol), and the resulting mixture was stirred at 85 °C for 1 h. Water (5 mL) was added, and the aqueous phase was extracted with AcOEt (3 × 15 mL). The combined organic extracts were washed with brine (3
× 10 mL), dried (Na₂SO₄) and concentrated in vacuo. The succinimides 8a-c were purified by flash column chromatography.

(S)-(−)-1-[1-(tert-Butyldiphenylsilyloxy)methyl]-2-(3,4-dimethoxyphenyl)ethyl|pyrrolidine-2,5-dione (9a). According to the general procedure, amine 8a (4.45 g, 9.9 mmol) was treated with succinic anhydride (1.78 g, 17.8 mmol), NaOAc (300 mg, 3.6 mmol) and Ac₂O (2.4 mL, 25 mmol). Flash column chromatography (silicagel, 50% hexane/ethyl acetate) afforded 9a, that was crystallized from pentane (3.9 g, 75%): [α]D²⁰ -23 (0.24, CH₂Cl₂); mp (n-pentane) 100-102 °C; IR (CHCl₃) 1774, 1704 cm⁻¹; ¹H NMR (CDCl₃) 0.09 (s, 9H), 2.43 (s, 4H), 2.89 (dd, J = 13.9, 6.1 Hz, 1H), 3.08 (dd, J = 13.9, 10.7 Hz, 1H), 3.82 (s, 3H)*, 3.83 (s, 3H)*, 3.79-3.95 (m, 1H)*, 4.20 (t, J = 9.7 Hz, 1H), 4.56-4.69 (m, 1H), 6.60-6.63 (m, 2H), 6.70 (d, J = 8.7 Hz, 1H), 7.35-7.47 (m, 6H), 7.58-7.64 (m, 4H) (*designates partially overlapped signals); ¹³C NMR (CDCl₃) 18.4, 26.1, 27.8, 32.4, 54.4, 55.1, 55.2, 61.8, 110.4, 111.0, 120.2, 127.1, 129.1, 129.2, 132.4, 132.6, 134.8, 134.9, 146.8, 148.0, 176.7; MS (EI) m/z (rel intensity) 531 (M⁺+1, 1), 506 (2), 474 (100), 432 (3), 396 (13), 375 (5), 319 (22), 280 (34), 199 (7), 177 (50), 151 (54), 107 (10), 91 (9), 77 (9), 57 (14). Anal. Calcd for C₃₁H₃₇NO₅Si: C, 70.02; H, 7.01; N, 2.63. Found: C, 69.45; H, 6.99; N, 2.09. ee > 99% (Chiralcel OD, hexane:2-propanol 93:7, 1 mL/min, t₁ (S) = 16.5 min > 99%, t₉ (R) = 15.0 min < 1%.

(S)-(−)-1-[1-(Benzyloxymethyl)-2-(3,4-dimethoxyphenyl)ethyl|pyrrolidine-2,5-dione (9b). According to the general procedure, amine 8b (267 mg, 0.88 mmol) was treated with succinic anhydride (88 mg, 0.88 mmol), NaOAc (43 mg, 0.53 mmol) and Ac₂O (0.33 mL, 3.5 mmol). Flash column chromatography (silicagel, 50% hexane/ethyl acetate) afforded 9b, that was crystallized from pentane (280 mg, 83%): [α]D²⁰ -31 (1.2, CH₂Cl₂); mp (n-pentane) 100; IR (CHCl₃) 1772, 1700 cm⁻¹; ¹H NMR (CDCl₃) 2.39 (s, 4H), 2.93 (dd, J = 14.0, 6.3 Hz, 1H), 3.08 (dd, J = 14.0, 10.3 Hz, 1H), 3.62 (dd, J = 9.9, 5.1 Hz, 1H), 3.77 (s, 3H), 3.78 (s, 3H), 3.99 (t, J = 9.9 Hz, 1H), 4.40 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.63-4.7 (m, 1H), 6.61-6.71 (m, 3H), 7.19-7.27 (m, 5H); ¹³C NMR (CDCl₃) 27.7, 33.4, 52.5, 55.7, 68.5, 72.7, 110.8, 111.6, 120.8, 127.5, 127.6, 128.3, 129.4, 137.8, 147.4, 148.5, 177.3; MS
(S)-(–)-1-[2-(3,4-Dimethoxyphenyl)-1-(methoxymethyl)ethyl]pyrrolidine-2,5-dione (9c).

According to the general procedure, amine 8c (302 mg, 1.34 mmol) was treated with succinic anhydride (243 mg, 2.4 mmol), NaOAc (66 mg, 0.8 mmol) and Ac₂O (0.50 mL, 5.3 mmol). Flash column chromatography (silicagel, ethyl acetate) afforded 9c (240 mg, 58%): [α]D₂₀ -23 (0.24, CH₂Cl₂); IR (CHCl₃) 1700 cm⁻¹; ¹H NMR (CDCl₃) 2.49 (s, 4H), 2.95 (dd, J = 13.9, 6.3 Hz, 1H), 3.10 (dd, J = 13.9, 10.7 Hz, 1H), 3.29 (s, 3H), 3.48 (dd, J = 9.9, 5.1 Hz, 1H), 3.82 (s, 6H), 3.97 (t, J = 9.9 Hz, 1H), 4.58-4.70 (m, 1H), 6.65-6.74 (m, 3H); ¹³C NMR (CDCl₃) 27.6, 33.2, 52.1, 55.5, 58.4, 70.6, 110.7, 111.4, 120.2, 129.2, 147.3, 148.5, 177.2; MS (EI) m/z (rel intensity) 307 (M⁺, 12), 244 (1), 208 (100), 193 (3), 177 (32), 165 (2), 151 (24), 91 (2). Anal. Calcd for C₁₆H₂₅NO₅: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.34; H, 6.85; N, 4.20. ee > 99% (Chiralcel OD, hexane:2-propanol 92:8, 1 mL/min, tᵣ (S) = 26.5 min > 99%, tᵣ (R) = 29.8 min < 1%.

(S)-(–)-1-[2-(3,4-Dimethoxyphenyl)-1-(hydroxymethyl)ethyl]pyrrolidine-2,5-dione (9d). TBAF (2.15 mL, 2.15 mmol) was added over a solution of succinimide 9a (570 mg, 1.07 mmol) in dry THF (20 mL) at 0 °C. The resulting solution was stirred for 10 minutes, allowed to reach rt, and stirred for 3 h. The solvent was evaporated in vacuo and the resulting crude mixture was purified by flash column chromatography (silicagel, ethyl acetate) to afford succinimide 9d, that was crystallized from hexane/ethyl acetate (160 mg, 50%): [α]D₂₀ -98 (0.14, CH₂Cl₂); mp (hexane/AcOEt 50%) 118 °C; IR (CHCl₃) 3447, 1700 cm⁻¹; ¹H NMR (CDCl₃) 2.53 (s, 4H), 3.00-3.05 (m, 2H), 3.10 (bs, 1H), 3.81 (s, 3H), 3.82 (s, 3H), 3.71-3.77 (m, 1H), 3.94 (m, 1H), 4.42-4.52 (m, 1H), 6.66-6.75 (m, 3H); ¹³C NMR (CDCl₃) 27.9, 33.1, 55.2, 55.5, 55.7, 62.0, 110.9, 111.8, 120.9, 129.4, 147.5, 148.6, 178.1; MS (EI) m/z (rel intensity) 294 (M⁺+1, 1), 293 (M⁺, 18), 195 (12), 194 (100), 166 (12), 151 (52), 138 (15), 107 (3), 91 (2), 55 (4). Anal. Calcd for C₁₅H₁₉NO₅: C, 61.42; H, 6.53; N, 4.78. Found: C, 60.54; H, 6.52; N, 4.62. ee
> 99% (Chiralcel OD, hexane:2-propanol 90:10, 1 mL/min, tᵣ (S) = 56.2 min > 99%, tᵣ (R) = 67.7 min < 1%.

References