A Versatile Chemo-Enzymatic Route to Enantiomerically Pure β -Branched- α -Amino Acids.

Geoffrey J. Roff^a, Richard C. Lloyd^b and Nicholas J. Turner^{*a}

^a*School of Chemistry, University of Edinburgh, King's Buildings, West Mains Road, Edinburgh, EH9 3JJ, UK*

^b*Dowpharma, Chirotech Technology Ltd., a subsidiary of The Dow Chemical Company, Unit 321 Cambridge Science Park, Milton Road, Cambridge, CB4 0WG, UK*

SUPPORTING INFORMATION

IR absorption spectra were recorded on a Jasco-FT/IR-410 Spectrophotometer using standard techniques. ¹H and ¹³C-NMR spectra were recorded on a Varian Gemini or Bruker AC250 spectrometer. Chemical shifts are reported in ppm. Mass spectra were recorded on a Micromass Platform-2 under electrospray conditions or Magnetic Sector MS250 machine for FAB-MS.

Analytical normal phase HPLC was performed on a Chiracel OD-H column eluting with 1ml/min 5% IPA in Hexane at 210nm at 10°C. Reverse phase HPLC was performed on a Chirobiotic T column eluting with 0.7ml/min 40% ethanol in Water at 210nm. Peak intensities are reported to an accuracy of 0.1%.

Optical rotation was measured on an AA1000 polarimeter from Optical Activity Ltd (measurements made at the sodium D-line). Concentrations are given in g/100ml.

Column chromatography was carried out using Fisher silica 60A, particle size 35-70 micron).

Melting points were carried out on a Gallenkamp melting point apparatus with no corrections.

All solvents and reagents are standard laboratory grade and were obtained from commercial sources. The *Trigonopsis variabilis* D-amino acid oxidase was obtained from Sandoz. The porcine kidney D-amino acid oxidase and snake venom L-amino acid oxidase were obtained from Sigma.

1) Synthesis of (Z)-2-Acetylamino-3-iodo-but-2-enoic acid methyl ester **5**

NIS (12.9g, 0.057mol) was added to a stirring solution of methyl 2-(N-acetylamino)-Z-butenoate **3** (7.50g, 0.048mol) in 2% TFA in CH₂Cl₂ (250ml with 5ml TFA). The mixture was stirred at room temperature overnight. The mixture was cooled in an ice bath before triethylamine (20ml) was added slowly. The mixture was allowed to stir for a further hour. The mixture was concentrated and taken up in CH₂Cl₂, washed with 1M KHSO₄, water and brine before concentrating and running down a column of silica (CH₂Cl₂/ethyl acetate 1:1) to obtain **5** as a yellow/brown solid (5.41g, 40%).

$\nu_{\max}$ (KBr) 1518 (NH bend), 1659 (C=O amide), 1717 (C=O ester), 3249 cm⁻¹ (NH stretch); δ_{H} (250MHz, CDCl₃) 2.15 (3H, s, CH₃), 2.80 (3H, s, Ac), 3.84 (3H, s, CO₂CH₃), 6.91 (1H, s br., NH); δ_{C} (63MHz, CDCl₃) 22.7 (CH₃), 28.8 (Ac), 52.5 (CO₂CH₃), 102.1, 131.4, 161.4, 168.1 (C); m/z (FAB) 284 (MH⁺); found (FAB) 283.97830 (MH⁺), C₇H₁₁INO₃ requires 283.97837.

2) General procedure for Suzuki couplings

A mixture of vinyl iodide **5**, boronic acid, palladium acetate and sodium carbonate in ethanol was heated at 55°C for 4 hours.

The mixture was concentrated and taken up in CH₂Cl₂/water (1:1). The CH₂Cl₂ layer was further washed once with water, once with brine and dried over MgSO₄ before concentrating to the crude product. Column chromatography (CH₂Cl₂/ethyl acetate 1:1) gave the pure product.

2.1) Synthesis of (Z)-2-Acetylamino-3-phenyl-but-2-enoic acid methyl ester **6a**

The general procedure was followed using vinyl iodide **5** (400mg, 1.41mmol), phenylboronic acid (259mg, 2.12mmol), palladium acetate (32mg, 0.141mmol), sodium carbonate (300mg, 2.83mmol) and ethanol (15ml).

Wet flash column chromatography (CH₂Cl₂/ethyl acetate 1:1) gave **6a** as a white solid (265mg, 81%).

$\nu_{\max}$ (nujol) 1532 (N-H bend), 1657 (C=O amide), 1720 (C=O ester), 3177cm⁻¹ (N-H stretch); δ_{H} (200MHz, CDCl₃) 1.85 (3H, s, CH₃), 2.24 (3H, s, Ac), 3.80 (3H, s, CO₂CH₃), 6.56 (1H, s br., NH), 7.32-7.41 (5H, m, ArH); δ_{C} (63MHz, CDCl₃) 20.5 (CH₃), 22.4 (Ac), 52.0 (CO₂CH₃), 127.2, 128.0, 128.7 (C_{Ar}), 123.5, 137.5, 139.8, 165.5, 168.6 (C); m/z (FAB) 234 (MH⁺); found (FAB) (MH⁺) 234.11316; C₁₃H₁₆NO₃ requires 234.11302; TLC 0.27 (CH₂Cl₂/ ethyl acetate 1:1).

2.2) Synthesis of (Z)-2-Acetylamino-3-(4-fluorophenyl)but-2-enoic acid methyl ester **6b**

The general procedure was followed using vinyl iodide **5** (500mg, 1.77mmol), 4-fluorophenylboronic acid (371mg, 2.65mmol), palladium acetate (40mg, 0.177mmol), sodium carbonate (375mg, 3.53mmol) and ethanol (15ml).

Wet flash column chromatography (CH₂Cl₂/ethyl acetate 1:1) gave **6b** as a white solid (341mg, 77%).

$\nu_{\max}$ (KBr) 1509 (NH bend), 1654 (C=O amide), 1723 (C=O ester), 3280 cm⁻¹ (NH stretch); δ_{H} (250MHz, CDCl₃) 2.09 (3H, s, CH₃), 2.45 (3H, s, Ac), 4.02 (3H, s, CO₂CH₃), 6.70 (1H, s br., NH), 7.23-7.46 (4H, m, ArH); δ_{C} (63MHz, CDCl₃) 21.2 (CH₃), 23.0 (Ac), 52.6 (CO₂CH₃), 116.1, 116.4, 129.6, 129.7 (C_{Ar}), 124.2, 236.3, 137.9, 164.7, 165.9, 169.1 (C); m/z (FAB) 252 (MH⁺); found (FAB) 252.10362 (MH⁺), C₁₃H₁₅FNO₃ requires 252.10360.

2.3) Synthesis of (Z)-2-Acetylamino-3-(4-trifluoromethylphenyl)but-2-enoic acid methyl ester **6c**

The general procedure was followed using vinyl iodide **5** (400mg, 1.41mmol), 4-trifluoromethylphenylboronic acid (403mg, 2.12mmol), palladium acetate (32mg, 0.141mmol), sodium carbonate (300mg, 2.83mmol) and ethanol (15ml).

Wet flash column chromatography (CH₂Cl₂/ethyl acetate 1:1) gave **6c** as a white solid (356mg, 84%).

$\nu_{\max}$ (KBr) 1508 (NH bend), 1682 (C=O amide), 1709 (C=O ester), 3306 cm⁻¹ (NH stretch); δ_{H} (250MHz, CDCl₃) 1.96 (3H, s, CH₃), 2.36 (3H, s, Ac), 3.90 (3H, s, CO₂CH₃), 6.57 (1H, s br., NH), 7.33-7.73 (4H, m, ArH); δ_{C} (63MHz, CDCl₃) 20.4 (CH₃), 22.5 (Ac), 52.2 (CO₂CH₃), 125.7, 127.7 (C_{Ar}), 124.2, 137.4, 143.8, 165.1, 168.7 (C); m/z (FAB) 302 (MH⁺); found (FAB) 302.10071 (MH⁺), C₁₄H₁₅F₃NO₃ requires 302.10040.

2.4) Synthesis of (Z)-2-Acetylamino-3-naphthalen-2-yl-but-2-enoic acid methyl ester **6d**

The general procedure was followed using vinyl iodide **5** (800mg, 2.82mmol), 2-naphthaleneboronic acid (729mg, 4.24mmol), palladium acetate (64mg, 0.242mmol), sodium carbonate (600mg, 5.66mmol) and ethanol (25ml).

Wet flash column chromatography (CH₂Cl₂/ethyl acetate 1:1) gave **6d** as a pale yellow solid (575mg, 72%).

$\nu_{\max}$ (KBr) 1509 (NH bend), 1650 (C=O amide), 1720 (C=O ester), 3298 cm⁻¹ (NH stretch); δ_{H} (250MHz, CDCl₃) 1.78 (3H, s, CH₃), 2.28 (3H, s, Ac), 3.77 (3H, s, CO₂CH₃), 6.52 (1H, s br., NH), 7.28-7.80 (7H, m, ArH); δ_{C} (63MHz, CDCl₃)

20.5 (CH₃), 22.4 (Ac), 52.1 (CO₂CH₃), 125.2, 126.4, 126.5, 127.6, 127.9, 128.5 (C_{Ar}), 123.9, 132.7, 133.1, 137.2, 137.3, 165.5, 168.6 (C); *m/z* (FAB) 284 (MH⁺); found (FAB) 284.12934 (MH⁺), C₁₇H₁₈NO₃ requires 284.12867.

2.5 Synthesis of (Z)-2-Acetylamino-3- (3,5-dimethylphenyl)but-2-enoic acid methyl ester **6e**

The general procedure was followed using vinyl iodide **5** (400mg, 1.41mmol), 3,5-dimethylphenylboronic acid (318mg, 2.12mmol), palladium acetate (32mg, 0.141mmol), sodium carbonate (300mg, 2.83mmol) and ethanol (15ml).

Wet flash column chromatography (CH₂Cl₂/ethyl acetate 1:1) gave **6e** as a white solid (301mg, 82%).

$\nu_{\max}$ (KBr) 1527 (NH bend), 1648 (C=O amide), 1728 (C=O ester), 3238 cm⁻¹ (NH stretch); δ_{H} (250MHz, CDCl₃) 2.08 (3H, s, CH₃), 2.40 (3H, s, Ac), 2.50 (6H, s, (CH₃)₂), 6.71 (1H, s br., NH), 7.14-7.27 (3H, m, ArH); δ_{C} (63MHz, CDCl₃) 20.4 (CH₃), 21.1 ((CH₃)₂), 22.5 (Ac), 52.0 (CO₂CH₃), 124.8, 129.7 (C_{Ar}), 123.4, 136.9, 138.4, 139.6, 165.5, 168.4 (C); *m/z* (FAB) 262 (MH⁺); (FAB) Found 262.14480 (MH⁺), C₁₅H₂₀NO₃ requires 267.14432.

2.6 Synthesis of (Z)-2-Acetylamino-3- (4-methoxyphenyl)but-2-enoic acid methyl ester **6f**

The general procedure was followed using vinyl iodide **5** (500mg, 1.77mmol), 4-methoxyphenylboronic acid (403mg, 2.65mmol), palladium acetate (40mg, 0.177mmol), sodium carbonate (375mg, 3.53mmol) and ethanol (15ml).

Wet flash column chromatography (CH₂Cl₂/ethyl acetate 1:1) gave **6f** a white solid (338mg, 73%).

$\nu_{\max}$ (KBr) 1519 (NH bend), 1637 (C=O amide), 1720 (C=O ester), 3244 cm⁻¹ (NH stretch); δ_{H} (200MHz, CDCl₃) 1.99 (3H, s, CH₃), 2.32 (3H, s, Ac), 3.91 (3H, s, CO₂CH₃), 6.55 (1H, s br., NH), 6.97-7.34 (4H, m, ArH); δ_{C} (63MHz, CDCl₃) 20.5 (CH₃), 22.5 (Ac), 52.0 (CO₂CH₃), 55.1 (OCH₃), 114.0, 128.7 (C_{Ar}), 123.2, 131.7, 137.4, 159.3, 165.7, 168.6 (C); *m/z* (FAB) 264 (MH⁺); found (FAB) 264.12316 (MH⁺), C₁₄H₁₈NO₄ requires 264.12358.

3) General procedure for asymmetric hydrogenations

A mixture of dihydroamino acid **Z-6** and either [Rh(*R,R*)-Et-DuPhos(COD)]BF₄ or [Rh(*S,S*)-Et-DuPhos(COD)]BF₄ (1 mol%) were stirred in degassed methanol under 100psi of hydrogen. The mixture was concentrated and run down a short column (EtOAc) of silica to yield the pure product.

3.1 Synthesis of (2*R*,3*S*)-2-Acetylamino-3-phenyl-butyric acid methyl ester (2*R*,3*S*)-**7a**

The general procedure was followed using alkene **6a** (300mg, 1.29mmol), [Rh(*R,R*)-Et-DuPhos(COD)]BF₄ (8.4mg, 0.013mmol) and methanol (5ml) at 100psi for 72 hours.

Work up yielded **(2*R*,3*S*)-7a** as a white solid (300mg, 99%).

M.p. 82-86°C; $\nu_{\max}$ (Film) 1541 (NH bend), 1657 (C=O amide), 1743 (C=O ester), 3289 cm⁻¹ (NH stretch); (200MHz, CDCl₃) 1.47 (3H, d $J=7.4$ Hz, CH₃), 2.06 (3H, s, COCH₃), 3.25 (1H, quin. $J=7.0$ Hz, CH), 3.62 (3H, s, CO₂CH₃), 4.87 (1H, dd $J=6.6$ &9.0Hz, CH), 6.20 (1H, d br. $J=8.6$ Hz, NH), 7.21-7.41 (5H, m, ArH); m/z (ES⁺) 236 (MH⁺); $[\alpha]_D^{21}$ -47.4° (c=0.27, CHCl₃).

HPLC: Chiracel OD-H; R_t (min) 16.34 (99.3%), 20.22 (0.7%).

3.2) Synthesis of (2*R*,3*S*)-2-Acetylamino-3-(4-fluorophenyl)butyric acid methyl ester (**(2*R*,3*S*)-7b**)

The general procedure was followed using alkene **6b** (300mg, 1.20mmol), [Rh(*R,R*)-Et-DuPhos(COD)]BF₄ (7.9mg, 0.012mmol) and methanol (5ml) at 100psi for 72 hours.

Workup yielded **(2*R*,3*S*)-7b** as a pale yellow solid (300mg, 99%).

M.p. 92-95°C; $\nu_{\max}$ (KBr) 1512 (NH bend), 1652 (C=O amide), 1738 (C=O ester), 3316cm⁻¹ (NH stretch); δ_H (250MHz, CDCl₃) 1.28 (3H, d $J=7.2$ Hz, CH₃), 1.94 (3H, s, Ac), 3.14 (1H, quin. $J=7.1$ Hz, CH), 3.50 (3H, s, CO₂CH₃), 4.71 (1H, dd $J=6.7$ & 8.9Hz, CH), 6.00 (1H, d br. $J=8.8$ Hz, NH), 6.87-7.20 (4H, m, ArH); δ_C (63MHz, CDCl₃) 17.5 (CH₃), 23.5 (Ac), 42.4 (CH), 52.5 (CO₂CH₃), 57.9 (CH), 115.4, 115.8, 129.4, 129.5 (C_{Ar}), 137.2, 160.3, 164.2, 170.0, 172.3 (C); m/z (FAB) 254 (MH⁺); found (FAB) 254.11962 (MH⁺), C₁₃H₁₇FO₃ requires 254.11925.

HPLC: Chiracel OD-H; R_t (min) 17.49 (99.0%), 27.05 (0.1%).

3.3) Synthesis of (2*R*,3*S*)-2-Acetylamino-3-(4-trifluoromethylphenyl)butyric acid methyl ester (**(2*R*,3*S*)-7c**)

The general procedure was followed using alkene **6c** (300mg, 1.00mmol), (*R,R*)-EtDuPhos (6.6mg, 0.010mmol) and methanol (5ml) at 100psi for 72 hours.

Workup yielded **(2*R*,3*S*)-7c** as a white solid (300mg, 99%).

M.p. 75-77 °C; $\nu_{\max}$ (KBr) 1564 (NH bend), 1654 (C=O amide), 1741 (C=O ester), 3318cm⁻¹ (NH stretch); δ_H (250MHz, CDCl₃) 1.32 (3H, d $J=7.2$ Hz, CH₃), 1.94 (3H, s, Ac), 3.22 (1H, quin. $J=7.1$ Hz, CH), 3.51 (3H, s, CO₂CH₃), 4.78 (1H, dd $J=6.6$ & 8.8Hz, CH), 6.01 (1H, d br. $J=8.4$ Hz, NH), 7.20-7.50 (4H, m, ArH); δ_C (63MHz, CDCl₃) 16.7 (CH₃), 23.0 (Ac), 42.5 (CH), 52.1 (CO₂CH₃), 57.1 (CH), 125.2, 127.9 (C_{Ar}), 145.2, 169.6, 171.5 (C); m/z (FAB) 304 (MH⁺); found (FAB) 304.11621 (MH⁺), C₁₄H₁₇F₃NO₃ requires 304.11605; $[\alpha]_D^{21}$ -49.5° (c=0.63, CHCl₃).

HPLC: Chiracel OD-H; R_t (min) 16.05 (99.2%), 21.66 (0.8%).

3.4) Synthesis of (2*R*,3*S*)-2-Acetylamino-3-naphthalen-2-yl-butyric acid methyl ester (2*R*,3*S*)-7d

The general procedure was followed using alkene **6d** (300mg, 0.99mmol), [Rh(*R,R*)-Et-DuPhos(COD)]BF₄ (6.5mg, 0.010mmol) and methanol (5ml) at 100psi for 72 hours.

Workup yielded (**2*R*,3*S***)-**7d** as a pale yellow solid (300mg, 99%).

M.p. 65-69°C; $\nu_{\max}$ (KBr) 1544 (NH bend), 1639 (C=O amide), 1739 (C=O ester), 3267cm⁻¹ (NH stretch); δ_H (250MHz, CDCl₃) 1.40 (3H, d $J=7.2$ Hz, CH₃), 1.91 (3H, s, Ac), 3.28 (1H, quin. $J=7.1$ Hz, CH), 3.44 (3H, s, CO₂CH₃), 4.83 (1H, dd $J=6.9$ & 8.9Hz, CH), 6.01 (1H, d br. $J=8.6$ Hz, NH), 7.18-7.74 (7H, m, ArH); δ_C (63MHz, CDCl₃) 16.5 (CH₃), 22.4 (Ac), 42.2 (CH), 51.3 (CO₂CH₃), 56.9 (CH), 125.0, 125.1, 125.4, 125.7, 127.0, 127.4 (C_{Ar}), 131.9, 132.4, 138.0, 169.1, 171.4 (C); m/z (FAB) 286 (MH⁺); found (FAB) 286.14219 (MH⁺), C₁₇H₂₀NO₃ requires 286.14432; $[\alpha]_D^{21}$ -58.4° (c=0.69, CHCl₃).

HPLC: Chiracel OD-H; R_t (min) 21.08 (99.7%), 26.62 (0.3%).

3.5) Synthesis of (2*R*,3*S*)-2-Acetylamino-3-(3,5-dimethylphenyl)butyric acid methyl ester (2*R*,3*S*)-7e

The general procedure was followed using alkene **6e** (300mg, 1.14mmol), [Rh(*R,R*)-Et-DuPhos(COD)]BF₄ (7.6mg, 0.011mmol) and methanol (5ml) at 100psi for 72 hours.

Workup yielded (**2*R*,3*S***)-**7e** as a pale yellow solid (300mg, 99%).

M.p. 115-118°C; $\nu_{\max}$ (KBr) 1540 (NH bend), 1650 (C=O amide), 1739 (C=O ester), 3320 cm⁻¹ (NH stretch); δ_H (250MHz, CDCl₃) 1.29 (3H, d $J=7.2$ Hz, CH₃), 1.92 (3H, s, Ac), 2.17 (6H, s, (CH₃)₂), 3.03 (1H, quin. $J=7.1$ Hz, CH), 3.49 (3H, s, CO₂CH₃), 4.69 (1H, dd $J=6.8$ & 8.9Hz, CH), 6.00 (1H, s br. $J=8.8$ Hz, NH), 6.69-6.80 (3H, m, ArH); (63MHz, CDCl₃) 16.9 (CH₃), 21.2 ((CH₃)₂), 23.0 (Ac), 42.4 (CH), 51.7 (CO₂CH₃), 57.5 (CH), 125.3, 137.6 (C_{Ar}), 128.7, 140.8, 169.5, 171.9 (C); (FAB) 264 (MH⁺); found (FAB) 264.15971 (MH⁺), C₁₅H₂₂NO₃ requires 264.15997; $[\alpha]_D^{21}$ -75.7° (c=0.44, CHCl₃).

HPLC: Chiracel OD-H; R_t (min) 17.25 (99.8%), 19.65 (0.2%).

3.6 Synthesis of (2*R*,3*S*)-2-Acetylamino-3-(4-methoxyphenyl)butyric acid methyl ester (2*R*,3*S*)-7f

The general procedure was followed using alkene **6f** (300mg, 1.14mmol), [Rh(*R,R*)-Et-DuPhos(COD)]BF₄ (7.5mg, 0.011mmol) and methanol (5ml) at 100psi for 72 hours.

Workup yielded (2*R*,3*S*)-**7f** as a pale yellow solid (300mg, 99%).

M.p. 101-105°C; $\nu_{\max}$ (KBr) 1514 (NH bend), 1650 (C=O amide), 1738 (C=O ester), 3252 cm⁻¹ (NH stretch); δ_H (250MHz, CDCl₃) 1.29 (3H, d $J=7.2$ Hz, CH₃), 1.93 (3H, s, Ac), 3.07 (1H, quin. $J=7.1$ Hz, CH), 3.50 (3H, s, CO₂CH₃), 3.79 (3H, s, OCH₃), 4.69 (1H, dd $J=6.7$ & 8.8Hz, CH), 6.02 (1H, d br. $J=9.0$ Hz, NH), 6.69-7.03 (4H, m, ArH); δ_C (63MHz, CDCl₃) 16.6 (CH₃), 22.5 (Ac), 41.3 (CH), 51.3 (CO₂CH₃), 54.5 (OCH₃), 57.1 (CH), 113.1, 127.9 (C_{Ar}), 132.4, 158.0, 169.0, 171.4 (C); m/z (FAB) 266 (MH⁺); found (FAB) 266.13870 (MH⁺), C₁₄H₂₀NO₄ requires 266.13923; $[\alpha]_D^{21}$ -48.0° (c=0.32, CHCl₃).

HPLC: Chiracel OD-H; R_t (min) 21.36 (98.0%), 27.71 (2.0%).

3.7 Synthesis of (2*S*,3*R*)-2-Acetylamino-3-phenyl-butyrac acid methyl ester (2*S*,3*R*)-7a

The general procedure was followed using alkene **6a** (300mg, 1.29mmol), [Rh(*S,S*)-Et-DuPhos(COD)]BF₄ (8.4mg, 0.013mmol) and methanol (5ml) at 100psi for 72 hours.

Workup yielded (2*S*,3*R*)-**7a** as a white solid (300mg, 99%).

M.p. 81-84°C; $\nu_{\max}$ (Film) 1544 (NH bend), 1657 (C=O amide), 1744 (C=O ester), 3285 cm⁻¹ (NH stretch); δ_H (200MHz, CDCl₃) 1.47 (3H, d $J=7.4$ Hz, CH₃), 2.06 (3H, s, COCH₃), 3.25 (1H, quin. $J=7.0$ Hz, CH), 3.62 (3H, s, CO₂CH₃), 4.87 (1H, dd $J=6.6$ & 9.0Hz, CH), 6.20 (1H, d br. $J=8.6$ Hz, NH), 7.21-7.41 (5H, m, ArH); m/z (ES⁺) 236 (MH⁺); $[\alpha]_D^{21}$ +49.3° (c=0.14, CHCl₃).

HPLC: Chiracel OD-H; R_t (min) 15.25 (0.1%), 15.25 (99.9%).

3.8 Synthesis of (2*S*,3*R*)-2-Acetylamino-3-(4-fluorophenyl)butyric acid methyl ester (2*S*,3*R*)-7b

The general procedure was followed using alkene **6b** (300mg, 1.20mmol), (S,S)-EtDuPhos (7.9mg, 0.012mmol) and methanol (5ml) at 100psi for 72 hours.

Workup yielded **(2S,3R)-7b** as a pale yellow solid (300mg, 99%).

M.p. 92-94°C; $\nu_{\max}$ (KBr) 1511 (NH bend), 1651 (C=O amide), 1738 (C=O ester), 3316 cm^{-1} (NH stretch); δ_{H} (250MHz, CDCl_3) 1.28 (3H, d $J=7.2\text{Hz}$, CH_3), 1.94 (3H, s, Ac), 3.14 (1H, quin. $J=7.1\text{Hz}$, CH), 3.50 (3H, s, CO_2CH_3), 4.71 (1H, dd $J=6.7$ & 8.9Hz , CH), 6.00 (1H, d br. $J=8.8\text{Hz}$, NH) 6.87-7.20 (4H, m, ArH); δ_{C} (63MHz, CDCl_3) 17.5 (CH_3), 23.5 (Ac), 42.4 (CH), 52.5 (CO_2CH_3), 57.9 (CH), 115.4, 115.8, 129.4, 129.5 (C_{Ar}), 137.2, 160.3, 164.2, 170.0, 172.3 (C); m/z (FAB) 254 (MH^+); found (FAB) 254.11925 (MH^+), $\text{C}_{13}\text{H}_{17}\text{FNO}_3$ requires 254.11925.

HPLC: Chiracel OD-H; R_t (min) 26.08% (100%).

3.9) Synthesis of (2S,3R)-2-Acetylamino-3-(4-trifluoromethylphenyl)butyric acid methyl ester (2S,3R)-7c

The general procedure was followed using alkene **6c** (300mg, 1.00mmol), $[\text{Rh}(\text{S,S})\text{-Et-DuPhos}(\text{COD})]\text{BF}_4$ (6.6mg, 0.010mmol) and methanol (5ml) at 100psi for 72 hours.

Workup yielded **(2S,3R)-7c** as a white solid (300mg, 99%).

M.p. 73-75°C; $\nu_{\max}$ (KBr) 1538 (NH bend), 1653 (C=O amide), 1741 (C=O ester), 3317 cm^{-1} (NH stretch); δ_{H} (250MHz, CDCl_3) 1.32 (3H, d $J=7.2\text{Hz}$, CH_3), 1.94 (3H, s, Ac), 3.22 (1H, quin. $J=7.1\text{Hz}$, CH), 3.51 (3H, s, CO_2CH_3), 4.78 (1H, dd $J=6.6$ & 8.8Hz , CH), 6.01 (1H, d br. $J=8.4\text{Hz}$, NH), 7.20-7.50 (4H, m, ArH); δ_{C} (63MHz, CDCl_3) 16.7 (CH_3), 23.0 (Ac), 42.5 (CH), 52.1 (CO_2CH_3), 57.1 (CH), 125.2, 127.9 (C_{Ar}), 145.2, 169.6, 171.5 (C); m/z (FAB) 304 (MH^+); found (FAB) 304.11558 (MH^+), $\text{C}_{14}\text{H}_{17}\text{F}_3\text{NO}_3$ requires 304.11605; $[\alpha]_{\text{D}}^{21} +41.7^\circ$ ($c=0.79$, CHCl_3).

HPLC: Chiracel OD-H; R_t (min) 17.00 (0.9%), 20.37 (99.1%).

3.10) Synthesis of (2S,3R)-2-Acetylamino-3-naphthalen-2-yl-butylbutyric acid methyl ester (2S,3R)-7d

The general procedure was followed using alkene **6d** (300mg, 0.99mmol), [Rh(*S,S*)-Et-DuPhos(COD)]BF₄ (6.5mg, 0.010mmol) and methanol (5ml) at 100psi for 72 hours.

Workup yielded (**2*S*,3*R***)-**7d** as a pale yellow solid (300mg, 99%).

M.p. 70-72 °C; $\nu_{\max}$ (KBr) 1544 (NH bend), 1639 (C=O amide), 1738 (C=O ester), 3266cm⁻¹ (NH stretch); δ_{H} (250MHz, CDCl₃) 1.40 (3H, d $J=7.2$ Hz, CH₃), 1.91 (3H, s, Ac), 3.28 (1H, quin. $J=7.1$ Hz, CH), 3.44 (3H, s, CO₂CH₃), 4.83 (1H, dd $J=6.9$ & 8.9Hz, CH), 6.01 (1H, d br. $J=8.6$ Hz, NH), 7.18-7.74 (7H, m, ArH); δ_{C} (63MHz, CDCl₃) 16.5 (CH₃), 22.4 (Ac), 42.2 (CH), 51.3 (CO₂CH₃), 56.9 (CH), 125.0, 125.1, 125.4, 125.7, 127.0, 127.4 (C_{Ar}), 131.9, 132.4, 138.0, 169.1, 171.4 (C); m/z (FAB) 286 (MH⁺); found (FAB) 286.14475 (MH⁺), C₁₇H₂₀NO₃ requires 286.14432; $[\alpha]_{\text{D}}^{21} +50.5^{\circ}$ (c=0.83, CHCl₃).

HPLC: Chiracel OD-H; R_t (min) 22.09 (0.9%), 25.09 (99.1%).

3.11) Synthesis of (2*S*,3*R*)-2-Acetylamino-3-(3,5-dimethylphenyl)butyric acid methyl (2*S*,3*R*)-**7e**

The general procedure was followed using alkene **6e** (300mg, 1.14mmol), [Rh(*S,S*)-Et-DuPhos(COD)]BF₄ (7.6mg, 0.011mmol) and methanol (5ml) at 100psi for 72 hours.

Workup yielded (**2*S*,3*R***)-**7e** as a pale yellow solid (300mg, 99%).

M.p. 112-114°C; $\nu_{\max}$ (KBr) 1541 (NH bend), 1650 (C=O amide), 1740 (C=O ester), 3319cm⁻¹ (NH stretch); δ_{H} (250MHz, CDCl₃) 1.29 (3H, d $J=7.2$ Hz, CH₃), 1.92 (3H, s, Ac), 2.17 (6H, s, (CH₃)₂), 3.03 (1H, quin. $J=7.1$ Hz, CH), 3.49 (3H, s, CO₂CH₃), 4.69 (1H, dd $J=6.8$ & 8.9Hz, CH), 6.00 (1H, s br. $J=8.8$ Hz, NH), 6.69-6.80 (3H, m, ArH); δ_{C} (63MHz, CDCl₃) 16.9 (CH₃), 21.2 ((CH₃)₂), 23.0 (Ac), 42.4 (CH), 51.7 (CO₂CH₃), 57.5 (CH), 125.3, 137.6 (C_{Ar}), 128.7, 140.8, 169.5, 171.9 (C); (FAB) 264 (MH⁺); found (FAB) 264.15971 (MH⁺), C₁₅H₂₂NO₃ requires 264.15997; $[\alpha]_{\text{D}}^{21} +71.6^{\circ}$ (c=0.71, CHCl₃).

HPLC: Chiracel OD-H; R_t (min) 18.93 (100%).

3.12) Synthesis of (2*S*,3*R*)-2-Acetylamino-3-(4-methoxyphenyl)butyric acid methyl ester (2*S*,3*R*)-**7f**

The general procedure was followed using alkene **6f** (300mg, 1.14mmol), [Rh(*S,S*)-Et-DuPhos(COD)]BF₄ (7.5mg, 0.011mmol) and methanol (5ml) at 100psi for 72 hours.

Workup yielded (**2*S*,3*R***)-**7f** as a pale yellow solid (300mg, 99%).

M.p. 108-110°C; $\nu_{\max}$ (KBr) 1514 (NH bend), 1650 (C=O amide), 1738 (C=O ester), 3252 cm⁻¹ (NH stretch); δ_{H} (250MHz, CDCl₃) 1.29 (3H, d $J=7.2$ Hz, CH₃), 1.93 (3H, s, Ac), 3.07 (1H, quin. $J=7.1$ Hz, CH), 3.50 (3H, s, CO₂CH₃), 3.79 (3H, s, OCH₃), 4.69 (1H, dd $J=6.7$ & 8.8Hz, CH), 6.02 (1H, d br. $J=9.0$ Hz, NH), 6.69-7.03 (4H, m, ArH); δ_{C} (63MHz, CDCl₃) 16.6 (CH₃), 22.5 (Ac), 41.3 (CH), 51.3 (CO₂CH₃), 54.5 (OCH₃), 57.1 (CH), 113.1, 127.9 (C_{Ar}), 132.4, 158.0, 169.0, 171.4 (C); m/z (FAB) 266 (MH⁺); found (FAB) 266.13926 (MH⁺), C₁₄H₂₀NO₄ requires 266.13923; $[\alpha]_{\text{D}}^{21} +45.0^\circ$ (c=0.38, CHCl₃).

HPLC: Chiracel OD-H; R_t (min) 22.52 (3.3%), 26.34 (96.7%).

4) General procedure for hydrolysis

HCl (4N, 20ml) was added to a stirring solution of protected amino acid **7** (250mg) in acetone (2.5ml) and the mixture was heated under reflux for 3 hours. The mixture was treated with decolourising charcoal before filtering and concentrating. Trituration with acetone gave the pure product.

4.1) Synthesis of (2R,3S)-2-Amino-3-phenyl-butyric acid hydrochloride (2R,3S)-1a

The general procedure was followed using (2R,3S)-**7a** (250mg, 1.06mmol), acetone (2.5ml) and HCl (20ml) and yielded (2R,3S)-**1a** as a white solid (201mg, 88%).

M.p. 195-198°C; $\nu_{\max}$ (nujol) 1603 (amino acid II), 1731 (amino acid I), 1951 and 2535 (NH₃⁺ overtones and combinations), 2975 (OH), 3437 cm⁻¹ (NH₃⁺); δ_{H} (250MHz, D₂O) 1.29 (3H, d $J=7.3$ Hz, CH₃), 3.80 (1H, m, $J=5.9$ Hz, CH), 4.70 (1H, d $J=5.7$ Hz, CH), 7.16-7.40 (5H, m, ArH); δ_{C} (63MHz, D₂O) 15.1 (CH₃), 40.1 (CH), 59.2 (CH), 128.2, 128.5, 129.6 (C_{Ar}), 139.5, 171.6 (C); m/z (FAB) 180 (MH⁺); found (FAB) 180.10245 (MH⁺), C₁₀H₁₄NO₂ requires 180.10245; $[\alpha]_{\text{D}}^{22} -5.0^\circ$ (c=0.50, H₂O).

HPLC: Chirobiotic T; R_t (min) 7.69 (0.2%), 9.55 (99.8%).

4.2) Synthesis of (2R,3S)-2-Amino-3-(4-fluorophenyl)butyric acid hydrochloride (2R,3S)-1b

The general procedure was followed using (2R,3S)-**7b** (253mg, 1.0mmol), acetone (2.5ml) and HCl (20.0ml) and yielded (2R,3S)-**1b** as a white solid (181mg, 78%).

M.p. 190-192°C; $\nu_{\max}$ (KBr) 1605 (amino acid II), 1732 (amino acid I), 2531 (NH₃⁺ overtones and combinations), 2992 (OH), 3448 cm⁻¹ (NH₃⁺); δ_{H} (200MHz, D₂O) 1.38 (3H, d $J=7.2$ Hz, CH₃), 3.49 (1H, quin. $J=6.2$ Hz, CH), 4.17 (1H, d $J=5.8$ Hz, CH), 7.05-7.34 (4H, m, ArH); δ_{C} (63MHz, D₂O) 15.5 (CH₃), 39.5 (CH), 59.2 (CH), 116.0, 116.4, 129.9, 130.1

(C_{Ar}), 135.3, 160.6, 164.5, 171.5 (C); *m/z* (FAB) 198 (MH⁺); found (FAB) 198.09337 (MH⁺), C₁₀H₁₃FNO₂ requires 198.09303; [α]_D²² -4.5° (c=1.00, H₂O).

HPLC: Chirobiotic T; R_t (min) 7.85 (0.3%), 9.21 (99.7%).

4.3 Synthesis of (2*R*,3*S*)-2-Amino-3-(4-trifluoromethylphenyl)butyric acid hydrochloride (2*R*,3*S*)-1c

The general procedure was followed using (2*R*,3*S*)-7c (250mg, 0.83mmol), acetone (2.5ml) and HCl (20.0ml) and ether trituration yielded (2*R*,3*S*)-1c as a white solid (168mg, 71%).

M.p. 183-186°C; *v*_{max} (KBr) 1623 (amino acid II), 1733 (amino acid I), 2998 (OH), 3443cm⁻¹ (NH₃⁺); δ_H (200MHz, D₂O) 1.36(3H, d *J*=6.8Hz, CH₃), 3.51(1H, quin. *J*=6.2Hz, CH), 4.07 (1H, d *J*=6.0Hz, CH), 7.41-7.67 (4H, m, ArH); δ_C (63MHz, D₂O) 15.3 (CH₃), 40.1 (CH), 58.9 (CH), 126.7, 128.8 (C_{Ar}), 143.9, 171.3 (C); *m/z* (FAB) 248 (MH⁺); found (FAB) 248.09024 (MH⁺), C₁₁H₁₃F₃NO₂ requires 248.08984; [α]_D²² -6.0° (c=1.00, H₂O).

HPLC: Chirobiotic T; R_t (min) 11.06 (100%).

4.4 Synthesis of (2*R*,3*S*)-2-Amino-3-naphthalen-2-yl-butyric acid hydrochloride (2*R*,3*S*)-1d

The general procedure was followed using (2*R*,3*S*)-7d (250mg, 0.88mmol), acetone (2.5ml) and HCl (20.0ml) and yielded (2*R*,3*S*)-1d as an off-white solid (158mg, 68%).

M.p. 200-203°C; *v*_{max} (KBr) 1588 (amino acid II), 1770 amino acid I), 1978 (NH₃⁺ overtones and combinations), 2981 (OH), 3419cm⁻¹ (NH₃⁺); δ_H (200MHz, D₂O) 1.46 (3H, d *J*=7.2Hz, CH₃), 3.64 (1H, quin. *J*=6.8Hz, CH), 4.22 (1H, d *J*=5.4Hz, CH), 7.41-7.91 (7H, m, ArH); *m/z* (FAB) 230 (MH⁺); found (FAB) 230.11857 (MH⁺), C₁₄H₁₆NO₂ requires 230.11810; [α]_D²² -10.0° (c=1.00, H₂O).

HPLC: Chirobiotic T; R_t (min) 17.12 (100%).

4.5 Synthesis of (2*R*,3*S*)-2-Amino-3-(3,5-dimethylphenyl)butyric acid hydrochloride (2*R*,3*S*)-1e

The general procedure was followed using **(2R,3S)-7e** (250mg, 0.95mmol), acetone (2.5ml) and HCl (20.0ml) and trituration with ether yielded **(2R,3S)-1e** as a white solid (205mg, 89%).

M.p. 183-186°C; $\nu_{\max}$ (KBr) 1607 (amino acid II), 1733 (amino acid I), 2975 (OH), 3435 cm^{-1} (NH_3^+); δ_{H} (200MHz, D_2O) 1.32 (3H, d $J=7.4\text{Hz}$, CH_3), 2.21 (6H, s, $(\text{CH}_3)_2$), 3.38 (1H, quin. $J=6.0\text{Hz}$, CH), 4.03 (1H, d $J=5.4\text{Hz}$, CH), 6.91-6.98 (3H, m, ArH); δ_{C} (63MHz, D_2O) 15.2 (CH_3), 20.8 ($(\text{CH}_3)_2$), 40.0 (CH), 59.1 (CH), 126.0, 129.8 (C_{Ar}), 139.7, 171.5 (C); m/z (FAB) 208 (MH^+); found (FAB) 208.13378 (MH^+), $\text{C}_{12}\text{H}_{18}\text{NO}_2$ requires 208.13375; $[\alpha]_{\text{D}}^{22}$ -6.0° ($c=1.00$, H_2O)
HPLC: Chirobiotic T; R_{t} (min) 10.01 (0.5%), 12.81 (99.5%).

4.6) Synthesis of (2R,3S)-2-Amino-3-(4-methoxyphenyl)butyric acid hydrochloride (2R,3S)-1f

The general procedure was followed using **(2R,3S)-7f** (250mg, 0.95mmol), acetone (2.5ml) and HCl (20.0ml) and yielded **(2R,3S)-1f** as a white solid (154mg, 66%).

M.p. 210-213°C; $\nu_{\max}$ (KBr) 1611 (amino acid II), 1732 (amino acid I), 1942 and 2532 (NH_3^+ overtones and combinations), 2988 (OH), 3442 cm^{-1} (NH_3^+); δ_{H} (200MHz, D_2O) 1.35 (3H, d $J=7.4\text{Hz}$, CH_3), 3.45 (1H, quin. $J=6.4\text{Hz}$, CH), 4.04 (1H, d $J=5.4\text{Hz}$, CH), 6.95-7.28 (4H, m, ArH); δ_{C} (63Hz, D_2O) 15.4 (CH_3), 39.4 (CH), 55.8 (OCH_3), 59.2 (CH), 114.9, 129.5 (C_{Ar}), 131.9, 158.9, 171.6 (C); m/z (FAB) 210 (MH^+); found (FAB) 210.11298 (MH^+), $\text{C}_{11}\text{H}_{16}\text{NO}_3$ requires 210.11302; $[\alpha]_{\text{D}}^{22}$ -6.0° ($c=1.00$, H_2O).

HPLC: Chirobiotic T; R_{t} (min) 9.83 (0.1%), 11.93 (99.9%).

4.7) Synthesis of (2S,3R)-2-Amino-3-phenyl-butyric acid hydrochloride (2S,3R)-1a

The general procedure was followed using **(2S,3R)-7a** (250mg, 1.06mmol), acetone (2.5ml) and HCl (20ml) and yielded **(2S,3R)-1a** as a white solid (204mg, 69%).

M.p. 190-192°C; $\nu_{\max}$ (nujol) 1603 (amino acid II), 1731 (amino acid I), 1951 and 2535 (NH_3^+ overtones and combinations), 2977 (OH), 3437cm^{-1} (NH_3^+); δ_{H} (250MHz, D_2O) 1.23 (3H, d $J=7.3\text{Hz}$, CH_3), 3.32 (1H, quin., $J=5.9\text{Hz}$, CH), 4.01 (1H, d $J=5.7\text{Hz}$, CH), 7.12-7.22 (5H, m, ArH); δ_{C} (63MHz, D_2O) 15.1 (CH_3), 40.1 (CH), 59.2 (CH), 128.2, 128.5, 129.6 (C_{Ar}), 139.5 171.6 (C); m/z (FAB) 180 (MH^+); found (FAB) 180.10256 (MH^+), $\text{C}_{10}\text{H}_{14}\text{NO}_2$ requires 180.10245; $[\alpha]_{\text{D}}^{22} +5.0^\circ$ ($c=0.50$, H_2O).

HPLC: Chirobiotic T; R_t (min) 7.56 (99.9%), 9.99 (0.1%).

4.8) Synthesis of (2*S*,3*R*)-2-Amino-3-(4-fluorophenyl)butyric acid hydrochloride (2*S*,3*R*)-1b

The general procedure was followed using (2*S*,3*R*)-7b (253mg, 1.0mmol), acetone (2.5ml) and HCl (20.0ml) and yielded (2*S*,3*R*)-1b as a white solid (178mg, 76%).

M.p. 186-190°C; $\nu_{\max}$ (KBr) 1604 (amino acid II), 1732 (amino acid I), 1950 and 2530 (NH_3^+ overtones and combinations), 2990 (OH), 3449cm^{-1} (NH_3^+); δ_{H} (200MHz, D_2O) 1.41(3H, d $J=7.2\text{Hz}$, CH_3), 3.51 (1H, quin. $J=6.2\text{Hz}$, CH), 4.18 (1H, d $J=6.0\text{Hz}$, CH), 7.08-7.36 (4H, m, ArH); δ_{C} (63MHz, D_2O) 15.4 (CH_3), 39.4 (CH), 59.1 (CH), 116.0, 116.4, 129.9, 130.1 (C_{Ar}), 135.4, 160.6, 164.5, 171.6 (C); m/z (FAB) 198 (MH^+); found (FAB) 198.09318 (MH^+), $\text{C}_{10}\text{H}_{13}\text{FNO}_2$ requires 198.09303; $[\alpha]_{\text{D}}^{22} +4.5^\circ$ ($c=1.00$, H_2O).

HPLC: Chirobiotic T; R_t (min) 7.69 (99.6%), 9.67 (0.4%).

4.9) Synthesis of (2*S*,3*R*)-2-Amino-3-(4-trifluoromethylphenyl)butyric acid hydrochloride (2*S*,3*R*)-1c

The general procedure was followed using (2*S*,3*R*)-7c (250mg, 0.83mmol), acetone (2.5ml) and HCl (20.0ml) and yielded (2*S*,3*R*)-1c as a white solid (198mg, 84%).

M.p. 181-184°C; $\nu_{\max}$ (KBr) 1622 (amino acid II), 1733 (amino acid I), 2998 (OH), 3443cm^{-1} (NH_3^+); δ_{H} (200MHz, D_2O) 1.40 (3H, d $J=6.8\text{Hz}$, CH_3), 3.54 (1H, quin. $J=6.2\text{Hz}$, CH), 4.14 (1H, d $J=6.0\text{Hz}$, CH), 7.43-7.69 (4H, m, ArH); δ_{C} (63MHz, D_2O) 15.3 (CH_3), 40.1 (CH), 58.9 (CH), 126.7, 128.8 (C_{Ar}), 143.9, 171.3 (C); m/z (FAB) 248 (MH^+); found (FAB) 248.08899 (MH^+), $\text{C}_{11}\text{H}_{13}\text{F}_3\text{NO}_2$ requires 248.08984; $[\alpha]_{\text{D}}^{22} +7.0^\circ$ ($c=1.00$, H_2O).

HPLC: Chirobiotic T; R_t (min) 7.51 (100%).

4.10) Synthesis of (2*S*,3*R*)-2-Amino-3-naphthalen-2-yl-butyric acid hydrochloride (2*S*,3*R*)-1d

The general procedure was followed using **(2S,3R)-7d** (250mg, 0.88mmol), acetone (2.5ml) and HCl (20.0ml) and yielded **(2S,3R)-1d** as an off-white solid (203mg, 87%).

M.p. 205-207°C; $\nu_{\max}$ (KBr) 1588 (amino acid II), 1770 (amino acid I), 1977 (NH_3^+ overtones and combinations), 2982 (OH), 3419cm^{-1} (NH_3^+); δ_{H} (200MHz, D_2O) 1.47 (3H, d $J=7.2\text{Hz}$, CH_3), 3.66 (1H, quin. $J=6.8\text{Hz}$, CH), 4.19 (1H, d $J=5.4\text{Hz}$, CH), 7.43-7.93 (7H, m, ArH); m/z (FAB) 230 (MH^+); found (FAB) 230.11834 (MH^+), $\text{C}_{14}\text{H}_{16}\text{NO}_2$ requires 230.11810; $[\alpha]_{\text{D}}^{22} +10.0^\circ$ ($c=1.00$, H_2O).

HPLC: Chirobiotic T; R_t (min) 8.87 (100%).

4.11) Synthesis of (2S,3R)-2-Amino-3-(3,5-dimethylphenyl)butyric acid hydrochloride (2S,3R)-1e

The general procedure was followed using **(2S,3R)-7e** (250mg, 0.95mmol), acetone (2.5ml) and HCl (20.0ml) and trituration with ether yielded **(2S,3R)-1e** as a white solid (170mg, 73%).

M.p. 180-185°C; $\nu_{\max}$ (KBr) 1608 (amino acid II), 1733 (amino acid I), 2975 (OH), 3437cm^{-1} (NH_3^+); δ_{H} (200MHz, D_2O) 1.33 (3H, d $J=7.4\text{Hz}$, CH_3), 2.24 (6H, s, $(\text{CH}_3)_2$), 3.43 (1H, quin. $J=6.0\text{Hz}$, CH), 4.04 (1H, d $J=5.4\text{Hz}$, CH), 6.95-7.00 (3H, m, ArH); δ_{C} (63MHz, D_2O) 15.2 (CH_3), 20.8 ($(\text{CH}_3)_2$), 40.0 (CH), 59.1 (CH), 126.0, 129.8 (C_{Ar}), 139.7, 171.5 (C); m/z (FAB) 208 (MH^+); found (FAB) 208.13419 (MH^+), $\text{C}_{12}\text{H}_{18}\text{NO}_2$ requires 208.13375; $[\alpha]_{\text{D}}^{22} +4.0^\circ$ ($c=1.00$, H_2O)

HPLC: Chirobiotic T; R_t (min) 9.15 (99.5%), 14.83 (0.5%).

4.12) Synthesis of (2S,3R)-2-Amino-3-(4-methoxyphenyl)butyric acid hydrochloride (2S,3R)-1f

The general procedure was followed using **(2S,3R)-7f** (250mg, 0.95mmol), acetone (2.5ml) and HCl (20.0ml) and yielded **(2S,3R)-1f** as a white solid (155mg, 67%).

M.p. 211-213°C; $\nu_{\max}$ (KBr) 1611(amino acid II), 1731 (amino acid I), 1947 and 2535 (NH_3^+ overtones and combinations), 2990 (OH), 3442cm^{-1} (NH_3^+); δ_{H} (200MHz, D_2O) 1.35(3H, d $J=7.4\text{Hz}$, CH_3), 3.45 (1H, quin. $J=6.4\text{Hz}$,

CH), 4.04 (1H, d $J=5.4$ Hz, CH), 6.95-7.29(4H, m, ArH); δ_c (63Hz, D₂O) 15.4 (CH₃), 39.4 (CH), 55.8 (OCH₃), 59.2 (CH), 114.9, 129.5 (C_{Ar}), 131.9, 158.9, 171.6 (C); m/z (FAB) 210 (MH⁺); found (FAB) 210.11318 (MH⁺), C₁₁H₁₆NO₃ requires 210.11302; $[\alpha]_D^{22} +5.0^\circ$ (c=1.00, H₂O).

HPLC: Chirobiotic T; R_t (min) 9.88 (100%).

5) General procedure for D-AAO stereoinversion

A mixture of amino acid hydrochloride (**(2R,3S)-1**) (2ml of a 5mM solution), *Trigonopsis variabilis* D-amino acid oxidase (5 drops of immobilised slurry, 222.7 U/g dry weight) and ammonia-borane complex (5mg, 0.16mmol) were shaken on a blood rotator at 30°C. Samples were filtered and analysed by HPLC at t=0 and t=20hr.

5.1) Synthesis of (2S,3S)-2-Amino-3-phenyl-butyric acid (2S,3S)-1a

The general procedure was followed using (**(2R,3S)-1a**).

HPLC: Chirobiotic T; R_t (min): t=0hr 6.60 (0.2%), 8.82 (99.8%); t=20hr 6.40 (99.9%), 8.94 (0.1%); 69% yield; >99% d.e.

5.2) Synthesis of (2S,3S)-2-Amino-3-(4-fluorophenyl)butyric acid (2S,3S)-1b

The general procedure was followed using (**(2R,3S)-1b**).

HPLC: Chirobiotic T; R_t (min): t=0hr 8.25 (100%); t=20hr 6.33 (100%); 68% yield; >99% d.e.

5.3) Synthesis of (2S,3S)-2-Amino-3-(4-trifluoromethylphenyl)butyric acid (2S,3S)-1c

The general procedure was followed using (**(2R,3S)-1c**).

HPLC: Chirobiotic T; R_t (min): t=0hr 6.30 (1%), 7.82 (99%); t=20hr 6.05 (100%); 81% yield; >99% d.e.

5.4) Synthesis of (2*S*,3*S*)-2-Amino-3-naphthalen-2-yl-butyric acid (2*S*,3*S*)-1d

The general procedure was followed using (2*R*,3*S*)-1d.

HPLC: Chirobiotic T; R_t (min): $t=0$ hr 8.02 (1.9%), 13.02 (98.1%); $t=20$ hr 7.83 (100%); 80% yield; >99% d.e.

5.5) Synthesis of (2*S*,3*S*)-2-Amino-3-(3,5-dimethylphenyl)butyric acid (2*S*,3*S*)-1e

The general procedure was followed using (2*R*,3*S*)-1e.

HPLC: Chirobiotic T; R_t (min) $t=0$ hr 6.73 (2.8%), 10.44 (97.2%); $t=20$ hr 6.53 (100%); 72% yield; >99% d.e.

5.6) Synthesis of (2*S*,3*S*)-2-Amino-3-(4-methoxyphenyl)butyric acid (2*S*,3*S*)-1f

The general procedure was followed using (2*R*,3*S*)-1f.

HPLC: Chirobiotic T; R_t (min): $t=0$ hr 6.99 (0.2%), 9.13 (99.8%); $t=20$ hr 6.76 (100%); 81% yield; >99% d.e.

6) General procedure for L-AAO stereoinversion

A mixture of amino acid hydrochloride (2*S*,3*R*)-1 (4ml of a 5mM solution), Snake venom L-amino acid oxidase (20mg of a 0.5U/mg enzyme) and ammonia-borane complex (10mg, 0.32mmol) were shaken on a blood rotator at 30°C. Samples were filtered and analysed by HPLC at $t=0$ and $t=20$ hr.

6.1) 6.1 Synthesis of (2*R*,3*R*)-2-Amino-3-phenyl-butyric acid (2*R*,3*R*)-1a

The general procedure was followed using **(2S,3R)-1a**.

HPLC: Chirobiotic T; R_t (min): $t=0$ hr 7.00 (100%); $t=20$ hr 8.88 (100%); 83% yield; >99% d.e.

6.2) Synthesis of (2R,3R)-2-Amino-3-(4-fluorophenyl)butyric acid (2R,3R)-1b

The general procedure was followed using **(2S,3R)-1b**.

HPLC: Chirobiotic T; R_t (min): $t=0$ hr 6.79 (100%); $t=20$ hr 8.69 (100%); 85% yield; >99% d.e.

6.3) Synthesis of (2R,3R)-2-Amino-3-(4-trifluoromethylphenyl)butyric acid (2R,3R)-1c

The general procedure was followed using **(2S,3R)-1c**.

HPLC: Chirobiotic T; R_t (min): $t=0$ hr 6.48 (100%); $t=20$ hr 7.94 (100%); 92% yield; >99% d.e.

6.4) Synthesis of (2R,3R)-2-Amino-3-naphthalen-2-yl-butyric acid (2R,3R)-1d

The general procedure was followed using **(2S,3R)-1d**.

HPLC: Chirobiotic T; R_t (min): $t=0$ hr 9.08 (100%); $t=20$ hr 9.82 (1.2%), 11.96 (98.8%); $t=40$ hr 12.50 (100%); 80% yield; >99% d.e.

6.5) Synthesis of (2R,3R)-2-Amino-3-(3,5-dimethylphenyl)butyric acid (2R,3R)-1e

The general procedure was followed using **(2S,3R)-1e**.

HPLC: Chirobiotic T; R_t (min): $t=0\text{hr}$ 7.28 (100%); $t=20\text{hr}$ 7.28 (52.8%), 8.26 (47.2%); $t=40\text{hr}$ 7.43 (32.6%), 8.41 (67.4%); $t=64\text{hr}$ 7.36 (25.5%), 8.27 (74.5%); 71% yield, 49% d.e.

6.6) Synthesis of (2R,3R)-2-Amino-3-(4-methoxyphenyl)butyric acid (2R,3R)-1f

The general procedure was followed using **(2S,3R)-1f**.

HPLC: Chirobiotic T; R_t (min): $t=0\text{hr}$ 7.56 (100%), $t=20\text{hr}$ 7.71 (2.7%), 9.95 (97.3%); $t=40\text{hr}$ 10.13 (100%); 80% yield; >99% d.e.

7) Stereoinversion on 1g scale

A mixture of β -methylphenylalanine hydrochloride **(2R,3R)-1a** (1.00g, 4.64mmol), ammonia-borane complex (3.10g, 100mmol), *T. variabilis* D-AAO (10ml of immobilised slurry, 222.7 U/g dry weight) in water (200ml) was shaken at 37°C for 96hr. HPLC showed complete conversion with 54% yield. The mixture was filtered and freeze dried, taken up in boiling ethanol and hot filtered to remove unreacted ammonia-borane. Recrystallisation from ethanol/ethyl acetate gave **(2S,3R)-1a** as a white solid (455mg 55%).

M.p. 188°C decomp.; δ_H (250MHz, D_2O) 1.41 (3H, d $J=7.3\text{Hz}$, CH_3), 3.55 (1H, quin. $J=7.3\text{Hz}$, CH), 3.93 (1H, d $J=5.0\text{Hz}$, CH), 7.32-7.45 (5H, m, ArH); δ_C (63MHz, D_2O) 14.2 (CH_3), 39.9 (CH), 61.1 (CH), 128.2, 129.5 (C_{Ar}), 140.7, 173.8 (C); m/z (ES+) 180 (MH^+); $[\alpha]_D^{20}$ 4.2° ($c=0.83$, $CHCl_3$).

HPLC: Chirobiotic T; R_t (min): $t=0\text{hr}$ 10.33 (100%), $t=96\text{hr}$ 8.46 (100%).