Total Synthesis of Stephanotic Acid Methyl Ester**David J. Bentley, Alexandra M. Z. Slawin, and Christopher J. Moody****SUPPORTING INFORMATION****TABLE OF CONTENTS**

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General Experimental Details

Commercially available reagents were used throughout without purification unless otherwise stated. Light petroleum refers to the fraction with bp 40-60 °C and was distilled before use. Ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen or argon atmosphere. Analytical thin layer chromatography was carried out on aluminum backed plates coated with Merck Kieselgel 60 GF₂₅₄, and visualized under UV light at 254 and/or 360 nm. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Fully characterized compounds were chromatographically homogeneous.

Infrared spectra were recorded in the range 4000-600 cm⁻¹ using a Nicolet Magna FT-550 or Perkin Elmer FT-1600 spectrometers. NMR spectra were carried out on Bruker 300 and 400 MHz instruments (¹H frequencies, corresponding ¹³C frequencies are 75 and 100 MHz).

Chemical shifts are quoted in ppm with TMS as internal standard. *J* values are recorded in Hz. In the ¹³C spectra, signals corresponding to CH, CH₂ or CH₃ groups, as assigned from DEPT, are noted; all others are C. High and low resolution mass spectra were recorded on a Micromass GCT TDF High Resolution mass spectrometer, or at the EPSRC Mass Spectrometry Service (Swansea). Specific rotations were measured on an AA-1000 polarimeter and values are quoted in 10⁻¹degcm²g⁻¹.

Indole-6-carbonitrile

Dimethylformamide dimethylacetal (32.0 ml, 241 mmol) was added to 4-methyl-3-nitrobenzonitrile (15.0 g, 92.6 mmol) in DMF (450 ml) and the mixture was heated

under reflux for 15 h. The reaction mixture was concentrated and the crude enamine split into two equal batches. Each batch was dissolved in anhydrous THF (150 ml) and added to a Parr tube containing palladium on carbon (10%; 7.50 g). The solutions were degassed and stirred under hydrogen pressure (50 psi) for 30 min. The reaction mixtures were filtered through Celite and the filtrates were combined and concentrated. The residue was dissolved in ethyl acetate (500 ml), washed with brine (2 $\times$ 300 ml), dried (MgSO₄) and concentrated. The residue was purified by column chromatography (dichloromethane) to give the *title compound* (9.07 g, 69%) as a yellow powder; mp 126-127 °C (from ethyl acetate / light petroleum), (lit.,¹ mp 132 °C); (Found: MH⁺, 143.0612. C₉H₆N₂ + H requires 143.0609); ν_{max} (KBr)/cm⁻¹ 3412 (NH), 2219 (C $\equiv$ N); δ_{H} (300 MHz; CDCl₃) 8.76 (1H, s, NH), 7.78 (1H, s, 7-H), 7.69 (1H, d, *J* 8.2, 4-H), 7.43 (1H, app t, *J* 2.7, 2-H), 7.34 (1H, dd, *J* 8.2, 0.9, 5-H), 6.63 (1H, m, 3-H); δ_{C} (75 MHz; CDCl₃) 133.9 (C), 130.5 (C), 127.5 (CH), 122.0 (CH), 120.9 (CH), 120.2 (C), 115.4 (CH), 103.4 (C), 102.7 (CH); *m/z* (CI) 143 (MH⁺, 100%), 142 (M⁺, 28).

***N*-tert-Butoxycarbonyl-6-isobutyrylindole 7**

(a) Isopropylmagnesium chloride in THF (2.0 M; 400 ml, 800 mmol) was added to a solution of indole-6-carbonitrile (9.07 g, 63.9 mmol) in anhydrous THF (50 ml) at 0 °C. The reaction mixture was heated under reflux for 24 h. The reaction mixture was cooled to 0 °C, hydrochloric acid (2 M; 400 ml) was added slowly until pH 4 was reached, and then the mixture was allowed to stir at room temperature for 30 min. The THF was removed under vacuum and the product was

extracted from the aqueous with ether (2 × 500 ml). The combined organics were washed with brine (500 ml), dried (MgSO₄) and concentrated.

The procedure above was repeated using a second batch of 6-cyanoindole (8.52 g, 60.0 mmol), and the two crude products were combined and purified by recrystallization from dichloromethane. This recrystallized product was combined with a further quantity obtained by column chromatography (dichloromethane) of the mother liquor to give *6-isobutyrylindole* (15.7 g, 68%) as a colorless powder; mp 165-167 °C (from ethyl acetate / light petroleum); (Found: C, 77.1; H, 7.0; N, 7.4. C₁₂H₁₃NO requires C, 77.0; H, 7.0; N, 7.5%); (Found: MH⁺, 188.1079. C₁₂H₁₃NO + H requires 188.1075); ν_{max} (KBr)/cm⁻¹ 3312 (NH), 2981 (CH), 1647 (CO); ν_{H} (300 MHz; CDCl₃) 8.73 (1H, br s, NH), 8.14 (1H, s, 7-H), 7.77 (1H, dd, *J* 8.4, 1.3, 4-H), 7.68 (1H, d, *J* 8.4, 5-H), 7.40 (1H, app t, *J* 2.8, 2-H), 6.60 (1H, m, 3-H), 3.66 (1H, m, *J* 6.8, CHMe₂), 1.25 (6H, d, *J* 6.8 CHMe₂); ν_{C} (75 MHz; CDCl₃) 205.0 (C), 135.5 (C), 131.6 (C), 130.3 (C), 128.0 (CH), 120.4 (CH), 120.1 (CH), 112.3 (CH), 102.9 (CH), 35.3 (CH), 19.5 (Me); *m/z* (CI) 188 (MH⁺, 100%), 187 (M⁺, 12), 144 (17).

(b) 6-Isobutyrylindole (12.2 g, 65.2 mmol), 4-dimethylaminopyridine (238 mg, 1.95 mmol) and di-*tert*-butyl dicarbonate (18.5 g, 85.0 mmol) were stirred for 15 h in anhydrous acetonitrile (250 ml). The acetonitrile was removed under vacuum and the residue was dissolved in ethyl acetate (500 ml), and was washed with saturated aqueous sodium hydrogen carbonate (250 ml) and brine (250 ml). The organics were dried (MgSO₄) and concentrated. The residue was purified by column chromatography (5% up to 15% ethyl acetate / light petroleum) to give the *title compound* (18.1 g, 97%) as a colorless oil; (Found: MH⁺, 288.1598. C₁₇H₂₁NO₃ + H requires 288.1599); ν_{max} (film)/cm⁻¹ 2975 (ArH), 2934, 2853 (CH), 1739, 1678 (CO), 1609, 1522 (C=C);

δ_{H} (300 MHz; CDCl_3) 8.82 (1H, s, 7-H), 7.89 (1H, dd, J 8.3, 1.5, 4-H), 7.76 (1H, d, J 3.7, 2-H), 7.61 (1H, d, J 8.3, 5-H), 6.62 (1H, dd, J 3.7, 0.6, 3-H), 3.69 (1H, m, J 6.8, CHMe_2), 1.71 (9H, s, CMe_3), 1.26 (6H, d, J 6.8, CHMe_2); δ_{C} (75 MHz; CDCl_3) 204.5 (C), 149.4 (C), 134.8 (C), 134.2 (C), 132.3 (C), 129.1 (CH), 122.8 (CH), 120.9 (CH), 116.0 (CH), 107.2 (CH), 84.4 (C), 35.3 (C), 28.1 (Me), 19.5 (Me); m/z (CI) 288 (MH^+ , 56%), 260 (15), 232 (100), 188 (13).

Ethyl 5-(1-*tert*-butoxycarbonylindol-6-yl)-5-isopropyl-2-thioxo-oxazolidine-4-carboxylate **8**

A premixed solution of *N*-*tert*-butoxycarbonyl-6-isobutyrylindole **7** (200 mg, 0.700 mmol) and ethyl isothiocyanatoacetate (35 μl , 2.8 mmol) in anhydrous THF (2 ml) was added dropwise to a suspension of a sodium hydride dispersion in mineral oil (60%; 120 mg, 2.9 mmol) in anhydrous THF (3 ml) at 0 °C. Water (10 ml) was added after 30 min at 0 °C. The THF was removed under vacuum and the residue was dissolved in ethyl acetate (20 ml) and washed with brine (2 $\times$ 10 ml). The ethyl acetate layer was dried (MgSO_4) and concentrated. The residue, containing a mixture *syn*- and *anti*-isomers, was purified and the isomers separated by column chromatography (30% ethyl acetate / light petroleum) to give the *title compounds*, *anti*-**8** (62 mg, 21%) as a colorless powder; mp 130-132 °C (from ethyl acetate / light petroleum); (Found: C, 60.7; H, 6.5; N, 6.5. $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_5\text{S}$ requires C, 61.1; H, 6.5; N, 6.5%); (Found: MH^+ , 433.1805. $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_5\text{S} + \text{H}$ requires 433.1797); ν_{max} (KBr)/ cm^{-1} 2978 (CH), 1734 (CO), 1207 (CS); δ_{H} (300 MHz; CDCl_3) 8.36 (1H, s, 7-H), 7.80-7.65 (1H, br m, NH), 7.64 (1H, d, J 2.6, 2-H), 7.56 (1H, d, J 6.2, 4-H), 7.41 (1H, dd, J 6.2, 1.2, 5-H), 6.55 (1H, d, J 2.6, 3-H), 4.79 (1H, s, CH), 4.39 (2H, m, CH_2Me),

2.66 (1H, m, J 5.0, CHMe₂), 1.69 (9H, s, CMe₃), 1.42 (3H, t, J 5.3, CH₂Me), 1.03 (3H, d, J 5.0, CHMeMe), 0.77 (3H, d, J 5.0, CHMeMe); δ_{C} (75 MHz; CDCl₃) 188.4 (C), 167.5 (C), 149.6 (C), 137.8 (C), 135.0 (C), 130.3 (C), 127.0 (CH), 121.1 (CH), 119.2 (CH), 111.7 (CH), 106.8 (CH), 98.0 (C), 84.3 (C), 67.8 (CH), 62.8 (CH₂), 35.0 (CH), 28.3 (Me), 18.0 (Me), 16.6 (Me), 14.0 (Me); m/z (CI) 433 (MH⁺, 0.9%), 188 (100), 146 (33), 118 (34), 109 (28), and *syn*-**8** (180 mg, 60%) as a colorless powder; mp 99-100 °C (from ethyl acetate / light petroleum); (Found: C, 61.4; H, 7.0; N, 6.2. C₂₂H₂₈N₂O₅S requires C, 61.1; H, 6.5; N, 6.5%); (Found: MH⁺, 433.1820. C₂₂H₂₈N₂O₅S + H requires 433.1797); ν_{max} (KBr)/cm⁻¹ 2978 (CH), 1735 (CO), 1188 (CS); δ_{H} (300 MHz; CDCl₃) 8.14 (1H, s, 7-H), 7.62 (1H, d, J 2.7, 2-H), 7.51 (1H, dd, J 6.2, 0.4, 4-H), 7.45 (1H, br s, NH) 7.21 (1H, dd, J 6.2, 0.9, 5-H), 6.53 (1H, d, J 2.7, 3-H), 4.70 (1H, s, CH), 3.70 (1H, m, CHHMe), 3.48 (1H, m, CHHMe), 2.66 (1H, m, J 5.0, CHMe₂), 1.69 (9H, s, CMe₃), 1.22 (3H, d, J 5.0, CHMeMe), 0.89 (3H, d, J 5.0, CHMeMe), 0.84 (3H, t, J 5.4, CH₂Me); δ_{C} (75 MHz; CDCl₃) 189.6 (C), 167.8 (C), 149.6 (C), 134.7 (C), 132.5 (C), 130.5 (C), 127.1 (CH), 120.6 (2 overlapping CH), 113.0 (CH), 106.9 (CH), 98.4 (C), 84.3 (C), 66.1 (CH), 62.0 (CH₂), 38.0 (CH), 28.2 (Me), 17.3 (Me), 16.2 (Me), 13.3 (Me); m/z (CI) 433 (MH⁺, 0.5%), 299 (12), 256 (12), 216 (11), 212 (17), 188 (100), 146 (20).

On a larger scale, the above procedure was followed using ketone **7** (18.1g, 63.1 mmol). The isomers were purified and collected together to give the *title compounds anti*-**8** and *syn*-**8** (22.5 g, 83%).

Ethyl 3-Benzyloxycarbonyl-5-(1-*tert*-butoxycarbonylindol-6-yl)-5-isopropyl-2-thioxo-oxazolidine-4-carboxylate **9**

(a) *Anti-9*

Triethylamine (51 μ l, 0.11 mmol) and benzyl chloroformate (51 μ l, 0.11 mmol) were respectively added dropwise to a solution of *anti-8* (47 mg, 0.11 mmol) in anhydrous THF (4 ml). The reaction mixture was stirred for 1 h at 0 °C and then allowed to warm to room temperature. The THF was removed under vacuum and the residue dissolved in ethyl acetate (10 ml), and washed with water (2 $\times$ 10 ml). The ethyl acetate layer was dried (MgSO₄) and concentrated. The residue was purified by column chromatography (20% ethyl acetate / light petroleum) to give the *title compound anti-9* (45 mg, 73%) as a colorless powder; mp 156-157 °C (from ethyl acetate / light petroleum); (Found: C, 63.5; H, 6.1; N, 4.9. C₃₀H₃₄N₂O₇S requires C, 63.6; H, 6.1; N, 5.0%); (Found: MH⁺, 567.2196. C₃₀H₃₄N₂O₇S + H requires 567.2165); ν_{max} (KBr)/cm⁻¹ 2974 (CH), 1775, 1743 (CO); δ_{H} (300 MHz; CDCl₃) 8.23 (1H, s, 7-H), 7.69 (1H, d, *J* 3.7, 2-H), 7.57 (1H, d, *J* 8.3, 4-H), 7.36-7.30 (6H, m, ArH, 5-H), 6.58 (1H, d, *J* 3.7, 3-H), 5.30 (2H, m, CHHAr, CH), 5.13 (1H, d, *J* 12.2, CHHAr), 4.23 (2H, q, *J* 5.5, CH₂Me), 2.30 (1H, m, *J* 6.7, CHMe₂), 1.71 (9H, s, CMe₃), 1.25 (3H, t, *J* 5.5, CH₂Me), 0.94 (6H, d, *J* 6.7, CHMe₂); δ_{C} (75 MHz; CDCl₃) 182.7 (C), 167.6 (C), 150.8 (C), 150.0 (C), 134.9 (C), 134.7 (C), 133.1 (C), 131.3 (C), 129.1 (CH), 129.0 (CH), 128.8 (CH), 127.7 (CH), 121.1 (CH), 120.9 (CH), 113.8 (CH), 107.2 (CH), 94.2 (C), 84.9 (C), 71.0 (CH), 69.7 (CH₂), 62.9 (CH₂), 34.2 (CH), 28.7 (Me), 18.0 (Me), 17.7 (Me), 14.3 (Me); *m/z* (CI) 567 (MH⁺, 3%), 423 (15), 343 (18), 301 (29), 299 (45), 258 (24), 256 (29), 232 (26), 212 (43), 188 (100).

(b) *Syn-9*

The above procedure was followed using *syn-8* (82 mg, 0.19 mmol). Purification gave the *title compound syn-9* (79 mg, 74%) as a colorless powder; mp 71-74 °C (from ethyl acetate / light petroleum); (Found: C, 63.4; H, 6.0; N, 4.8. C₃₀H₃₄N₂O₇S requires C, 63.6; H, 6.1; N, 5.0%); (Found: MH⁺, 567.2156. C₃₀H₃₄N₂O₇S + H requires 567.2165); ν_{max} (KBr)/cm⁻¹ 2978 (CH), 1775, 1734 (CO); δ_{H} (300 MHz; CDCl₃) 8.17 (1H, s, 7-H), 7.63 (1H, d, *J* 3.6, 2-H), 7.50 (1H, d, *J* 8.1, 4-H), 7.45-7.31 (5H, m, ArH), 7.20 (1H, d, *J* 8.1, 5-H), 6.53 (1H, d, *J* 3.6, 3-H), 5.36 (1H, d, *J* 12.2, CHHAr), 5.20 (1H, d, *J* 12.2, CHHAr), 5.07 (1H, s, CH), 3.46 (1H, m, CHHMe), 3.27 (1H, m, CHHMe), 2.59 (1H, m, *J* 6.7, CHMe₂), 1.69 (9H, s, CMe₃), 1.14 (3H, d, *J* 6.7, CHMeMe), 0.85 (3H, d, *J* 6.7, CHMeMe), 0.67 (3H, t, *J* 7.2, CH₂Me); δ_{C} (75 MHz; CDCl₃) 183.2 (C), 167.1 (C), 150.5 (C), 150.0 (C), 135.0 (C), 134.7 (C), 132.2 (C), 131.0 (C), 129.1 (CH), 129.0 (CH), 128.8 (CH), 127.5 (CH), 120.9 (CH), 120.8 (CH), 113.5 (CH), 107.2 (CH), 93.8 (C), 84.8 (C), 69.8 (CH₂), 69.1 (CH), 62.1 (CH₂), 39.5 (CH), 28.6 (Me), 17.5 (Me), 16.4 (Me), 13.6 (Me); *m/z* (CI) 567 (MH⁺, 35%), 523 (33), 511 (21), 467 (82), 423 (100), 407 (27), 300 (14), 256 (24).

(c) On a larger scale, the above procedure was followed using a mixture of *anti-8* and *syn-8* (11.4 g, 26.3 mmol) in the same ratio in which they were formed. The isomers of the product were purified and collected together to give the *title compounds anti-9* and *syn-9* (14.0 g, 94%).

Ethyl 2-benzyloxycarbonylamino-3-(1-*tert*-butoxycarbonylindol-6-yl)-4-methylpent-2-enoate **10**

(a) From *anti*-*N*-benzyloxycarbonyl thioxo-oxazolidine **9**

A solution of *anti*-oxazolidine **9** (43 mg, 0.08 mmol) in anhydrous THF (0.5 ml) was added dropwise to a solution of potassium *tert*-butoxide (13 mg, 0.12 mmol) in anhydrous THF (1 ml) at -78 °C. The reaction mixture was stirred for 30 min at this temperature and then quenched with water (1 ml) and allowed to warm to room temperature. The THF was removed under vacuum and water (10 ml) was added to the residue. The product was extracted with ether (2 × 10 ml) and the combined organics were washed with brine (20 ml), dried (MgSO₄), and concentrated. The residue was purified and the isomers separated by column chromatography (15% ethyl acetate / light petroleum) to give the alkenes, (*Z*)-**10** (8 mg, 21%) as a colorless oil; (Found: MH⁺, 507.2491. C₂₉H₃₄N₂O₆ + H requires 507.2495); ν_{max} (film)/cm⁻¹ 3424 (NH), 2976 (CH), 1734 (CO); δ_{H} (300 MHz; CDCl₃) 7.88 (1H, s, 7-H), 7.62 (1H, d, *J* 3.6, 2-H), 7.56 (1H, d, *J* 8.0, 4-H), 7.35-7.23 (5H, m, ArH), 6.91 (1H, d, *J* 8.0, 5-H), 6.57 (1H, d, *J* 3.6, 3-H), 5.83 (1H, br s, NH), 4.99 (2H, s, CH₂Ar), 4.35 (2H, m, CH₂Me), 3.30 (1H, m, CHMe₂), 1.66 (9H, s, CMe₃), 1.35 (3H, m, CH₂Me), 1.00 (6H, d, *J* 6.8, CHMe₂); δ_{C} (75 MHz; CDCl₃) 165.5 (C), 153.7 (C), 149.9 (C), 140.4 (C), 136.2 (C), 135.6 (C), 131.2 (C), 130.4 (C), 128.9 (CH), 128.64 (CH), 128.59 (CH), 126.9 (CH), 124.7 (C), 123.9 (CH), 121.7 (CH), 115.7 (CH), 107.4 (CH), 84.4 (C), 67.6 (CH₂), 61.7 (CH₂), 30.7 (CH), 28.6 (Me), 21.9 (Me), 14.5 (Me); *m/z* (CI) 567 (MH⁺, 2%), 407 (33), 361 (36), 299 (100), 298 (37), 253 (67), and (*E*)-**10** (9 mg, 23%), as a colorless oil; (Found: M⁺,

506.2426. C₂₉H₃₄N₂O₆ requires 506.2417); ν_{max} (film)/cm⁻¹ 2975 (CH), 1734 (CO); ν_{H} (300 MHz; CDCl₃) 7.87 (1H, s, 7-H), 7.58 (1H, d, *J* 3.6, 2-H), 7.47 (1H, d, *J* 8.0, 4-H), 7.40-7.31 (5H, m, ArH), 6.96 (1H, d, *J* 8.0, 5-H), 6.55 (1H, d, *J* 3.6, 3-H), 6.25 (1H, br s, NH), 5.18 (2H, s, CH₂Ar), 3.78 (2H, m, CH₂Me), 3.14 (1H, m, CHMe₂), 1.65 (9H, s, CMe₃), 1.01 (6H, d, *J* 6.8, CHMe₂), 0.66 (3H, t, *J* 7.0, CH₂Me); ν_{C} (75 MHz; CDCl₃) 164.3 (C), 153.5 (C), 148.6 (C), 140.0 (C), 135.0 (C), 133.5 (C), 131.7 (C), 128.5 (C), 127.5 (CH), 127.4 (CH), 127.2 (CH), 125.1 (CH), 123.1 (C), 122.9 (CH), 118.6 (CH), 114.4 (CH), 106.1 (CH), 82.6 (C), 66.4 (CH₂), 59.5 (CH₂), 29.6 (CH), 27.1 (Me), 19.5 (Me), 12.3 (Me); *m/z* (CI) 506 (M⁺, 4%), 361 (18), 343 (22), 299 (100), 298 (28), 253 (83).

(b) From *syn*-*N*-benzyloxycarbonyl thioxo-oxazolidine **9**:

The above procedure was followed using *syn*-oxazolidine **9** (61 mg, 0.11 mmol). The isomers were purified and separated to give the alkenes (*Z*)-**10** (17 mg, 31%), and (*E*)-**10** (10 mg, 18%), characterized as above.

(c) On a larger scale, the above procedure was followed using a mixture of *anti*-**10** and *syn*-**10** (14.0 g, 24.7 mmol) in the same ratio in which they were formed. The isomers were purified and collected together to give the alkenes (*Z*)-**10** and (*E*)-**10** (9.27 g, 74%).

Ethyl 2-benzyloxycarbonylamino-3-(1-*tert*-butoxycarbonylindol-6-yl)-4-methylpentanoate

11

(a) From (Z)-**10**

Coarse magnesium powder (47 mg, 1.98 mmol) was added to (Z)-**10** (100 mg, 0.198 mmol) in anhydrous methanol (2 ml). The reaction mixture was stirred vigorously for 1 h ensuring the temperature did not exceed room temperature by use of an ice bath. The solvent was removed under vacuum and the residue dissolved in ethyl acetate (20 ml) was washed with hydrochloric acid (2 M; 15 ml) and brine (15 ml). The organic layer was dried (MgSO₄) and concentrated. The crude product was purified and the diastereomers separated by column chromatography (5% up to 10% ethyl acetate / light petroleum) to give *diastereomer 1*-(±)-(2*S*, 3*S*)-**11** (17 mg, 17%) as a colorless oil; (Found: MH⁺, 509.2656. C₂₉H₃₆N₂O₆ + H requires 507.2651); ν_{max} (film)/cm⁻¹ 3431 (NH), 2978 (CH), 1728 (CO); δ_{H} (400 MHz; CDCl₃) 7.95 (1H, s, 7-H), 7.55 (1H, d, *J* 3.4, 2-H), 7.45 (1H, d, *J* 8.0, 4-H), 7.32 (5H, m, ArH), 6.95 (1H, d, *J* 8.0, 5-H), 6.51 (1H, d, *J* 3.4, 3-H), 5.13 (3H, m, NH and CH₂Ar), 4.97 (1H, dd, *J* 10.2, 3.9, □-CH), 4.12 (2H, q, *J* 8.0, CH₂Me), 3.03 (1H, dd, *J* 10.2, 3.8, □-CH), 2.19 (1H, m, CHMe₂), 1.63 (9H, s, CMe₃), 1.25 (6H, m, CH₂Me, CHMeMe), 0.79 (3H, d, *J* 6.6, CHMeMe); δ_{C} (100 MHz; CDCl₃) 172.0 (C), 156.4 (C), 149.6 (C), 136.2 (C), 135.5 (C), 134.7 (C), 129.7 (C), 128.5 (CH), 128.14 (CH), 128.13 (CH), 126.0 (CH), 123.3 (CH), 120.9 (CH), 115.3 (CH), 107.0 (CH), 83.6 (C), 67.1 (CH₂), 61.3 (CH₂), 55.8 (CH), 55.5 (CH), 28.5 (CH), 28.1 (Me), 21.4 (Me), 21.3 (Me), 14.2 (Me); *m/z* (CI) 509 (MH⁺, 27%), 453 (17), 409 (49), 272 (18), 244 (100), 216 (77), 158 (39), 57 (20), and *diastereomer 2*-(±)-(2*S*, 3*R*)-**11** (52 mg, 52%) as a colorless oil; (Found: M⁺, 508.2567. C₂₉H₃₆N₂O₆ requires 508.2573); ν_{max} (film)/cm⁻¹ 3352 (NH), 2976 (CH), 1732 (CO); δ_{H} (300 MHz; CDCl₃) 7.93 (1H, s, 7-H), 7.54 (1H, d, *J* 3.6, 2-H), 7.44 (1H, d, *J* 8.1, 4-H), 7.33 (5H, m, ArH), 6.91 (1H, dd, *J* 8.1, 1.1, 5-H), 6.51 (1H, d, *J* 3.6, 3-H), 5.17 (1H, m, NH), 5.12 (2H, s, CH₂Ar), 4.91 (1H, m, □-CH), 4.09 (2H, q, *J* 7.0, CH₂Me), 2.76 (1H, m, □-CH), 2.38 (1H, m, CHMe₂), 1.64 (9H, s, CMe₃), 1.23 (3H,

d, J 6.5, CHMeMe), 1.16 (3H, t, J 7.0, CH₂Me), 0.77 (3H, d, J 6.5, CHMeMe); δ_c (75 MHz; CDCl₃) 171.0 (C), 155.6 (C), 149.6 (C), 136.3 (C), 135.3 (C), 134.7 (C), 129.7 (C), 128.5 (CH), 128.14 (CH), 128.09 (CH), 125.9 (CH), 123.8 (CH), 120.5 (CH), 115.7 (CH), 107.0 (CH), 83.5 (C), 66.9 (CH₂), 61.2 (CH₂), 57.5 (CH), 55.9 (CH), 29.1 (CH), 28.2 (Me), 21.4 (Me), 21.2 (Me), 13.9 (Me); m/z (FI) 509 (MH⁺, 13%), 508 (M⁺, 33) 202 (21), 108 (100).

(b) From (*E*)-**10**

The above procedure was followed using (*E*)-**10** (60 mg, 0.12 mmol). The isomers were purified and separated to give the *diastereomer* 1-(±)-(2*S*, 3*S*)-**11** (16 mg, 26%) and *diastereomer* 2-(±)-(2*S*, 3*R*)-**11** (25 mg, 41%), characterized as above.

(c) On a larger scale, the above procedure was followed using a mixture of **Z-29** and **E-29** (9.27 g, 18.3 mmol) in the same ratio in which they were formed. The isomers were purified and separated to give the *diastereomer* 1-(±)-(2*S*, 3*S*)-**11** (2.44 g, 26%) and *diastereomer* 2-(±)-(2*S*, 3*R*)-**11** (4.01 g, 43%), characterized as above.

(±)-(2*S*/*R*, 3*R*/*S*)-Ethyl 2-benzyloxycarbonylamino-3-(3-formylindol-6-yl)-4-methylpentanoate (±)-**12**

Dichloromethyl methyl ether (**CAUTION**) (390 μ l, 4.27 mmol) was added to a solution of *diastereomer* 2-(±)-(2*S*, 3*R*)-**11** (867 mg, 1.71 mmol) in dichloromethane (10 ml) at 0 °C. A

solution of titanium tetrachloride (670 μ l, 6.15 mmol) in dichloromethane (7 ml) was added slowly over 1 h to the cold mixture. The reaction mixture was kept at 0 °C for a further 5 min before water (15 ml) followed by saturated aqueous sodium hydrogen carbonate (15 ml) was added. The organic phase was separated and the aqueous was extracted with dichloromethane (3 $\times$ 20 ml). The combined organic layers were washed with brine (60 ml), dried (MgSO_4) and concentrated. The residue was purified by column chromatography (40% up to 50% ethyl acetate / light petroleum) to give ($\pm$)-**12** (340 mg, 46%), as a colorless powder; mp 151-153 °C (from ethyl acetate / pentane); (Found: C, 68.8; H, 6.6; N, 6.3. $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_5$ requires C, 68.8; H, 6.5; N, 6.4%); (Found: M^+ , 436.2007. $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_5$ requires 436.1998); ν_{max} (KBr)/ cm^{-1} 3312 (NH), 2960 (CH), 1723, 1645, 1526 (CO); ^1H (300 MHz; CDCl_3) 9.98 (1H, s, CHO), 9.31 (1H, br s, NH), 8.18 (1H, d, J 8.1, 4-H), 7.75 (1H, d, J 2.8, 2-H), 7.32 (5H, m, ArH), 7.11 (1H, s, 8.2, 7-H), 7.00 (1H, d, J 8.1, 5-H), 5.24 (1H, br d, J 8.9, NHCbz), 5.11 (2H, m, CH_2Ar), 4.88 (1H, m, $\square$ -CH), 4.07 (2H, m, CH_2Me), 2.78 (1H, m, $\square$ -CH), 2.34 (1H, m, CHMe_2), 1.13 (6H, m, CH_2Me , CHMeMe), 0.73 (3H, d, J 6.6, CHMeMe); ^{13}C (75 MHz; CDCl_3) 185.6 (CH), 171.6 (C), 156.2 (C), 137.2 (C), 136.6 (C), 136.4 (CH), 135.2 (C), 129.0 (CH), 128.7 (CH), 128.6 (CH), 124.4 (CH), 124.0 (C), 122.0 (CH), 119.7 (C), 112.8 (CH), 67.5 (CH_2), 61.8 (CH_2), 57.2 (CH), 56.4 (CH), 29.4 (CH), 21.8 (Me), 21.3 (Me), 14.4 (Me); m/z (EI) 436 (M^+ , 4%), 368 (2), 285 (6), 212 (6), 201 (56), 200 (100), 172 (39), 158 (56), 130 (35), 98 (45), 91 (82), 80 (85), 79 (48), 55 (58).

Compound 14

(a) Cesium carbonate (13.0 g, 39.9 mmol) and (±)-(2S/R, 3R/S)-ethyl 2-benzyloxycarbonylamino-3-(3-formylindol-6-yl)-4-methylpentanoate **12** (457 mg, 0.78 mmol) in water (12 ml) and methanol (12 ml) were heated under reflux for 3.5 h. The methanol was removed under vacuum, ethyl acetate (20 ml) and aqueous sodium hydroxide (1 M; 20 ml) were added and the layers separated. The organic layer was extracted with aqueous sodium hydroxide (1M; 20 ml) and the combined aqueous layers were acidified to pH 5 using hydrochloric acid. The aqueous was extracted with ethyl acetate (3 × 30 ml) and the combined organic layers were dried (MgSO₄) and concentrated to give 2-benzyloxycarbonylamino-3-(3-formylindol-6-yl)-4-methylpentanoic acid (390 mg, 91%) as a colorless crystalline powder; mp 150-152 °C (from ethyl acetate / pentane); (Found: C, 67.1; H, 6.1; N, 6.8. C₂₃H₂₄N₂O₅·0.25H₂O requires C, 66.9; H, 6.0; N, 6.8%); (Found: MH⁺, 409.1757. C₂₃H₂₄N₂O₅ + H requires 409.1758); ν_{max} (KBr)/cm⁻¹ 3295, 1573 (NH), 2962 (CH), 1718, 1646, 1526 (CO); δ_{H} (300 MHz; MeOD) 9.74 (1H, s, CHO), 7.94 (2H, m, 2-H, 4-H), 7.24 (6H, m, ArH, 7-H), 6.97 (1H, d, *J* 7.7, 5-H), 5.02 (1H, d, *J* 18.2, CHHAr), 4.98 (1H, d, *J* 18.2, CHHAr), 4.63 (1H, m, □-CH), 2.87 (1H, m, □-CH), 2.26 (1H, m, CHMe₂), 0.91 (3H, d, *J* 5.9, CHMeMe), 0.66 (3H, d, *J* 5.9, CHMeMe); δ_{C} (75 MHz; MeOD) 187.8 (CH), 158.7 (C), 140.3 (CH), 139.3 (C), 138.7 (C), 136.9 (C), 129.9 (CH), 129.4 (CH), 129.2 (CH), 126.1 (CH), 125.1 (C), 122.2 (CH), 120.4 (C), 114.4 (CH), 68.1 (CH₂), 58.3 (CH), 56.7 (CH), 30.2 (CH), 22.4

(Me), 20.6 (Me), (one quaternary carbon is not visible); m/z (CI) 409 (MH^+ , 2%), 318 (15), 132 (25), 126 (28), 108 (100), 106 (53), 98 (45).

(b) Benzotriazole-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP) (642 mg, 1.28 mmol) was added to a solution of the above carboxylic acid (375 mg, 0.920 mmol) in dichloromethane (9 ml) at 0 °C. A premixed solution of (*S*)-isoleucine *tert*-butyl ester hydrochloride salt (288 mg, 1.29 mmol) and diisopropylethylamine (450 μ l, 2.57 mmol) in dichloromethane (9 ml) was added dropwise over 1 h. The reaction mixture was left to warm to room temperature overnight. The solvent was removed under vacuum and the residue dissolved in ethyl acetate (20 ml), washed with saturated aqueous sodium hydrogen carbonate (20 ml) and brine (20 ml), dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (50% ethyl acetate / light petroleum) to give the *title compound* **14** (502 mg, 94%) as an inseparable 1:1 mixture of diastereomers, as a colorless sticky foam; (Found: MH^+ , 578.3229. $C_{33}H_{43}N_3O_6 + H$ requires 578.3225); ν_{max} (KBr)/ cm^{-1} 3417 (NH), 2966 (CH), 1725, 1652, 1529 (CO); δ_H (300 MHz; $CDCl_3$) 10.00, 9.96 (1H, s, CHO), 9.22, 9.05 (1H, br s, NH), 8.19 (1H, m, IndH), 7.78 (1H, m, IndH), 7.35 (6H, m, IndH, 5ArH), 7.09 (1H, m, IndH), 6.41, 6.29 (1H, m, NH(Ile)), 5.40 (1H, m, $NHCbz$), 5.14 (2H, m, CH_2Ar), 4.73 (1H, m, $\square$ -CH(Leu)), 4.17 (1H, m, $\square$ -CH(Ile)), 2.93 (1H, m, $\square$ -CH(Leu)), 2.35 (1H, m, $CHMe_2$), 1.70 (1H, m, $\square$ -CH(Ile)), 1.39, 1.25 (9H, s, CMe_3), 0.97-0.75, 0.68, 0.50, 0.18 (14H, m, 4 $\square$ Me, CH_2Me); m/z (CI) 578 (MH^+ , <1%), 188 (11), 140 (20), 128 (37), 114 (56), 112 (71), 100 (92), 86 (100), 72 (68).

Dehydrotryptophans 15

(a) Di-*tert*-butyl dicarbonate (208 mg, 0.960 mmol) in acetonitrile (10 ml) was added slowly over 1 h to a solution **14** (502 mg, 0.870 mmol) and 4-dimethylaminopyridine (11 mg, 0.090 mmol) in acetonitrile (10 ml). The reaction mixture was stirred for 3 h and the solvent removed under vacuum. The residue was dissolved in ethyl acetate (30 ml), washed with saturated aqueous sodium hydrogen carbonate (30 ml) and brine (30 ml), dried (MgSO₄) and concentrated. The residue was purified by column chromatography (50% ethyl acetate / light petroleum) to give *N*-Boc-**14** (445 mg, 76%) as an inseparable 1:1 mixture of diastereomers, as a colorless sticky foam; (Found: M^+ , 677.3665. C₃₈H₅₁N₃O₈ requires 677.3676); $\nu_{\max}$ (KBr)/cm⁻¹ 3350 (NH), 2967 (CH), 1735, 1678, 1548, 1520 (CO); δ_{H} (300 MHz; CDCl₃) 10.06 (1H, s, CHO), 8.20, (2H, m, IndH), 8.00 (1H, m, IndH), 7.34 (5H, m, ArH), 7.16 (1H, m, IndH), 6.30, 6.17 (1H, m, NH(Ile)), 5.28 (1H, m, NHCBz), 5.15 (2H, m, CH₂Ar), 4.74 (1H, m, α -CH(Leu)), 4.20 (1H, m, α -CH(Ile)), 2.95 (1H, m, α -CH(Leu)), 2.40 (1H, m, CHMe₂), 1.70, 1.60 (10H, m, α -CH(Ile), CMe₃), 1.38, 1.30 (9H, s, CMe₃), 1.10 (2H, m, CH₂Me), 1.03, 0.92 (3H, m, Me), 0.84, 0.70 (6H, m, Me), 0.61, 0.29 (3H, m, Me); m/z (EI) 677 (M^+ , <1%), 647 (8), 526 (3), 466 (12), 244 (43), 200 (100), 158 (923), 111 (29), 97 (50).

(a) The above indole-3-carboxaldehyde **14** (437 mg, 0.645 mmol) in dichloromethane (8 ml) was added dropwise to a solution of phosphonoglycine **13**² (460 mg, 1.16 mmol) and distilled

1,8-diazabicyclo[5.4.0]undec-7-ene (190 μ l, 1.26 mmol) in dichloromethane (8 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight, and the solvent removed under vacuum. The residue was dissolved in ethyl acetate (20 ml), washed with saturated aqueous sodium hydrogen carbonate (10 ml) and brine (10 ml), and the organic layer dried (MgSO₄) and concentrated. The residue was purified and the diastereomers separated by column chromatography (20% up to 30% ethyl acetate / light petroleum) to give the *dehydrotryptophans* **D1-15** (207 mg, 34%) as a colorless powder; mp 111-112 °C (from ethyl acetate / pentane); (Found: C, 64.2; H, 7.9; N, 7.1. C₅₁H₇₃N₅O₁₂·0.33H₂O requires C, 64.2; H, 7.8; N, 7.3%); (Found: MH⁺, 948.5322. C₅₁H₇₃N₅O₁₂ + H requires 948.5328); ν_{max} (KBr)/cm⁻¹ 3348 (NH), 2969 (CH), 1728, 1693 (CO), 1499 (Aryl CC); δ_{H} (400 MHz; CDCl₃) 7.91 (1H, s, NH), 7.86 (1H, s, 7-H), 7.70 (1H, s, 2-H), 7.42 (2H, m, =CH, 4-H or 5-H), 7.33 (5H, m, ArH), 7.16 (1H, d, *J* 7.9, 4-H or 5-H), 6.90 (1H, br d, *J* 7.7, NH(Ile)), 5.38 (1H, br d, *J* 9.1, NHCBz), 5.23 (1H, br d, *J* 9.6, NHBoc), 5.13 (2H, m, CH₂Ar), 4.70 (1H, m, $\square$ -CH(Leu)), 4.40 (1H, m, $\square$ -CH(Val)), 4.06 (1H, m, $\square$ -CH(Ile)), 3.84 (3H, s, OMe), 2.87 (1H, m, $\square$ -CH(Leu)), 2.32 (1H, m, $\square$ -CH(Val)), 2.07 (1H, m, $\square$ -CH(Ile)), 1.66 (10H, m, CMe₃, $\square$ -CH(Ile)), 1.54 (9H, s, CMe₃), 1.40 (2H, m, CH₂Me), 1.11 (9H, s, CMe₃), 0.99 (3H, d, *J* 6.8, Me(Leu)), 0.95 (3H, d, *J* 6.8, Me(Leu)), 0.88 (6H, m, (Me)₂(Val)), 0.78 (3H, t, *J* 7.3, CH₂Me), 0.72 (3H, d, *J* 6.8, CHMe(Ile)); δ_{C} (100 MHz; CDCl₃) 171.6 (C), 171.3 (C), 170.8 (C), 169.9 (C), 165.1 (C), 155.7 (C), 148.9 (C), 136.5 (C), 135.3 (C), 134.7 (C), 128.5 (CH), 128.03 (CH), 127.96 (CH), 127.5 (CH), 126.7 (C), 125.1 (C), 124.1 (CH), 122.7 (CH), 120.6 (CH), 117.3 (CH), 114.1 (CH), 84.4 (C), 81.5 (C), 80.2 (C), 66.8 (CH₂), 58.9 (CH), 57.1 (CH), 56.9 (CH), 55.5 (CH), 52.4 (Me), 37.2 (CH), 31.7 (CH), 28.5 (Me), 28.3 (CH), 28.1 (Me), 27.6 (Me), 25.3 (CH₂), 21.8 (Me), 18.8 (Me), 18.0 (2 overlapping Me), 15.1 (Me), 11.0 (Me); *m/z* (ES) 971 (M+Na⁺, 100%), 949 (M+H⁺, 91), 849 (99), 792 (52), 91 (23), and **D2-**

15 (237 mg, 39%) as a colorless powder; mp 124-126 °C (from ethyl acetate / pentane); (Found: C, 63.9; H, 8.0; N, 7.2. $C_{51}H_{73}N_5O_{12} \cdot 0.5H_2O$ requires C, 64.0; H, 7.8; N, 7.3%); (Found: MH^+ , 948.5327. $C_{51}H_{73}N_5O_{12} + H$ requires 948.5328); ν_{max} (KBr)/ cm^{-1} 3337 (NH), 2968 (CH), 1728 (CO), 1506 (Aryl CC); δ_H (400 MHz; $CDCl_3$) 7.99 (1H, s, 7-H), 7.92 (1H, s, 2-H), 7.63 (1H, s, =CH), 7.60 (1H, s, NH), 7.56 (1H, d, J 8.0, 4-H, or 5-H), 7.33 (5H, m, ArH), 7.12 (1H, d, J 8.0, 4-H or 5-H), 6.15 (1H, br d, J 6.5, NH(Ile or Val)), 5.37 (1H, d, J 9.0, $NH\text{Cbz}$), 5.13 (2H, m, $CH_2\text{Ar}$), 5.07 (1H, d, J 9.2, NH(Ile or Val)), 4.72 (1H, m, $\square\text{-CH(Leu)}$), 4.19 (1H, m, $\square\text{-CH(Ile or Val)}$), 4.12 (1H, m, $\square\text{-CH(Ile or Val)}$), 3.85 (3H, s, OMe), 2.97 (1H, m, $\square\text{-CH(Leu)}$), 2.35 (2H, m, $\square\text{-CH(Ile or Val)}$, $CHMe_2$), 1.68 (10H, m, CMe_3 , $\square\text{-CH(Ile or Val)}$), 1.45 (9H, s, CMe_3), 1.37 (9H, s, CMe_3), 1.31 (2H, m, CH_2Me), 1.03 (3H, d, J 6.8, Me), 0.99 (3H, d, J 6.8, Me), 0.90 (3H, d, J 6.8, Me), 0.86 (3H, d, J 6.8, Me), 0.58 (3H, d, J 6.8, Me), 0.26 (3H, d, J 6.8, Me(Ile)); δ_C (100 MHz; $CDCl_3$) 170.38 (C), 170.37 (C), 170.3 (C), 170.1 (C), 165.3 (C), 156.0 (C), 149.0 (C), 136.2 (C), 135.3 (C), 134.9 (C), 128.7 (C), 128.5 (CH), 128.13 (CH), 128.07 (CH), 127.6 (CH), 125.2 (CH), 123.8 (CH), 123.1 (C), 118.5 (CH), 116.2 (CH), 113.7 (C), 84.7 (C), 81.9 (C), 80.2 (C), 67.1 (CH_2), 61.8 (CH), 57.1 (CH), 56.6 (CH), 54.9 (CH), 52.6 (Me), 38.0 (CH), 30.2 (CH), 28.3 (Me), 28.2 (CH), 28.1 (Me), 28.0 (Me), 24.7 (CH_2), 21.7 (Me), 19.5 (Me), 18.4 (Me), 17.5 (Me), 14.5 (Me), 11.4 (Me); m/z (ES) 971 ($M+Na^+$, 100%), 949 ($M+H^+$, 20), 849 (31), 793 (14), 91 (12), 46 (20).

Compounds 16

(a) **D1-16**

Anhydrous methanol (12 ml) was added to dehydrotryptophan **D1-15** (164 mg, 0.173 mmol) and (+)-1,2-bis((2*S*,5*S*)-2,5-diethylphospholano)benzene (cyclooctadiene) rhodium(I) trifluoromethanesulfonate (6.5 mg, 5 mol%) contained in a dry Parr tube. The system was evacuated and flushed with nitrogen 5 times, and evacuated and flushed with hydrogen 5 times. The hydrogen pressure was increased to 90 psi. The reaction mixture was left to stir for 42 h and the solvent was removed under vacuum. The residue was purified by column chromatography (30% ethyl acetate / light petroleum) to give **D1-16** (161 mg, 98%, 99% de) as colorless crystals; mp 107-109 °C (from ethyl acetate / pentane); $[\alpha]_D^{30}$ 28.6 (*c* 0.42, CHCl₃) (Found: MH⁺, 950.5489. C₅₁H₇₅N₅O₁₂ + H requires 950.5485); $\bar{\nu}_{\max}$ (KBr)/cm⁻¹ 3371 (NH), 2968, 2934, 2876 (CH), 1732, 1668 (CO), 1505 (Aryl CC); δ_{H} (400 MHz; CDCl₃) 7.73 (1H, s, 7-H), 7.32 (6H, m, ArH, 4-H or 5-H), 7.23 (1H, s, 2-H), 7.11 (1H, d, *J* 7.8, 4-H or 5-H), 6.98 (1H, d, *J* 9.2, NH(Ile)), 6.91 (1H, d, *J* 8.3, NH(Trp)), 5.41 (1H, d, *J* 9.0, NHCBz), 5.33 (1H, d, *J* 9.9, NHBoc), 5.14 (3H, m, CH₂Ar, $\square$ -CH(Trp)), 4.69 (1H, m, $\square$ -CH(Leu)), 4.33 (1H, m, $\square$ -CH(Val)), 4.02 (1H, m, $\square$ -CH(Ile)), 3.75 (3H, s, OMe), 3.29 (2H, m, $\square$ -CH₂(Trp)), 2.86 (1H, m, $\square$ -CH(Leu)), 2.28 (1H, m, CHMe₂), 1.86 (1H, m, $\square$ -CH(Val)), 1.77 (1H, m, $\square$ -CH(Ile)), 1.63 (9H, s, CMe₃), 1.59 (9H, s, CMe₃), 1.46 (1H, m, CHHMe), 1.11 (9H, s, CMe₃), 1.01 (1H, m, CHHMe), 0.85 (9H, m, 3 $\square$ Me), 0.75 (9H, m, 3 $\square$ Me); δ_{C} (100 MHz; CDCl₃) 171.8 (C), 171.6 (C), 171.2 (C), 171.0 (C),

155.6 (C), 155.4 (C), 149.3 (C), 136.6 (C), 135.0 (C), 133.8 (C), 130.0 (C), 128.4 (CH), 128.0 (CH), 127.9 (CH), 123.4 (2 overlapping CH), 118.7 (CH), 117.5 (CH), 115.2 (C), 83.4 (C), 81.3 (C), 80.0 (C), 66.7 (CH₂), 58.4 (CH), 57.3 (CH), 56.9 (CH), 54.4 (CH), 53.0 (CH), 52.2 (Me), 36.2 (CH), 32.5 (CH), 28.6 (Me), 28.2 (Me), 27.9 (CH), 27.3 (Me), 26.7 (CH₂), 25.1 (CH₂), 21.8 (Me), 18.6 (Me), 18.3 (Me), 17.4 (Me), 15.1 (Me), 10.7 (Me); *m/z* (ES) 973 (M+Na⁺, 100%), 951 (M+H⁺, 38), 851 (72), 164 (13), 91 (15).

(b) D2-16

An identical procedure to above was followed using dehydrotryptophan **D2-15** (161 mg, 0.170 mmol). Purification gave **D2-16** (162 mg, >99%, >99% de) as colorless crystals; mp 94-96 °C (from ethyl acetate / pentane); $[\alpha]_D^{30}$ 23.5 (*c* 0.51, CHCl₃) (Found: MH⁺, 950.5478.

C₅₁H₇₅N₅O₁₂ + H requires 950.5485); $\nu_{\max}$ (KBr)/cm⁻¹ 3427, 3328 (NH), 2968, 2934, 2876 (CH), 1733, 1678 (CO), 1511 (Aryl CC); δ_{H} (400 MHz; CDCl₃) 7.95 (1H, s, 7-H), 7.33 (7H, m, 5ArH, 2-H, 4-H or 5-H), 7.05 (1H, d, *J* 7.7, 4-H or 5-H), 6.67 (1H, br s, NH(Trp)), 6.20 (1H, d, *J* 7.5, NH(Ile)), 5.57 (1H, br s, NHCBz), 5.11 (2H, s, CH₂Ar), 5.05 (1H, d, *J* 7.6, NHBoc), 4.84 (1H, m, □-CH(Trp)), 4.72 (1H, m, □-CH(Leu)), 4.18 (1H, m, □-CH(Ile)), 3.96 (1H, m, □-CH(Val)), 3.62 (3H, s, OMe), 3.13 (2H, m, □-CH₂(Trp)), 2.96 (1H, m, □-CH(Leu)), 2.33 (1H, m, CHMe₂), 2.09 (1H, m, □-CH(Val)), 1.65 (9H, s, CMe₃), 1.40 (9H, s, CMe₃), 1.36 (9H, s, CMe₃), 1.30 (1H, m, □-CH(Ile)), 1.00 (1H, m, CHHMe), 0.87 (12H, m, 2 □ Me(Val), 2 □ Me(Leu)), 0.61 (1H, m, CHHMe), 0.55 (3H, m, CH₂Me), 0.22 (3H, d *J* 6.0, CHMe); δ_{C} (100 MHz; CDCl₃) 171.8 (C), 171.5 (C), 170.4 (C), 170.1 (C), 156.0 (C), 155.7 (C), 149.3 (C), 136.3 (C), 134.63 (C), 134.60 (C), 129.4 (C), 128.5 (CH), 128.1 (CH), 128.0 (CH), 124.8 (CH), 124.0 (CH), 118.4 (CH), 116.1 (CH), 114.7 (C), 83.8 (C), 81.8 (C), 79.9 (C), 67.0 (CH₂), 59.7 (CH), 57.0 (CH), 56.6 (CH), 54.6

(CH), 52.4 (overlapping CH and Me), 37.9 (CH), 30.9 (CH), 28.25 (Me), 28.19 (overlapping CH and Me), 27.9 (Me), 27.6 (CH₂), 24.6 (CH₂), 21.7 (Me), 19.2 (Me), 18.3 (Me), 17.6 (Me), 14.4 (Me), 11.4 (Me); *m/z* (ES) 973 (M+Na⁺, 100%), 951 (M+H⁺, 15), 851 (78), 795 (11), 91 (8).

(c) Achiral hydrogenation using **D1-15**

Anhydrous methanol (1 ml) was added to dehydrotryptophan **D1-15** (9 mg, 0.009 mmol) and 1,1'-bis(di-*iso*-propylphosphino)ferrocene (1,5-cyclooctadiene) rhodium(I) tetrafluoroborate (1.5 mg, 2 mol%) contained in a dry Parr tube. The system was evacuated and flushed with nitrogen 5 times, and evacuated and flushed with hydrogen 5 times. The hydrogen pressure was increased to 90 psi. The reaction mixture was left to stir for 20 h and the solvent was removed under vacuum. The residue was purified by column chromatography (30% ethyl acetate / light petroleum) to give a 1:1 mixture of diastereomers (9 mg, 100%) as a colorless powder.

(d) Achiral hydrogenation using using **D2-15**

An identical procedure to above was followed using dehydrotryptophan **D2-15** (8 mg, 0.008 mmol). Purification gave a 1:1 mixture of diastereomers (8 mg, 100%) as a colorless powder.

Compounds 17

(a) **D1-17**

Trifluoroacetic acid (0.7 ml) was added slowly to a solution of **D1-16** (43 mg, 0.045 mmol) in dichloromethane (0.7 ml) at room temperature. After 2.5 h the reaction mixture was concentrated ensuring all excess trifluoroacetic had been removed. The residue was dissolved in anhydrous DMF (45 ml), cooled to 0 °C and HOAt (47 mg, 0.344 mmol), diisopropylethylamine (90 μ l, 0.52 mmol) and HATU (65 mg, 0.17 mmol) were added sequentially. The reaction mixture was allowed to warm to room temperature and, after stirring for 4 days, was concentrated. The residue was dissolved in ethyl acetate (20 ml) and was washed with hydrochloric acid (1 M; 10 ml), saturated aqueous sodium hydrogen carbonate (2 $\times$ 10 ml) and brine (10 ml). The organic layer was dried (MgSO₄) and concentrated. The residue was purified by column chromatography (50% up to 80% ethyl acetate) to give **D1-17** (15 mg, 49%) as a colorless solid; (Found: MH⁺, 676.3698. C₃₇H₄₉N₅O₇ + H requires 676.3705); δ_{H} (400 MHz; MeOD) 7.38 (1H, d, *J* 8.9, 4-H), 7.22 (5H, m, ArH), 6.85 (3H, m, 2-H, 5-H, 7-H), 5.36 (1H, m, α -CH(Trp)), 5.00 (2H, m, CH₂Ar), 4.52 (1H, m, α -CH(Leu)), 3.86 (1H, d, *J* 8.4, α -CH(Ile or Val)), 3.76 (1H, d, *J* 6.6, α -CH(Ile or Val)), 3.67 (3H, s, OMe), 3.39 (1H, m, β -CHH(Trp)), 3.10 (1H, m, β -CHH(Trp)), 2.93 (1H, m, β -CH(Leu)), 2.18 (1H, m, CHMe₂), 1.95 (1H, m, β -CH(Ile or Val)), 1.57 (1H, m, CHHMe), 1.51 (1H, m, β -CH(Ile or Val)), 0.93 (1H, m, CHHMe), 0.89 (3H, d, *J* 6.8, Me(Leu)), 0.84 (6H, m, 2 $\times$ Me(Ile or Val)), 0.73 (3H, d, *J* 6.8, Me(Leu)), 0.66 (6H, m, 2 $\times$ Me(Ile or Val)); δ_{C} (100 MHz; MeOD) 172.3 (C), 172.2 (C), 171.4 (C), 170.5 (C), 156.8 (C), 137.1 (C), 136.9 (C), 130.3 (C), 128.1 (CH), 127.6 (CH), 127.2 (CH), 125.7 (C), 123.8 (CH), 118.3 (CH), 118.0 (CH), 114.5 (CH), 108.5 (C), 66.1 (CH₂), 58.5 (CH), 58.2 (CH), 58.1 (CH), 52.2 (CH), 51.3 (Me), 50.8 (CH), 37.7 (CH), 31.0 (CH), 27.6 (CH), 27.2 (CH₂), 24.3 (CH₂), 20.8 (Me), 17.7 (Me), 17.5 (Me), 16.7 (Me), 14.5 (Me), 9.5 (Me), containing 35% of an impurity which suggested that epimerization

had occurred during the reaction. The product was used in the next step without further purification.

(b) D2-17

An identical procedure to above was followed using **D2-16** (30 mg, 0.032 mmol). Purification gave **D2-17** (12 mg, 56%) as a colorless solid; $[\alpha]_D^{29}$ 28.6 (*c* 0.21, MeOH); (Found: MH^+ , 676.3706. $\text{C}_{37}\text{H}_{49}\text{N}_5\text{O}_7 + \text{H}$ requires 676.3705); ^1H (400 MHz; MeOD) 7.34 (1H, d, *J* 8.4, 4-H), 7.26 (5H, m, ArH), 7.04 (1H, s, 2-H), 6.99 (1H, s, 7-H), 6.47 (1H, d, *J* 8.4, 5-H), 4.99 (2H, app q, *J* 10.0, 12.0, CH_2Ar), 4.66 (1H, d, *J* 4.0, $\square$ -CH(Leu)), 4.53 (1H, d, *J* 10.0, $\square$ -CH(Trp)), 4.43 (1H, d, *J* 5.3, $\square$ -CH(Val)), 4.23 (1H, d, *J* 11.0, $\square$ -CH(Ile)), 3.70 (3H, s, OMe), 3.21 (1H, m, $\square$ -CHH(Trp)), 2.91 (1H, m, $\square$ -CHH(Trp)), 2.44 (1H, m, CHMe₂), 2.27 (1H, m, $\square$ -CH(Leu)), 1.88 (1H, m, $\square$ -CH(Val)), 1.45 (1H, m, $\square$ -CH(Ile)), 1.36 (1H, m, CHHMe), 1.21 (3H, d, *J* 6.3, Me(Leu)), 0.95 (1H, m, CHHMe), 0.86 (3H, d, *J* 6.9, Me(Val)), 0.81 (3H, d, *J* 6.6, CHMe), 0.73 (6H, m, Me(Ile), Me(Val)), 0.51 (3H, d, *J* 6.3, Me(Leu)); ^{13}C (100 MHz; MeOD) 171.6 (C), 171.1 (C), 170.9 (C), 169.9 (C), 156.0 (C), 136.7 (C), 131.5 (C), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.5 (C), 126.5 (C), 123.1 (CH), 119.3 (CH), 117.1 (CH), 113.4 (CH), 112.7 (C), 66.9 (CH₂), 59.12 (CH), 59.07 (CH), 57.9 (CH), 55.7 (CH), 55.5 (CH), 51.5 (Me), 36.5 (CH), 32.1 (CH), 29.5 (CH₂), 29.1 (CH), 24.6 (CH₂), 21.3 (Me), 20.9 (Me), 17.9 (Me), 17.1 (Me), 14.5 (Me), 9.1 (Me).

Stephanotic acid methyl ester 6

Palladium(II) hydroxide on carbon (20%; 10mg) was added to a solution of **D1-17** (15 mg, 0.022 mmol) in ethanol (0.5 ml). The system was evacuated and flushed with nitrogen 5 times, and evacuated and flushed with hydrogen 5 times. The reaction mixture was left stirring under hydrogen at atmospheric pressure for 2 h, and filtered through Celite. The filter pad was washed with ethanol (3 $\times$ 10 ml) and the combined washings were concentrated. The amine was dissolved in DMF (0.8 ml) and cooled to 0 °C. (*S*)-Pyroglutamic acid (4 mg, 0.031 mmol), HOAt (4 mg, 0.029 mmol), diethylisopropylamine (10 μ l, 0.058 mmol) and HATU (11mg, 0.029 mmol) were sequentially added to the solution. The reaction mixture was allowed to warm to room temperature overnight and the solvent was removed under vacuum. The residue was dissolved in ethyl acetate (20 ml) and was washed with hydrochloric acid (1M; 10 ml), saturated aqueous sodium hydrogen carbonate (10 ml) and brine (10 ml). The organic layer was dried (MgSO₄) and concentrated. The residue was purified and the product isolated by normal phase followed by reversed phase preparative HPLC to give **stephanotic acid methyl ester 6** (2 mg, 14%) as a colorless solid; mp 196-201 °C, (lit.,³ mp 202-204 °C); $[\alpha]_D^{28}$ -106 (*c* 0.09, MeOH), (lit.,³ $[\alpha]_D^{25}$ -119 (*c* 1.7, MeOH)); (Found: MH⁺, 653.3669. C₃₄H₄₈N₆O₇ + H requires 653.3663); δ_H (400 MHz; DMSO) 10.72 (1H, s, NH(Ind)), 8.56 (1H, *J*, 10.8, NH(Leu)), 8.34 (1H, d, *J*, 8.5, NH(Ile)), 7.91 (1H, s, NH(PyroGlu)), 7.48 (1H, d, *J* 8.5, NH(Trp)), 7.41 (1H, d, *J* 8.5, 4-H(Ind)), 7.03 (3H, m, NH(Val), 5-H(Ind), 2-H(Ind)), 6.93 (1H, s, 7-H), 5.28 (1H, m, α -CH(Trp)), 4.90 (1H, app t, *J*

10.8, α -CH(Leu)), 4.16 (1H, dd, J 9.0, 3.4, α -CH(PyroGlu)), 3.93 (1H, dd, J 7.6, 6.0, α -CH(Val)), 3.82 (1H, dd, J 10.3, 8.5, α -CH(Ile)), 3.70 (3H, s, OMe), 3.32 (1H, m, α -CHH(Trp)), 3.19 (1H, m, α -CHH(Trp)), 3.04 (1H, dd, J 10.8, 3.5, α -CH(Leu)), 2.29 (1H, m, α -CHH(PyroGlu)), 2.18 (1H, m, CHMe₂), 2.13 (2H, m, α -CH₂(PyroGlu)), 2.05 (1H, m, α -CH(Val)), 1.76 (1H, m, α -CHH(PyroGlu)), 1.66 (1H, m, α -CH(Ile)), 1.27 (2H, m, CH₂Me), 0.97 (3H, d, J 6.9, Me(Val)), 0.94 (3H, d, J 6.8, Me(Val)), 0.90 (3H, d, J 7.1, Me(Leu)), 0.82 (3H, d, J 6.8, Me(Leu)), 0.72 (3H, t, J 8.3, CH₂Me), 0.69 (3H, d, J 6.9, CHMe); δ_{C} (100 MHz; DMSO) 178.4 (CONH-PyroGlu), 173.2 (CO-PyroGlu), 172.7 (CO-Trp), 171.6 (CO-Val), 170.9 (CO-Leu), 170.7 (CO-Ile), 137.0 (8-C-Ind), 130.8 (6-C-Ind), 126.5 (9-C-Ind), 124.4 (2-CH-Ind), 120.0 (5-CH-Ind), 118.7 (4-CH-Ind), 115.5 (7-CH-Ind), 109.5 (3-C-Ind), 58.9 (α -CH-Val), 58.6 (α -CH-Ile), 56.1 (α -CH-Leu), 56.0 (α -CH-PyroGlu), 52.9 (Me-Trp), 52.8 (α -CH-Leu), 52.0 (α -CH-Trp), 38.1 (α -CH-Ile), 31.5 (α -CH-Val), 30.0 (α -CH₂-PyroGlu), 28.1 (CH₂-Ile), 27.8 (α -CH₂-Trp), 26.5 (α -CH-Leu), 25.0 (α -CH₂-PyroGlu), 22.8 (Me-Leu), 19.6 (Me-Val), 18.9 (Me-Val), 18.3 (Me-Leu), 16.3 (CHMe-Ile), 11.3 (CH₂Me-Ile); m/z (ES) 675 (M+Na⁺, 38%), 653 (M+H⁺, 26), 360 (100), 338 (87), 204 (31), 150 (47).

Carbon assignments made by HMQC spectroscopy, (quaternary carbons assigned by comparison with the literature report).³

Diastereomer of Stephanotic acid methyl ester Diast-6

An identical procedure to above was followed using **D2-17** (12 mg, 0.018 mmol). Purification of the crude product was by column chromatography (2% up to 5% methanol / ethyl acetate) to give **Diast-6** (4 mg, 34%) as a colorless solid; mp 220-225 °C; $[\alpha]_{\text{D}}^{30}$ 22 (c 0.09, MeOH), δ_{H} (400 MHz; MeOD) 7.53 (1H, d, J 8.4, 4-H), 7.19 (1H, s, 7-H), 7.15 (1H, s, 2-H), 6.64 (1H, dd, J 8.4,

1.4, 5-H), 4.96 (1H, d, J 3.9, $\square$ -CH(Leu)), 4.65 (1H, d, J 11.4, $\square$ -CH(Trp)), 4.52 (1H, d, J 5.3, $\square$ -CH(Val)), 4.29 (1H, d, J 11.6, $\square$ -CH(Ile)), 4.21 (1H, dd, J 8.4, 6.5, $\square$ -CH(PyroGlu)), 3.80 (3H, s, OMe), 3.36 (1H, m, $\square$ -CHH(Trp)), 3.04 (1H, dd, J 14.4, 11.2, $\square$ -CHH(Trp)), 2.55 (1H, m, CHMe₂), 2.48 (1H, m, $\square$ -CHH(PyroGlu)), 2.38 (3H, m, $\square$ -CH(Leu), $\square$ -CH₂(PyroGlu)), 2.08 (2H, m, $\square$ -CHH(PyroGlu), $\square$ -CH(Val)), 1.53 (1H, m, $\square$ -CH(Ile)), 1.40 (1H, m, CHHMe), 1.30 (3H, d, J 6.4, Me(Leu)), 1.01 (3H, d, J 6.8, Me(Val)), 0.96 (1H, m, CHHMe), 0.88 (6H, m, Me(Ile), Me(Val)), 0.79 (3H, t, J 7.3, Me(Ile)), 0.63 (3H, d, J 6.6, Me(Leu)); $\square_c$ (100 MHz; MeOD) 180.5 (C), 172.8 (C), 171.7 (C), 171.0 (C), 170.1 (C), 169.5 (C), 136.8 (C), 131.5 (C), 126.7 (C), 123.3 (CH), 119.8 (CH), 117.4 (CH), 113.2 (CH), 112.6 (C), 59.3 (CH), 58.20 (CH), 58.17 (CH), 57.0 (CH), 55.2 (CH), 54.4 (CH), 51.4 (Me), 35.9 (CH), 31.6 (CH), 29.4 (CH₂), 29.3 (CH₂), 29.2 (CH), 25.1 (CH₂), 24.5 (CH₂), 21.2 (Me), 20.8 (Me), 18.0 (Me), 16.8 (Me), 14.4 (Me), 8.8 (Me).

X-ray crystal data of ($\pm$)-12

Crystal data

Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	$a = 14.248(3)$ Å	$\square = 90^\circ$.
	$b = 7.7909(16)$ Å	$\square = 108.455(3)^\circ$.
	$c = 22.151(5)$ Å	$\square = 90^\circ$.
Volume	2332.5(9) Å ³	
Z	4	
Density (calculated)	1.243 Mg/m ³	
Absorption coefficient	0.087 mm ⁻¹	
F(000)	928	

Crystal size	0.2000 x 0.2000 x 0.0300 mm ³
Theta range for data collection	2.79 to 25.36°.
Index ranges	-16<=h<=17, -9<=k<=8, -26<=l<=22
Reflections collected	16112
Independent reflections	3944 [R(int) = 0.0329]
Completeness to theta = 25.36°	92.1 %
Absorption correction	None
Max. and min. transmission	1.0000 and 0.2692
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3944 / 2 / 299
Goodness-of-fit on F ²	1.046
Final R indices [I>2sigma(I)]	R1 = 0.0368, wR2 = 0.0855
R indices (all data)	R1 = 0.0438, wR2 = 0.0902
Extinction coefficient	0.0039(17)
Largest diff. peak and hole	0.225 and -0.184 e.Å ⁻³

References

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- (3) Yoshikawa, K.; Tao, S.; Arihara, A. *J. Nat. Prod.* **2000**, 63, 540-542.