Supplementary Material for Organic & Biomolecular Chemistry

Asymmetric synthesis of the central tryptophan residue of stephanotic acid

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Supplementary data

Experimental procedures

6-Bromo-1-*tert*-butoxycarbonylindole-3-carbaldehyde 11

Di-*tert*-butyl dicarbonate (1.95 g, 8.93 mmol) was added to 6-bromoindole-3-carbaldehyde (2.00g, 8.93 mmol) and 4-dimethylaminopyridine (32 mg, 0.262 mmol) in acetonitrile (25 ml). The mixture was stirred for 5 min at room temperature and the solvent evaporated *in vacuo*. The residue was dissolved in ethyl acetate (50 ml), washed with saturated sodium hydrogen carbonate (50 ml) and brine (50 ml), dried over magnesium sulfate and concentrated to give the *title compound* (2.89 g, 98%) as a colourless powder; mp 144-145 °C (from ethyl acetate / light petroleum), (lit.,[1] mp 148 °C); (Found: MH^+, 324.0239. $C_{14}H_{14}{}^{79}BrNO_3$ + H requires 324.0235); ν_{max} (KBr)/cm^{-1} 1736 (CO), 1673 (CO); δ (300 MHz; $CDCl_3$) 10.07 (1H, s, CHO), 8.37 (1H, d, *J* 1.6, 7-H), 8.19 (1H, s, 2-H), 8.15 (1H, dd, *J* 8.5, 1.6, 5-H), 7.49 (1H, d, *J* 8.5, 4-H), 1.71 (9H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 185.9 (CHO), 148.4 (CO), 136.6 (C), 136.5 (CH), 128.0 (CH), 124.9 (C), 123.3 (CH), 121.3 (C), 119.9 (C), 118.5 (CH), 86.3 (C), 28.0 ($C\underline{Me}_3$); *m/z* (CI) 326/324 (MH^+, 7/7%), 298/296 (10/10), 286 (29), 270/268 (89/100), 226/224 (93/98).

N-tert-Butoxycarbonyl (*S*)-valinamide 7

Ethyl chloroformate (4.65 ml, 48.4 mmol) was added slowly to a stirred solution of *N-tert*-butoxycarbonyl (*S*)-valine (10.0 g, 46.1 mmol) and triethylamine (6.73 ml, 48.4 mmol) in tetrahydrofuran (150 ml) at 0 °C. The reaction mixture was stirred for 30 min and aqueous ammonia (35%; 15 ml) in tetrahydrofuran (8 ml) was added. The reaction mixture was allowed to warm to room temperature over 2.5 h and the solvent evaporated *in vacuo* to give a colourless solid that was partitioned between ethyl acetate (250 ml) and water (200 ml). The aqueous layer was extracted with ethyl acetate (3 × 50 ml) and the combined organics were washed with saturated sodium hydrogen carbonate (2 × 30 ml), brine (20 ml), citric acid solution (1 M; 2 × 30 ml), brine (20 ml), copper sulfate solution (1 M; 2 × 30 ml) and brine (20 ml). The organic layer was dried over magnesium sulfate and concentrated to give the *title compound* (9.71 g, 98%) as a

colourless powder; mp 158-160 °C (from ethyl acetate / light petroleum), (lit.,[2a] mp 158-159 °C); $[\alpha]_D^{32}$ -5.33 (*c* 0.60, $CHCl_3$) {lit.,[2b] $[\alpha]_D^{25}$ -4.73 (*c* 0.66, $CHCl_3$)} (Found: MH^+, 217.1561. $C_{10}H_{20}N_2O_3$ + H requires 217.1552); ν_{max} (KBr)/cm^{-1} 3387 (NH), 3348 (NH), 3207 (NH), 2979 (CH), 1680 (CO), 1641 (CO); δ_H (300 MHz; $CDCl_3$) 7.28 (1H, br s, NHH), 6.34 (1H, br s, NHH), 5.19 (1H, br d, *J* 8.9, BocNH), 4.02 (1H, br app t, *J* 7.5, α-CH), 2.11 (1H, m, $CHMe_2$), 1.44 (9H, s, CMe_3), 0.99 (3H, d, *J* 6.8, $CHCH_3Me$), 0.94 (3H, d, *J* 6.8, $CHMeCH_3$); δ_C (75 MHz; $CDCl_3$) 174.4 (CO), 156.0 (CO), 80.0 (C), 59.4 (CH), 30.7 (CH), 28.0 (CMe_3), 19.3 (Me), 17.8 (Me); *m/z* (CI) 217 (MH^+, 2%), 189 (15), 161 (28), 157 (11), 144 (15), 143 (37), 117 (82), 116 (29), 115 (10), 98 (10), 73 (12), 72 (100), 57 (31).

***N-tert*-Butoxycarbonyl (*S*)-isoleucine (*S*)-valinamide 9**

(a) *N,N*'-Dicyclohexylcarbodiimide (472 mg, 2.29 mmol) in anhydrous tetrahydrofuran (1 ml) was added dropwise to a solution of (*S*)-valine methyl ester hydrochloride (349 mg, 2.08 mmol), *N-tert*-butoxycarbonyl (*S*)-isoleucine hemihydrate (500 mg, 2.08 mmol), 1-hydroxybenzotriazole (281 mg, 2.08 mmol) and *N*-ethylmorpholine (0.27ml, 2.08 mmol) in anhydrous tetrahydrofuran (5 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature after 1 h and then stirred for 1 h. The colourless solid formed was removed by filtration and the filtrate was concentrated. The residue was dissolved in ethyl acetate (50 ml) and washed with saturated aqueous sodium hydrogen carbonate (30 ml), citric acid solution (10%; 30 ml), saturated aqueous sodium hydrogen carbonate (30 ml) and water (30 ml). The organic layer was dried over magnesium sulfate and concentrated. The residue was purified by column chromatography (25% ethyl acetate / light petroleum) to give *N-tert*-butoxycarbonyl (*S*)-isoleucine (*S*)-valine methyl ester (574 mg, 80%) as a colourless powder; mp 167-168 °C (from ethyl acetate / light petroleum), (lit.,[3] mp 169-170 °C); $[\alpha]_D^{27}$ -7.00 (c 0.57, $CHCl_3$) {lit.,[3] $[\alpha]_D^{25}$ -15.4 (*c* 0.57, $CHCl_3$)} (Found: C, 59.0; H, 9.7; N, 8.1. $C_{17}H_{32}N_2O_5$ requires C, 59.3; H, 9.4; N, 8.1%) (Found: MH^+ 345.2384. $C_{17}H_{32}N_2O_5$ + H requires 345.2389); ν_{max} (KBr)/cm^{-1} 3323 (NH), 2967 (CH), 1750 (CO), 1684 (CO), 1649 (CO); δ_H (300 MHz; $CDCl_3$) 6.81 (1H, br d, *J* 8.5, NH-Val), 5.40 (1H, br d, *J* 8.1, NH-Ile), 4.54 (1H, dd, *J* 5.4, 8.5, α-CH-Val), 4.04 (1H, app t, *J* 8.1, α-CH-Ile), 3.73 (3H, s, OMe), 2.17 (1H, m, β-CH-Val), 1.85 (1H, br m, β-CH-Ile), 1.52 (1H, br m, CHH-Ile), 1.44 (9H, s, Me_3), 1.15 (1H, br m, CHH-Ile), 0.90 (12H, m, $CHMe_2$-Val, 2 × Me-Ile);

δ_C (75 MHz; $CDCl_3$) 172.4 (CO), 172.3 (CO), 156.2 (CO), 81.0 (C), 60.7 (CH), 59.6 (CH), 52.3 (Me), 37.2 (CH), 31.4 (CH), 28.6 ($C\underline{Me}_3$), 25.1 (CH_2), 19.2 (Me), 18.1 (Me), 15.7 (Me), 11.6 (Me); *m/z* (CI) 345 (MH^+, 63%), 290 (10), 289 (73), 245 (100), 130 (14), 86 (38), 57 (97).

(b) *N-tert*-Butoxycarbonyl (*S*)-isoleucine (*S*)-valine methyl ester (861 mg, 2.51 mmol) was dissolved in tetrahydrofuran (12 ml) and cooled to 0 °C. Lithium hydroxide monohydrate (263 mg, 6.26 mmol) dissolved in water (3 ml) was added dropwise to the ester and the reaction mixture was stirred at room temperature for 15 h. The solvent was evaporated *in vacuo* and water (20 ml) was added to the residue. The basic aqueous layer was washed with ethyl acetate (2 × 10 ml) and then acidified to pH 4 with citric acid solution (10%) at 0 °C. The product was extracted with ethyl acetate (3 × 20 ml) and the combined organic layers were dried over magnesium sulfate and concentrated. The residue was purified by column chromatography (10% methanol / dichloromethane) to give *N-tert*-butoxycarbonyl (*S*)-isoleucine (*S*)-valine (805 mg, 97%) as a colourless foam; mp 74-77 °C (not recrystallized); ν_{max} (KBr)/cm^{-1} 3326 (NH, OH), 2967 (CH), 1716 (CO), 1660 (CO); δ (300 MHz; $CDCl_3$) 6.91 (1H, br d, *J* 8.8, NH-Val), 5.33 (1H, br d, *J* 8.8, NH-Ile), 4.61 (1H, dd, *J* 8.7, 8.8, α-CH-Val), 4.02 (1H, t, *J* 8.8, α-CH-Ile), 2.25 (1H, m, β-CH-Val), 1.81 (1H, br m, β-CH-Ile), 1.53 (1H, br m, C<u>H</u>H-Ile), 1.43 (9H, s, $(Me)_3$), 1.11 (1H, br m, CH<u>H</u>-Ile), 0.90-0.82 (12H, m, $CH\underline{Me}_2$-Val, 2 × Me-Ile); δ_C (75 MHz; $CDCl_3$) 174.6 (CO), 172.3 (CO), 156.3 (CO), 80.4 (C), 59.2 (CH), 56.8 (CH), 36.5 (CH), 31.0 (CH), 28.2 ($C\underline{Me}_3$), 24.9 (CH_2), 19.0 (Me), 17.4 (Me), 15.3 (Me), 11.0 (Me); *m/z* (CI) 285 ($M-CO_2H$, 10%), 275 (12), 257 (29), 232 (13), 231 (89), 211 (100), 185 (20), 115 (15), (M^+ not observed). This compound is described in the literature but without characterization.[4]

(c) The above acid (257 mg, 0.779 mmol) and *N*-hydroxysuccinimide ammonium salt[6] (154 mg, 1.17 mmol) were stirred in dimethylformamide (10 ml) at 0 °C. *N,N*'-Dicyclohexylcarbodiimide (241 mg, 1.17 mmol) was added and the reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 15 h. The solvent was removed *in vacuo* and ethyl acetate (20 ml) was added to the residue. The colourless precipitate was filtered and the organic filtrate washed with saturated aqueous sodium hydrogen carbonate (20 ml) and brine (20 ml). The organic layer was dried over magnesium sulfate and concentrated. The residue was purified by column

chromatography (5% methanol / dichloromethane) to give the *title compound* (155 mg, 60%) as a colourless powder; mp 191 °C (from ethanol / water); $[\alpha]_D^{32}$ 46.9 (*c* 0.50, $CHCl_3$) (Found: MH^+, 330.2389. $C_{16}H_{31}N_3O_4$ + H requires 330.2393); ν_{max} (KBr)/cm^{-1} 3328 (NH), 2968 (CH), 1689 (CO), 1650 (CO), 1526 (CO); $\delta_{\square}$ (300 MHz; $CDCl_3$) 6.80 (1H, br d, *J* 8.5, NH-Val), 6.60 (1H, br s, NHH), 5.77 (1H, br s, NHH), 5.10 (1H, d, *J* 7.2, NH-Ile), 4.33 (1H, dd, *J* 5.8, 8.5, α-CH-Val), 3.97 (1H, app t, *J* 7.2, α-CH-Ile), 2.27 (1H, m, β-CH-Val), 1.89 (1H, m, β-CH-Ile), 1.51 (1H, m, CHH-Ile), 1.44 (9H, s, CMe_3), 1.15 (1H, m, CHH-Ile), 0.98-0.88 (12H, m, $CHMe_2$-Val, 2 × Me-Ile); δ_C (75 MHz; $CDCl_3$) 173.5 (CO), 171.8 (CO), 156.2 (CO), 80.5 (C), 59.9 (CH), 57.9 (CH), 36.6 (CH), 29.9 (CH), 28.1 (CMe_3), 24.8 (CH_2), 19.4 (Me), 17.5 (Me), 15.7 (Me), 11.4 (Me); *m/z* (CI) 330 (MH^+, 7%), 302 (18), 274 (45), 258 (30), 257 (100), 256 (27), 230 (53), 229 (23), 213 (38), 212 (21), 211 (99), 185 (39), 140 (23), 86 (47), 57 (95).

N-tert-Butoxycarbonyl (_S_)-valine phosphonoglycine 8

Trimethyl diazophosphonoacetate[5] (3.34 g, 16.1 mmol) in anhydrous chloroform (10 ml) was added slowly to a solution of *N-tert*-butoxycarbonyl (*S*)-valinamide **7** (2.67 g, 12.3 mmol) and rhodium octanoate (192 mg, 0.25 mmol) in anhydrous chloroform (40 ml). The reaction mixture was heated under reflux for 21 h and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (90% ethyl acetate / light petroleum up to 100% ethyl acetate) to give the *title compound* (3.13 g, 64%) as a mixture of two diastereomers, as a pale grey sticky solid used without further purification; (Found: MH^+, 397.1742. $C_{15}H_{29}N_2O_8P$ + H requires 397.1740); ν_{max} (KBr)/cm^{-1} 3397 (NH), 2966 (CH), 1756 (CO), 1711 (CO), 1685 (CO); $\delta_{\square}$ (300 MHz; $CDCl_3$) 6.98 (1H, br t, NH-CHP), 5.24 (1H, dd, *J* 8.9, 22.1, CHP), 5.06 (1H, br d, Val NH), 4.08 (1H, m, Val α-CH), 3.86-3.78 (9H, m, 3 × OMe), 2.20 (1H, m, Val β-CH), 1.45 (9H, s, CMe_3), 0.99 (3H, d, *J* 6.8, $CHCH_3Me$), 0.93 (3H, d, *J* 6.8, $CHMeCH_3$); *m/z* (CI) 397 (MH^+, 8%), 341 (15), 298 (9), 297 (100), 198 (21), 150 (11), 111 (9),

N-tert-Butoxycarbonyl (_S_)-isoleucine (_S_)-valine phosphonoglycine 10

(a) From the dipeptide amide **9**

Trimethyl diazophosphonoacetate[5] (210 mg, 1.01 mmol) in anhydrous chloroform (2 ml) was added slowly to a solution of *N-tert*-butoxycarbonyl (*S*)-isoleucine (*S*)-valinamide **9** (166 mg,

0.505 mmol) and rhodium octanoate (20 mg, 0.025 mmol) in anhydrous chloroform (6 ml). The reaction mixture was heated under reflux for 21 h and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (ethyl acetate) to give the *title compound* (104 mg, 40%) as a mixture of two diastereomers, as a colourless sticky solid used without further purification; (Found: MH^+, 510.2563. $C_{21}H_{40}N_3O_9P$ + H requires 510.2580); ν_{max} (KBr)/cm^{-1} 3288 (NH), 2964 (CH), 1752 (CO), 1692 (CO), 1647 (CO), 1527 (CO), 1247 (P=O), 1044 (P-O); δ (300 MHz; $CDCl_3$) 6.90 (1H, N<u>H</u>-CHP), 6.55 (1H, Val NH), 5.20 (1H, CHP), 5.00 (1H, Ile NH), 4.42 (1H, Val α-CH) 3.92 (1H, Ile α-CH), 3.80 (9H, 3 × OMe), 2.15 (1H, Val β-CH), 1.90 (1H, Ile β-CH), 1.52 (1H, C<u>H</u>H), 1.44 (9H, s, C<u>Me</u>$_3$), 1.15 (1H, CH<u>H</u>), 0.95 (12H, Me); *m/z* (CI) 510 (MH^+, 12%), 454 (14), 411 (18), 410 (100), 198 (15), 185 (15), 140 (11), 124 (18).

(b) From the phosphonopeptide **8**

Trifluoroacetic acid (3.0 ml, 71.0 mmol) was added dropwise to a solution of *N-tert*-butoxycarbonyl (*S*)-valine phosphonoglycine **8** (287 mg, 0.725 mmol) in anhydrous chloroform (2 ml). The reaction mixture was stirred at room temperature for 5 h and the solvent was evaporated *in vacuo* ensuring all excess trifluoroacetic acid had been removed. Dichloromethane (3 ml) was added to the trifluoroacetic acid amine salt and Hunigs base (1.26 ml, 7.25 mmol) was added dropwise. The subsequent free amine was cooled to 0 °C. *N-tert*-Butoxycarbonyl (*S*)-isoleucine (226 mg, 0.943 mmol) and bromotrispyrrolidinophosphonium hexafluorophosphate (405 mg, 0.870 mmol) were added and the reaction mixture was allowed to slowly warm to room temperature over night. The reaction mixture was concentrated and the residue dissolved in ethyl acetate (20 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (10 ml) and the aqueous layer was back-extracted with ethyl acetate (10 ml). The combined organic layers were washed with brine (20 ml), dried over magnesium sulfate and concentrated. The residue was purified by column chromatography (ethyl acetate) to give the *title compound* (210 mg, 57%) as a mixture of two diastereomers, as a colourless sticky solid used without further purification; data as above.

N-tert-Butoxycarbonyl (_S_)-valine (6-bromo-1-_tert_-butoxycarbonyl)-(_Z_)-dehydrotryptophan methyl ester 12

6-Bromo-1-*tert*-butoxycarbonylindole-3-carbaldehyde **11** (315 mg, 0.927 mmol) in dichloromethane (3 ml) was added dropwise to a solution of *N*-*tert*-butoxycarbonyl (*S*)-valine phosphonoglycine **8** (500 mg, 1.26 mmol) and distilled 1,8-diazabicyclo[5.4.0]undec-7-ene (0.21 ml, 1.41 mmol) in dichloromethane (3 ml) at 0 °C. The reaction mixture was allowed to slowly warm to room temperature and was left stirring for 20 h. The reaction mixture was concentrated and the residue dissolved in ethyl acetate (20 ml) and washed with saturated aqueous sodium hydrogen carbonate (10 ml) and brine (10 ml). The organic layer was dried over magnesium sulfate and concentrated, and the residue purified by column chromatography (25% ethyl acetate / light petroleum) to give the *title compound* (479 mg, 83%) as a colourless powder; mp 116-118 °C (from methanol); $[\alpha]_D^{30}$ -1.82 (*c* 0.55, $CHCl_3$) (Found: MH^+, 594.1808. $C_{27}H_{36}{}^{79}BrN_3O_7$ + H requires 594.1815); ν_{max} (KBr)/cm^{-1} 3324 (NH), 2976 (CH), 1733 (CO); δ□ (300 MHz; $CDCl_3$) 8.27 (1H, s, 7-H), 8.02 (1H, s, Trp NH), 7.86 (1H, s, 2-H), 7.54 (1H, s, CH=C), 7.46 (1H, d, *J* 8.5, 5-H), 7.36 (1H, d, *J* 8.5, 4-H), 5.25 (1H, br d, *J* 8.4, Val NH), 4.20 (1H, br dd, *J* 6.0, 8.4, Val α-CH), 3.82 (3H, s, OMe), 2.31 (1H, m, Val β-CH), 1.67 (9H, s, CMe_3), 1.44 (9H, s, CMe_3), 1.03 (3H, d, *J* 6.8, $CHC\underline{H}_3Me$), 0.96 (3H, d, *J* 6.8, $CHMeC\underline{H}_3$); δ_C (75 MHz; $CDCl_3$) 171.1 (C), 165.5 (C), 156.3 (C), 149.1 (C), 135.7 (C), 128.6 (C), 128.4 (CH), 126.7 (CH), 124.1 (CH), 123.7 (C), 120.4 (CH), 119.1 (C), 118.9 (CH), 114.1 (C), 85.5 (C), 80.4 (C), 60.4 (CH), 53.0 (Me), 30.9 (CH), 28.7 ($C\underline{Me}_3$), 28.4 ($C\underline{Me}_3$), 19.9 (Me), 17.9 (Me); *m/z* (CI) 596/594 (MH^+, 5/5%), 595/593 (M^+, 8/8), 496/494 (67/69), 440/438 (95/98), 408/406 (47/49), 396/394 (100/97), 364/362 (47/49), 347 (84), 345 (50), 283 (35), 249/247 (88/89), 169 (51), 168 (37), 167 (23).

_N_-*tert*-Butoxycarbonyl (*S*)-isoleucine (*S*)-valine (6-bromo-1-*tert*-butoxycarbonyl)-(*Z*)-dehydrotryptophan methyl ester 13

6-Bromo-1-*tert*-butoxycarbonylindole-3-carbaldehyde **11** (122 mg, 0.375 mmol) in dichloromethane (2 ml) was added dropwise to a solution of *N*-*tert*-butoxycarbonyl (*S*)-isoleucine (*S*)-valine phosphonoglycine **10** (210 mg, 0.413 mmol) and distilled 1,8-diazabicyclo[5.4.0]undec-7-ene (0.062 ml, 0.413 mmol) in dichloromethane (2 ml) at 0 °C. The reaction mixture was allowed to slowly warm to room temperature and was left stirring for 20 h. The reaction mixture was concentrated and the residue dissolved in ethyl acetate (15 ml) and washed with saturated aqueous sodium hydrogen carbonate (5 ml) and brine (5 ml). The

organic layer was dried over magnesium sulfate and concentrated, and the residue purified by column chromatography (40% ethyl acetate / light petroleum) to give the *title compound* (239 mg, 90%) as a colourless powder; mp 227-228 °C (from ethanol); $[\alpha]_D^{30}$ -62.9 (*c* 0.35, $CHCl_3$) (Found: MH^+, 707.2642. $C_{33}H_{47}{}^{79}BrN_4O_8$ + H requires 707.2650); ν_{max} (KBr)/cm^{-1} 3429 (NH), 2968 (CH), 1730 (CO), 1649 (CO); δ□ (300 MHz; $CDCl_3$) 8.34 (1H, s, 7-H), 8.03 (1H, br s, Trp NH), 7.98 (1H, s, 2-H), 7.61 (1H, s, CH=C), 7.53 (1H, d, *J* 8.4, 5-H), 7.40 (1H, dd, *J* 1.6, 8.4, 4-H), 6.52 (1H, br d, *J* 8.4, Val NH), 4.98 (1H, br d, *J* 5.1, Ile NH), 4.45 (1H, m, Val α-CH), 3.96 (1H, m, Ile α-CH), 3.83 (3H, s, OMe), 2.18 (1H, m, Val β-CH), 1.94 (1H, m, Ile β-CH), 1.69 (9H, s, Ind-CMe_3), 1.50 (1H, m, C<u>H</u>H), 1.50 (9H, s, Ile-CMe_3), 1.15 (1H, m, CH<u>H</u>), 1.03-0.87 (12H, m, *J* 6.8, 4 × Me); δ_C (75 MHz; $CDCl_3$); 171.7 (CO), 170.1 (CO), 165.1 (CO), 156.4 (CO Boc), 149.0 (CO Boc), 135.5 (C), 128.5 (C), 128.1 (2-CH), 126.4 (4-CH), 123.7 (alkene CH), 120.0 (5-CH), 118.7 (7-CH or C), 118.6 (C or 7-CH), 113.6 (C), 85.2 (C Boc), 80.8 (C Boc), 60.2 (α CH Ile), 58.6 (α CH Val), 52.5 (Me ester), 36.4 (β CH Ile), 29.6 (β CH Val), 28.2 (C<u>Me</u>$_3$), 28.1 (C<u>Me</u>$_3$), 24.9 (CH_2), 19.7 (Me), 17.2 (Me), 15.8 (Me), 11.5 (Me), (one quaternary carbon, either α-C of Trp or aromatic C, is not visible), assignments made using HMBC spectroscopy; *m/z* (ES) 731/729 ($M+Na^+$, 11/11%), 709/707 (MH^+, 6/6), 313 (34), 258 (15), 257 (100), 229 (26), 213 (10), 72 (19).

N-tert-Butoxycarbonyl (_S_)-valine (6-bromo-1-_tert_-butoxycarbonyl)-(_S_)-tryptophan methyl ester 5

Anhydrous methanol (4 ml) was added to *N-tert*-butoxycarbonyl (*S*)-valine (6-bromo-1-*tert*-butoxycarbonyl)-(*Z*)-dehydrotryptophan methyl ester **12** (100 mg, 0.168 mmol) and (+)-1,2-bis((2S,5S)-2,5-diethylphospholano)benzene(cyclooctadiene) rhodium(I) trifluoromethanesulfonate (2.4 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 and over 5 min the orange suspension changed to a clear yellow solution. The reaction mixture was left to stir for 16 h and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (30% ethyl acetate / light petroleum) to give the *title compound* (98 mg, 98%, >99% de) as a colourless powder; mp 86-88 °C (from ethyl acetate / light petroleum); $[\alpha]_D^{32}$ 22.7 (*c* 0.22, $CHCl_3$) (Found: MH^+,

596.1983. $C_{27}H_{38}{}^{79}BrN_3O_7$ + H requires 596.1971); λ_{max} (MeCN)/nm 297 (ε 7009), 264 (21211), 233 (22811); ν_{max} (KBr)/cm^{-1} 3324 (NH), 2976 (CH), 1739 (CO), 1658 (CO); $\delta_{\square}$ (300 MHz; $CDCl_3$) 8.33 (1H, s, 7-H), 7.37 (3H, m, 2-H, 4-H, 5-H), 6.50 (1H, br d, *J* 7.5, Trp NH), 4.98 (1H, br d, *J* 8.0 Val NH), 4.91 (1H, m, Trp α-CH), 3.90 (1H, m, Val α-CH), 3.67 (3H, s, OMe), 3.21 (2H, d, *J* 5.7, Trp β-CH_2) 2.12 (1H, m, Val β-CH), 1.67 (9H, s, CMe_3), 1.43 (9H, s, CMe_3), 0.94 (3H, d, *J* 6.7, CHC$\underline{H}_3$Me), 0.87 (3H, d, *J* 6.7, CHMeC$\underline{H}_3$); δ_C (75 MHz; $CDCl_3$) 171.7 (C), 171.4 (C), 155.7 (C), 149.1 (C), 136.0 (C), 129.2 (C), 125.9 (CH), 124.5 (CH), 120.0 (CH), 118.6 (CH) 118.4 (C), 114.7 (C), 84.3 (C), 80.0 (C), 59.9 (CH), 52.5 (CH), 52.4 (CH), 30.8 (Me) 28.3 (C$\underline{Me}_3$), 28.1 (C$\underline{Me}_3$), 27.6 (CH_2), 19.2 (Me), 17.7 (Me); *m/z* (CI) 598/596 (MH^+, 11/12%), 498/496 (94/100), 442/440 (65/72), 398/396 (81/85).

N-tert-Butoxycarbonyl (_S_)-valine (6-bromo-1-_tert_-butoxycarbonyl)-(_R/S_)-tryptophan methyl ester

Anhydrous methanol (2 ml) was added to *N-tert*-butoxycarbonyl (*S*)-valine (6-bromo-1-*tert*-butoxycarbonyl)-(*Z*)-dehydrotryptophan methyl ester **12** (50 mg, 0.084 mmol) and 1,1'-bis(di-*iso*-propylphosphino)ferrocene (1,5-cyclooctadiene) rhodium(I) tetrafluoroborate (3.0 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 17 h and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (30% ethyl acetate / light petroleum) to give the *title compound* (47 mg, 94%) as a 1:1 mixture of diastereomers, as a colourless powder.

N-tert-Butoxycarbonyl (_S_)-isoleucine (_S_)-valine (6-bromo-1-_tert_-butoxycarbonyl)-(_S_)-tryptophan methyl ester 6

Anhydrous methanol (4 ml) was added to *N-tert*-butoxycarbonyl (*S*)-isoleucine (*S*)-valine (6-bromo-1-*tert*-butoxycarbonyl)-(*Z*)-dehydrotryptophan methyl ester **13** (50 mg, 0.071 mmol) and (+)-1,2-bis((2S,5S)-2,5-diethylphospholano)benzene(cyclooctadiene) rhodium(I) trifluoromethanesulfonate (1.0 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 and the reaction mixture was left to stir for 40 h. The solvent was removed *in vacuo* to give the crude product which was purified by column

chromatography (40% ethyl acetate / light petroleum) to give the *title compound* (48 mg, 95%, 89% de) as a colourless powder; mp 124-128 °C; $[\alpha]_D^{31}$ 10.8 (*c* 0.48, $CHCl_3$) (Found: $M+NH_4^+$, 726.3075. $C_{33}H_{49}{}^{79}BrN_4O_8 + NH_4$ requires 726.3072); λ_{max} (MeCN)/nm 297 (ε 3010), 272 (12126), 232 (25699); ν_{max} (KBr)/cm^{-1} 3316 (NH), 2968 (CH), 1740 (CO), 1692 (CO), 1648 (CO); δ (300 MHz; $CDCl_3$) 8.33 (1H, s, 7-H), 7.40-7.35 (3H, m, 2-H, 4-H, 5-H), 6.69 (1H, br d, *J* 7.2, Trp NH), 6.52 (1H, d, *J* 8.5, Val NH), 5.07 (1H, br d, *J* 7.7, Ile NH), 4.88 (1H, m, Trp α-CH), 4.27 (1H, m, Val α-CH), 3.90 (1H, m, Ile α-CH), 3.66 (3H, s, OMe), 3.18 (2H, d, *J* 5.8, CH_2-Ind), 2.16 (1H, m, Val β-CH), 1.86 (1H, m, Ile β-CH), 1.67 (9H, s, CMe_3), 1.49 (1H, m, Ile C<u>H</u>H), 1.42 (9H, s, CMe_3), 1.11 (1H, m, Ile CH<u>H</u>), 0.94-0.80 (12H, m, 4 × Me); δ_C (75 MHz; $CDCl_3$) 171.7 (C), 171.6 (C), 170.7 (C), 155.9 (C), 149.1 (C), 136.0 (C), 129.1 (C), 125.9 (CH), 124.6 (CH), 120.0 (CH), 118.5 (CH) 118.4 (C), 114.7 (C), 84.3 (C), 80.1 (C), 59.6 (CH), 58.4 (CH), 52.5 (Me), 52.3 (Me), 36.7 (CH), 30.6 (CH), 28.3 (C<u>Me</u>$_3$), 28.1 (C<u>Me</u>$_3$), 27.6 (CH_2), 24.7 (CH_2), 19.2 (Me), 17.8 (Me), 15.6 (Me), 11.3 (Me).

N-tert-Butoxycarbonyl (_S_)-isoleucine (_S_)-valine (6-bromo-1-_tert_-butoxycarbonyl)-(_R/S_)-tryptophan methyl ester

Anhydrous methanol (3 ml) was added to *N-tert*-butoxycarbonyl (*S*)-isoleucine (*S*)-valine (6-bromo-1-*tert*-butoxycarbonyl)-(*Z*)-dehydrotryptophan methyl ester **13** (31 mg, 0.044 mmol) and 1,1'-bis(di-*iso*-propylphosphino)ferrocene (1,5-cyclooctadiene) rhodium(I) tetrafluoroborate (2.0 mg, 6 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 and the reaction mixture was left to stir for 66 h. The solvent was removed *in vacuo* to give the crude product that was purified by column chromatography (40% ethyl acetate / light petroleum) to give the *title compound* (30 mg, 96%) as a 1:1 mixture of diastereomers, as a colourless powder.

References

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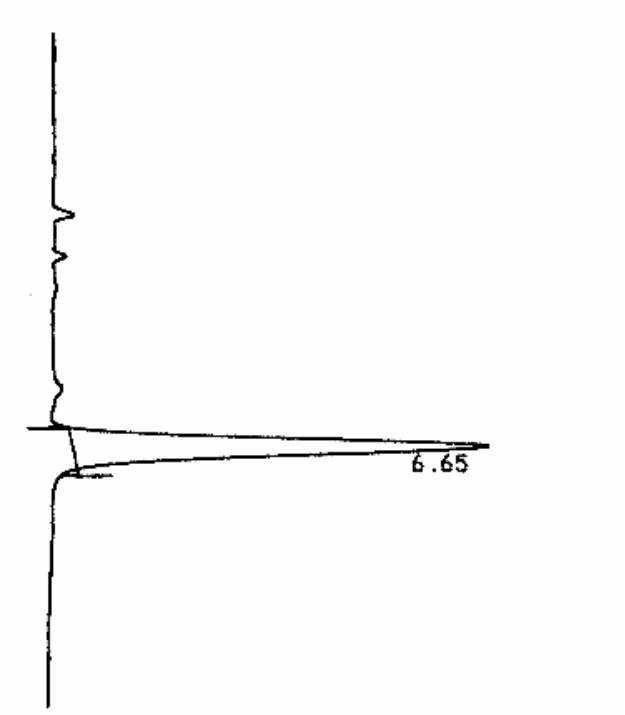
HPLC DATA

***N-tert*-Butoxycarbonyl (*S*)-valine (6-bromo-1-*tert*-butoxycarbonyl)-(*S*)-tryptophan methyl ester 5** from asymmetric hydrogenation of *N-tert*-butoxycarbonyl (*S*)-valine (6-bromo-1-*tert*-butoxycarbonyl)-(*Z*)-dehydrotryptophan methyl ester **12** using (+)-1,2-bis((2S,5S)-2,5-diethylphospholano)benzene(cyclooctadiene) rhodium(I) trifluoromethanesulfonate catalyst.

λ 254 nm; Column type OD-R; Eluent solvent 5% IPA / Hexane; Flow rate 0.7 ml / min.



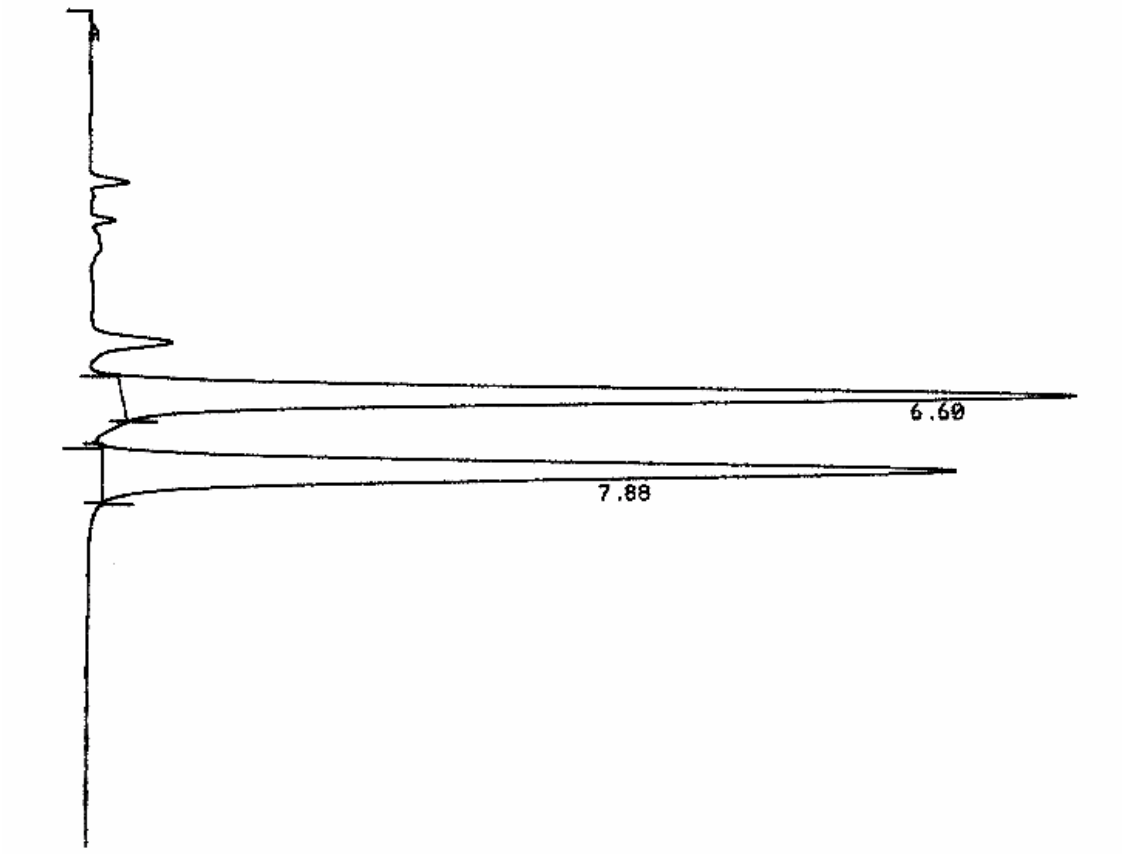
PEAK#	AREA%	RT	AREA	BC
1	100.	6.65	1652239	01
TOTAL	100.		1652239	

D1 6.65 min; D2 not visible.

Diastereomeric excess >99.9%

***N-tert*-Butoxycarbonyl (*S*)-valine (6-bromo-1-*tert*-butoxycarbonyl)-(*R/S*)-tryptophan methyl ester** from "racemic" hydrogenation of *N*-*tert*-butoxycarbonyl (*S*)-valine (6-bromo-1-*tert*-butoxycarbonyl)-(*Z*)-dehydrotryptophan methyl ester **12** using 1,1'-bis(di-*iso*-propylphosphino)ferrocene (1,5-cyclooctadiene)rhodium(I) tetrafluoroborate achiral catalyst.

λ 254 nm; Column type OD-R; Eluent solvent 5% IPA / Hexane; Flow rate 0.7 ml / min.

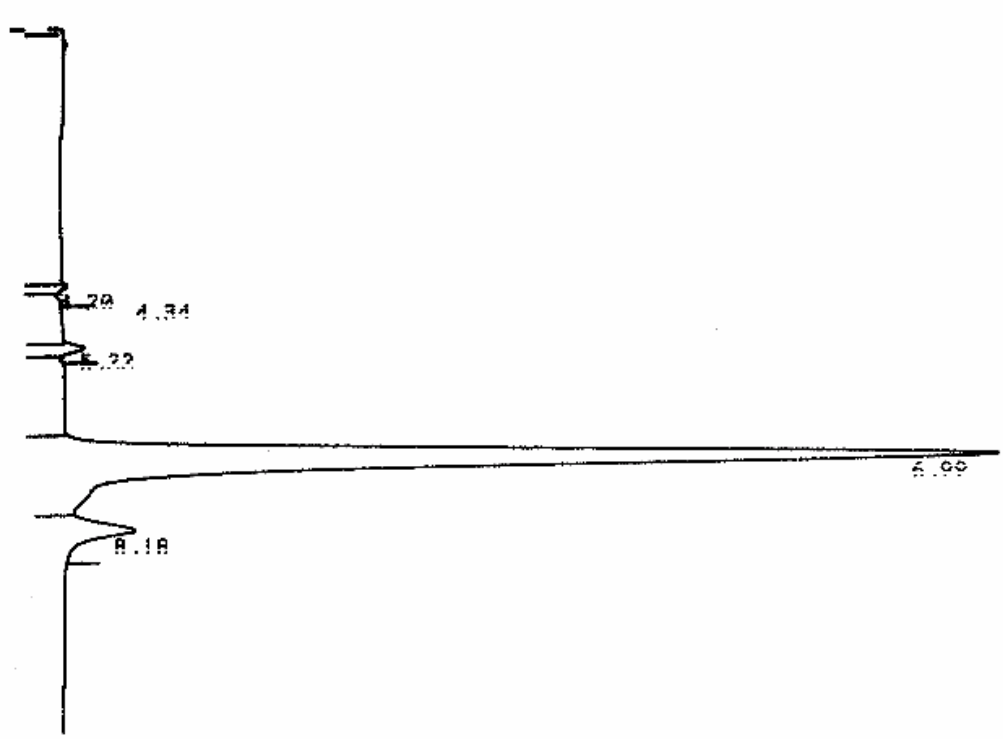


1	50.028	6.6	2102084 01
2	49.972	7.88	2099744 01
TOTAL	100.		4201828

D1 6.60 min; D2 7.88 min.

***N-tert*-Butoxycarbonyl (*S*)-isoleucine (*S*)-valine (6-bromo-1-*tert*-butoxycarbonyl)-(*S*)-tryptophan methyl ester 6** from asymmetric hydrogenation of *N-tert*-butoxycarbonyl (*S*)-isoleucine (*S*)-valine (6-bromo-1-*tert*-butoxycarbonyl) (*Z*)-dehydrotryptophan methyl ester **13** using (+)-1,2-bis((2S,5S)-2,5-diethylphospholano)benzene(cyclooctadiene) rhodium(I) trifluoromethanesulfonate catalyst.

λ 254 nm; Column type OD; Eluent solvent 4.0% IPA / Hexane; Flow rate: 0.7 ml / min.



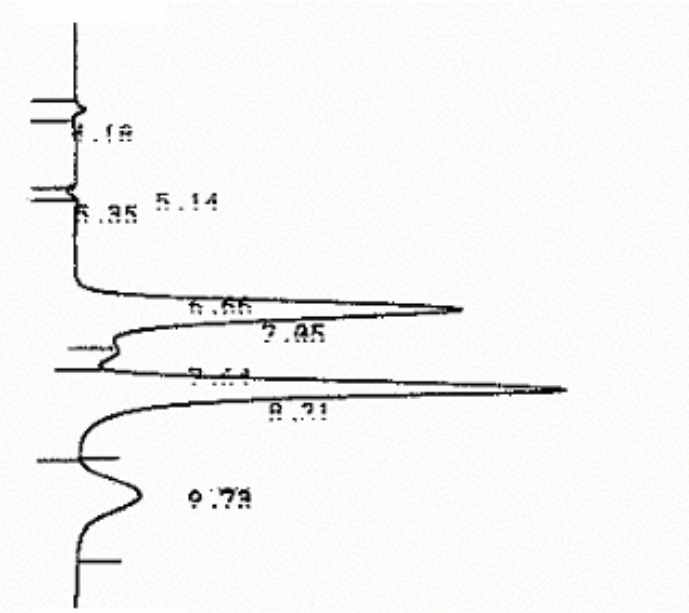
PEAK#	AREA%	RT	AREA	RC
1	0.149	4.3	12877	02
2	0.158	4.34	13695	13
3	0.785	5.22	68657	03
4	99.454	6.99	8111183	00
5	5.304	8.18	459411	05
TOTAL	100.		8660823	

D1 6.99 min; D2 8.18 min.

Diastereomeric excess = 89%

***N-tert*-Butoxycarbonyl (*S*)-isoleucine (*S*)-valine (6-bromo-1-*tert*-butoxycarbonyl)-(*R*/*S*)-tryptophan methyl ester** from "racemic" hydrogenation of *N-tert*-butoxycarbonyl (*S*)-isoleucine (*S*)-valine (6-bromo-1-*tert*-butoxycarbonyl)-(*Z*)-dehydrotryptophan methyl ester **13** using 1,1'-bis(di-*iso*-propylphosphino)ferrocene (1,5-cyclooctadiene)rhodium(I) tetrafluoroborate achiral catalyst

λ 254 nm; Column type OD; Eluent solvent 4.0% IPA / Hexane; Flow rate 0.7 ml / min.



PEAK#	AREA%	RT	AREA BC
1	0.369	4.18	28507 BV
2	0.4	5.14	30882 VV
3	0.201	5.35	15484 VV
4	0.073	6.66	5635 BV
5	38.842	7.05	2998442 BV
6	3.756	7.64	289949 BV
7	46.76	8.21	3609982 VB
8	9.599	9.73	741052 BV
TOTAL	100.		7720953

D1 7.05 min; D2 8.21min.

Note: Broad peak at 9.73 min corresponds to starting alkene **13**