Synthesis of 2-substituted indolines using sequential Pd-catalyzed processes †

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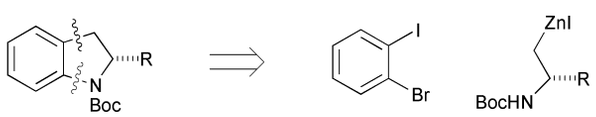
Received (in Cambridge, UK) 2nd January 2002, Accepted 11th February 2002
First published as an Advance Article on the web 25th February 2002

A concise route to enantiomerically pure 2-substituted indolines **4a**–**g** and a 2-substituted tetrahydroquinoline **4h** has been developed by application of the Pd-catalyzed coupling of amino functionalised organozinc reagents with 2-bromoiodobenzene, followed by Buchwald's palladium-catalyzed intramolecular amination reaction. The yields in the initial coupling are modest (36–52%), but the cyclisation yields are satisfactory (63–87%). The stereochemical integrity of a representative example was established by chiral phase HPLC.

Introduction

Indolines are commonly found as constituents of biologically active molecules[1–4] and natural products that have been the subject of extensive studies.[5–9] Routes to 2-substituted indolines have been summarized in a paper that describes their enantioselective synthesis from *N*-Boc indoline, using an asymmetric deprotonation strategy.[10] The palladium(0)-catalyzed cyclization of an enantiomerically pure *o*-bromophenylalanine derivative has also been reported.[11]

This latter method, which has recently been optimized,[12] suggested to us that it might be possible to combine it with our method for the preparation of ω-functionalised amines that involves the coupling of aromatic iodides with amino-substituted organozinc reagents.[13–16] Such a combination would then constitute a simple, but potentially very effective, ring-annelation process, Scheme 1. We now wish to report the preparation of a range of 2-substituted indolines **4a**–**g** and the 2-substituted tetrahydroquinoline **4h** by using this approach.



Scheme 1 Strategy for ring-annelation.

Results and discussion

The intramolecular amination of aryl bromides is a very efficient reaction.[11,12] This allowed us to select 2-bromoiodobenzene as the electrophile in our cross-coupling reaction with amino-functionalised organozinc reagents, since the rate of the cross-coupling reaction of organozinc reagents with aryl bromides using conventional palladium catalysts is substantially lower than with aryl iodides, allowing selective couplings to take place.[17,18]

The organozinc reagents **2a**–**h** were prepared by treatment of iodides **1a**–**h** with activated zinc dust in DMF at 0 °C, a process which is complete within 5–60 minutes, depending on the particular substrate.[13–16] Palladium(0)-catalyzed cross-coupling with 2-bromoiodobenzene at room temperature furnished the arylated intermediates **3a**–**h** in moderate yield after purification (Table 1) (Scheme 2). The yields in this step are at the low end of the range that we normally encounter in cross-coupling of aryl iodides with amino-functionalised organozinc reagents. The major by-products are derived from decomposition of the zinc reagents, either by protonation or elimination, rather than due to double coupling. We therefore suggest that the relatively hindered 2-bromoiodobenzene is not an especially effective coupling partner. Notwithstanding the modest yields in the initial coupling, the derived aryl bromides **3a**–**h** were converted efficiently into the cyclic products **4a**–**h** in satisfactory to excellent yield (Table 1), when treated with catalytic palladium(0) and caesium carbonate in toluene and heated at 100 °C for 15 h. Buchwald has previously prepared the *N*-benzoyl analogue of **4a** with high ee.[11]

Table 1 Preparation of enantiomerically pure dihydroindoles **4b**–**g**

Entry	R	**3** (Yield %)[a]	**4** (Yield %)[b]
b	CH_2CO_2Me	39	82
c	$(CH_2)_2CO_2Me$	37	66
d	Me	38	63
e	Et	36	68
f	^{i}Pr	42	65
g	Bn	39	74

[a] Yield based on iodides **1a**–**h**. [b] Yield based on bromides **3a**–**h**.

The enantiomeric excess of a representative product **4d** (R = Me) was established by chiral phase HPLC analysis. Comparison of **4d** with a racemic sample indicated an enantiomeric excess of >99%. In addition, the specific rotation compared favourably with that reported in the literature.[10] This, together with Buchwald's observation that the conditions used for cyclisation do not cause racemisation of amino acid derivatives,[11] suggest strongly that all the products **4a**–**h** are enantiomerically pure.

Unsurprisingly, the NMR spectra of all the cyclised compounds **4** indicated the presence of hindered rotation about the N–Boc bond, which was especially evident from the substantial broadening of the aromatic proton at C-7, to the extent that the signal was only evident through integration. Decoupling experiments at room temperature on compound **4c** allowed an unambiguous assignment to be made. Moreover, variable temperature NMR experiments on the same compound

† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for all products without elemental analysis data (**3c**–**g** and **4d**–**g**). See http://www.rsc.org/suppdata/p1/b2/b200163b/

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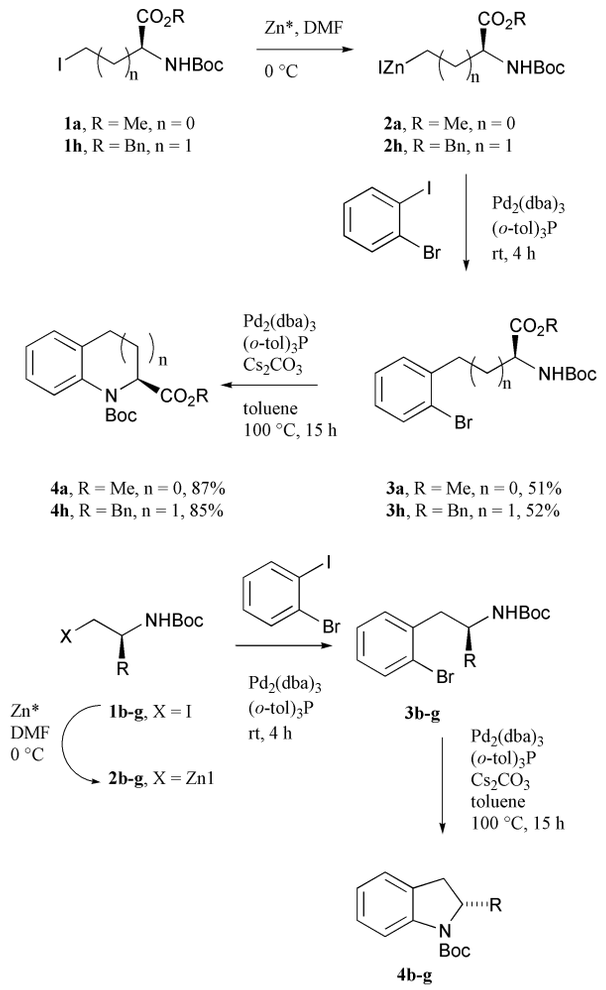
DOI: 10.1039/b200163b



Scheme 2 Preparation of 2-substituted indolines.

revealed the presence of two easily resolved rotameric forms which first became distinct at −15 °C, and were sharply resolved at −55 °C. The very low intensity of some of the signals in the ^{13}C NMR spectra can also be ascribed to the presence of rotameric forms. Thus, the ^{13}C NMR spectrum of **4c** at −55 °C revealed a pair of signals at 129.8 and 130.6, and another pair at 140.8 and 141.67, where no signals were evident above the noise in the corresponding room temperature spectrum. This type of behaviour is also evident in the supplementary material provided for Beak's paper.[10]

In summary, a concise route to enantiomerically pure 2-substituted indolines and a 2-substituted tetrahydroquinoline has been developed by application of our Pd-catalysed coupling of amino functionalised organozinc reagents, followed by application of the intramolecular amination protocol.

Experimental

General methods

General experimental procedures have already been described.[15] Iodides **1a**–**d** and **1f**–**h** were prepared as previously described.[13–16] Iodide **1e** was prepared using these general methods and had ^{1}H NMR data consistent with the literature compound.[19]

(2*S*)-2-*N*-*tert*-Butoxycarbonylamino-1-iodobutane 1e

Compound **1e** (4.17 g, 59%) was isolated as white needles, mp 54–55 °C (lit.[19] 51–52 °C). ν_{max} 3309, 2973, 1673, 1534, and 1167; δ_C 10.2, 14.7, 28.4, 40.5, 51.2, 79.6 and 155.2; *m*/*z* (EI) 299.0368 (27%, M^+; $C_9H_{18}INO_2$ requires 299.0382), 284 (17), 270 (13), 243 (14), 183 (7), 170 (27), 158 (34), 126 (21), and 57 (100). $[\alpha]_D$ −27.3 (*c* 1.00 in CH_2Cl_2) [lit.[19] −36.7 (*c* 0.49 in $CHCl_3$)].

Generation of zinc reagents 2a–h. General procedure

Zinc dust (325 mesh, 0.147 g, 2.25 mmol, 3 equiv.) was weighed into a 50 mL round bottom flask with side arm which was repeatedly evacuated (with heating using a hot air gun) and flushed with nitrogen. Dry DMF (0.5 mL) and trimethylsilyl chloride (6 μL, 0.046 mmol) were added, and the resultant mixture was stirred for 30 min at room temperature. Iodides **1a**–**h** (0.75 mmol) were dissolved in dry DMF (0.5 mL) under nitrogen. The iodide solution was transferred *via* syringe to the zinc suspension at 0 °C, and the mixture was then stirred. TLC analysis (petroleum ether–ethyl acetate, 2 : 1) showed complete consumption of the iodide within 5–60 min.

Preparation of arylated intermediates 3a–h. General procedure

2-Bromoiodobenzene (129 μL, 1.0 mmol, 1.3 equiv.), tris-(dibenzylideneacetone)dipalladium (0.023 g, 0.025 mmol, 3.3 mol%) and tri-*o*-tolylphosphine (0.030 g, 0.10 mmol, 13.3 mol%), were added sequentially to the solution of zinc reagent prepared above. The reaction mixture was stirred at room temperature for 4 h and was subsequently diluted with ethyl acetate (50 mL) and filtered through a pad of Celite®. The filtrate was washed successively with aqueous sodium thiosulfate (1 M, 20 mL), water (2 × 20 mL), and brine (40 mL), dried, and evaporated to dryness. Flash column chromatography over silica eluting with an appropriate petroleum ether–ethyl acetate gradient furnished the intermediates **3a**–**h**.

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(2′-bromophenyl)propanoate 3a. Compound **3a** (0.137 g, 51%) was isolated as a pale orange powder, mp 53–54 °C. Found: C, 50.5; H, 5.5; N, 3.8. $C_{15}H_{20}BrNO_4$ requires C, 50.3; H, 5.6 and N, 3.9%. ν_{max} 3370, 3058, 2978, 1746, 1717, 1507, 1207, 1169, 1055, and 754; δ_H 1.38 (9H, s), 3.11 (1H, dd, *J* 8, 13.5), 3.30 (1H, dd, *J* 6, 14), 3.72 (3H, s), 4.61–4.69 (1H, m), 5.07 (1H, d, *J* 8), 7.11 (1H, t, *J* 7), 7.21 (1H, d, *J* 7), 7.25 (1H, t, *J* 7), 7.55 (1H, d, *J* 8); δ_C 28.3, 38.7, 52.4, 53.5, 79.9, 125.1, 127.4, 128.6, 131.3, 132.9, 136.1, 155.1 and 172.4; *m*/*z* (EI) 300.9952 (4, $M^+ - C_4H_8$; $C_{11}H_{12}BrNO_4$ requires 300.9952), 258 (6), 242 (16), 222 (8), 200 (9), 161 (18), 118 (8), 88 (34), and 57 (100). $[\alpha]_D$ +3.5 (*c* 1.01 in CH_2Cl_2).

Methyl (3*R*)-3-[(*tert*-butoxycarbonyl)amino]-4-(2′-bromophenyl)butanoate 3b. Compound **3b** (0.146 g, 39%) was isolated as a light orange powder, mp 81–82 °C. Found: C, 52.0; H, 5.9; N, 3.6. $C_{16}H_{22}BrNO_4$ requires C, 51.6; H, 6.0 and N, 3.8%. ν_{max} 3377, 3053, 2977, 1730, 1682, 1521, 1195, 1165, 1047, and 751; δ_H 1.36 (9H, s), 2.55 (1H, dd, *J* 5, 16), 2.61 (1H, dd, *J* 5, 16), 3.04 (2H, d, *J* 7), 3.70 (3H, s), 4.23–4.31 (1H, m), 5.16 (1H, d, *J* 8), 7.08 (1H, dt, *J* 3, 7), 7.21–7.26 (2H, m), 7.54 (1H, d, *J* 8); δ_C 28.3, 38.0, 40.2, 47.9, 51.7, 79.3, 125.0, 127.5, 128.3, 131.5, 132.9, 137.6, 155.0 and 172.1; *m*/*z* (EI) 316.0178 (0.2%, $M^+ - C_4H_7$; $C_{12}H_{15}BrNO_4$ requires 316.0184), 298 (2), 284 (3), 256 (3), 102 (86), 90 (7), and 57 (100). $[\alpha]_D$ +33.0 (*c* 0.99 in CH_2Cl_2).

Methyl (4*S*)-4-[(*tert*-butoxycarbonyl)amino]-5-(2′-bromophenyl)pentanoate 3c. Compound **3c** (0.143 g, 37%) was isolated as a pale orange powder, mp 82–83 °C. ν_{max} 3369, 3053, 2970, 1728, 1684, 1520, 1171, 1046, and 751; δ_H 1.34 (9H, s), 1.73–1.82 (1H, m), 1.88–1.96 (1H, m), 2.38–2.47 (2H, m), 2.89 (1H, dd, *J* 8, 14), 2.96 (1H, dd, *J* 6, 14), 3.67 (3H, s), 3.88–3.96 (1H, m), 4.44 (1H, d, *J* 9), 7.07 (1H, dt, *J* 5, 8), 7.20–7.25 (2H, m), and 7.53 (1H, d, *J* 8); δ_C 28.3, 29.9, 31.0, 41.6, 51.0, 51.7, 79.1, 125.0, 127.4, 128.1, 131.3, 132.8, 137.7, 155.3 and 174.0; *m*/*z* (EI) 312.0224 (0.7%, $M^+ - C_4H_9O$; $C_{13}H_{15}BrNO_3$ requires 312.0235), 286 (0.3), 271 (0.8), 254 (3), 160 (14), 130 (11), 116 (55), 84 (21), and 57 (100). $[\alpha]_D$ +27.8 (*c* 1.01 in CH_2Cl_2).

(2*S*)-2-*N*-*tert*-Butoxycarbonyl-1-(2′-bromophenyl)-2-propylamine 3d. Compound **3d** (0.090 g, 38%) was isolated as a pale yellow solid, mp 91–92 °C. ν_{max} 3377, 2972, and 1689; δ_H 1.22 (3H, d, *J* 7), 1.43 (9H, s), 2.90–2.96 (2H, m), 4.01–4.09 (1H, m), 4.49–4.57 (1H, br s), 7.09–7.14 (1H, m), 7.25–7.30 (2H, m), and 7.57 (1H, d, *J* 8); δ_C 20.7, 28.3, 42.7, 47.1, 79.0, 125.3, 127.3, 127.9, 131.3, 132.8, 138.1 and 155.1; *m*/*z* (EI) 313.0706 (44%, M^+; $C_{14}H_{20}BrNO_2$ requires 313.0677), 144 (57), and 57 (100). $[\alpha]_D$ +54.4 (*c* 0.25 in CH_2Cl_2).

2-(*S*)-*N*-*tert*-Butoxycarbonyl-1-(2′-bromophenyl)-2-butylamine 3e. Compound **3e** (0.089 g, 36%) was isolated as an off white solid, mp 95–96 °C. ν_{max} 3376, 2980, and 1689; δ_H 0.98 (3H, t, *J* 7), 1.36 (9H, s), 1.40–1.50 (1H, m), 1.57–1.65 (1H, m), 2.82–2.86 (1H, m), 2.97 (1H, dd, *J* 3, 14), 3.78–3.87 (1H, m), 4.35–4.44 (1H, m), 7.06 (1H, t, *J* 6.5), 7.11–7.27 (2H, m), and 7.53 (1H, d, *J* 8); δ_C 10.7, 28.1, 28.6, 41.3, 52.9, 79.1, 125.3, 127.5, 128.1, 131.6, 133.0, 138.6 and 155.7; *m*/*z* (EI) 312.0596 (14, $M^+ - CH_3$; $C_{14}H_{19}BrNO_2$ requires 312.0599), 211 (67), 158 (43), and 57 (100). $[\alpha]_D$ −23.9 (*c* 1.25 in CH_2Cl_2).

(2*S*)-2-*N*-*tert*-Butoxycarbonyl-1-(2′-bromophenyl)-3-methyl-2-butylamine 3f. Compound **3f** (0.108 g, 42%) was isolated as an off white solid, mp 96–97 °C. ν_{max} 3373, 2978, and 1690; δ_H 1.05 (6H, t, *J* 5.5), 1.36 (9H, s), 1.89 (1H, m), 2.74–2.80 (1H, m), 3.00–3.09 (1H, m), 3.84–3.92 (1H, m), 4.50 (1H, br d, *J* 8), 7.08 (1H, m), 7.23–7.32 (2H, m), and 7.57 (1H, d, *J* 7.5); δ_C 17.8, 19.3, 28.2, 38.6, 55.9, 78.7, 125.0, 127.2, 127.8, 131.1, 132.6, 138.5 and 155.5; *m*/*z* (EI) 225.0002 (35%, $M^+ - C_5H_{11}NO_2$; $C_{11}H_{13}Br$ requires 225.0064), and 57 (100). $[\alpha]_D^{18}$ +50.1 (*c* 0.43 in CH_2Cl_2).

(2*S*)-2-*N*-*tert*-Butoxycarbonyl-1-(2′-bromophenyl)-3-phenyl-2-propylamine 3g. Compound **3g** (0.114 g, 39%) was isolated as a white solid, mp 101–103 °C. ν_{max} 3369, 2981, and 1683; δ_H 1.38 (9H, s), 2.87–3.08 (4H, m), 4.18–4.27 (1H, m), 4.47–4.56 (1H, br s), 7.10–7.15 (1H, m), 7.24–7.38 (7H, m), 7.57 (1H, d, *J* 8); δ_C 28.4, 40.5, 41.3, 52.4, 79.2, 120.3, 125.1, 126.5, 127.4, 128.1, 128.5, 129.5, 131.3, 132.8, 138.2 and 155.3; *m*/*z* (EI) 389.0983 (43%, M^+; $C_{20}H_{24}BrNO_2$ requires 389.0990), 220 (4), 120 (52), 91 (36), and 57 (100). $[\alpha]_D$ +3.2 (*c* 1.00 in CH_2Cl_2).

Benzyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-(2′-bromophenyl)butanoate 3h. Compound **3h** (0.233 g, 52%) was isolated as a pale yellow oil which solidified on standing, mp 58–60 °C; Found: C, 59.2; H, 5.9; N, 3.3. $C_{22}H_{26}BrNO_4$ requires C, 58.9; H, 5.8 and N, 3.1%. ν_{max} 3365, 3065, 3034, 2977, 1739, 1713, 1499, 1167, 1049, and 751; δ_H 1.43 (9H, s), 2.52–2.68 (2H, m), 2.98–3.06 (2H, m), 4.24–4.32 (1H, m), 5.09–5.20 (3H, m), 7.02–7.10 (1H, m), 7.19 (1H, d, *J* 5), 7.30–7.40 (6H, m), 7.52 (1H, d, *J* 8); δ_C 28.4, 38.2, 40.3, 48.1, 66.6, 79.4, 125.1, 127.6, 128.1, 128.4, 128.5, 128.7, 131.6, 133.0, 135.9, 137.7, 155.1 and 171.6; *m*/*z* (EI) 392.0489 (0.75%, $M^+ - C_4H_9$; $C_{18}H_{17}BrNO_4$ requires 392.0497), 348 (3), 278 (5), 234 (14), 222 (10), 178 (21), 91 (100), and 57 (66). $[\alpha]_D$ +21.7 (*c* 1.01 in CH_2Cl_2).

Preparation of 4a–g *via* the intramolecular aryl amination reaction. General procedure

Bromides **3a**–**h** (0.75 mmol) were dissolved in dry toluene (2 mL under nitrogen) in a 10 mL round bottom flask fitted with an air condenser (Vigreux column). Caesium carbonate (0.579 g, 3.0 mmol, 4 equiv.), tris(dibenzylideneacetone)dipalladium (0.023 g, 0.025 mmol, 3.3 mol%) and tri-*o*-tolylphosphine (0.030 g, 0.10 mmol, 13.3 mol%), were added sequentially to the reaction mixture. The mixture was heated to 100 °C and stirring was continued for 15 h. The reaction mixture was diluted with ethyl acetate (50 mL) and filtered through a pad of Celite®. The filtrate was washed with water (2 × 20 mL) and brine (40 mL), dried and evaporated to dryness. Purification by flash column chromatography over silica with a suitable petroleum ether–ethyl acetate gradient furnished the pure indoline products **4a**–**g**, and the tetrahydroquinoline **4h**.

(2*S*)-*N*-*tert*-Butoxycarbonyl-2-methoxycarbonylindoline 4a. Compound **4a** (0.241 g, 87%) was isolated as a yellow oil. Found: C, 64.9; H, 7.0; N, 5.0. $C_{15}H_{19}NO_4$ requires C, 65.0; H, 6.9 and N, 5.1%. ν_{max} 3051, 2974, 2954, 2928, 1755, 1713, 1486, 1169, 1150, and 752; δ_H 1.49 (9H, s), 3.11 (1H, dd, *J* 4, 16.5), 3.50 (1H, dd, *J* 12, 16), 3.75 (3H, s), 4.80–4.98 (1H, m), 6.94 (1H, t, *J* 7), 7.10 (1H, d, *J* 6), 7.17–7.22 (1H, m), and 7.30–7.50 (1H, br); δ_C 28.3, 29.7, 52.3, 60.4, 81.3, 114.7, 122.6, 125.4, 127.9, 128.4, 128.9 and 143.3 (the signals for the carbonyl carbons were not detectable above the noise); *m*/*z* (EI) 277.1302 (8%, M^+; $C_{15}H_{19}NO_4$ requires 277.1314), 220 (1), 199 (6), 177 (20), 118 (100), and 57 (39). $[\alpha]_D$ −45.6 (*c* 0.50 in CH_2Cl_2).

(2*R*)-*N*-*tert*-Butoxycarbonyl-2-methoxycarbonylmethylindoline 4b. Compound **4b** (0.239 g, 82%) was isolated as a yellow oil which solidified on standing, mp 50–51 °C. Found: C, 66.8; H, 7.3; N, 4.3. $C_{16}H_{21}NO_4$ requires C, 67.0; H, 7.3 and N, 4.8%. ν_{max} 3032, 2981, 1735, 1695, 1188, 1169, and 753; δ_H 1.57 (9H, s), 2.51 (1H, dd, *J* 10, 15), 2.81 (1H, dd, *J* 2,16.5), 2.89–2.97 (1H, m), 3.41 (1H, dd, *J* 9.5, 16.5), 3.67 (3H, s), 4.70–4.85 (1H, br s), 6.95 (1H, dt, *J* 1, 7.5), 7.14 (1H, d, *J* 8), 7.17 (1H, t, *J* 7.5), and 7.32–7.49 (1H, br s); δ_C 28.4, 34.3, 39.3, 51.7, 56.1, 79.3, 115.3, 122.6, 125.2, 128.4, 130.5, 143.3 and 171.5 (the signal for the urethane carbonyl was not detectable above the noise); *m*/*z* (EI) 291.1473 (6%, M^+; $C_{16}H_{21}NO_4$ requires 291.1471), 234 (10), 204 (3), 191 (33), 130 (16), 118 (100), 103 (11), 91 (8), 77 (11), and 57 (66). $[\alpha]_D$ +87.6 (*c* 1.02 in CH_2Cl_2).

(2*R*)-*N*-*tert*-Butoxycarbonyl-2-methoxycarbonylethylindoline 4c. Compound **4c** (0.202 g, 66%) was isolated as a yellow oil which solidified on standing, mp 44–46 °C. Found: C, 66.9; H, 7.6; N, 4.3. $C_{17}H_{23}NO_4$ requires C, 66.9; H, 7.6 and N, 4.6%. ν_{max} 3049, 2975, 1739, 1700, 1168, and 752; δ_H 1.57 (9H, s), 1.90–2.00 (1H, m), 1.97–2.06 (1H, m), 2.28–2.40 (2H, m), 2.69 (1H, d, *J* 15.5), 3.33 (1H, dd, *J* 9.5, 16), 3.65 (3H, s), 4.42–4.57 (1H, br s), 6.94 (1H, t, *J* 7.5), 7.13 (1H, d, *J* 7.5), 7.16 (1H, t, *J* 7.5), 7.35–7.45 (1H, br s); δ_C 28.4, 29.8, 30.1, 33.5, 51.6, 58.4, 81.2, 115.6, 122.6, 124.7, 127.4, 152.6 and 173.5 (two signals were not detectable above the noise, but when the spectrum was run at −55 °C, pairs of signals at 129.8 and 130.6, and 140.8 and 141.7, were detected); *m*/*z* (EI) 305.1630 (4%, M^+; $C_{17}H_{23}NO_4$ requires 305.1627), 232 (2), 205 (18), 174 (6), 130 (7), 118 (100), and 57 (60). $[\alpha]_D$ +44.3 (*c* 0.99 in CH_2Cl_2).

(2*S*)-*N*-*tert*-Butoxycarbonyl-2-methylindoline 4d. Compound **4d** (0.111 g, 63%) was isolated as a green oil. ν_{max} 3072, 2975, and 1700; δ_H 1.28 (3H, d, *J* 6.5), 1.55 (9H, s), 2.61 (1H, dd, *J* 2, 16), 3.34 (1H, dd, *J* 10, 16), 4.51–4.54 (1H, br s), 6.93 (1H, t, *J* 7.5), 7.15–7.21 (2H, m), 7.71–7.74 (1H, br s); δ_C 21.1, 28.4, 35.6, 55.1, 80.5, 115.2, 122.2, 124.9, 127.2, 129.9, 141.7 and 152.2 (the signals at 129.9 and 141.7 were broad and of very low intensity); *m*/*z* (EI) 233.1410 (20%, M^+; $C_{14}H_{19}NO_2$ requires 233.1416), 177 (100), 162 (37), 133 (15), 118 (82), and 57 (86). $[\alpha]_D$ −42 (*c* 0.52 in $CHCl_3$), (lit.[10] +39, enantiomer (*c* 0.01 in $CHCl_3$)).

A racemic sample *rac*-**4d** of the above material was prepared *via* Boc protection of racemic 2-methylindoline. *rac*-**4d** exhibited identical spectroscopic data to the enantiomerically pure sample **4d**. The racemic sample was analysed by chiral phase HPLC (Ceramospher RU-1 column, eluent 95 : 5 hexane–ethanol, flow rate 1 mL min^{-1}, detection at 215 nm), which gave baseline enantiomer separation. Analysis of **4d** indicated an enantiomeric excess >99%.

(2*S*)-*N*-*tert*-Butoxycarbonyl-2-ethylindoline 4e. Compound **4e** (0.126 g, 68%) was isolated as a green oil. ν_{max} 3033, 2970 and

1700, and; δ_H 0.91 (3H, t, *J* 7.5), 1.59 (9H, s), 1.65–1.85 (2H, m), 2.75 (1H, dd, *J* 2, 16), 3.29 (1H, dd, *J* 9.5, 16), 4.33–4.39 (1H, br s), 6.95 (1H, t, *J* 7.5), 7.13–7.20 (3H, m); δ_C 9.4, 27.7, 28.6, 33.0, 60.7, 80.1, 115.3, 122.4, 124.9, 127.4, 130.5, 142.0 and 152.6 (the signals at 130.0 and 142.0 were broad and of very low intensity); *m*/*z* (EI) 247.1581 (23%, M^+; $C_{15}H_{21}NO_2$ requires 247.1572), 191 (100), 174 (9), and 57 (24); $[\alpha]_D$ −83.8 (*c* 1.00 in CH_2Cl_2).

(2*S*)-*N*-*tert*-Butoxycarbonyl-2-isopropylindoline 4f. Compound **4f** (0.128 g, 65%) was isolated as a green oil. ν_{max} 3033, 2963, and 1699; δ_H 0.68 (3H, d, *J* 7), 0.81 (3H, d, *J* 7), 1.51 (9H, s), 2.16–2.25 (1H, m), 2.77 (1H, dd, *J* 2.5, 16), 3.11 (1H, dd, *J* 10, 16), 4.27–4.36 (1H, br s), 6.88 (1H, t, *J* 7), 7.04–7.12 (3H, m); δ_C 15.5, 16.1, 18.5, 28.4, 31.1, 64.0, 80.5, 115.22, 122.3, 124.2, 127.1, 131.0, 143.0 and 152.8 (the signals at 131.0 and 143.0 were broad and of very low intensity); *m*/*z* (EI) 261.1733 (28%, M^+; $C_{16}H_{23}NO_2$ requires 261.1729), 205 (84), 188 (6), 163 (12), 132 (13), 118 (100), and 57 (20). $[\alpha]_D$ +126.6 (*c* 1.00 in CH_2Cl_2).

(2*S*)-*N*-*tert*-Butoxycarbonyl-2-benzylindoline 4g. Compound **4g** (0.171 g, 74%) was isolated as a green oil. ν_{max} 3027, 2974, and 1702; δ_H 1.51 (9H, s), 2.51–2.56 (1H, m), 2.72 (1H, d, *J* 15.5), 2.95 (1H, dd, *J* 9.5, 16), 3.15–3.25 (1H, br s), 4.52–4.61 (1H, br s), 6.91 (1H, t, *J* 7), 7.09–7.29 (8H, m); δ_C 28.3, 32.4, 40.8, 60.7, 80.8, 115.3, 122.4, 125.0, 126.4, 127.4, 128.5, 129.5, 130.5, 137.9, 142.0 and 152.2 (the signals at 130.5 and 142.0 were broad and of very low intensity); *m*/*z* (EI) 309.1733 (11%, M^+; $C_{20}H_{23}NO_2$ requires 309.1729), 253 (23), 236 (7), 218 (13), 132 (4), 118 (100), 91 (23), and 57 (55). $[\alpha]_D$ −65.7 (*c* 1.00 in CH_2Cl_2).

(2*S*)-*N*-(*tert*-Butoxycarbonyl)-2-(benzyloxycarbonyl)-1,2,3,4-tetrahydroquinoline 4h. Compound **4h** (0.312 g, 85%) was isolated as a yellow oil. Found: C, 72.0; H, 6.9; N, 3.9. $C_{22}H_{25}NO_4$ requires C, 71.9; H, 6.9 and N, 3.8%. ν_{max} 3065, 3034, 2974, 2926, 1735, 1705, 1484, 1392, 1169, and 751; δ_H 1.56 (9H, s), 2.57 (1H, dd, *J* 10, 15), 2.83 (1H, dd, *J* 2, 16.5), 2.88–3.03 (1H, br s), 3.39 (1H, dd, *J* 10, 16.5), 4.70–4.87 (1H, br s), 5.07 (1H, d, *J* 12.5), 5.11 (1H, d, *J* 12.5), 6.94 (1H, dt, *J* 1, 7.5), 7.12 (1H, d, *J* 7.5), 7.16 (1H, t, *J* 7.5), 7.30–7.38 (5H, m), 7.40–7.45 (1H, m); δ_C 28.4, 29.7, 39.2, 56.1, 66.4, 81.3, 115.3, 122.6, 125.0, 127.5, 128.3, 128.6, 128.9, 134.8, 135.7, 143.3, 151.9 and 170.9; *m*/*z* (EI) 367.1779 (5%, M^+; $C_{22}H_{25}NO_4$ requires 367.1784), 257 (64), 233 (8), 208 (14), 130 (20), 118 (100), 91 (87), 77 (8), and 57 (73). $[\alpha]_D$ +5.4 (*c* 1.25 in CH_2Cl_2).

Acknowledgements

This work was supported by Medivir (UK), (partial funding of a studentship to HJCD) and EPSRC and GlaxoSmithKline, through a CASE award (to CH). We thank Dr U. Grabowska (Medivir) and Dr H. K. Rami (GlaxoSmithKline) for helpful advice, Professor W. McFarlane (University of Newcastle upon Tyne) for the variable temperature NMR studies, and Dr M.G. Sanders (GlaxoSmithKline) for the HPLC ee determination.

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