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Concise synthesis of (±)-horsfiline and (±)-coerulescine by tandem cyclisation of iodoaryl alkenyl azides†

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A brief, efficient and economical synthesis of the spiropyrrolidinyloxindoles, horsfiline and coerulescine, has been achieved, starting from itaconic acid and, respectively, *p*-anisidine or *o*-iodoaniline. Tandem radical cyclisation of iodoaryl alkenyl azides is the key step in both syntheses.

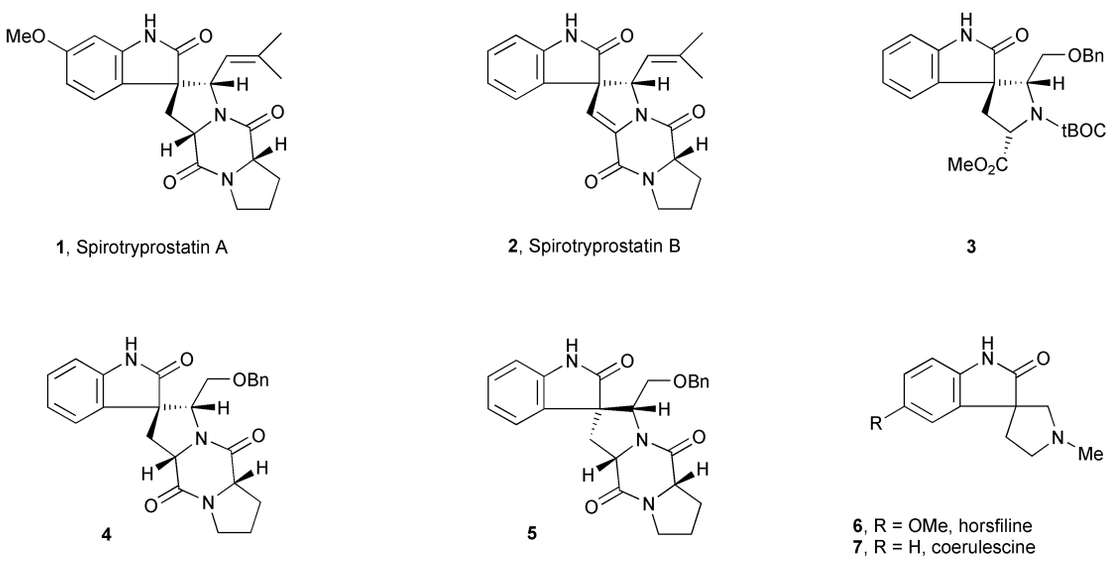
Introduction

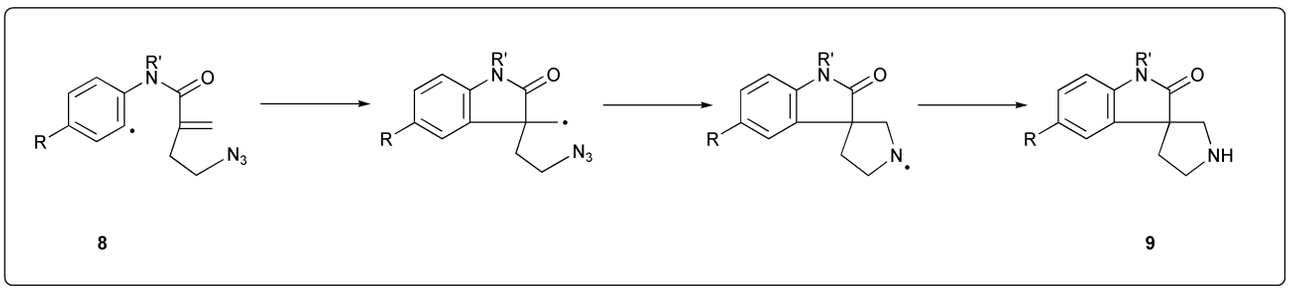
The recent isolation of the natural products[1] spirotryprostatin A **1** and spirotryprostatin B **2** (Scheme 1), and the discovery of their activity (albeit mild activity) as cell cycle inhibitors has added considerable impetus to research on the spiropyrrolidinyloxindole alkaloids. Total syntheses[2] of the spirotryprostatins A and B have been achieved, but it transpires that synthetic intermediates prepared during Danishefsky's synthetic studies[3] on these compounds, may be more interesting than the spirotryprostatins themselves. Three compounds, **3**–**5**, were identified to have potent and selective action on human breast cancer cell lines.

Among these, tricyclic compound **3** is exciting since it is a relatively uncomplicated potential lead for development of novel anti-tumour agents. Also highly active was the pair of diastereomers **4** and **5**. The discovery of equal activity for the diastereomeric pair shows that the stereochemistry of the spiro centre in these molecules is not crucial for anti-tumour action. Although the cellular site of action of these three compounds has not yet been disclosed, if it is assumed that they act at a common locus, as a working hypothesis, then the anti-tumour activity of tricyclic spiropyrrolidinyloxindoles requires further investigation, and therefore synthetic routes that provide easy access to these classes of compounds become important.

It is not surprising therefore that there has been a significant and increasing interest in the synthesis of the tricyclic natural

† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra are provided for the compounds; the preparations of compounds **19**, **20** and **21** and the conversion of **20** to **16** are also included. See http://www.rsc.org/suppdata/ob/b2/b208114h/





Scheme 1

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products, horsfiline[4a–h,4j] **6** (isolated by Bodo and co-workers[4a]) and coerulescine[4d,i–l] **7** (isolated[5] by Colegate and co-workers) that bear the same tricyclic skeleton as **3**. A range of synthetic approaches has been used. With respect to horsfiline, Jones and Wilkinson[4b] used a free radical cyclisation as the key step in their synthesis. Lévy and co-workers produced[4d] two routes featuring (i) oxidative rearrangement of a tetrahydrocarboline (see also ref. 4*a*) and (ii) oxidation and formaldehyde-treatment of an appropriately substituted tryptamine. In a synthesis of (−)-horsfiline as well as, separately, the unnatural enantiomer, Borschberg and co-workers[4c] studied the stereospecific conversion of tryptamine derivatives firstly to tetrahydrocarbolines and thence to spiropyrrolidinylindolones, while Palmisano *et al.* prepared[4e] (−)-**6** *via* the (chiral auxiliary-directed) cycloaddition of azomethine ylides onto 3-methyleneindolones. Meanwhile, Fuji and co-workers used[4f] asymmetric nitroolefination of indolones to introduce the correct stereochemistry at what would become the spiro-carbon, subsequently making the pyrrolidine ring. More recently, in preparations of (±)-**6**, Carreira's group[4g] have ring-expanded a spiro-cyclopropylindolone to the requisite spiropyrrolidine, and Kumar *et al.* rearranged[4j] an (aziridinoethylidene)indolone to a pyrrolidinylindolone.

From our perspective, the spiropyrrolidinyl-oxindole skeleton should be an ideal target for synthesis using the iodoaryl azide tandem radical cyclisation strategy that we recently exploited in the total synthesis of aspidospermidine[6] and in the formal total synthesis of vindoline.[7] Thus tandem cyclisation of a radical, **8**, should afford the tricyclic system, **9**, in a single process. This paper reports[8] the realisation of that goal.

Results and discussion

To synthesise horsfiline, dilithiated *t*-BOC-*p*-anisidine **10a** was iodinated[9] with 1,2-diiodoethane, to give **11a** (86%). Deprotection of the *t*-BOC group gave **12a** (89%), which was reductively alkylated with benzaldehyde[10] (94%). (Conversion of the primary amine **12a** to a secondary amine such as **13a** is necessary since the radical cyclisations about to be undertaken on the amide substrates, *e.g.* **17** in Scheme 2 do not succeed[4b] with secondary amides. We chose benzylation for this conversion, because of the later easy removal of the benzyl group). Condensation of the benzylamine **13a** with the acid chloride[11] **14** of the monomethyl ester of itaconic‡ acid (in turn readily available[11] from commercially available itaconic acid) afforded the amide **15a** (94%). It was now necessary to reduce the ester group in amide **15a** to an alcohol, **16a**, before conversion to azide **17a** and cyclisation. Initial attempts to reduce the ester to alcohol **16a** with DIBAL-H led to the desired product **16a** as the major product, but it was contaminated with a minor compound that, based on examination of the NMR spectrum, we propose to be **18**, where unexpected reduction of the alkene has occurred. Unfortunately the two compounds had similar physical properties, so separation was not possible. To overcome this problem, protection of the alkene double bond in **15a** was undertaken. Reaction of **15a** with PhSeNa, formed *in situ* by reduction of diphenyl diselenide with sodium borohydride, surprisingly led to no reaction, and we attribute this to steric hindrance to attack on the alkene by the large phenylseleno group. To decrease the steric problems, PhSH was instead reacted with ester **15a** in the presence of base to give an excellent yield of product **19** (96%). Reduction of **19** afforded the desired alcohol **20** (55%) together with a small amount of unexpected amine **21** (10%). Alcohol **20** was purified and oxidized to the corresponding sulfoxide, which was directly subjected to thermal elimination affording the alcohol **16a** (72%).

‡ The IUPAC name for itaconic acid is methylenesuccinic acid.

Although **16a** had now been produced, the process of protecting and later deprotecting the alkene detracted from the directness of the synthetic route. With this in mind, we returned to investigate further whether a clean reduction of **15a** to **16a** could be found. Gratifyingly, success was achieved with $LiBH_4$, generated *in situ* from lithium chloride and sodium borohydride.[12] This afforded the desired product cleanly and in high yield (83%). Conversion to the azide **17a** (68%) was accomplished using diphenylphosphoryl azide, and this was followed by tandem cyclisation to afford the tricyclic product **22a**; this was subjected to *in situ* methylation to yield **23a** (60% over two steps). Finally deprotection under Birch conditions afforded horsfiline **6** (87%).

Significantly, the tandem radical cyclisation afforded solely the desired tricyclic skeleton; no product arising from apparent 6-*endo-trig* cyclisation of the aryl radical onto the alkene was seen. In studies related to the synthesis of these same alkaloids, Jones *et al.* had shown[13] how the balance of 5-*exo* to apparent 6-*endo* cyclisation is determined by kinetic and thermodynamic factors. At lower temperatures, the 5-*exo* predominates,[14] but at higher temperatures, rearrangement to 6-*endo* can occur through a neophyl rearrangement. In our case, the product of the initial 5-*exo* cyclisation is likely to be trapped by the azide group, preventing side-products from forming.

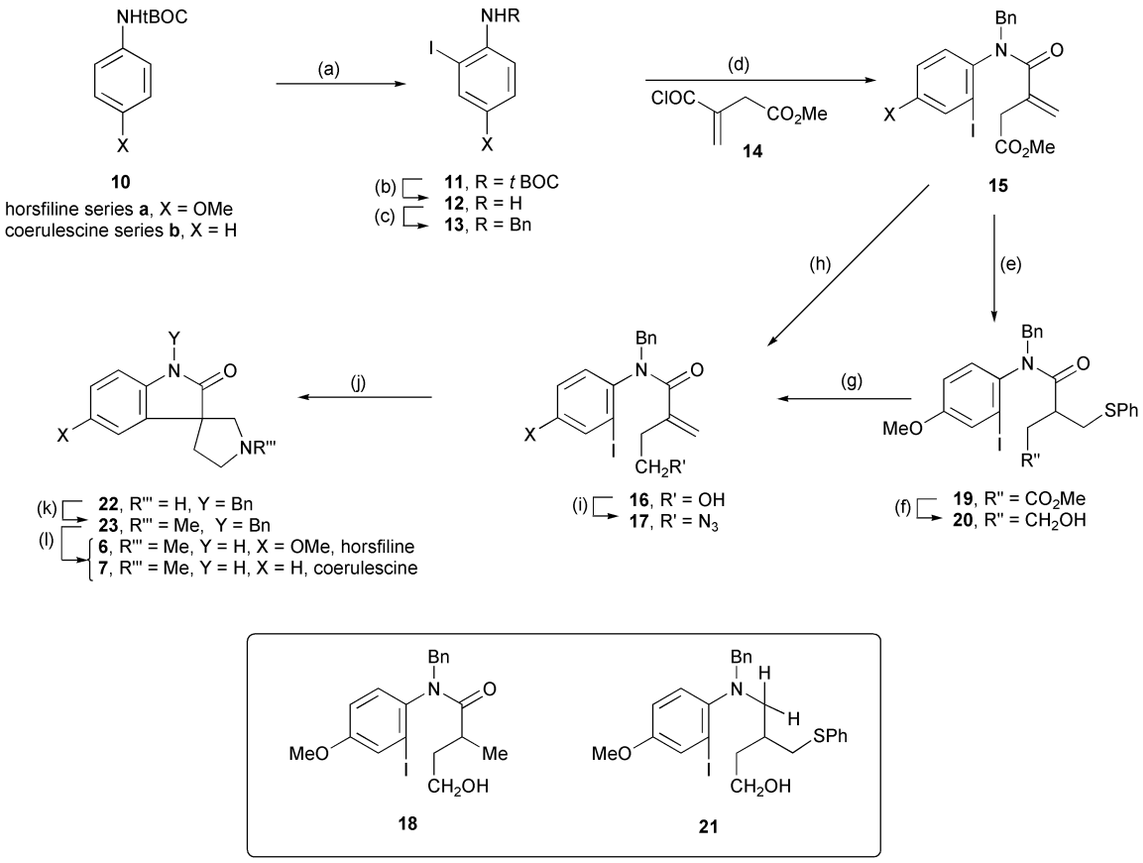
The same protocol was then followed for the synthesis of coerulescine and with generally excellent yields, producing intermediates **13b** (92%), **15b** (94%), **16b** (84%), **17b** (70%) and **23b** (68%). We were a little concerned about the final deprotection step to afford coerulescine. Debenzylation of **23a** in the horsfiline case involves selective addition of solvated electrons to the aromatic ring of the benzyl protecting group. It is entirely reasonable that this should be a very selective process, since the aromatic ring in the horsfiline skeleton is likely to be far more electron-rich, and hence more difficult to reduce, than that of the benzyl group, due to the electron-donating properties of the methoxy and amide groups. With coerulescine, the absence of the methoxy group should make the difference between the two rings less pronounced, but the benzyl group should still bear the more electron-poor ring. In practice, the selectivity was maintained and the reaction proceeded in an excellent (83%) yield.

It is seen that the iodoaryl alkenyl azide tandem radical cyclisation reaction affords a rapid route to (±)-horsfiline in 20% yield from *t*-BOC-*p*-anisidine [18% from anisidine], and (±)-coerulescine in 29% yield from 2-iodoaniline. An acid chloride derived from the economical itaconic acid is the key partner reagent for both syntheses. The efficiency of this route ranks with the highest reported.

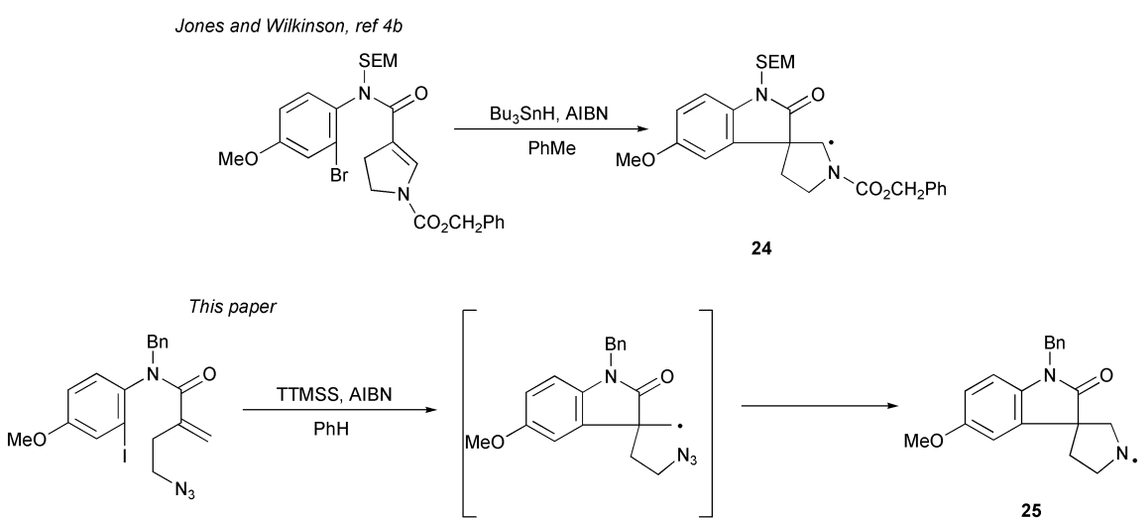
In mechanistic terms, this route shows greatest similarities with the route of Jones and Wilkinson,[4b] since both use radical cyclisations as the key steps (Scheme 3). However, the two routes differ considerably in all other facets, (*e.g.* single cyclisation *versus* tandem cyclisation) and most particularly in the nature and reactivity of the final radicals, carbon radical **24** in their case, *versus* nitrogen radical **25** in this case. Importantly, in designing the synthesis of more complex spiropyrrolidinylindolones, the diversity of efficient routes should now allow access to a wide variety of substitution patterns of analogues for anti-tumor testing.

Experimental section

Melting points were carried out on a Reichert hot stage apparatus and are uncorrected. Infra red spectra were obtained on a Perkin Elmer 1720-X FTIR. Mass spectra were recorded on a JEOL JMS-AX505 HA instrument using, electron impact ionisation (EI^+), chemical ionisation (CI), electrospray (ES) or fast atom bombardment (FAB). Some low and high resolution mass spectra were obtained on JLSX 102 and VG ZAB-E instruments using peak-matching techniques at the EPSRC



Scheme 2 Syntheses of horsfiline and coerulescine. *Reagents and conditions*: (a) *t*-BuLi, Et_2O, −20 °C then ICH_2CH_2I, 86% for **11a**; (b) TFA, DCM, 0 °C, 89% for **12a**; (c) $ZnCl_2$, PhCHO, MeOH, $NaCNBH_3$, 94% for **13a**, 92% for **13b**; (d) Et_3N, PhH, 94% for **15a**; 94% for **15b**; (e) PhSH, DBU, THF, Δ, 96% for **19**; (f) DIBAL-H, PhMe, −78 °C, 55% for **20**; (g) *m*-CPBA, DCM, then PhMe, Δ, 72 h, 72% for **16a**; (h) LiCl, $NaBH_4$, EtOH, THF, 83% for **16a**, 84% for **16b**; (i) PPh_3, $(PhO)_2P(O)N_3$, DEAD, THF, 68% for **17a**; 70% for **17b**; (j) $(Me_3Si)_3SiH$, AIBN, PhH; (k) CH_2O, $NaCNBH_3$, MeCN, yield over 2 steps: 60% for **23a**, 68% for **23b**; (1) Na, NH_3, 86% for **6**, 83% for **7**.



Scheme 3 The different regiochemical outcomes of the two radical cyclisation approaches to spiropyrrolidinylindolones.

Mass Spectrometry Centre, Swansea. ^{1}H NMR spectra were recorded at 400 MHz on a Bruker DPX 400 spectrometer. ^{13}C{H} NMR spectra were similarly recorded at 100.61 MHz on a Bruker DPX400 machine. NMR experiments were carried out in deuterochloroform with tetramethylsilane as internal reference unless otherwise stated. ^{13}C NMR spectra were acquired in a broadband decoupled mode with the multiplicities obtained using a DEPT or Jmod sequence. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane. The following abbreviations are used for multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet, br = broad. Coupling constants (J) are reported in Hertz (Hz).

tert-Butyl (2-iodo-4-methoxyphenyl)carbamate 11a[9]

Addition of *tert*-butyllithium in pentane (1.7 M, 39.6 cm^{-3}, 67.2 mmol, 2.5 equiv.) to a solution of *tert*-butyl (4-methoxyphenyl)carbamate (6.0 g, 26.9 mmol, 1.00 equiv.), in dry diethyl ether (60 cm^{-3}), was performed under a nitrogen atmosphere at −20 °C, followed by stirring for 3 h at the same temperature. To this mixture was added 1,2-diiodoethane (11.4 g, 40.3 mmol,

1.5 equiv.) in dry diethyl ether (80 cm^{-3}) at −78 °C, and the reaction was gradually warmed to room temperature and stirred for 16 h. After addition of a saturated aqueous solution of sodium thiosulfate (200 cm^{-3}), the mixture was extracted with diethyl ether. The organic extracts were then washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (10 : 1 petroleum ether–ethyl acetate) to yield *tert*-butyl (2-iodo-4-methoxyphenyl)carbamate **11a** as colourless prisms (8.1 g, 86%); mp 48–49 °C (lit.[9] mp 49–50 °C); [Found (EI) M^+ 349.0172. $C_{12}H_{16}INO_3$ requires *M*, 349.0175]. ν_{max} (film)/cm^{-1} 3399, 2976, 2933, 2834, 1725, 1511, 1367, 1250, 1161, 1037; δ_H 1.51 (9H, s, 3 × CH_3), 3.72 (3H, s, CH_3), 6.55 (1H, br s, NH), 6.84–6.87 (1H, dd, *J* 9.0, 2.8 ArH), 7.28 (1H, d, *J* 2.8, ArH) 7.76 (1H, d, *J* 9.0, ArH); δ_C 28.5 (q), 55.9 (q), 80.9 (s), 90.5 (s), 115.1 (d), 122.3 (d), 123.9 (d), 132.6 (s), 153.3 (s), 156.3 (s). *m*/*z* (EI) 349 (29%, M^+), 293 (96), 249 (46), 166 (34), 106 (22) and 57 (100).

4-Amino-3-iodoanisole 12a

Trifluoroacetic acid (21.2 cm^{-3}, 274.9 mmol, 12.00 equiv.) was added to a solution of *tert*-butyI (2-iodo-4-methoxyphenyl)-carbamate (8.0 g, 22.9 mmol, 1.00 equiv.) in dry DCM (120 cm^{-3}) at 0 °C and the reaction was stirred at room temperature for 2 h. Sodium hydroxide (2 M) was added followed by hydrochloric acid (2 M) until neutral pH had been attained. The two layers were separated and the aqueous one was extracted with DCM. The organic layers were washed with brine, dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (4 : 1 petroleum ether–ethyl acetate) giving *4-amino-3-iodoanisole* **12a** as a colourless oil (5.1 g, 89%); [Found (ES): MH^+ 249.9732 C_7H_9INO, requires *MH*, 249.9729]; ν_{max} (film)/cm^{-1} 3431, 3348, 2939, 2830, 1596, 1493, 1232, 1037; δ_H 3.62 (2H, br s, NH_2), 3.77 (3H, s, CH_3), 6.74 (1H, d, *J*, 8.7, ArH), 6.82 (1H, dd, *J* 8.7, 2.7, ArH), 7.26 (1H, d, *J* 2.7, ArH); δ_C 56.4 (q), 84.7 (s), 115.9 (d), 116.5 (d), 124.0 (d), 141.3 (s), 153.1 (s); *m*/*z* (CI) 267 (MNH_4^+, 63%), 250 (M^+, 100).

Benzyl(2-iodo-4-methoxyphenyl)amine 13a

A stirred mixture of 4-amino-3-iodoanisole **12** (3 g, 12.00 mmol, 1.00 equiv.), zinc(II) chloride (1.97 g, 14.45 mmol, 1.20 equiv.) and benzaldehyde (1.47 cm^{-3}, 14.45 mmol, 1.20 equiv.) in methanol, (50 cm^{-3}) was treated with sodium cyanoborohydride (0.91 g, 14.45 mmol, 1.20 equiv.) and warmed at reflux under nitrogen for 2 h. The cooled reaction mixture was diluted with sodium hydroxide (1 M, 50 cm^{-3}) and extracted with diethyl ether. The combined ether layers were washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo*. *Benzyl(2-iodo-4-methoxyphenyl)amine* **13a** was purified by column chromatography on silica gel eluting with petroleum ether–ethyl acetate 5 : 1 to give pure title compound as a yellow oil (3.85 g, 94%); Found: C, 49.87; H, 4.15; N, 4.06. $C_{14}H_{14}INO$ requires C, 49.56; H, 4.16; N, 4.13%; (Found (ES): MH^+ 340.0196, $C_{14}H_{15}INO$ requires *MH* 340.0198); ν_{max} (film)/cm^{-1} 3401, 3028, 2998, 2830, 1603, 1504, 1282, 1039; δ_H 3.75 (3H, s, CH_3), 4.33 (1H, br s, NH), 4.39 (2H, d, *J* 4.2, CH_2), 6.54 (1H, d, *J* 8.9, ArH), 6.84, (1H, dd, *J* 2.9, 8.9, ArH), 7.30–7.42 (6H, m, ArH); δ_C 49.2 (t), 56.1 (q), 85.5 (s), 111.7 (d), 115.7 (d), 124.8 (d), 127.4 (d), 128.8 (d), 139.1 (s), 142.0 (s), 152.2 (s); *m*/*z* (CI) 340.1 ([MH]$^+$, 100%).

3-Chlorocarbonylbut-3-enoic acid methyl ester 14[11]

Thionyl chloride (7.1 cm^{-3}, 97.2 mmol, 1.40 equiv.) was added to a solution of 2-methylenesuccinic acid 4-methyl ester (10 g, 69.4 mmol, 1.00 equiv.) in dry diethyl ether (8 cm^{-3}) and the reaction mixture was refluxed gently until gas evolution was essentially complete (15 min). Distillation gave 3-chlorocarbonylbut-3-enoic acid methyl ester **14** as a colourless oil (10.8 g, 96%) bp 84–87 °C (11 mmHg) (Found: M^+ 162.0080, $C_6H_7ClO_3$ requires *M* 162.0084); ν_{max} (film)/cm^{-1} 3004, 2955, 2847, 1740, 1638, 1437, 1343, 1206; δ_H 3.39 (2H, d, *J* 0.8, CH_2), 3.72 (3H, s, CH_3), 6.17 (1H, t, *J* 0.8, CH_2), 6.70 (1H, s, CH_2); δ_C 37.8 (t), 52.8 (q), 136.5 (t), 138.7 (s), 168.6 (s), 170.3 (s); *m*/*z* (EI) 163 ([MH]$^+$, 5%), 127 (60), 113 (95), 99 (50), 85 (100).

3-[Benzyl(2-iodo-4-methoxyphenyl)carbamoyl]but-3-enoic acid methyl ester 15a

Triethylamine (1.6 cm^{-3}, 11.4 mmol, 1.10 equiv.) was added to a stirred solution of benzyl(2-iodo-4-methoxyphenyl)amine (3.5 g, 10.3 mmol, 1.00 equiv.) in dry benzene (10 cm^{-3}) at room temperature. 3-Chlorocarbonylbut-3-enoic acid methyl ester (2.18 g, 13.4 mmol, 1.30 equiv.) in dry benzene (10 cm^{-3}) was added dropwise. The resulting solution was stirred at rt for 30 min, then heated under reflux for 90 min. After cooling, the solvent was removed under reduced pressure and the residue dissolved in diethyl ether (50 cm^{-3}). The ether was washed with water, dried over anhydrous sodium sulfate and concentrated. Column chromatography eluting with petroleum ether–ethyl acetate 4 : 1 gave pure *3-[benzyl(2-iodo-4-methoxyphenyl)-carbamoyl]but-3-enoic acid methyl ester* **15a** as a white solid mp 107–110 °C (4.5 g, 94%); Found C, 51.68; H, 4.36; N, 3.03. $C_{20}H_{20}INO_4$ requires C, 51.61; H, 4.33; N, 3.01%; [Found: (ES) MH^+ 466.0521, $C_{20}H_{21}INO_4$ requires *MH* 466.0515]; ν_{max} (film)/cm^{-1} 3065, 2998, 2841, 1736, 1651, 1622, 1491, 1287, 1175; δ_H 3.06 (1H, d, *J* 16.5, CH_2), 3.64–3.69 (4H, CH_3 + CH_2), 3.78 (3H, s, CH_3), 4.17 (1H, d, *J* 14.3, CH_2), 5.16 (1H, s, CH_2), 5.27 (1H, s, CH_2), 5.77 (1H, d, *J* 14.3, CH_2), 6.70 (1H, dd, *J* 2.8, 8.7, ArH), 6.81 (1H, d, *J* 8.7, ArH), 7.23–7.31 (5H, m, ArH), 7.42 (1H, d, *J* 2.8, ArH); δ_C 40.1 (t), 52.0 (q), 52.1 (t), 55.7 (q), 100.1 (s), 114.4 (d), 123.2 (t), 125.0 (d), 127.6 (d), 128.4 (d), 129.6 (d), 132.0 (d), 136.5 (s), 136.8 (s), 137.5 (s), 159.0 (s), 169.2 (s), 171.3 (s); *m*/*z* (ES) 466 [(MH)$^+$, 60%], 340 (100).

Reduction of 3-[benzyl(2-iodo-4-methoxyphenyl)carbamoyl]but-3-enoic acid methyl ester 15a using $NaBH_4$ and LiCl

Lithium chloride (16.2 mg, 0.43 mmol, 2.00 equiv.) was added to a solution of 3-[benzyl(2-iodo-4-methoxyphenyl)carbamoyl]but-3-enoic acid methyl ester **15a** (100 mg, 0.21 mmol, 1.00 equiv.) in dry THF–EtOH (2 : 1 mixture, 3 cm^{-3}). When it had dissolved, $NaBH_4$ (16.2 mg, 0.43 mmol, 2.00 equiv.) was added and the reaction mixture was stirred at room temperature for 16 h. Then the solvent was evaporated near dryness and H_2O (4 cm^{-3}) was added. The organic phase was extracted with ethyl acetate, washed with H_2O, dried over anhydrous sodium sulfate and concentrated under vacuum. The reaction mixture was subjected to column chromatography eluting with petroleum ether–ethyl acetate 1 : 1 to afford *N-benzyl-2-(2-hydroxyethyl)-N-(2-iodo-2-methoxyphenyl)acrylamide* **16a** as a colourless oil (76 mg, 83%); [Found (ES): MH^+ 438.0563, $C_{19}H_{21}INO_3$ requires *MH* 438.0566]; ν_{max} (film)/cm^{-1} 3409, 2938, 1614, 1487, 1287, 1030; δ_H 2.01 (1H, br s, OH) 2.25–2.31 (1H, m, CH_2), 2.48–2.54 (1H, m, CH_2), 3.62–3.77 (5H, m, CH_2 and CH_3), 4.10 (1H, d, *J* 14.1, CH_2), 5.10 (1H, s, CH_2), 5.14 (1H, s, CH_2), 5.71 (1H, d, *J* 14.1, CH_2), 6.56 (1H, d, *J* 8.7 ArH), 6.68 (1H, dd, *J* 2.7, 8.7, ArH), 7.21–7.39 (5H, m, ArH), 7.40 (1H, d, *J* 2.7, ArH); δ_C 38.2 (t), 52.4 (t), 55.7 (q), 62.6 (t), 100.1 (s), 114.4 (d), 120.2 (t), 125.0 (d), 127.9 (d), 128.6 (d), 129.6 (d), 131.6 (d), 136.6 (s), 137.1 (s), 142.0 (s), 159.1 (s), 172.2 (s); *m*/*z* (El) 438.1 [(MH)$^+$, 100%]

2-(2-Azidoethyl)-*N*-benzyl-*N*-(2-iodo-4-methoxyphenyl)-acrylamide 17a

Triphenylphosphine (363 mg, 1.38 mmol, 1.10 equiv.), DEAD (0.22 cm^{-3}, 1.38 mmol, 1.10 equiv.) and diphenylphosphoryl azide (0.3 cm^{-3}, 1.38 mmol, 1.10 equiv.) were added sequen-

tially to a solution of alcohol **16a** in dry THF (12 cm^{-3}), and the solution was stirred at rt for 24 h. Then the solvent was evaporated and the residue was subjected to column chromatography using petroleum ether–ethyl acetate 5 : 1 to afford pure *2-(2-azidoethyl)-N-benzyl-N-(2-iodo-4-methoxyphenyl) acrylamide* **17a** as a slightly yellow oil (396 mg, 68%); [Found (ES): MH^+ 463.0622, $C_{19}H_{20}IN_4O_2$ requires *MH* 463.0631]; ν_{max} (film)/cm^{-1} 3030, 2938, 2838, 2096, 1651, 1622, 1488, 1287, 1030; δ_H 2.34–2.41 (1H, m, CH_2), 2.55–2.62 (1H, m, CH_2), 3.43 (2H, t, *J* 6.9, CH_2), 3.78 (3H, s, CH_3), 4.09 (1H, d, *J* 14.1, CH_2), 5.12 (1H, s, CH_2), 5.17 (1H, s, CH_2), 5.71 (1H, d, *J* 14.1, CH_2), 6.55 (1H, d, *J* 8.7, ArH), 6.69 (1H, dd, *J* 2.7, 8.7, ArH), 7.21–7.35 (5H, m, ArH), 7.41 (1H, d, *J* 2.7, ArH); δ_C 33.9 (t), 50.1 (t), 52.3 (t), 55.8 (q), 100.4 (s), 114.5 (d), 120.3 (t), 125.1 (d), 127.8 (d), 128.6 (d), 129.7 (d), 131.7 (d), 136.9 (s), 137.1 (s), 140.7 (s), 159.2 (s), 170.5 (s); *m/z* (CI) 463 [$(MH)^+$, 35%], 115 (100).

Tandem radical cyclisation of 2-(2-azidoethyl)-*N*-benzyl-*N*-(2-iodo-4-methoxyphenyl)acrylamide 17a

2-(2-Azidoethyl)-*N*-benzyl-*N*-(2-iodo-4-methoxyphenyl)acrylamide **17a** (295 mg, 0.64 mmol, 1.00 equiv.) was dissolved in dry benzene (20 cm^{-3}) and the solution was purged with argon for 30 min. The solution was brought to reflux and tristrimethylsilylsilane (TTMSS) (0.22 cm^{-3}, 0.70 mmol, 1.10 equiv.) and AIBN (21 mg, 0.13 mmol, 0.2 equiv.) were added and the mixture was refluxed for 5 h. The reaction mixture was allowed to cool down to room temperature and the solvent was removed *in vacuo*. Ethyl acetate (50 cm^{-3}) was added and the mixture extracted with hydrochloric acid (2 M). The aqueous phase was basified with sodium hydroxide (2 M) and then it was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo.* The crude 1-benzyl-5-methoxy-1*H*-spiro[indole-3,3′-pyrrolidin]-2-one **22a** (150 mg, 0.49 mmol, 1.00 equiv.) from the previous step was dissolved in acetonitrile (7 cm^{-3}) and treated[5f] with formaldehyde [(0.24 cm^{-3}, 2.92 mmol, 6.00 equiv.) 37% in water] and $NaCNBH_3$ (61 mg, 0.97 mmol, 2.00 equiv.) at rt. The mixture was stirred for 15 min and neutralised with acetic acid. After stirring was continued for another 1 h, the mixture was basified with ammonia solution and the solvent was removed *in vacuo*. The residue was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Column chromatography eluting with ethyl acetate: acetone 4 : 1 gave pure 1-benzyl-5-methoxy-1′-methyl-1*H*-spiro[indole-3,3′-pyrrolidin]-2-one **23a** as a colourless oil (123 mg, 60% over two steps) (Found MH^+ 323.1761, $C_{20}H_{23}N_2O_2$ requires *MH* 323.1759); ν_{max} (film)/cm^{-1} 2941, 2836, 2787, 1707, 1601, 1491, 1177, 1035; δ_H 2.12–2.20 (1H, m, CH_2), 2.40–2.46 (1H, m, CH_2), 2.51 (3H, s, CH_3), 2.78–2.85 (1H, m, CH_2), 2.91 (1H, d, *J* 9.4, CH_2), 3.01 (1H, d, *J* 9.4, CH_2), 3.15–3.20 (1H, m, CH_2), 3.77 (3H, s, CH_3), 4.88 (2H, s, CH_2), 6.59 (1H, d, *J* 8.5, ArH), 6.68 (1H, dd, *J* 2.6, 8.5, ArH), 7.11 (1H, d, *J* 2.6, ArH), 7.24–7.33 (5H, m, ArH); δ_C 38.4 (t), 42.0 (q), 44.1 (t), 53.9 (s), 56.1 (q), 56.8 (t), 66.2 (t), 109.3 (d), 110.6 (d), 112.5 (d), 127.4 (d), 127.8 (d), 129.0 (d), 135.6 (s), 136.2 (s), 137.0 (s), 156.6 (s), 180.2 (s); *m/z* (CI) 323 [$(MH)^+$, 100%].

(±)-Horsfiline 6[4g]

Ammonia (*ca.* 5 cm^{-3}) was condensed at −50 °C and sodium (31 mg) was added with vigorous stirring. 1-Benzyl-5-methoxy-1′-methyl-1*H*-spiro[indole-3,3′-pyrrolidin]-2-one **23a** (29.4 mg, 0.09 mmol, 1.00 equiv.) was added in THF (1 cm^{-3}). After 12 min, a small amount of NH_4Cl was added and the ammonia left to evaporate. Water (25 cm^{-3}) was added and the reaction was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated *in vacuo*. Column chromatography on silica gel with DCM–MeOH 9 : 1 afforded pure (±)-horsfiline as a white solid (18.2 mg, 87%); mp 154–156 °C (lit.[4g] mp 156–157 °C) [Found (ES): MH^+ 233.1287, $C_{13}H_{17}N_2O_2$ requires *MH* 233.1290]; ν_{max} (film)/cm^{-1} 3400, 2944, 2849, 1704, 1604, 1491, 1304, 1209, 1031; δ_H 2.05–2.18 (1H, m, CH_2), 2.38–2.44 (1H, m, CH_2), 2.49 (3H, s, CH_3), 2.77–2.84 (1H, m, CH_2), 2.90 (1H, d, *J* 9.4, CH_2), 2.97 (1H, d, *J* 9.4, CH_2), 3.06–3.11 (1H, m, CH_2), 3.80 (3H, s, CH_3), 6.72 (1H, dd, *J* 2.5, 8.4, ArH), 6.80 (1H, d, *J* 8.4, ArH), 7.06 (1H, d, *J* 2.5, ArH), 8.32 (1H, br s, NH); δ_C 38.3 (t), 41.9 (q), 54.3 (s), 56.1 (t), 56.8 (q), 66.2 (t), 110.0 (d), 110.6 (d), 112.9 (d), 133.6 (s), 137.4 (s), 156.5 (s), 182.8 (s); *m/z* (CI) 233 [$(M + H)^+$), 100%].

Benzyl(2-iodophenyl)amine 13b

12b (5 g, 22.80 mmol, 1.00 equiv.), was treated as for **12a** and afforded benzyl(2-iodophenyl)amine **13b** as a yellow oil (6.5 g, 92%) [Found (ES): MH^+ 310.0095, $C_{13}H_{13}IN$ requires *MH* 310.0093]; ν_{max} (film)/cm^{-1} 3400, 3060, 3027, 2854, 1589, 1502, 1318, 1004; δ_H 4.52 (2H, d, *J* 5.6, CH_2), 4.74 (1H, br s, NH) 6.56 (1H, ddd, *J* 1.4, 7.3, 7.8, ArH), 6.64 (1H, dd, *J* 1.3, 8.1, ArH), 7.26 (1H, ddd, *J* 1.4, 7.3, 8.1, ArH), 7.39–7.48 (5H, m, ArH), 7.78–7.80 (1H, dd, *J* 1.4, 7.8, ArH); δ_C 48.5 (t), 85.5 (s), 111.1 (d), 119.0 (d), 127.4 (d), 127.5 (d), 128.9 (d), 129.6 (d), 138.8 (s), 139.2 (d), 147.3 (s); *m/z* (EI) 309 [$(MH)^+$, 18%], 180 (20), 91 (100) and 65 (22).

3-[Benzyl(2-iodophenyl)carbamoyl]but-3-enoic acid methyl ester 15b

Benzyl(2-iodophenyl)amine **13b** (4.5 g, 14.55 mmol, 1.00 equiv.) was reacted as for **13a** and gave *3-[benzyl(2-iodophenyl)carbamoyl]but-3-enoic acid methyl ester* **15b** as a white solid mp 60–62 °C (5.96 g, 94%); [Found (EI): M^+ 435.0339, $C_{19}H_{18}INO_3$ requires *M* 435.0331]; ν_{max} (film)/cm^{-1} 2949, 1736, 1653, 1625, 1470, 1172; δ_H 3.06 (1H, d, *J* 16.5, CH_2), 3.67–3.70 (4H, m, CH_2 and CH_3), 4.23 (1H, d, *J* 14.3, CH_2), 5.15 (1H, s, CH_2), 5.27 (1H, s, CH_2), 5.78 (1H, d, *J* 14.3, CH_2), 6.94–7.00 (2H, m, ArH), 7.16–7.20 (1H, m, ArH), 7.24–7.30 (5H, m, ArH), 7.91 (1H, d, *J* 7.9, ArH); δ_C 40.0 (t), 52.0 (q), 52.5 (t), 99.8 (s), 123.4 (t), 127.7 (d), 128.4 (d), 129.0 (d), 129.4 (d), 129.6 (d), 132.0 (d), 136.4 (s), 136.6 (s), 140.2 (d), 144.7 (s), 168.9 (s), 171.3 (s); *m/z* (EI) 435 (M^+, 5%), 376 (9), 308 (18), 180 (19) and 91 (100).

N-Benzyl-2-(2-hydroxyethyl)-*N*-(2-iodophenyl)acrylamide 16b

3-[Benzyl(2-iodophenyl)carbamoyl]but-3-enoic acid methyl ester **15b** (12.1 g, 27.8 mmol, 1.00 equiv.) was treated as for **15a** to afford *N-benzyl-2-(2-hydroxyethyl)-N-(2-iodophenyl)-acrylamide* **16b** as a colourless oil (9.5 g, 84%) [Found (ES): MH^+ 408.0461, $C_{18}H_{19}INO_2$ requires *MH* 408.0460]; ν_{max} (film)/cm^{-1} 3401, 2931, 1647, 1619, 1469, 1030; δ_H 2.27–2.31 (1H, m, CH_2), 2.50–2.57 (1H, m, CH_2), 3.20 (1H, br s, OH), 3.74–3.81 (2H, m, CH_2), 4.14 (1H, d, *J* 14.3, CH_2), 5.10 (1H, s, CH_2), 5.13 (1H, s, CH_2), 5.70 (1H, d, *J* 14.3, CH_2), 6.68 (1H, d, *J* 7.6, ArH), 6.97–7.00 (1H, m, ArH), 7.15–7.28 (6H, m, ArH), 7.92 (1H, dd, *J* 1.4, 7.9, ArH); δ_C 38.3 (t), 52.2 (t), 62.8 (t), 99.9 (s), 120.7 (t), 127.9 (d), 128.7 (d), 128.9 (d), 129.6 (d), 129.7 (d), 131.6 (d), 136.6 (s), 140.4 (d), 141.9 (s), 144.4 (s), 171.9 (s); *m/z* (EI) 407 (2%, M^+), 376 (12), 280 (17), 180 (17), 91 (100) and 65 (25).

2-(2-Azidoethyl)-*N*-benzyl-*N*-(2-iodophenyl)acrylamide 17b

Alcohol **16b** (480 mg, 1.18 mmol, 1.00 equiv.) was treated as for alcohol **16a** to afford pure *2-(2-azidoethyl)-N-benzyl-N-(2-iodophenyl)acrylamide* **17b** as a slightly yellow oil (357 mg, 70%); [Found (EI): M^+ 432.0446, $C_{18}H_{17}IN_4O$ requires *M* 432.0447]; ν_{max} (film)/cm^{-1} 3031, 2934, 2875, 2095, 1651, 1624, 1469, 1385; δ_H 2.37–2.41 (1H, m, CH_2), 2.57–2.64 (1H, m, CH_2), 3.44 (2H, t, *J* 6.7, CH_2), 4.16 (1H, d, *J* 14.2, CH_2), 5.12 (1H, s, CH_2), 5.17 (1H, s, CH_2), 5.70 (1H, d, *J* 14.2, CH_2), 6.70 (1H, d, *J* 7.5, ArH), 6.96–7.00 (1H, m, ArH), 7.16–7.38 (6H, m, ArH),

7.90 (1H, dd, *J* 1.4, 7.8, ArH); δ_C 33.9 (t), 50.1 (t), 52.2 (t), 99.9 (s), 120.3 (d), 120.7 (t), 125.8 (d), 127.9 (d), 128.6 (d), 129.0 (d), 129.6 (d), 130.1 (d), 131.7 (d), 136.9 (s), 140.5 (d), 140.5 (s), 145.4 (s) 170.5 (s); *m*/*z* (CI) 432 (100%, M^+).

Tandem radical cyclisation of 2-(2-azidoethyl)-*N*-benzyl-*N*-(2-iodophenyl)acrylamide 17b

2-(2-Azidoethyl)-*N*-benzyl-*N*-(2-iodophenyl)acrylamide **17b** (160 mg, 0.37 mmol, 1.00 equiv.) when treated as for azide **17a** gave pure 1-benzyl-1′-methyl-1*H*-spiro[indole-3,3′-pyrrolidin]-2-one **23b** as a colourless oil (73.6 mg, 68% over two steps) [Found (ES): MH^+ 293.1652, $C_{19}H_{21}N_2O$ requires *MH* 293.1654]; ν_{max} (film)/cm^{-1} 2940, 2838, 2786, 1711, 1611, 1486, 1467, 1359, 1183; δ_H 2.11–2.18 (1H, m, CH_2), 2.41–2.46 (1H, m, CH_2), 2.50 (3H, s, CH_3), 2.77–2.83 (1H, m, CH_2), 2.89 (1H, d, *J* 9.4, CH_2), 2.95 (1H, d, *J* 9.4, CH_2), 3.09–3.14 (1H, m, CH_2), 4.9 (2H, s, CH_2), 6.71 (1H, d, *J* 7.7, ArH), 7.04 (1H, ddd, *J* 1.5, 7.3, 7.7, ArH), 7.14 (1H, ddd, *J* 0.8, 7.7, 7.7, ArH), 7.24–7.33 (5H, m, ArH), 7.44 (1H, dd, *J* 1.4, 7.8, ArH); δ_C 38.3 (t), 42.0 (q), 44.0 (t), 53.5 (s), 56.9 (t), 66.6 (t), 108.9 (d), 123.1 (d), 123.2 (d), 127.4 (d), 127.7 (d), 127.8 (d), 129.0 (d), 136.0 (s), 136.2 (s), 142.1 (s), 180.6 (s); *m*/*z* (EI) 292 [$(M)^+$, 30%], 235 (100), 91 (80).

(±)-Coerulescine 7

1-Benzyl-1′-methyl-1*H*-spiro[indole-3,3′-pyrrolidin]-2-one **23b** (22 mg, 0.075 mmol, 1.00 equiv.) was treated as for **23a** and afforded pure (±)-coerulescine **7** as a pale yellow gum (12.7 mg, 83%); [Found (ES): MH^+ 203.1182, $C_{12}H_{14}N_2O$ requires *MH* 203.1184]; ν_{max} (film)/cm^{-1} 3385, 2969, 2793, 1711, 1619, 1471, 1336, 1196, 1047; δ_H 2.10–2.18 (1H, m, CH_2), 2.39–2.45 (1H, m, CH_2), 2.50 (3H, s, CH_3), 2.80–2.86 (1H, m, CH_2), 2.89–2.96 (2H, m, CH_2), 3.05–3.11 (1H, m, CH_2), 6.88 (1H, d, *J* 7.7, ArH), 7.07 (1H, ddd, *J* 0.9, 7.2, 7.7, ArH), 7.20 (1H, ddd, *J* 1.2, 7.7, 7.7, ArH), 7.42 (1H, d, *J* 7.2, ArH), 8.16 (1H, br s, NH); δ_C 38.1 (t), 41.9 (q), 53.9 (s), 56.9 (t), 66.2 (t), 109.8 (d), 123.1 (d), 123.5 (d), 128.0 (d), 136.1 (s), 140.4 (s), 183.3 (s); *m*/*z* (EI) 202 (40%, M^+), 145 (25), 130 (28), 57 (100) and 51 (12).

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