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Synthesis of the dibenzopyrrocoline alkaloid skeleton: indolo-[2,1-*a*]isoquinolines and related analogues

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Abstract—The indolo[2,1-*a*]isoquinoline and pyrrolo[2,1-*a*]isoquinoline nuclei have been synthesized from *N*-benzylindole or ethyl 1*H*-indol-1-ylacetate and *N*-benzylpyrrole precursors, respectively. Firstly, at C-2 of either the indole or pyrrole nucleus, aromatic rings containing a carbonyl substituent *ortho* to the newly formed biaryl axis were introduced using the Suzuki–Miyaura coupling reaction. Thereafter, under basic conditions the nucleophile that formed at the acidic methylene protons of the *N*-benzylindole, ethyl 1*H*-indol-1-ylacetate or *N*-benzylpyrrole intermediate reacted with the internal aromatic carbonyl to yield (after the expulsion of water) the title compounds. For example, exposure of ethyl 2-(2-(2-formylphenyl)-1*H*-indol-1-yl)acetate to potassium *tert*-butoxide resulted in the formation of ethyl indolo[2,1-*a*]isoquinoline-6-carboxylate.

1. Introduction

The dibenzopyrrocoline alkaloids contain an indole ring fused to the isoquinoline moiety where they share a common nitrogen atom.

For example, the natural products cryptaustoline **1** and cryptowoline **2** (Fig. 1) isolated from the bark of *Cryptocarya bowie* fit into this category.[1] These types of alkaloids have been reported to possess antileukemic,[2] tubulin polymerization inhibitory[3] and antitumour activities.[4,5] Related synthetic acetoxy-substituted 5,6-dihydro[2,1-*a*]isoquinolines such as **3** exhibit strong binding affinities for the estrogen receptor of MDA-MB 231 and MCF-7 mammary tumour cell lines.[6] It has also been reported that hydroxy-substituted indolo[2,1-*a*]isoquinolines bind to the colchicine binding site and inhibit the polymerization of tubulin.[6]

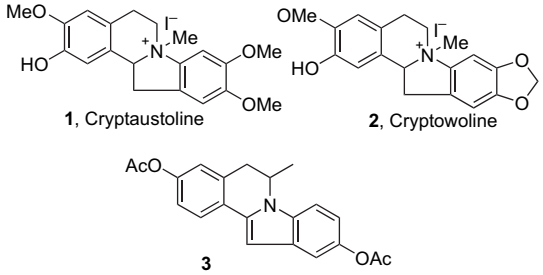

Figure 1. Examples of biologically active indolo[2,1-*a*]isoquinolines.

Related compounds containing a hexahydropyrrolo[2,1-*a*]-isoquinoline such as compounds **4** and **5**, lacking the additional fused benzene ring, have been reported to be potential candidates for the treatment of depression (Fig. 2). Studies show that they inhibit the neuronal uptake of dopamine (DA), norepinephrine (NE) and serotonin (5 HT).[7,8]

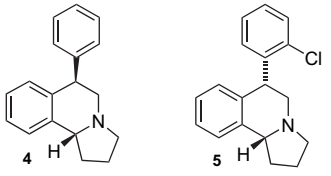

Figure 2. Examples of biologically active pyrrolo[2,1-*a*]isoquinolines.

A number of different strategies have been utilized to synthesize both the indolo[2,1-*a*]isoquinolines and the pyrrolo[2,1-*a*]isoquinolines. Shown in Scheme 1 are some of the general methods used for the formation of the final ring of the indolo[2,1-*a*]isoquinolines nucleus. A common initial disconnection is between the isoquinoline nitrogen and the benzene ring, which ultimately forms part of the

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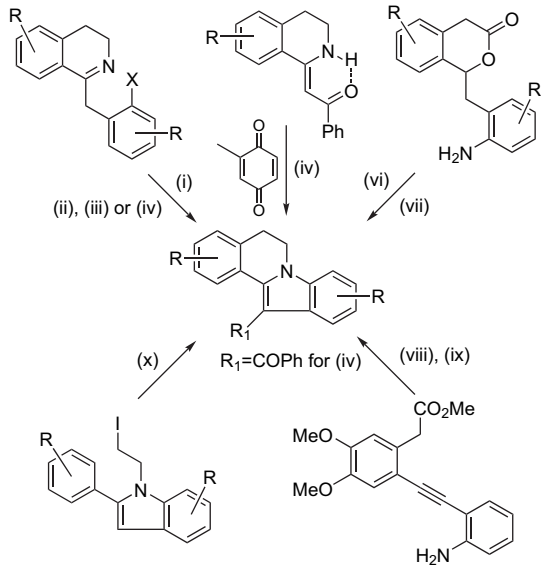
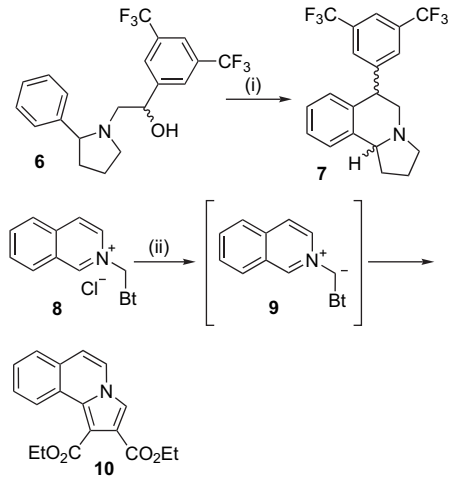
indole nucleus. This bond in the syntheses has then been formed by base-, radical- and benzyne-mediated ring closures or by palladium-catalyzed methods [see Scheme 1, (i), (ii), (iii) or (iv)]. However, as shown in Scheme 1 other approaches have been successfully used for the assembly of this nucleus.



Scheme 1. (i) X=Br, K_2CO_3, DMF, reflux, 3 days[9] or (ii) X=Br, AIBN, Bu_3SnH[6,10] or (iii) X=Cl, *n*-BuLi, THF, −100 °C, 98%;[11] (iv) Pd catalysis; e.g., 8% $Pd_2(dba)_3$, 16% SIPr, NaO^{t}Bu, PhMe;[12] (v) $MeNO_2$, rt, 2 days, 72%;[13] (vi) TFA/CH_2Cl_2, 18 h, 53%; (vii) BH_3/THF;[14] (viii) CuI, DMF, reflux, 2 h, (ix) *p*-TsOH, CH_2Cl_2;[15] (x) dicumylperoxide, chlorobenzene, heat, 69–85%.[16]

The pyrrolo[2,1-*a*]isoquinoline skeleton can be obtained by using, for example, acid-catalyzed reactions. Cyclization of **6** in the presence of polyphosphoric acid gave **7** as a mixture of cis and trans diastereomers (Scheme 2).[7]



Scheme 2. (i) PPA, heat, 47%; (ii) $EtCO_2C{\equiv}CCO_2Et$, Et_3N, MeCN, 67%.

As also shown in Scheme 2, 1,3-dipolar cycloadditions have been used quite extensively to construct this skeleton (Elwan et al.,[17] Hershenson,[18] Anderson et al.[2] and Zhao et al.[19]). For example, Katritzky et al.[20] has described the regioselective synthesis of pyrrolo[2,1-*a*]isoquinolines using his benzotriazole methodology. Reaction of **8** with diethyl acetylene dicarboxylate, in the presence of triethylamine gave the compound of interest, pyrrolo[2,1-*a*]isoquinoline **10**. The reaction is postulated to occur by way of intermediate **9**.

In this paper, we wish to report a novel synthesis of both the indolo[2,1-*a*]isoquinolines and pyrrolo[2,1-*a*]isoquinolines with the ultimate aim of synthesizing the indolo[2,1-*a*]isoquinoline skeleton of cryptaustoline **1** and cryptowoline **2**. One of the key steps in our synthesis is that the final ring forming reaction (as shown in the retrosynthesis) involves a novel disconnection at the C-5 and C-6 of the indolo-[2,1-*a*]isoquinoline or pyrrolo[2,1-*a*]isoquinoline nucleus (i.e., Fig. 3, **11**⇒**12**). Aspects of this work have been reported in a communication.[21]

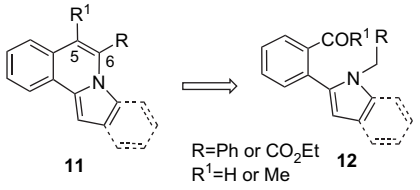
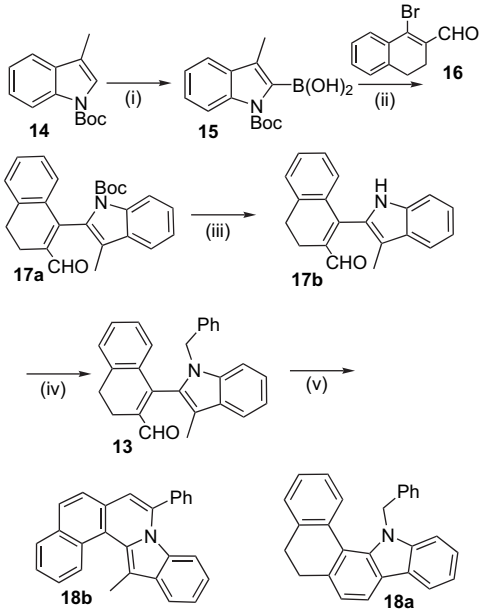


Figure 3. Retrosynthesis.

2. Results and discussion

While working on the synthesis of benzo- and naphtho-fused carbazoles,[22] we had reason to synthesize the substituted *N*-benzyl-protected indole **13**[23] from the Boc-protected indole **14** (Scheme 3). Reaction of **14** with *n*-BuLi and trimethyl borate followed by work-up with aqueous acid afforded boronic acid **15**. Dihydronaphthalene **16** was then reacted with boronic acid **15** in the presence of catalytic $Pd(PPh_3)_4$ under



Scheme 3. *Reagents and conditions*: (i) (a) *n*-BuLi, THF, −78 °C, (b) $B(OMe)_3$, THF, −78 °C, (c) H_3O^+, extract into Et_2O; (ii) 10% $Pd(PPh_3)_4$, aq Na_2CO_3/DME (Et_2O removed by bubbling N_2 through reaction mixture), 96% (two steps); (iii) $AlCl_3$, CH_2Cl_2, rt, 2 h, 100%; (iv) BnBr, 50% aq NaOH, DMF, 53%; (v) KO^{t}Bu, DMF, *hν*, 80 °C, **18a**: 0%, **18b**: 65%.

Suzuki–Miyaura coupling reaction conditions to afford the desired coupled product **17a**.[16] In addition to the peaks at δ 1.29 and 2.10 due to the Boc group and the aromatic methyl group, respectively, the ^{1}H NMR spectrum of compound **17a** also showed evidence for the presence of the methylene protons (δ 2.72–3.01) and the aldehyde group at δ 9.70. The HRMS showed a molecular ion peak at *m*/*z* 387.1834 ($C_{25}H_{25}NO_3$ requires 387.1830). The compound was crystalline and gave good quality crystals suitable for X-ray crystallography, after recrystallization from an EtOAc/hexane solution.[24] The X-ray crystal structure of **17a** is shown in Figure 4. It is clear from the X-ray crystal structure that the steric crowding due to the Boc, methyl and aldehyde groups forces the molecule to adopt a solid state structure that minimizes steric interactions.

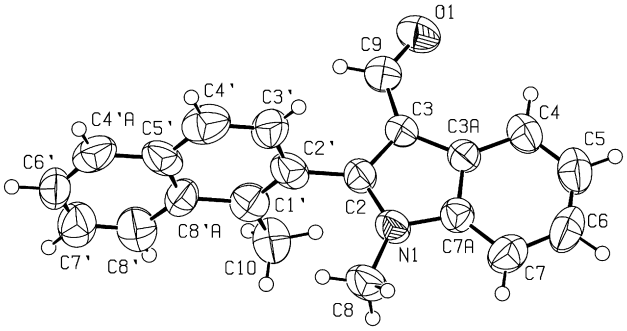


Figure 4. ORTEP diagram of *tert*-butyl-2-(2-formyl-3,4-dihydro-1-naphthalenyl)-3-methyl-1*H*-indole-1-carboxylate **17a** (ellipsoids at 50% probability).

Exposure of **17a** to the Lewis acid $AlCl_3$ yielded the intermediate deprotected indole **17b**. The ^{1}H NMR spectrum of the product showed a broad peak at δ 7.99 due the NH proton, thus indicating that the desired product had been formed. In addition, the peaks due to the methyl protons of the Boc group were no longer present in the spectrum. Treatment of the intermediate with benzyl bromide gave the required benzyl-protected **13**. In the ^{1}H NMR spectrum of this product the broad peak due to the NH proton was no longer evident. Instead, two doublets due to the non-equivalent methylene protons of the benzyl group were now observed at δ 4.75 and 5.23.

Utilizing the reaction conditions[25,26] developed for the formation of aromatic rings (KO^{t}Bu, *hν*, DMF, 80 °C), we treated **13** using this procedure. However, none of the expected naphtho[*a*]carbazole **18a** was isolated, and isoquinoline **18b** was obtained instead. Subjecting substrate **13** to the same reaction conditions as described before but without the light source resulted in the formation of the identical product **18b** in a similar yield. Therefore, the base is abstracting an *N*-benzyl proton of **13** and the resulting anion is condensing with the electrophilic aldehyde to afford the fused isoquinoline **18b** after aromatization of the putative dihydronaphthalene intermediate.

The structure of the product **18b** was confirmed by X-ray crystallography.[27] X-ray crystallography shows that **18b** is not flat as seen from selected bond angles in the crystal structure (Fig. 5).

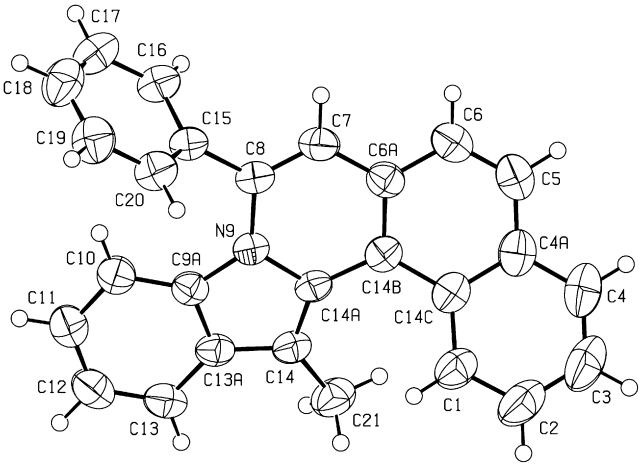
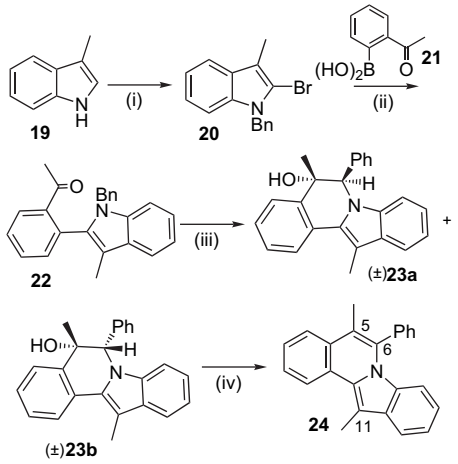


Figure 5. ORTEP diagram of 14-methyl-8-phenylbenzo[*h*]indolo[2,1-*a*]-isoquinoline **18b** (ellipsoids at 50% probability).

In light of this result, we decided to test the generality of this reaction by synthesizing a number of indole and pyrrole analogues. An obvious extension to this methodology would be to exchange the functional groups of the substrates required for the coupling reaction. Therefore, bromoindole **20** was synthesized using published chemistry from commercially available 3-methylindole **19**.[28] Suzuki–Miyaura coupling of **20** with the commercially available boronic acid **21** gave the desired precursor **22** on which the ring forming reaction was attempted (Scheme 4). The ^{1}H NMR spectrum of **22** provided evidence for the identity of the product as there were two methyl groups at δ 1.83 and 2.17. In addition to this, two doublets corresponding to the non-equivalent methylene protons of the benzyl group at δ 5.04 and 5.24 were also evident. In the ^{13}C NMR spectrum the peak at δ 202.8 due to the carbonyl group also suggested the formation of the expected product. Exposure of **22** to KO^{t}Bu in DMF afforded the ring-closed alcohols **23a** and **23b** as diastereoisomers (~1:3 ratio). The IR spectra of the two separated diastereoisomers showed stretching bands at

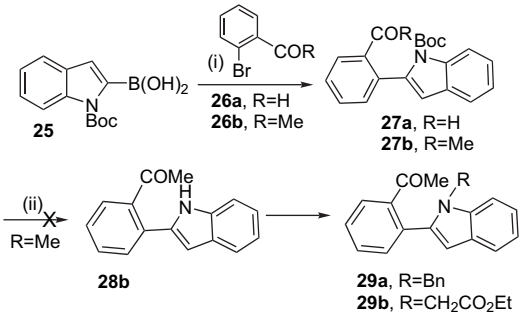


Scheme 4. *Reagents and conditions*: (i) (a) NBS, CCl_4, 3 h, 98%; (b) aq NaOH, BnBr, 66%; (ii) 10% $Pd(PPh_3)_4$, aq Na_2CO_3/DME, 64%; (iii) KO^{t}Bu, DMF, 80 °C, **23a**: 26%, **23b**: 74%; (iv) **23b**, 15 mol % TsOH, CH_2Cl_2, rt, 24 h, 79%.

3417 and 3447 cm^{-1}, respectively, for **23a** and **23b**, indicating the presence of the alcohol functional groups. The major diastereoisomer was shown to be **23b** by NOE spectroscopy. Exposure of **23b** to 15 mol % TsOH afforded the dibenzopyrrocoline **24** in very good yield. The HRMS for this compound showed a molecular ion peak at *m/z* 321.1517 ($C_{24}H_{19}N$ requires 321.1516).

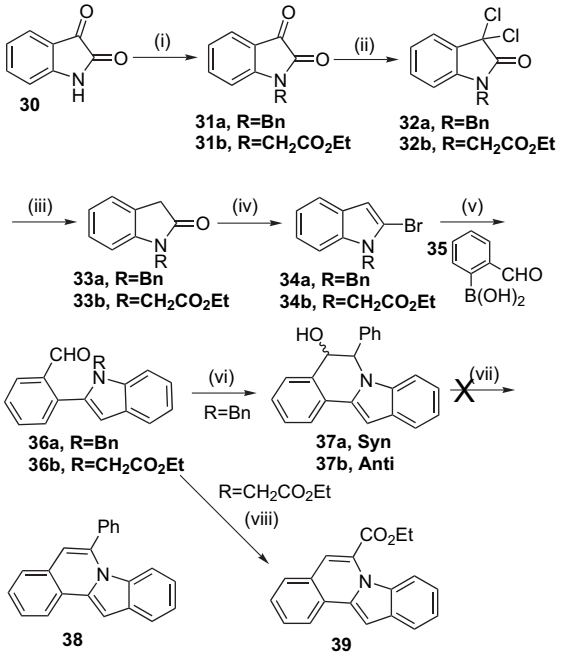
In summary, at this stage as far as the synthesis of cryptaustoline **1** and cryptowoline **2** nuclei was concerned, we had synthesized compound **24**, which possesses additional methyl substituents at C-5 and C-11 as well as a phenyl substituent at C-6. The next phase of this project was to adapt our methodology to assemble the basic nucleus of **1** and **2**.

Logically, we thought that the best way to tackle this problem using our methodology was to commence with the known Boc-protected indole boronic acid **25**. Using Suzuki–Miyaura coupling methodology we hoped to access **27**. The next step would be the removal of the Boc protecting group and this would be replaced by a benzyl substituent to yield **29a**. However, as the phenyl at C-6 of **24** is derived from the benzyl we thought that this could be replaced by a methylene ester to give **29b**. This would then result in the formation of the ester derivative of **24**. In other words, the phenyl substituent at C-6 of **24** would be substituted by CO_2Et. This should be easier to remove by decarboxylation than the phenyl substituent. Both **27a** and **27b** were easy to synthesize using standard methodology from **25** and **26** but the removal of the Boc group to give **28** proved to be problematic (Scheme 5). After considerable experimentation by using a variety of methods (e.g., NaOMe in MeOH[29]) none of the desired product **28b** was obtained and therefore, we needed to modify our synthesis.



Scheme 5. *Reagents and conditions*: (i) **27a**, R=H, 10% $Pd(PPh_3)_4$, aq Na_2CO_3/DME, 63%; **27b**, R=Me, 85%; (ii) NaOMe, MeOH.

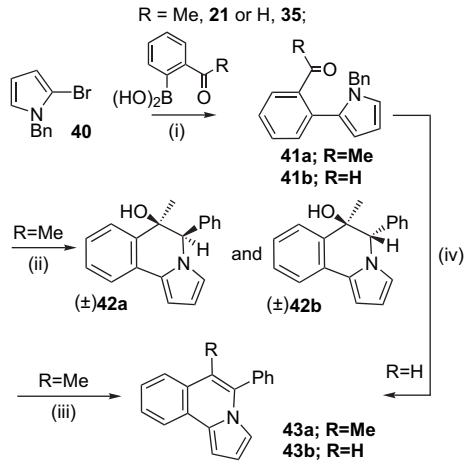
Initially, attempts were made to *N*-benzylate oxindole but this proved fruitless as a result of *N*- and C-3 alkylation. Isatin **30** was thus treated with both benzyl bromide and ethyl bromacetate in separate reactions in the presence of CaH_2 to provide both **31a** and **31b**.[30] Exposure of **31a** and **31b** to PCl_5 provided **32a** and **32b** (Scheme 6). Separate reactions of **32a** and **32b** with Zn in AcOH[31] afforded the desired oxindoles **33a** and **33b** on which we attempted the formation of the desired 2-bromoindoles **34a** and **34b**. After considerable experimentation, we found that treatment of **33a** with $POBr_3$ and imidazole[32] in CH_2Cl_2 gave a mediocre yield (55%) of the required bromide **34a**. In a similar fashion **33b** was treated with $POBr_3$ in CH_2Cl_2[33] to give a 50% yield of the desired indole **34b**. Suzuki–Miyaura coupling of both **34a** and **34b** with benzaldehyde boronic acid **35** afforded good yields of the desired products **36a** and **36b**. Subjecting **36a** to KO^{t}Bu in DMF for 1 min gave the desired ring-closed alcohols **37a** and **37b** as a mixture of diastereoisomers. Unfortunately, exposure of **37a** and **37b** to *p*-TsOH did not give the desired aromatic compound **38** but a complex mixture of uncharacterizable products. However, subjecting **36b** to the same conditions afforded the targeted product **39** in good yield.



Scheme 6. *Reagents and conditions*: (i) BnBr or $BrCH_2CO_2Et$, CaH_2, DMF, 100 °C, **31a**: 89%, **31b**: 100%; (ii) PCl_5, benzene, 25 °C, **32a**: 81%, **32b**: 65%; (iii) Zn, AcOH, rt, **33a**: 76%, **33b**: 100%; (iv) $POBr_3$, CH_2Cl_2, imidazole, reflux, **34a**: 55%; $POBr_3$, CH_2Cl_2, reflux, **34b**: 50%; (v) 10% $Pd(PPh_3)_4$, aq Na_2CO_3/DME, **36a**: 92%, **36b**: 77%; (vi) KO^{t}Bu, DMF, 80 °C, 76%; (vii) 15 mol % TsOH, CH_2Cl_2, rt, 24 h; (viii) KO^{t}Bu, DMF, 80 °C, 59%.

As a next step, we thought it would be useful to see if the same type of chemistry could be done on pyrrole derivatives to assemble pyrroloisoquinolines.

The synthesis of the required bromopyrrole **40** was achieved using literature procedures.[34,35] Coupling this compound under Suzuki–Miyaura conditions with either the boronic acid **21** or the aldehyde equivalent **35** resulted in the formation of both desired precursors **41a** (R=Me) and **41b** (R=H). The ^{1}H NMR spectrum of **41a** showed two singlets at δ 1.83 and 4.91 corresponding to the ketone methyl substituent and methylene protons of the benzyl group, respectively. The HRMS of **41a** showed a molecular ion peak at *m/z* 339.1623 corresponding to the expected product ($C_{24}H_{21}NO$ requires 339.1623). Subjecting **41a** to KO^{t}Bu in DMF afforded a diastereomeric mixture of alcohols **42a** and **42b** (ratio ~1:2.5). The major product **42b** was dehydrated under acidic conditions to give the desired product **43a**. In the same manner when **41b** was treated with KO^{t}Bu, **43b** was produced, presumably by way of the intermediate alcohol (Scheme 7).



Scheme 7. *Reagents and conditions*: (i) 10% $Pd(PPh_3)_4$, aq Na_2CO_3/DME, **41a**: 82%, **41b**: 52%; (ii) KO^{t}Bu, DMF, *hν*, 80 °C, **42a**: 56%, **42b**: 23%; (iii) R=Me, 15 mol % TsOH, CH_2Cl_2, rt, 24 h, **43a**: 74%; (iv) R=H, KO^{t}Bu, DMF, 80 °C, **43b**: 68%.

3. Conclusion

In conclusion, we have been able to synthesize both indolo- and pyrrolo[2,1-*a*]isoquinoline including the dibenzopyrrocoline skeleton, starting from simple *N*-benzylated indoles or pyrroles.

We are presently using this methodology to assemble the desired cryptaustoline nucleus with the correct oxygenation pattern.

4. Experimental

4.1. General

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 (300.13 MHz) and chemical shifts are reported in parts per million (ppm) with TMS as the internal standard in ^1H NMR spectrum and using δ 77.00 ($CDCl_3$) as reference peak in ^{13}C NMR spectrum. Spectra were recorded in deuterated chloroform ($CDCl_3$) unless otherwise specified. CH-correlated, NOE, NOESY and DEPT spectra were run on some samples for the complete assignments of signals. IR spectra were recorded on a Bruker IFS-25 Fourier transform spectrometer or on a Bruker Vector-22 Fourier transform spectrometer. The infra-red signals are reported in wavenumbers (ν/cm^{-1}). For liquid samples NaCl plates were used to run the IR spectrum while KBr pellets were made for solid samples. High-resolution mass spectra (HRMS) were recorded on a VG70 MS (Mass Spectrum CC Pyramid data system) or on a VG70 SEQ (VG 11-250J or Marc II data systems). The melting points were determined on a Reichert hot-stage microscope and are uncorrected. For silica gel chromatography Macherey–Nagel Kieselgel 60 (particle size 0.063–2.00 mm) was used. Aluminium-backed Macherey–Nagel ALUGRAM Sil G/UV$_{254}$ was used for thin layer chromatography (TLC). All the solvents used for reactions and chromatography were distilled prior to use according to the standard procedures. Tetrahydrofuran and diethylether were distilled from sodium/benzophenone, dichloromethane and dimethylformamide were distilled from calcium hydride and toluene and benzene were distilled from sodium. Potassium *tert*-butoxide was sublimed prior to use.

4.2. Crystal structure data and refinement

Intensity data were collected on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo Kα radiation (50 kV, 30 mA). The collection method involved ω-scans of width 0.3°. Data reduction was carried out using the program *SAINT+*. The crystal structure was solved by direct methods using *SHELXTL*. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using *SHELXTL*. Hydrogen atoms were first located in the difference map, then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL and PLATON.

4.2.1. *tert*-Butyl-2-(2-formyl-3,4-dihydro-1-naphthalenyl)-3-methyl-1*H*-indole-1-carboxylate 17a. A solution of 1-bromo-3,4-dihydronaphthalene-2-carbaldehyde **16** (0.20 g, 0.84 mmol) in DME (4 cm^3) was deoxygenated by passing nitrogen through the mixture for 5 min. The solution was then added to $Pd(PPh_3)_4$ (10 mol %, 0.096 g, 0.08 mmol) and stirred under an atmosphere of N_2 for 10 min at rt. A solution of 1-(*tert*-butoxycarbonyl)-3-methyl-1*H*-indol-2-ylboronic acid **15** (0.346 g, 1.27 mmol) in ethanol (1.5 cm^3) was deoxygenated and added to the reaction mixture. The mixture was stirred for further 10 min. A deoxygenated 2 M aq Na_2CO_3 solution (3.6 cm^3, 7.12 mmol) was then added to the reaction mixture, which was stirred at rt for further 5 min before being heated at reflux for 2 days. The mixture was cooled to rt and quenched with H_2O (20 cm^3) after which the organic material was extracted with CH_2Cl_2 (3×30 cm^3) and the solvent was evaporated under reduced pressure. The crude product was subjected to column chromatography (5–10% EtOAc/hexane) to afford the product, *tert*-butyl-2-(2-formyl-3,4-dihydro-1-naphthalenyl)-3-methyl-1*H*-indole-1-carboxylate **17a** as a yellow solid (0.313 g, 96%): mp 141–142 °C; ν_{max} ($CHCl_3$)/cm^{-1}: 1725 and 1660 (C=O) and 1559 (ArC=C); ^1H NMR (300 MHz, C0DCl_3, Me_4Si) 1.29 (9H, s, Boc), 2.10 (3H, s, $ArCH_3$), 2.72–2.82 (2H, m, CH_2), 2.96–3.00 (2H, m, CH_2), 6.78 (1H, d, *J*=7.8 Hz, ArH), 7.08–7.11 (1H, m, ArH), 7.25–7.45 (4H, m, 4×ArH), 7.57 (1H, d, *J*=7.4 Hz, ArH), 8.29 (1H, d, *J*=8.3 Hz, ArH) and 9.70 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) 9.3 ($ArCH_3$), 20.2 (CH_2), 27.1 (CH_2), 27.8 (Boc), 83.9 [$C(CH_3)_3$], 115.7 (CH), 119.1 (CH), 120.7 (C), 123.0 (CH), 125.4 (CH), 126.7 (CH), 126.9 (CH), 128.0 (CH), 129.8 (C), 130.2 (CH), 134.5 (C), 135.5 (C), 136.5 (C), 137.8 (C), 146.5 (C), 149.5 (NC=O) and 192.0 (CHO); MS *m*/*z* (EI): 387 (M^+, 47%), 287 (83), 273 (30), 272 (100), 269 (32), 258 (50) and 241 (16); HRMS calcd for $C_{25}H_{25}NO_3$: 387.1830, found: 387.1834.

4.2.2. 1-(3-Methyl-1*H*-indol-3-yl)-3,4-dihydro-2-naphthalenecarbaldehyde 17b. $AlCl_3$ (0.152 g, 0.34 mmol) was added to a solution of **17a** (0.133 g, 0.34 mmol) in dry CH_2Cl_2 (5 cm^3) under an N_2 atmosphere in portions at 0 °C. The suspension was vigorously stirred at rt for 2 h.

After completion of the reaction, it was neutralized with aq $NaHCO_3$ solution and the product was extracted with EtOAc (3×30 cm^3). The organic phase was separated, dried ($MgSO_4$), filtered and the solvent was removed in vacuo to afford the crude product. The product was then purified by column chromatography (5% EtOAc/hexane) to afford 1-(3-methyl-1*H*-indol-3-yl)-3,4-dihydro-2-naphthalenecarbaldehyde **17b** as a reddish brown solid (0.098 g, quantitative): mp 150–152 °C; ν_{max} ($CHCl_3$)/cm^{-1}: 1638 (C=O), 1601 and 1566 (ArC=C); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 2.22 (3H, s, $ArCH_3$), 2.55–2.92 (4H, m, $2\times CH_2$), 6.92 (1H, d, J=7.7 Hz, ArH), 7.11–7.38 (6H, m, $6\times$ArH), 7.65 (1H, d, J=7.7 Hz, ArH), 7.99 (1H, s, NH) and 9.66 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) 9.3 ($ArCH_3$), 20.5 (CH_2), 27.4 (CH_2), 110.7 (CH), 115.1 (C), 119.2 (CH), 119.9 (CH), 123.2 (CH), 127.0 (CH), 127.2 (C), 128.0 (CH), 128.1 (CH), 128.4 (C), 130.5 (CH), 133.9 (C), 136.1 (C), 137.2 (C), 138.5 (C), 144.8 (C) and 193.3 (CHO); MS *m*/*z* (EI): 287 (M$^+$, 100%), 272 (86), 269 (32), 258 (73) and 244 (19); HRMS calcd for $C_{20}H_{17}NO$: 287.1313, found: 287.1310.

4.2.3. 1-(1-Benzyl-3-methyl-1*H*-indol-2-yl)-3,4-dihydro-2-naphthalenecarbaldehyde 13. 2-Naphthalenecarbaldehyde **17b** (0.10 g, 0.35 mmol) was dissolved in dry THF (6 cm^3) and mixed with 50% aq NaOH (1.5 g in 3 cm^3 H_2O). Benzyl bromide (0.082 cm^3, 0.70 mmol) was added over 20 min and the mixture was treated with a catalytic amount of the phase transfer catalyst, $(n\text{-Bu})_4NBr$ (0.02 g). The reaction mixture was stirred vigorously for 1.5 h. The reaction mixture was then extracted with EtOAc ($3\times$ 30 cm^3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was then purified by column chromatography (5–20% EtOAc/hexane) to give 1-(1-benzyl-3-methyl-1*H*-indol-2-yl)-3,4-dihydro-2-naphthalenecarbaldehyde **13** as a brown oil (0.068 g, 52%): ν_{max} (film)/cm^{-1}: 1663 (C=O) and 1603 (ArC=C); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 2.20 (3H, s, $ArCH_3$), 2.42–2.52 [1H, m, C(*H*)H], 2.74–2.91 (3H, m, C(*H*)H, CH_2), 4.75 (1H, d, J=16.3 Hz, PhCH), 5.23 (1H, d, J=16.3 Hz, PhCH), 6.75 (1H, d, J=7.6 Hz, ArH), 6.81–6.83 (2H, m, $2\times$ArH), 7.05–7.19 (4H, m, $4\times$ArH), 7.22–7.36 (5H, m, $5\times$ArH), 7.67 (1H, d, J=7.7 Hz, ArH) and 9.39 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) 9.2 ($ArCH_3$), 20.1 (CH_2), 27.2 (CH_2), 48.0 (NCH_2Ph), 109.8 (CH), 114.6 (C), 119.2 (CH), 119.6 (CH), 122.8 (CH), 126.4 ($2\times$CH), 127.0 (CH), 127.3 (CH), 127.5 (CH), 127.9 (CH), 128.1 (C), 128.5 ($2\times$CH), 129.6 (C), 130.4 (CH), 133.7 (C), 137.5 (C), 137.7 (C), 137.9 (C), 138.0 (C), 143.8 (C) and 192.6 (CHO); MS *m*/*z* (EI): 377 (M$^+$, 28%), 286 (100), 256 (7) and 91 (23); HRMS calcd for $C_{27}H_{23}NO$: 377.1779, found: 377.1780.

4.2.4. 14-Methyl-8-phenylbenzo[*h*]indolo[2,1-*a*]isoquinoline 18b. KO^{t}Bu (0.119 g, 1.06 mmol) was added to **13** (0.105 g, 0.33 mmol) dissolved in dry DMF (10 cm^3) and heated under N_2 at 80 °C for 10 min. The reaction mixture was quenched with H_2O (50 cm^3) and the organic material was extracted into Et_2O (3×50 cm^3). The combined organic layers were dried ($MgSO_4$) and filtered. The solvent was then evaporated in vacuo and the residue was subjected to column chromatography (5–20% EtOAc/hexane) to afford the product, 14-methyl-8-phenylbenzo[*h*]indolo[2,1-*a*]isoquinoline **18b** (0.076 g, 65%) as a yellow solid: mp 96–98 °C; ν_{max} ($CHCl_3$)/cm^{-1}: 1663 (C=O), 1594 and 1551 (ArC=C); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 2.55 (3H, s, $ArCH_3$), 6.53 (1H, s, ArH), 6.58 (1H, d, J=8.6 Hz, ArH), 6.95–7.00 (1H, m, ArH), 7.29–7.34 (1H, m, ArH), 7.52–7.65 (8H, m, $8\times$ArH), 7.81 (1H, d, J=8.0 Hz, ArH), 7.90 (1H, d, J=8.4 Hz, ArH), 7.94 (1H, d, J=7.9 Hz, ArH) and 8.32 (1H, d, J=8.3 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 14.5 ($ArCH_3$), 108.2 (C), 111.3 (CH), 114.0 (CH), 118.3 (CH), 120.8 (CH), 121.7 (CH), 124.1 (CH), 125.1 (CH), 125.5 (CH), 127.9 ($2\times$CH), 128.3 (CH), 128.9 ($2\times$CH), 128.9 (C), 129.0 ($2\times$CH), 129.2 (CH), 129.7 (C), 131.2 (C), 131.6 (C), 132.9 (C), 137.0 (C) and 139.1 (C) (two quaternary carbons missing); MS *m*/*z* (EI): 358 (36%), 357 (M$^+$, 100), 356 (54), 354 (21), 278 (11) and 171 (11); HRMS calcd for $C_{27}H_{19}N$: 357.1518, found: 357.1517.

4.2.5. 1-[2-(1-Benzyl-3-methyl-1*H*-indol-2-yl)phenyl]-1-ethanone 22. A solution of 1-benzyl-2-bromo-3-methyl-1*H*-indole[21] (0.470 g, 1.58 mmol) in DME (10 cm^3) was deoxygenated by passing nitrogen through the mixture for 5 min. The solution was then added to $Pd(PPh_3)_4$ (10 mol %, 0.194 g, 0.16 mmol) and stirred under an atmosphere of N_2 for 10 min at rt. A solution of 2-acetylphenylboronic acid **21** (0.388 g, 2.40 mmol) in ethanol (3.75 cm^3) was deoxygenated and added to the reaction mixture. The mixture was stirred for further 10 min. A deoxygenated 2 M aq Na_2CO_3 solution (6.7 cm^3, 13.2 mmol) was then added to the reaction mixture, which was stirred at rt for further 5 min before being heated at reflux for 2 days. The mixture was cooled to rt and quenched with water (20 cm^3) after which the organic material was extracted with CH_2Cl_2 (3×30 cm^3) and the solvent was evaporated under reduced pressure. The crude product was subjected to column chromatography (5–10% EtOAc/hexane) to afford the product, 1-[2-(1-benzyl-3-methyl-1*H*-indol-2-yl)phenyl]-1-ethanone **22** as a yellow oil (0.343 g, 64%): ν_{max} (film)/cm^{-1}: 3059, 1684 (C=O), 1598 (ArC=C) and 742; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 1.83 (3H, s, $ArCH_3$), 2.17 (3H, s, $ArCOCH_3$), 5.01 (1H, d, J=16.5 Hz, PhCH), 5.24 (1H, d, J=16.5 Hz, PhCH), 6.81–6.85 (2H, br m, $2\times$ArH), 7.14–7.28 (7H, m, $7\times$ArH), 7.42–7.50 (2H, m, $2\times$ArH) and 7.61–7.63 (1H, m, ArH), 7.68–7.71 (1H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 9.1 ($ArCH_3$), 28.7 ($ArCOCH_3$), 47.5 (CH_2), 110.2 (CH), 110.8 (C), 119.1 (CH), 119.6 (CH), 122.4 (CH), 126.4 ($2\times$CH), 127.2 (CH), 128.2 (CH), 128.5 ($2\times$CH), 128.6 (C), 128.7 (CH), 130.1 (C), 130.8 (CH), 132.2 (CH), 135.4 (C), 136.9 (C), 137.8 (C), 142.0 (C) and 202.8 (C=O); MS *m*/*z* (EI): 339 (M$^+$, 91%), 248 (33), 232 (25), 204 (31) and 91 (100); HRMS calcd for $C_{24}H_{21}NO$: 339.1623, found: 339.1623.

4.2.6. 5,12-Dimethyl-6-phenyl-5,6-dihydroindolo[2,1-*a*]isoquin-5-ols 23a and 23b. KO^{t}Bu (0.082 g, 1.27 mmol) was added to **22** (0.062 g, 0.32 mmol) dissolved in dry DMF (6 cm^3) and heated under N_2 at 80 °C for 10 min. The reaction mixture was quenched by adding H_2O (50 cm^3) and then the organic material was extracted with Et_2O (3×50 cm^3). The combined organic layers were dried over $MgSO_4$ and filtered. The organic solvent was then evaporated in vacuo and subjected to column chromatography (5–20%

EtOAc/hexane) to afford firstly the product **23b** (0.046 g, 74%) as a yellow solid: mp 61–63 °C; ν_{max} ($CHCl_3$)/cm^{-1}: 3417 (OH), 1603, 1575 and 1555 (ArC=C); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) 1.63 (3H, s, $ArCH_3$), 2.54 (1H, s, OH), 2.72 (3H, s, CH_3), 5.51 (1H, s, CH), 6.93–6.97 (2H, m, 2×ArH), 7.06–7.17 (5H, m, 5×ArH), 7.23–7.30 (2H, m, 2×ArH), 7.43–7.53 (2H, m, 2×ArH), 7.62 (1H, d, J=7.3 Hz, ArH) and 8.03 (1H, d, J=7.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 11.0 ($ArCH_3$), 23.7 (CH_3), 67.3 (CH), 72.7 (C–OH), 108.5 (C), 109.2 (CH), 119.0 (CH), 119.6 (CH), 122.6 (CH), 125.7 (CH), 125.8 (CH), 127.2 (CH), 127.5 (2×CH), 127.8 (CH), 128.3 (2×CH), 128.5 (C), 129.0 (CH), 129.4 (C), 129.8 (C), 135.4 (C), 136.0 (C) and 137.7 (C); MS *m*/*z* (EI): 340 (49%), 339 (M^+, 100), 324 (38), 296 (26), 248 (33) and 216 (19); HRMS calcd for $C_{24}H_{21}NO$: 339.1623, found: 339.1623.

The second product **23a** was isolated as a yellow solid (0.015 g, 26%): mp 123–126 °C; ν_{max} (solid)/cm^{-1}: 3447 (OH), 1602 and 1577 (ArC=C); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) 1.53 (3H, s, $ArCH_3$), 2.15 (1H, s, OH), 2.71 (3H, s, CH_3), 5.41 (1H, s, CH), 6.97–7.0 (2H, m, 2×ArH), 7.10–7.30 (7H, m, 7×ArH), 7.35–7.45 (1H, m, ArH), 7.54 (1H, d, J=7.6 Hz, ArH), 7.62 (1H, d, J=7.0 Hz, ArH) and 7.93 (1H, d, J=7.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 10.7 ($ArCH_3$), 29.7 (CH_3), 60.4 (CH), 73.5 (C–OH), 108.3 (C), 108.8 (CH), 118.9 (CH), 119.6 (CH), 122.5 (CH), 124.5 (CH), 125.0 (CH), 127.4 (CH), 127.8 (CH), 128.0 (2×CH), 128.2 (C), 128.3 (CH), 128.6 (2×CH), 129.0 (C), 129.8 (C), 135.5 (C), 136.3 (C) and 139.0 (C); MS *m*/*z* (EI): 340 (M^+, 27%), 339 (100), 324 (20), 296 (15) and 248 (17); HRMS calcd for $C_{24}H_{21}NO$: 339.1623, found: 339.1624.

4.2.7. 5,12-Dimethyl-6-phenylindolo[2,1-*a*]isoquinoline 24. To a solution of 5,12-dimethyl-6-phenyl-5,6-dihydroindolo[2,1-*a*]isoquin-5-ol **23b** (0.030 g, 0.09 mmol) in CH_2Cl_2 (10 cm^3) were added molecular sieves and *p*TSA (15 mol %, 0.003 g, 0.005 mmol). The reaction mixture was stirred at rt for 18 h. The reaction mixture was then filtered, evaporated and subjected to column chromatography (5–10% EtOAc/hexane) to afford the product, 5,12-dimethyl-6-phenylindolo[2,1-*a*]isoquinoline **24** (0.022 g, 79%) as a yellow oil; ν_{max} (film)/cm^{-1}: 1637 and 1599 (ArC=C); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) 2.15 (3H, s, $ArCH_3$), 2.89 (3H, s, $ArCH_3$), 5.90 (1H, d, J=8.7 Hz, ArH), 6.77–6.80 (1H, m, ArH), 7.19 (1H, t, J=7.5 Hz, ArH), 7.42–7.62 (7H, m, 7×ArH), 7.75–7.77 (2H, m, 2×ArH) and 8.50 (1H, d, J=8.2 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 12.0 ($ArCH_3$), 14.8 ($ArCH_3$), 104.8 (C), 112.2 (C), 114.1 (CH), 117.8 (CH), 120.2 (CH), 120.7 (CH), 123.5 (CH), 124.6 (CH), 126.5 (2×CH), 127.6 (C), 129.1 (CH), 129.4 (2×CH), 130.0 (C), 130.1 (2×CH), 130.8 (C), 131.2 (C), 135.4 (C) and 136.7 (C) (one quaternary C missing); MS *m*/*z* (EI): 322 (M^+, 27%), 321 (100), 320 (21) and 304 (6); HRMS calcd for $C_{24}H_{19}N$: 321.1518, found: 321.1517.

4.2.8. 1-(*tert*-Butoxycarbonyl)-1*H*-indol-2-yl-2-boronic acid 25. A flask equipped with a dropping funnel, rubber septum and N_2 adaptor was flame dried. THF of 25 and 100 cm^3 was added to the dropping funnel and round bottom flask, respectively. Tetramethylpiperidine (2.04 cm^3, 11.96 mmol, 1.3 equiv) was added to the flask using a syringe and *tert*-butyl 1*H*-indole-1-carboxylate (2.00 g, 9.20 mmol) was added to the dropping funnel. The solution was lowered to −78 °C and *n*-butyl lithium (7.9 cm^3, 11.04 mmol, 1.2 equiv) was added drop wise, over 5 min. The solution was warmed to 0 °C over 30 min and then recooled to −78 °C. The solution in the dropping funnel was now added drop wise to the flask and the resulting mixture was stirred for 1.5 h at −78 °C. $B(OMe)_3$ (5.16 cm^3, 46.00 mmol, 5 equiv) was added and the solution was stirred at −78 °C for further 30 min before allowing to warm up to rt. Water (150 cm^3) was added, the solution was acidified using a 1 M HCl solution and then extracted with Et_2O (3×100 cm^3). The organic layers were combined, washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed, in vacuo, until approximately 15 cm^3 remained. Cold hexane was added, which resulted in 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl-2-boronic acid **25**,[26,36] precipitating as a white solid (1.57 g, 65%). The solid **25** was obtained by filtration, dried overnight under N_2 and stored in a refrigerator. ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) 1.74 (9H, s, 9×CH_3), 7.25 (1H, t, J=7.4 Hz, ArH), 7.35 (1H, m, ArH), 7.50 (1H, s, 3-H), 7.54 (2H, s, 2×OH), 7.60 (1H, d, J=7.6 Hz, ArH) and 8.02 (1H, d, J=8.4 Hz, ArH).

4.2.9. *tert*-Butyl 2-(2-formylphenyl)-1*H*-indole-1-carboxylate 27a. $Pd(PPh_3)_4$ (0.53 g, 0.46 mmol, 10 mol %) was added to a flame dried round bottom flask equipped with a condenser and dropping funnel. Boronic acid **25** (1.80 g, 6.89 mmol, 1.5 equiv), 2-bromobenzaldehyde (0.85 g, 4.60 mmol) and DME (12.65 cm^3) were combined in the dropping funnel and degassed before adding to the flask. A 2 M Na_2CO_3 solution (2.44 g, 23.00 mmol) was added to the dropping funnel, degassed and also added to the flask. The dropping funnel was closed and the resulting mixture was degassed once more before heating under reflux for 60 h. Water (50 cm^3) was added to the reaction mixture and the solution was extracted with EtOAc (3×50 cm^3). The organic layers were combined and dried over anhydrous $MgSO_4$. The organic solvent was removed in vacuo and the residue was purified by column chromatography (2% EtOAc/hexane) to afford *tert*-butyl 2-(2-formylphenyl)-1*H*-indole-1-carboxylate **27a** as a white solid (1.26 g, 85%): mp 127–128 °C; ν_{max} (film)/cm^{-1}: 1733 and 1698 (C=O) and 1600 (ArC=C); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) 1.24 (9H, s, Boc), 6.60 (1H, s, 3-H), 7.26–7.47 (3H, m, 3×ArH), 7.51–7.66 (3H, m, 3×ArH), 8.01 (1H, d, J=7.7 Hz, ArH), 8.28 (1H, d, J=8.3 Hz, ArH) and 10.01 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) 27.5 (Boc), 83.9 [$C(CH_3)_3$], 112.6 (CH), 115.7 (CH), 120.6 (CH), 123.3 (CH), 124.9 (CH), 127.3 (CH), 128.5 (CH), 128.8 (C), 131.0 (CH), 133.1 (CH), 134.9 (C), 135.2 (C), 137.0 (C), 138.3 (C), 149.7 (NC=O) and 191.6 (PhC=O); MS *m*/*z* (EI): 321 (M^+, 16%), 221 (24), 193 (100), 165 (17), 57 (53) and 41 (13); HRMS $C_{20}H_{19}NO_3$ requires: 321.1365, found: 321.1323.

4.2.10. *tert*-Butyl 2-(2-acetylphenyl)-1*H*-indole-1-carboxylate 27b. $Pd(PPh_3)_4$ (0.53 g, 0.46 mmol, 10 mol %) was added to a flame dried round bottom flask equipped with a condenser and dropping funnel. Boronic acid **25** (1.80 g, 6.89 mmol, 1.5 equiv), 1-(2-bromophenyl)ethanone (0.92 g, 4.60 mmol) and DME (12.65 cm^3) were combined in the dropping funnel and degassed before adding to the flask.

A 2 M Na_2CO_3 solution (2.44 g, 23.00 mmol) was added to the dropping funnel, degassed and then added to the flask. The dropping funnel was closed and the resulting mixture was degassed once more before heating under reflux for 3 days. Water (50 cm^3) was added and the solution was extracted with EtOAc (3×50 cm^3). The organic layers were combined and dried over anhydrous $MgSO_4$. The organic solvent was removed in vacuo and the residue was purified by column chromatography (2% EtOAc/hexane) to afford *tert*-butyl 2-(2-acetylphenyl)-1*H*-indole-1-carboxylate **27b** as an orange-pink viscous oil that eventually solidified (0.97 g, 63%): mp 91–92 °C; ν_{max} (film)/cm^{-1}: 1731 and 1688 (C═O) and 1598 (ArC═C); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 1.29 (9H, s, Boc), 2.33 (3H, s, CH_3C═O), 6.48 (1H, s, 3-H), 7.22–7.55 (6H, m, 6×ArH), 7.73 (1H, d, *J*=7.4 Hz, ArH) and 8.24 (1H, d, *J*=8.3 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 27.4 (Boc), 28.6 (*C*H_3C═O), 83.2 [*C*(CH_3)$_3$], 110.3 (CH), 115.5 (CH), 120.3 (CH), 122.8 (CH), 124.3 (CH), 127.9 (CH), 128.0 (CH), 129.0 (C), 130.6 (CH), 130.8 (CH), 133.7 (C), 136.6 (C), 138.2 (C), 139.0 (C), 149.6 (NC═O) and 200.8 (PhC═O); MS *m*/*z* (EI): 335 (M^+, 30%), 235 (100), 220 (65), 165 (13), 57 (58), 41 (16) and 30 (12); HRMS $C_{21}H_{21}NO_3$ requires: 335.1521, found: 335.1530.

4.2.11. 1-Benzylindoline-2,3-dione 31a. Isatin **30** (8.00 g, 54.00 mmol) and CaH_2 (2.29 g, 54.00 mmol, 1 equiv) were dissolved in DMF (27.00 cm^3) in a round bottom flask. The solution was stirred at 100 °C for 1 h and then cooled to 40 °C so that benzyl bromide (7.10 cm^3, 60.00 mmol, 1.1 equiv) could be added slowly. The resulting mixture was heated to 100 °C for 4 h and then allowed to cool to rt. The solution was poured into an aqueous 0.5 M HCl solution (200 cm^3) with vigorous stirring, which resulted in an orange precipitate. The precipitate was filtered off and washed with H_2O. The crude product was further purified by recrystallization (CH_2Cl_2/hexane) to afford 1-benzylindoline-2,3-dione **31a** as orange needle-like crystals (11.44 g, 89%): mp 133–134 °C (lit. mp 126–127 °C);[37] ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ_H (ppm) 4.94 (2H, s, $PhCH_2N$), 6.78 (1H, d, *J*=7.9 Hz, ArH), 7.09 (1H, t, *J*=7.6 Hz, ArH), 7.25–7.38 (5H, m, 5×ArH), 7.48 (1H, dt, *J*=1.2 and 7.8 Hz, ArH) and 7.61 (1H, d, *J*=7.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 44.0 ($PhCH_2N$), 110.0 (CH), 117.6 (C), 123.8 (CH), 125.3 (CH), 127.4 (2×CH), 128.1 (CH), 129.0 (2×CH), 134.5 (C), 138.3 (CH), 150.7 (C), 158.2 (BnNC═O) and 183.2 (C═O).

4.2.12. 1-Benzyl-3,3-dichloroindolin-2-one 32a. Dione **31a** (6.40 g, 27.00 mmol) was dissolved in benzene (70 cm^3) in a round bottom flask. Phosphorus pentachloride (12.80 g, 62.10 mmol, 2.3 equiv) was added and the solution was warmed to 25 °C for 24 h. The solvent was removed in vacuo to obtain a yellow brown residue, which was further purified by column chromatography (5% EtOAc/hexane) to afford 1-benzyl-3,3-dichloroindolin-2-one **32a** as a light yellow oil. On addition of ethanol **32a** precipitated as a white solid (6.37 g, 81%): mp 125–126 °C (lit. mp 126–127 °C);[38] ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 4.94 (2H, s, $PhCH_2N$), 6.72 (1H, d, *J*=7.9 Hz, ArH), 7.14 (1H, t, *J*=7.6 Hz, ArH), 7.22–7.39 (6H, m, 6×ArH) and 7.64 (1H, d, *J*=7.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 44.5 ($PhCH_2N$), 110.1 ($ArCCl_2$), 124.2 (CH), 124.9 (CH), 127.1 (2×CH), 128.1 (CH), 129.0 (2×CH), 129.3 (C), 131.8 (CH), 134.4 (C), 139.8 (C) and 169.2 (C═O).

4.2.13. 1-Benzylindolin-2-one 33a. 1-Benzyl-3,3-dichloroindolin-2-one **32a** (3.00 g, 10.30 mmol) was dissolved in AcOH (90 cm^3). Activated Zn (10.00 g, 154.5 mmol, 15 equiv) was added over a 10 min period and the resulting mixture was stirred for further 10 min at rt. The Zn was filtered off and washed with AcOH and EtOAc. Most of the solvent was removed in vacuo and concentrated. Solid $NaHCO_3$ was then added until effervescence ceased. The solution was extracted with Et_2O (3×50 cm^3), the organic layers were combined and the solvent was dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the resulting residue was purified by column chromatography (20% EtOAc/hexane) to afford 1-benzylindolin-2-one **33a** as a white solid (1.75 g, 76%): mp 60–62 °C (lit. mp 66.5–67 °C);[39] ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 3.62 (2H, s, $PhCH_2C$═O), 4.91 (2H, s, $PhCH_2N$), 6.72 (1H, d, *J*=7.8 Hz, ArH), 7.00 (1H, t, *J*=7.5 Hz, ArH), 7.16 (1H, t, *J*=7.8 Hz, ArH), 7.21–7.34 (6H, m, 6×ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 35.7 ($PhCH_2C$═O), 43.7 ($PhCH_2N$), 109.0 (CH), 122.3 (CH), 124.3 (CH), 124.4 (C), 127.3 (2×CH), 127.6 (CH), 127.8 (CH), 128.7 (2×CH), 135.9 (C), 144.3 (C) and 175.1 (BnNC═O).

4.2.14. 1-Benzyl-2-bromo-1*H*-indole 34a. $POBr_3$ (0.19 g, 0.68 mmol, 1.5 equiv) was added to a solution of 1-benzylindolin-2-one **33a** (0.10 g, 0.45 mmol) in dichloromethane (10.00 cm^3). The resulting mixture was stirred at reflux for 1 h. The solution was cooled to rt and imidazole (0.04 g, 0.54 mmol, 1.2 equiv) was added before refluxing for further 48 h. A 2 M $NaHCO_3$ solution was added until the reaction stopped and the solution was extracted with CH_2Cl_2 (3× 30 cm^3). The organic layers were combined, washed with brine and dried over anhydrous $MgSO_4$ before removing the solvent in vacuo. The resulting orange residue was purified by column chromatography (2% EtOAc/hexane) to afford the brominated compound **34a** as a white solid (0.07 g, 88%) and starting material (0.02 g): mp 87–89 °C; ν_{max} (film)/cm^{-1}: 1497, 1450, 737 and 722; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 5.41 (2H, s, $PhCH_2N$), 6.65 (1H, s, 3-H), 7.06–7.13 (4H, m, 4×ArH), 7.20–7.28 (4H, m, 4×ArH) and 7.55 (1H, dd, *J*=2.2 and 6.4 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 48.1 ($PhCH_2N$), 104.5 (3-C), 109.0 (CH), 113.5 (C), 119.8 (CH), 120.3 (CH), 122.0 (CH), 126.4 (2×CH), 127.5 (CH), 128.2 (C), 128.7 (2×CH), 136.7 (C) and 137.0 (C); MS *m*/*z* (EI): 285 (M^+, 42%), 204 (11), 91 (100), 65 (9); HRMS $C_{15}H_{12}N^{79}Br$ requires: 285.0153, found: 285.0091.

4.2.15. 2-(1-Benzyl-1*H*-indol-2-yl)benzaldehyde 36a. $Pd(PPh_3)_4$ (0.10 g, 0.087 mmol, 10 mol %) was added to a 50 cm^3 flame dried round bottom flask equipped with a condenser and dropping funnel. Bromide **34a** (0.25 g, 0.87 mmol), 2-formylphenylboronic acid **35** (0.15 g, 1.31 mmol) and DME (2.4 cm^3) were combined in the dropping funnel and degassed before adding to the flask. A 2 M Na_2CO_3 solution (0.46 g, 4.35 mmol, 5 equiv) was added to the dropping funnel, degassed and then added to the flask. The dropping funnel was closed and the resulting mixture was degassed once more before refluxing for 24 h. Water (10 cm^3) was added and the solution was extracted with

EtOAc (3×20 cm^3). The organic layers were combined and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (2% EtOAc/hexane) to afford 2-(1-benzyl-1*H*-indol-2-yl)benzaldehyde **36a** as a yellow, viscous oil (0.25 g, 92%); ν_{max} ($CHCl_3$)/cm^{-1}: 1701 (C=O) and 1597 (ArC=C); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) 5.26 (2H, s, $PhCH_2N$), 6.63 (1H, s, 3-H), 6.80–6.83 (2H, m, 2×ArH), 7.16–7.27 (5H, m, 5×ArH), 7.32 (1H, d, *J*=8.0 Hz, ArH), 7.40 (1H, dd, *J*=1.2 and 7.4 Hz, ArH), 7.50–7.61 (2H, m, 2×ArH), 7.69 (1H, dd, *J*=1.1 and 6.9 Hz, ArH), 8.01 (1H, dd, *J*=1.4 and 7.6 Hz, ArH) and 9.85 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) 47.6 ($PhCH_2N$), 106.8 (3-C), 110.4 (CH), 120.5 (CH), 120.8 (CH), 122.7 (CH), 126.1 (2×CH), 127.4 (CH), 127.5 (CH), 128.7 (2×CH), 129.0 (CH), 131.4 (CH), 133.2 (CH), 135.4 (C), 135.5 (C), 135.8 (C), 137.4 (C), 137.8 (C) and 191.6 (C=O); MS *m*/*z* (EI): 311 (M^+, 33%), 283 (58), 282 (65), 221 (19), 220 (100), 206 (39), 182 (53), 181 (72), 180 (20), 153 (20), 152 (30), 91 (87), 86 (27), 84 (41), 76 (15), 57 (22), 43 (18); HRMS $C_{22}H_{17}NO$ requires: 311.1310, found: 311.1335.

4.2.16. 5,6-Dihydro-6-phenylindolo[2,1-*a*]isoquinolin-5-ols 37a and 37b. To a solution of 2-(1-benzyl-1*H*-indol-2-yl)benzaldehyde **36a** (0.20 g, 0.64 mmol) in DMF (20 cm^3) was added ^{t}BuOK (0.086 g, 0.77 mmol) and the resulting mixture was stirred for 2 min at rt. The solution was quenched with H_2O (40 cm^3) and the reaction mixture was extracted with Et_2O (3×40 cm^3). After the organic layers were combined and dried, the solvent was removed in vacuo. The residue obtained was purified by column chromatography (2–5% EtOAc/hexane) to afford the *syn*- and *anti*-diastereomer **37a** and **37b** as yellow-green resins in a 7:3 ratio (53% *anti* and 22% *syn*). *anti*-Diastereoisomer **37a**: ν_{max} (film)/cm^{-1}: 3423 (OH) and 1605 (ArC=C); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) 1.66 (1H, d, *J*=11.0 Hz, OH), 5.38 (1H, dd, *J*=7.0 and 11.0 Hz, PhC*H*OH), 5.71 (1H, d, *J*=7.0 Hz, PhC*H*N), 6.85–6.82 (2H, m, 2×ArH), 6.92 (1H, s, 3-H), 6.97–7.05 (5H, m, 5×ArH), 7.11–7.21 (2H, m, 2×ArH), 7.29 (1H, t, *J*=7.4 Hz, ArH), 7.38 (1H, d, *J*=7.8 Hz, ArH), 7.54 (1H, dd, *J*=2.2 and 6.4 Hz, ArH) and 7.75 (1H, d, *J*=7.6 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 59.5 (Ph*C*HOH), 69.5 (Ph*C*HN), 97.4 (CH), 109.4 (CH), 120.5 (CH), 120.8 (CH), 122.3 (CH), 123.9 (CH), 125.0 (CH), 127.3 (C), 127.9 (2×CH), 128.0 (CH), 128.1 (CH), 128.4 (CH), 128.6 (2×CH), 129.1 (C), 133.4 (C), 134.5 (C), 135.0 (C) and 136.4 (C); MS *m*/*z* (EI): 311 (M^+, 100%), 310 (18), 283 (17), 282 (47), 280 (14), 234 (17), 220 (42), 206 (41), 204 (30), 178 (15), 165 (18), 155 (14) and 91 (20); HRMS $C_{22}H_{17}NO$ requires: 311.1310, found: 311.1302.

syn-Diastereoisomer **37b**: ν_{max} (film)/cm^{-1}: 3364 (OH) and 1607 (ArC=C); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) 2.18 (1H, br s, OH), 4.91 (1H, s, PhCHOH), 5.81 (1H, d, *J*=1.5 Hz, PhCHN), 6.72–6.69 (2H, m, 2×ArH), 6.97 (1H, s, ArH), 7.00–7.09 (5H, m, 5×ArH), 7.12–7.18 (3H, m, 3×ArH), 7.29–7.35 (1H, m, ArH), 7.58–7.60 (1H, m, ArH) and 7.79 (1H, d, *J*=7.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 62.0 (Ph*C*HOH), 73.9 (Ph*C*HN), 97.6 (CH), 109.6 (CH), 120.5 (CH), 120.9 (CH), 122.4 (CH), 124.4 (CH), 125.9 (2×CH), 127.7 (CH), 128.0 (C), 128.1 (CH), 128.7 (2×CH), 129.1 (C), 129.7 (CH), 129.9 (CH), 131.0 (C), 133.7 (C), 137.4 (C) and 137.8 (C); MS *m*/*z* (EI): 311 (M^+, 100%), 310 (20), 283 (18), 282 (47), 280 (14), 234 (18), 220 (42), 217 (14), 206 (42), 204 (31), 178 (16), 165 (19), 155 (15) and 91 (21); HRMS $C_{22}H_{17}NO$ requires: 311.1310, found: 311.1339.

4.2.17. Ethyl 2-(2,3-dioxoindolin-1-yl)acetate 31b. Isatin **30** (10.00 g, 68.00 mmol) and CaH_2 (2.86 g, 68.00 mmol, 1 equiv) were dissolved in DMF (35.00 cm^3) in a round bottom flask. The solution was stirred at 100 °C for 1 h and then cooled to 40 °C so that ethyl 2-bromoacetate (22.62 cm^3, 204.00 mmol, 3 equiv) could be added slowly. The resulting mixture was heated to 100 °C for 4 h and then allowed to cool to rt. The solution was poured into an aqueous 0.5 M HCl solution (200 cm^3) with vigorous stirring, which resulted in a yellow precipitate. The precipitate was filtered off and washed with H_2O. The crude product was further purified by recrystallization (CH_2Cl_2/hexane) to afford ethyl 2-(2,3-dioxoindolin-1-yl)acetate **31b** as yellow crystals in quantitative yield: mp 132–133 °C (lit. mp 116–118 °C);[40] ν_{max} ($CHCl_3$)/cm^{-1}: 1740 (C=O) and 1615 (ArC=C); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) 1.29 (3H, t, *J*=7.1 Hz, CH_2CH_3), 4.25 (2H, q, *J*=7.1 Hz, CH_2CH_3), 4.49 (2H, s, $O{=}CCH_2N$), 6.79 (1H, d, *J*=7.9 Hz, ArH), 7.16 (1H, t, *J*=7.5 Hz, ArH), 7.57–7.62 (1H, m, ArH) and 7.66 (1H, d, *J*=7.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 14.1 (CH_3), 41.3 ($O{=}CCH_2N$), 62.2 (CH_3CH_2), 110.1 (CH), 117.7 (C), 124.1 (CH), 125.6 (CH), 138.4 (CH), 150.3 (C), 158.0 (NC=O), 166.7 (OC=O) and 182.4 (PhC=O); MS *m*/*z* (EI): 233 (M^+, 35%), 132 (100), 77 (24) and 51 (9); HRMS $C_{12}H_{11}NO_4$ requires: 233.0688, found: 233.0675.

4.2.18. Ethyl 2-(3,3-dichloro-2-oxoindolin-1-yl)acetate 32b. Dione **31b** (2.50 g, 10.70 mmol) was dissolved in benzene (40 cm^3) in a round bottom flask. PCl_5 (5.00 g, 24.61 mmol, 2.3 equiv) was added and the solution was warmed to 25 °C for 24 h. The solvent was removed in vacuo to obtain a light yellow residue, which was further purified by column chromatography (hexane→2% EtOAc/hexane) to afford ethyl 2-(3,3-dichloro-2-oxoindolin-1-yl)acetate **32b** as a white solid (3.10 g, 100%): mp 115–116 °C; ν_{max} ($CHCl_3$)/cm^{-1}: 1746 (C=O), 1613 (ArC=C) and 670 (C–Cl); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) 1.26 (3H, t, *J*=7.1 Hz, CH_2CH_3), 4.23 (2H, q, *J*=7.1 Hz, CH_3CH_2), 4.48 (2H, s, $O{=}CCH_2N$), 6.77 (1H, d, *J*=7.9 Hz, ArH), 7.19 (1H, t, *J*=7.7 Hz, ArH), 7.39 (1H, dt, *J*=1.0 and 7.8 Hz, ArH) and 7.66 (1H, d, *J*=7.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 14.0 (CH_3), 41.8 ($O{=}CCH_2N$), 62.1 (CH_3CH_2), 73.9 (CH), 109.1 (CCl_2), 124.5 (CH), 125.0 (CH), 129.0 (C), 131.8 (CH), 139.4 (C), 166.4 (NC=O) and 168.9 (OC=O); MS *m*/*z* (EI): 287 (M^+, 39%), 254 (37), 252 (100), 216 (23), 214 (36), 188 (11), 186 (18), 173 (23), 151 (21) and 89 (18); HRMS $C_{12}H_{11}NO^{35}Cl_2$ requires: 287.0116, found: 287.0151.

4.2.19. Ethyl 2-(2-oxoindolin-1-yl)acetate 33b. In a round bottom flask, ethyl 2-(3,3-dichloro-2-oxoindolin-1-yl)acetate **32b** (0.15 g, 0.52 mmol) was dissolved in AcOH (5 cm^3). Activated Zn (0.50 g, 7.29 mmol, 14 equiv) was added over a 10 min period and the resulting mixture was stirred for further 5 min at rt. The Zn was filtered off and washed with AcOH and EtOAc. Most of the solvent was removed in vacuo and concentrated $NaHCO_3$ was added until

effervescence stopped. The solution was extracted with Et_2O (3×20 cm^3), the organic layers were combined and the solvent was dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the resulting residue was purified by column chromatography ($2\rightarrow5\%$ EtOAc/hexane) to afford ethyl 2-(2-oxoindolin-1-yl)acetate **33b** as a white solid in quantitative yield: mp 127–129 °C (lit. mp 125–127.5 °C);[41] ν_{max} ($CHCl_3$)/cm^{-1}: 1740 and 1715 (C=O) and 1615 (ArC=C); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 1.27 (3H, t, J=7.1 Hz, CH_2CH_3), 3.60 (1H, s, $PhCH_2$), 4.22 (2H, q, J=7.1 Hz, CH_3CH_2), 4.47 (2H, s, O=CCH_2N), 6.70 (1H, d, J=7.8 Hz, ArH), 7.03–7.05 (1H, m, ArH) and 7.23–7.28 (2H, m, 2×ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 14.1 (CH_3), 35.5 ($PhCH_2$), 41.3 (O=CCH_2N), 61.7 (CH_3CH_2), 108.1 (CH), 122.7 (CH), 124.2 (C), 124.5 (CH), 127.9 (CH), 143.8 (C), 167.6 (NC=O) and 174.9 (OC=O); MS m/z (EI): 219 (M$^+$, 45%), 146 (49), 119 (11), 118 (100), 91 (39), 65 (14), 43 (12) and 21 (24); HRMS $C_{12}H_{13}NO_3$ requires: 219.0895, found: 219.0896.

4.2.20. Ethyl 2-(2-bromo-1*H*-indol-1-yl)acetate 34b. $POBr_3$ (0.60 g, 2.22 mmol, 1.2 equiv) was added to a solution of ethyl 2-(2-oxoindolin-1-yl)acetate **33b** (0.40 g, 1.84 mmol) in dichloromethane (40 cm^3). The resulting mixture was stirred at reflux for 9 days. A 2 M $NaHCO_3$ solution was added until effervescence ceased and the solution was extracted with CH_2Cl_2 (3×50 cm^3). The organic layers were combined, washed with brine and dried over anhydrous $MgSO_4$ before removing the solvent in vacuo. The resulting purple residue was purified by column chromatography (2% EtOAc/hexane) to afford the brominated compound **34b** as a white solid (0.25 g, 89%) and starting material (0.12 g): mp 61–63 °C; ν_{max} (film)/cm^{-1}: 1737 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 1.23 (3H, t, J=7.2 Hz, CH_3CH_2), 4.19 (2H, q, J=7.1 Hz, CH_3CH_2), 4.87 (2H, s, O=CCH_2N), 6.63 (1H, s, 3-H), 7.08–7.21 (3H, m, 3×ArH) and 7.53 (1H, d, J=7.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 14.1 (CH_2CH_3), 46.0 (O=CCH_2N), 61.7 (CH_3CH_2), 105.1 (CH), 109.0 (CH), 113.4 (C), 120.0 (CH), 120.6 (CH), 122.2 (CH), 128.1 (C), 136.9 (C) and 167.9 (OC=O); MS m/z (EI): 281 (M$^+$, 19%), 213 (15), 210 (35), 208 (36), 201 (35), 143 (12), 129 (19), 128 (10), 127 (18), 115 (66), 87 (15), 81 (41), 69 (14), 43 (21), 41 (100), 39 (13), 29 (42), 28 (18) and 27 (10); HRMS $C_{12}H_{12}NO_2{}^{79}Br$ requires: 281.0051, found: 281.0052.

4.2.21. Ethyl 2-[2-(2-formylphenyl)-1*H*-indol-1-yl]acetate 36b. $Pd(PPh_3)_4$ (0.11 g, 0.089 mmol, 10 mol %) was added to a flame dried round bottom flask equipped with a condenser and dropping funnel. Bromide **34b** (0.25 g, 0.89 mmol), 2-formylphenylboronic acid **35** (0.20 g, 1.14 mmol) and DME (2.6 cm^3) were combined in the dropping funnel and degassed before adding to the flask. A 2 M Na_2CO_3 solution (0.47 g, 4.45 mmol, 5 equiv) was added to the dropping funnel, degassed and then added to the flask. The dropping funnel was closed and the resulting mixture was degassed once more before refluxing for 10 min. Water (10 cm^3) was added and the solution was extracted with EtOAc (3×20 cm^3). The organic layers were combined and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (2% EtOAc/hexane) to afford ethyl 2-(2-(2-formylphenyl)-1*H*-indol-1-yl)acetate **36b** as an orange viscous oil (0.21 g, 77%); ν_{max} (film)/cm^{-1}: 1748 and 1693 (C=O) and 1600 (ArC=C); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 1.15 (3H, t, J=7.1 Hz, CH_2CH_3), 4.10 (2H, q, J=7.1 Hz, CH_3CH_2) 4.71 (2H, s, O=CCH_2N), 6.63 (1H, s, 3-H), 7.18–7.33 (3H, m, 3×ArH), 7.51 (1H, d, J=7.6 Hz, ArH), 7.58–7.62 (1H, m, ArH), 7.65–7.70 (2H, m, 2×ArH), 8.08 (1H, dd, J=1.1 and 7.7 Hz, ArH) and 10.00 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) 14.0 (CH_3), 45.7 (O=CCH_2N), 61.7 (CH_3CH_2), 107.1 (CH), 109.3 (CH), 120.9 (CH), 120.9 (CH), 121.0 (CH), 123.0 (CH), 127.9 (C), 129.2 (CH), 131.5 (CH), 133.3 (CH), 135.2 (C), 135.4 (C), 135.8 (C), 137.9 (C), 168.3 (OC=O) and 192.1 (CHO); MS m/z (EI): 307 (M$^+$, 65%), 279 (33), 278 (39), 250 (24), 235 (13), 234 (47), 233 (25), 220 (19), 219 (23), 210 (12), 207 (20), 206 (54), 205 (43), 204 (47), 203 (15), 192 (13), 182 (36), 181 (100), 178 (20), 177 (14), 165 (19), 153 (31), 152 (49), 151 (23), 150 (16), 149 (56), 136 (24), 102 (12), 86 (34), 84 (45), 77 (19), 76 (23), 51 (10), 47 (12) and 29 (12); HRMS $C_{19}H_{17}NO_3$ requires: 307.1208, found: 307.1200.

4.2.22. Ethyl indolo[2,1-*a*]isoquinoline-6-carboxylate 39. To a solution of ethyl 2-(2-(2-formylphenyl)-1*H*-indol-1-yl)acetate **36b** (0.15 g, 0.49 mmol) in DMF (15 cm^3) was added ^{t}BuOK (0.006 g, 0.049 mmol, 10 mol %) at rt. The resulting mixture was stirred for 2 min before it was quenched with H_2O (25 cm^3) and then extracted with Et_2O (3×25 cm^3). The organic layers were combined, dried over $MgSO_4$ and the solvent was removed in vacuo. The resulting residue was purified by column chromatography (2% EtOAc/hexane) to afford ethyl indolo[2,1-*a*]isoquinoline-6-carboxylate **39** (0.083 g, 59%) as a yellow solid: mp 109–111 °C; ν_{max} (film)/cm^{-1}: 1724 (C=O) and 1601 (ArC=C); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 1.41 (3H, t, J=7.1 Hz, CH_3CH_2), 4.51 (2H, q, J=7.1 Hz, CH_3CH_2), 7.12 (1H, s, 3-H), 7.17–7.26 (3H, m, 3×ArH), 7.30–7.38 (1H, m, ArH), 7.44–7.53 (2H, m, 2×ArH), 7.61 (1H, d, J=8.2 Hz, ArH), 7.74 (1H, d, J=7.6 Hz, ArH) and 8.07 (1H, d, J=7.9 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 14.2 (CH_3CH_2), 62.2 (CH_3CH_2), 95.4 (CH), 113.8 (CH), 115.2 (CH), 120.7 (CH), 121.0 (CH), 122.2 (CH), 123.4 (CH), 126.9 (C), 127.3 (C), 127.7 (CH), 127.8 (CH), 128.8 (C), 129.2 (CH), 129.3 (C), 131.7 (C), 135.5 (C) and 164.1 (OC=O); MS m/z (EI): 289 (M$^+$, 100%), 261 (67), 216 (19), 187 (5), 131 (7) and 108 (8); HRMS $C_{19}H_{15}NO_2$ requires: 289.1103, found: 289.1081.

4.2.23. 1-[2-Benzyl-3-1*H*-pyrrol-2-ylphenyl]-1-ethanone 41a. A solution of 1-benzyl-2-bromo-1*H*-pyrrole **40**[35] (0.350 g, 1.48 mmol) in DME (4 cm^3) was deoxygenated by passing nitrogen through the mixture for 5 min. The solution was then added to $Pd(PPh_3)_4$ (10 mol %, 0.170 g, 0.15 mmol) and stirred under an atmosphere of N_2 for 10 min at rt. A solution of 2-acetylphenylboronic acid (0.365 g, 2.22 mmol) in EtOH (2.6 cm^3) was deoxygenated and added to the reaction mixture. The mixture was stirred for further 10 min. A deoxygenated 2 M aq Na_2CO_3 solution (6.3 cm^3, 12.6 mmol) was then added to the reaction mixture, which was stirred at rt for further 5 min before being heated at reflux for 2 days. The mixture was cooled to rt and quenched with H_2O (20 cm^3) after which the organic material was extracted with CH_2Cl_2 (3×30 cm^3) and the solvent was evaporated under reduced pressure. The crude

product was subjected to column chromatography (5–10% EtOAc/hexane) to afford the product 1-[2-benzyl-3-1*H*-pyrrol-2-ylphenyl]-1-ethanone **41a** as a yellow oil (0.335 g, 82%); ν_{max} (film)/cm^{-1}: 1682 (C=O), 1597 (ArC=C) and 709; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 1.86 (3H, s, $ArCOCH_3$), 4.91 (2H, s, CH_2), 6.15–6.17 (1H, m, ArH), 6.24–6.26 (1H, m, ArH), 6.79–6.80 (1H, m, ArH), 6.88–6.90 (2H, m, 2×ArH), 7.19–7.27 (4H, m, 4×ArH), 7.38–7.42 (2H, m, 2×ArH) and 7.56–7.59 (1H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 28.9 ($ArCOCH_3$), 50.9 (CH_2), 108.8 (CH), 111.0 (CH), 122.8 (CH), 127.0 (2×CH), 127.5 (CH), 127.8 (CH), 127.9 (CH), 128.2 (C), 128.5 (2×CH), 130.6 (CH), 131.3 (CH), 131.7 (C), 137.8 (C), 141.8 (C) and 204.1 (C=O); MS *m/z* (EI): 275 (M$^+$, 96%), 232 (49), 198 (45), 192 (20), 184 (63), 156 (60) and 91 (100); HRMS calcd for $C_{19}H_{17}NO$: 275.1310, found: 275.1320.

4.2.24. 6-Methyl-5-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquin-6-ols 42a and 42b. KO^{t}Bu (0.164 g, 1.50 mmol) was added to 1-[2-benzyl-3-1*H*-pyrrol-2-ylphenyl]-1-ethanone **41a** (0.103 g, 0.37 mmol) dissolved in dry DMF (10 cm^3) and heated under N_2 at 80 °C. The reaction mixture was quenched by adding H_2O (50 cm^3) and the organic material was extracted with Et_2O (3×50 cm^3). The organic layer was dried over $MgSO_4$ and filtered. The organic solvent was then evaporated in vacuo and the residue was subjected to column chromatography (5–20% EtOAc/hexane) to afford firstly the product **42a** (0.056 g, 56%) as a yellow oil; ν_{max} (film)/cm^{-1}: 3401 (OH) and 1605 and 1580 (ArC=C); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 1.50 (3H, s, CH_3), 1.54 (1H, s, OH), 5.15 (1H, s, CH), 6.24–6.26 (1H, m, ArH), 6.66–6.68 (2H, m, 2×ArH), 7.01–7.05 (2H, m, 2×ArH), 7.14–7.23 (4H, m, 4×ArH), 7.25–7.44 (2H, m, 2×ArH) and 7.66–7.69 (1H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 23.9 (CH_3), 70.2 (CH), 73.0 (C), 104.8 (CH), 109.7 (CH), 121.9 (CH), 122.8 (CH), 124.9 (CH), 126.3 (CH), 127.9 (2×CH), 128.2 (CH), 128.3 (C), 128.4 (2×CH), 128.8 (CH), 134.1 (C) and 137.3 (2×C); MS *m/z* (EI): 275 (M$^+$, 100%), 274 (33), 232 (28), 198 (23) and 156 (36); HRMS calcd for $C_{19}H_{17}NO$: 275.1310, found: 275.1311.

The second product **42b** was also isolated as a yellow oil (0.023 g, 23%); ν_{max} (film)/cm^{-1}: 3448 (OH), 1605 and 1579 (ArC=C); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 1.58 (3H, s, CH_3), 1.63 (1H, s, OH), 5.06 (1H, s, CH), 6.25–6.26 (1H, m, ArH), 6.64–6.67 (2H, m, 2×ArH), 6.82–6.93 (2H, m, 2×ArH), 7.11–7.19 (4H, m, 4×ArH), 7.24–7.31 (1H, m, ArH), 7.43 (1H, d, *J*=7.7 Hz, ArH) and 7.61 (1H, d, *J*=7.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 29.7 (CH_3), 68.9 (CH), 73.4 (C), 104.5 (CH), 109.8 (CH), 121.5 (CH), 122.0 (CH), 124.2 (CH), 126.4 (CH), 127.5 (C), 127.7 (2×CH), 127.9 (CH), 128.3 (CH), 128.6 (C), 128.6 (2×CH), 136.4 (C) and 136.9 (C); MS *m/z* (EI): 275 (M$^+$, 94%), 257 (37), 232 (31), 198 (28), 156 (48), 91 (47), 86 (85) and 84 (100); HRMS calcd for $C_{19}H_{17}NO$: 275.1310, found: 275.1311.

4.2.25. 6-Methyl-5-phenylpyrrolo[2,1-*a*]isoquinoline 43a. To a solution of 6-methyl-5-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquin-6-ol **42b** (0.020 g, 0.07 mmol) in CH_2Cl_2 (5 cm^3) were added molecular sieves and *p*TSA (15 mol %, 0.001 g, 0.004 mmol). The reaction mixture was stirred at rt for 18 h. The mixture was then filtered, evaporated and subjected to column chromatography (5–10% EtOAc/hexane) to afford the product 6-methyl-5-phenylpyrrolo[2,1-*a*]isoquinoline **43a** (0.014 g, 74%) as a pale yellow oil; ν_{max} (film)/cm^{-1}: 1655 and 1613 (ArC=C); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 2.22 (3H, s, $ArCH_3$), 6.56–6.58 (1H, m, ArH), 6.66–6.68 (1H, m, ArH), 6.99–7.01 (1H, m, ArH), 7.38–7.58 (7H, m, 7×ArH), 7.75 (1H, d, *J*=8.2 Hz, ArH) and 8.10 (1H, d, *J*=7.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 14.8 ($ArCH_3$), 99.8 (CH), 110.7 (CH), 114.1 (C), 114.8 (CH), 122.1 (CH), 124.0 (CH), 125.4 (CH), 126.0 (C), 127.0 (CH), 128.0 (C), 128.9 (CH), 129.2 (2×CH), 130.1 (2×CH), 133.5 (C) and 135.0 (2×C); MS *m/z* (EI): 259 (M$^+$, 28%), 257 (100), 256 (46), 254 (21), 241 (17) and 121 (8); HRMS calcd for $C_{19}H_{15}N$: 257.1205, found: 257.1205.

4.2.26. 2-(1-Benzyl-1*H*-pyrrol-2-yl)benzaldehyde 41b. A solution of 1-benzyl-2-bromo-1*H*-pyrrole **40** (0.305 g, 1.29 mmol) in DME (6 cm^3) was deoxygenated by passing N_2 through the mixture for 5 min. The solution was then added to $Pd(PPh_3)_4$ (10 mol %, 0.146 g, 0.13 mmol) and stirred under an atmosphere of N_2 for 10 min at rt. A solution of 2-formylphenylboronic acid (0.38 g, 1.9 mmol) in ethanol (2.3 cm^3) was deoxygenated and added to the reaction mixture. The mixture was stirred for further 10 min. A deoxygenated 2 M aq Na_2CO_3 solution (5.4 cm^3, 10.8 mmol) was then added to the reaction mixture, which was stirred at rt for further 5 min before being heated at reflux for 2 days. The reaction mixture was cooled to rt and quenched with H_2O (20 cm^3) after which the organic material was extracted with CH_2Cl_2 (3×30 cm^3) and then the organic solvent was evaporated under reduced pressure. The crude product was subjected to column chromatography (5–10% EtOAc/hexane) to afford the product 2-(1-benzyl-1*H*-pyrrol-2-yl)benzaldehyde as a yellow oil **41b** (0.172 g, 52%); ν_{max} (film)/cm^{-1}: 1693 (C=O) and 1599 (ArC=C); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 5.00 (2H, s, CH_2), 6.23–6.32 (2H, m, 2×ArH), 6.81–6.88 (3H, m, 3×ArH), 7.18–7.24 (3H, m, 3×ArH), 7.33 (1H, d, *J*=6.9 Hz, ArH), 7.35–7.46 (1H, m, ArH), 7.51–7.57 (1H, m, ArH), 7.93 (1H, dd, *J*=1.1 and 7.7 Hz, ArH) and 9.81 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) 51.1 (CH_2), 108.5 (CH), 113.5 (CH), 123.6 (CH), 126.6 (2×CH), 127.3 (CH), 127.6 (CH), 128.1 (CH), 128.6 (2×CH and one C), 131.6 (CH), 133.2 (CH), 135.4 (C), 136.6 (C), 137.9 (C) and 192.3 (CHO); MS *m/z* (EI): 261 (M$^+$, 91%), 233 (37), 179 (25), 170 (97), 156 (54) and 91 (100); HRMS calcd for $C_{18}H_{15}NO$: 261.1154, found: 261.1154.

4.2.27. 5-Phenylpyrrolo[2,1-*a*]isoquinoline 43b. KO^{t}Bu (0.086 g, 0.76 mmol) was added to 2-(1-benzyl-1*H*-pyrrol-2-yl)benzaldehyde **41b** (0.050 g, 0.19 mmol) dissolved in dry DMF (9 cm^3) and heated under N_2 at 80 °C for 10 min. The reaction mixture was quenched with H_2O (50 cm^3) and then extracted with Et_2O (3×50 cm^3). The organic layer was dried over $MgSO_4$ and filtered. The organic layers were then evaporated and subjected to column chromatography (5–20% EtOAc/hexane) to afford the product 5-phenylpyrrolo[2,1-*a*]isoquinoline **43b** (0.032 g, 68%) as a yellow oil; ν_{max} (film)/cm^{-1}: 1635 and 1557 (ArC=C); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) 6.68–6.70 (2H, m, 2×ArH), 7.04 (1H, m, ArH), 7.04–7.06 (1H, m, ArH),

7.31–7.36 (1H, m, ArH), 7.37–7.57 (5H, m, 5×ArH), 7.64–7.67 (2H, m, 2×ArH) and 8.06 (1H, d, J=8.0 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 110.4 (CH), 111.4 (CH), 111.5 (CH), 114.1 (CH), 121.9 (CH), 125.5 (C), 125.6 (CH), 125.8 (C), 126.8 (CH), 127.2 (CH), 127.3 (C), 128.8 (2×CH), 128.9 (2×CH), 129.2 (CH), 135.3 (C) and 136.6 (C); MS *m*/*z* (EI): 243 (M^+, 100%), 220 (21), 205 (63) and 170 (14); HRMS calcd for $C_{18}H_{13}N$: 243.1048, found: 243.1048.

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23. The work in this paper is taken from the Ph.D. of R. Pathak, University of the Witwatersrand, November 2004, the M.Sc. of A. N. C. Lötter, April 2006 and the ongoing M.Sc. of T. S. Sello, University of the Witwatersrand.
24. Crystal data for **17a**: $C_{21}H_{17}NO$, M=299.36, monoclinic, a=13.5387(17) Å, b=8.8623(11) Å, c=13.8000(18) Å, U=1602.0(4) Å^3, T=293(2) K, space group $P2(1)/n$, Z=4, μ(Mo Kα)=0.076 mm^{-1}; 9101 reflections measured, 3140 unique [R(int)=0.0291], which were used in all calculations. Final R indices [$I>2\sigma(I)$], R_1=0.0705, $wR(F^2)$=0.2051. CCDC number: 612525.
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27. Crystal data for **18b**: $C_{27}H_{19}N$, M=357.43, monoclinic, a=12.904(3) Å, b=17.260(4) Å, c=8.679(2) Å, U=1886.1(8) Å^3, T=293(2) K, space group $P2(1)/c$, Z=4, μ(Mo Kα)=0.073 mm^{-1}; 1079 reflections measured, 3704 unique [R(int)=0.0363], which were used in all calculations. Final R indices [$I>2\sigma(I)$], R_1=0.0477, $wR(F^2)$=0.1180. CCDC number: 612524.
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