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Applications of NHC-mediated O- to C-carboxyl transfer: synthesis of (\pm) -N-benzyl-coerulescine and (\pm) -horsfiline

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ABSTRACT

NHC-promoted O- to C-carboxyl transfer of 3-allyl indolyl phenyl carbonates generates 3-allyl-3-phenoxycarbonyl-oxindoles with good catalytic efficiency, which are readily converted into (\pm) -N-benzyl-coerulescine and (\pm) -horsfiline.

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1. Introduction

A diverse array of naturally occurring polycyclic alkaloids bear a quaternary stereocentre at the 3-position of an oxindole. The spiro[pyrrolidine-3,3'-oxindole] motif is among the many structural classes encompassed within this classification, with a range of natural products of varying complexity such as alstonisine $\mathbf{1}^1$ and spirotryprostatin 2^2 that contain this ring junction possessing significant biological activity (Fig. 1).³ Given the biological profile and structural interest in these targets, the synthesis of the spiro[pyrrolidine-3,3'oxindole] system has been used as a test-bed for the development of a range of synthetic methodologies in order to tackle the total syntheses of these molecules.⁴ The simplest examples of alkaloids containing the spiro[pyrrolidine-3,3'-oxindole] motif include coerulescine **3** and the structurally related horsfiline **4**. Horsfiline was first isolated in 1991 by Bodo et al. from the Malaysian medical plant Horsfildea superba warb,⁵ while coerulescine was isolated in 1998 by Colegate et al.⁶ Several different strategies have been developed for the synthesis of these natural products in either racemic or enantiomerically enriched form. Approaches based upon MgI₂ promoted ring expansions,^{7,8} oxidative rearrangement of tetrahydro-β-carbolines (using *N*-bromosuccinimide,⁹ dimethyldioxirane,¹⁰ lead tetra-acetate,⁵ sodium tungstate,¹¹ or *tert*-butylhypochlorite¹²), dipolar cycloaddition reactions,¹³ radical cyclisations,^{14,15} asymmetric

nitroolefination reactions,¹⁶ intramolecular Mannich reactions,¹⁷ iodine-induced rearrangement of 3-[(aziridin-1-yl)(methylthio)-methylene]-2-oxindoles¹⁸ and palladium catalysed asymmetric allylic alkylation¹⁹ have all been utilised previously.



Figure 1. Representative natural products that contain the spiro[pyrrolidine-3,3'-ox-indole] system.





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As part of a programme of research aimed at developing alternative Lewis-base mediated catalysts,²⁰ we have shown that *N*-heterocyclic carbenes (NHCs)^{21,22} can promote the *O*- to *C*-carboxyl transfer reaction (the Steglich rearrangement) of a range of oxazolyl, indolyl and benzofuranyl carbonate derivatives with good catalytic efficiency.^{23,24} A number of elegant asymmetric versions of this process have been developed for the asymmetric synthesis of 3-carboxyl oxindoles from indolyl carbonates.²⁵ As a demonstration of the utility of this methodology, its application to the syntheses of coerulescine and horsfiline was investigated. Our planned retrosynthetic route to these products targeted a suitably protected diol **G** as a viable precursor to the spiro[pyrrolidine-3,3'-oxindole] motif. Diol **6** could be generated by selective reduction and functional group manipulation of a 3-allyl-3-phenoxycarbonyl oxindole **7**, prepared by NHC-promoted O-to *C*-carboxyl transfer of an indolyl carbonate **8** (Fig. 2).



Figure 2. Proposed synthetic route to spiro[pyrrolidine-3,3'-oxindole] products.

This strategy is related to that employed by Trost et al. in their asymmetric synthesis of horsfiline, who prepared 3-allyl-3-ethoxycarbonyl oxindole **9** as a key intermediate in 98% ee after crystallisation using an asymmetric allylation strategy.¹⁹ In this case, however, attempts to access diol **10** from **9** proved impossible; following oxidative cleavage of the allyl functionality, selective reduction of the ethyl ester could not be accomplished. The completed synthesis involved oxidative cleavage of the allyl functionality within **9** and subsequent reductive amination to give **11** after N-deprotection, followed by selective reduction to give the desired natural product **4** in 11% overall yield (Fig. 3).

Building upon these precedents, we detail herein the successful selective realisation of our synthetic strategy to prepare the spiro[pyrrolidine-3,3'-oxindole] motif via a diol such as **6**, and its application to the synthesis of (\pm) -*N*-benzyl-coerulescine and (\pm) -horsfiline.

2. Results and discussion

2.1. Model studies: synthesis of (±)-N-benzyl-coerulescine

Initial studies focused upon the preparation of 3-allyloxindole **15** from *N*-benzylisatin **12**. Addition of allylmagnesium bromide to *N*-benzyl isatin gave 3-allyl-3-hydroxyisatin **13**.²⁶ Attempted reduction of **13** to generate **15** in one step through treatment with SnCl₂ proved sluggish, giving 60% conversion to a ~50:50 mixture of 3-chlorooxindole **14** and the desired product **15** even after



Figure 3. Trost's successful asymmetric route to horsfiline employing 3-allyl-3-ethoxycarbonyl oxindole 9.

extended reaction times. To overcome this problem, initial conversion of alcohol **13** to chloride **14**, and subsequent reduction with zinc powder²⁷ gave **15** in greatly improved yields and purity. Treatment of 3-allyloxindole **15** with KHMDS and O-carboxylation with phenyl chloroformate furnished phenyl carbonate **16** in good yield. The ability of the NHC derived from triazolium salt **17** to promote the desired *O*-to *C*-carboxyl transfer was next evaluated, with deprotonation of triazolium salt **17** with KHMDS used to prepare the corresponding NHC in situ. Good conversion of **16** to the desired 3-allyl-3-phenoxycarbonyl oxindole **18** was observed with variation in the catalyst loading of the NHC derived from **17** (from 9 mol % to 1.5 mol %), although trace quantities of 3-allyloxindole **15** (typically <5%) and diphenylcarbonate were observed, with the desired product **18** isolated in 49–73% yield (Scheme 1). In practice, and on a >2 g scale, an NHC catalyst loading of 9 mol % was



Scheme 1. Reagents and conditions: (i). allylMgBr, THF, -78 °C (10 min) then warm to 0 °C (20 min); (ii). SOCl₂, N(*i*-Pr)₂Et, CH₂Cl₂, rt, 25 min then Zn (powder), AcOH, THF, 0 °C to rt; (iii). KHMDS, THF, -78 °C then PhOCOCl; (iv). KHMDS (1.5 to 9 mol %), salt **17** (2 to 10 mol %), THF, 15 min then indolyl carbonate **16**, rt, 1 h.

used to promote rearrangement of **16**, giving **18** in 73% yield.²⁸ Unambiguous verification of the molecular structure of **18** was confirmed by X-ray crystallographic analysis (Fig. 4).



Figure 4. Molecular representation of the X-ray crystal structure of 18. The X-ray crystal structure shows disorder of the allyl group, but only one representation is shown.

Functional group manipulation of **18** to generate the corresponding diol as a key intermediate towards the preparation of the spiro[pyrrolidine-3,3'-oxindole] skeleton was next investigated. Oxidative functionalisation of **18** using OsO₄ under standard Upjohn conditions gave spirocyclic lactone **19** (66:34 dr), with purification giving the separable diastereoisomers, whose relative configurations were not identified, in 62% overall yield.²⁹ As an alternative strategy, selective reduction of the ester functionality within **18** was attempted. Treatment of **18** with LiAlH₄ at rt resulted in over-reduction, generating *N*-benzyl-3-allylindole **21** in 44% isolated yield, while

selective reduction was achieved through treatment with sodium borohydride and calcium chloride in methanol,³⁰ giving alcohol **20** in 80% yield (Scheme 2). At the moment we cannot distinguish between the over-reduction process to give **21** proceeding either via direct reductive retro-Claisen reaction of the ester, or retro-aldol reaction of in situ formed alcohol **20**. The molecular structure of **20** was confirmed by X-ray crystallographic analysis (Fig. 5).



Figure 5. Molecular representation of the X-ray crystal structure of 20. There are two molecules of 20 in the asymmetric unit cell, but only one representation is shown.

Further functionalisation of alcohol **20** was achieved by dihydroxylation with OsO₄ to give triol **22** in 92% yield, with oxidative cleavage with sodium periodate giving the spirocyclic lactol **23**



Scheme 2. Reagents and conditions: (i). OsO₄ (1% wt solution in H₂O), NMO, CH₂Cl₂, rt; (ii). LiAlH₄, THF, 0 °C to rt; (iii). NaBH₄, CaCl₂, MeOH, rt.



Figure 6. Molecular representation of the X-ray crystal structure of 24.

(78:22 dr). Reduction with NaBH₄ gave the desired diol **24** in 67% yield, whose molecular structure was confirmed unambiguously by X-ray crystallographic analysis (Fig. 6). Subsequent bis-mesylation generated **25** in high yield, with addition of methylamine,³¹ followed by purification on silica to promote cyclisation, giving *N*-benzyl-coerulescine **26** with comparable spectroscopic properties to the literature (Scheme 3).¹⁵ As N-debenzylation of **26** has previously been demonstrated, this represents a formal synthesis of coerulescine **3**.¹⁵



Scheme 3. Reagents and Conditions: (i). OsO_4 (1% solution in H₂O), rt; (ii). $NaIO_4$, acetone/H₂O (4.5:1), THF, rt; (iii). $NaBH_4$, MeOH, rt; (iv). MsCl, NEt₃, CH₂Cl₂, rt; (v). MeNH₂ (2.0 M solution in THF), EtOH, 105 °C, sealed tube then chromatography on silica.

2.2. Synthesis of (±)-horsfiline 4

Having optimised reaction conditions and demonstrated the utility of this approach for the synthesis of (\pm) -*N*-benzyl-coerulescine **26**, this methodology was applied to the synthesis of (\pm) -horsfiline **4**. Addition of allylmagnesium bromide to *N*-benzyl-5-methoxyisatin **27** gave **28**, which was transformed to 3-allyl-5-methoxyoxindole **30** via chloride **29** in 70% overall yield over two steps. Indolyl carbonate formation, followed by *O*- to *C*-carboxyl transfer using 4 mol% of the NHC derived from triazolium salt **17** gave **32** in excellent yield (Scheme 4).

Subsequent ester reduction of **32** using NaBH₄/CaCl₂ in methanol gave a 55:45 mixture of the desired alcohol **33**: methyl ester **34** (presumably arising from competitive transesterification), with chromatographic separation giving **33** in 39% yield and **34** in 35% yield (Scheme 5). The molecular structures of **33** and **34** were both



Scheme 4. Reagents and conditions: (i). allyIMgBr, THF, -78 °C (10 min) then warm to 0 °C (20 min); (ii). SOCl₂, N(*i*-Pr)₂Et, CH₂Cl₂, rt, 25 min; then Zn (powder), AcOH, THF, 0 °C to rt; (iii). KHMDS, THF, -78 °C then PhOCOCl; (iv). KHMDS (4 mol %), salt **17** (5 mol %), THF, 15 min then indolyl carbonate **31**, rt, 1 h.

confirmed by X-ray diffraction (Figs. 7 and 8). Attempted conversion of methyl ester **34** to alcohol **33** under a range of conditions gave preferentially 3-allyl-5-methoxyoxindole **30** rather than the desired alcohol **33**, although further optimisation showed that reduction of phenyl ester **32** with LiAlH₄ in THF at -78 °C gave predominantly alcohol **33** in an improved 61% yield (Scheme 5).



Having optimised the preparation of key alcohol **33**, subsequent dihydroxylation, oxidative cleavage and reduction with NaBH₄ gave diol **35** in 83% yield over three steps. Bis-mesylation and treatment with methylamine, followed by purification on silica, gave *N*-benzylhorsfiline **37** in 65% yield over two steps.^{7,15} N-debenzylation following the procedure of Carreira et al.⁷ gave (\pm)-horsfiline **4** with comparable spectroscopic properties to the literature in 57% yield (Scheme 6).



Figure 7. Molecular representation of the X-ray crystal structure of 33. There are two molecules of 33 in the asymmetric unit cell, but only one representation is shown.



Figure 8. Molecular representation of the X-ray crystal structure of 34.

3. Conclusion

In conclusion, we have shown that NHC-mediated *O*-to *C*-carboxyl transfer of indolyl carbonates can be used to generate (\pm) -3-allyl-3-phenoxycarbonyloxindoles containing a quaternary stereocentre in good yield and with excellent catalytic efficiency. These products are readily functionalised to generate the spiro[pyrrolidine-3,3'-oxindole] motif, and have been used in the synthesis of (\pm) -*N*-benzyl-coerulescine **26** and (\pm) -horsfiline **4**. Current research is focused upon developing applications of NHCs and other Lewis-bases in asymmetric catalysis, and utilising this methodology in complex natural product synthesis.



Scheme 6. Reagents and conditions: (i). OsO₄ (1% wt solution in H₂O), rt; (ii). NalO₄, acetone/H₂O (4.5:1), THF, rt; (iii). NaBH₄, MeOH, rt; (iv). MsCl, NEt₃, CH₂Cl₂, rt; (v). MeNH₂ (2.0 M solution in THF), EtOH, 105 °C, sealed tube then chromatography on silica; (vi) Na, NH₃(l), -33 °C, 15 min.

4. General experimental

4.1. General

All reactions involving moisture sensitive reagents were performed under an atmosphere of argon using standard vacuum line techniques and with freshly distilled solvents. All glassware was flame dried and allowed to cool under vacuum.

Solvents were dried and purified either by distillation (under an atmosphere of nitrogen as described below) or obtained from a solvent purification system (MBraun, SPS-800). Methanol (MeOH) was distilled from CaH₂. Petrol refers to the fraction of petroleum ether boiling between 40 °C and 60 °C. Osmium tetroxide was prepared as a 1% wt solution in H₂O. All other reagents were used directly as supplied without further purification.

Flash column chromatography was carried out according to the method of Still³² with silica gel 60 (0.043–0.060 mm) (Merck) in the solvent system stated. Analytical thin layer chromatography was performed on commercially available pre-coated aluminium-backed plates (Merck silica Kieselgel 60 F₂₅₄). TLCs were visualised either by UV fluorescence (254 nm), or by staining with basic KMnO₄ solution.

Melting points were recorded on an Electrothermal apparatus and are uncorrected. Microanalyses were carried out on a Carlo Erba CHNS analyser. Infrared spectra were recorded on a Perkin-Elmer Spectrum GX FT-IR Spectrometer and analysed either as thin films between NaCl plates (thin film) or KBr discs (KBr disc) as stated. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm⁻¹) and only structurally significant peaks are quoted.

¹H and ¹³C nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (300 MHz ¹H, 75.4 MHz ¹³C), a Bruker Avance 400 (400 MHz ¹H, 100 MHz ¹³C) or a Bruker Avance 500 (500 MHz ¹H, 125 MHz ¹³C) spectrometer in the deuterated solvent stated. ¹³C NMR spectra were recorded with proton decoupling. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to residual solvent peaks or to SiMe₄ as an internal standard (δ =0.00). Coupling constants, *J*, are quoted in Hz. The abbreviations s, d, dd, dt, td, q and m denote singlet, doublet, doublet of doublets, doublet of triplets, triplet of doublets, quartet and multiplet, respectively. The abbreviation Ar is used to denote aromatic.

Mass spectrometric (m/z) data was acquired by electrospray ionisation (ESI) or chemical ionisation (CI), either at the University of St Andrews Mass Spectrometry facility ([M+Na] quoted) or at the EPSRC National Mass Spectrometry Service Centre, Swansea ([M+H]⁺, [2M+H]⁺, [M+Na]⁺ or [2M+Na]⁺ quoted). At the University of St Andrews, low and high resolution ESI MS was carried out on a Micromass LCT spectrometer. At the EPSRC National Mass Spectrometry Service Centre, CIMS was carried out on a Micromass Quattro II spectrometer. High resolution ESI was carried out on a Finnigan MAT 900 XLT; a Thermofisher LTQ Orbitrap XL spectrometer was used to obtain high resolution ESI MS for accurate mass determination but also provided fragmentation data for the characterisation of samples. Values are quoted as a ratio of mass to charge in Daltons.

Temperatures of 0 °C were obtained using an ice/water bath and of -78 °C were obtained using a dry ice/acetone bath.

Crystallographic data (excluding structure factors) for compounds **18**, **20**, **24**, **33** and **34** have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 746509, 746510, 746511, 746512 and 746513, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.2. General procedure A: rearrangement of carbonates

KHMDS (9, 4, or 1.5 mol%) was added to a stirred solution of triazolium salt **17** (10, 5 or 2 mol%, respectively) in THF (~10 mL/g of substrate) and stirred at rt for 30 min. The required carbonate was then added to the reaction mixture and stirred for 1 h at rt before concentration in vacuo.

4.3. General procedure B: dihydroxylation with OsO₄

Following the method described by Trost et al.,¹⁹ osmium tetroxide (0.02 equiv) was added to a solution of oxindole (1 equiv) and *N*-methylmorpholine-*N*-oxide (2.55 equiv) in CH₂Cl₂ (10 mL/mmol) and stirred at rt until deemed complete by TLC (typically 8–24 h). The reaction was quenched with satd aq Na₂SO₃ solution. The solution was diluted with CH₂Cl₂, the layers separated and the aqueous phase further extracted with CH₂Cl₂. The organic extracts were combined, dried (MgSO₄), filtered and concentrated in vacuo.

4.3.1. 3-Allyl-1-benzyl-3-hydroxy-2-oxo-2,3-dihydroindole 13.



To a stirred solution of *N*-benzylisatin (10.0 g, 50.6 mmol) in THF (210 mL) at -78 °C was slowly added allylmagnesium

bromide (1.0 M solution in Et₂O, 46.4 mL, 46.4 mmol) and the reaction mixture stirred at -78 °C for 10 min and then at 0 °C for 20 min. After this time, the reaction was quenched with satd aq NH₄Cl solution (210 mL) and extracted with EtOAc (150 mL×3). The organic extracts were combined, washed with H₂O (150 mL), brine (150 mL), dried (MgSO₄), filtered and concentrated in vacuo. Trituration with Et₂O gave **13** (6.55 g, 56%) as a yellow solid with spectroscopic data in accordance with the literature.³³ Mp 142–143 °C (Et₂O) (lit. Mp 124–126 °C);³³ $\delta_{\rm H}$ (300 MHz, CDCl₃) 7.43–7.38 (1H, m, ArH), 7.35–7.25 (5H, m, ArH), 7.25–7.17 (1H, m, ArH), 7.10–7.03 (1H, m, ArH), 6.72–6.68 (1H, m, ArH), 5.72–5.57 (1H, m, HC=CH₂), 5.20–5.08 (2H, m, HC=CH₂), 5.03 (1H, ABq, J_{AB}=15.6, CH_AH_BPh), 4.73 (1H, ABq, J_{AB}=15.6, CH_AH_BPh), 2.85 (1H, s, OH), 2.84–2.77 (1H, m, CH₂CH=CH₂), 2.73–2.65 (1H, m, CH₂CH=CH₂).

4.3.2. 3-Allyl-1-benzyl-2-oxo-2,3-dihydroindole 15.



Method 1: To a stirred suspension of **13** (589 mg, 2.11 mmol) in a solution of glacial AcOH (20 mL) and concd HCl (1.3 mL) was added stannous chloride dihydrate (1.43 g, 6.33 mmol) and the reaction mixture heated to 80 °C overnight. After cooling to rt, the solution was poured into H₂O and the aqueous phase extracted with Et₂O (50 mL×3). The organic extracts were combined, washed with 2 M NaOH (aq) solution (100 mL×3), dried (MgSO₄), filtered and concentrated in vacuo. Residual AcOH was removed azeotropically with toluene (×3). ¹H NMR analysis of the crude residue indicated it to be a 41:29:29 mixture of **13:14:15**.

Method 2: Following the method of Trost et al.,²⁷ to a stirred solution of 13 (6.07 g, 21.8 mmol) in anhydrous CH₂Cl₂ (200 mL) was added Hünig's base (11.4 mL, 65.3 mmol) and thionyl chloride (1.91 mL, 26.1 mmol) and the resulting solution stirred for 25 min. After this time, the reaction mixture was poured into satd aq NaHCO₃ solution (100 mL) and extracted with Et_2O (100 mL×3). The organic extracts were combined, dried (MgSO₄), filtered and concentrated in vacuo. The crude residue (chloride 14) was dissolved in THF (220 mL) and glacial acetic acid (22 mL) and cooled to 0 °C. Zinc powder (16.9 g, 259 mmol) was added and the resulting mixture allowed to warm to rt while stirring for 2 h. The reaction mixture was then filtered through a pad of Celite[®], the filtrate diluted with Et₂O (100 mL) then washed with H₂O (200 mL) and satd aq NaHCO₃ solution (3×150 mL), dried (MgSO₄), filtered and concentrated in vacuo. Chromatographic purification (petrol/Et₂O 80:20) gave 15 (6.81 g, 87%), as an off-white solid. Mp 59-62 °C (petrol); Found: C, 81.85; H, 6.25; N, 5.0; C₁₈H₁₇NO requires C, 82.1; H, 6.5; N, 5.3%; ν_{max} (KBr)/cm⁻¹ 3060, 2921, 1712, 1612, 1466, 750; $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.33–7.22 (6H, m, Ar*H*), 7.18–7.13 (1H, m, Ar*H*), 7.03–6.98 (1H, m, ArH), 6.70 (1H, d, J=7.7, C(7)H), 5.81–5.70 (1H, m, $HC=CH_2$), 5.17–5.10 (1H, m, $HC=CH_2$), 5.09–5.04 (1H, m, $HC=CH_2$), 4.99 (1H, ABq, J_{AB}=15.7, CH_AH_BPh), 4.83 (1H, ABq, J_{BA}=15.7, CH_AH_BPh), 3.61 (1H, dd, J=7.2 and 5.0, C(3)H), 2.93-2.84 (1H, m, CH₂CH=CH₂), 2.70-2.60 (1H, m, CH₂CH=CH₂); δ_C (100 MHz, CDCl₃) 177.3, 143.4, 135.9, 133.9, 128.7, 128.6, 127.9, 127.6, 127.3, 124.2, 122.3, 118.2, 109.0, 45.2, 43.7, 35.0; *m*/*z* (CI) 264 ([M+H]⁺, 100%); HRMS (ESI⁺) 264.1384 ([M+H]⁺ C₁₈H₁₈NO requires 264.1383 (+0.3 ppm)).

4.3.3. 3-Allyl-1-benzylindol-2-yl phenyl carbonate 16.



A solution of 15 (3.90 g, 14.8 mmol) in THF (28 mL) at $-78 \degree$ C was added slowly to a stirred solution of KHMDS (0.42 M solution in toluene, 42.3 mL, 17.8 mmol) in THF (28 mL) at -78 °C and stirred for 30 min. This solution was then transferred via cannula to a stirred solution of phenyl chloroformate (2.24 mL, 17.8 mmol) in THF (34 mL) at -78 °C and the resulting solution allowed to warm slowly to rt while stirring for 3 h. The reaction mixture was then poured into 0.1 N aq HCl (50 mL) and extracted with Et₂O (75 mL×3). The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo. Chromatographic purification (petrol/Et₂O 80:20) gave 16 (4.28 g, 76%) as a fluffy colourless solid. Mp 58–61 °C (petrol); v_{max} (KBr)/cm⁻¹ 3055, 1788, 1624, 1465, 1229, 1201, 739; δ_H (300 MHz, CDCl₃) 7.65-7.60 (1H, m, ArH), 7.46-7.07 (13H, m, ArH), 6.14-5.99 (1H, m, HC=CH₂), 5.31 (2H, s, CH₂Ph), 5.28-5.19 (1H, m, HC=CH₂), 5.16-5.09 (1H, m, HC= CH_2), 3.54 (2H, dt, *J*=6.3 and 1.5, CH₂CH= CH_2); δ_C (75 MHz, CDCl₃) 150.8, 150.6, 139.0, 137.0, 136.1, 132.4, 129.6, 128.8, 127.6, 126.7, 126.6, 126.0, 122.1, 120.6, 120.0, 119.4, 115.5, 109.6, 99.5, 46.0, 27.8; m/z (CI) 384 ([M+H]⁺, 30%), 264 ([M-CO₂Ph+H]⁺, 100%); HRMS (ESI⁺) 384.1597 ([M+H]⁺ C₂₅H₂₂NO₃ requires 384.1594 (+0.7 ppm)).

4.3.4. Phenyl-3-allyl-1-benzyl-2-oxo-2,3-dihydroindole carboxylate 18.



Catalyst loading (9 mol %): following general procedure A, KHMDS (0.5 M in toluene, 1.67 mL, 0.835 mmol, 9 mol %), triazolium salt **17** (253 mg, 0.927 mmol, 10 mol %), THF (35 mL) and 3allyl-1-benzylindol-2-yl phenyl carbonate **16** (3.55 g, 9.26 mmol) gave, after chromatographic purification (petrol/Et₂O 90:10), compound **18** (2.60 g, 73%) as a colourless solid.

Catalyst loading (4 mol %): following general procedure A, KHMDS (0.5 M in toluene, 46 μ L, 0.023 mmol, 4 mol %), triazolium salt **17** (8 mg, 0.029 mmol, 5 mol %), THF (1.1 mL) and 3-allyl-1-benzylindol-2-yl phenyl carbonate **16** (221 mg, 0.577 mmol) gave, after chromatographic purification (petrol/Et₂O 90:10), compound **18** (154 mg, 70%) as a colourless solid.

Catalyst loading (1.5 mol %): following general procedure A, KHMDS (0.5 M in toluene, 27 µL, 0.014 mmol, 1.5 mol %), triazolium salt **17** (5 mg, 0.018 mmol, 2 mol %), THF (0.9 mL) and 3-allyl-1-benzylindol-2-yl phenyl carbonate **16** (346 mg, 0.902 mmol) gave, after chromatographic purification (petrol/Et₂O 90:10), compound **18** (170 mg, 49%) as a colourless solid. Mp 62–64 °C (petrol); Found: C, 78.6; H, 5.25; N, 3.9. C₂₅H₂₁NO₃ requires C, 78.3; H, 5.5; N, 3.65%; ν_{max} (KBr)/cm⁻¹ 3061, 2902, 1754, 1721, 1609, 1466, 1210, 1186, 753; $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.40–7.18 (10H, m, ArH), 7.13–7.06 (1H, m, ArH), 7.00–6.95 (2H, m, ArH),

6.76–6.71 (1H, m, C(7)*H*), 5.53–5.41 (1H, m, *HC*=CH₂), 5.18–5.12 (1H, m, HC=CH₂), 5.04 (1H, ABq, J_{AB} =15.8, CH_AH_BPh), 5.02–4.98 (1H, m, HC=CH₂), 4.94 (1H, ABq, J_{BA} =15.8, CH_AH_BPh), 3.21–3.10 (2H, m, CH₂CH=CH₂); δ_{C} (100 MHz, CDCl₃) 173.5, 167.7, 150.4, 143.5, 135.4, 130.9, 129.4 (2C), 128.8, 127.7, 127.2 (2C), 126.2, 123.6, 123.0, 121.2, 120.3, 109.7, 59.4, 44.0, 38.0; *m/z* (CI) 401 ([M+NH₄]⁺, 55%), 384 ([M+H]⁺, 100%); HRMS (ESI⁺) 384.1593 ([M+H]⁺ C₂₅H₂₂NO₃ requires 384.1594 (–0.2 ppm)).

4.3.5. 1'-Benzyl-5-(hydroxymethyl)-4,5-dihydro-2H-spiro[furan-3,3'-indolin]-2,2'-dione **19**.



Following general procedure B, osmium tetroxide (130 µL, 1% solution in H₂O), 18 (100 mg, 0.26 mmol) and N-methylmorpholine-N-oxide (78 mg, 0.66 mmol) in CH₂Cl₂ (2 mL) gave, after chromatographic purification (petrol/Et₂O 80:20), both diastereomers of 19, major (33 mg, 39%); minor (19 mg, 23%) as colourless gums. Major diastereomer: ν_{max} (KBr)/cm⁻¹ 3430, 2928, 1767, 1714, 1611, 1489, 1468, 1170, 734; $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.28-7.12 (7H, m, ArH), 7.02-6.95 (1H, m, ArH), 6.70-6.65 (1H, m, C(7)H), 4.98–4.88 (1H, m, CHCH₂OH), 4.98 (1H, ABq, J_{AB}=15.8, CH_AH_BPh), 4.77 (1H, ABq, J_{BA}=15.8, CH_AH_BPh), 3.96 (1H, dd, J=12.6 and 4.0, CH_AH_BOH), 3.90 (1H, dd, J=12.6 and 3.9, CH_AH-_BOH), 2.85 (1H, dd, *I*=13.5 and 7.9, CH_AH_BCHCH₂OH), 2.56 (1H, dd, J=13.5 and 7.5, $CH_AH_BCHCH_2OH$; δ_C (75 MHz; $CDCl_3$) 173.9, 172.3, 143.0, 135.0, 129.8, 129.0, 128.6, 127.9, 127.1, 123.6, 122.7, 110.2, 79.5, 64.3, 56.8, 44.3, 34.0; *m/z* (ESI⁺) 346 ([M+Na], 100%); HRMS (ESI⁺) 346.1064 ([M+Na] C₁₉H₁₇NNaO₄ requires 346.1055 (+2.6 ppm)); Minor diastereomer: $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.36–7.21 (7H, m, ArH), 7.11-7.05 (1H, m, ArH), 6.77-6.72 (1H, m, C(7)H), 5.24–5.16 (1H, m, CHCH₂OH), 4.99 (1H, ABq, J_{AB}=15.8, CH_AH_BPh), 4.85 (1H, ABq, J_{BA}=15.8, CH_AH_BPh), 4.19-4.11 (1H, m, CH₂OH), 3.80-3.70 (1H, m, CH2OH), 2.87-2.74 (2H, m, CH2CHCH2OH) and 2.24 (1H, s, OH).

4.3.6. 3-Allyl-1-benzyl-3-(hydroxymethyl)-2-oxo-2,3-dihydroindole **20**.



Following the method described by Loreto et al.,³⁰ sodium borohydride (163 mg, 4.30 mmol) was added to a suspension of **18** (550 mg, 1.43 mmol) and calcium chloride (239 mg, 2.15 mmol) in MeOH (3.5 mL) at 0 °C and the resulting mixture stirred for 4 h then warmed to rt and stirred overnight before concentration in vacuo. 3 N citric acid was added dropwise until reaching pH 2–3 before extracting with CH₂Cl₂ (25 mL×3). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo to give, after chromatographic purification (petrol/Et₂O 90:10), **20** (340 mg, 80%) as a colourless solid. Mp 136–138 °C (petrol); ν_{max} (KBr)/cm⁻¹ 3440, 3053, 2923, 1691, 1614, 1490, 1465, 1182, 743; $\delta_{\rm H}$ (300 MHz, CDCl₃) 7.35–7.24 (6H, m, ArH), 7.19 (1H, td, *J*=7.7 and 1.3, ArH), 7.07 (1H, td, *J*=7.5 and 0.9, ArH), 6.73 (1H, d, *J*=7.7, C(7)H), 5.55–5.41 (1H, m, HC=CH₂), 5.13–5.05 (1H, m, HC=CH₂), 5.03–4.95 (1H, m, HC=CH₂), 4.99 (1H, ABq, *J*_{AB}=15.7, CH_AH_BPh), 4.88 (1H, ABq, *J*_{BA}=15.7, CH_AH_BPh), 4.88 (1H, ABq, *J*_{BA}=15.7, CH_AH_BPh), 3.98 (1H, dd, *J*=11.0 and 9.4, CH₂OH), 3.84 (1H, dd, *J*=11.0 and 3.5, CH₂OH), 2.82–2.74 (1H, m, CH₂CH=CH₂), 2.72–2.64 (1H, m, CH₂CH=CH₂), 2.32 (1H, dd, *J*=9.4 and 3.5, CH₂OH); $\delta_{\rm C}$ (75 MHz, CDCl₃) 179.3, 143.7, 136.0, 132.3, 129.8, 129.2, 128.8, 128.0, 127.6, 123.7, 123.1, 119.7, 109.8, 67.2, 54.7, 44.1, 37.8; *m/z* (ESI⁺) 316 ([M+Na], 100%); HRMS (ESI⁺) 316.1303 ([M+Na] C₁₉H₁₉NNaO₂ requires 316.1313 (–3.3 ppm)).

4.3.7. 3-Allyl-1-benzyl-1H-indole 21.



Lithium aluminium hydride (1.0 M solution in THF, 0.156 mL, 0.156 mmol) was added to a suspension of **18** (60 mg, 0.156 mmol) in THF (0.6 mL) at 0 °C and stirred for 2 h. The reaction was then warmed to rt and stirred overnight before being quenched with ice/water and extracted with CH₂Cl₂ (25 mL×3). The organic extracts were combined, dried (MgSO₄) and concentrated in vacuo to give, after chromatographic purification (petrol/Et₂O 80:20), **21** (17 mg, 44%) as a colourless gum with spectroscopic data in accordance with the literature.³⁴ $\delta_{\rm H}$ (300 MHz, CDCl₃) 7.57–7.50 (1H, m, C(4)H), 7.25–7.13 (4H, m, ArH), 7.12–7.06 (1H, m, ArH), 7.06–6.99 (3H, m, ArH), 6.84 (1H, s, C(2)H), 6.06–5.92 (1H, m, HC=CH₂), 5.19 (2H, s, NCH₂Ph), 5.12–5.04 (1H, m, HC=CH₂), 5.01–4.95 (1H, m, HC=CH₂), 3.45 (2H, ddd, *J*=6.5, 2.4 and 1.3, CH₂CH=CH₂).

4.3.8. 1-Benzyl-3-(2,3-dihydroxypropyl)-3-(hydroxymethyl)-2-oxo-2,3-dihydroindole **22**.



ABq, J_{AB} =10.7, CH_AH_BOH), 3.86 (1H, ABq, J_{BA} =10.7, CH_AH_BOH), 3.62– 3.55 (1H, m, $CH(OH)CH_2OH$), 3.33–3.29 (2H, m, $CH(OH)CH_2OH$), 2.13–1.99 (2H, m, $CH_2CH(OH)CH_2OH$); δ_C (75 MHz, CD_3OD) 181.8, 145.3, 137.6, 131.7, 129.6, 128.9, 128.3 (2C), 124.8, 123.5, 110.4, 70.1, 68.8, 67.7, 55.1, 44.7, 37.0; m/z (ESI⁺) 350 ([M+Na], 100%); HRMS (ESI⁺) 350.1375 ([M+Na] $C_{19}H_{21}NNaO_4$ requires 350.1368 (+2.0 ppm)).

4.3.9. 1'-Benzyl-5-hydroxy-2',3',4,5-tetrahydro-2H-spiro[furan-3,3'-indolin]-2'-one **23**.



Sodium periodate (73 mg, 0.341 mmol) was added to a solution of 22 (60 mg, 0.183 mmol) in acetone (0.9 mL) and H₂O (0.2 mL) and the solution stirred at rt for 4 h. The solution was then diluted with H₂O (20 mL) and Et₂O (20 mL), the lavers separated and the aqueous phase further extracted with $Et_2O(25 \text{ mL} \times 3)$. The organic extracts were combined, dried (MgSO₄) and concentrated in vacuo to give, after chromatographic purification (EtOAc/petrol 50:50), a 78:22 mixture of diastereomers of lactol 23 (45 mg, 83%) as a colourless foam. $\nu_{\rm max}$ (KBr)/cm⁻¹ 3365, 3062, 2942, 1685, 1613, 1489, 1467, 1174, 1028, 730; δ_H (300 MHz, CDCl₃) 7.39–7.07 (8H, m, ArH), 6.83–6.79 (1H, m, C(7)H), 6.28 (1H, d, J=12.1, OH), 5.75 (1H, dd, J=12.1 and 4.8, CHOH), 4.96 (2H, s, CH2Ph), 4.48 (1H, ABq, J_{AB}=9.0, CH_AH_BOCHOH), 4.11 (1H, ABq, J_{BA}=9.0, CH_AH_BOCHOH), 2.55 (1H, dd, J=13.5 and 4.8, CH_AH_BCHOH), 2.41 (1H, d, J=13.5, CH_A*H*_BCHOH); δ_C (75 MHz, CDCl₃) 181.6, 142.7, 135.2, 130.2, 129.0, 128.8, 128.0, 127.4, 123.8, 122.6, 109.7, 100.6, 76.0, 53.7, 44.4, 44.2; m/z (ESI⁺) 318 ([M+Na], 100%); HRMS (ESI⁺) 318.1112 ([M+Na] C₁₈H₁₇NaNO₃ requires 318.1106 (+2.0 ppm)).

4.3.10. 1-Benzyl-3-(2-hydroxyethyl)-3-(hydroxymethyl)-2-oxo-2,3-dihydroindole **24**.



Following general procedure B, osmium tetroxide (187 µL, 1% solution in water), **20** (110 mg, 0.38 mmol) and *N*-methylmorpholine-*N*-oxide (112 mg, 0.96 mmol) in CH₂Cl₂ (3 mL) gave, after trituration with EtOAc, a 61:39 mixture of diastereomers of **22** (50 mg, 41%) as a colourless solid. The mother liquor was concentrated in vacuo to give, after chromatographic purification (EtOAc/petrol 80:20 \rightarrow 100% EtOAc \rightarrow EtOAc/MeOH 95:5), a further 21:79 mixture of diastereoisomers of **22** (62 mg, 51%). Mp 146–150 °C (EtOAc); ν_{max} (KBr)/cm⁻¹ 3495, 3444, 2933, 2917, 1658, 1611, 1492, 1467, 1183, 1077, 763; $\delta_{\rm H}$ (400 MHz, CD₃OD) 7.44–7.13 (7H, m, ArH), 7.11–7.05 (1H, m, ArH), 6.82–6.76 (1H, m, C(7)H), 5.05 (1H, ABq, J_{AB} =15.9, CH_AH_BPh), 4.89 (1H, ABq, J_{AB} =15.9, CH_AH_BPh), 3.99 (1H, Sodium borohydride (0.01 g, 0.264 mmol) was added to a solution of **23** (40 mg, 0.135 mmol) in MeOH (0.2 mL) and the solution stirred at rt for 1.5 h. The solution was then quenched with 1 N HCl (1.5 mL) diluted with H₂O (20 mL), extracted with EtOAc (25 mL×3), dried (MgSO₄) and concentrated in vacuo to give, after chromatographic purification (EtOAc/petrol 80:20), **24** (27 mg, 67%) as a colourless solid. Mp 142–146 °C; ν_{max} (KBr)/cm⁻¹ 3460, 2920, 2875, 1675, 1612, 1491, 1466, 1185, 1028, 743; δ_{H} (300 MHz, CD₃OD) 7.39–7.14 (7H, m, ArH), 7.08 (1H, td, *J*=7.5 and 1.0, ArH), 6.81–6.75 (1H, m, C(7)H), 4.99 (1H, ABq, *J*_{AB}=15.9, CH_AH_BPh), 4.91 (1H, ABq, *J*_{BA}=15.9, CH_AH_BPh), 3.84 (1H, ABq, *J*_{AB}=10.6, CH_AH_BOH), 3.33–3.22 (2H, m, CH₂CH₂OH), 2.23–2.01 (2H, m, CH₂CH₂OH); δ_{C}

(75 MHz, CD₃OD) 181.9, 145.6, 138.3, 132.4, 130.5, 129.9, 129.3, 129.1, 125.4, 124.6, 111.3, 69.1, 59.7, 55.9, 45.4, 37.4; m/z (ESI⁺) 320 ([M+Na], 100%); HRMS (ESI⁺) 320.1274 ([M+Na] C₁₈H₁₉NNaO₃ requires 320.1263 (+3.6 ppm)).

4.3.11. 2-(1-Benzyl-3-((methylsulfonyloxy)methyl)-2-oxo-2,3-dihydroindol-3-yl)ethyl methanesulfonate **25**.



To a solution of 24 (295 mg, 0.990 mmol) and triethylamine (0.290 mL, 2.08 mmol) in CH₂Cl₂ (6.5 mL) at 0 °C was added dropwise mesyl chloride (0.160 mL, 2.08 mmol) and the resulting mixture stirred for 2 h. The reaction mixture was then warmed to rt and stirred overnight before quenching with satd ag NaHCO₃ solution (10 mL), CH₂Cl₂ (25 mL) and brine (10 mL) were added. the layers separated and the aqueous phase further extracted with CH_2Cl_2 (15 mL×3). The organic extracts were combined, dried (MgSO₄) and concentrated in vacuo to give, after chromatographic purification (EtOAc/petrol $50:50 \rightarrow 100\%$ EtOAc), **25** (383 mg, 85%) as a colourless foam. v_{max} (KBr)/cm⁻¹ 2921, 1708, 1612, 1174; δ_{H} (300 MHz, CDCl₃) 7.39-7.22 (7H, m, ArH), 7.13 (1H, td, J=7.5 and 0.8, ArH), 6.82 (1H, d, J=7.8, ArH), 5.15 (1H, ABq, J_{AB}=15.8, CH_AH_BPh), 4.77 (1H, ABq, J_{BA}=15.8, CH_AH_BPh), 4.58 (1H, ABq, J_{AB}=9.7, CH_AH_BOMs), 4.43 (1H, ABq, J_{BA}=9.7, CH_AH_BOMs), 4.18-3.98 (2H, m, CH2OMs), 2.75 (3H, s, CH3), 2.68 (3H, s, CH3), 2.58-2.44 (1H, m, CH₂), 2.35–2.25 (1H, m, CH₂); δ_{C} (75 MHz, CDCl₃) 176.0, 143.7, 135.8, 130.0, 129.4, 128.3, 127.6, 127.3, 124.4, 123.7, 110.3, 72.8, 65.3, 50.9, 44.5, 37.6 (2C), 32.3; m/z (ESI⁺) 476 ([M+Na], 100%); HRMS (ESI⁺) 476.0811 ([M+Na] C₂₀H₂₃NaNO₇S₂ requires 476.0814 (-0.2 ppm)).

4.3.12. N-Benzyl-coerulescine 26.



To a solution of **25** (35 mg, 0.077 mmol) in EtOH (0.4 mL) was added methylamine (2.0 M solution in THF, 0.12 mL, 0.23 mmol) and the solution heated to 105 °C in a sealed tube overnight. The solution was concentrated in vacuo, the residue dissolved in CH₂Cl₂ (10 mL), washed with 0.1 N HCl (aq) (5 mL×2), dried (MgSO₄), filtered and concentrated in vacuo. Chromatographic purification (EtOAc/petrol 50:50 \rightarrow 100% EtOAc) gave **26** (55 mg, 71%) as a colourless gum with spectroscopic data in accordance with the literature.¹⁵ $\delta_{\rm H}$ (300 MHz, CDCl₃) 7.45 (1H, dd, *J*=7.3 and 0.9, Ar*H*), 7.36–7.24 (5H, m, PhH), 7.15 (1H, td, *J*=7.7 and 1.4, Ar*H*), 7.04 (1H, td, *J*=7.5 and 1.0, Ar*H*), 6.70 (1H, d, *J*=7.3, Ar*H*), 4.92 (2H, s, CH₂Ph), 3.15–3.07 (1H, m, CH₂), 2.94 (1H, ABq, *J*=9.2, CH_AH_B), 2.79 (1H, q, *J*=8.3, CH₂), 2.49 (3H, s, NCH₃), 2.48–2.40 (1H, m, CH₂), 2.14 (1H, dt, *J*=12.7 and 7.7, CH₂); $\delta_{\rm C}$ (75 MHz, CDCl₃)

180.6, 142.1, 136.1, 136.0, 128.9, 127.7, 127.7, 127.4, 123.2, 123.0, 108.9, 66.7, 56.9, 53.5, 43.9, 42.1, 38.2.

4.3.13. 3-Allyl-1-benzyl-3-hydroxy-5-methoxy-2-oxo-2,3-dihy-droindole **28**.



To a stirred solution of 27^{35} (5.50 g, 1.87 mmol) in THF (100 mL) cooled to -78 °C was slowly added allylmagnesium bromide (22.6 mL, 22.6 mmol, 1.0 M solution in Et₂O) and the reaction mixture stirred at -78 °C for 10 min and then at 0 °C for 20 min. After this time, the reaction was guenched with satd ag NH₄Cl solution (210 mL) and extracted with EtOAc (150 mL×3). The organic extracts were combined, washed with H₂O (150 mL), brine (150 mL), dried (MgSO₄), filtered and concentrated in vacuo. Trituration with Et₂O gave 28 as a yellow solid (3.89 g). Chromatographic purification (petrol/EtOAc 80:20) of the mother liquor also gave 28 as an orange solid (806 mg). Total yield: 4.70 g, 74%. Mp 151–153 °C; v_{max} (KBr)/cm⁻¹ 3277, 2935, 1694, 1610, 1184, 811; $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.37–7.24 (5H, m, ArH), 7.05 (1H, d, J=2.5, C(4)H), 6.74 (1H, dd, J=8.5 and 2.5, C(6)H), 6.61 (1H, d, J=8.5, C(7)H), 5.72-5.59 (1H, m, C(3)CH₂CHCH₂), 5.23-5.10 (2H, m, C(3)CH₂CHCH₂), 5.03 (1H, ABq, J_{AB}=15.7, CH_AH_BPh), 4.73 (1H, ABq, I_{BA}=15.7, CH_AH_BPh), 3.79 (3H, s, OCH₃), 3.48 (1H, s, OH), 2.88–2.68 (2H, m, C(3)CH₂CHCH₂); δ_C (75 MHz, CDCl₃) 177.9, 156.3, 135.7, 135.5, 131.0, 130.6, 128.8, 127.7, 127.3, 120.6, 114.2, 111.3, 110.1, 76.4, 55.8, 43.9, 43.1; *m*/*z* (ESI⁺) 619 ([2M+H]⁺, 65%), 310.1 ([M+H]⁺, 100%); HRMS (ESI⁺) 310.1443 ([M+H]⁺ C₁₉H₂₀NO₃⁺ requires 310.1438 (+1.7 ppm)).

4.3.14. 3-Allyl-1-benzyl-3-chloro-5-methoxy-2-oxo-2,3-dihydro-indole **29**.



To a solution of **28** (0.326 g, 1.06 mmol) in CH₂Cl₂ (10 mL) was added Hünig's base (0.550 mL, 3.16 mmol) and thionyl chloride (90 µL, 1.26 mmol). The resultant solution was stirred at rt for 15 min, then poured into satd aq NaHCO₃ solution and the mixture extracted with Et₂O (25 mL×3). The organic extracts were combined, dried (MgSO₄), filtered and concentrated to afford, after chromatographic purification (petrol/Et₂O 85:15), chloride 29 (260 mg, 75%) as a dark yellow oil. ν_{max} (thin film)/cm⁻¹ 2927, 1726, 1603, 1496, 1178, 732, 697; δ_H (300 MHz, CDCl₃) 7.28–7.15 (5H, m, ArH), 6.94 (1H, d, J=2.5, C(4)H), 6.66 (1H, dd, J=8.6 and 2.5, C(6)H), 6.51 (1H, d, J=8.6, C(7)H), 5.54-5.39 (1H, m, C(3)CH₂CHCH₂), 5.14-5.00 (2H, m, C(3)CH₂CHCH₂), 4.90 (1H, ABq, J_{AB}=15.7, CH_AH_BPh), 4.74 (1H, ABq, J_{BA}=15.7, CH_AH_BPh), 3.70 (3H, s, OCH₃), 3.04–2.89 (2H, m, C(3)CH₂CHCH₂); δ_C (100 MHz, CDCl₃) 173.5, 156.4, 135.2, 135.1, 130.2 (2C), 128.8, 127.8, 127.2, 121.2, 114.7, 111.5, 110.3, 64.2, 55.9, 44.2, 43.3; m/z (ESI⁺) 328 ([M (³⁵Cl)+H]⁺, 100%), 330 ([M $(^{37}\text{Cl})+\text{H}]^+,$ 30%); HRMS (ESI⁺) 328.1102 ([M+H]^+ C_{19}\text{H}_{19}{}^{35}\text{ClNO}_2^+ requires 328.1099 (+1.0 ppm)).

4.3.15. 3-Allyl-1-benzyl-5-methoxy-2-oxo-2,3-dihydroindole 30.



Method 1: To a stirred solution of **29** (353 mg, 1.08 mmol) in THF (11 mL) was added glacial acetic acid (1.1 mL) and the resultant solution cooled to 0 °C. Zinc powder (1.06 g, 16.2 mmol) was then added and the resulting mixture allowed to warm to rt while stirring for 2 h. The reaction mixture was filtered through a pad of Celite[®], the filtrate diluted with Et₂O (20 mL), washed with H₂O (20 mL), satd aq NaHCO₃ solution (3×40 mL), dried (MgSO₄), filtered and concentrated in vacuo. Chromatographic purification (petrol/Et₂O 80:20) gave **30** as a yellow oil (260 mg, 82%).

Method 2: Following the method of Trost et al.,²⁷ to a stirred solution of 28 (4.45 g, 14.4 mmol) in anhydrous CH₂Cl₂ (140 mL) was added Hünig's base (7.50 mL, 43.2 mmol) and thionyl chloride (1.26 mL, 17.3 mmol) and the resulting solution stirred for 15 min. After this time, the reaction mixture was poured into satd aq NaHCO₃ solution (100 mL) and extracted with Et₂O (50 mL×3). The organic extracts were combined, dried (MgSO₄), filtered and concentrated in vacuo. The crude residue (chloride 29) was dissolved in THF (140 mL) and glacial acetic acid (10 mL) then cooled to 0 °C. Zinc powder (14.1 g, 216 mmol) was added and the resulting mixture allowed to warm to rt while stirring for 2 h. The reaction mixture was filtered through a pad of Celite[®], the filtrate diluted with Et₂O (100 mL), washed with H₂O (200 mL), satd aq NaHCO₃ solution (3×100 mL), dried (MgSO₄), filtered and concentrated in vacuo. Chromatographic purification (petrol/Et₂O 80:20) gave **30** as a yellow-brown oil, which solidified on standing (2.96 g, 70% over two steps). Mp 46–48 °C; ν_{max} (thin film)/ cm^{-1} 2925, 1707, 1600, 1493, 1177, 694; δ_H (300 MHz, CDCl₃) 7.38–7.22 (5H, m, ArH), 6.94 (1H, dd, J=2.5 and 0.9, C(4)H), 6.73-6.67 (1H, m, C(6)H), 6.63-6.59 (1H, m, C(7)H), 5.86-5.70 (1H, m, C(3)CH₂CHCH₂), 5.22–5.07 (2H, m, C(3)CH₂CHCH₂), 4.99 (1H, ABq, J_{AB}=15.7, CH_AH_BPh), 4.83 (1H, ABq, J_{BA}=15.7, CH_AH_BPh), 3.77 (3H, s, OCH₃), 3.61 (1H, dd, J=7.3 and 4.9, C(3)H), 2.96-2.85 (1H, m, C(3)CH₂CHCH₂), 2.73-2.61 (1H, m, C(3)CH₂CHCH₂); δ_C(100 MHz, CDCl₃) 176.9, 155.7, 136.9, 136.0, 133.9, 130.0, 128.7, 127.5, 127.3, 118.3, 111.9 (2C), 109.2, 55.8, 45.6, 43.8, 35.0; m/z (ESI⁺) 609 ([2M+Na]⁺, 15%), 587 ([2M+H]⁺, 20%), 316 $([M+Na]^+, 10\%), 294 ([M+H]^+, 100\%); HRMS (ESI^+) 294.1491$ $([M+H]^+ C_{19}H_{20}NO_2^+ requires 294.1489 (+0.8 ppm)).$

4.3.16. 3-Allyl-1-benzyl-5-methoxyindol-2-yl phenyl carbonate 31.



A solution of **30** (2.78 g, 9.47 mmol) in THF (20 mL) at -78 °C was added slowly to a stirred solution of KHMDS (0.5 M solution in toluene, 22.8 mL, 11.4 mmol) at -78 °C and stirred for 30 min. This solution was then transferred via cannula to a stirred solution of phenyl chloroformate (1.43 mL, 11.4 mmol) in THF (20 mL) at -78 °C and the

resulting solution allowed to warm slowly to rt while stirring for 3 h. The reaction mixture was then poured into 0.1 N aq HCl (50 mL) and extracted with Et₂O (50 mL×3). The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo. Recrystallisation (Et₂O/petrol) afforded **31** (1.52 g, 39%) as a beige solid. Mp 90–92 °C; ν_{max} (KBr)/cm⁻¹ 2956, 1792, 1591, 1224, 1199, 741; $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.44–7.37 (2H, m, ArH), 7.35–7.25 (4H, m, ArH), 7.22–7.18 (2H, m, ArH), 7.14–7.06 (4H, m, ArH), 6.88–6.83 (1H, m, ArH), 6.11–5.99 (1H, m, C(3)CH₂CHCH₂), 5.27 (2H, s, CH₂Ph), 5.27–5.20 (1H, m, C(3)CH₂CHCH₂), 5.15–5.10 (1H, m, C(3)CH₂CHCH₂), 3.87 (3H, s, OCH₃), 3.53–3.48 (2H, m, C(3)CH₂CHCH₂); $\delta_{\rm C}$ (75 MHz, CDCl₃) 154.3, 150.8, 150.6, 139.4, 136.0, 137.0, 129.6, 128.8, 127.6, 127.4, 126.7, 126.6, 126.4, 120.6, 115.5, 111.7, 110.6, 101.8, 99.3, 55.9, 46.2, 27.9; m/z (ESI⁺) 414 ([M+H]⁺, 100%); HRMS (ESI⁺) 414.1698 ([M+H]⁺ C₂₆H₂₄NO₄⁺ requires 414.1700 (–0.4 ppm)).

4.3.17. Phenyl-3-allyl-1-benzyl-5-methoxy-2-oxo-2,3-dihydroindole-3-carboxylate **32**.



Following general procedure A, KHMDS (0.50 M solution in toluene, 0.090 mL, 0.045 mmol, 9 mol %), triazolium salt **17** (13.7 mg, 0.050 mmol, 10 mol %), THF (1.0 mL) and **31** (206 mg, 0.500 mmol) gave, after 1 h and chromatographic purification (petrol/Et₂O 90:10 \rightarrow 80:20), **32** (205 mg, 0.496 mmol, 99%) as a yellow solid. Mp 101–103 °C; v_{max} (KBr)/cm⁻¹ 2922, 1751, 1717, 1599, 1187, 1160, 702; δ_{H} (400 MHz, CDCl₃) 7.28–7.10 (8H, m, ArH), 6.94–6.89 (3H, m, ArH), 6.69–6.67 (1H, m, ArH), 6.56–6.53 (1H, m, ArH), 5.47–5.34 (1H, m, C(3)CH₂CHCH₂), 5.12–5.05 (1H, m, C(3)CH₂CHCH₂), 4.96–4.80 (3H, m, CH₂Ph, C(3)CH₂CHCH₂), 3.69 (3H, s, OCH₃), 3.06 (2H, d, *J*=7.3, C(3)CH₂CHCH₂); δ_{C} (125 MHz, CDCl₃) 172.1, 166.7, 155.1, 149.3, 135.7, 134.4, 129.8, 128.4, 127.7, 127.3, 126.6, 126.2, 125.1, 120.2, 119.3, 112.6, 109.8, 109.1, 58.7, 54.8, 43.0, 37.0; *m*/*z* (ESI⁺) 414 ([M+H]⁺, 100%); HRMS (ESI⁺) 414.1699 ([M+H]⁺ C₂₆H₂₄NO⁺₄ requires 414.1700 (–0.2 ppm)).

4.3.18. 3-Allyl-1-benzyl-3-hydroxymethyl-5-methoxy-2-oxo-2,3-dihydroindole **33** and methyl 3-allyl-1-benzyl-5-methoxy-2-oxo-2,3dihydroindole-3-carboxylate **34**.



Method 1: Following the method described by Loreto et al.,³⁰ sodium borohydride (0.192 g, 5.08 mmol) was added to a suspension of **32** (1.05 g, 2.54 mmol) and calcium chloride (0.282 g, 2.54 mmol) in MeOH (5 mL) at 0 °C and the resulting mixture stirred for 4 h. The reaction was then warmed to rt and stirred overnight before concentration in vacuo. 3 N citric acid was added dropwise until reaching pH 2–3 before extracting with CH₂Cl₂ (25 mL×3). The organic extracts were combined, dried (Na₂SO₄) and concentrated in vacuo to give, after chromatographic purification (petrol/Et₂O 80:20 \rightarrow 40:60), **33** (318 mg, 39%) as a colourless solid and **34** (316 mg, 35%) as a yellow solid.

Method 2: To a stirred solution of **32** (103 mg, 0.250 mmol) in THF (2.0 mL) at -78 °C was added LiAlH₄ (2.0 M solution in THF, 0.075 mL, 0.150 mmol) dropwise and the resulting solution stirred at -78 °C for 45 min before the addition of EtOAc (10 mL) and 0.1 N HCl (10 mL). The mixture was allowed to warm to rt, the organic layer separated and the aqueous layer extracted with EtOAc (10 mL×3). The combined organic layers were washed with brine (10 mL), dried (MgSO₄) and concentrated in vacuo to give, after chromatographic purification (petrol/Et₂O 80:20→40:60), **33** as a colourless solid (49 mg, 0.152 mmol, 61%).

Data for **33**: mp 94–96 °C; ν_{max} (KBr)/cm⁻¹ 3449, 2947, 1691, 1601, 1180, 695; $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.32–7.22 (5H, m, Ar*H*), 6.85 (1H, d, *J*=2.5, Ar*H*), 6.71–6.66 (1H, m, Ar*H*), 6.61–6.57 (1H, m, Ar*H*), 5.54–5.42 (1H, m, C(3)CH₂CHCH₂), 5.12–5.05 (1H, m, C(3)CH₂CHCH₂), 5.00–4.95 (1H, m, C(3)CH₂CHCH₂), 4.96 (1H, ABq, *J*_{AB}=15.8, CH_AH_BPh), 4.84 (1H, ABq, *J*_{BA}=15.8, CH_AH_BPh), 3.99–3.91 (1H, m, CH_AH_BOH), 3.81 (1H, dd, *J*=10.9 and 3.4, CH_AH_BOH), 3.76 (3H, s, OCH₃), 2.80–2.72 (1H, m, C(3)CH₂CHCH₂), 2.68–2.61 (1H, m, C(3)CH₂CHCH₂), 2.34 (1H, dd, *J*=9.3 and 3.4, CH₂OH); $\delta_{\rm C}$ (75 MHz, CDCl₃) 178.6, 156.0, 136.7, 135.7, 131.9, 130.9, 128.7, 127.6, 127.2, 119.3, 112.3, 111.1, 109.7, 66.8, 55.8, 54.6, 43.8, 37.4; *m/z* (ESI⁺) 346 ([M+Na]⁺, 30%), 324 ([M+H]⁺, 100%); HRMS (ESI⁺) 324.1598 ([M+H]⁺ C₂₀H₂₂NO₃⁺ requires 324.1599 (-0.4 ppm)).

Data for **34**: mp 109–111 °C; ν_{max} (KBr)/cm⁻¹ 2957, 1743, 1701, 1604, 1228, 1200, 695; $\delta_{\rm H}$ (300 MHz, CDCl₃) 7.31–7.26 (5H, m, Ar*H*), 6.88 (1H, d, *J*=2.5, Ar*H*), 6.71 (1H, dd, *J*=8.5 and 2.6, Ar*H*), 6.59–6.55 (1H, m, Ar*H*), 5.47–5.30 (1H, m, C(3)CH₂CHCH₂), 5.14–5.06 (1H, m, C(3)CH₂CHCH₂), 4.99–4.95 (1H, m, C(3)CH₂CHCH₂), 4.91 (2H, s, CH₂Ph), 3.75 (3H, s, OCH₃), 3.70 (3H, s, OCH₃), 3.07–3.01 (2H, m, C(3)CH₂CHCH₂); $\delta_{\rm C}$ (75 MHz; CDCl₃) 173.5, 169.6, 156.1, 136.7, 135.5, 131.0, 128.7 (2C), 127.6, 127.3, 120.1, 113.5, 110.8, 109.9, 59.6, 55.8, 53.1, 44.0, 38.2; *m*/*z* (ESI⁺) 352 ([M+H]⁺, 100%); HRMS (ESI⁺) 352.1545 ([M+H]⁺ C₂₁H₂₂NO₄⁺ requires 352.1543 (+0.5 ppm)).

4.3.19. 1-Benzyl-3-(2-hydroxyethyl)-3-(hydroxymethyl)-5-methoxy-2-oxo-2,3-dihydroindole **35**.



Following general procedure B, osmium tetroxide (234 µL, 1% wt solution in H₂O), **33** (149 mg, 0.461 mmol) and *N*-methylmorpholine-*N*-oxide (138 mg, 1.18 mmol) in CH₂Cl₂ (5 mL) gave after chromatographic purification (petrol/EtOAc 20:80), a 62:38 mixture of diastereoisomers of triol 1-benzyl-3-(2,3-dihydroxypropyl)-3-(hydroxymethyl)-5-methoxy-2-oxo-2,3-dihydroindole (153 mg, 93%) as a yellow gum. Major diastereoisomer: $\delta_{\rm H}$ (300 MHz, CDCl₃) 7.26–7.17 (5H, m, ArH), 6.89 (1H, d, *J*=2.3, C(4)H), 6.63–6.53 (2H, m, C(6)H and C(7)H), 4.89 (1H, ABq, *J*_{AB}=15.7, NCH₂Ph), 4.77 (1H, d, *J*_{BA}=15.7, NCH₂Ph), 3.67 (3H, s, OMe), 3.59–3.51 (1H, m, CHOH), 3.47–3.38 (2H, m, CH₂OH), 3.35–3.27 (2H, m, CH₂OH), 2.36–2.21 (1H, m, CH₂CHOH), 1.80–1.75 (1H, m, CH₂CHOH). Characteristic peaks for minor diastereoisomer: $\delta_{\rm H}$ (300 MHz, CDCl₃) 6.78 (1H, d, *J*=2.4, C(4)H), 4.85 (1H, ABq, *J*_{AB}=15.7, NCH₂Ph), 4.77 (NCH₂Ph).

Sodium periodate (567 mg, 2.65 mmol) was added to a solution of triol 1-benzyl-3-(2,3-dihydroxypropyl)-3-(hydroxymethyl)-5methoxy-2-oxo-2,3-dihydroindole (509 mg, 1.42 mmol) in acetone

(7 mL) and H₂O (1.5 mL) and the solution stirred at rt for 4 h. The solution was then diluted with H₂O (20 mL) and Et₂O (20 mL), the layers separated and the aqueous phase further extracted with Et₂O (25 mL×3). The organic extracts were combined, dried (MgSO₄) and concentrated in vacuo. The crude residue was dissolved in MeOH (14 mL), sodium borohydride (108 mg, 2.85 mmol) was added and the solution stirred at rt for 1.5 h. The solution was then guenched with 1 N HCl (15 mL), concentrated in vacuo to remove the MeOH. diluted with H₂O (40 mL), extracted with EtOAc (40 mL×3), dried (MgSO₄) and concentrated in vacuo to give, after chromatographic purification (EtOAc/petrol 80:20), 35 (415 mg, 89% over two steps) as a colourless oil. v_{max} (thin film)/cm⁻¹ 3399, 2925, 1687, 1603, 1180, 1046, 737; δ_H (300 MHz, CD₃OD) 7.39–7.20 (5H, m, ArH), 7.02 (1H, d, J=2.4, ArH), 6.78–6.66 (2H, m, ArH), 4.97 (1H, ABq, J_{AB}=15.8, CH_AH_BPh), 4.89 (1H, ABq, J_{BA}=15.8, CH_AH_BPh), 3.89 (1H, ABq, J_{AB}=10.6, C(3)CH_AH_BOH), 3.85 (1H, ABq, J_{BA}=10.6, C(3)CH_AH_BOH), 3.77 (3H, s, OCH₃), 3.37–3.20 (2H, m, C(3)CH₂CH₂OH), 2.24–2.00 (2H, m, C(3)CH₂CH₂OH); δ_C (75 MHz, CD₃OD) 180.7, 157.8, 138.1, 137.5, 133.0, 129.7, 128.5, 128.3, 113.5, 112.1, 110.9, 68.3, 58.9, 56.2, 55.5, 44.7, 36.6; *m*/*z* (ESI⁺) 350 ([M+Na]⁺, 45%), 328 ([M+H]⁺, 100%); HRMS (ESI⁺) 328.1547 ([M+H]⁺ C₁₉H₂₂NO⁺₄ requires 328.1543 (+1.1 ppm)).

4.3.20. 2-(1-Benzyl-5-methoxy-3-((methylsulfonyloxy)methyl)-2oxo-2,3-dihydroindol-3-yl)ethyl methanesulfonate **36**.



To a solution of 35 (197 mg, 0.602 mmol) and triethylamine (175 μL , 1.26 mmol) in CH_2Cl_2 (6 mL) at 0 $^\circ C$ was added dropwise mesyl chloride (98 µL, 1.26 mmol) and stirred for 2 h. The reaction mixture was then warmed to rt and stirred overnight before quenching with satd aq NaHCO₃ solution (10 mL). CH₂Cl₂ (25 mL) and brine (10 mL) were added, the layers separated and the aqueous phase further extracted with CH_2Cl_2 (15 mL×3). The organic extracts were combined, dried (MgSO₄) and concentrated in vacuo to give, after chromatographic purification (EtOAc/petrol 80:20), 36 (201 mg, 69%) as a yellow oil. ν_{max} (thin film)/cm⁻¹ 2937, 1709, 1603, 1356, 1175, 736; δ_H (300 MHz, CDCl₃) 7.37–7.23 (5H, m, ArH), 6.92 (1H, d, *I*=2.4, ArH), 6.77 (1H, dd, *I*=8.6 and 2.5, ArH), 6.69 (1H, d, J=8.6, ArH), 5.10 (1H, ABq, J_{AB}=15.8, CH_AH_BPh), 4.73 (1H, ABq, J_{BA}=15.8, CH_AH_BPh), 4.53 (1H, ABq, J_{AB}=9.7, C(3)CH_AH_BOMs), 4.40 (1H, ABq, J_{BA}=9.7, C(3)CH_AH_BOMs), 4.16–3.99 (2H, m, C(3)CH₂CH₂OMs), 3.77 (3H, s, OCH₃), 2.79 (3H, s, OSO₂CH₃), 2.73 (3H, s, OSO₂CH₃), 2.56–2.44 (1H, m, C(3)CH_AH_BCH₂OMs), 2.31–2.21 (1H, m, C(3)CH_AH_BCH₂OMs); δ_C(75 MHz, CDCl₃) 175.2, 156.4, 136.5, 135.4, 129.0, 128.2, 127.9, 127.2, 113.8, 111.4, 110.4, 72.2, 64.8, 55.9, 50.9, 44.2, 37.3 (2C), 32.1; *m*/*z*(ESI⁺) 501 ([M+NH₄]⁺, 100%), 484 ([M+H]⁺, 45%); HRMS (ESI⁺) 501.1353 ([M+NH₄]⁺ C₂₁H₂₉N₂O₈S⁺₂ requires 501.1360 (-1.4 ppm)).

4.3.21. N-Benzylhorsfiline 37.



To a solution of **36** (97 mg, 0.200 mmol) in EtOH (1.0 mL) was added methylamine (2.0 M solution in THF, 0.30 mL, 0.60 mmol) and the solution heated to 105 °C in a sealed tube overnight. The solution was concentrated in vacuo, the residue dissolved in CH₂Cl₂ (10 mL), washed with 0.1 N HCl (2 mL×2), dried (MgSO₄), filtered and concentrated in vacuo. Chromatographic purification (EtOAc/ acetone $100:0 \rightarrow 75:25$) gave **37** (61 mg, 0.190 mmol, 95%) as a colourless oil with spectroscopic data in accordance with the literature.⁷ $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.25–7.15 (5H, m, ArH), 7.01 (1H, d, *J*=2.5, C(4)H), 6.58 (1H, dd, J=8.5 and 2.5, C(6)H), 6.50 (1H, d, J=8.5, C(7)H), 4.80 (2H, s, CH₂Ph), 3.69 (3H, s, OCH₃), 3.02 (1H, td, *J*=8.2, 3.9, C(5')H_AH_B), 2.87 (1H, AB q, J_{AB}=9.3, C(2')H_AH_B), 2.80 (1H, AB q, J_{BA}=9.3, C(2')H_AH_B), 2.70 (1H, app q, J=8.2, C(5')H_AH_B), 2.40 (3H, s, NCH₃), 2.32–2.38 (1H, m, C(4') H_AH_B), 2.02–2.09 (1H, m, C(4') H_AH_B); $\delta_{\rm C}$ (100 MHz, CDCl₃) 180.2, 156.4, 137.2, 136.1, 135.4, 128.8, 127.6, 127.2, 112.2, 110.4, 109.1, 66.4, 56.7, 55.9, 53.8, 43.9, 41.9, 38.2.

4.3.22. Horsfiline 4.



NH₃ (~5 mL) was condensed at $-78 \degree$ C and Na (~20 mg) was added with vigorous stirring at -33 °C until the deep blue colour persisted. A solution of **37** (10.0 mg, 0.031 mmol) in THF (0.50 mL) was added dropwise and the mixture stirred at -33 °C for 15 min before the addition of NH₄Cl (~50 mg). The ammonia was allowed to evaporate, H₂O (10 mL) was added and the mixture extracted with EtOAc (3×10 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Chromatographic purification (CH₂Cl₂/MeOH $100:0 \rightarrow 90:10$) gave **4** (4.1 mg, 0.018 mmol, 57%) as an off-white solid with spectroscopic data in accordance with the literature.⁷ mp 140-142 °C (lit. Mp 156-157°C); δ_H (400 MHz, CDCl₃) 7.87 (1H, br s, NH), 7.04 (1H, d, J=2.4, C(4)H), 6.77 (1H, d, J=8.4, C(7)H), 6.58 (1H, dd, J=8.4 and 2.4, C(6)H), 3.79 (3H, s, OCH₃), 3.07-3.01 (1H, m, C(5')H_AH_B), 2.91-2.85 (2H, m, J_{AB}=9.3, C(2')H₂), 2.76 (1H, app q, J=8.2, C(5')H_AH_B), 2.46 (3H, s, NCH₃), 2.40 (1H, ddd, J=12.6, 7.9 and 4.6, C(4')H_AH_B), 2.14-2.06 (1H, m, C(4')H_AH_B); δ_C (100 MHz, CDCl₃) 182.4, 156.4, 133.3, 112.9, 110.5, 109.9, 66.0, 56.7, 56.1, 54.1, 41.8, 38.2 [C(3) not observed].

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Supplementary data

¹H and ¹³C NMR data is available for all products. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.03.047.

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