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From One to Two Quaternary Centers: Ester or Nitrile α-Alkylation applied to Bioactive Alkaloids

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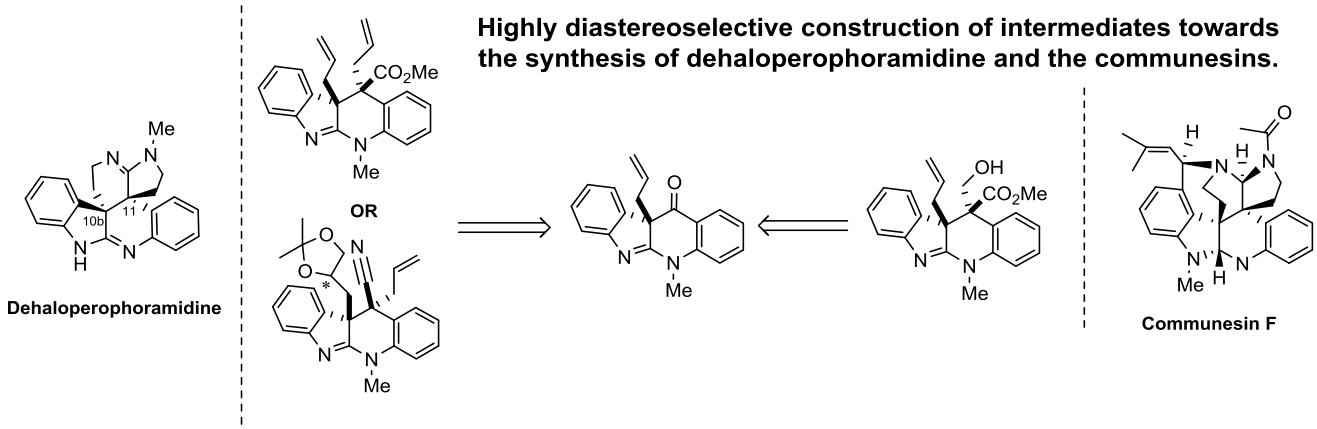

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From One to Two Quaternary Centers: Ester or Nitrile α-Alkylation applied to Bioactive Alkaloids

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Dehaloperophoramidine
Diastereoselective
Quaternary
Stereocenter

ABSTRACT

The synthesis of all-carbon quaternary centers remains a challenge. Here we describe studies on the formation of two adjacent all-carbon quaternary centers in the context of the planned synthesis of the bioactive natural products perophoramidine and the communesins. In one approach the key step involves ester-alkylation using either allyl bromide or formaldehyde as the electrophile. An unexpected rapid auto-oxidation reaction during the synthesis of the alkylation substrates limited the scalability of this approach. In a second route, alkylation of a nitrile-containing precursor was planned. The use of the TosMIC reagent on a complex substrate gave the nitrile for alkylation. The assignment of the relative stereochemistry of the products was done through the extensive use of small molecule X-ray crystallography.

1. Introduction

The natural product perophoramidine (**1**) and its dehalogenated derivative **2** were first reported by Ireland in 2002.[1] These compounds are structurally related to another family of alkaloids known as the communesins (for example **3F**, Figure 1).[2] Since their isolation, **1**-**3** have proved an inspiration to synthetic chemists resulting in numerous total syntheses and a wide range of elegant approaches.[3-5]

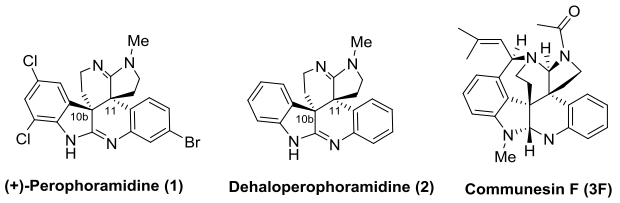
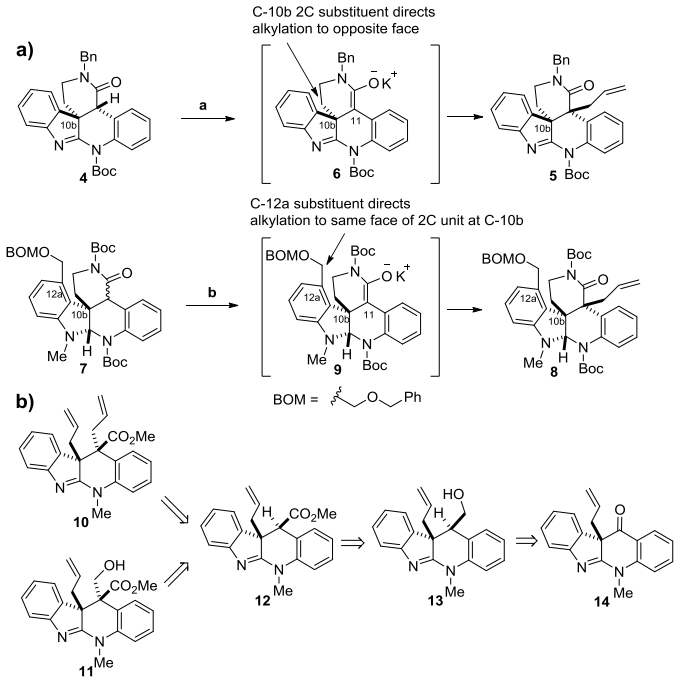


Figure 1: Structures of the natural products (**1**-**3F**) relevant to this work.

These natural products all possess an indolo[2,3-*b*]quinoline core structure but it is the vicinal all-carbon quaternary centers that present the major synthetic challenge. Early work on the synthesis of dehaloperophoramidine (**2**) by Rainier[4a] involved alkylation of lactam **4** to give **5** under basic conditions *via* enolate **6** (Scheme 1a). This reaction occurred to give a single diastereomer with addition of allyl iodide occurring from the opposite side to the $CH_2CH_2NR_2$ group on C-10b. In addition, Weinreb has reported the conversion of **7** to **8** via enolate **9**.[5c] In Weinreb's example it was argued that the bulky BOM protected primary alcohol at C-12a controlled C11- alkylation of **9** leading to the allyl group being

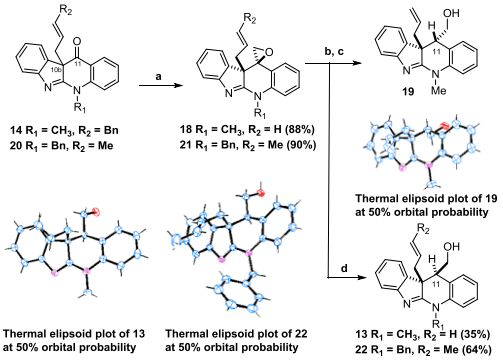


Scheme 1: a) The previously reported alkylation methods by Rainier[4a] and Weinreb[5c]; Reagents and conditions:a) KO^{t}Bu, allyl iodide, THF, 0 °C 89%, b) KO^{t}Bu, allyl iodide, THF, -78 °C – rt, 87%. **b)** Two proposed methods for installing the required all-carbon quaternary stereocenters from our ketone **14**.

directed onto the same face as the existing $CH_2CH_2NR_2$ group at C-10b. These results suggest that the stereochemical outcome of alkylation at C11, in the absence of a C12a-substituent, is highly likely to lead to the new substituent being place on the opposite face to the $CH_2CH_2NR_2$ group at C-10b. We therefore considered an approach towards both ester **10** (in a plan to prepare dehaloperophoramidine (**2**)) and ester **11** (for the communesins) *via* a common intermediate **12** (Scheme 1b). Ester **12** could be constructed from alcohol **13** which could itself be formed from ketone **14**.[6] Here we describe the outcome of this plan and discuss a series of interesting issues that arose during these studies.

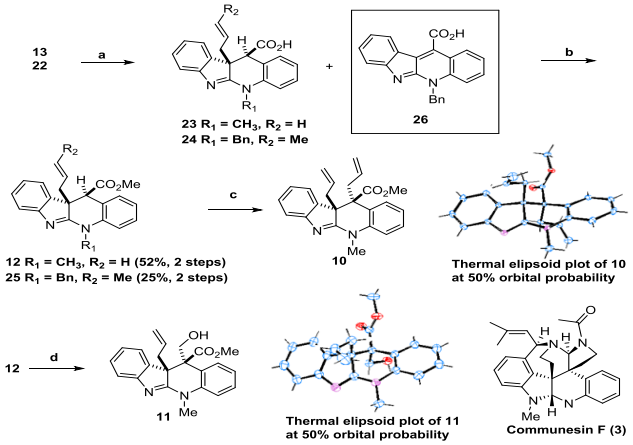
2. Results and Discussion

We have previously reported the synthesis of ketone **14** (Scheme 1b).[6] In this new work, preliminary investigations involved nucleophilic addition to **14** to assess the stereochemical outcome (Scheme 2). Reduction of **14** with $NaBH_4$ led to alcohol **15** in high yield (89%) as a single diastereoisomer. The relative stereochemistry of **15** was confirmed by X-ray crystallographic analysis and indicated hydride attack on **14** had occurred on the opposite face to the allyl group at C-10b, as expected. Furthermore, treatment of the *N*-benzylated analogue **16** led to the formation of **17** (95%) as a single diastereoisomer. The relative stereochemistry of **17** was proposed to be the same as **15** (see Table S1 for ^{1}H NMR comparison of **15** and **17** and further discussion).



Scheme 2: Diastereoselective reductions of ketones **14** and **16**. In each case the nucleophile approached from the opposite face to the allyl group at C-10b. The structure of **15** was confirmed by X-ray crystallographic analysis and this was used to infer the relative stereochemistry in **17**.

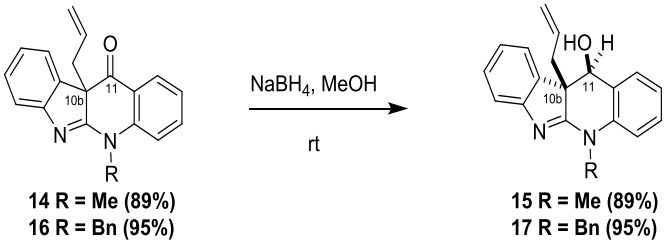
This result encouraged us to continue our approach to installing the all-carbon quaternary stereocenters in **1** and **2** using the C10b stereocenter as the control unit. In brief, as this section of our approach has been previously described in a communication format,[4d] **14** was converted to **18** using MeLiBr in the presence of chloroiodomethane (Scheme 3). With **18** in hand, attempts were made to perform an acid-catalysed rearrangement of the epoxide. The addition of 5 equivalents of $BF_3\cdot OEt_2$ to **18** led to a complex mixture of products. However, treatment of the crude sample with $NaBH_4$ and subsequent recrystallisation from $CDCl_3$/ hexane afforded alcohol **19**. The relative configuration of **19** was assigned using X-ray crystallographic analysis. Alternatively, reductive opening of **18** with 2.5 equivalents of $BF_3\cdot OEt_2$ in the presence of $NaBH_3CN$ gave alcohol **13** in an unoptimised 35% yield after recrystallisation from methanol. X-ray crystallographic analysis confirmed the structure of **13** and demonstrated that it was the C-11 epimer of alcohol **19**. Analogous reaction conditions were applied to ketone **20** (Scheme 3). The change in the N-R_1 protecting group from methyl to benzyl was required to enable a late stage deprotection to give the required unprotected amidine.[4d] The change from the allyl to the crotyl side chain was part of one potential solution to the challenge of developing an asymmetric approach to **2**.[6] Ketone **20** was converted to **21** in an optimized 90% yield and underwent successful reductive epoxide opening to alcohol **22**.

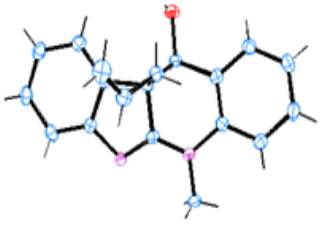


Scheme 3: Formation of alcohols **19**, **13** and **22**. The structures of these compounds were confirmed by X-ray crystallographic analysis. Reaction conditions: **a** MeLi-LiBr, $ClCH_2I$, THF, -78 °C, 0.5 h, rt, 12 h; **b** $BF_3\cdot OEt_2$, THF, -78 °C, 3 h; **c** $NaBH_4$, MeOH, rt, 2 h; **d** BF_3OEt_2, $NaBH_3CN$, -78 °C -rt, 18 h.

Again, X-ray crystallographic analysis of **22** confirmed the relative stereochemistry of the new C-11 stereocenter.

With alcohols **13** and **22** in hand, attempts were made to install the required all-carbon quaternary stereocenters at C10b and C11. Alcohol **13** underwent Jones oxidation to carboxylic acid **23**, followed by methylation to give ester **12** in 52% yield (2 steps, Scheme 4). Loss of product likely occurred during the work up stage as the zwitterionic nature of **23** probably renders it soluble in the aqueous phase. Encouragingly, alkylation of **12** with allyl bromide under basic conditions afforded the desired ester **10** as a single diastereoisomer in 59% yield. X-ray crystallographic analysis of **10** confirmed that alkylation had been directed to the opposite face of the existing C-10b $CH_2CH_2NR_2$ group, as expected. Therefore **10** was viewed as a potentially suitable intermediate en route to dehaloperophoramidine (**2**).





Thermal elipsoid plot of 15 at 50% orbital probability

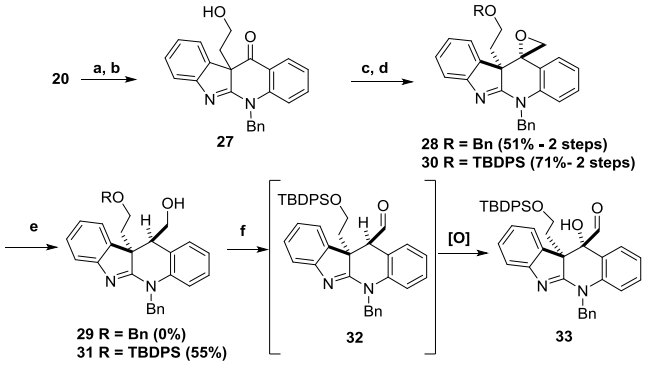
Scheme 4: Formation of all-carbon quaternary stereocenters with the desired relative stereochemistry in dehaloperophoramidine and the communesins. Reagents and conditions: **a** CrO_3, H_2SO_4, H_2O, Me_2CO, rt; **b** Me_3SiCHN_2, MeOH, rt; **c** LiHMDS, allyl bromide, THF, -78 °C to rt, 16 h, 59%; **d** LDA, H_2CO, THF, -78 °C to rt, 1.5 h, 76%.

Ester **12** was also considered as a possible intermediate towards members of the communesin family of natural products. Alkylation of **12** with formaldehyde in the presence of LDA

afforded **11** in good yield (76%) as a single diastereoisomer. X-ray crystallographic analysis confirmed the structure of **11** and showed that it possessed 1-carbon units at different oxidation levels that afforded **11** in good yield (76%) as a single diastereoisomer. X-ray crystallographic analysis confirmed the structure of **11** and showed that it possessed 1-carbon units at different oxidation levels that were either *syn*-(CO_2Me) or *anti*-(CH_2OH) to the allyl group at C-10b. Selective functionalisation of the ester would be required to generate the necessary *syn*-2-carbon unit required in the communesins.

However, when the analogous reactions were carried out on the crotyl-containing alcohol **22**, Jones oxidation of carboxylic acid **24**, followed by methylation to ester **25** could only be achieved in an overall yield of 25%. The low yield rendered this approach unsuitable for the planned approach to **2**. Unfortunately, the yield could not be improved despite an extensive screen of reaction conditions and oxidising agents (Table S2). Further analysis of the Jones oxidation reaction of **22** by LCMS and LRMS indicated significant accumulation of a degradation product during the reaction (*m/z* = 352.96). After isolation *via* semi-preparative HPLC, this compound was tentatively assigned as achiral **26** (Scheme 4). ^{1}H NMR analysis of **26** indicated loss of the crotyl group. Furthermore, the diastereotopic benzyl C$\underline{H}_2$ protons present in **22** (two doublets) now appeared as a singlet in **26** (see SI for a further discussion and one proposed mechanism for this reaction). As the presence of the crotyl group in **22** appeared to have a detrimental effect on the yield of **23**, it was decided to modify this group by oxidative cleavage (Scheme **5**). This transformation would be required at some stage in any synthesis of **2** to remove the one excess carbon atom.

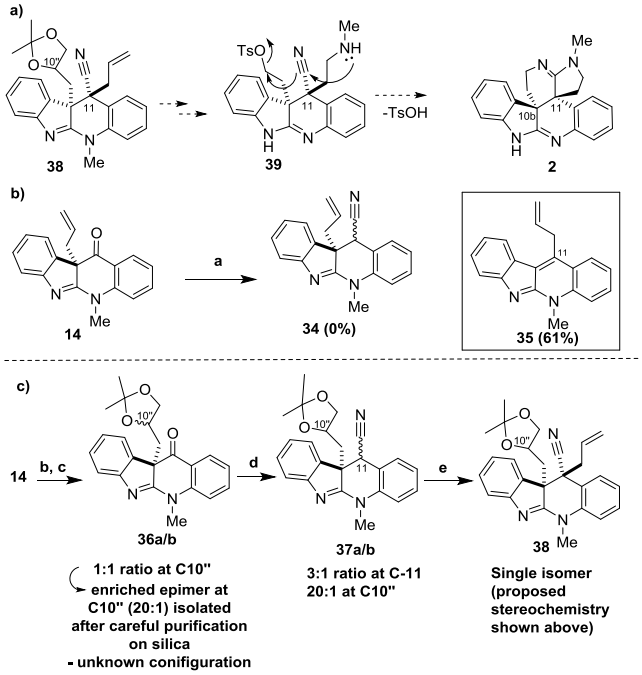
Dihydroxylation followed by oxidative cleavage of the alkene in **20**, followed by *in-situ* reduction of the intermediate aldehyde afforded **27** in high yield (88%). Alcohol **27** was initially *O*-benzylated before undergoing epoxide formation to give **28** in an analogous manner to the synthesis of **18** and **21** (Scheme 3). Disappointingly, the conversion of **28** to alcohol **29** in the presence of $BF_3\cdot OEt_2$ could not be achieved and a complex mixture of unassignable products was isolated. This was likely due to initial Lewis-acid mediated *O*-benzyl deprotection prior to degradation of the starting material. To overcome this issue, TBDPS protected epoxide **30** was synthesized. Gratifyingly, **30** underwent the desired reductive epoxide opening to give **31** in a 55% yield**.** Due to its acid labile silyl protecting group (TBDPS), **31** was deemed unsuitable for oxidation under the highly acidic Jones conditions.



Scheme 5: Synthesis of **31** and unexpected air oxidation of intermediate **32** to **33**. Reagents and conditions: **a** OsO_4, NMO, THF:H_2O (9:1), 18 h, rt. **b** $PhI(OAc)_2$, DCM, 2h, rt then $NaBH(OAc)_3$, EtOAc, 2 h, rt, 88% (2 steps). **c i)** Benzyl TCA, TMSOTf, DCM, 0 °C – rt, 4 h; **c ii)** TPDBS-Cl, imidazole, DCM, rt, 1 h. **d** $ClICH_2$, MeLi:LiBr, THF, 6 h, -78 °C – rt, 51% for **28** (2 steps); 71% for **30** (2 steps). **e** $BF_3.Et_2O$, $NaBH_3CN$, THF, - 78°C – rt, 16 h, 55%. **f** DMP, $CDCl_3$, rt, 48 h, 65%.

Instead, Dess-Martin periodinane (DMP) was chosen in an attempt to form aldehyde **32**. Interestingly, whilst **32** was the initial product formed upon the addition of 1.2 equivalents of DMP to **31** (full consumption of the starting material was observed after 0.5 hours, Figure SI1) it was found that α-hydroxylation occurred at C-11 to form **33** after extended reaction times (48 h, Figure SI1. See Figure SI2 for further discussion of the oxidation and assignment of the stereochemistry in **33**). Furthermore, α-hydroxylation was still found to occur even after isolation and rapid purification by column chromatography of aldehyde **32**. This indicated **32** was air sensitive and that molecular oxygen was the likely source of the undesired oxidation. Air oxidation at benzylic positions α- to an aldehyde has been reported previously in the total synthesis of Fredericamycin A by Boger and co-workers.[7]

Whilst the transformation of **31** to **33** was intriguing, it prevented further progress towards the desired natural products **1**-**3**. Having struggled to develop a reproducible and scalable method for the construction of the all-carbon quaternary stereocenters *via* the above methods, a new approach was investigated. Reassessment of the structure of key intermediate **12** (Scheme 1b) showed that whilst the presence of the ester moiety adjacent to C-11 ultimately permitted alkylation to give **10** and was at the correct oxidation level for this atom in **2**, significant further development of the ester would be required to incorporate the necessary nitrogen atoms. It was therefore proposed that the installation of a cyano group at C-11 could achieve the analogous acidification of the C-11 proton to facilitate alkylation and that it may be possible to incorporate the cyano nitrogen into advanced intermediates (Scheme 6a). After initial attempts to convert the alcohol in **17** to a cyano group (*via* a C-11 bromide) proved unsuccessful, it was decided to try and incorporate the cyano group using tosylmethyl isocyanide (TosMIC). An initial attempt to convert the ketone in **14** to the cyano group with TosMIC failed to yield the desired nitrile **34** (Scheme 6b). Instead, the achiral **35,** in which the allyl group had migrated from C-10b to C-11, was isolated in 61% yield (see SI for further discussion on the structural assignment of **35** and two possible mechanisms).



Scheme 6: A) Synthesis of achiral **35**. Reagents and conditions: **a** TosMIC, DME *t*-BuOK, 0 °C to rt, 1.5 h; **B)** Synthesis of allyl-nitrile **38** and proposed di-cyclisation of target intermediate **39**. Reagents and conditions: **b** OsO_4, NMO, THF, H_2O, rt, 24 h, PPTS; **c** $Me_2C(OMe)_2$, CH_2Cl_2, rt, 48 h, 70% (2 steps); d TosMIC, t-BuOK, t-BuOH, DME, 0 °C to rt, 1 h; **e** LiHMDS, allyl bromide, THF, - 78 °C to rt, 34% (2 steps).

As the presence of the allyl side chain at C-10b again appeared to be providing an alternative reaction pathway, it was decided to

functionalise this group prior to attempting the TosMIC-mediated reductive cyanation (Scheme 6c). Dihydroxylation of ketone **14**, followed by protection of the resulting diol via acetal formation with 2,2-dimethoxypropane led to formation of **36** and its C10'' epimer. Careful chromatographic purification of the resulting the diastereomeric mixture **36a/b**, gave a highly enriched sample of **36a** (20:1). The relative stereochemistry at C10'' in **36a** could not be assigned. Reductive cyanation of **36a** gave **37a/b** as a mixture of C-11 epimers in ratio of 3:1 with only trace signals corresponding to the C10'' epimers being observed in the ^{1}H NMR spectrum.

Finally, allylation of the diastereomeric mixture of **37a/b** was achieved by treatment with allyl bromide in the presence of LiHMDS to give **38** (34%, 2 steps) as essentially a single isomer after purification. Although **38** was obtained as a single diastereoisomer, it was not possible to obtain X-ray crystallographic data to assign the relative stereochemistry (the structure currently assigned to **38** is tentative and is based on the assumption that alkylation was directed by the CH_2CH-acetal group on C-10b in the absence of a C12-substituent (see Scheme 1)).

Having successfully synthesized allyl-nitrile **38**, future work will focus on the synthesis of intermediate **39** (Scheme 6a) *via* functionalization of the C-3 units at C-10b and C-11 and de-methylation of the amidine moiety. It is hoped that **39** could be a direct precursor to **2** upon undergoing a double cyclisation to construct the second required amidine.

3. Conclusions

In conclusion, we have described the construction of all-carbon quaternary stereocenters within intermediates aimed at both dehaloperophoramidine (**2)** and the communesins. The reactions involved have included highly diastereoselective base mediated alkylation at the C-11 position of ester **12** with both allyl bromide and formaldehyde. In addition, a 2-steps protocol for the construction of all-carbon quaternary stereocenters *via* TosMIC addition to **36** and alkylation is described. Further investigations into the synthesis of the target natural products *via* these intermediates will be reported in due course.

4. Experimental

General methods

All chemicals and solvents were purchased from Sigma Aldrich (UK) or Alfa-Aesar and used without further purification. All reactions were carried out under a positive pressure of nitrogen or argon in flame or oven-dried glassware. Thin layer chromatography (TLC) analysis was performed on silica pre-coated SIL G-25 UV_{254} sheets (layer: 0.25 mm silica gel with fluorescent indicator UV_{254}, Alugram, UK). Compounds were visualized by UV light (UV lamp, model UVGL-58, Mineralight LAMP, Multiband UV-254/365 nm) and stained with potassium permanganate. Flash column chromatography was carried out on silica gel (40-63 µm, Fluorochem, UK). Melting points were measured with an Electrothermal 9100 capillary melting point apparatus and are uncorrected. Fourier Transform infra-red spectra (FT-IR) were acquired on a Perkin Elmer paragon 1000 FT spectrometer. Absorption maxima are reported in wavenumbers (cm $^{-1}$). Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were measured at room temperature (298 K) on a Bruker DPX 400 (^{1}H = 400 MHz, ^{13}C = 100 MHz); Bruker Avance 300 (^{1}H = 300 MHz, ^{13}C = 75 MHz) and a Bruker Avance 500 (^{1}H = 500.1 MHz, ^{13}C = 125 MHz). Deuterated solvents were used and ^{1}H NMR chemical shifts were internally referenced to $CHCl_3$ (7.26 ppm) in chloroform-d_1 solution. Chemical shifts are expressed as δ in unit of ppm and coupling constants are recorded in Hz. Data processing was carried out using TOPSPIN 2 NMR version (Bruker UK, Ltd) or MestreNova 9.0 program (Bruker UK Ltd). In ^{1}H NMR assignment the multiplicity used is indicated by the following abbreviations: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, brs = broad singlet. Signals of protons and carbons were assigned, as far as possible, by using the following two-dimensional NMR spectroscopy techniques: [^{1}H-^{1}H] COSY, [^{1}H-^{13}C] HSQC (Heteronuclear Single Quantum Coherence) and long range [^{1}H-^{13}C] HMBC (Heteronuclear Multiple Bond Connectivity). Mass spectrometry analysis (electrospray mode, ES; chemical ionization mode, CI) were performed by Ms Caroline Hosburgh and were recorded on a high performance orthogonal acceleration reflecting TOF mass spectrometer operating in positive and negative mode, coupled to a Waters 2975 HPLC.

Experimental procedures

*(±)-10b-allyl-5-methyl-5,11-dihydro-10bH-indolo[2,3-b]quinoline-11-ol (**15**)*

$NaBH_4$ (164 mg, 4.34 mmol) was added to a solution of **14** (250 mg, 0.867 mmol) and MeOH (10 mL). After 2 hours, water (2 mL) was added and the MeOH was evaporated at reduced pressure. The aqueous residue was extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were dried ($MgSO_4$) and the CH_2Cl_2 was concentrated i*n vacuo*. The residue was purified by flash chromatography (10% to 20% EtOAc/hexane) the afford the title compound **15** as a colourless crystalline solid (224 mg, 0.771 mmol, 89%). Crystals suitable for X-ray analysis were obtained from EtOH. Mp 181-182 ^{o}C; IR (KBr) ν_{max}: 3416, 3076, 1557 cm^{-1}; HRMS (CI) m/z calcd for $C_{19}H_{19}N_2O$ 291.1497, found 291.1496; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.38-7.24 (m, 3H), 7.13 (td, *J* = 7.5, 1.0 Hz, 1H), 7.05-6.99 (m, 2H), 5.26-5.12 (m, 1H), 4.98 (d, *J* = 7.5 Hz, 1H), 4.78-4.71 (m, 2H), 3.57 (s, 3H), 2.94 (d, *J* = 7.5 Hz, 1H), 2.63 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.32 (dd, *J* = 13.5, 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 155.8, 140.1, 137.2, 132.7, 128.94, 128.87, 126.7, 125.8, 123.1, 123.0, 122.6, 118.5, 117.5, 114.3, 72.1, 57.0, 33.6, 32.9.

*(±)-10b-allyl-5-benzyl-10b,11-dihydro-5H-indolo[2,3-b]quinolin-11-ol (**17**)*

$NaBH_4$ (164 mg, 4.34 mmol) was added to a solution of **16** (100 mg, 0.275 mmol) and MeOH (5 mL). After 2 hours, water (5 mL) was added and the mixture was diluted with DCM (10 mL). The organic layer was washed with brine; dried ($MgSO_4$) then concentrated *in vacuo*. The residue was purified by flash chromatography (10% to 20% EtOAc/hexane) the afford the title compound **17** as a colourless crystalline solid (91 mg, 0.249 mmol, 91%). IR (ATR) ν_{max}: 3293, 1631, 1553 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{25}H_{23}N_2O$ 367.1810, found 367.1813; ^{1}H NMR (500 MHz,$CDCl_3$) δ 7.59 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.50 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.36 – 7.27 (m, 6H), 7.26 – 7.17 (m, 2H), 7.08 (dtd, *J* = 13.5, 7.5, 1.0 Hz, 2H), 6.92 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.77 (d, *J* = 16.5 Hz, 1H), 5.31 – 5.20 (m, 1H), 5.04 (d, *J* = 7.0 Hz, 1H), 4.94 (d, *J* = 16.5 Hz, 1H), 4.87 – 4.80 (m, 2H), 2.77 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.67 (d, *J* = 7.0 Hz, 1H), 2.44 (dd, *J* = 14.0, 7.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 155.9, 139.6, 137.4, 136.9, 132.8, 128.8, 127.4, 126.7, 126.6, 125.6, 123.3, 123.1, 122.7, 118.7, 117.8, 115.2, 72.1, 57.0, 49.8, 33.4.

*(±)-10b-allyl-11-hydroxymethyl-5-methyl-5,11-dihydro-10bH-indolo[2,5-b]quinoline (**19**)*

An impure sample of **SI1** (7 mg) was dissolved in MeOH (0.5 mL) and $NaBH_4$ (5 mg, 0.132 mmol) was added. After 2 h, water (0.5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 1 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated at reduced pressure to give the title compound **19** as a colourless solid (7 mg). A crystal suitable for X-ray analysis was obtained from $CDCl_3$/hexane. IR (film) ν_{max}: 3192, 1556, 1493, 1469, 1455, 1403, 1219, 1132, 1063, 922, 753, 737 cm^{-1}; HRMS (CI) m/z calcd for $C_{20}H_{20}N_2O$ 304.1576, found 304.1577; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.21 (m, 5H), 7.08-6.99 (m, 3H), 5.52-5.38 (m, 1H), 4.98-4.94 (m, 1H), 4.81-4.74 (m, 1H), 3.61 (s, 3H), 3.51 (dd, *J* = 14.0, 8.5 Hz, 1H), 3.39-3.31 (m, 2H), 2.47 (dd, *J* = 13.5, 8.0 Hz, 1H), 2.25 (dd, *J* = 13.5, 7.0 Hz, 1H).

*(±)-10b-allyl-11-hydroxymethyl-5-methyl-5,11-dihydro-10bH-indolo[2,5-b]quinoline (**13**)*

A stirred mixture of **18** (560 mg, 1.84 mmol) and $NaBH_3CN$ (291 mg, 4.63 mmol) in THF (20 mL), maintained under an argon atmosphere, was cooled to -10 °C. A solution of $BF_3.OEt_2$ (0.51 mL, 4.06 mmol) in THF (5 mL) was added over a period of 20 min. After 2 hours, an additional portion of $BF_3.OEt_2$ (0.12 mL, 0.955 mmol) in THF (1 mL) was added and stirring was continued for 1 hour at -10 °C. $NaHCO_{3(aq)}$ (50 mL) was added and the reaction mixture was allowed to warm to room temperature. The aqueous solution was extracted with CH_2Cl_2 (4 x 30 mL), the combined extracts were washed with brine (50 mL), dried ($MgSO_4$), and the CH_2Cl_2 was evaporated at reduced pressure. The residue was crystallised from MeOH/water to afford the title compound **13** as a colourless crystalline solid (196 mg, 0.644 mmol, 35%). Crystals from MeOH were suitable for X-ray analysis. Mp 190-191 ºC; Anal. calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.99; H, 6.66; N, 9.53; IR (KBr) ν_{max}: 3201, 2928, 2876, 1616, 1557, 1495, 1472, 1456, 1401, 1316, 1222, 1139, 1105, 1051, 986, 931, 809, 758, 652, 499 cm^{-1}; HRMS (CI) m/z calcd for $C_{20}H_{20}N_2O$ 304.1576, found 304.1569; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H), 7.26-7.23 (m, 4H), 7.14-6.98 (m, 3H), 5.10-4.96 (m, 1H), 4.73-4.62 (m, 3H), 4.48-4.39 (m, 1H), 3.58 (s, 3H), 3.12-3.07 (m, 1H) 2.38-2.35 (m, 2H), 2.01 (dd, *J* = 7.5, 3.5, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 156.0, 141.4, 136.7, 132.6, 128.8, 128.2, 127.4, 125.4, 123.7, 123.2, 122.3, 118.2, 117.4, 114.6, 61.7, 54.3, 44.2, 35.0, 33.1.

*(±)-5,10b-dihydro-10b-crotyl-5-benzyl-10bH-indolo[2,3-b]quinolin-11-one (**20**)*

A solution of alkoxide was prepared by the careful addition of sodium (1.72 g, 75 mmol, 2 eq.) to 3-buten-2-ol (21.0 g, 243 mmol, 3.2 eq.) in THF (5 mL). This solution was added to a stirring solution of **SI2** (10 g, 37.5 mmol, 1 eq.; the synthesis of **SI2** has been reported previously[4d]) in THF (200 mL). The resulting reaction mixture was stirred at room temperature for 18 h. Saturated aqueous NH_4Cl was then added (100 mL) and the solvent removed at reduced pressure. The resulting residue was suspended in water (100 mL) and extracted with DCM (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed at reduced pressure. The crude material was dissolved in THF (150 mL) and stirred at reflux for 5 h. After cooling to room temperature, the residue was purified by column chromatography (Hexane/EtOAc, 95:5 to 90:10) to afford the desired product **20** as a yellow microcrystalline powder (8.50 g, 22.5 mmol, 60%). Mp 148-150 °C; IR (KBr) ν_{max} cm^{-1} 1697, 1558, 1469; HRMS (ES^+) *m/z* calcd for $C_{23}H_{20}O_4Na$ 401.1630, found 401.1614; ^1H NMR δ_H (300 MHz, $CDCl_3$) 7.95 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.70 (dd, *J* = 7.5 Hz, 0.5 Hz, 1H), 7.53-7.21 (m, 8H), 7.20-6.97 (m, 3H), 5.92 (d, *J* = 16.5 Hz, 1H), 5.35-5.19 (m, 1H), 5.11-4.96 (m, 2H), 2.87 (dd, *J* = 13.5 Hz, 6.5 Hz, 1H), 2.46 (dd, *J* = 13.5 Hz, *J* = 8.0 Hz, 1H), 1.53 (dd, *J* = 6.0 Hz, *J* = 0.5 Hz, 3H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 192.9, 172.3, 153.5, 144.8, 136.9, 133.6, 131.6, 129.0, 128.7, 128.4, 127.8, 127.6, 126.7 (2C), 124.8, 123.1, 122.6, 122.5, 119.3, 118.7, 115.5, 66.5, 49.6, 44.3, 17.9.

*(±)-10b-crotyl-5-benzyl-5,11-dihydro-10bH-indolo[2,5-b]quinolin-11-spiro-2'-oxirane (**21**)*

To a mixture of **20** (4.90 g, 12.9 mmol, 1 eq.) in THF (50 mL) at -78 °C was added slowly MeLi-LiBr (12.2 mL of a 1.5 M solution, 19.4 mmol, 1.5 eq) over a period of 20 minutes. Chloroiodomethane (1.22 mL, 19.4 mmol, 1.5 eq.) was added and the reaction mixture stirred for 30 min at -78 °C before allowing to warm to room temperature. After stirring for 18 h at room temperature, saturated aqueous NH_4Cl solution (50 mL) was added and the solvent removed at reduced pressure. Water (50 mL) and Et_2O (50 ml) were added, the organic phase was separated and the aqueous phase further extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and filtered through a plug of silica. The resulting organic solution was left to slowly evaporate at ambient temperature until nearly dry (*ca*. 10 mL of Et_2O remaining). The desired product **21** was obtained as large colourless crystals (4.45 g, 11.35 mmol, 88%). Mp 138-141 °C; IR (KBr) ν_{max} 3029, 2938, 1813, 1689, 1558, 1491 cm^{-1}; HRMS *m/z* (ES^+) calcd for $C_{27}H_{25}N_2O$ 393.1967, found 393.1956; ^1H NMR δ_H (400 MHz, $CDCl_3$) 7.43-7.16 (m, 10H), 7.07-6.97 (m, 2H), 6.91 (dd, *J* = 8.0 Hz, 0.5 Hz, 1H), 5.91 (d, *J* = 16.5 Hz, 1H), 5.33-5.21 (m, 1H), 4.97-4.83 (m, 2H), 3.07 (d, *J* = 5.5 Hz, 1H), 2.81 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.62 (dd, *J* = 14.0, 8.5 Hz 1H), 2.53 (d, *J* = 5.5 Hz, 1H), 1.45 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 172.6, 155.5, 141.5, 137.0, 134.6, 129.7, 129.4, 128.9, 128.8, 127.4, 126.6, 124.2, 123.8, 123.5, 123.3, 122.8, 122.8, 118.0, 115.1, 60.2, 55.3, 53.6, 49.9, 37.3, 17.9.

*(±)-10b-crotyl-11-hydroxymethyl-5-benzyl-5,11-dihydro-10bH-indolo[2,5-b]quinoline (**22**)*

To a stirring solution of **21** (5.30 g, 13.5 mmol, 1 eq.) in THF (150 mL) at -78 °C was added $NaBH_3CN$ (2.12 g, 33.7 mmol, 2.5 eq.). A solution of $BF_3.OEt_2$ (6.78 mL, 54.0 mmol, 4 eq.) was then added over a period of 20 min and the resulting reaction mixture allowed to warm to room temperature. After stirring for 18 h at room temperature, the reaction was quenched by the addition of water (50 mL) and the aqueous solution extracted with DCM (4 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and the solvent removed at reduced pressure to afford the crude product. Purification by basic silica gel column chromatography (Hexane/EtOAc, 80:20) afforded the desired product **22** as a yellow oily solid (3.49 g, 8.64 mmol, 64%). Crystals suitable for X-ray analysis were obtained by slow evaporation from methanol. Mp 130-133 °C; IR (KBr) ν_{max} 3375, 3029, 2931, 1615, 1558, 1494, 1454, 1408, 1326, 1214 102 cm^{-1}; HRMS (ES^+) *m/z* calcd for $C_{27}H_{26}N_2ONa$ 419.1943, found 417.1939; ^1H NMR δ_H (300 MHz, $CDCl_3$) 7.68-7.62 (d, *J* = 7.5 Hz, 1H), 7.42-7.16 (m, 9H), 7.11-6.98 (m, 2H), 6.93 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.79 (d, *J* = 16.5 Hz, 1H), 5.25-5.09 (m, 1H), 4.86 (d, *J* = 16.5 Hz, 1H), 4.76-4.58 (m, 2H), 4.52-4.35 (m, 1H), 3.15 (d, *J* = 5.0 Hz, 1H), 2.40 (d, *J* = 7.0 Hz, 2H), 1.94,

1.38 (dd, J = 6.5 Hz, 1.5 Hz, 3H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 173.6, 153.2, 140.6, 136.2, 135.9, 129.8, 129.0, 128.9, 128.4, 127.6, 127.3, 126.7, 125.7, 124.5, 124.2, 124.0, 123.1, 116.9, 116.0, 61.4, 54.9, 51.1, 44.0, 33.9, 17.8.

*(±)-10b-allyl-5-methyl-5,11-dihydro-10bH-indolo[2,5-b]quinoline-11-carboxylic acid methyl ester (**12**)*

A solution of **13** (470 mg, 1.54 mmol) in acetone (20 mL) was added to a stirred mixture of CrO_3 (772 mg, 7.72 mmol) and celite (2.00 g) in 1.5 M H_2SO_4 (10 mL). After 5 hours, *i*-PrOH (2.0 mL, 26 mmol) was added and stirring was continued for 0.5 hours. The reaction mixture was filtered through celite and the celite was washed with EtOAc (50 mL). Brine (50 mL) was added to the filtrate followed by sufficient $NaHCO_{3(aq)}$ to neutralise (pH 7) the aqueous phase. The EtOAc was separated and the aqueous phase was further extracted with EtOAc (4 x 50 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated at reduced pressure to afford crude 23. The crude material was dissolved in MeOH (20 mL) and Me_3SiCHN_2 (1.54 mL of a 2.0 M solution in Et_2O, 3.08 mmol) was added. After stirring for 0.5 hours, AcOH (0.5 mL) was added and stirring was continued for an additional 0.5 hours. The solvent was evaporated at reduced pressure and the residue was partitioned between $NaHCO_{3(aq)}$ (10 mL) and CH_2Cl_2 (10 mL). The CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography (5% EtOAc/hexane) to afford the title compound **12** as a colourless crystalline solid (267 mg, 0.80 mmol, 52%). Mp 137-138 °C; IR (KBr) ν_{max}: 2951, 1740, 1618, 1560, 1495, 1470, 1400, 1215, 1161, 921, 751 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{21}N_2O_2$ 333.1603, found 333.1599; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.24 (m, 3H), 7.12-6.99 (m, 4H), 4.97-5.11 (m, 1H), 4.66-4.76 (m, 2H), 4.09 (s, 1H), 3.94 (s, 3H), 3.61 (s, 3H), 2.87 (dd, J = 14.0, 6.5 Hz, 1H), 2.55 (dd, J = 14.0, 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 172.0, 156.0, 141.0, 136.4, 132.4, 129.2, 129.0, 127.5, 123.0, 122.7, 122.4, 121.2, 118.4, 117.6, 114.8, 53.3, 52.2, 49.2, 34.7, 33.0.

*(±)-10b,11-diallyl-5-methyl-5,11-dihydro-10bH-indolo[2,5-b]quinoline-11-carboxylic acid methyl ester (**10**)*

LiHMDS (0.36 mL of a 1.0 M solution in THF, 0.36 mmol) was added to a solution of **12** (60 mg, 0.181 mmol) in THF (2 mL) at -78 °C, maintained under an argon atmosphere. The reaction mixture was warmed to 0 °C and then, after 1 hour, cooled to -78 °C. Allyl bromide (0.047 mL, 0.543 mmol) was added and the reaction mixture was slowly warmed to room temperature. After 16 hours, $NH_4Cl_{(aq)}$ (0.3 mL) was added and the THF was evaporated at reduced pressure. The residue was partitioned between water (1 mL) and CH_2Cl_2 (2 mL), the CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 x 2 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and the CH_2Cl_2 was evaporated at reduced pressure. The crude product was purified by flash chromatography (5% to 15% EtOAc/hexane) followed by crystallisation from EtOAc/hexane to afford the title compound **10** as a colourless crystalline solid (39 mg, 0.105 mmol, 59%). Crystals form EtOAc/hexane were suitable for X-ray analysis. Mp 171-173 °C; IR (KBr) ν_{max}: 2984, 2955, 1728, 1617, 1562, 1495, 1468, 1455, 1400, 1316, 1292, 1233, 1220, 935, 759 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{25}N_2O_2$ 373.1916, found 373.1907; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.23 (m, 3H), 7.06-6.97 (m, 5H), 5.47-5.32 (m, 1H), 5.07-4.93 (m, 1H), 4.84-4.57 (m, 4H), 3.96 (s, 3H), 3.61 (s, 3H), 2.76 (dd, J = 13.5, 8.0 Hz, 1H), 2.63 (dd, J = 14.0, 7.0 Hz, 1H), 2.39 (dd, J = 13.5, 6.0 Hz, 1H), 2.03 (dd, J = 14.0, 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 171.7, 156.3, 140.0, 134.7, 133.3, 132.3, 131.3, 129.0, 128.7, 123.7, 122.9, 122.6, 121.9, 119.0, 118.5,, 117.5, 114.5, 58.3, 57.1, 52.2, 38.5, 38.1, 33.0.

*(±)-10b-allyl-11-hydroxymethyl-5-methyl-5,11-dihydro-10bH-indolo[2,5-b]quinoline-11-carboxylic acid methyl ester (**11**)*

n-BuLi (0.27 mL of a 1.46 M solution, 0.394 mmol) was added to a mixture of *i*-Pr_2NH (0.058 mL, 0.412 mmol) and THF (1 mL) at -78 °C, maintained under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and then, after 0.5 hours, was cooled to -78 °C before a solution of **12** (65 mg, 0.196 mmol) in THF (2 mL) was added. The reaction mixture was warmed to -10 °C and after 1 hour formaldehyde, generated by heating paraformaldehyde (59 mg) to 150 °C, was bubbled through the vigorously stirred reaction mixture. The reaction mixture was then allowed to warm to room temperature and was stirred for 1 hour. $NH_4Cl_{(aq)}$ (0.5 mL) was added and the THF was evaporated at reduced pressure. The aqueous residue was extracted with CH_2Cl_2 (3 x 4 mL) and the combined CH_2Cl_2 extracts were dried ($MgSO_4$). The CH_2Cl_2 was evaporated at reduced pressure and the residue was purified by flash chromatography (20% to 40% EtOAc/hexane) to afford the title compound **11** as colourless crystals (55 mg, 0.152 mmol, 76%). Crystals suitable for X-ray analysis were obtained from EtOAc/hexane. Mp 202-203 °C; IR (KBr) ν_{max}: 3240, 2954, 1733, 1618, 1561, 1497, 1470, 1455, 1406, 1311, 1235, 1162, 1116, 1066, 923, 805, 760, 731, 643 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{22}N_2O_3Na$ 385.1528, found 385.1527; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.25-7.28 (m, 2H), 6.97-7.15 (m, 5H), 4.92-5.07 (m, 1H), 4.67-4.79 (m, 2H), 4.01 (s, 3H), 3.91 (dd, J = 11.5, 6.5 Hz, 1H), 3.59 (s, 3H), 3.38 (dd, J = 11.5, 8.0 Hz, 1H), 2.77 (dd, J = 13.5, 8.0 Hz, 1H), 2.51 (dd, J = 13.5, 6.5 Hz, 1H), 1.75 (dd, J = 6.5, 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 171.5 155.9, 140.4, 134.3, 131.7, 131.0, 129.2, 129.2, 122.8, 122.7, 122.53, 122.50, 118.9, 117.7, 114.8, 64.3, 58.8, 55.8, 52.6, 38.7, 33.0.

*(±)-10b-crotyl-5-benzyl-5,11-dihydro-10bH-indolo[2,5-b]quinoline-11-carboxylic acid methyl ester (**25**)*

To a stirring mixture of CrO_3 (630 mg, 6.3 mmol, 5 eq.) and celite (2 g) in 1.5M H_2SO_4 (10 mL) was added in one portion a solution of **22** (500 mg, 1.18 mmol, 1 eq.) in acetone (20 mL). After stirring for 5 h at room temperature, *i*-PrOH (10 mL) was added and the reaction stirred for further 30 min. The mixture was then filtered through celite and the celite washed with additional EtOAc (10 mL). After adding brine (10 mL) to the filtrate, and the pH of the aqueous layer adjusted to pH 7 by addition of saturated aqueous $NaHCO_3$ solution. The organic phase was separated and the aqueous phase further extracted with EtOAc (4 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed at reduced pressure to afford the crude acid **24**. The acid was then dissolved in MeOH (20 mL) and Me_3SiCHN_2 (1.25 mL of a 2.0M solution in Et_2O, 2.36 mmol) was added. After stirring for 30 min at room temperature, AcOH (0.5 mL) was added and the reaction mixture stirred for a further 30 min. After this time the solvent was removed at reduced pressure and the residue partitioned between layers of saturated aqueous $NaHCO_3$ solution (10 mL) and DCM (10 mL). The organic phase was separated and the aqueous phase further extracted with DCM (3 x 10 mL). The combined extracts were dried ($MgSO_4$) and the solvent removed at reduced pressure. The crude product was purified by flash column chromatography (Hexane/EtOAc, 95:5 to 90:10) to afford the desired product **25** as a colourless crystalline solid (124 mg, 0.29 mmol, 25% over two steps).

Mp 145-147 °C; IR (KBr) ν_{max} 3453, 3026, 2953, 2850, 1735, 1558, 1493 cm^{-1}; HRMS (ES^+) *m/z* calcd for $C_{28}H_{27}N_2O_2$ 423.2073, found 423.2071; ^1H NMR δ_H (400 MHz, $CDCl_3$) 7.41-7.14 (m, 8H, ArH), 7.11-7.09 (m, 1H), 7.06-6.93 (m, 4H), 5.76 (d, *J* = 16.5 Hz, 1H), 5.27-5.14 (m, 1H), 4.94 (d, *J* = 16.5 Hz, 1H), 4.73-4.60 (m, 1H), 4.14 (s, 1H), 3.94 (s, 3H), 2.91 (dd, *J* = 14.0 Hz, 6.0 Hz, 1H), 2.62 (dd, *J* = 14.5, 8.0 Hz, 1H), 1.37 (dd, *J* = 6.5, 0.5 Hz, 3H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 172.9, 171.9, 155.9, 140.7, 137.0, 136.8, 129.1, 128.9, 128.8 (2C), 127.4, 127.3, 126.9, 124.5, 123.1, 122.7, 122.3, 121.5, 117.7, 115.8, 53.6, 52.1, 50.2, 49.4, 33.4, 17.9.

*(±)-5-benzy-10b-(2-hydroxyethyl)-5H-indolo[2,3-b]quinolin-11(10bH)-one (**27**)*

To a solution of **20** (1.00 g, 2.74 mmol) in THF : H_2O (9:1, 20 mL) was added osmium tetroxide (2.5M solution in ^{t}BuOH, 0.2 mL, cat.) and NMO (0.97 g, 5.29 mmol, 2 eq.) and the mixture stirred at room temperature for 18 h. $Na_2SO_{3\ (aq.)}$ (20 mL) was added and the resulting mixture stirred for 30 min. Brine (20 mL) was added and the mixture extracted with DCM (3 × 50 mL) before the combined organic layer was dried ($MgSO_4$), filtered and concentrated to afford the crude diol as a mixture of diastereoisomers. The crude product was purified by column chromatography (0-5 % MeOH / DCM) to give the diol as a yellow solid. To a solution of the diol in DCM (20 mL) was added iodosobenzene diacetate (1.06 g, 3.29 mmol) and the mixture stirred at room temperature for 2 hours. Sodium triacetoxyborohydride (1.16 g, 5.49 mmol) was then added and the mixture stirred for a further 2 hours. $NaHCO_{3\ (aq.)}$ (20 mL) was added and the mixture extracted with DCM (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed at reduced pressure to give the crude product. Purification by column chromatography (20-30% EtOAc / Hexane) gave **27** as a yellow solid (890 mg, 88%, 2 steps). Mp 95-97 °C; IR (KBr) ν_{max} 3200, 1695, 1468, 799, 755 cm^{-1}; HRMS (ES^+): *m/z* calcd for $C_{24}H_{21}N_2O_2$ 369.1603, found: 369.1609. ^1H NMR δ ($CDCl_3$, 400 MHz) 7.95 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.76 (dd, *J* = 7.5, 0.5 Hz, 1H), 7.51-6.92 (m, 11H), 5.85 (d, *J* = 16.5 Hz, 1H), 5.15 (d, *J* = 16.5 Hz, 1H), 2.54-2.40 (m, 2H), 2.21-2.07 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.3, 172.6, 153.2, 144.2, 135.9, 135.7, 132.5, 129.2, 129.0, 128.6, 127.6, 126.6 (2C), 124.7, 123.6, 123.0, 119.1, 118.7, 115.7, 64.7, 60.4, 50.0, 43.2.

*(±)-5-benzyl-10b-(2-(benzyloxy)ethyl)-5,10b-dihydrospiro[indolo[2,3-b]quinoline-11,2'-oxirane] (**28**)*

To a solution of **27** (50 mg, 0.136 mmol) and benzyl TCA (41 mg, 0.163 mmol) in DCM (3 mL) was added TMS-OTf (30 mg, 0.136 mmol) at 0 °C. After stirring for 30 minutes, the ice bath was removed and the reaction stirred for a further 18 hours at room temperature before $NaHCO_{3\ (aq.)}$ (3 mL) was added. The mixture was extracted with DCM (3 x 3 mL) before the combined organic extracts were dried ($MgSO_4$) filtered and concentrated to give the crude product. The crude was purified by column chromatography (10–20 % EtOAc / Hexane) to give a yellow oil.

To the yellow oil (122 mg, 0.266 mmol) in THF (4 mL) at -78 °C was added chloroiodomethane (29 µL, 0.399 mmol) followed by methyl lithium – lithium bromide (1.5 M in THF, 266 µL, 0.399 mmol). The mixture was stirred at -78 °C for 30 minutes before the cold bath was removed and the reaction stirred for a further 5 hours at room temperature before $NH_4Cl_{\ (aq.)}$ (10 mL) was added. The mixture was extracted with DCM (3 x 10 mL) before the combined organic extracts were dried ($MgSO_4$) filtered and concentrated to give the crude product. The crude was purified by column chromatography (10–20 % EtOAc / Hexane) to give **28** as a yellow oil (83 mg, 51% - 2 steps).

IR (KBr) ν_{max}: 1719, 1555, 1492, 1467, 1451, 1208, 750, 695 cm^{-1}; HRMS (ES^+): *m/z* calcd for $C_{32}H_{29}N_2O_2$ 473.2224, found 473.2217 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.04 (m, 16H), 6.93 (td, *J* = 7.5, 1.0 Hz, 1H), 6.81 (dd, *J* = 8.0, 0.5 Hz, 1H), 5.66 (d, *J* = 16.5 Hz, 1H), 4.89 (d, *J* = 16.5 Hz, 1H), 4.10 (s, 2H), 3.15 – 3.02 (m, 2H), 2.97 (d, *J* = 5.5 Hz, 1H), 2.46 (d, *J* = 5.5 Hz, 1H), 2.42 – 2.27 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 155.6, 141.1, 138.1, 136.8, 134.0, 129.4, 129.0 (2C), 128.8 (2C), 128.3, 127.6 (2C), 127.5, 127.2, 126.4 (2C), 123.7, 123.2, 123.1, 122.9, 122.8, 118.2, 115.1, 73.1, 66.5, 60.5, 53.7, 53.3, 49.6, 33.6.

*(±)-5-benzyl-10b-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5,10b-dihydrospiro[indolo[2,3-b]quinoline-11,2'-oxirane] (**30**)*

To a solution of **27** (4.60 g, 12.5 mmol) in DCM (140 mL) at room temperature was added *tert*-butyl diphenyl silyl chloride (4.12 g, 15.0 mmol) and imidazole (1.88 g, 27.6 mmol). The mixture was stirred at room temperature for 60 minutes before $NH_4Cl_{\ (aq.)}$ (100 mL) was added and the mixture extracted with DCM (3 x 100 mL). The combined organic layer dried ($MgSO_4$), filtered and concentrated to give the crude product. Purification by column chromatography (5–15 % EtOAc / Hexane) to give a yellow solid.

The yellow solid (380 mg, 0.626 mmol) was taken up in THF (10 mL) at -78 °C was added chloroiodomethane (69 µL, 0.939 mmol) followed by the dropwise addition of methyl lithium – lithium bromide (1.5 M in THF, 626 µL, 0.939 mmol). The mixture was stirred at -78 °C for 15 minutes before the cold bath was removed and the reaction stirred for a further 5 hours at room temperature. $NH_4Cl_{\ (aq.)}$ (30 mL) was added and the mixture extracted with DCM (3 x 30 mL) before the combined organic extracts were dried ($MgSO_4$) filtered and concentrated to give the crude product. The crude was purified by column chromatography (10–20 % EtOAc / Hexane) to give **30** as a yellow solid (330 mg, 71% - 2 steps). Mp 46-49 °C; IR (KBr) ν_{max}: 3069, 3044, 2926, 2852, 1807, 1558, 1452, 1108, 700 cm^{-1}; HRMS (ES^+) *m/z* calcd for $C_{41}H_{40}N_2O_2NaSi$ 643.2757, found 643.2762 $[M+Na]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.08 (m, 19H), 7.08 – 6.93 (m, 2H), 6.93 – 6.75 (m, 2H), 5.53 (d, *J* = 16.5 Hz, 1H), 5.03 (d, *J* = 16.5 Hz, 1H), 3.50 – 3.38 (ddd, *J* = 10.0, 9.0, 5.5 Hz, 1H), 3.26 (ddd, *J* = 10.0, 9.0, 5.5 Hz, 1H), 2.93 (d, *J* = 5.5 Hz, 1H), 2.43 (d, *J* = 5.5 Hz, 1H), 2.25 (tdd, *J* = 13.5, 9.0, 6.0 Hz, 2H), 0.83 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 155.3, 140.8, 136.6, 135.4 (4C), 133.9, 133.5, 133.4, 129.5, 129.4, 129.3, 128.8 (3C), 127.6 (2C), 127.5 (2C), 127.2, 126.5 (2C), 123.7, 123.2, 122.9, 122.7, 118.1, 115.1, 60.4, 60.1, 53.5, 53.1), 49.4, 36.3, 26.8, 19.0.

*(±)-(-5-benzyl-10b-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-10b,11-dihydro-5H-indolo[2,3-b]quinolin-11-yl)methanol (**31**)*

To a solution of **30** (135 mg, 0.218 mmol) in THF (4 mL) at -78 °C was added boron trifluoride diethyl etherate (135 µL, 1.090 mmol) followed by sodium cyanoborohydride (34 mg, 0.545 mmol). The mixture was slowly allowed to warm to room temperature over a period of 4 hours before stirring for a further 12 hours at room temperature. $NH_4Cl_{\ (aq.)}$ (10 mL) was added before the mixture being extracted with DCM (3 x 10 mL) and the combined organic layer dried ($MgSO_4$), filtered and concentrated to give the crude product. Purification by column chromatography (20–40 % EtOAc / Hexane) gave **31** as a white solid (74 mg, 55%). Mp 112-115 °C; I.R. (KBr) ν_{max}: 3212, 2926, 2251, 1644, 1555, 1496, 1191, 1103, 700 cm^{-1}; HRMS (ES^+): m/z calcd for $C_{41}H_{43}N_2O_2Si$ 623.3088, found 623.0383 $[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.5 Hz, 1H), 7.39 – 7.00 (m, 19H),

6.94 (t, *J* = 7.5 Hz, 1H), 6.87 – 6.77 (m, 2H), 5.28 (d, *J* = 16.5 Hz, 1H), 4.96 (d, *J* = 16.5 Hz, 1H), 4.53 – 4.39 (m, 1H), 4.31 – 4.17 (m, 1H), 3.30 – 3.12 (m, 1H), 3.01 – 2.81 (m, 2H), 2.01 (ddd, *J* = 13.5, 9.0, 5.0 Hz, 1H), 1.80 (ddd, *J* = 13.5, 9.0, 5.0 Hz, 1H), 0.80 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 156.0, 140.6, 136.9, 136.5, 135.4, 135.3 (2C), 133.6, 133.5, 129.5, 128.7 (2C), 127.9, 127.5 (2C), 127.1 (2C), 126.7 (2C), 125.4, 123.5, 123.3, 122.3, 117.7, 115.6, 61.7, 60.2, 52.3, 49.6, 44.9, 33.0, 26.8, 19.0.

*(±)-5-benzyl-10b-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-11-hydroxy-10b,11-dihydro-5H-indolo[2,3-b]quinoline-11-carbaldehyde (**33**)*

To a solution of **31** (75 mg, 0.120 mmol) in $CDCl_3$ (3 mL) was added Dess-Martin periodinane (61 mg, 0.144 mmol) and the mixture was stirred at room temperature for 48 hours. $Na_2S_2O_{3\,(aq.)}$ (3 mL) and $NaHCO_{3\,(aq.)}$ (3 mL) were added and the mixture stirred for a further 30 minutes before the mixture was extracted with DCM (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give the crude product **32**. Purification by column chromatography (10–25 % EtOAc / Hexane) gave **33** as a white solid (50 mg, 65%). M.p. 101-103 °C; I.R. (KBr) ν_{max}: 3435, 3063, 2928, 2855, 1725, 1556, 1467, 1453, 1207, 1110, 821, 737, 701, 503 cm^{-1}; HRMS (ES$^-$): m/z calcd for $C_{41}H_{39}N_2O_3Si$ 635.2730, found 635.2722 [M-H]$^-$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (d, *J* = 1.0 Hz, 1H), 7.50 (m, 2H), 7.44 – 7.22 (m, 18H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.01 – 6.95 (m, 2H), 5.53 (d, *J* = 16.5 Hz, 1H), 5.25 (s, 1H), 5.20 (d, *J* = 16.5 Hz, 1H), 3.43 (t, *J* = 7.0 Hz, 2H), 2.43 (dt, *J* = 14.0, 7.0 Hz, 1H), 1.97 (dt, *J* = 14.0, 6.0 Hz, 1H), 0.98 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.7, 172.6, 155.6, 140.0, 136.6, 135.5 (2C), 135.4 (2C), 134.0, 132.9, 132.7, 130.2, 129.7, 129.7, 129.2, 128.8 (2C), 127.7 (2C), 127.6 (2C), 127.4, 127.0, 126.9 (2C), 123.7, 123.4, 123.1, 122.3, 118.3, 115.5, 81.6, 60.0, 55.4, 49.3, 34.6, 26.8, 19.1.

*11-allyl-5-methyl-5H-indolo[2,3-b]quinoline (**35**)*

t-BuOK (0.83 mL of a 1.0 M solution in *t*-BuOH, 0.830 mmol) was added to a stirred mixture of 5,10b-dihydro-10b-allyl-5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (**14**) (100 mg, 0.347 mmol), TosMIC (88 mg, 0.451 mmol) and DME (2.5 mL) that was cooled to 0 °C and maintained under an argon atmosphere. After 0.5 hours, the reaction mixture was allowed to warm to room temperature and the stirring was continued for 1 hour. Water (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were washed with brine (10 mL) and then dried ($MgSO_4$). The solvent was evaporated at reduced pressure and the residue was purified by flash chromatography (50% to 80% EtOAc/hexane) to afford the title compound **35** as an orange solid (57 mg, 0.209 mmol, 61%). Mp 125-127 ºC; IR (KBr) ν_{max}: 3049, 1627, 1608, 1565, 1525 cm^{-1}; HRMS (EI) m/z calcd for $C_{19}H_{16}N_2O$ 272.1313, found 272.1317; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 7.5 Hz, 1H), 7.78-7.73 (m, 3H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.49-7.45 (m, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 6.19 (ddt, *J* = 16.5, 10.5, 5.5 Hz, 1H), 5.18-5.13 (m, 2H), 4.35-4.31 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 155.3, 141.0, 137.1, 133.3, 130.4, 128.9, 126.0, 124.3, 123.3, 122.0, 120.8, 120.0, 117.82, 117.79, 114.7, 33.3, 33.0.

*(±)-10b-(2',2'-dimethyl[1,3]dioxolan-4'-ylmethyl)-5-methyl-5,10b-dihydroindolo[2,3-b]quinolin-11-one (**36**) and (±)-10b-(2',2'-dimethyl[1,3]dioxolan-4'-ylmethyl)-5-methyl-5,10b-dihydroindolo[2,3-b]quinolin-11-one (**36***)*

Osmium tetroxide (3.26 mL of a 2.5% solution in *t*-BuOH) was added to a vigorously stirred solution of 5,10b-dihydro-10b-allyl-5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (**130**) (1.50 g, 5.20 mmol) and NMO (1.28 g, 10.9 mmol) in THF/water (9:1, 40 mL). After 24 hours a saturated solution of sodium sulphite (90 mL) was added and stirring was continued for 0.5 hours before the reaction mixture was extracted with CH_2Cl_2 (3 x 150 mL). The combined CH_2Cl_2 extracts were washed with brine (200 mL), dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The residue was triturated with Et_2O and the yellow solids were collected by filtration.

2,2-dimethoxypropane (9.57 mL, 78.0 mmol) and PPTS (1.31 g, 5.21 mmol) were added to a stirred suspension of the crude solid in CH_2Cl_2 (100 mL), maintained under an argon atmosphere. After 2 days, when all the solids had gone into solution, $NaHCO_{3(aq)}$ (50 mL) was added and the CH_2Cl_2 was separated. The aqueous phase was further extracted with CH_2Cl_2 (3 x 25 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography (5% to 10% EtOAc/hexane) to yield the title compounds **36/36*** as a 1:1 mixture of diastereomers (1.32 g, 3.64 mmol, 70%). Whilst complete separation of the diastereomers could not be achieved, small highly enriched samples of each diastereomer could be obtained (122 mg of the less polar isomer and 50 mg of the more polar) by careful flash chromatography. Less polar isomer: IR (film) ν_{max}: 2986, 2937, 1694, 1563 cm^{-1}; HRMS (CI) m/z calcd for $C_{22}H_{23}N_2O_3$ 363.1709, found 363.1698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.70 (d, *J* = 7.0 Hz 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.36 (td, *J* = 7.5, 1.5 Hz, 1H), 7.18-7.06 (m, 3H), 3.69 (s, 3H), 3.58-3.51 (m, 1H), 3.27 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.01 (dd, *J* = 8.5, 6.0 Hz, 1H), 2.45 (dd, *J* = 13.5, 5.5 Hz, 1H), 2.18 (dd, *J* = 13.5, 7.0 Hz, 1H), 1.22 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2, 172.3, 153.9, 145.4, 136.1, 132.4, 129.3, 128.6, 124.7, 123.4, 122.3, 118.8, 118.4, 114.5, 108.4, 72.0, 69.3, 64.4, 44.6, 33.3, 26.8, 25.6.

More polar isomer: IR (film) ν_{max}: 2986, 2937, 1696, HRMS (CI) m/z calcd for $C_{22}H_{23}N_2O_3$ 363.1709, found 363.1700; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.61 (td, *J* = 8.0, 1.5 Hz, 1H), 7.44-7.34 (m, 2H), 7.21-7.11 (m, 3H), 3.91-3.82 (m, 2H), 3.71 (s, 3H), 3.33-3.26 (m, 1H), 2.51 (dd, *J* = 13.5, 6.0 Hz, 1H), 1.88 (dd, *J* = 13.5, 6.0 Hz, 1H), 1.89 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.1, 173.0, 153.7, 145.0, 135.8, 133.0, 129.2, 128.9, 125.0, 123.5, 122.7, 119.5, 118.9, 114.6, 109.0, 72.1, 69.3, 64.6, 45.6, 33.3, 26.8, 25.4.

*Preparation of (±)-11-allyl-10b-(2,2-dimethyl[1,3]dioxolan-4-ylmethyl)-5-methyl-5,11-dihydro-10bH-indolo[2,3-b]quinolin-11-carbonitrile (**38**) via (±)-10b-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-5-methyl-10b,11-dihydro-5H-indolo[2,3-b]quinoline-11-carbonitrile (**37**) and epi (±)-10b-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-5-methyl-10b,11-dihydro-5H-indolo[2,3-b]quinoline-11-carbonitrile (**37***)*

t-BuOK (0.73 mL of a 1.0 M solution in *t*-BuOH, 0.730 mmol) was added to a stirred mixture of enriched **36** (110 mg, 0.304 mmol), TosMIC (77 mg, 0.396 mmol) and DME (2.5 mL), cooled to 0 °C and maintained under an argon atmosphere. After 0.5 hours, the reaction mixture was allowed to warm to room temperature and the stirring was continued for 0.5 hour. Water (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were washed with brine (10 mL) and then dried ($MgSO_4$). The solvent was evaporated at reduced pressure and the residue was purified by flash chromatography (5% to 10% EtOAc/hexane) to afford a sample that was

predominantly **37** as a mixture of diastereomers (**37*** = minor isomer) that could not be separated (59 mg). IR (KBr) ν_{max}: 2985, 2934, 2243, 1562 cm^{-1}; HRMS (CI) m/z calcd for $C_{23}H_{24}N_3O_2$ 374.1869, found 374.1858; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.54 (m, 2H-major and 2H-minor), 7.45 – 7.30 (m, 3H-major and 3H-minor), 7.28 – 7.25 (m, 1H-minor), 7.22 (d, *J* = 7.2 Hz, 1H-minor), 7.16 – 7.04 (m, 3H-major and 1H-minor), 4.23 (s, 1H-major), 4.16 (s, 1H-minor), 3.67 (s, 3H-minor), 3.59 (s, 3H-major), 3.50 (q, *J* = 6.0 Hz, 1H-minor), 3.42 (q, *J* = 6.0 Hz, 1H-major), 3.26 – 3.18 (m, 1H-major and 1H-minor), 3.07 – 3.02 (m, 1H-major), 2.95 (dd, *J* = 8.5, 6.5 Hz, 1H-minor), 2.29 – 2.21 (m, 1H-major and 1H minor), 2.12 – 2.05 (m, 1H-major), 1.75 (dd, *J* = 13.5, 6.5 Hz, 1H-minor), 1.19 – 1.13 (m, 6H major and 6H minor).

This mixture of diastereomers (59 mg) was dissolved in THF (1 mL) and cooled to -78 °C, under an argon atmosphere. LiHMDS (0.24 mL of a 1.0 M solution in THF) was added and the reaction mixture was warmed to 0 °C for 0.5 hours. The orange reaction mixture was then cooled to -78 °C and allyl bromide (27 μL, 0.312 mmol) was added. After stirring -78 °C for 2 hours, the reaction mixture slowly warmed to room temperature and stirred for a further 16 hours. $NH_4Cl_{(aq)}$ (0.5 mL) was added and the solvent was evaporated at reduced pressure. The residue was partitioned between CH_2Cl_2 (1 mL) and water (1 mL). The CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 x 1 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated at reduced pressure. The residue was purified by chromatography (5% to 10% EtOAc/hexane) to afford **38** as a colourless oil (43 mg, 0.104 mmol, 34%). IR (film) ν_{max}: 2985, 2241, 1564; HRMS (EI) m/z calcd for $C_{26}H_{27}N_3O_2$ 413.2103, found 413.1998; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.5 Hz, 1H), 7.43-7.31 (m, 4H), 7.12-7.03 (m, 3H, 3 x ArH), 5.49-5.38 (m, 1H,), 5.05-5.01 (m, 1H), 4.87-4.82 (m, 1H), 3.61 (s, 3H), 3.43-4.39 (m, 1H), 3.26 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.06 (dd, *J* = 8.5, 6.5 Hz, 1H), 2.39 (dd, *J*= 14.0, 6.5 Hz, 1H), 2.24-2.33 (m, 2H), 2.18 (dd, *J* = 14.0, 7.0 Hz, 1H), 1.18 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 156.4, 138.8, 133.3, 130.7, 130.20, 130.17, 129.3, 123.4, 123.0, 122.5, 121.0, 120.5, 119.6, 118.2, 115.3, 108.5, 72.2, 69.6, 55.3, 49.5, 38.9, 38.6, 33.0, 26.9, 25.7.

Acknowledgments

We would like to acknowledge EPSRC for PhD funding through the Doctoral Training Schemes and the EPSRC National Mass Spectrometry Service Center, Swansea for mass spec analysis.

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Supplementary Material

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1582892 (**10**); CCDC 1582893 (**22**); CCDC 1582894 (**15**); CCDC 1582895 (**19**); CCDC 1582896 (**11**); CCDC 1582897 (**13**).

Additional results, discussion and discussion of supplementary compounds are discussed in the ESI.