Studies on the Claisen rearrangements in the indolo[2,3-*b*]quinoline system†

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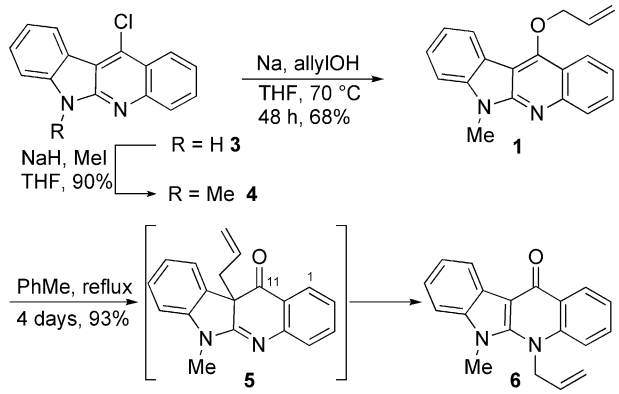
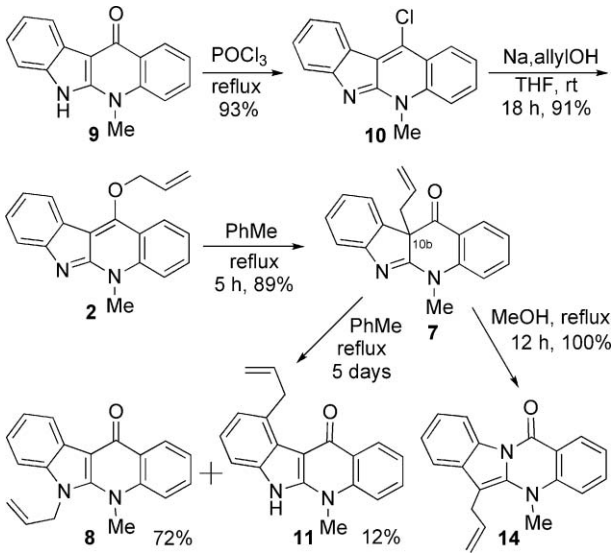
A study of the effect of substrate structure on a Claisen-aza-Cope reaction is presented including a rationalisation of the reaction outcome using DFT calculations. An asymmetric version of the reaction is also described that is of relevance to a proposed approach to the communesin family of natural products.

Introduction

Establishing quaternary centres in an asymmetric manner remains a key challenge.[1] An approach that has received relatively little attention is the formation of non-aromatic products by means of the Claisen rearrangement operating on aromatic substrates.[2] Here, we report the first application of this reaction type to the indolo[2,3-*b*]quinoline system and highlight its applicability in natural product synthesis. Initial studies focused on the rearrangement of **1** (Scheme 1) with the reaction outcome being rationalised computationally. Insights from these studies led to the attempted Claisen rearrangement of **2** (Scheme 2), an isomer of **1**. In this second-generation system, a stable product containing an all-carbon quaternary centre was isolated in high yield and the scope of this rearrangement was assessed as a function of the structure of the migrating allyl unit. Further computational studies provided an interesting insight into the difference in behaviour of **1** and **2**. Finally, an asymmetric version of this reaction, important in our approach to the communesin family of bioactive natural products,[3] is described.



Scheme 1 Attempted synthesis of **5**.



Scheme 2 Synthesis of indolo[2,3-*b*]quinoline **7**.

Results and discussion

Compound **1** was prepared by the regioselective methylation of the known indolo[2,3-*b*]quinoline **3**[4] to give **4**, followed by treatment with sodium allyloxide. Attempts to convert **1** to **5** led to the isolation of quinolone **6**, the result of formal allyl migration from oxygen to nitrogen. The rate of this reaction was found to be independent of the initial concentration of **1**, consistent with a tandem Claisen–aza-Cope process,[5] most likely *via* **5**. Interestingly, a detailed analysis of the crude reaction mixture using 2D-NMR techniques showed the presence of trace quantities of a compound that showed a signal at 195 ppm in the ^{13}C dimension. This signal is tentatively assigned to the carbonyl carbon of **5**, and a correlation between this carbon and H1 in **5** was also observed.[5,6]

Due to the lack of significant accumulation of **5** and in order to better understand the reaction outcome, the entire sequence of rearrangement reactions was investigated using DFT calculations using the B3LYP functional and a 6-31G(d,p) basis set (see the ESI for details†). The transition states located for the two rearrangements both have the classical chair-like structure.[5,7] The calculated barrier for the conversion of **1** into **5** is 27.3 kcal mol^{-1} (Fig. 1A). Intermediate **5** is calculated to be 6.7 kcal mol^{-1} higher in energy than **1**. The computed barrier for the conversion of intermediate **5** into **6** is significantly lower (23.0 kcal mol^{-1}) than

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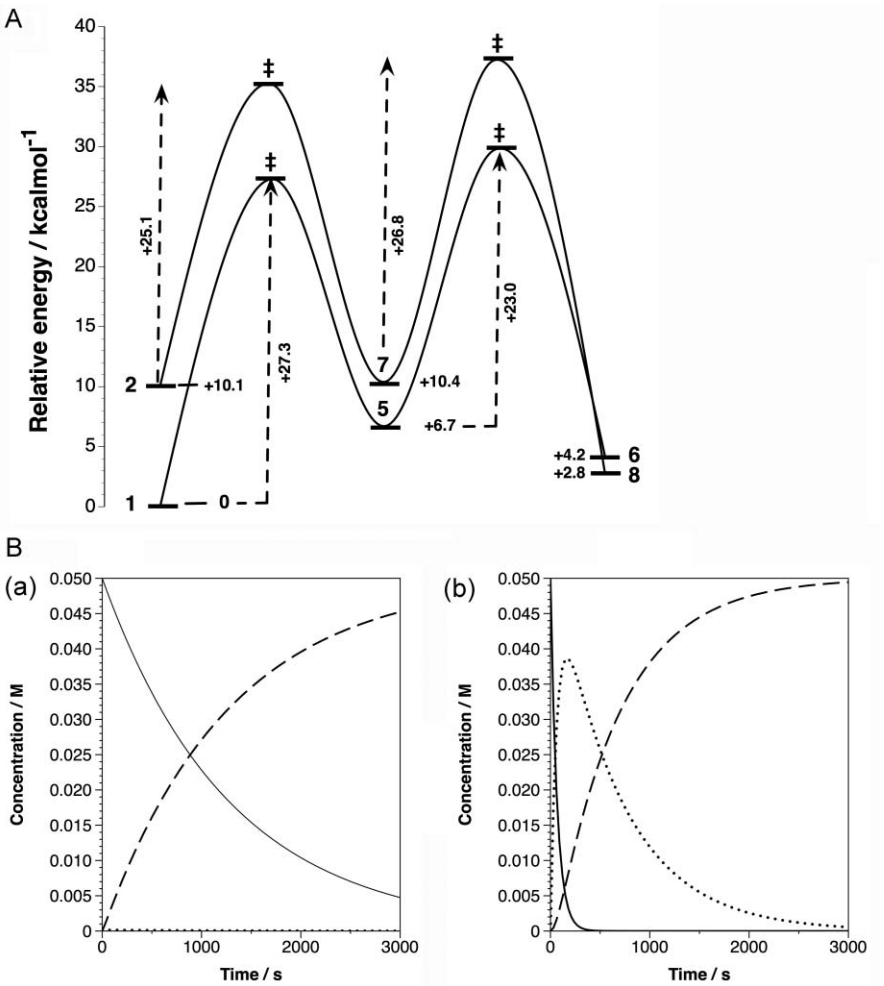


Fig. 1 **A** Calculated energy profile for the conversion of **1** to **5** to **6** and **2** to **7** to **8**. All energies are in kcal mol^{-1}. **B** Simulated reaction profiles generated using COPASI[5b] for the conversion of: (a) **1** (full line) through **5** (dotted line) to **6** (dashed line); (b) **2** (full line) through **7** (dotted line) to **8** (dashed line). First order rate constants at 373 K were estimated using the Eyring equation and the activation parameters derived from the described DFT calculations and a starting concentration of **1** or **2** of 50 mM was used.

that for the first rearrangement. These calculations are consistent with the efficient conversion of **1** to **6** *via* intermediate **5**. The first rearrangement step is rate limiting and therefore no useful accumulation of **5** occurs as a result of the much faster second rearrangement. This was best illustrated when the reaction profile was simulated using COPASI (Fig. 1B, chart (a)).[5b] A kinetic model consisting of two consecutive first order processes can be used to describe the overall transformation of **1** to **6**. The results demonstrate clearly that for the transformation of **1** to **6**, intermediate **5** is predicted to only ever be present at a very low level in agreement with the observed experimental result. The basis for this behaviour would appear to be the relative stability of the aromatic quinoline ring system present in **1**.

We reasoned that by changing the structure of the starting material, it might be possible to alter the balance of the rates of the two rearrangement reactions so that the overall process would lead to the accumulation of an intermediate analogous to **5**. Compound **2** (Scheme 2) was therefore considered as a potential substrate for the Claisen rearrangement. The methyl group in **2** is present on the quinoline ring nitrogen, in contrast to the situation in **1** where it is on the indole nitrogen. This minor structural change leads to a considerable perturbation of the ground state electronic structure of **2** as compared to **1**. The entire sequence of rearrangement reactions was again investigated computationally. As before, the two relevant transition states for the Claisen–aza-Cope reaction have the classical chair-like structures.[5] In this system, however, the barrier to the conversion of **2** into **7** is 25.1 kcal mol^{-1} higher in energy than **2** and the process is now essentially thermoneutral, with **7** being just 0.3 kcal mol^{-1} higher in energy than **2**. The computed barrier for the conversion of **7** into **8** (26.8 kcal mol^{-1}) is now higher than that for the first rearrangement step as required for the accumulation of **7** to occur. Whilst care must be taken over the interpretation of these computational studies, given the relatively low level of theory employed, it was clear that on moving from **1** to **2**, a potential solution to the problem was at hand. For example, simulation of the reaction profile in an analogous manner to that described for the conversion of **1** to **6** *via* **5** suggested that in the transformation of **2** to **8**, **7** is present as the dominant species in the early stages of the reaction (Fig. 1B, chart (b)). We therefore decided to prepare **2** and study how it behaved in this reaction.

Novel allyl ether **2** was synthesised from known indolo[2,3-*b*]quinolone **9**,[4] *via* chloride **10** (Scheme 2). Interestingly, substitution of the chlorine in **10** was found to occur under milder conditions than those required to convert **4** to **1** (Scheme 1), probably reflecting the decrease in ground state stability of **2** compared to **1**. As predicted, **2** underwent clean rearrangement to give **7** in 89% yield after 5 h in refluxing toluene. The structural assignment of **7** was confirmed by X-ray crystallographic analysis.[8] Prolonged heating of **7** in toluene was required to form **8** and a minor product **11**, resulting from a Cope rearrangement of **7**, was also isolated in this reaction.

To the best of our knowledge, **7** is the first example of the isolation of a 10b-substituted indolo[2,3-*b*]quinolin-11-one. Whilst similar compounds, including **12** (Fig. 2), have been reported by Coppola,[9] it was later demonstrated that their structural assignment was incorrect and that the compounds in question were in fact the corresponding indolo[2,1-*b*]quinazololin-12-ones (for example **13**).[10] The indolo[2,1-*b*]quinazololin-12-one **13** was reported to be formed by reaction of 3-methylthiooxindol with *N*-methylisotoic anhydride.[9] This reaction could have led to **13** directly; however, in our hands, **7** was converted to **14**[8] in quantitative yield when heated at reflux in methanol. This is consistent with an alternative route to **13** involving initial formation of **12**, as proposed by Coppola,[9] followed by rearrangement of **12** to give **13** *in situ*.

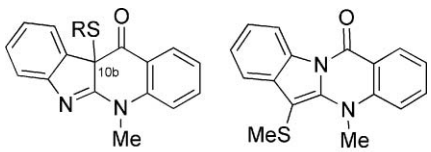
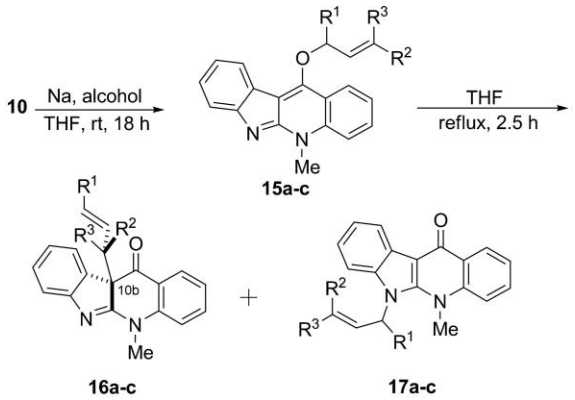


Fig. 2 Structures of **12** and **13**.

The scope of the Claisen rearrangement described in Scheme 2 was explored further by assessing the effect of alkyl substituents in the allyl moiety on the attempted preparation and rearrangement of **15a–c** (Scheme 3). In all three cases, pure samples of **15a–c** could not be obtained from the reaction of **10** with the corresponding alkoxide due to the rearrangement of **15a–c** at room temperature. In the case of **15a**, only low yields of **16a** could be obtained due to the formation of **17a**. This was even more pronounced in the case of **15b** where it proved impossible to prepare **16b**, with **17b** being the only isolated product. These observations are consistent both with the expected increase in the rate of the Claisen rearrangement due to the presence of the alkyl substituents,[11] and with a further increase in the rate of the aza-Cope rearrangement due to release in steric strain on transformation of **16a** and **16b** into **17a** and **17b**, respectively. Importantly, **16c** could be prepared directly from **10** in 83% yield with no formation of **17c**.

The presence of the *E*-geometry for the alkene in **16c** was confirmed by ^{1}H NMR (^3J (alkene protons) = 15.2 Hz) and is consistent with the reaction proceeding through the expected chair transition state in which the methyl substituent in **15c** occupies an equatorial position. This observation paved the way for the use of an optically enriched secondary alkoxide to enable the asymmetric synthesis of the quaternary centre (C10b, see structures **16a–c** in Scheme 3 for numbering) *via* intramolecular chirality transfer.[12,13]

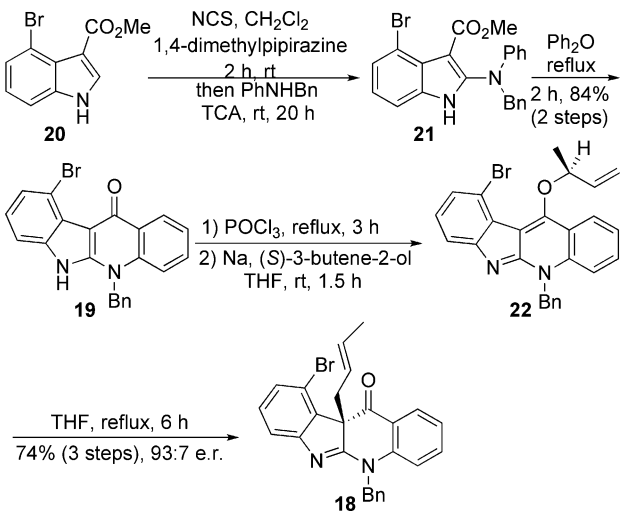


Entry	R^1	R^2	R^3	Allyl ether[a]	Rearrangement Products (yield)[b]	
1	H	H	H	**2**	**7** (89%)	**8** (0%)
2	H	H	Me	**15a**	**16a** (40%)	**17a** (16%)
3	H	Me	Me	**15b**	**16b** (0%)	**17b** (88%)
4[c]	Me	H	H	**15c**	**16c** (83%)	**17c** (0%)

[a] not isolated; [b] isolated yield (from **10**) after chromatography; [c] racemic 3-buten-2-ol was used

Scheme 3 The effect of substituents in the migrating allyl substituent on the Claisen rearrangement.

Scheme 4 illustrates this concept through the preparation of the highly optically enriched **18**, a versatile intermediate of potential relevance to the synthesis of the communesin group of natural products (Fig. 3).[3,14,15] Indoloquinolone **19**, prepared from 4-bromomethyl indole-3-carboxylate **20**[16] *via* **21**,[17] was converted to **18** in 74% yield using the readily available[18] (*S*)-(+)-3-buten-2-ol (96 : 4 e.r.[5,19]) without the need to purify the intermediate chloride and butenyl ether **22**.



Scheme 4 Synthesis of the highly optically enriched bromoindolo[2,3-*b*]quinoline **18**.

It was shown by the use of the chiral shift reagent Eu(hfc)$_3$[20] that the sample of **18** prepared by this method was formed as a 93 : 7 mixture of the two enantiomers, consistent with a slight erosion of optical purity, presumably resulting from the Claisen rearrangement of **18** proceeding *via* an alternative boat transition state in which the methyl group occupies an equatorial position.[5]

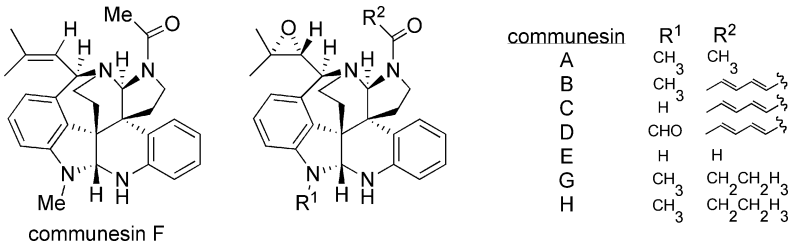


Fig. 3 The communesin family of natural products.

Crystallographic analysis confirmed the absolute stereochemistry of **18** to be the expected (*S*) configuration.[8]

This novel application of the Claisen rearrangement in the indolo[2,3-*b*]quinoline system therefore culminates in access to **18**, a versatile intermediate of relevance to the synthesis of the communesin group of natural products. In particular, the presence of both the C11 ketone and C1 bromo functional groups in **18** provides handles for subsequent incorporation of the second quaternary centre and the 7-membered ring that make up other key structural features in the communesins. Whilst differing in the specifics from our *N*6-benzyl protection strategy, precedent for the removal of an *N*-benzyl protecting group at a late stage in the synthesis of dehaloperophoramidine does exist.[15b] The novel approach reported here was developed through a detailed understanding of the effect of structural changes in the indolo[2,3-*b*]quinoline system on a tandem Clasien–aza-Cope reaction. Further studies on reactions of the C11 ketone functionality will be reported in the near future.

Experimental

Chemicals and solvents were purchased from commercial suppliers and were used as received unless otherwise stated. Air and moisture sensitive reactions were carried out under an inert atmosphere of dried argon, and glassware was oven-dried. Analytical thin-layer chromatography (TLC) was performed on pre-coated TLC plates SIL G-25 UV_{254} (layer 0.25 mm silica gel with fluorescent indicator UV_{254}). Developed plates were air-dried and analysed under a UV lamp and where necessary, stained with a solution of potassium permanganate to aid identification. Flash column chromatography was performed using silica gel (40–63 μm). Melting points are quoted to the nearest 1 °C and are uncorrected. ^{1}H NMR spectra were recorded at 300 and 400 MHz. ^{13}C NMR spectra using the PENDANT sequence were recorded at 75 and 100 MHz. Chemical shifts (δ) are recorded using the residual solvent as the internal reference in all cases ($CDCl_3$ δ_H 7.27 ppm, δ_C 77.16 ppm). Coupling constants (J) are quoted to the nearest 0.1 Hz. The following abbreviations are used; s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; t, triplet; m, multiplet and br, broad. Where inseparable mixtures of diastereoisomers were obtained, ^{1}H NMR and ^{13}C NMR spectra for the major diastereoisomer only are reported. Low resolution and high resolution (HR) electrospray mass spectral (ES-MS) analyses were recorded on a high performance orthogonal acceleration reflecting TOF mass spectrometer, coupled to a HPLC. Optical rotation measurements were recorded using the D-line of sodium at 20 °C in a 1 ml solution cell with a 10 cm path length. The concentration (c) is expressed in g ml^{-1}.

11-Allyloxy-6-methyl-6*H*-indolo[2,3-*b*]quinoline (1)

A solution of the alkoxide generated from allyl alcohol (25.5 ml, 375 mmol) and sodium (2.6 g, 113 mmol) in THF (70 mL) was added to 11-chloro-6-methyl-6*H*-indolo[2,3-*b*]quinoline (**4**) (2.00 g, 7.52 mmol) in THF (25 mL), maintained under an argon atmosphere, and the reaction mixture was heated at 70 °C (bath temperature). After 48 h the reaction was cooled to room temperature and $NH_4Cl_{(aq)}$ (10 mL) was added. The excess of allyl alcohol and THF were evaporated under reduced pressure and the residue was partitioned between water (25 mL) and CH_2Cl_2 (25 mL). The organic phase was separated and the aqueous phase was further extracted with CH_2Cl_2 (2 × 25 mL). All the organic extracts were combined, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (10% to 20% EtOAc–hexane) followed by crystallisation from EtOAc–hexane to afford the title compound **1** as pale yellow crystals (1.47 g, 5.10 mmol, 68%): m.p. 75-76 °C; Anal. calc'd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 78.86; H, 5.66; N, 9.72; ν_{max} (KBr) 3057, 2928, 1638, 1608, 1570, 1492, 1474, 1428, 1395, 1292, 1245, 1099, 993, 922, 765, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (dd, J = 8.5, 1.1, 1H, H-1), 8.24 (d, J = 7.5, 1H, H-10), 8.12 (d, J = 8.5, 1H, H-4), 7.72 (ddd, J = 8.5, 7.0, 1.1, 1H, H-3), 7.56 (ddd, J = 8.0, 7.5, 1.0, 1H, H-8), 7.45 (ddd, J = 8.5, 7.0, 1.0, 1H, H-2), 7.39 (d, J = 8.0, 1H, H-7), 7.31 (td, J = 7.5, 1.0, 1H, H-9), 6.29 (ddt, J = 17.0, 10.5, 5.5, 1H, C*H*=CH$_2$), 5.56 (dq, J = 17.0, 1.5, 1H, CH=C*H*$_2$), 5.37 (dq, J = 10.5, 1.5, 1H, CH=C*H*$_2$), 4.89 (td J = 5.5, 1.5, 2H, OCH$_2$), 3.97 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5 (C), 154.8 (C), 148.6 (C), 142.2 (C), 133.4 (CH), 129.4 (CH), 127.8 (CH), 127.7 (CH), 123.8 (CH), 122.71 (CH), 122.68 (CH), 120.7 (CH), 120.1 (C), 119.3 (C), 118.6 (CH_2), 109.4 (C), 108.6 (CH), 75.2 (CH_2), 28.0 (CH_3); LRMS (ESI) m/z 288 (MH^+, 100); HRMS (ESI) m/z calc'd for $C_{19}H_{16}N_2O$ 288.1262, found 288.1263.

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

A solution of the alkoxide generated from allyl alcohol (7.50 mL, 110 mmol) and sodium (650 mg, 28.3 mmol) in THF (10 mL) was added to 11-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (**10**) (1.50 g, 5.62 mmol) in THF (30 mL), maintained under an argon atmosphere. After stirring the reaction mixture at room temperature for 18 h a saturated solution of NH_4Cl (3 mL) was added. The THF and allyl alcohol were removed by evaporation under reduced pressure, water (10 mL) was added and the mixture was extracted with ether (3 × 40 mL). The ether extracts were combined, dried ($MgSO_4$) and were evaporated under reduced pressure. The residue was purified by flash chromatography (the product was eluted with 80% EtOAc–hexane) to afford the title

compound (**2**) as a dark yellow solid. (1.46 g, 5.06 mmol, 90%): m.p. 93-94 °C; ν_{max} (KBr) 1643, 1571, 1522, 1492, 1460, 1352, 1283, 1240, 1177, 1149, 1118, 1098, 1059, 965, 909, 750, 661, 595, 468 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (dd, J = 8.0, 1.5, 1H, H-1), 8.08 (d, J = 8.0, 1H, H-10), 7.63-7.77 (m, 3H, H-7, H-3, H-4), 7.52 (td, J = 8.0, 1.0, 1H, H-8), 7.40 (ddd, J = 8.0, 7.0, 1.0, 1H, H-2), 7.24 (td, J = 8.0, 1.0, 1H, H-9), 6.23 (ddt, J = 17.0, 10.5, 1.5, 1H, C*H*=CH$_2$), 5.54 (dq, J = 17.0, 1.5, 1H, CH=C*H*$_2$), 5.35 (dq, J = 10.5, 1.5, 1H, CH=C*H*$_2$), 4.92 (dt, J = 5.5, 1.5, 2H, OCH$_2$), 4.28 (s, 3H, CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4 (C), 156.6 (C), 153.9 (C), 138.1 (C), 132.8 (CH), 130.9 (CH), 128.3 (CH), 124.3 (CH), 123.2 (CH), 122.5 (C), 121.6 (CH), 120.0 (CH), 118.8 (CH$_2$), 117.9 (C), 117.5 (CH), 116.4 (C), 114.2 (CH), 75.1 (CH$_2$), 33.0 (CH$_3$); LRMS (CI) m/z 289 (MH$^+$, 100), 249 (27); HRMS (CI) m/z calc'd for $C_{19}H_{17}N_2O$ 289.1341 found 289.1339.

11-Chloro-6-methyl-6*H*-indolo[2,3-*b*]quinoline (4)

Sodium hydride (1.58 g of a 60% dispersion in oil, 39.5 mmol) was added to a stirred suspension of 11-chloro-6*H*-indolo[2,3-*b*]quinoline (**3**) (2.00 g, 7.91 mmol) in THF (70 mL), maintained under an argon atmosphere. When effervescence ceased, methyl iodide (2.50 mL, 40.1 mmol) was added and the reaction was heated to 50 °C (bath temperature) for 1 h. After cooling, a saturated solution of ammonium chloride (20 mL) was added and the solvent was removed under reduced pressure. The residue was partitioned between DCM (30 mL) and water (30 mL). The organic phase was separated and the aqueous phase was further extracted with DCM (2 × 30 mL). All the DCM extracts were combined, dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (the product was eluted with 20% EtOAc–hexane) to afford the title compound (**4**) as a pale yellow crystalline solid (1.89 g, 7.09 mmol, 90%); m.p. 141-142 °C; ν_{max} (KBr) 1603, 1560, 1489, 1470, 1422, 1393, 1322, 1260, 1121, 1073, 944, 863, 763, 749, 629 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 7.5, 1H, H-10), 8.39 (dd, J = 8.3, 1.2, 1H, H-1), 8.11 (d, J = 8.3, 1H, H-4), 7.74 (ddd, J = 8.3, 6.8, 1.2, 1H, H-3), 7.60 (ddd, J = 8.3, 7.5, 1.2, 1H, H-8), 7.53 (ddd, J = 8.3, 6.8, 1.0, 1H, H-2), 7.38 (d, J = 8.3, 1H, H-7), 7.33 (td, J = 7.5, 0.8, 1H, H-9), 3.95 (s, 3H, CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5 (C), 147.0 (C), 142.8 (C), 135.7 (C), 129.5 (CH), 128.6 (CH), 127.9 (CH), 124.3 (CH), 124.2 (CH), 123.7 (CH), 122.4 (C), 120.4 (CH), 119.8 (C), 115.6 (C), 108.6 (CH), 27.9 (CH$_3$); LRMS (ESI) m/z 267 (MH$^+$, 100); HRMS (ESI) m/z calc'd for $C_{16}H_{12}N_2{}^{35}Cl$ 267.0689, found 267.0681.

5,6-Dihydro-5-allyl-6-methylindolo[2,3-*b*]quinolin-11-one (6)

11-Allyloxy-6-methyl-6*H*-indolo-[2,3-*b*]quinoline (**1**) (50 mg, 0.173 mmol) was heated at 170 °C (bath temperature) for 1 h, under an argon atmosphere. After cooling the product was purified by flash chromatography (the product was eluted with 80% EtOAc–hexane) to yield the title compound (**6**) as a colourless crystalline solid (46 mg, 0.160 mmol, 92%); m.p. 196-197 °C; ν_{max} (KBr) 1613, 1591, 1535, 1510, 1467, 1396, 1242, 1126, 929, 751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (dd, J = 7.5, 0.7, 1H, H-10), 8.40 (dd, J = 7.9, 1.6, 1H, H-1), 7.44 (td, J = 8.7, 1.6, 1H, H-3), 7.30 (td, J = 7.5, 1.0, 1H, H-9), 7.16-7.26 (m, 3H, H-4, H-2, H-8), 6.97 (d, J = 8.0, 1H, H-7), 6.28 (m, 1H, C*H*=CH$_2$), 5.43 (m, 1H, CH=C*H*$_2$), 5.15 (m, 1H, CH=C*H*$_2$), 4.92 (m, 2H, NCH$_2$), 3.74 (s, 3H, CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3 (C, C-11), 147.4 (C, C-5a), 140.5 (C), 137.4 (C), 133.6 (CH), 131.2 (CH), 126.0 (CH), 125.1 (C), 123.5 (C), 123.2 (CH), 122.4 (CH), 122.2 (CH), 121.2 (CH), 118.2 (CH$_2$), 115.6 (CH), 108.9 (CH), 104.4 (C), 51.7 (CH$_2$), 32.8 (CH$_3$); LRMS (EI) m/z 288 (M$^+$, 13), 247 (44), 219 (26), 86 (65), 84 (100); HRMS (EI) m/z calc'd for $C_{19}H_{16}N_2O$ 288.1263, found 288.1255.

5,10b-Dihydro-10b-allyl-5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (7)

A solution of 11-allyloxy-5-methyl-5*H*-indolo[2,3-*b*]quinoline (**2**) (1.46 g, 5.06 mmol) in toluene (50 mL) was refluxed under an argon atmosphere for 5 h. The toluene was removed under reduced pressure and the residue was purified by flash chromatography (the product was eluted with 20% EtOAc–hexane) to afford the title compound (**7**) as a bright yellow crystalline solid (1.30 g, 4.51 mmol, 89%); m.p. 94-95 °C; Anal. calc'd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.09; H, 5.33; N, 9.56; ν_{max} (KBr) 3070, 2901, 1692, 1560, 1471, 1386, 1344, 1296, 1207, 1167, 1068, 1038, 985, 922, 844, 777, 762, 670, 676, 629, 504, 468 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, J = 7.8, 1.4, 1H, H-1), 7.70 (d, J = 7.3, 1H, H-10), 7.63 (ddd, J = 8.8, 7.3, 1.4, 1H, H-3), 7.42 (d, J = 7.3, 1H, H-7), 7.35 (td, J = 7.3, 1.3, 1H, H-8), 7.12-7.19 (m, 3H, H-4, H-9, H-2), 5.28-5.42 (m, 1H, C*H*=CH$_2$), 4.99 (m, 1H, CH=C*H*$_2$), 4.83 (m, 1H, CH=C*H*$_2$), 3.72 (s, 3H, CH$_3$), 2.80 (dd, J = 13.2, 6.8, 1H, CCH$_2$), 2.46 (dd, J = 13.2, 7.8, 1H, CCH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9 (C), 172.4 (C), 153.6 (C), 145.4 (C), 140.0 (CH), 133.1 (C), 130.4 (CH), 128.9 (CH), 128.6 (CH), 124.7 (CH), 123.3 (CH), 122.5 (CH), 120.3 (CH$_2$), 119.0 (C), 118.7 (CH), 114.6 (CH), 66.2 (C), 45.1 (CH$_2$), 33.2 (CH$_3$); LRMS (ESI) m/z 289 (MH$^+$, 100); HRMS (ESI) m/z calc'd for $C_{19}H_{17}N_2O$ 289.1341 found 289.1346.

5,6-Dihydro-6-allyl-5-methylindolo[2,3-*b*]quinolin-11-one (8) and 5,6-dihydro-10-allyl-5-methylindolo[2,3-*b*]quinolin-11-one (11)

5,10b-Dihydro-10b-allyl-5-methyl-10b*H*-indolo[2,3-*b*]-quinolin-11-one (**7**) (200 mg, 0.694 mmol) and PhMe (10 mL) were heated at reflux, under an argon atmosphere, for 4 d. After cooling, the PhMe was evaporated under reduced pressure and the residue was purified by flash chromatography. The first, colourless crystalline solid, compound to be eluted (1% MeOH–$CHCl_3$) was 5,6-dihydro-6-allyl-5-methylindolo[2,3-*b*]quinolin-11-one (**8**) (143 mg, 0.496 mmol, 72%); m.p. 187-188 °C; ν_{max} (KBr) 1619, 1594, 1509, 1467, 1384, 1311, 1242, 1158, 1125, 1039, 1014, 983, 925, 878, 740, 675, 654, 584, 545, 452 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (dd, J = 8.0, 1.5, 1H, H-10), 8.43 (dd, J = 8.0, 1.5, 1H, H-1), 7.49 (ddd, J = 8.5, 7.0, 1.5, 1H, H-3), 7.12-7.30 (m, 4H, H-9 H-8, H-4, H-2), 7.00 (d, J = 8.0, 1H, H-7), 6.05-6.18 (m, 1H, C*H*=CH$_2$), 5.30-5.37 (m, 1H, CH=C*H*$_2$), 5.08-5.17 (m, 1H, CH=C*H*$_2$), 4.72-4.76 (m, 2H, NCH$_2$), 3.84 (s, 3H, CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3 (C), 148.5 (C), 141.3 (C), 137.5 (C), 132.9 (CH), 131.2 (CH), 126.3 (CH), 125.5 (C), 124.0 (C), 123.5 (CH), 122.6 (CH), 122.4 (CH), 121.3 (CH), 117.9 (CH$_2$), 115.4 (CH), 109.4 (CH), 105.0 (C), 49.2 (CH$_2$), 37.1 (CH$_3$); LRMS (EI) m/z 288 (M$^+$, 12), 247 (42), 86 (66), 84 (100); HRMS (EI) m/z calc'd for $C_{19}H_{16}N_2O$ 288.1263 found 288.1268. The

second, colourless crystaline solid, compound to be eluted (2% MeOH–$CHCl_3$) was 5,6-dihydro-10-allyl-5-methylindolo[2,3-*b*]quinolin-11-one (**11**) (24 mg, 0.083 mmol, 12%); m.p. 270-280 °C (dec.); ν_{max} (KBr) 3052, 1617, 1576, 1546, 1510, 1433, 1380, 1303, 1273, 1217, 1165, 1133, 1057, 997, 911, 875, 787, 753, 708, 625, 490 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 12.08 (s, 1H, NH), 8.42 (d, J = 8.0, 1H, H-1), 7.70-7.78 (m, 2H, H-4, H-3), 7.36 (ddd, J = 8.0, 6.5, 1.0, 1H, H-2), 7.32 (dd, J = 7.5, 1.0, 1H, H-9), 7.20 (t, J = 7.5, 1H, H-8), 7.00 (d, J = 7.5, 1H, H-7), 6.02-6.12 (m, 1H, C*H*=CH_2), 4.96-5.02 (m, 1H, CH=C*H*$_2$), 4.87-4.91 (m, 1H, CH=C*H*$_2$), 4.52 (d, J = 6.5, 2H, *C*H_2CH=CH_2), 3.96 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 170.7 (C), 147.3 (C), 140.3 (CH), 138.7 (C), 135.5 (C), 133.8 (C), 131.2 (CH), 126.5 (CH), 124.9 (C), 123.3 (CH), 123.1 (C), 122.7 (CH), 121.6 (CH), 114.8 (CH), 113.8 (CH_2), 108.7 (CH), 103.1 (C), 39.6 (CH_2), 33.2 (CH_3); LRMS (ESI) m/z 311 (MNa^+, 100); HRMS (ESI) m/z calc'd for $C_{19}H_{16}N_2ONa$ 311.1160 found 311.1154.

11-Chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (10)

A mixture of 6-methyl-5*H*,6*H*-indolo[2,3-*b*]quinolin-11-one (**9**) (2.50 g, 10.1 mmol) and $POCl_3$ (50 mL) were heated at reflux, under an argon atmosphere, for 1 h and then cooled to room temperature. The excess of $POCl_3$ was removed under reduced pressure and crushed ice (*ca.* 50 g) was added to the residue. The mixture was basified with $NaHCO_{3(aq)}$ and the orange solid product was collected by filtration. The solids were washed with water and then thoroughly dried (an alternative to collecting the product by filtration is to extract it into DCM and dry the extracts with $MgSO_4$). There was thus obtained the title compound (**10**) as a bright orange solid of sufficient purity for subsequent reactions (2.56 g, 9.60 mmol, 95%); m.p. 182-183 °C; ν_{max} (KBr) 1632, 1610, 1572, 1523, 1491, 1438, 1272, 1235, 1193, 1139, 1076, 950, 887, 850, 751, 598, 465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42-8.47 (m, 2H, H-10, H-1), 7.72-7.84 (m, 3H, H-7, H-3, H-4), 7.49-7.62 (m, 2H, H-8, H-2), 7.26-7.31 (m, 1H, H-9), 4.35 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6 (C), 155.2 (C), 137.1 (C), 136.0 (C), 131.2 (CH), 129.9 (CH), 126.2 (CH), 125.0 (C), 124.1 (CH), 124.0 (C), 122.4 (CH), 120.4 (CH), 119.3 (C), 117.8 (CH), 114.4 (CH), 33.3 (CH_3); LRMS (ESI) m/z 267 (MH^+, 100); HRMS (ESI) m/z calc'd for $C_{16}H_{12}N_2Cl$ 267.0689 found 267.0688.

Preparation of 6-allyl-5-methyl-5*H*-indolo[2,1-*b*]quinazolin-12-one (14)

5,10b-Dihydro-10b-allyl-5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (**7**) (25 mg, 0.087 mmol) and MeOH (2.5 mL) were heated at reflux for 12 h. The reaction mixture was cooled to room temperature and the MeOH was evaporated under reduced pressure to afford the title compound **14** as a bright yellow crystalline solid (25 mg, 0.087 mmol, 100%). Crystals suitable for X-ray analysis were obtained from MeOH; m.p. 160-161 °C; Anal. calc'd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.04; H, 5.54; N, 9.75; ν_{max} (KBr) 1673, 1618, 1585, 1491, 1463, 1397, 1371, 1253, 1170, 1073, 1020, 912, 879, 775, 738, 684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.67-8.72 (m, 1H, H-10), 8.29 (dd, J = 7.8, 1.5, 1H, H-1), 7.57 (ddd, J = 8.5, 7.3, 1.5, 1H, H-3), 7.34-7.38 (m, 1H, H-7), 7.28 (td, J = 7.3, 1.3, 1H, H-8), 7.18-7.24 (m, 1H, H-9), 7.02-7.12 (m, 2H, H-2, H-4), 6.01-6.14 (ddt, J = 16.9, 10.1, 5.1, 1H, C*H*=CH_2), 5.13 (dq, J = 10.1, 1.7, 1H, CH=C*H*$_2$), 5.04 (dq, J = 16.9, 1.7, 1H, CH=C*H*$_2$), 3.73 (s, 3H, CH_3), 3.69 (dt, J = 5.1, 1.7, 1H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4 (C, C-12), 142.6 (C), 136.8 (CH), 135.6 (C), 134.6 (CH), 131.1 (C), 129.8 (C), 128.7 (CH), 124.2 (CH), 121.5 (CH), 120.4 (CH), 116.3 (CH), 116.14 (CH), 116.09 (CH_2), 114.0 (C), 112.5 (CH), 92.5 (C, C-6), 36.2 (CH_3), 28.8 (CH_2); LRMS (CI) m/z 289 (MH^+, 100); HRMS (CI) m/z calc'd for $C_{19}H_{17}N_2O$ 289.1341 found 289.1341.

Rac-(1′*R*,10b*S*)-5,10b-dihydro-10b-(1′-methylallyl)-5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (16a) and 5,6-dihydro-6-(*E*-but-2-enyl)-5-methylindolo[2,3-*b*]quinolin-11-one (17a)

Crude 11-(*E*-but-2-enyloxy)-5-methyl-5*H*-indolo[2,3-*b*]quinoline (**15a**) was prepared from 11-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (**10**) (200 mg, 0.750 mmol) in THF (10 mL), with the alkoxide generated from *trans*-2-buten-1-ol (0.51 mL, 6.01 mmol) and sodium (35 mg, 1.52 mmol) in THF (0.5 mL), using the following general method: alkoxides were formed by slowly adding the appropriate alcohol, at a rate that maintained a steady reaction, to sodium in THF with stirring and under an argon atmosphere. When all the sodium had dissolved, the alkoxide was added *via* cannula to a stirred mixture of the appropriate 11-chloro-5*H*-indolo[2,3-*b*]quinoline in THF (1 vol.). The reaction mixture was then stirred at room temperature, under an argon atmosphere, for 18 h. After adding a saturated solution of $NH_4Cl_{(aq)}$ (0.1 vol.), the solvent was removed under reduced pressure and the residue was partitioned between water (1 vol.) and CH_2Cl_2 (1 vol.). The organic phase was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 × 1 vol.). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and the CH_2Cl_2 was removed under reduced pressure. Purification by chromatography afforded **15a**. ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (dd, J = 8.2, 1.3, 1H, H-1), 8.11 (d, J = 7.5, 1H, H-10), 7.72-7.83 (m, 3H, H-7, H-3, H-4), 7.46-7.56 (m, 2H, H-8, H-2), 7.24-7.29 (m, 1H, H-9), 5.91-5.96 (m, 1H, CH_2CH), 5.66-5.70 (m, 1H, $CHCH_3$), 4.89-4.92 (m, 2H, CH_2), 4.35 (s, 3H, NCH_3), 1.76-1.78 (m, 3H $CHCH_3$). Crude **15a** was dissolved in THF (10 mL) and the mixture was heated at reflux for 2.5 h. The reaction was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography. The first, bright yellow crystalline solid, compound to be eluted ($CHCl_3$) was rac-(1′*R*,10b*S*)-5,10b-dihydro-10b-(1-methylallyl)-5-methylindolo[2,3-*b*]quinolin-11-one (**16a**) (91 mg, 0.301 mmol, 40%); m.p. 123-124 °C (dec.); ν_{max} (KBr) 3080, 2977, 2932, 1698, 1559, 1470, 1469, 1388, 1342, 1304, 1206, 1194, 1156, 1122, 1066, 1036, 970, 920, 872, 857, 801, 763, 748, 700, 644, 524, 456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, J = 7.5, 1.5, H-10), 7.58-7.64 (m, 2H, H-1, H-3), 7.33-7.43 (m, 2H, H-7, H-8), 7.10-7.17 (m, 3H, H-9, H-4, H-2), 5.79 (ddd, J = 17.0, 10.5, 8.5, 1H, C*H*=CH_2), 5.11 (ddd, J = 10.5, 1.5, 1.0, 1H, CH_2), 4.78 (dt, J = 17.0, 1.5, 1H, CH_2), 3.73 (s, 3H, NCH_3), 2.83-2.92 (m, 1H, $CHCH_3$), 0.56 (d, J = 7.0, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.3 (C, C-11), 172.1 (C), 154.6 (C), 145.2 (C), 136.7 (CH), 135.7 (CH), 130.8 (C), 129.0 (CH), 128.5 (CH), 125.6 (CH), 123.0 (CH), 122.6 (CH), 119.8 (C), 118.5 (CH), 117.7 (CH_2), 114.5 (CH), 70.5 (C), 46.3 (CH), 33.2 (CH_3), 14.1 (CH_3); LRMS (CI) m/z 303 (MH^+, 68), 249 (100); HRMS (CI) m/z calc'd for $C_{20}H_{19}N_2O$

303.1497 found 303.1488. The second, colourless crystalline solid, compound to be eluted (1% MeOH–$CHCl_3$) was 5,6-dihydro-6-(*E*-but-2-enyl)-5-methylindolo[2,3-*b*]quinolin-11-one (**17a**); m.p. 165-166 °C; Anal. calc'd for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.11; H, 5.80; N, 9.15; ν_{max} (KBr) 3053, 2915, 1617, 1590, 1538, 1506, 1461, 1394, 1362, 1323, 1285, 1262, 1189, 1168, 1125, 1069, 1036, 981, 927, 879, 753, 675, 606, 542, 487, 456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (dd, J = 8.5, 2.0, 1H, H-1), 8.50 (d, J = 7.5, 1H, H-10), 7.52 (ddd, J = 8.5, 7.5, 2.0, 1H, H-3), 7.16-7.32 (m, 4H, H-8, H-4, H-2, H-9), 7.08 (d, J = 8.0, 1H, H-7), 5.69-5.79 (m, 1H, CH_2CH), 5.54-5.67 (m, 1H, $CHCH_3$), 4.68-4.73 (m, 2H, CH_2), 3.90 (s, 3H, NCH_3), 1.72 (dd, J = 6.5, 1.5, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4 (C), 148.5 (C), 141.4 (C), 137.6 (C), 131.2 (CH), 129.0 (CH), 126.4 (CH), 125.7 (CH), 125.6 (C), 124.1 (C), 123.4 (CH), 122.6 (CH), 122.4 (CH), 121.4 (CH), 115.4 (CH), 109.5 (CH), 105.1 (C), 48.5 (CH_2), 37.3 (CH_3, NCH_3), 17.9 (CH_3, $CHCH_3$); LRMS (CI) m/z 303 (MH^+, 100); HRMS (CI) m/z calc'd for $C_{20}H_{19}N_2O$ 303.1497 found 303.1488.

5,6-Dihydro-5-methyl-6-(3-methyl-2-butenyl)indolo[2,3-*b*]quinolin-11-one (17b)

Crude 5-methyl-11-(3-methyl-2-butenyloxy)-5*H*-indolo[2,3-*b*]quinoline (**15b**) was prepared from 11-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (**10**) (200 mg, 0.750 mmol) in THF (10 mL), with the alkoxide generated from 3-methyl-2-buten-1-ol (0.61 mL, 6.01 mmol) and sodium (35 mg, 1.52 mmol) in THF (0.5 mL), using the following general method: alkoxides were formed by slowly adding the appropriate alcohol, at a rate that maintained a steady reaction, to sodium in THF with stirring and under an argon atmosphere. When all the sodium had dissolved, the alkoxide was added *via* cannula to a stirred mixture of the appropriate 11-chloro-5*H*-indolo[2,3-*b*]quinoline in THF (1 vol.). The reaction mixture was then stirred at room temperature, under an argon atmosphere, for 18 h. After adding a saturated solution of $NH_4Cl_{(aq)}$ (0.1 vol.), the solvent was removed under reduced pressure and the residue was partitioned between water (1 vol.) and CH_2Cl_2 (1 vol.). The organic phase was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 × 1 vol.). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and the CH_2Cl_2 was removed by evaporation under reduced pressure. Purification by chromatography afforded **15b**. ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (dd, J = 8.2, 1.0, 1H, H-1), 8.15 (d, J = 7.3, 1H, H-10), 7.68-7.77 (m, 3H, H-7, H-3, H-4), 7.40-7.55 (m, 2H, H-8, H-2), 7.20-7.28 (m, 1H, H-9), 5.71-5.77 (m, 1H, CH_2CH), 4.97 (d, J = 7.1, 2H, CH_2), 4.31 (s, 3H, NCH_3), 1.81 (s, 3H, CCH_3), 1.68 (s, 3H, CCH_3). Crude **15b** was dissolved in THF (10 mL) and the mixture was heated at reflux for 2.5 h. The reaction was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (1% MeOH–$CHCl_3$) to afford the title compound **17b** as a colourless crystalline solid (208 mg, 0.657, 88%); m.p. 220-221 °C; Anal. calc'd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.50; H, 6.28; N, 8.78; ν_{max} (KBr) 3057, 2980, 2912, 1621, 1594, 1539, 1509, 1460, 1389, 1372, 1327, 1264, 1211, 1182, 1155, 1039, 984, 926, 880, 745, 673, 610, 488, 463 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45-8.50 (m, 2H, H-1, H-10), 7.50 (ddd, J = 8.5, 7.0, 2.0, 1H, H-3), 7.17-7.30 (m, 4H, H-8, H-4, H-2, H-9), 7.05 (d, J = 8.0, 1H, H-7), 5.30-5.34 (m, 1H, $CHC(CH_3)_2$), 4.66 (d, J = 5.0, 2H, NCH_2), 3.83 (s, 3H, NCH_3), 1.81 (s, 3H, $C(CH_3)_2$), 1.78 (d, J = 1.0, 3H, $C(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4 (C), 148.3 (C), 141.4 (C), 137.5 (C), 136.2 (C), 131.1 (CH), 126.4 (CH), 125.5 (C), 124.1 (C), 123.3 (CH), 122.5 (CH), 122.4 (CH), 121.5 (CH), 120.4 (CH), 115.3 (CH), 109.3 (CH), 105.0 (C), 45.7 (CH_2), 37.6 (CH_3), 25.7 (CH_3), 18.6 (CH_3); LRMS (ESI) m/z 339 (MNa^+, 100); HRMS (ESI) m/z calcd for $C_{21}H_{20}N_2ONa$ 339.1473 found 339.1470.

5,10b-Dihydro-10b-(*E*-but-2-enyl)-5-methyl-10b*H*-indolo[2,3-*b*]quinolin-11-one (16c)

Crude 5-methyl-11-(1-methylallyloxy)-5*H*-indolo[2,3-*b*]quinoline (**15c**) was prepared from 11-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinoline (**10**) (100 mg, 0.375 mmol) in THF (5 mL), with the alkoxide generated from 3-buten-2-ol (0.25 mL, 2.91 mmol) and sodium (20 mg, 0.870 mmol) in THF (0.5 mL), using the following general method: alkoxides were formed by slowly adding the appropriate alcohol, at a rate that maintained a steady reaction, to sodium in THF with stirring and under an argon atmosphere. When all the sodium had dissolved, the alkoxide was added *via* cannula to a stirred mixture of the appropriate 11-chloro-5*H*-indolo[2,3-*b*]quinoline in THF (1 vol.). The reaction mixture was then stirred at room temperature, under an argon atmosphere, for 18 h. After adding a saturated solution of $NH_4Cl_{(aq)}$ (0.1 vol.), the solvent was removed under reduced pressure and the residue was partitioned between water (1 vol.) and CH_2Cl_2 (1 vol.). The organic phase was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 × 1 vol.). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and the CH_2Cl_2 was removed by evaporation at reduced pressure. Purification by chromatography afforded **15c**. ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (dd, J = 8.4, 1.4, 1H, H-1), 8.11 (d, J = 7.7, 1H, H-10), 7.69-7.78 (m, 3H, H-7, H-3, H-4), 7.53 (ddd, J = 8.2, 7.7, 1.7, 1H, H-8), 7.42 (ddd, J = 8.4, 6.4, 1.6, 1H, H-2), 7.22-7.27 (m, 1H, H-9), 6.10 (ddd, J = 17.2, 10.5, 6.4, 1H, $CH{=}CH_2$), 5.32-5.41 (m, 1H, $CHCH_3$), 5.18 (dt, J = 17.2, 1.1, 1H, $CH{=}CH_2$), 5.08 (dt, J = 10.5, 1.1, 1H, $CH{=}CH_2$), 4.33 (s, 3H, NCH_3), 1.60 (d, J = 10.4, 3H, $CHCH_3$). Crude **15c** was dissolved in THF and heated at reflux for 2.5 h under an argon atmosphere. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (10% to 20% EtOAc–hexane) to afford the title compound **15c** as a bright yellow crystalline solid (94 mg, 0.311 mmol, 83%); m.p. 114-116 °C; ν_{max} (KBr) 3027, 2936, 1693, 1559, 1472, 1453, 1387, 1344, 1289, 1204, 1164, 1121, 1054, 1016, 964, 845, 764, 746, 690, 654, 583, 504 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, J = 8.0, 1.5, 1H, H-1), 7.67 (d, J = 7.5, 1H, H-10), 7.62 (ddd, J = 8.5, 7.5, 1.5, 1H, H-8), 7.14 (d, J = 7.5, 1H, H-4), 7.34 (ddd, J = 7.5, 7.5, 1.5, 1H, H-3), 7.11-7.17 (m, 3H, H-2, H-7, H-9), 5.17-5.29 (m, 1H, $CHCH_3$), 4.96-5.07 (m, 1H, CH_2CH), 3.72 (s, 3H, NCH_3), 2.72 (dd, J = 13.0, 6.5, 1H, CH_2), 2.36 (dd, J = 13.0, 8.0, 1H, CH_2), 1.52 (d, J = 6.5, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0 (C), 172.6 (C), 153.5 (C), 145.4 (C), 135.9 (CH), 133.4 (C), 131.4 (CH), 128.8 (CH), 128.5 (CH), 124.7 (CH), 123.1 (CH), 122.7 (CH), 122.4 (CH), 119.2 (C), 118.6 (CH), 114.5 (CH), 66.6 (C), 44.4 (CH_2), 33.1 (CH_3), 18.0 (CH_3); LRMS (EI) m/z 302 (M^+, 28), 248 (100), 219 (45); HRMS (EI) m/z calc'd for $C_{20}H_{18}N_2O$ 302.1419 found 302.1426.

(*S*)-(−)-5-Benzyl-10-bromo-10b-(*E*-but-2-enyl)-5*H*-indolo[2,3-*b*]quinolin-11-one (18)

A mixture of 5,6-dihydro-5-benzyl-10-bromoindolo[2,3-*b*]quinolin-11-one (**19**) (200 mg, 0.496 mmol) and $POCl_3$ (3 mL) were heated at reflux for 3 h, under an argon atmosphere. After the excess of $POCl_3$ had been evaporated under reduced pressure (the addition and evaporation of a small amount of dry PhMe was used to remove the last remaining traces of $POCl_3$), CH_2Cl_2 (10 mL) and $NaHCO_{3(aq)}$ (10 mL) were added and the mixture was stirred until completely orange with no remaining yellow solids. The organic phase was separated and the aqueous phase was further extracted with CH_2Cl_2 (2 × 10 mL). The extracts were combined, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The resulting bright orange residue was dissolved in THF (10 mL), under an argon atmosphere, and the alkoxide generated from (*S*)-(+)-3-buten-2-ol (1.50 mL of a 2.7 M solution in THF, 0.556 mmol) and sodium (34 mg, 1.48 mmol) in THF (5 mL) was added. After stirring for 1.5 h, $NH_4Cl_{(aq)}$ (0.5 mL) was added and the solvent was evaporated under reduced pressure. The residue was partitioned between CH_2Cl_2 (5 mL) and water (5 mL), the CH_2Cl_2 was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 × 5 mL), the organic phase was combined, dried ($MgSO_4$) and the organic phase was evaporated under reduced pressure. The residue was dissolved in THF and heated at reflux under an argon atmosphere for 6 h. The THF was evaporated under reduced pressure and the crude product was purified by flash chromatography (10% EtOAc–hexane) to yield the title compound **18** as a bright yellow crystalline solid (167 mg, 0.365 mmol, 74%, $[\alpha]_D^{20}$ −347.1 (*c* 5.80, $CHCl_3$)). This material was crystallised from Et_2O–hexane to give a sample for X-ray analysis; m.p. 124-125 °C; ν_{max} (KBr) 1700, 1602, 1560, 1467, 1415, 1391, 1323, 1240, 1212, 1163, 1042, 965, 856, 785, 765, 693, 533 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, J = 8.0, 1.5, 1H, H-1), 7.00-7.51 (m, 11H, 11 x ArH), 5.85 (d, J = 16.5, 1H, NCH_2), 5.31-5.46 (m, 1H, $CHCH_3$), 5.04 (d, J = 16.5, 1H, NCH_2), 4.63-4.78 (m, 1H, CH_2CH), 3.49 (dd, J = 13.5, 7.0, 1H, CH_2CH), 2.86 (dd, J = 13.5, 7.5, 1H, CH_2CH), 1.37 (dd, J = 6.5, 1.5, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2 (C, C-11), 171.4 (C), 156.6 (C), 144.3 (C), 136.4 (C), 135.5 (CH), 132.0 (C), 131.3 (CH), 130.5 (CH), 129.0 (2 x CH), 128.6 (CH), 128.1 (CH), 127.7 (CH), 126.9 (2 x CH), 123.0 (CH), 122.2 (CH), 120.4 (C), 119.0 (C), 117.7 (CH), 115.4 (CH), 69.7 (C), 50.1 (CH_2), 38.4 (CH_2), 17.9 (CH_3); LRMS (CI) m/z 456 ($^{79}BrM^+$, 30), 457 ($^{79}BrMH^+$, 42), 458 ($^{81}BrM^+$, 41), 459 ($^{81}BrMH^+$, 39), 405 (65), 403 (100), 325 (75); HRMS (CI) m/z calc'd for $C_{26}H_{22}N_2O^{79}Br$ 457.0915 found 457.0915.

5,6-Dihydro-5-benzyl-10-bromoindolo[2,3-*b*]quinolin-11-one (19)

A solution of 2-(benzylphenylamino)-4-bromo-indole-3-carboxylic acid methyl ester (310 mg, 0.714 mmol) in Ph_2O (2.5 mL) was heated at 250 °C, under an argon atmosphere, for 2 h. After cooling to room temperature, the formed solids were collected by filtration and washed with Et_2O to yield the title compound **19** as a light brown crystalline solid (241 mg, 0.598 mmol, 84%); m.p. *ca.* 320 °C (dec.); ν_{max} (KBr) 3031, 1616, 1546, 1508, 1454, 1431, 1371, 1325, 1115, 1053, 871, 755, 739, 692, 538, 505, 458 cm^{-1}; ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 12.46 (s, 1H, NH), 8.39 (d, J = 8.0, 1H, H-1), 7.12-7.64 (m, 11H, 11 × ArH) 5.77 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 170.5 (C, C-11), 147.6 (C), 138.1 (C), 136.7 (C), 135.7 (C), 131.5 (CH), 128.9 (2 x CH), 127.5 (CH), 126.7 (CH), 126.6 (CH), 126.0 (2 x CH), 125.6 (C), 124.5 (C), 124.2 (CH), 122.0 (CH), 115.2 (CH), 112.7 (C), 110.3 (CH), 101.2 (C), 48.6 (CH_2); LRMS (CI) m/z 402 ($^{79}BrM^+$, 60), 403 ($^{79}BrMH^+$, 85), 404 ($^{81}BrM^+$, 78), 405 ($^{81}BrMH^+$, 60), 325 (70), 315 (87), 314 (100), 313 (90), 312 (89), 234 (35); HRMS (CI) m/z calc'd for $C_{22}H_{16}N_2O^{79}Br$ 403.0446 found 403.0436.

Preparation of 2-(benzylphenylamino)-4-bromoindole-3-carboxylic acid methyl ester (21)

N-Chlorosuccinimide (116 mg, 0.869 mmol) and *N*,*N*′-dimethylpiperazine (0.06 mL, 0.436 mmol) were added to a mixture of 4-bromo-1*H*-indole-3-carboxylic acid methyl ester (**20**) (200 mg, 0.787 mmol) and powdered 4 Å molecular sieves (400 mg) in CH_2Cl_2 (4 mL) at 0 °C, maintained under an argon atmosphere. After stirring for 2 h a solution of *N*-benzylaniline (288 mg, 1.57 mmol) and trichloroacetic acid (0.02 mL 0.0196 mmol) in CH_2Cl_2 (4 mL) was added. The reaction mixture was allowed to warm to room temperature and the stirring was continued for 20 h. The molecular sieves were removed by filtration and the filtrate was washed sequentially with 1.0 M $HCl_{(aq)}$ (4 mL), $NaHCO_{3(aq)}$ (4 mL) and water (4 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (5% to 10% EtOAc–hexane) to afford the title compound **21** as a colourless crystalline solid (310 mg, 0.712 mmol, 90%); m.p. 156-157 °C; ν_{max} (KBr) 3267, 1672, 1599, 1543, 1498, 1446, 1325, 1253, 1172, 1127, 1083, 1029, 950, 772, 743, 690, 622, 506, 459, 437 cm^{-1}; LRMS (CI) m/z 434 ($^{79}BrM^+$,8 6), 435 ($^{79}BrMH^+$, 97), 436 ($^{81}BrM^+$, 100), 437 ($^{81}BrMH^+$, 85), 405 (25), 403 (26), 356 (40); HRMS (CI) m/z calc'd for $C_{23}H_{20}N_2O_2{}^{81}Br$ 437.0688, found 437.0678; The NMR data presented shows both the 3*H**- and 1*H*-indole tautomer. ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 0.8H, NH), 6.85-7.39 (m, 13H, 7.5 x ArH, 7.5 ArH*), 5.22 (d, J = 14, 0.2H, CH_2*), 5.12 (d, J = 14, 0.2H, CH_2*), 4.58 (s, 0.2H, H-3*), 3.65 (s, 2.4H, CH_3), 3.37 (s, 0.6H, CH_3*).

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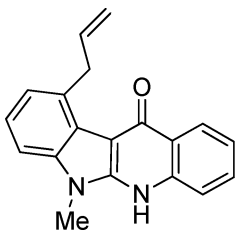

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