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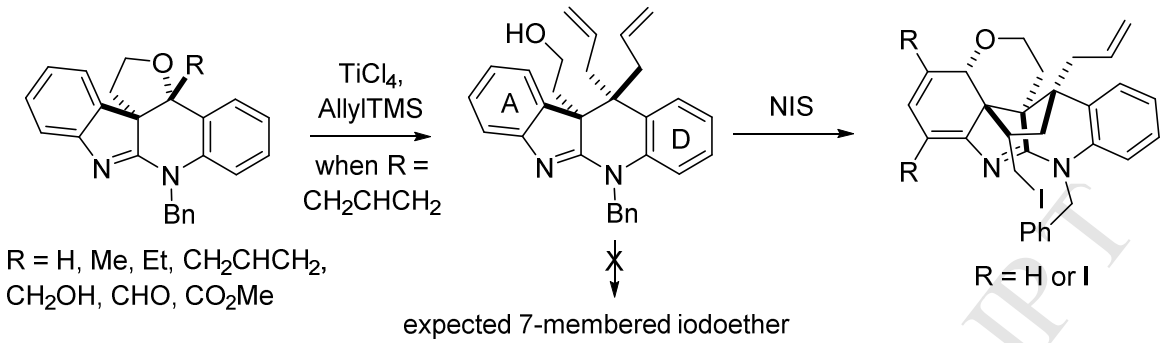

Graphical Abstract

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Polycyclic Ethers and an Unexpected Dearomatisation Reaction during studies towards the Bioactive Alkaloid, Perophoramidine

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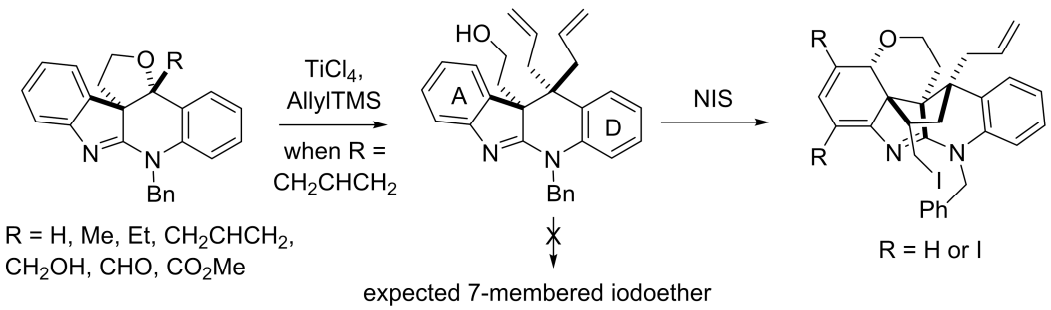

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Polycyclic Ethers and an Unexpected Dearomatisation Reaction during studies towards the Bioactive Alkaloid, Perophoramidine

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ABSTRACT

The bioactive alkaloid natural product perophoramidine and the related family of compounds known as the communesins have inspired the synthesis community for more than a decade. Many of the elegant approaches have required the synthesis of complex intermediates that have not always reacted in the expected manner. In this study we describe a series of cyclic ether-containing precursors that were prepared during our synthetic studies towards these natural products. Attempts to open the cyclic ether ring and trap the resulting stabilised carbocation with a carbon nucleophile ultimately led to the preparation of a diallyl-substituted all carbon quaternary centre. Subsequent attempts to differentiate between the two allyl groups resulted in a relatively clean transformation to an unexpected compound. Extensive structural characterisation, including small molecule X-ray crystallography, showed that a dearomatisation reaction had occurred.

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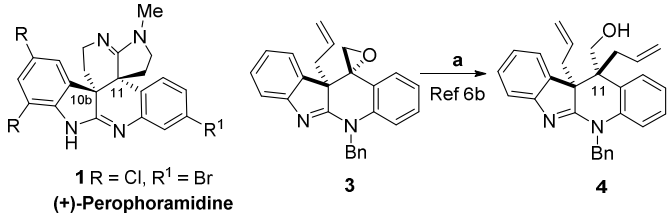
1. Introduction

Perophoramidine (**1**) and the family of alkaloids known as the communesins have provided a significant challenge to the synthesis community for more than a decade (Figure 1).[1-5] Their complex polycyclic structures and the abundance of stereogenic centres, two of them being all carbon quaternary centres, have tested a range of synthetic methodologies to the full. We have reported a total synthesis of the simplified dehaloperophoramidine (**2**) structure which involved, as a key carbon-carbon bond forming step, the Lewis-acid catalysed opening of epoxides of the general type **3** and subsequent trapping with allyl-trimethylsilane to give **4**.[6,7] This strategy was inspired by a series of observations on structurally related cyclic ethers. The synthesis and studies on the reactivity of these

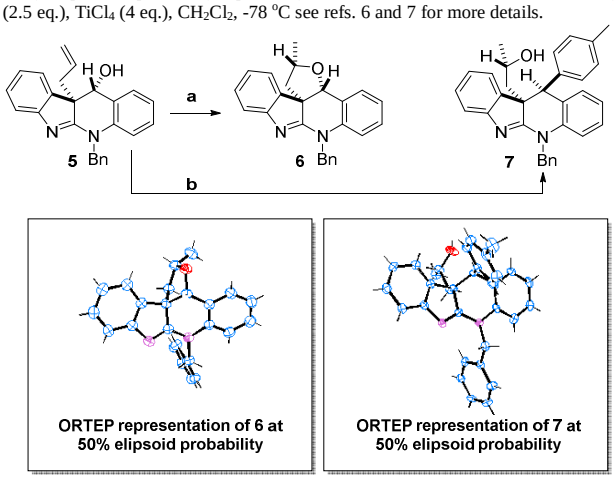


1 R = Cl, R^1 = Br
(+)-Perophoramidine
2 R = R^1 = H
(+)-Dehaloperophoramidine

3 **4**

previously unreported ethers are described here.

Figure 1: Structures of Perophoramidine (**1**), the related Dehaloperophoramidine (**2**) and a key step in our previously reported synthesis of **2**. Reaction conditions: a) Allyl-TMS (2.5 eq.), $TiCl_4$ (4 eq.), CH_2Cl_2, -78 ^oC see refs. 6 and 7 for more details.

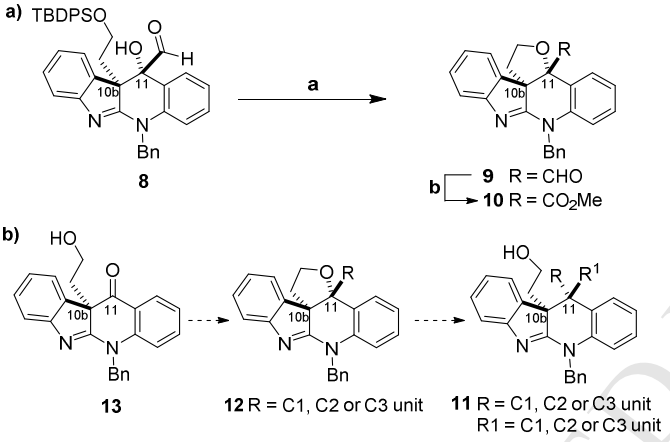


Scheme 1: Synthesis and subsequent reaction of cyclic ether **6**; Reagents and conditions: a) $AlCl_3$ (7 eq.), CH_2Cl_2, rt, 95%; b) $AlCl_3$ (7 eq.), CH_2Cl_2, rt then after work up $AlCl_3$ (7 eq.), PhMe, rt, 46% over 2 steps. The structures of **6** (left) and **7** (in box) were confirmed by X-ray crystallographic analysis.

2. Results and Discussion

Our interest in cyclic ethers in this context was first aroused when allylic alcohol **5** was treated with an excess of aluminium trichloride at room temperature in dichloromethane. In line with previous literature precedent using $AlCl_3$[8] and work using

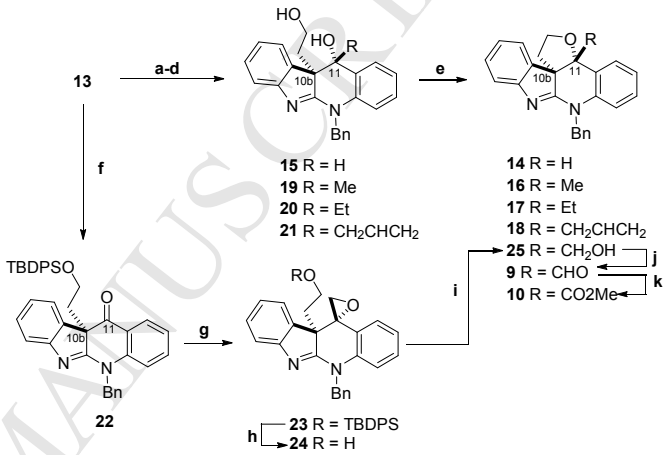
$BF_3.Et_2O$,[9] both on unrelated structures, we observed highly diastereoselective formation of cyclic ether **6** in 95% yield (Schemes 1 and S1). Small molecule X-ray crystallographic analysis of **6** confirmed the structure as drawn. A limited screen of alternative Lewis acids (Table S1) suggested that the use of $AlCl_3$ was important for the formation of **6** from **5**. Interestingly, when toluene was used as a solvent in place of dichloromethane in the $AlCl_3$ reaction, a second product assigned as structure **7**, resulted from ring opening of the cyclic ether ring. The ^{1}H NMR of **7** was noteworthy due to the presence of an apparent doublet (with a small coupling constant of J = 1.3 Hz) equating to 4 protons in the aromatic region. Combined with the presence of a new signal corresponding to an aromatic methyl group and other analytical data, it was concluded that a molecule of the solvent (toluene) had been incorporated into the product during this reaction. Small molecule X-ray crystallographic analysis of **7** confirmed the structure and the observed signal in the ^{1}H NMR spectrum of **7** was rationalised based on a small chemical shift difference between the aromatic protons in the toluene ring in **7** leading to a small coupling constant. Exposure of a crude sample of **6** prepared in dichloromethane to excess $AlCl_3$ in toluene gave exclusively **7** as a single diastereomer (Scheme S1).



Scheme 2: 5-membered cyclic ethers **12** were viewed as a central unit in a plan to form an all-carbon quaternary centre at position C11 in **11**. **a)** Conversion of previously reported aldehyde **8** to ethers **9** and **10.** Reaction conditions: **a** TBAF, *p*-TsCl, DMAP, CH_2Cl_2, rt, 82%; **b** (i) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, ^{t}BuOH, H_2O, rt, 2h; (ii) $TMSCHN_2$, MeOH, rt, 1h, 54% over two steps. **b)** proposed route from **13** via cyclic ethers of general structure **12** to **11** inspired by the experimental observations shown in Schemes 1 and 2a.

A second interesting observation came following our previously reported synthesis of the α-hydroxy aldehyde **8** (Scheme 2a).[7] Reaction of **8** with TBAF in the presence of tosyl chloride and DMAP resulted in the formation of another 5-membered cyclic ether **9** (Scheme S2 for a more detailed discussion). In contrast to cyclic ether **6** (Scheme 1), ether **9** does not possess a hydrogen atom at the C11 position. The conversion of **8** to **9** was assumed to occur via tosylation of the initial formed primary alkoxide followed by nucleophilic substitution involving attack of the tertiary alcohol/alkoxide at the tosyl-substituted carbon. Subsequent oxidation of aldehyde **9** and esterification gave cyclic ether **10** in moderate yield over the two steps. Combining the two observations described in Schemes 1 and 2a led us to consider a new approach for establishing the C11 all carbon quaternary centre in compounds of general type **11** (Scheme 2b). This strategy would involve the synthesis of relevant C11-substituted cyclic ethers of the general type **12** which could potentially undergo ring opening and trapping with a suitable carbon nucleophile. The conversion of the ketone **13** to **12** became the next challenge.

Rapid access to the C11-H cyclic ether **14** was achieved following reduction of **13** using sodium borohydride to give **15.** Reaction of **15** with tosyl chloride in pyridine (2 hours at room temperature
followed by heating at 60 ^{o}C), inspired by existing literature on unrelated structures,[10] gave **14**. Cyclic ethers **16**-**18** were prepared in excellent yields and as single diastereomers by an analogous route using greater than two equivalents of the corresponding Grignard reagent to give alcohols **19**-**21**. Cyclisation of **19**-**21** using tosyl chloride gave **16**-**18**. Finally, increased quantities of cyclic ether **10** were prepared from **13** via



O-silylation to give **22**, diastereoselective conversion to the epoxide **23** followed by deprotection to give **24**. Reaction of epoxide **24** with *p*-toluenesulfonic acid[11] at room temperature gave the cyclic ether **25** in excellent yield. Dess-Martin oxidation[12] of **25** to **9** followed by Pinnick oxidation[13] and esterification gave **10**.

Scheme 3: Formation of cyclic ethers **14**, **16**-**18**, **25**, **9** and **10**. Reaction conditions: **a** $NaBH_4$, MeOH, 0 ^{o}C to rt, 1h 95% for **15**; **b** MeMgCl (2.2 eq.), THF, 0 ^{o}C to rt, 1h, 98% for **19**; **c** EtMgCl (4 eq.), THF, 0 ^{o}C to rt, 1h, 96% for **20**; **d** allyl MgCl (3.0 eq.), THF, 0 ^{o}C to rt, 1h, 92% for **21**; **e** *p*-TsCl, pyridine, rt, 2hs then 60 ^{o}C for 5 hs., 70% for **14**, 81% for **16**, 84% for **17**, 70% for **18**; **f** TPDBS-Cl, imid., DCM, rt, 1 h; **g**; $ClICH_2$, MeLi:LiBr, THF, 6 h, -78 ^{o}C – rt, 71% (2 steps); **h** TBAF, THF rt, 2 hs, 98%; **i** *p*-TsOH, CH_2Cl_2, rt, 18hs, 94%; **j** Dess-Martin periodinane,[12] CH_2Cl_2, rt, 1h, 90%; **k** (i) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, ^{t}BuOH, H_2O, rt, 2h; (ii) $TMSCHN_2$, MeOH, rt, 1h, 54% (2 steps).

Having accessed a number of cyclic ethers of general structure **12** (Scheme 2b), attempts to open the ether ring with concomitant trapping of the resulting carbocation with a carbon nucleophile were carried out. Initially we returned to the $AlCl_3$-mediated opening in toluene. Encouragingly, cyclic ethers **14**, **16** and **17** were converted under these conditions to **26**, **27** and **28** respectively (Figure 2) in an analogous manner to the conversion of **6** to **7** (Scheme 1). Evidence to support the assigned relative stereochemistry of **26**-**28** came from NOESY experiments (Figures S1-S3). It was determined that greater than 3 eqs. of $AlCl_3$ were required for these reactions to proceed possibly due to competing coordination of the Lewis acid to other heteroatoms.

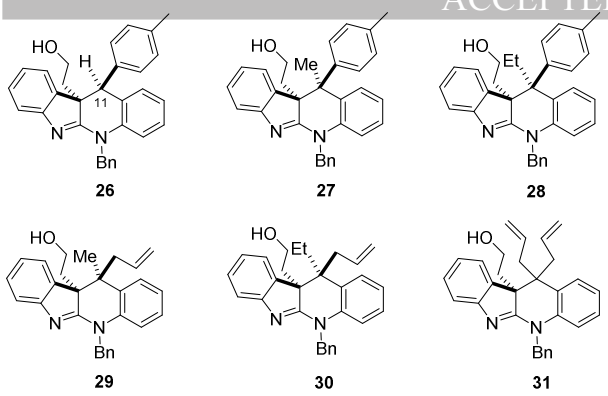
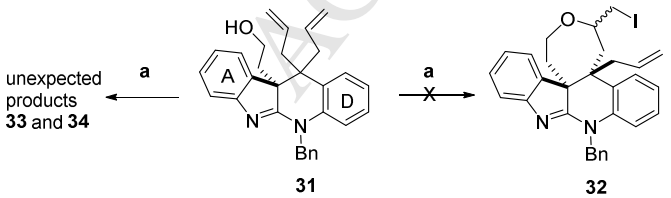


Figure 2: Structures of compounds obtained from ring opening of cyclic ethers followed by trapping with a carbon-based nucleophile. Reagents and conditions: $AlCl_3$ (7 eq.), PhMe, rt, 77% for **26** from **14**; 83% for **27** from **16**; 70% for **28** from **17**. $AlCl_3$ (7 eq.), allylTMS (10 eq.), CH_2Cl_2, rt, 1h. 87% for **29** from **16**; 68% for **30** from **17**; $TiCl_4$ (5 eq.), allylTMS (5 eq.), CH_2Cl_2, -78 °C, 4.5hs. 87% for **31** from **18**.

The reaction of cyclic ether **18** (Scheme 3) with $AlCl_3$ in toluene led to full consumption of the starting material but a complex mixture of products was formed and the expected product could not be isolated. Unfortunately, cyclic ethers **10** and, perhaps more surprisingly, **25** did not react at room temperature even after extended reaction times (up to 18 hours). Increasing the number of equivalents of $AlCl_3$ and/or heating the reaction using conventional or microwave methods had no effect. Use of a p-toluenesulfonic acid-mediated protocol, that had been successful for the conversion of **14** to **26**, did not work in the case of **25** (Scheme S3) Use of the Hosomi-Sakuri protocol[14] with $AlCl_3$ and allyltrimethylsilane as the nucleophile in dichloromethane enabled the synthesis of **29** and **30** from **16** and **17** respectively (Figures 2, S4 and S5). Again, the attempted reaction of **18** gave a complex mixture and, despite considerable efforts (Table S2), none of the desired products could be obtained when **10** and **25** were used under these conditions. However a change of Lewis acid from $AlCl_3$ to $TiCl_4$, inspired by a report from Heathcock,[15] did enable the synthesis of **31** (Figure 2) from **18** in 87% yield. Having successfully established a robust route to an all carbon quaternary centre at C11 in **31**, it became clear that to progress further towards the natural products it would be necessary to differentiate between the two allyl groups present at the C11 position. One possible approach to this was to attempt a selective iodoetherification reaction on **31** in the hope that a 7-membered cyclic ether ring (as in **32**, Scheme 4) would form on reaction of the primary alcohol in **31** with the allyl group that was on the same face (as opposed to the other more distant C11-allyl group). The remainder of this report describes the unexpected outcome of the attempted iodoetherification reaction of **31**.



Scheme 4: The attempted conversion of **31** to **32**. Reagents and conditions: **a** NIS (1.2 eqs.), CH_2Cl_2, rt, 1h, 40% recovered starting material **31**; 15% of **33** and 9% of **34**. See Figure 3 and Scheme 5 for the structures of **33** and **34**. The use of the A and the D-ring nomenclature is highlighted in the structure of the starting material **31**.

Preliminary studies on the reaction of **31** with iodine or N-iodosuccinimde (NIS) in a range of solvents including acetonitrile and dichloromethane, with or without the addition of base ($NaHCO_3$ or NaHMDS), resulted in the partial reaction of **31** to give on all occasions what appeared to be a mixture of 3 major products along with some unreacted starting material **31**. It proved possible to isolate 2 of the new products (**33** and **34**) in sufficient quantities for detailed analysis. ^{1}H NMR analysis of the first of these products indicated that only one allyl group was still present (Figure 3a, red section in structure). It was also clear that the C-10b CH_2-CH_2-O substituent present in **31** was retained, but that the signals corresponding to the CH_2-O group had shifted from 2.85 and 3.11 ppm in **31** to 3.65 and 3.99 ppm (Figures 3a and S6). The significant downfield shift of these types of signals had been observed on several occasions during this work following cyclic ether formation. A new singlet at 4.27 ppm corresponding to a CH proton was also observed, with the proton being bonded to a carbon atom with a ^{13}C NMR chemical shift of 88.0 ppm (data not shown). This peak was not present in the starting material **31** and would not be expected in **32**. There was also (i) a CH_2I group (as observed by a characteristic ^{13}C peak at 9.0 ppm), (ii) an additional CH_2 group and (iii) a CH (observed as a multiplet at around 2.4 ppm) bonded to a carbon atom with a ^{13}C chemical shift of 45.7 ppm. Analysis of the COSY spectrum indicated that the CH multiplet at 2.4 ppm correlated with both the CH_2I and the other CH_2 group. This suggested that the atoms corresponding to these signals were connected in the sequence CH_2I-CH-CH_2 with this fragment most likely coming from the reaction of one of the allyl substituents with iodine. The CH proton did not correlate with any other signal (Figure 3 blue section in structure). The aromatic region of the ^{1}H NMR spectrum contained only 10 protons with 8 CH environments observed in the HSQC spectrum. This was lower than the 13 aromatic protons present in the starting material **31** and the expected product **32**, suggesting that some change to the molecule had taken place in one or more of the aromatic rings.

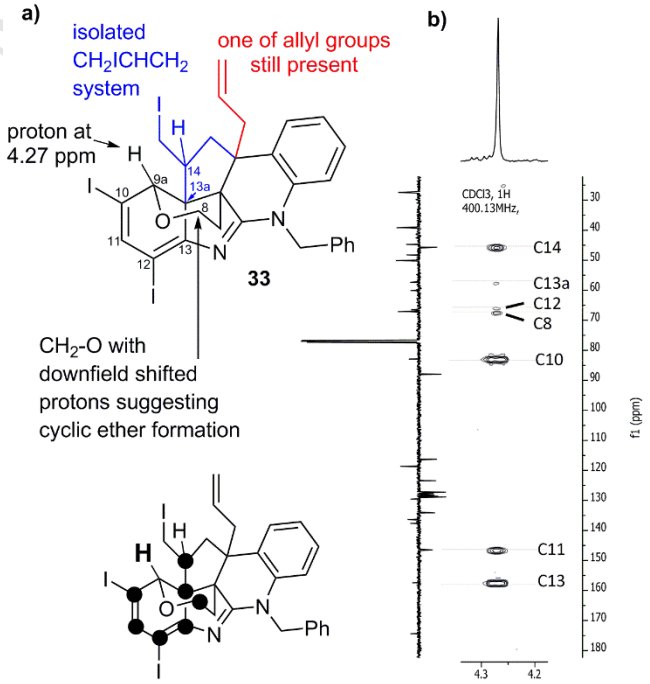
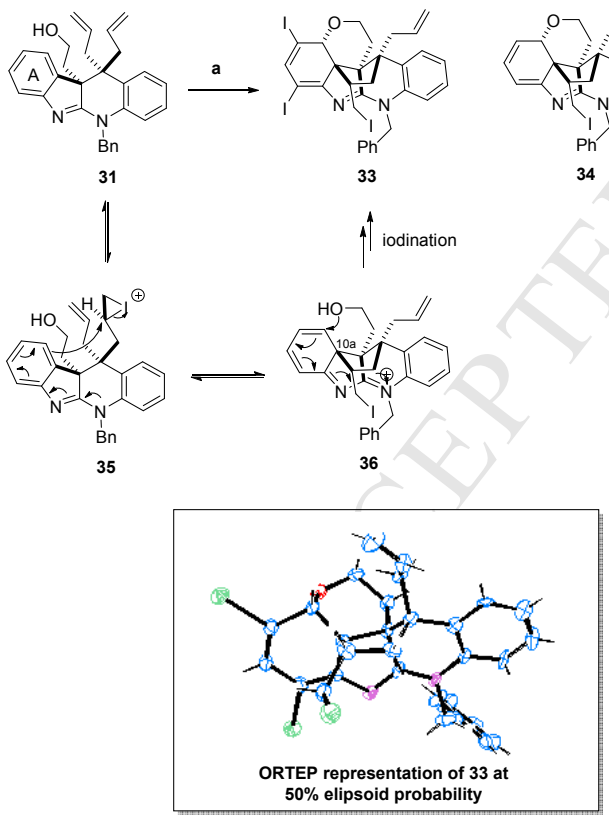


Figure 3: The attempted conversion of **31** to **32**. Reagents and conditions: **a** NIS (1.2 eqs.), CH_2Cl_2, rt, 1h, 40% recovered starting material **31**; 15% of **33** and 9% of **34**. See above and Figure 4 for the structures of **33** and **34**.

Analysis of the ^{13}C NMR spectrum indicated that there were 30 carbon atoms present in the product, suggesting that no carbon atoms were lost or gained in the reaction. DEPTQ analysis identified a CH signal with a chemical shift of 146.5 ppm, which was much higher than any CH carbon observed in related compounds. It was thought that this signal may have originated from the A ring of **31**. It was also noted that the signals

corresponding to the three other aromatic protons in the A ring of **31** were not observed (Scheme 4), suggesting that reaction had taken place on this ring. There also appeared to be 7 CH_2 carbon environments present and 10 quaternary carbon environments. This was 2 more quaternary carbons than in **31** or would be expected in **32**. With this information in mind, the HMBC spectrum of the product was analysed to try to determine the atom connectivity. The CH singlet at 4.27 ppm correlated with seven other carbon atoms (Figure 3) including a CH_2O (67.2 ppm), CH (45.7 ppm) and a CH (146.5 ppm). These correlations suggested that this CH group was within 2-3 bonds of the C-10b substituent, the signals corresponding to the reacted allyl and the A ring. The close bonding proximity of all of these groups, and the large number of HMBC correlations observed for this CH singlet suggested that a multi-ring system may have been formed. Surprisingly, it seemed likely that the A ring was no longer aromatic and now contained four quaternary carbons. High resolution mass spectrometric analysis of the product found a m/z of 812.9329, which was much higher than that of the starting material **31** (435.2430 $[M+H]^+$) and the expected product **32** (561.1403, expected $[M+H]^+$). This mass corresponded to a molecular formula of $C_{30}H_{28}O_1N_2I_3$ which suggested the addition of 3 iodine atoms and the loss of three hydrogen atoms had occurred relative to **31**. This data, as well as that obtained from the NMR analysis, led to the proposal that this product was **33** (Figure 3, Scheme 5 and Tables S3 and S4 for full assignments of ^1H and ^{13}C NMR). This proposed structure of **33** was found to be consistent with all of the characterisation data obtained including the key HMBC correlations.



Scheme 5: Optimised formation of **33** from **31**. Reagents and conditions: **a** NIS (3.6 eq), CH_2Cl_2, rt, 6 h, 65%. One possible mechanism for the reaction is shown. The structure of **33** was confirmed by X-ray crystallographic analysis.

The unusual structure proposed for **33** contained three contiguous all carbon quaternary carbon centres, as well as two additional stereocentres. It was thought that at least 3 equivalents of NIS were required to produce **33** and so the reaction of **31** was repeated with 3.6 equivalents of NIS resulting in the production of **33** as a single product in reasonably high yield (65%). Upon recrystallisation of **33** from ethyl acetate and methanol, a crystal was obtained that was suitable for X-ray crystallographic analysis. The analysis found a pair of enantiomers present in the unit cell in line with the fact that the starting material **31** was racemic. This analysis confirmed that the connectivity in the structure of **33** was as assigned by NMR and mass spectrometric analysis and enabled the relative stereochemistry of **33** to be assigned (Scheme 5). One possible mechanism for the formation of **33** could involve reversible reaction of **31** with NIS to form a series of iodonium ions, one of which (**35** in Scheme 5) could undergo nucleophilic attack from the aromatic A ring to give **36**. This would lead to formation of a new ring by linking one of the two allyl substituents and the C-10a position. The alcohol substituent could then add to the extended iminium system in **36** to form the cyclic ether ring. Subsequent iodination of the diene unit by the remaining NIS could form **33**. Evidence to support this mechanism came from the observation that the second product from the original studies was assigned the structure **34** based on comparison of the NMR analysis with that of **33**. The three signals corresponding to the diene protons in **34** were all found in the 5.6 – 6.4 ppm region of the ^1H NMR spectrum (Figure S7), as expected. Treatment of a crude sample of **34** with NIS led to formation of **33** (Figure S8).

3. Conclusions

In conclusion, we have described the synthesis of a series of cyclic ether containing compounds that are structurally related to the bioactive alkaloid natural product perophoramidine (**1**). Attempts to open the ether rings and trap the resulting carbocations with carbon nucleophiles proved successful in several cases leading us to the C11-diallylated compound **31**. In order to progress further towards the target molecules **1** and **2**, an attempt was made to differentiate between the two allyl substitutents using an intramolecular iodoetherification protocol. Unexpectedly, this led to a major structural change involving an unusual dearomatisation reaction. The hexacyclic core structure that results contains 3 contiguous all carbon quaternary centres and five stereogenic centres in total. To the best of our knowledge, the closest literature precedent (Scheme S4) proceeds via radical intermediates rather than likely carbocation intermediates involved in the chemistry described here.[16] We remain surprised by the complexity of the compounds formed during, what appeared on paper at least, to be a reasonable synthetic plan.

4. Experimental

4.1. 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 visualised 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.

4.2. General Procedures

4.2.1. Aluminum trichloride-mediated opening of cyclic ether compounds in touene

To a solution of the cyclic ether compound (1 eq.) in toluene (1 vol) was added $AlCl_3$ (7 eq.). The mixture was stirred at rt for 1h before 1M NaOH (1 vol) was added and the mixture extracted with ethyl acetate (3 x 1 vol). The organic extracts were dried ($MgSO_4$), filtered and concentrated before purification by column chromatography (EtOAc/hexanes) to give the desired product.

4.2.2. Aluminum trichloride-mediated opening of cyclic ether compounds in the presence of allyltrimethyl silane.

To a solution of the cyclic ether compound (1eq.) in DCM (1 vol) was added allyltrimethylsilane (10 eq.) followed by $AlCl_3$ (7 eq.). The mixture was stirred at rt for 1h before 1M NaOH (10 vol) was added and the mixture extracted with DCM (3 x 10 vol). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated before the crude product was purified by column chromatography (EtOAc/hexanes) to give the alcohol product.

4.3. Compounds synthesised

*4.3.1. (±)-(2R,10bS,11S)-5-benzyl-2'-methyl-1',2',10b,11-tetrahydrofuro[3,2-c]indolo[2,3-b]quinoline (**6**)*

To a stirred solution of **5**[7] (0.05 g, 0.137 mmol) in CH_2Cl_2 (10 mL) was added $AlCl_3$ (0.131 g, 0.985 mmol). The suspension was stirred at rt for 18h before sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction. The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic extracts were washed with water (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (20% EtOAc/hexane) afforded **6** (0.048 g, 0.133 mmol, 95%). Crystals suitable for X-ray analysis were obtained. I.R. (ATR) ν_{max}: 1555, 1456, 1045, 999, 802 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (1H, ddd, *J*=7.5, 1.5, 1.0 Hz), 7.50 – 7.44 (2H, m), 7.38 – 7.30 (5H, m), 7.30 – 7.24 (1H, m), 7.24 – 7.17 (1H, m), 7.15 – 7.07 (2H, m), 6.96 (1H, dd, *J*=8.0, 1.0 Hz), 5.96 (1H, d, *J*=16.5 Hz), 5.27 (1H, s), 5.10 (1H, d, *J*=16.5 Hz), 4.74 (1H, qd, *J*=9.5, 6.0 Hz), 2.31 – 2.23 (1H, m), 2.12 (1H, dd, *J*=12.0, 6.5, 0.5 Hz), 1.19 (3H, d, *J*=6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 154.4, 139.7, 138.1, 137.0, 129.7, 129.1, 129.0, 128.7, 127.4, 126.5, 126.0, 122.9, 122.7, 121.6, 118.0, 115.0, 79.2, 75.1, 58.3, 49.3, 44.3, 22.9; LRMS (ESI) *m/z* 367 ([M+H]$^+$, 100), 389 ([M+Na]$^+$, 60); HRMS (ESI) *m/z* [M+H]$^+$ calcd. for $C_{25}H_{23}N_2O^+$ 367.1805, found 367.1794.

*4.3.2. (±)-1-((10bS,11R)-5-benzyl-11-(p-tolyl)-5,11-dihydro-10bH-indolo[2,3-b]quinolin-10b-yl)propan-2-ol (**7**)*

To a stirred solution of **5** (0.05 g, 0.137 mmol) in PhMe (10 mL) was added $AlCl_3$ (0.131 g, 0.985 mmol). The suspension was stirred at rt for 18h before sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction. The aqueous layer was separated and extracted with EtOAc (2 x 10 mL) and the combined organic extracts were washed with water (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc/hexane) afforded **7** (0.029 g, 0.063 mmol, 45%). Crystals suitable for X-ray analysis were obtained. I.R. (ATR) ν_{max}: 3250, 1558, 1541, 1456, 1215, 1140 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.42 (2H, m), 7.38 (2H, dd, *J*=8.0, 7.0 Hz), 7.36 – 7.26 (2H, m), 7.24 – 7.13 (3H, m), 7.13 (1H, ddd, *J*=7.5, 1.0 Hz), 7.08 (1H, d, *J*=8.0 Hz), 7.02 – 6.89 (2H, m), 6.79 (4H, d, *J*=1.5 Hz), 5.98 (1H, d, *J*=16.0 Hz), 5.06 (1H, d, *J*=16.5 Hz), 4.60 (1H, s), 3.71 – 3.62 (1H, m), 2.29 – 2.10 (2H, m), 2.11 (3H, d, *J*=1.0 Hz), 0.99 (3H, dd, *J*=6.5, 1.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 155.5, 140.0, 137.3, 136.4, 136.4, 136.3, 130.8, 128.9, 128.6, 128.3, 127.9, 127.6, 127.0, 126.4, 123.5, 123.5, 122.2, 118.1, 115.4, 65.5, 57.0, 50.9, 49.7, 45.9, 24.2, 21.0; LRMS (ESI) *m/z* 459 ([M+H]$^+$, 100), 481 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* [M+H]$^+$ calcd. for $C_{32}H_{31}N_2O^+$ 459.2431, found 459.2417.

6 (0.016 g, 0.044 mmol, 31%) was also isolated from this reaction. An alternative protocol for the preparation of **7** was also used: To a stirred solution of **5** (0.04 g, 0.109 mmol) in CH_2Cl_2 (2 mL) was added $AlCl_3$ (0.102 g, 0.765 mmol). The suspension was stirred at rt for 18h before sat. aq. $NaHCO_3$ (5 mL) was added to quench the reaction. The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic extracts were washed with water (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford **6** which was used without further purification. To a stirred solution of **6** (0.109 mmol) in PhMe (3 mL) was added $AlCl_3$ (0.106 g, 0.797 mmol). The suspension was stirred at rt for 18h before sat. aq. $NaHCO_3$ (5 mL) was added to quench the reaction. The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic extracts were washed with water (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc/hexane) afforded **7** (0.023 g, 0.05 mmol, 46%, 2 steps).

*4.3.3. (±)-(3aR,13bR)-9-Benzyl-2,3,9,13b-tetrahydrofuro[3,2-c]indolo[2,3-b]quinoline-13b-carbaldehyde (**9**)*

To a solution of **8**[7] (45 mg, 0.071 mmol) in DCM (1 mL) was added *p*-toluenesulfonyl chloride (20 mg, 0.106 mmol), 4-dimethylaminopyridine (15 mg, 0.120 mmol) and tetra-*n*-butylammonium fluoride (2M in THF, 70 µL, 0.141 mmol). The mixture was stirred at room temperature for 2h before NH_4Cl (aq.) (3 mL) was added and the mixture extracted with DCM (3 x 3 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to give the crude product. Purification

by column chromatography (10–20 % EtOAc/hexanes) gave **9** as an orange-brown solid (22 mg, 82%).
m.p. 82-85 °C; I.R. (KBr) νmax: 2921, 1732, 1558, 1453, 1206, 754, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.30 – 7.12 (m, 9H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 5.66 (d, *J* = 16.5 Hz, 1H), 5.17 (d, *J* = 16.5 Hz, 1H), 4.41 (q, *J* = 8.5 Hz, 1H), 4.08 – 4.01 (m, 1H), 2.67 (dt, *J* = 12.0, 9.5 Hz, 1H), 2.13 – 2.05 (dt, *J* = 12.0, 9.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.0, 170.1, 154.3, 139.7, 136.3, 135.9, 130.4, 129.2, 128.9, 128.2, 127.4, 126.4, 123.3, 123.1, 122.0, 121.6, 118.5, 115.6, 89.6, 66.0, 57.7, 49.1, 37.5; HR MS [ES+]: *m/z* calcd. for $C_{25}H_{21}N_2O_2$ 381.1603, found 381.1596 $[M+H]^+$.
Compound **9** was also prepared as follows: To a solution of **25** (50 mg, 0.131 mmol) in DCM (1.5 mL) was added Dess-Martin periodinane (67 mg, 0.158 mmol) and the mixture stirred at rt for 1h. $Na_2S_2O_3$ (aq.) (2 mL) and $NaHCO_3$ (aq.) (2 mL) were added and the mixture was stirred for a further 30 minutes before being extracted with DCM (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) filtered and concentrated before purification by column chromatography (EtOAc/hexanes) to give **9** as an orange-brown solid (45 mg, 90%). All characterisation data were as reported above.

*4.3.4. (±)-rac-(3aS,13bS–Methyl 9–benzyl-2,3,9,13b–tetra-hydrofuro[3,2-c]indolo[2,3-b]quinoline-13b-carboxylate (**10**)*

To a solution of **9** (40 mg, 0.105 mmol) in ^{t}BuOH : H_2O (1:1, 2 mL) was added 2-methylbut-2-ene (0.11 mL, 0.210 mmol), NaH_2PO_4 (213 mg, 1.367 mmol) and sodium chlorite (124 mg, 1.367 mmol). The mixture was stirred at rt for 2h before water (5 mL) was added and the mixture extracted with EtOAc (4 x 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude acid product. The crude was redissolved in anhydrous methanol (2 mL) and (trimethyl-silyl)diazomethane (2M in diethyl ether, 105 μL, 0.210 mmol) was added. The solution was stirred for 1h at rt before acetic acid was added (50 μL) and the mixture stirred for a further 0.5h. $NaHCO_3$ (aq.) (5 mL) was added and the mixture extracted with DCM (4 x 5 mL) before the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude ester. Purification by column chromatography (10-20% Ethyl acetate/hexanes) gave **10** as a pale orange solid (23 mg, 54%).
m.p. 69-71 °C; I.R. (KBr) ν_{max}: 2950, 1764, 1722, 1557, 1491, 1468, 1451, 1204, 1101, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.41 – 7.19 (m, 9H), 7.08 – 7.00 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 5.64 (d, *J* = 16.5 Hz, 1H), 5.42 (d, *J* = 16.5 Hz, 1H), 4.43 (q, *J* = 8.5 Hz, 1H), 4.02 (ddd, *J* = 10.0, 8.5, 3.0 Hz, 1H), 3.33 (s, 3H), 2.69 (dt, *J* = 12.5, 10.0 Hz, 1H), 2.15 (ddd, *J* = 12.0, 8.0, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 168.5, 153.7, 138.9, 137.0, 136.3, 130.2, 129.0, 128.8, 127.4, 127.4, 126.6, 123.3, 123.2, 123.0, 121.4, 117.9, 115.6, 86.6, 65.5, 58.0, 52.4, 49.0, 37.0; HRMS [ES+]: *m/z* calcd. for $C_{26}H_{23}N_2O_3$ 411.1703, found 411.1704 $[M+H]^+$.

*4.3.5. (±)-(10bR,11R)-5-Benzyl-10b-(2-hydroxyethyl)-10b,11-dihydro-5H-indolo[2,3-b]quinolin-11-ol (**15**)*

To a solution of **13**[7] (1.00 g, 2.71 mmol) in MeOH (30 mL) at 0 °C was added $NaBH_4$ (0.21 g, 5.42 mmol). The mixture was stirred at 0 °C for 5 minutes before removing the ice-bath and allowing the mixture to stir at rt for a further 1h. NH_4Cl (aq.) (30 ml) was added and the organic solvent was removed under reduced pressure before the mixture extracted with DCM (3 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to give the crude product. The crude product was purified by column chromatography (EtOAc/hexanes) to give **15** as a white solid (0.98 g, 97%). m.p. 180-181 °C; I.R. (KBr) ν_{max}: 3320, 2143, 1555, 1469, 1452, 1206, 1059, 761, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 – 7.57 (m, 2H), 7.39 – 7.16 (m, 8H), 7.13 – 7.04 (m, 2H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.75 (d, *J* = 16.5 Hz, 1H), 4.97 (d, *J* = 16.5 Hz, 1H), 4.89 (s, 1H), 3.70 (t, *J* = 9.5 Hz, 1H), 3.54 (t, *J* = 10.0 Hz, 1H), 2.39 (s, 1H), 2.34 – 2.26 (m, 1H), 1.75 – 1.46 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.7, 155.6, 138.9, 136.7, 128.8, 128.8, 128.5, 127.5, 127.3, 126.3, 125.5, 124.2, 123.4, 122.4, 117.8, 114.8, 70.9, 58.9, 56.0, 49.7, 32.8. HRMS [ES-]: *m/z* calcd. for $C_{24}H_{21}N_2O_2$ 369.1603, found 369.1603 $[M-H]^-$.

*4.3.6. (±)-(3aR,13bR)-9-Benzyl-2,3,9,13b-tetrahydrofuro[3,2-c]indolo[2,3-b]quinoline (**14**)*

To a solution of **15** (100 mg, 0.270 mmol) in pyridine (5 mL) was added *p*-toluenesulfonyl chloride (57 mg, 0.297 mmol) and the solution stirred at rt for 2h. The mixture was then heated to 60 °C for a further 5h before cooling to rt and adding 1M HCl (75 mL). The mixture was extracted with DCM (3 x 30 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated to give the crude product. Purification by column chromatography (EtOAc/hexanes) gave **14** as a pale yellow solid (67 mg, 70%). m.p. 122- 124 °C; I.R. (KBr) ν_{max}: 2921, 1737, 1555, 1464, 1199, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.30 – 7.16 (m, 6H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.05 – 6.98 (m, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 5.85 (d, *J* = 16.5 Hz, 1H), 5.26 (s, 1H), 4.97 (d, *J* = 16.5 Hz, 1H), 4.22 (q, *J* = 8.5 Hz, 1H), 3.91 (td, *J* = 10.0, 9.0, 3.0 Hz, 1H), 2.57 – 2.45 (m, 1H), 2.00 (ddd, *J* = 11.5, 7.5, 3.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 154.2, 140.1, 139.0, 136.9, 129.2, 128.9, 128.5, 128.3, 127.3, 126.4, 123.9, 123.1, 122.7, 121.4, 117.9, 115.1, 79.9, 65.2, 56.5, 49.2, 36.7; HRMS [APCI+]: *m/z* calcd. for $C_{24}H_{21}N_2O$ 353.1648, found 353.1644 $[M+H]^+$.

*4.3.7. (±)-(10bR,11R)-5-Benzyl-10b-(2-hydroxyethyl)-11-methyl-10b,11-dihydro-5H-indolo[2,3b]quinolin- 11-ol (**19**)*

To a solution of **13**[7] (360 mg, 0.977 mmol) in THF (12 mL) at 0 °C was added methylmagnesium bromide (3M in THF, 0.72 mL, 2.150 mmol). The mixture was stirred for 10 minutes before the ice-bath was removed and stirring continued for a further 1h at rt. NH_4Cl (aq.) (10 ml) was added and the organic solvent was removed under reduced pressure before the mixture was extracted with DCM (3 x 10 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to give the crude product. The crude product was purified by column chromatography (EtOAc/hexanes) to give **19** as a yellow solid (367 mg, 98%). m.p. 114-117 °C; I.R. (KBr) ν_{max}: 2921, 2852, 1552, 1467, 1452, 1204, 754, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.52 (dt, *J* = 6.5, 0.5 Hz, 1H), 7.38 – 7.21 (m, 7H), 7.16 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H), 7.10 – 7.02 (m, 2H), 6.89 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.70 (d, *J* = 16.5 Hz, 1H), 5.01 (d, *J* = 16.5 Hz, 1H), 3.68 (ddd, *J* = 11.5, 9.5, 3.5 Hz, 1H), 3.53 (dt, *J* = 11.5, 4.5 Hz, 1H), 2.39 (ddd, *J* = 14.5, 9.5, 4.5 Hz, 1H), 1.71 (ddd, *J* = 14.5, 5.0, 3.5 Hz, 1H), 1.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 155.9, 138.3, 137.0, 135.6, 132.6, 128.8, 128.7, 128.4, 127.3, 126.6, 124.7, 123.8, 123.6, 122.4, 117.8, 114.8, 74.3, 60.1, 59.2, 49.1, 35.2, 25.7; HRMS [ES+]: *m/z* calcd. for $C_{25}H_{24}N_2O_2Na$ 407.1735, found 407.1743 $[M+Na]^+$.

*4.3.8 (±)-(10bR,11R)-5-Benzyl-11-ethyl-10b-(2-hydroxy-ethyl)-10b,11-dihydro-5H-indolo[2,3-b]quinolin- 11-ol (**20**)*

To a solution of **13**[7] (160 mg, 0.434 mmol) in THF (16 mL) at 0 °C was added ethylmagnesium bromide (3M in THF, 0.58 mL, 1.74 mmol). The mixture was stirred for 10 minutes before the ice-bath was removed and stirring continued for a further 1h at rt. NH_4Cl (aq.) (15 ml) was added and the organic solvent was removed under reduced pressure before the mixture was extracted with DCM (3 x 15 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to give the crude product. The crude product was purified by column chromatography (EtOAc/hexanes) to give **20** as a white solid (166 mg, 96%). m.p. 115-117 °C; I.R. (KBr) ν_{max}: 3232, 3054, 2921, 1555, 1469, 1452, 1209, 751 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.37 – 7.17 (m, 8H), 7.13 – 7.03 (m, 2H), 6.95 (d, *J* = 7.5 Hz, 1H), 5.73 (d, *J* = 16.5 Hz, 1H), 5.07 (d, *J* = 15.5 Hz, 1H), 4.57 (s, 1H), 3.68 – 3.58 (m, 1H), 3.51 – 3.44 (m, 1H), 2.40 (ddd, *J* = 14.5, 9.0, 4.0 Hz, 1H), 1.77 – 1.69 (m, 1H), 1.50 (dq, *J* = 14.5, 7.5 Hz, 1H), 1.42 (dq, *J* = 12.0, 6.0, 5.0 Hz, 1H), 0.58 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 154.8, 138.1, 136.5, 134.7, 130.0, 128.8, 128.5, 127.5, 126.8, 126.7, 124.0, 123.4, 122.9, 117.4, 115.4, 76.3, 60.6, 58.8, 49.7, 35.3, 28.6, 7.6; HRMS [ES+]: *m/z* calcd. for $C_{26}H_{26}N_2O_2Na$ 421.1892, found 421.1892 $[M+H]^+$.

*4.3.9. (±)-(10bR,11R)-11-Allyl-5-benzyl-10b-(2-hydroxy-ethyl)-10b,11-dihydro-5H-indolo[2,3-b]quinolin- 11-ol (**21**)*

To a solution of **13**[7] (2.65 g, 7.20 mmol) in THF (100 mL) at 0 °C was added allylmagnesium bromide (2M in THF, 10.8 mL, 21.61 mmol). The mixture was stirred for 10 minutes before the ice-bath was removed and stirring continued for a further 1h at rt. NH_4Cl (aq.) (100 ml) was added and the organic solvent was removed under reduced pressure before the mixture was extracted with DCM (3 x 100 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to give the crude product. The crude product was purified by column chromatography (EtOAc/hexanes) to give **21** as a pale yellow solid (2.72 g, 92%). m.p. 88-91 °C; I.R. (KBr) ν_{max}: 3069, 2926, 2852, 1553, 1467, 1452, 1214, 1108, 737, 700, 503 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.46 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.40 – 7.25 (m, 7H), 7.20 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H), 7.08 (tdd, *J* = 7.5, 2.5, 1.5 Hz, 2H), 6.94 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.69 (d, *J* = 16.5 Hz, 1H), 5.45 (dddd, *J* = 16.5, 10.0, 8.0, 6.5 Hz, 1H), 5.07 (d, *J* = 16.5 Hz, 1H), 4.98 (ddt, *J* = 10.0, 2.0, 1.0 Hz, 1H), 4.85 – 4.78 (m, 1H), 4.39 (s, 1H), 3.60 (d, *J* = 10.0 Hz, 1H), 3.47 (d, *J* = 7.0 Hz, 1H), 2.51 – 2.38 (m, 1H), 2.31 – 2.17 (m, 2H), 1.79 (ddd, *J* = 14.5, 5.5, 4.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 155.8, 138.4, 136.8, 135.4, 132.6, 129.9, 128.8, 128.5, 127.4, 126.7, 126.4, 124.0, 123.0, 122.6, 119.5, 117.8, 115.0, 75.6, 60.0, 59.0, 49.2, 41.0, 35.2; HRMS [APCI+]: *m/z* calcd. for $C_{27}H_{26}N_2O_2$ 410.1989, found 410.1983 $[M]^+$.

4.3.10. *(±)-(3aR,13bR)-9-Benzyl-13b-methyl-2,3,9,13b-tetrahydrofuro[3,2-c]indolo[2,3-b]quinoline (**16**)*

To a solution of **19** (367 mg, 0.955 mmol) in pyridine (10 mL) was added *p*-toluenesulfonyl chloride (113 mg, 1.145 mmol) and the solution stirred at rt for 2h. The mixture was then heated to 60 °C for a further 5h before cooling to room temperature and adding 1M HCl (150 mL). The mixture was extracted with DCM (3 x 60 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated to give the crude product. Purification by column chromatography (EtOAc/hexanes) gave **16** as a pale yellow solid (282 mg, 81%). m.p 158- 160 °C; I.R. (KBr) ν_{max}: 2921, 1552, 1469, 1449, 1204, 1120, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.31 – 7.15 (m, 9H), 7.10 – 7.05 (m, 1H), 7.01 – 6.95 (m, 2H), 6.80 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.74 (d, *J* = 16.5 Hz, 1H), 5.01 (d, *J* = 16.5 Hz, 1H), 4.20 (q, *J* = 8.5 Hz, 1H), 3.81 (ddd, *J* = 10.0, 8.5, 3.5 Hz, 1H), 2.61 (ddd, *J* = 12.5, 10.0, 8.0 Hz, 1H), 2.07 (ddd, *J* = 12.0, 8.0, 3.5 Hz, 1H), 1.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 154.7, 138.2, 138.1, 136.9, 129.3, 128.8, 128.4, 127.3, 126.7, 126.4, 123.3, 122.7, 122.3, 117.9, 114.9, 84.9, 64.6, 60.1, 49.0, 37.2, 22.7; HRMS [ES+]: *m/z* calcd. for $C_{25}H_{23}N_2O$ 367.1810, found 367.1803 $[M+H]^+$.

4.3.11. *(±)-(3aR,13bR)-9-Benzyl-13b-ethyl-2,3,9,13b-tetrahydro-furo[3,2-c]indolo[2,3-b]quinoline (**17**)*

To a solution of **20** (50 mg, 0.125 mmol) in pyridine (2 mL) was added p-toluenesulfonyl chloride (26 mg, 0.138 mmol) and the solution stirred at rt for 2h. The mixture was then heated to 60 °C for a further 5 hours before cooling to rt and adding 1M HCl (30 mL). The mixture was extracted with DCM (3 x 15 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated to give the crude product. Purification by column chromatography (EtOAc/hexanes) gave **17** as a white solid (40 mg, 84%). m.p. 177-180 °C; I.R. (KBr) ν_{max}: 2921, 1552, 1467, 1452, 1204, 1098, 1024, 798, 759 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.33 – 7.15 (m, 8H), 7.11 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H), 7.03 – 6.96 (m, 2H), 6.84 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.78 (d, *J* = 16.5 Hz, 1H), 4.94 (d, *J* = 16.5 Hz, 1H), 4.17 (q, *J* = 8.5 Hz, 1H), 3.79 (ddd, *J* = 10.0, 8.5, 3.5 Hz, 1H), 2.59 (ddd, *J* = 12.5, 10.0, 8.5 Hz, 1H), 2.03 (ddd, *J* = 12.5, 8.0, 3.5 Hz, 1H), 1.84 – 1.66 (m, 2H), 0.38 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 154.6, 139.5, 137.8, 137.0, 128.9, 128.8, 128.3, 127.4, 127.3, 127.3, 126.5, 123.1, 122.6, 122.4, 118.1, 114.7, 87.6, 64.4, 59.2, 49.2, 38.3, 30.1, 7.9; HRMS [ES+]: *m/z* calcd. for $C_{26}H_{25}N_2O$ 381.1967, found 381.1967 $[M+H]^+$.

*4.3.12. (±)-(3aR,13bR)-13b-Allyl-9-benzyl-2,3,9,13b-tetrahydrofuro[3,2-c]indolo[2,3-b]quinoline (**18**)*

To a solution of **21** (1.00 g, 2.436 mmol) in pyridine (25 mL) was added *p*-toluenesulfonyl chloride (0.56 g, 2.923 mmol) and the solution stirred at rt for 2h. The mixture was then heated to 60 °C for a further 5h before cooling to rt and adding 1M HCl (320 mL). The mixture was extracted with DCM (4 x 150 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated to give the crude product. Purification by column chromatography (EtOAc/hexanes) gave **18** as a yellow solid (0.67 g, 70%). m.p. 48-51 °C; I.R. (KBr) ν_{max}: 2926, 1555, 1467, 1452, 1327, 1295, 1204, 919, 751, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.34 – 7.14 (m, 8H), 7.09 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H), 6.99 (tdd, *J* = 7.5, 4.0, 1.0 Hz, 2H), 6.81 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.68 (d, *J* = 16.5 Hz, 1H), 5.18 – 5.03 (m, 1H), 4.97 (d, *J* = 16.5 Hz, 1H), 4.64 (ddt, *J* = 10.0, 2.0, 1.0 Hz, 1H), 4.37 (dq, *J* = 17.0, 1.5 Hz, 1H), 4.18 (q, *J* = 8.5 Hz, 1H), 3.80 (ddd, *J* = 10.0, 8.5, 3.5 Hz, 1H), 2.64 – 2.51 (m, 1H), 2.51 – 2.39 (m, 2H), 2.03 (ddd, *J* = 12.5, 8.0, 3.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 154.8, 139.3, 137.7, 136.9, 130.9, 129.0, 128.8, 128.4, 127.4, 127.3, 127.1, 126.6, 123.1, 122.6, 122.3, 119.4, 118.1, 114.7, 86.1, 64.4, 59.2, 49.2, 41.7, 38.0. HRMS [ES+]: *m/z* calcd. for $C_{27}H_{25}N_2O$ 393.1961, found 393.1959 $[M+H]^+$.

*4.3.13. (±)-2-((2'R,10bR)-5-Benzyl-5,10b-dihydrospiro-[indolo[2,3-b]quinoline-11,2'-oxirane]-10b-yl) ethanol (**24**)*

To a solution of **23** (500 mg, 0.805 mmol) in THF (25 mL) was added TBAF (1 M in THF, 1.6 mL, 1.611 mmol) and the mixture stirred at rt for 2h. NH_4Cl (aq.) (25 mL) was added and the organic solvent was removed under reduced pressure before the mixture was extracted with DCM (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to give the crude product which was purified by column chromatography (EtOAc/hexanes) to give **24** as a yellow-orange solid (302 mg, 98%). m.p. 86-88 °C; I.R. (KBr) ν_{max}: 2921, 1671, 1607, 1555, 1489, 1452, 1403, 1204, 1027, 909, 754, 729, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.11 (m, 10H), 7.00 – 6.94 (m, 2H), 6.87 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.76 (d, *J* = 16.5 Hz, 1H), 4.94 (d, *J* = 16.5 Hz, 1H), 3.44 – 3.27 (m, 2H), 3.05 (d, *J* = 5.5 Hz, 1H), 2.52 (d, *J* = 5.5 Hz, 1H), 2.36 (dt, *J* = 13.5, 6.5 Hz, 1H), 2.10 (dt, *J* = 14.0, 6.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 155.1, 140.9, 136.6, 133.8, 129.5, 129.2, 128.9, 127.4, 126.4, 123.7, 123.5, 123.0, 122.9, 118.3, 115.2, 60.2, 59.1, 54.1, 53.6, 49.7, 36.6; HRMS [ES+]: *m/z* calcd. for $C_{25}H_{23}N_2O_2$ 383.1760, found 383.1745 $[M+H]^+$.

*4.3.14. (±)-((3aR,13bR)-9-Benzyl-2,3,9,13b-tetrahydrofuro-[3,2-c]indolo[2,3-b]quinolin-13b-yl)methanol (**25**)*

To a solution of **24** (1.20 g, 3.138 mmol) in DCM (70 mL) was added *p*-toluenesulfonic acid (1.62 g, 9.413 mmol) and the mixture stirred at rt for 18h. $NaHCO_3$ (aq.) (70 mL) was added and the mixture extracted with DCM (3 x 50 mL) before the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The crude product which was purified by column chromatography (EtOAc/hexanes) to give **25** as a yellow-orange solid (1.13 g, 94%). m.p. 151-155 °C; I.R. (KBr) ν_{max}: 3320, 2921, 1555, 1491, 1469, 1452, 1413, 1324, 1206, 1147, 1064, 756, 692 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.46 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.31 – 7.14 (m, 8H), 7.09 – 6.96 (m, 2H), 6.88 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.66 (d, *J* = 16.5 Hz, 1H), 5.31 (br. s, 1H), 4.89 (d, *J* = 16.5 Hz, 1H), 3.55 (ddd, *J* = 11.0, 9.0, 3.5 Hz, 1H), 3.49 – 3.34 (m, 3H), 2.42 (ddd, *J* = 14.5, 9.0, 4.5 Hz, 1H), 1.66 (ddd, *J* = 14.5, 5.0, 3.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 155.6, 138.7, 136.7, 134.1, 129.4, 129.2, 128.9, 127.9, 127.5, 127.3, 126.5, 124.2, 123.1, 122.8, 118.1, 115.0, 75.2, 59.1, 58.6, 50.1, 49.4, 35.9; HRMS [ES+]: *m/z* calcd. for $C_{25}H_{23}N_2O_2$ 383.1760, found 383.1765 $[M+H]^+$.

4.3.15. *(±)-2-((10bR,11S)-5-Benzyl-11-(p-tolyl)-10b,11-dihydro-5H-indolo[2,3-b]quinolin-10b-yl)ethanol (**26**)*

26 was synthesised from the reaction of **14** (40 mg, 0.113 mmol) with $AlCl_3$ (106 mg, 0.794 mmol) in toluene (3 mL) using general procedure 4.2.1. **26** was obtained as a pale yellow solid (39 mg, 77%). m.p. 63-65 °C; I.R. (KBr) ν_{max}: 2921, 2852, 1555, 1469, 1454, 1078, 776, 692, 459 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 2H), 7.39 – 7.33 (m, 2H), 7.32 – 7.07 (m, 7H), 7.01 – 6.92 (m, 2H), 6.79 – 6.71 (m, 4H), 5.86 (d, *J* = 16.5 Hz, 1H), 5.16 (d, *J* = 16.5 Hz, 1H), 4.46 (s, 1H), 3.38 – 3.26 (m, 2H), 2.36 (dt, *J* = 13.5, 6.5 Hz, 1H), 2.26 – 2.17 (m, 1H), 2.10 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 153.8, 139.4, 136.6, 136.4, 135.5, 135.5, 135.4, 130.5, 128.8, 128.4, 127.8, 127.6, 127.3, 126.4, 123.9, 122.8, 122.4, 117.3, 115.9, 59.1, 56.2, 50.8, 50.1, 39.8, 20.9; HRMS [ES+]: *m/z* calcd. for $C_{31}H_{29}N_2O$ 445.2280, found 445.2275 $[M+H]^+$.

*4.3.16. (±)-2-((10bR,11S)-5-Benzyl-11-methyl-11-(p-tolyl)-10b,11-dihydro-5H-indolo[2,3-b]quinolin-10b-yl)ethanol (**27**)*

27 was synthesised from the reaction of **16** (29 mg, 0.079 mmol) with $AlCl_3$ (74 mg, 0.552 mmol) in toluene (1.5 mL) using general procedure 4.2.1. **27** was obtained as a pale yellow solid (30 mg, 83%). m.p. 108- 111 °C; I.R. (KBr) ν_{max}: 3374, 2956, 2916, 1555, 1491, 1449, 1408, 1245, 1211, 1027, 835, 751, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.51 (m, 1H), 7.37 – 7.15 (m, 8H), 7.14 – 7.02 (m, 4H), 6.75 – 6.64 (m, 2H), 6.54 – 6.41 (m, 2H,), 5.48 (d, J = 16.5 Hz, 1H), 5.01 (d, *J* = 16.5 Hz, 1H), 3.23 (dt, *J* = 11.0, 7.0 Hz, 1H), 3.03 (dt, *J* = 11.0, 6.5 Hz, 1H), 2.29 (t, *J* = 7.0 Hz, 2H), 2.13 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 156.0, 141.3, 139.2, 137.2, 136.5, 136.0, 131.2, 128.6, 128.6, 128.3, 128.0, 127.3, 127.3, 126.9, 123.6, 123.0, 122.4, 117.7, 115.3, 59.6, 58.6, 50.1, 47.4, 35.6, 22.3, 20.8; HRMS [ES+]: *m/z* calcd. for C32H30N2ONa 481.2256, found 481.2247 $[M+Na]^+$.

*4.3.17. (±)-2-((10bR,11S)-5-Benzyl-11-ethyl-11-(p-tolyl)-10b,11-dihydro-5H-indolo[2,3-b]quinolin-10b-yl)ethanol (**28**)*

28 was synthesised from the reaction of **17** (30 mg, 0.079 mmol) with $AlCl_3$ (74 mg, 0.552 mmol) in toluene (1.5 mL) using general procedure 4.2.1. **17** was obtained as a pale yellow solid (26 mg, 70%). m.p. 140- 143 °C; I.R. (KBr) ν_{max}: 3261, 2921, 1555, 1449, 1407, 1209, 1019, 751, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.53 (m, 1H), 7.53 – 7.44 (m, 1H), 7.39 – 6.98 (m, 11H), 6.77 – 6.65 (m, 2H), 6.42 – 6.30 (m, 2H), 5.33 (d, *J* = 16.5 Hz, 1H), 4.94 (d, *J* = 16.5 Hz, 1H), 3.18 (dt, *J* = 11.0, 7.0 Hz, 1H), 3.04 (dt, *J* = 11.0, 6.5 Hz, 1H), 2.75 (dq, *J* = 15.0, 7.5 Hz, 1H,), 2.63 (dq, *J* = 14.0, 7.0 Hz, 1H), 2.28 (dd, *J* = 8.0, 6.0 Hz, 2H), 2.19 (s, 3H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 156.3, 141.5, 137.1, 136.5, 136.0, 135.9, 131.7, 128.8, 128.5, 128.2, 128.0, 127.3, 127.2, 127.1, 123.6, 123.4, 122.5, 117.6, 115.8, 59.8, 59.5, 51.5, 50.2, 35.0, 26.2, 20.9, 12.0; HRMS [ES+]: *m/z* calcd. for $C_{33}H_{33}N_2O$ 473.2593, found 473.2590 $[M+H]^+$.

*4.3.18. (±)-2-((10bR,11S)-11-Allyl-5-benzyl-11-methyl-10b,11-dihydro-5H-indolo[2,3-b]quinolin-10b-yl)ethanol (**29**)*

29 was synthesised from the reaction of **16** (30 mg, 0.082 mmol) with allyltrimethylsilane (94 mg, 0.819 mmol) and $AlCl_3$ (76 mg, 0.573 mmol) in DCM (0.2 mL) using general procedure 4.2.2. **29** was obtained as a pale yellow solid (29 mg, 87%). m.p. 169-171 °C; I.R. (KBr) ν_{max}: 3394, 2931, 1543, 1467, 1449, 1206, 1039, 102, 751, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.20 (m, 8H), 7.17 – 7.09 (m, 2H), 7.05 – 6.94 (m, 3H), 5.63 (d, *J* = 16.5 Hz, 1H), 5.28 – 5.17 (m, 1H), 5.14 (d, *J* = 16.5 Hz, 1H), 4.87 – 4.79 (m, 1H), 4.69 – 4.61 (m, 1H), 3.24 (dt, *J* = 11.0, 7.0 Hz, 1H), 3.04 (dt, *J* = 11.0, 7.0 Hz, 1H), 2.21 – 2.07 (m, 3H), 1.81 (dd, *J* = 13.5, 9.0 Hz, 1H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 156.7, 139.8, 137.5, 136.4, 134.1, 130.1, 129.2, 129.1, 128.2, 127.8, 127.7, 127.4, 123.4, 123.2, 122.9, 118.5, 118.1, 115.9, 59.7, 58.6, 50.0, 43.2, 40.4, 35.1, 18.5; HRMS [APCI+]: *m/z* calcd. for $C_{28}H_{28}N_2O$ 408.2196, found 408.2192 $[M]^+$.

*4.3.19. (±)-2-((10bR,11S)-11-Allyl-5-benzyl-11-ethyl-10b,11-dihydro-5H-indolo[2,3-b]quinolin-10b-yl)ethanol (**30**)*

30 was synthesised from the reaction of **17** (20 mg, 0.053 mmol) with allyltrimethylsilane (60 mg, 0.526 mmol) and $AlCl_3$ (49 mg, 0.368 mmol) in DCM (0.15 mL) using general procedure 3. **30** was obtained as a pale yellow solid (15 mg, 68%). m.p. 65-67 °C;

I.R. (KBr) ν_{max}: 3411, 3063, 2923, 1701, 1554, 1491, 1467, 1450, 1205, 1041, 836, 754, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.21 (m, 10H), 7.19 – 7.13 (m, 2H), 7.07 – 6.99 (m, 3H), 5.61 (d, *J* = 16.5 Hz, 1H), 5.19 – 5.09 (m, 2H), 4.72 (dt, J = 10.0, 1.5 Hz, 1H), 4.62 – 4.54 (m, 1H), 3.23 (dq, J = 11.0, 7.0, 6.5 Hz, 1H), 3.01 (ddd, J = 11.0, 7.5, 6.0 Hz, 1H), 2.40 (dq, J = 15.5, 7.5 Hz, 1H), 2.29 – 2.13 (m, 4H), 1.87 (dd, J = 14.5, 8.5 Hz, 1H), 1.34 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 155.9, 140.0, 136.8, 136.1, 134.2, 128.8, 128.7, 128.4, 128.0, 127.7, 127.3, 127.1, 123.1, 122.8, 122.7, 117.5, 117.5, 116.0, 59.4, 59.1, 49.8, 45.9, 40.4, 35.9, 25.8, 11.8; LRMS [ES+]: m/z calcd. for $C_{29}H_{31}N_2O$ 423.24, found 423.39 $[M+H]^+$.

*4.3.20. (±)-2-(11,11-Diallyl-5-benzyl-10b,11-dihydro-5H-indolo[2,3-b]quinolin-10b-yl)ethanol (**31**)*

To a solution of **18** (663 mg, 1.689 mmol) in DCM (14 mL) at -78 °C was added allyltrimethylsilane (1.34 mL, 8.446 mmol) followed by $TiCl_4$ (dropwise addition, 0.93 mL, 8.446 mmol). The mixture was stirred at -78 °C for 4.5h before methanol (1 mL) was added and the mixture stirred for an additional 10 minutes. The mixture was removed from the cold bath and NH_4Cl (aq.) (15 mL) was added before the mixture was extracted with DCM (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated before the crude product was purified by column chromatography (EtOAc/hexanes) to give **31** as a yellow solid (636 mg, 87%). m.p. 116- 118 °C; I.R. (KBr) ν_{max}: 3355, 2931, 1641, 1469, 919, 759, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 3H), 7.34 – 7.14 (m, 7H), 7.08 – 6.98 (m, 3H), 6.23 (dtd, *J* = 17.0, 10.0, 4.0 Hz, 1H), 5.61 (d, *J* = 16.5 Hz, 1H), 5.39 (d, *J* = 17.0 Hz, 1H), 5.21 – 5.08 (m, 3H), 4.81 (d, *J* = 10.0 Hz, 1H), 4.65 (d, *J* = 17.0 Hz, 1H), 3.26 – 3.12 (m, 2H), 2.99 – 2.81 (m, 2H), 2.46 (ddd, *J* = 13.5, 8.0, 6.0 Hz, 1H), 2.21 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.10 (tdd, *J* = 14.5, 9.5, 6.0 Hz, 1H), 1.84 (dd, *J* = 14.0, 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 157.3, 140.4, 137.3, 137.1, 136.4, 134.1, 129.2, 129.1, 128.5, 128.3, 128.0, 127.7, 127.5, 123.7, 123.1, 118.7, 118.0, 116.7, 116.4, 59.8, 59.6, 50.1, 46.3, 40.8, 37.9, 36.2; HRMS [ES+]: *m/z* calcd. for $C_{30}H_{31}N_2O$ 435.2431, found 435.2430 $[M+H]^+$.

*4.3.21. (±)-(6aR,9aR,13aR,14R,15aS)-15a-Allyl-5-benzyl-10,12-diiodo-14-(iodomethyl)-7,8,9a,14,15,15a-hexahydro-5H-6,13-(azeno)chromeno[4',4a':1,5]cyclopenta[1,2-c]quinoline (**33**) and (±)-(6aR,9aS,13aR,14R,15aS)-15a-Allyl-5-benzyl-14-(iodomethyl)-7,8,9a,14,15,15a-hexahydro-5H-6,13-(azeno)-chromeno[4',4a':1,5]cyclopenta[1,2-c]quinoline (**34**)*

To a solution of **31** (50 mg, 0.115 mmol) in DCM (2.3 mL) was added NIS (31 mg, 0.138 mmol) and the mixture stirred at rt for 1h. $Na_2S_2O_3$ (aq.) (2 mL) was added and the mixture stirred for a further 10 minutes before being extracted with DCM (3 x 2mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated before purification by column chromatography (EtOAc/hexanes) giving a mixture of products including recovered **31** (20 mg, 40%). **33** was obtained as a yellow solid (14 mg, 15%). m.p. 150-152 °C; I.R. (KBr) ν_{max}: 2921, 1567, 1520, 1494, 1462, 1327, 1211, 1076, 744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.38 – 7.25 (m, 5H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.11 – 7.01 (m, 3H), 6.12 – 6.00 (m, 1H), 5.74 (d, *J* = 16.0 Hz, 1H), 5.34 (d, *J* = 17.0 Hz, 1H), 5.27 (d, *J* = 10.5 Hz, 1H), 5.00 (d, *J* = 16.0 Hz, 1H), 4.27 (s, 1H), 4.05 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.72 (td, *J* = 12.5, 2.5 Hz, 1H), 3.44 (dd, *J* = 9.5, 3.5 Hz, 1H), 2.93 – 2.83 (m, 2H), 2.73 (dd, *J* = 11.5, 9.5 Hz, 1H), 2.56 – 2.42 (m, 2H), 1.77 – 1.71 (m, 1H), 1.68 – 1.59 (m, 1H), 1.41 – 1.33 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 157.4, 146.5, 137.6, 136.4, 134.2, 129.6, 128.9, 128.6, 128.2, 127.7, 127.2, 123.4, 118.7, 116.3, 88.0, 82.9, 67.2, 66.5, 60.1, 57.4, 50.2, 48.3, 45.7, 44.7, 39.2, 27.5, 9.0; HRMS [ES+]: *m/z* calcd. for $C_{30}H_{28}I_3N_2O$ 812.9330, found 812.9329 $[M+H]^+$. **34** was obtained as a green solid (6 mg, 9%). m.p. 126-128 °C (dec.); I.R. (KBr) ν_{max}: 2921, 1722, 1639, 1533, 1491, 1459, 1410, 1327, 1073, 914, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.29 – 7.23 (m, 3H), 7.19 – 7.13 (m, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.38 (dd, *J* = 9.5, 5.5 Hz, 1H), 6.13 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H), 5.91 (d, *J* = 5.5 Hz, 1H, C12-H), 5.82 – 5.72 (m, 2H, CH2N, C10-H), 5.33 (d, *J* = 17.0 Hz, 1H), 5.26 (d, *J* = 10.0 Hz, 1H), 4.87 (d, *J* = 16.0 Hz, 1H), 4.15 (d, *J* = 6.0 Hz, 1H), 4.01 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.78 (td, *J* = 12.5, 2.5 Hz, 1H), 3.45 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.04 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.95 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.86 (dd, *J* = 12.0, 9.5 Hz, 1H), 2.56 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.50 – 2.40 (m, 1H), 1.83 – 1.77 (m, 1H), 1.71 – 1.63 (m, 1H), 1.50 – 1.41 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 155.4, 138.3, 136.7, 134.7, 131.8, 129.7, 128.9, 128.5, 128.0, 127.4, 126.4, 122.7, 118.3, 116.7, 115.7, 105.6, 77.4, 67.0, 57.3, 53.4, 49.9, 48.3, 45.4, 44.7, 39.6, 28.0, 10.7; LRMS [ES+]: *m/z* calcd. for $C_{30}H_{29}IN_2O$ 561.14, found 561.02 $[M+H]^+$.

*4.3.22. (±)-(6aR,9aR,13aR,14R,15aS)-15a-Allyl-5-benzyl-10,12-diiodo-14-(iodomethyl)-7,8,9a,14,15,15a-hexahydro-5H-6,13-(azeno)chromeno[4',4a':1,5]cyclopenta[1,2-c]quinoline (**33**)*

To a solution of **31** (50 mg, 0.115 mmol) in DCM (2.3 mL) was added NIS (93 mg, 0.414 mmol) and the mixture stirred at rt for 1h. $Na_2S_2O_3$ (aq.) (2 mL) was added and the mixture stirred for a further 10 minutes before being extracted with DCM (3 x 2 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated before purification by column chromatography (EtOAc/hexanes) giving **33** as a yellow solid (60 mg, 64%). All characterisation data were in agreement with that reported above for **33**. Crystals suitable for X-ray crystallographic analysis were obtained by the slow evaporation of a solution of **33** in EtOAc/MeOH.

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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 1811883 (**6**); CCDC 1811882 (**7**); CCDC 1811884 (**33**).

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