New asymmetric routes to ajmaline and suaveoline indole alkaloids

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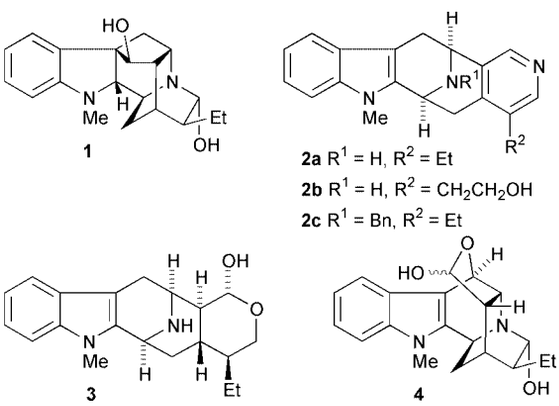
The tetracyclic advanced intermediates **6**, **8** and **9** obtained from L-tryptophan *via* a *cis*-selective Pictet–Spengler reaction and a Dieckmann–Thorpe cyclisation are used in a range of new approaches to polycyclic monoterpenoid indole alkaloids such as ajmaline and suaveoline. Structural modifications designed to facilitate a key intermolecular addition to C15 (ajmaline numbering) are described, followed by two intramolecular routes based on the addition of a suitable carbon fragment to a remote nitrogen atom prior to bond formation at C15.

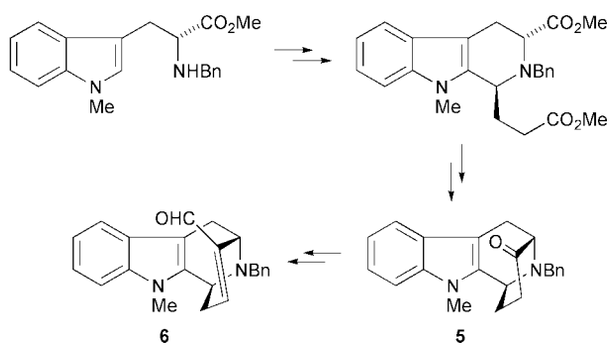
Introduction

Indole alkaloids are a structurally diverse family of natural products that attract considerable interest because of their well established, wide-ranging medicinal properties. Clinically important examples include the heteroyohimboid alkaloids such as the vasodilatory ajmalicine,[1] the macroline/sarpagine alkaloids such as the anti-cancer bisindoles vincristine and vinblastine,[2] and the established anti-arrhythmic ajmaline **1**.[3] The intricate cage-like indole alkaloids typified by ajmaline and the related alkaloids suaveoline **2a** and raumacline **3**, have recently been the focus of much synthetic excitement.



Suaveoline **2a** was first isolated from the bark of *Rauwolfia suaveolens* in 1972,[4] but has since been found in other *Rauwolfia* species along with structural analogues such as macrophylline **2b**.[5] Biotransformations in *Rauwolfia serpentina* cell cultures fed with ajmaline produce a range of alkaloids including suaveoline **2a**, raumacline **3** and alkaloid G **4**.[6] The biosynthetic interconversion of members of the ajmaline family emphasises the fact that advanced intermediates can often be exploited in the synthesis of several alkaloids and analogues.

The first total synthesis of racemic suaveoline was achieved by Trudell and Cook in 1989; the key steps in this ingenious synthesis from D/L-tryptophan (overall yield 2.3%) include a *trans*-specific Pictet–Spengler reaction to gain access (after epimerisation) to the bridged ketone **5**, an unusual homologation to the α,β-unsaturated aldehyde **6** (Scheme 1), and an anionic Cope rearrangement in order to introduce the final carbons of the suaveoline skeleton.[7] Related anionic Cope rearrangements have since been employed by Cook *et al*. in the asymmetric synthesis of ajmaline[3] and other structurally



Scheme 1

related indole alkaloids.[8] Cook's asymmetric synthesis of (−)-suaveoline started from D-tryptophan, and included modified procedures to improve the overall yield considerably.[9] Nevertheless, these syntheses use non-proteinogenic D-tryptophan as the starting material, and construction of the carbon skeletons is lengthy and awkward.

We achieved the formal asymmetric synthesis of ajmaline and suaveoline in 1993 starting from L-tryptophan,[10] by exploiting the *cis*-selective kinetically controlled Pictet–Spengler reaction;[11] our route gave access to the bridged ketone **5** used by Cook.[7,9] We later developed an independent asymmetric route to the α,β-unsaturated aldehyde **6** (ee ≥ 97%) which is also an intermediate in Cook's syntheses, in which the aldehyde carbon was introduced at the start of the synthesis by homologation of L-tryptophan to the nitrile **7**. Further key steps included a *cis* selective Pictet–Spengler reaction and a Thorpe cyclisation to the ketone **8** (Scheme 2).[12]

However, we wished to develop an independent total synthesis of one or more of these alkaloids, and our new synthetic approaches are described here and in the following paper (DOI: 10.1039/b005695m).

Results and discussion

With a total synthesis of ajmaline and suaveoline in mind and with homochiral α,β-unsaturated aldehyde **6** available,[12] our initial synthetic efforts were directed towards the intermolecular 1,4-addition of a suitable four-carbon fragment to C15 (ajmaline numbering). Earlier work by ourselves[13] and others[14] had hinted at the difficulty of this 1,4-addition; for example, simple alkyl Grignards, enamines and organocuprates were all known to fail. One set of conditions that is successful

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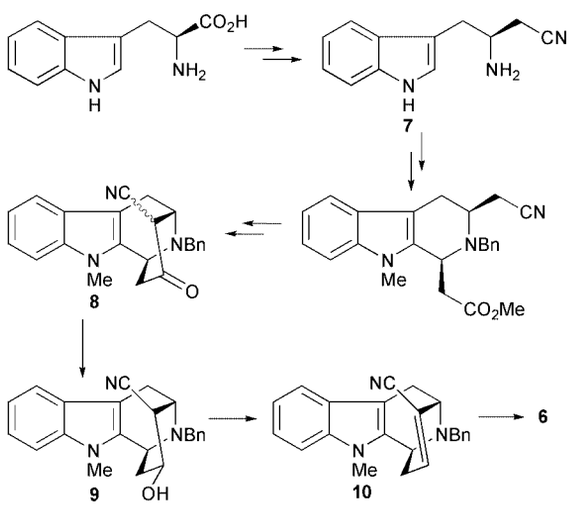
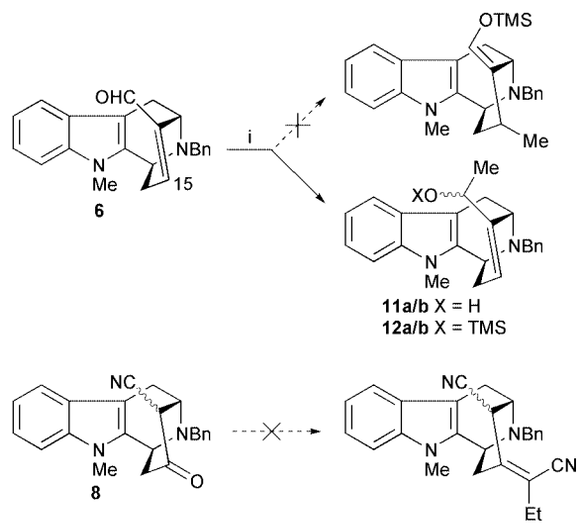
with other α,β-unsaturated aldehydes is a Cu(I) catalysed Grignard 1,4-addition in which the intermediate enolate is trapped as a TMS enol ether.[15] However, this procedure did not lead to any 1,4-addition and the only products isolated were the result of direct 1,2-attack on the aldehyde (Scheme 3).

We therefore decided to look back into our established synthetic route (Scheme 2) for earlier synthetic intermediates that might be amenable to bond formation at C15. As a first approach, the ketone **8** was proposed as a substrate for direct nucleophilic addition. This material was known to be readily enolisable, as confirmed by our earlier observation that reduction with sodium borohydride leads to a single diastereoismer of the alcohol **9** *via* the interconvertion of ketone stereoisomers.[16] However, a suitably non-basic nucleophile would lead to a much shortened synthetic route and the Reformatsky addition of 2-bromobutyronitrile to the ketone could lead to an ideal advanced intermediate with the carbon skeletons of ajmaline and suaveoline largely in place (Scheme 3). However, no reaction between the ketone **8** and 2-bromopropionitrile (employed as a model reagent) was observed under standard Reformatsky conditions, or even under the accelerating influence of sonication[17] or when using a highly reactive form of dispersed zinc, namely a zinc/silver/graphite matrix.[18] A simple lithium cuprate addition also failed with this ketone, again presumably because of the acidity of the α-proton.

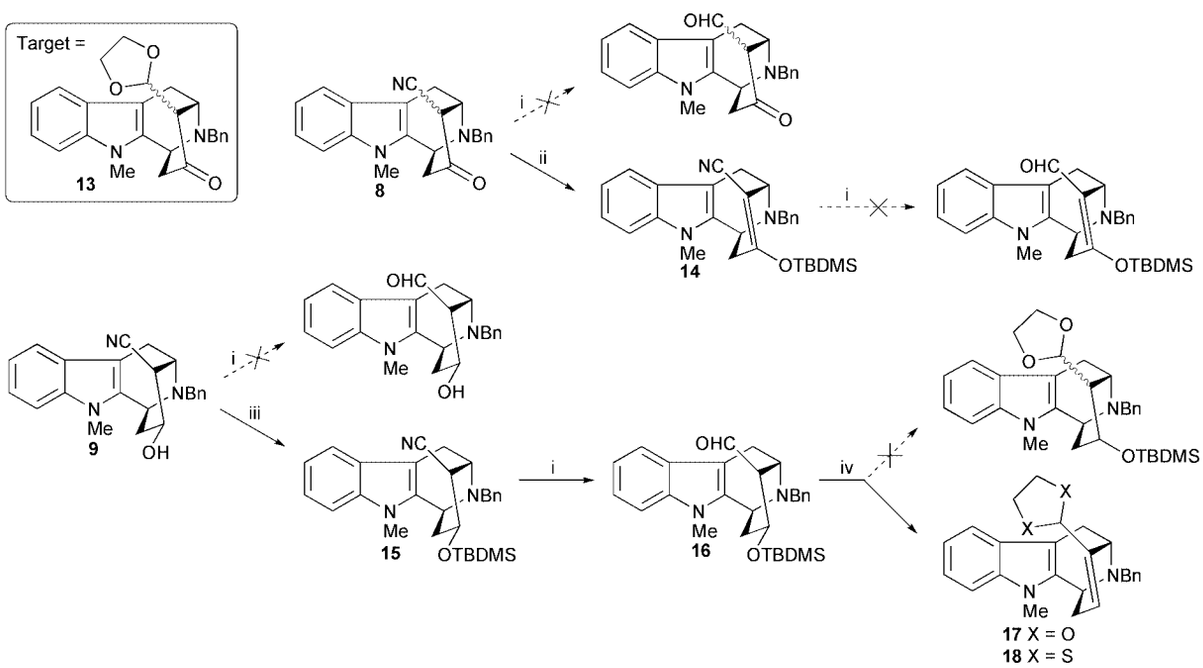
We reasoned that conversion of the electron-withdrawing nitrile to an aldehyde masked as an acetal (as in **13**) would reduce the acidity of the α-proton and thus allow nucleophilic addition of a suitable four-carbon unit to the ketone functionality. Not surprisingly, direct DIBAL-H reduction of the ketone **8** gave complex product mixtures, from which no aldehyde could be isolated. Temporary masking of the ketone functionality as a silyl enol ether **14** was achieved in high yield with TBDMSCl and imidazole in DCM (Scheme 4). These conditions also allowed the selective protection of the ketone **8** in the presence of the alcohol **9**, and thus eased the chromatographic separation of these two established intermediates. The silyl enol ether **14** proved surprisingly inert towards reduction with DIBAL-H, with no reaction being observed even with several equivalents of the reducing agent. For another approach to the acetal **13**, DIBAL-H reduction of the nitrile moiety of the alcohol **9** followed by acetal formation and oxidation to the



Scheme 2



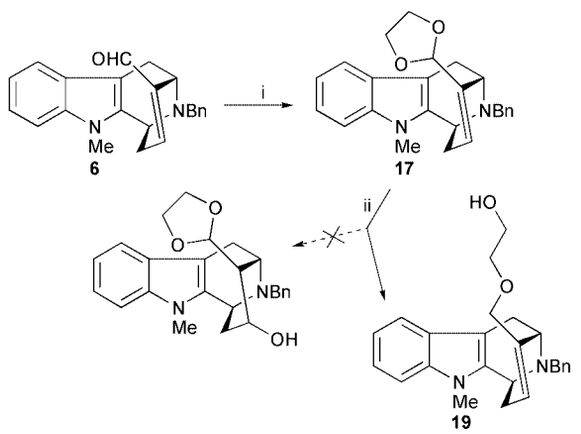
Scheme 3 *Reagents and conditions*: i, MeMgI, CuBr·Me_2S, TMS–Cl, HMPA, THF, −78 °C (30% for **11a/b** and 29% for **12a/b**).



Scheme 4 *Reagents and conditions*: i, DIBAL-H, DCM, −78 °C; ii, TBDMS–Cl, imidazole, DCM, room temp., 24 h (92%); iii, TBDMS–OTf, 2,6-dimethylpyridine, room temp., 24 h (80%); iv, $HO(CH_2)_2OH$, PTSA, reflux, 2 h (65%).

ketone was proposed. Direct reduction of the nitrile moiety of the alcohol **9** again failed, but masking of the alcohol functionality was achieved by reaction with TBDMSOTf and 2,6-dimethylpyridine in DCM. This protected alcohol was then treated with DIBAL-H in DCM at −78 °C to afford the corresponding aldehyde which was isolated and immediately protected as the acetal. However, the forcing conditions required for complete acetal formation also caused desilylation and dehydration to afford the unsaturated acetal **17** in low overall yield, as outlined in Scheme 4. Even the milder conditions required to form a thioacetal led solely to the formation of the unsaturated thioacetal **18**.

These initially disappointing results led us to propose two possible applications for the unsaturated acetal **17**; firstly, hydroboration followed by Swern oxidation to afford the desired protected ketone **13** and secondly, epoxidation of the double bond. In fact, the acetal **17** was found to be readily available from the established α,β-unsaturated aldehyde intermediate **6** in 89% yield (Scheme 5), thus offering a potentially



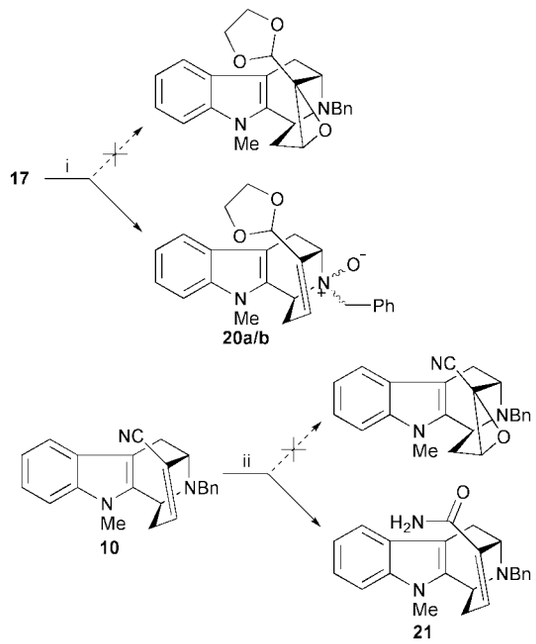
Scheme 5 *Reagents and conditions*: i, $HO(CH_2)_2OH$, $BF_3{\cdot}OEt_2$, DCM, room temp., 4 h (89%); ii, 9-BBN, THF, room temp., 24 h then alkaline peroxide, 15 min (55%).

high overall yield for the production of the desired ketone **13**. Hydroboration of the acetal **17** with $BH_3{\cdot}THF$ gave a complex product mixture by TLC and the reaction was not pursued further.

Reaction of the acetal **17** with 9-BBN in DCM followed by an alkaline peroxide work-up afforded a single product. Unfortunately, this material was not derived from the expected hydroboration reaction but simply from acetal ring opening. The thioacetal **18** failed to react under similar (and more forcing) conditions.

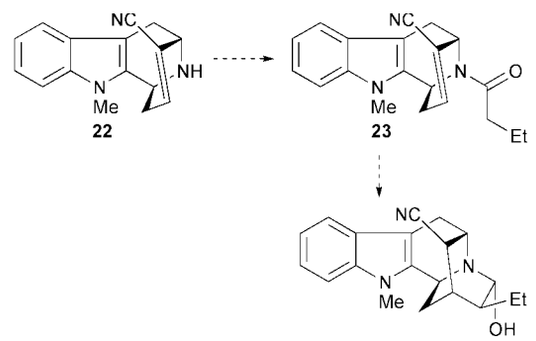
Next the acetal **17** was treated with MCPBA in DCM in an effort to produce the corresponding epoxide which might itself be open to nucleophilic attack of a suitable four carbon fragment. TLC analysis of the reaction mixture indicated the presence of two products, which were separable by careful flash chromatography. However, instead of the expected epoxides, both diastereoisomers of the *N*-oxide **20a/b** in the ratio of *ca.* 3:1 were isolated. (Scheme 6). Extended reaction times and/or excess MCPBA produced complex mixtures of products from which no trace of an epoxide could be isolated. Related attempts to epoxidise another established synthetic intermediate, the nitrile **10**, with alkaline hydrogen peroxide[19] also failed, with nitrile hydrolysis[20] leading solely to the corresponding α,β-unsaturated amide **21**. At this point, the intermolecular addition of a suitable four-carbon fragment to advanced intermediates was abandoned in favour of two new intramolecular approaches.

Our first intramolecular approach was based on the initial addition of a four-carbon unit to the N^b nitrogen. In earlier synthetic studies we had shown that an electron-withdrawing



Scheme 6 *Reagents and conditions*: i, MCPBA, $NaHCO_3$, DCM, 0 °C, 30 min (76%); ii, alkaline peroxide, acetone, room temp., 48 h (79%).

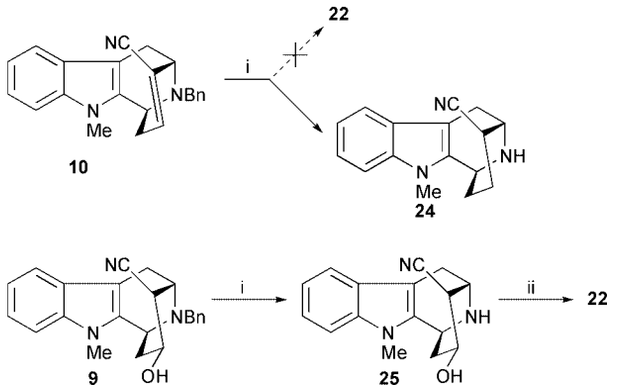
group such as butyryl could not be employed as a N^b protecting group in the early stages of the synthesis because of problems of carboline ring-opening in the Thorpe cyclisation step.[12] Thus, the addition of a butyryl group to a tetracyclic advanced intermediate such as the nitrile **22** was proposed, as outlined in Scheme 7.



Scheme 7

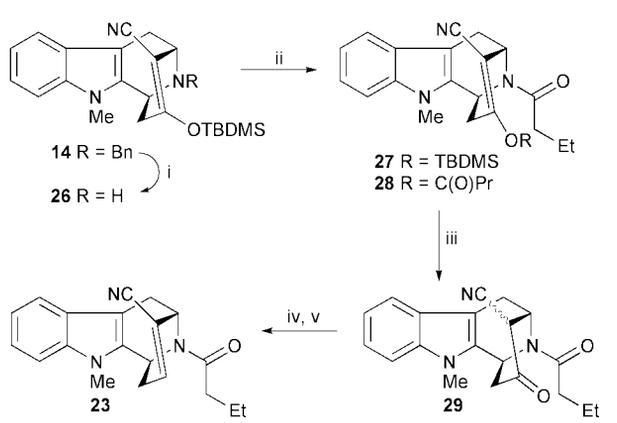
We were of course concerned that the stereo-electronic factors might disfavour the desired Michael attack, but the presumed thermodynamic stability of the cyclised product and the brevity of the route encouraged us to attempt it. The free amine **22** proved difficult to obtain: hydrogenation of the N^b-benzyl α,β-unsaturated nitrile **10** led to reduction of the double bond prior to benzyl cleavage, whilst cleavage of the benzyl group from the alcohol **9** led to the formation of the highly insoluble amino alcohol **25** which could only be dehydrated to the required amine **22** in poor overall yield (Scheme 8).

Since the amine **22** was not readily available and to avoid the solubility difficulties encountered with the free amino alcohol **25** the versatile silyl enol ether **14** was again employed *en route* to the tetracyclic intermediate **23** proposed in Scheme 7. Initially, the required debenzylation proved troublesome, but dissolving the TBDMS enol ether **14** in MeOH, followed by rigorous rotary evaporation afforded an amorphous solid which reacted very cleanly to afford a quantitative yield of the free amine **26** (Scheme 9). This evaporation procedure presumably removed small traces of chlorinated solvents which otherwise poisoned the palladium catalyst. The free amine **26** was found to be unstable and was not fully characterised.



Scheme 8 *Reagents and conditions*: i, Pd–C, H_2, MeOH (80% for **24** and 67% for **25**); ii, $POCl_3$, pyridine, benzene, reflux, 48 h (25%).

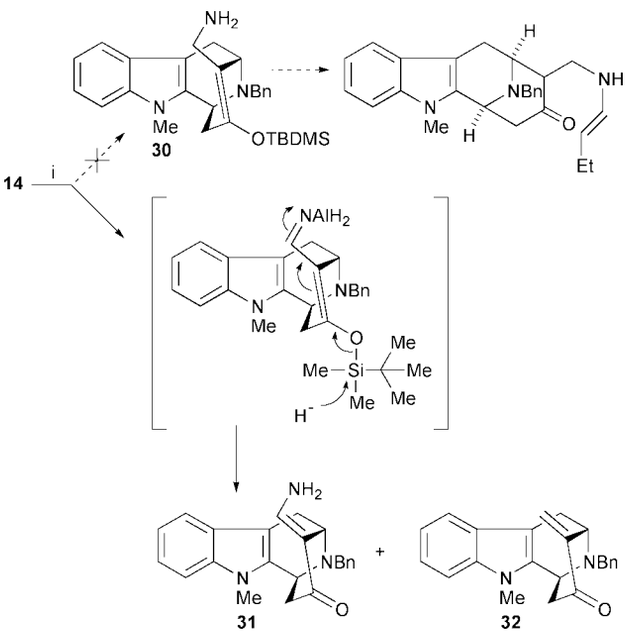
Reaction with butyryl chloride to afford the amide **27**, proceeded in good yield. A small quantity of the ester **28** was also isolated, presumably *via* desilylation and trapping of the resultant ketone. Desilylation of the TBDMS enol **27** with TBAF proceeded quantitatively to afford the corresponding ketone **29**. As expected, the NMR spectra of this compound were very broad, presumably due to keto–enol equilibration and the presence of amide rotamers about N^b. It was envisaged that reduction–dehydration of this ketone would proceed in high overall yield, based on our earlier work with the N^b-benzyl series.[12] However, sodium borohydride reduction of the ketone **29** in methanol afforded complex mixtures of products from which no corresponding alcohol was readily isolated. Dehydration of the crude reaction mixtures with phosphoryl chloride and pyridine in refluxing benzene again afforded complex mixtures of products. However, some of the α,β-unsaturated nitrile **23** could be obtained in low yield by careful flash chromatography, along with some recovered ketone **29** (Scheme 9).



Scheme 9 *Reagents and conditions*: i, Pd–C, H_2, MeOH, 45 min; ii, PrCOCl, Cs_2CO_3, DCM, room temp., 30 min (61% overall for **27** and 17% for **28**); iii, TBAF, MeOH, room temp., 30 min (100%); iv, $NaBH_4$, MeOH, room temp., 72 h; v, $POCl_3$, pyridine, benzene, reflux, 24 h (24% overall from **29**).

The base-induced ring closure postulated in Scheme 7 was now attempted with 1, 2, 5 and 10 equivalents of LDA in THF. No reaction was observed at −78 °C, and at higher temperatures steady decomposition of starting material was the only observed process. The amides **27** and **29** were also subjected to the same conditions, but again no ring closure was observed. The failure of these reactions was presumably due to the conformational constraints placed upon the ring system by the amide functionality and in light of the surprisingly difficult and low yielding sequence to the N^b-butyryl α,β-unsaturated nitrile **23**, this approach was not investigated further.

We envisaged a second intramolecular route towards suaveoline **2a**, again starting from the TBDMS enol ether **14**. The first step proposed was a simple LAH reduction of the nitrile moiety of the silyl enol ether **14** to the corresponding amine. The amine **30** would then be ideally set up for condensation with butyraldehyde, or an equivalent, and following desilylation, intramolecular enamine cyclisation to the ketone functionality at C15 (Scheme 10). However, an initial small scale LAH

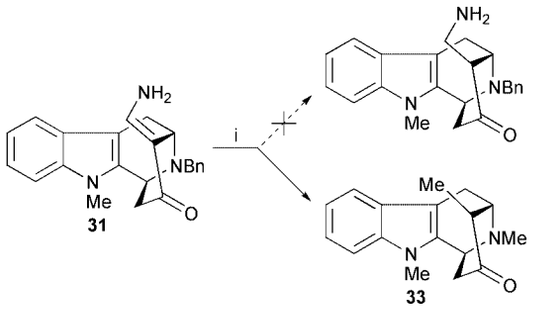


Scheme 10 *Reagents* (for conditions see text): i, LAH, THF.

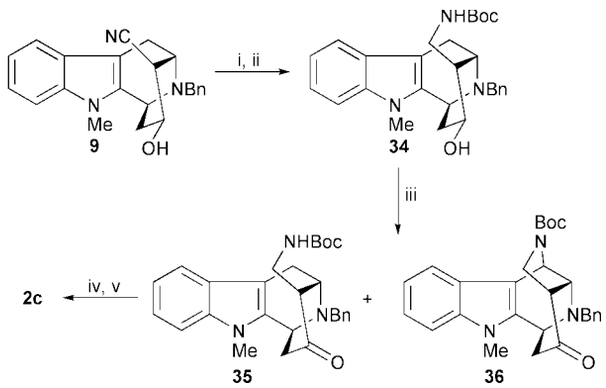
reduction (over 24 h) gave a single product which was not the expected amine **30**, but was eventually identified as the vinylogous amide **31** (45% yield). A larger scale reduction (over 72 h) afforded some of the same product **31** in 20% yield, along with a higher running component in 55% yield which was assigned as the ketone **32**. Unfortunately, this material rapidly dimerised, thus preventing full characterisation. The structure of the dimer ($M_r = 684$) remains unknown due to the complexity of the available NMR data. Another larger scale reduction, carefully monitored to ensure that just enough LAH was added to consume the starting material, afforded some of the vinylogous amide **31** in 26% yield but mostly returned the desilylated ketone **8** in 67% yield. Thus, a possible mechanism for the formation of the vinylogous amide is *via* the hydride promoted desilylation of the intermediate aldimine.

We reasoned that the vinylogous amide **31** was structurally close to suaveoline and could also undergo the enamine reaction postulated in Scheme 10. Unfortunately no reaction with butyraldehyde was observed under standard conditions for imine formation. Thus we attempted to increase the nucleophilicity of the nitrogen by reducing the double bond. However, the vinylogous amide **31** proved surprisingly robust towards hydrogenation in methanol; an excess of 10% Pd–C catalyst along with a 24 h reaction time was required to effect complete consumption of the starting material. A single product was obtained in 66% yield (Scheme 11). Remarkably, NMR indicated the presence of 3 methyl groups and this material was identified as the ketone **33**. This result confirms a report by Cook and Fu[14a] where an N^b-benzyl in related systems is converted to N^b-methyl under similar conditions. A full mechanism to account for this transformation is elusive, but presumably involves formaldehyde, which can be generated from the solvent under similar reaction conditions.[21]

Nevertheless, by returning to the hydroxynitrile **9**, reduction of the nitrile to the primary amine was more straightforward,



Scheme 11 *Reagents and conditions*: i, Pd–C, H_2, MeOH, 24 h (66%).



Scheme 12 *Reagents and conditions*: i, LAH, THF, room temp. 24 h then reflux 5 h; ii, BOC_2O, $NaHCO_3$, $CHCl_3$, room temp., 90 min (64% overall from **9**); iii, PCC–Florosil, DCM, room temp., 24 h (41%); iv, 1:9 water–TFA, room temp., 1 h then PrCHO, DCM, 72 h.

and selective protection to the *N*-Boc derivative **34** proceeded in an overall yield of 65% from the alcohol **9** (Scheme 12). Next we envisaged a simple oxidation from the alcohol back to the ketone, so that this slightly circuitous route could proceed in high overall yield. Standard Swern and TPAP oxidation conditions failed, but the use of excess Swern reagent did yield some of the ketone **35** (37%), along with a complex mixture of rearrangement products which could not be characterised (although we have since applied related Swern conditions in synthetically valuable oxidations and alkylations of tryptamine derivatives).[22] Oxidation of the alcohol to the ketone **35** was therefore more conveniently achieved using PCC. Unexpectedly, this reaction also generated the 3′-cyclised derivative **36** as the major product,[23] which bears an interesting structural similarity to alkaloid G **4** (Scheme 12). Finally, deprotection of **35** with TFA afforded an unstable ketone (which could not be isolated and characterised), but which was treated with butanal in the presence of oxygen in an effort to promote the intramolecular enamine reaction proposed earlier. Although a complex reaction mixture was generated, traces of N^b-benzylsuaveoline **2c** could be identified by TLC/MS comparison with authentic material.[9,14a]

Conclusion

In this paper we present a range of transformations from bridged intermediates such as **6**, **8** and **9**. A number of unusual reactions were observed, in particular: (a) the hydride-promoted desilylation leading to a range of compounds including the vinylogous amide **31**, (b) the reductive alkylations occurring during the hydrogenation of **31**, (c) the formation of the 3′-cyclised derivative **36**. We were successful in the production of small amounts of N^b-benzylsuaveoline **2c**; however, problems with introducing the required carbons at C15 are a specific issue that needs addressing. Our efficient solution to this long term problem is described in the next paper.

Experimental

Melting points were determined on a Reichert microscope hot-stage apparatus, and are uncorrected. Elemental analysis was performed by CHN Ltd. NMR spectra were recorded on a Bruker WP80 at 80 MHz (^{1}H), a JEOL FX90 at 90 MHz (^{1}H) and 22.5 MHz (^{13}C), a Bruker MSL300 spectrometer at 300 MHz (^{1}H) and 75 MHz (^{13}C), a Bruker WP200 at 200 MHz (^{1}H) and 50 MHz (^{13}C) or a Bruker DPX400 at 400 MHz (^{1}H) and 100 MHz (^{13}C). Chemical shifts were measured in ppm on the δ scale downfield from tetramethylsilane as internal standard. The solvent employed was $CDCl_3$, unless otherwise stated. When pairs of diastereoisomers were not separated the diastereomeric NMR resonances are bracketed thus {}. All ^{13}C data are quoted with ^{1}H multiplicities (off resonance results) in brackets thus (), although this multiplicity was inferred from DEPT experiments. Infrared spectra were recorded on a Perkin-Elmer 1420 ratio recording spectrophotometer. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter at room temp. and are reported in units of 10^{-1} deg cm^2 g^{-1}. Mass spectra were obtained by electron impact at 70 eV on an AEI MS-3074, or a VG AUTOSPEC spectrometer. Analytical TLC was carried out on Merck aluminium sheet silica gel 60 F_{254} plates (thickness 0.2 mm). Spots were visualised with a UV hand lamp. Flash chromatography was performed using silica gel 60 (230–400 mesh) as the stationary phase, purchased from Camlab.

THF was dried by distillation from sodium or obtained anhydrous from Aldrich. DMF was obtained anhydrous from Aldrich and was stored under dry argon. HPLC grade $CHCl_3$, DCM and MeOH used in the large scale preparations were obtained from Rathburn Chemicals Ltd. For small scale work, chlorinated solvents were distilled from phosphorus pentaoxide. Benzene, toluene and ethoxyethane were distilled and stored over sodium. Pyridine and 2,6-dimethylpyridine were distilled and stored over potassium hydroxide pellets. Triethylamine and phosphoryl chloride were distilled and stored under dry argon. LAH 1 M solution in THF, DIBAL-H 1 M solution in DCM, 9-BBN 0.5 M solution in THF, BH_3·THF 1 M solution in THF, LDA 1.5 M solution in THF and *n*-BuLi 2.5 M solution in hexanes were obtained from Aldrich and stored under dry argon.

Attempted Michael addition to the tetracyclic aldehyde 6

Methyl iodide (250 mg, 1.75 mmol) was added dropwise to clean magnesium turnings (40.5 mg, 1.75 mmol) in dry THF (1.5 ml) at room temp. When all the magnesium was consumed (*ca.* 10 min) HMPA (540 mg, 3.0 mmol) and CuBr·Me_2S (1.5 mg, 7 μmol) were added and a portion of the resulting solution (200 μl, *ca.* 0.17 mmol, 1.5 eq. of Grignard reagent) was added dropwise to a solution of the aldehyde **6** (40 mg, 0.12 mmol) and TMSCl (33 mg, 0.3 mmol) in THF (1 ml) maintained at −78 °C. After 4 h TLC indicated complete consumption of starting material and saturated aqueous NH_4Cl was added to quench the reaction. Upon warming to room temperature, the solution was extracted 3 times with EtOAc and the combined organic extracts were washed with water and then dried over $MgSO_4$. Filtration and evaporation afforded a yellow oil (39 mg). Flash chromatography on silica eluted with a solvent gradient (DCM to 1:9 ether–DCM) afforded 2 pairs of diastereoisomers (each *ca.* 1:1): the free alcohol **11a/b** (15 mg, 30%) and the TMS ether **12a/b** (12 mg, 29%).

Data for the alcohol 11a/b. R_f 0.11 and 0.07 (1:9 ether–$CHCl_3$); ^{1}H NMR (300 MHz) δ 1.29 (3H, dd, *J* 6.5, 2.4 Hz, $CHCH_3$), 1.97–2.05 (1H, m, one of $ArCHCH_2$), 2.67–2.81 (2H, m, one of $ArCHCH_2$ and one of $ArCH_2CH$), 3.07–3.15 (1H, m, one of $ArCH_2CH$), {3.54, 3.56} (3H, s, indole NCH_3), 3.62–4.01 (4H, m, $ArCHCH_2$ and NCH_2Ph and $ArCH_2CH$),

4.23 (1H, q, *J* 6.5 Hz, C*H*OH), {5.61, 5.71} (1H, br s, ArCHCH$_2$C*H*), 7.05–7.49 (9H, m, Ar*H*); ^{13}C NMR (75 MHz) δ 20.8 (q), {22.3, 23.0} (t), 28.9 (q), {29.4, 30.3} (t), {48.6, 47.4} (d), {52.2, 52.5} (d), 56.3 (t), 68.8 (d), 104.9 (s), 108.9 (d), 118.1 (d), 118.9 (d), 119.4 (d), 121.0 (d), 127.1 (d), 128.3 (d), 128.8 (d), 135.4 (s), 138.1 (s), 138.9 (s), 142.6 (s), 144.1 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 1700, 1670, 1620, 1470; MS *m*/*z* 358 (M^+, 100%), 343 (15), 313 (32), 273 (21), 249 (64), 222 (26), 181 (40), 157 (19), 144 (21), 91 (96); found *m*/*z* 358.2048, calc. for $C_{24}H_{26}N_2O$ 358.2045.

Data for 12a/b. R_f 0.48 and 0.38 (1:9 ether–$CHCl_3$); ^{1}H NMR (300 MHz) δ 0.03 (9H, s, SiC(C*H*$_3$)$_3$), 1.24 (3H, d, *J* 6.4 Hz, CHC*H*$_3$), 2.00 (1H, dd, *J* 13.5, 5.5 Hz, one of ArCHC*H*$_2$), 2.67–2.78 (2H, m, one of ArCHC*H*$_2$ and one of ArC*H*$_2$CH), 3.05 (1H, dt, *J* 15.9, 7.4 Hz, one of ArC*H*$_2$CH), 3.57 (3H, s, indole NC*H*$_3$), 3.65–3.82 (3H, m, NC*H*$_2$Ph and ArCH$_2$C*H*), 4.03 (1H, d, *J* 5.9 Hz, ArC*H*CH$_2$), 4.19–4.27 (1H, m, C*H*OTMS), {5.52, 5.62} (1H, br s, ArCHCH$_2$C*H*), 7.07–7.48 (9H, m, Ar*H*); ^{13}C NMR (75 MHz) δ 0.1 (q), 21.7 (q), 22.4 (t), 28.8 (q), 29.6 (t), 48.4 (d), 50.9 (d), 57.6 (t), {68.6, 69.1} (d), 104.8 (s), 108.2 (d), 117.4 (d), 117.6 (d), 118.5 (d), 120.2 (d), 126.7 (d), 127.5 (d), 128.5 (d), 135.2 (s), 136.5 (s), 138.6 (s), 141.7 (s), 142.6 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 1525, 1425; MS *m*/*z* 430 (M^+, 65%), 415 (87), 339 (17), 313 (19), 273 (23), 249 (24), 181 (31), 144 (22), 91 (100); found *m*/*z* 430.2440, calc. for $C_{27}H_{34}N_2OSi$ 430.2426.

Attempted Reformatsky reactions with the ketone 8

The ketone **8** (35.5 mg, 0.10 mmol), 2-bromopropionitrile (19 mg, 0.14 mmol) and an excess of acid washed zinc powder were suspended in dioxane (3 ml). The flask was suspended in a sonic bath for 2 h and then left to stand for 24 h. TLC indicated that no reaction had occurred.

Formation of zinc/silver/graphite matrix. Graphite (300 mg, 25 mmol) was degassed under a stream of dry argon for 10 min at 150 °C and then cooled to room temp. Finely divided, freshly cut potassium metal (120 mg, 3.06 mmol) was added and the mixture heated until the metal melted (oil bath *ca.* 175 °C). Vigorous stirring then afforded a bronze powder of KC_8. After cooling to room temp. dry THF (10 ml) was added, followed by anhydrous $ZnCl_2$ (200 mg, 1.47 mmol) and AgOAc (20 mg, 0.12 mmol) in small portions. The resulting mixture was refluxed with stirring to afford a black suspension of zinc/silver/graphite which was used immediately.

For a second Reformatsky attempt, the ketone **8** (230 mg, 0.65 mmol) and 2-bromopropionitrile (19 mg, 0.14 mmol) were added to freshly prepared zinc/silver/graphite (1.47 mmol of zinc) in THF at −20 °C. After stirring for 1 h the reaction was allowed to warm to room temperature and stirred for 72 h. TLC indicated that no reaction had occurred.

Attempted cuprate addition to the tetracyclic ketone 8

n-BuLi (0.42 ml of 2.5 M solution in hexanes) was added to a suspension of CuBr·Me_2S (43.2 mg, 0.21 mmol) in dry THF (2 ml) maintained at −78 °C. This mixture was allowed to warm to *ca.* −40 °C (until homogeneous) and again cooled to −78 °C, then a solution of the ketone **8** (40 mg, 0.11 mmol) in dry THF (2 ml) was added dropwise. TLC analysis indicated that no reaction had occurred after 2 h, and so the mixture was allowed to warm gradually to room temperature. After a further 24 h the only process observed was slight decomposition of the ketone **8**.

General procedure for the attempted DIBAL-H reduction of the ketone 8 or the alcohol 9

The tetracyclic material was dissolved in dry DCM and cooled to −78 °C. Sufficient DIBAL-H to consume the starting material (3.5 eq. of 1 M solution in DCM) was added dropwise. After stirring for 30 min the reaction was allowed to warm to room temperature and stirred for a further 1 h. The solution was then cooled to −78 °C and MeOH, saturated NH_4Cl (aq), and 0.1 M aqueous sulfuric acid were added sequentially and the mixture allowed to warm to room temperature. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and evaporated to afford a yellow oil. TLC indicated that these oils contained at least 4 products and none of the desired aldehydes could be isolated from the mixtures.

Preparation of (6*S*,10*S*)-12-benzyl-9-cyano-8-*tert*-butyldimethylsilyloxy-5-methyl-6,7,10,11-tetrahydro-5*H*-6,10-iminocycloocta[*b*]indole 14 from the pure ketone 8

The ketone **8** (25 mg, 0.07 mmol) was dissolved in dry DCM (10 ml) and stirred at 0 °C. Imidazole (10 mg, 0.14 mmol) and TBDMSCl (22 mg, 0.14 mmol) were added and the resulting solution allowed to warm to room temperature and stirred for 24 h. The solution was then washed with brine, dried over $MgSO_4$, filtered and evaporated to afford a yellow foam. Flash chromatography on silica eluted with DCM afforded the TBDMS enol ether ether **14** as colourless foam (30 mg, 92%).

R_f 0.88 (1:9 ether–$CHCl_3$); ^{1}H NMR (300 MHz) δ 0.10–0.15 (6H, m, Si(C*H*$_3$)$_2$), 0.89–0.91 (9H, m, SiC(C*H*$_3$)$_3$), 2.03 (1H, d, *J* 17.6 Hz, one of ArCHC*H*$_2$), 2.77–2.90 (1H, m, one of ArCHC*H*$_2$), 2.86 (1H, d, *J* 15.8 Hz, one of ArC*H*$_2$CH), 3.16 (1H, dd, *J* 15.8, 5.3 Hz, one of ArC*H*$_2$CH), 3.57 (3H, s, indole NC*H*$_3$), 3.67–3.84 (2H, m, NC*H*$_2$Ph), 3.94 (1H, d, *J* 5.3 Hz, ArCH$_2$C*H*), 4.12 (1H, br s, ArC*H*CH$_2$), 7.11–7.54 (9H, m, Ar*H*); ^{13}C NMR (75 MHz) δ −4.0 (q), −3.9 (q), −3.6 (q), 18.0 (s), 23.5 (t), 25.3 (q), 25.6 (q), 29.3 (q), 34.4 (t), 48.9 (d), 53.2 (d), 56.4 (t), 93.6 (s), 104.6 (s), 108.8 (d), 118.5 (d), 119.4 (d), 121.6 (s), 126.8 (s), 127.6 (d), 128.6 (d), 128.7 (d), 133.5 (s), 137.2 (s), 162.6 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 2205, 1635, 1495, 1470, 1415, 1370; MS *m*/*z* 469 (M^+, 44%), 412 (88), 378 (16), 363 (7), 337 (15), 312 (14), 295 (11), 273 (17), 246 (22), 91 (100), 73 (82); found *m*/*z* 469.2550, calc. for $C_{29}H_{35}N_3OSi$ 469.2549.

Large-scale formation of the TBDMS enol ether 14 from a mixture of the ketone 8 and the alcohol 9

A mixture of ketone **8** and alcohol **9** (1 g) was stirred in dry DCM (40 ml) and imidazole (250 mg, 3.7 mmol) was added. When the imidazole had fully dissolved TBDMSCl (426 mg, 2.82 mmol) was added in portions. After 1 h TLC indicated that the reaction was complete. Work-up as for the small scale procedure above followed by flash chromatography on silica eluted with DCM afforded the TBDMS enol ether **14** (894 mg) and the alcohol **9** (317 mg) both as colourless foams in essentially quantitative overall yield. The spectral data for this TBDMS enol ether were identical to those quoted above and evaporation of a methanolic solution afforded a white solid which was amenable to elemental analysis.

Mp 149–150 °C (MeOH); $[\alpha]_D$ −140 (*c* 1, MeOH); found C 74.12, H 7.52; and N 9.00; calc. C 74.16, H 7.51; and N 8.95%.

Attempted DIBAL-H reduction of the TBDMS enol ether 14

The TBDMS enol ether **14** (150 mg, 0.32 mmol) was dissolved in dry DCM (2 ml) and cooled to −78 °C. DIBAL-H (1.5 ml of 1 M solution in DCM, 1.5 mmol, 5 eq.) was added dropwise and the solution stirred at this temperature for 30 min. The reaction was then allowed to warm to room temperature and stirred for 24 h. No reaction was observed by TLC and work-up as for the previous DIBAL-H reductions afforded starting material, contaminated with traces of decomposition products.

Preparation of (6*S*,8*S*,9*R*,10*S*)-12-benzyl-9-cyano-8-*tert*-butyldimethylsilyloxy-5-methyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-iminocycloocta[*b*]indole 15

The alcohol **9** (300 mg, 0.84 mmol) was dissolved in DCM (10 ml) and 2,6-dimethylpyridine added (270 mg, 2.52 mmol) followed by TBDMSOTf (444 mg, 1.68 mmol). After stirring at room temp. for 24 h TLC indicated the reaction was complete, evaporation and flash chromatography on silica eluted with DCM then afforded the TBDMS protected alcohol **15** as a white foam (315 mg, 80%).

R_f 0.88 (1:9 ether–$CHCl_3$); ^{1}H NMR (300 MHz) δ −0.36 (3H, s, one of $Si(CH_3)_2$), −0.14 (3H, s, one of $Si(CH_3)_2$), 0.33 (9H, s, $SiC(CH_3)_3$), 1.91 (1H, dt, *J* 14.1, 2.4 Hz, one of $ArCHCH_2$), 2.13 (1H, dt, *J* 14.1 4.1 Hz, one of $ArCHCH_2$), 3.08 (1H, d, *J* 16.4 Hz, one of $ArCH_2CH$), 3.18 (1H, dd, *J* 17.0, 7.0 Hz, one of $ArCH_2CH$), 3.33 (1H, dd, *J* 5.3, 4.1 Hz, CHCN), 3.54 (3H, s, indole NCH_3), 3.54–3.57 (1H, m, $ArCH_2CH$), 3.60–3.70 (2H, ABq, *J* 13.5 Hz, NCH_2Ph), 3.87 (1H, dd, *J* 4.8, 2.4 Hz, $ArCHCH_2$), 4.22–4.24 (1H, m, CHOTBDMS), 7.05–7.34 (8H, m, Ar*H*), 7.48 (1H, d, *J* 7.6Hz, Ar*H*); ^{13}C NMR (75 MHz) δ −5.5 (q), −5.2 (q), 17.4 (s), 18.9 (t), 24.9 (q), 28.9 (q), 37.0 (t), 40.9 (d), 47.3 (d), 51.7 (d), 57.6 (t), 64.6 (d), 105.5 (s), 108.5 (d), 118.2 (d), 118.7 (d), 119.8 (s), 120.6 (d), 127.0 (s), 127.3 (d), 128.4 (d), 128.6 (d), 134.0 (s), 137.0 (s), 138.4 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 2200, 1495, 1420, 1415, 1370; MS *m*/*z* 471 (M^+, 100%), 414 (15), 348 (10), 339 (12), 313 (13), 273 (81), 222 (17), 183 (16), 170 (26), 154 (37), 91 (67), 75 (23); found *m*/*z* 471.2706, calc. for $C_{29}H_{37}N_3OSi$ 471.2706.

Preparation of (6*S*,8*S*,9*R*,10*S*)-12-benzyl-8-*tert*-butyldimethylsilyloxy-5-methyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-iminocycloocta[*b*]indole-9-carbaldehyde 16

The TBDMS ether **15** (144 mg, 0.31 mmol) was dissolved in DCM (5 ml) and cooled to −78 °C. DIBAL-H (0.9 ml of 1 M solution, 0.9 mmol, 3 eq.) was added dropwise and the reaction stirred for 1 h at this temperature, then for 1.5 h at room temp. Work-up as for the previous attempted DIBAL-H reductions followed by flash chromatography on silica eluted with DCM afforded the aldehyde **16** (125 mg, 85%). Since we envisaged this material being less stable than the related acetal or nitrile, an exhaustive characterisation was not undertaken.

R_f 0.59 (1:9 ether–$CHCl_3$); ^{1}H NMR (80 MHz) δ −0.51 (3H, s, one of $Si(CH_3)_2$), −0.17 (3H, s, one of $Si(CH_3)_2$), 0.28 (9H, s, $SiC(CH_3)_3$), 1.78–2.19 (2H, m, $ArCHCH_2$), 2.68–3.37 (4H, m, $ArCH_2CH$ and CHCHO), 3.52 (3H, s, indole NCH_3), 3.58–3.89 (3H, m, CH_2Ph and ArC*H*), 4.56–4.81 (1H, m, CHOTBDMS), 6.87–7.54 (9H, m, Ar*H*), 9.65 (1H, s, CHO); MS *m*/*z* 474 (M^+, 56%), 342 (16), 313 (25), 273 (87), 251 (13), 181 (45), 170 (26), 129 (34), 91 (100), 75 (96); found *m*/*z* 474.2689, calc. for $C_{29}H_{38}N_2O_2Si$ 474.2703.

Formation of (6*S*,9*R*,10*S*)-12-benzyl-5-methyl-6,7,10,11-tetrahydro-5*H*-6,10-iminocycloocta[*b*]indole-9-carbaldehyde ethylene acetal 17 and ethylene dithioacetal 18

The aldehyde **16** (30 mg, 0.06 mmol) was dissolved in ethylene glycol (10 ml) and refluxed for 2 h with a trace of PTSA, by which time TLC indicated complete consumption of starting material. The reaction mixture was diluted with benzene and washed twice with aqueous 1 M $NaHCO_3$ then once with brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to afford a brown oil. Flash chromatography on silica eluted with DCM afforded the unsaturated acetal **17** (15 mg, 65%) as a white foam.

R_f 0.39 (1:9 ether–$CHCl_3$); ^{1}H NMR (300 MHz) δ 2.05 (1H, dd, *J* 17.6, 5.3 Hz, one of $ArCHCH_2$), 2.73 (1H, br dd, *J* 17.6, 5.3 Hz, one of $ArCHCH_2$), 2.93 (1H, d, *J* 15.8 Hz, one of $ArCH_2CH$), 3.08 (1H, dd, *J* 15.8, 5.9 Hz, one of $ArCH_2CH$), 3.54 (3H, s, indole NCH_3), 3.67–3.81 (2H, AB system, *J* 13.5 Hz, NCH_2Ph), 3.83–4.03 (6H, m, $ArCH_2CH$ and $ArCHCH_2$ and $CH(OCH_2)_2$), 5.19 (1H, s, $CH(OCH_2)_2$), 5.89 (1H, br d, *J* 2.9 Hz, $ArCHCH_2CH$), 7.04–7.51 (9H, m, Ar*H*); ^{13}C NMR (75 MHz) δ 23.1 (t), 29.1 (q), 29.6 (t), 38.3 (t), 48.2 (d), 51.1 (d), 59.4 (t), 64.8 (t), 104.9 (d), 105.3 (s), 108.6 (d), 118.2 (d), 118.7 (d), 120.8 (d), 124.1 (d), 126.9 (d), 127.1 (s), 128.2 (d), 128.8 (d), 135.4 (s), 136.1 (s), 137.0 (s), 139.0 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 1675, 1495, 1470, 1370, 1320; MS *m*/*z* 386 (M^+, 100%), 342 (7), 313 (45), 295 (30), 273 (32), 251 (17), 222 (21), 207 (14), 181 (46), 91 (67); found *m*/*z* 386.1989, calc. for $C_{25}H_{26}N_2O_2$ 386.1994.

The aldehyde **16** (200 mg, 0.42 mmol) and ethane-1,2-dithiol (119 mg, 1.26 mmol, 3 eq.) were dissolved in DCM and $BF_3{\cdot}OEt_2$ (59.6 mg, 52 ml, 0.42 mmol, 1 eq.) was added slowly and the reaction stirred for 24 h at room temp., when TLC indicated complete consumption of starting material. Aqueous saturated $NaHCO_3$ was added and the organic layer separated, washed with saturated $NaHCO_3$ (aq), dried over $MgSO_4$, filtered and evaporated to afford a smelly yellow oil. Flash chromatography on silica eluted with DCM afforded the unsaturated dithioacetal **18** as a pale yellow foam (115 mg, 66%).

R_f 0.78 (1:9 ether–$CHCl_3$); ^{1}H NMR (300 MHz) δ 1.95 (1H, dd, *J* 17.6, 5.3 Hz, one of $ArCHCH_2$), 2.61–2.70 (1H, m, one of $ArCHCH_2$), 2.83 (1H, d, *J* 16.9 Hz, one of $ArCH_2CH$), 2.97–3.22 (5H, m, $CH(SCH_2)_2$ and one of $ArCH_2CH$), 3.46 (3H, s, indole NCH_3), 3.59–3.73 (2H, AB system, *J* 13.5 Hz, NCH_2Ph), 3.74 (1H, d, *J* 5.9 Hz, $ArCH_2CH$), 3.95 (1H, d, *J* 5.9 Hz, $ArCHCH_2$), 5.02 (1H, s, $CH(SCH_2)_2$), 5.95–5.98 (1H, m, $ArCHCH_2CH$), 6.95–7.42 (9H, m, Ar*H*); ^{13}C NMR (75 MHz) δ 23.6 (t), 29.1 (q), 29.4 (t), 38.3 (t), 39.1 (t), 48.2 (d), 53.8 (d), 56.2 (d), 56.3 (t), 105.1 (s), 108.6 (d), 118.0 (d), 118.7 (d), 120.8 (d), 121.3 (d), 126.9 (s), 126.9 (d), 128.1 (d), 128.8 (d), 135.8 (s), 136.8 (s), 139.9 (s), 138.8 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 1510, 1470, 1380; MS *m*/*z* 418 (M^+, 39%), 357 (34), 327 (14), 313 (32), 273 (30), 181 (29), 91 (100); found *m*/*z* 418.1536, calc. for $C_{25}H_{26}N_2S_2$ 418.1537.

Acetal 17 formation from the α,β-unsaturated aldehyde 6

The α,β-unsaturated aldehyde **6** (303 mg, 0.88 mmol) and excess ethylene glycol (1 ml) were stirred in dry DCM (20 ml) at room temp. $BF_3{\cdot}OEt_2$ (640 mg, 4.4 mmol, 5 eq.) was added dropwise and the reaction stirred at ambient temperature for 4 h, when TLC indicated complete consumption of starting material. Saturated $NaHCO_3$ (aq) was added and the organic layer separated, washed sequentially with $NaHCO_3$ (aq) and brine, then dried over $MgSO_4$. Silica (250 mg) was added to remove baseline colouration. Filtration and evaporation then afforded more of the acetal **17** as a white foam (302 mg, 89%).

Attempted hydroboration of the acetal 17 with $BH_3{\cdot}THF$

The α,β-unsaturated acetal **17** (27 mg, 0.07 mmol) was dissolved in dry THF (2 ml) and cooled to 0 °C. $BH_3{\cdot}THF$ (0.5 ml of 1 M solution in THF, 0.5 mmol) was added dropwise and the reaction stirred for 24 h. TLC at regular intervals indicated that a mixture of products was produced simultaneously, and this reaction was not pursued further.

Attempted hydroboration of the acetal 17 with 9-BBN

To the acetal **17** (64 mg, 0.16 mmol) was added 9-BBN (0.5 ml of 0.5 M solution in THF, 0.25 mmol). The resulting solution was stirred at ambient temperature for 24 h then aqueous 2 M NaOH (0.5 ml) and aqueous 35% H_2O_2 (0.2 ml) were added and the solution stirred for a further 15 min. The reaction mixture was then extracted into benzene, washed with water then brine, dried over $MgSO_4$, filtered and evaporated to afford a yellow oil (70 mg). Flash chromatography on silica eluted with a solvent gradient (DCM to 1:9 ether–DCM) afforded the ring-opened

material **19** as a white foam (34 mg, 55%) and also some starting material **17** (9 mg, 14%).

R_f 0.58 (1:9 MeOH–$CHCl_3$); ^{1}H NMR (300 MHz) δ 2.04 (1H, dd, *J* 17.3, 4.4 Hz, one of ArCHCH_2), 2.71 (1H, d, *J* 15.8 Hz, one of ArCH_2CH), 2.80 (1H, br d, *J* 17.3 Hz, one of ArCHCH_2), 3.10 (1H, dd, *J* 15.8, 5.9 Hz, one of ArCH_2CH), 3.41–3.57 (2H, m, $CH_2OCH_2CH_2OH$), 3.58 (3H, s, indole NCH_3), 3.68–3.69 (3H, m, $ArCH_2CH$ and $CH_2OCH_2CH_2OH$), 3.66–3.82 (2H, ABq, *J* 5.9 Hz, CCH_2O), 3.80–3.86 (2H, ABq, *J* 13.5 Hz, NCH_2Ph), 4.05–4.11 (2H, m, ArC*H* and O*H*), 5.64 (1H, br s, $ArCHCH_2CH$), 7.07–7.51 (9H, m, Ar*H*); ^{13}C NMR (75 MHz) δ 21.6 (t), 29.3 (q), 30.4 (t), 48.4 (d), 52.3 (d), 56.4 (t), 61.9 (t), 70.8 (t), 73.2 (t), 105.0 (s), 108.8 (d), 118.0 (d), 118.9 (d), 121.0 (d), 122.4 (d), 126.9 (s), 127.1 (d), 128.3 (d), 128.8 (d), 135.0 (s), 136.5 (s), 137.0 (s), 138.6 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 1705, 1655, 1615, 1495, 1470, 1380; MS *m*/*z* 388 (M^+, 100%), 344 (8), 327 (37), 297 (14), 273 (19), 235 (58), 220 (24), 181 (57), 91 (66); found *m*/*z* 388.2153, calc. for $C_{25}H_{28}N_2O_2$ 388.2151.

Attempted hydroboration of the dithioacetal 18 with 9-BBN

To the dithioacetal **18** (50 mg, 0.12 mmol) was added 9-BBN (0.5 ml of 0.5 M solution in THF, 0.25 mmol) and the resulting solution stirred at ambient temperature for 24 h. When TLC indicated that no reaction had occurred 9-BBN (1 ml of 0.5 M solution in THF, 0.5 mmol) was added and the reaction mixture refluxed for 24 h. No reaction, other than slight decomposition, was observed by TLC.

Attempted epoxide formation from acetal 17: formation of the *N*-oxides 20a/b

The acetal **17** (120 mg, 0.31 mmol) was dissolved in DCM (15 ml) and stirred over excess $NaHCO_3$ at 0 °C. Commercially available MCPBA (201 mg of 50% pure solid, 0.59 mmol) was added and stirring maintained for 30 min at this temperature. Saturated $NaHCO_3$ (aq) was added and the organic layer separated, washed with $NaHCO_3$ (aq) and then twice with brine, then dried over $MgSO_4$, filtered and evaporated to afford a yellow oil (175 mg). Flash chromatography on silica eluted with a careful gradient (1:20 ether–DCM to 1:1:18 ether–MeOH–DCM) afforded white foams for both isomers of the *N*-oxide **20a** (71 mg, 57%) and **20b** (24 mg, 19%).

Data for 20a (major isomer by *ca.* 3:1). R_f 0.52 (1:9 MeOH–$CHCl_3$); ^{1}H NMR (90 MHz) δ 2.09 (1H, dd, *J* 18.3, 4.7 Hz, one of ArCHCH_2), 3.13–3.70 (2H, m, one of ArCHCH_2 and one of ArCH_2CH), 3.55 (3H, s, indole NCH_3), 3.86–4.05 (5H, m, $CH(OCH_2)_2$ and one of ArCH_2CH), 4.24–4.33 (2H, m, $ArCH_2CH$ and ArC*H*CH_2), 4.35–4.67 (2H, ABq, *J* 10.4 Hz, NCH_2Ph), 5.29 (1H, s, C*H*$(OCH_2)_2$), 5.89–6.00 (1H, m, $ArCH$-CH_2CH), 7.09–7.64 (9H, m, Ar*H*); ^{13}C NMR (75 MHz) δ 25.9 (t), 28.9 (q), 29.2 (t), 60.4 (d), 64.5 (2 × t), 67.3 (d), 67.9 (t), 103.0 (s), 104.0 (d), 109.1 (d), 118.4 (d), 119.4 (d), 122.0 (d), 123.9 (d), 125.6 (s), 127.9 (d), 129.1 (d), 129.6 (s), 130.7 (s), 132.6 (d), 132.6 (s), 137.5 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 1615, 1495, 1470, 1455, 1400, 1385, 1350; MS *m*/*z* 402 (M^+, 9%), 386 (36), 313 (20), 311 (6), 295 (23), 273 (11), 251 (7), 242 (8), 222 (16), 207 (11), 194 (12), 181 (26), 157 (21), 91 (100), 73 (26); found *m*/*z* 402.1950, calc. for $C_{25}H_{26}N_2O_3$ 402.1943.

Data for 20b. R_f 0.57 (1:9 MeOH–$CHCl_3$); ^{1}H NMR (90 MHz) δ 2.45 (1H, dd, *J* 19.9, 4.7 Hz, one of ArCHCH_2), 2.97–3.22 (3H, m, ArCH_2CH and one of ArCHCH_2), 3.52 (3H, s, indole NCH_3), 3.84–4.30 (6H, m, $CH(OCH_2)_2$ and NCH_2Ph), 4.47–4.59 (2H, m, $ArCH_2CH$ and ArC*H*CH_2), 5.28 (1H, s, C*H*$(OCH_2)_2$), 5.90–6.02 (1H, m, $ArCHCH_2CH$), 7.01–7.52 (7H, m, Ar*H*), 7.77–7.89 (2H, m, Ar*H*); ^{13}C NMR (75 MHz) δ 24.1 (t), 29.4 (q), 31.5 (t), 63.9 (d), 65.2 (t), 65.4 (t), 66.0 (d), 68.7 (t), 104.0 (d), 104.5 (s), 108.8 (d), 118.6 (d), 119.1 (d), 121.2 (d), 123.2 (d), 126.2 (s), 128.1 (d), 129.4 (d), 130.0 (s), 131.8 (s), 133.1 (d), 135.5 (s), 137.4 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 1600, 1495, 1470, 1455, 1400, 1385, 1365, 1350; MS *m*/*z* 402 (M^+, 56%), 386 (13), 313 (7), 311 (16), 295 (100), 251 (8), 242 (54), 223 (19), 208 (15), 194 (14), 181 (24), 91 (68), 73 (49); found *m*/*z* 402.1953, calc. for $C_{25}H_{26}N_2O_3$ 402.1943.

Attempted epoxide formation from the *N*-oxides 20a/b

The *N*-oxides **20a/b** (20 mg, 0.05 mmol) were dissolved in DCM (2 ml) and stirred over excess $NaHCO_3$ at 0 °C. MCPBA (28 mg of 50% pure, 0.08 mmol) was added and the reaction stirred for 24 h. TLC during this time indicated that a complex mixture of products was produced. The same work-up procedure as the previous reaction was employed to afford a yellow oil. None the desired epoxide could be detected, or isolated from these products.

Attempted epoxide formation from the α,β-unsaturated nitrile 10: formation of the amide 21

The nitrile **10** (25 mg, 0.07 mmol) was dissolved in acetone (1 ml). Aqueous 2 M NaOH (0.18 ml) was added, followed by dropwise addition of aqueous 35% H_2O_2 (0.15 ml). After stirring at ambient temperature for 48 h the solution was diluted with saturated $NaHCO_3$ (aq), extracted into DCM, washed with brine and dried over $MgSO_4$. Filtration and evaporation afforded a yellow oil (30 mg). Flash chromatography on silica eluted with 1:9 MeOH–DCM afforded the amide **21** as a white foam (21 mg, 79%).

R_f 0.57 (1:9 MeOH–$CHCl_3$); ^{1}H NMR (90 MHz) δ 2.12 (1H, dd, *J* 18.5, 5.8 Hz, one of ArCHCH_2), 2.70–3.37 (3H, m, ArCH_2CH and one of ArCHCH_2), 3.56 (3H, s, indole NCH_3), 3.58–4.09 (3H, m, NCH_2Ph and $ArCH_2CH$), 4.29 (1H, d, *J* 5.8 Hz, ArC*H*CH_2), 5.31 (1H, br s, one of C(O)NH_2), 6.36 (1H, dd, *J* 4.9, 2.2 Hz, $ArCHCH_2CH$), 7.05–7.54 (10H, m, Ar*H* and one of C(O)NH_2); ^{13}C NMR (22.5 MHz) δ 22.6 (t), 29.4 (q), 31.1 (t), 47.4 (d), 51.7 (d), 56.5 (t), 105.3 (s), 108.8 (d), 118.4 (d), 119.1 (d), 121.3 (d), 127.0 (d), 127.2 (d), 128.5 (d), 128.8 (d), 129.6 (d), 134.6 (s), 136.5 (s), 137.1 (s), 138.6 (s), 169.0 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 3520, 3415, 1675, 1645, 1585, 1495, 1475, 1375; MS *m*/*z* 357 (M^+, 100%), 340 (17), 313 (10), 273 (26), 266 (19), 249 (41), 221 (68), 206 (22), 181 (43), 91 (79); found *m*/*z* 357.1834, calc. for $C_{23}H_{23}N_3O$ 357.1841.

Attempted debenzylation of the α,β-unsaturated nitrile 10: formation of the amine 24

The nitrile **10** (25 mg, 0.07 mmol) was dissolved in dry MeOH and stirred over 10% Pd–C under an atmosphere of hydrogen whilst being monitored by TLC. After 24 h, filtration and evaporation afforded a clear oil (21 mg). Flash chromatography on silica eluted with a solvent gradient (DCM to 1:19 MeOH–DCM) afforded the free amine **24** as a white foam (16 mg, 80%).

R_f 0.41 (1:9 MeOH–$CHCl_3$); ^{1}H NMR (90 MHz) δ 1.61–2.10 (4H, m, $ArCHCH_2CH_2$), 2.99–3.17 (3H, m, ArCH_2CH and C*H*CN), 3.56 (3H, s, indole NCH_3), 3.48–3.73 (1H, m, $ArCH_2$-C*H*), 4.14 (1H, br s, ArC*H*CH_2), 7.05–7.58 (4H, m, Ar*H*); ^{13}C NMR (22.5 MHz) δ 18.6 (t), 21.0 (t), 29.2 (q), 29.3 (t), 34.2 (d), 49.3 (d), 50.6 (d), 106.8 (s), 109.0 (d), 118.2 (d), 119.3 (d), 121.3 (s), 121.5 (d), 126.2 (s), 133.2 (s), 137.1 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 2245, 1615, 1470, 1450, 1425, 1380, 1355; MS *m*/*z* 251 (M^+, 14%), 250 (46), 233 (17), 183 (100), 168 (24), 84 (28); found *m*/*z* 251.1420, calc. for $C_{16}H_{17}N_3$ 251.1422.

Preparation of (6*S*,8*S*,9*R*,10*S*)-9-cyano-8-hydroxy-5-methyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-iminocycloocta[*b*]indole 25

The alcohol **9** (50 mg, 0.14 mmol) was dissolved in MeOH (10 ml) and stirred under an atmosphere of H_2 with catalytic 10% Pd–C for 48 h. Filtration and evaporation afforded a colourless oil (36 mg). Flash chromatography on silica eluted

with 1:19 MeOH–DCM afforded the amino alcohol **25** as a white foam (25 mg, 67%).

R_f 0.35 (1:9 MeOH–$CHCl_3$); ^{1}H NMR (90 MHz) δ 1.83–1.98 (1H, m, one of ArCHCH_2), 2.15–2.26 (1H, m, one of ArCHCH_2), 3.20–3.49 (3H, m, ArCH_2CH and C*H*CN), 3.62 (3H, s, indole NCH_3), 3.90–4.28 (3H, m, ArCH$_2$C*H*, ArC*H*CH$_2$ and C*H*OH), 7.01–7.54 (4H, m, Ar*H*); ^{13}C NMR (22.5 MHz) δ 23.2 (t), 28.8 (q), 35.3 (t), 38.3 (d), 41.3 (d), 46.2 (d), 62.8 (d), 105.0 (s), 108.9 (d), 117.0 (d), 118.1 (d), 119.9 (d), 120.6 (s), 126.7 (s), 136.2 (s), 139.3 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 3520, 2231; MS *m*/*z* 267 (M$^+$, 15%), 183 (100); found *m*/*z* 267.1368, calc. for $C_{16}H_{17}N_3O$ 267.1372.

Preparation of (6*S*,10*S*)-9-cyano-5-methyl-6,7,10,11-tetrahydro-5*H*-6,10-iminocycloocta[*b*]indole 22

The amino alcohol **25** (150 mg, 0.56 mmol), phosphoryl chloride (343.4 mg, 2.24 mmol) and pyridine (885 mg, 11.2 mmol) were refluxed together in dry benzene (25 ml) for 48 h. The solution was then cooled, treated with water and stirred for 30 min. The organic layer was separated, twice washed with saturated $NaHCO_3$ (aq) then dried over $MgSO_4$, filtered and evaporated to afford a yellow oil (148 mg). Flash chromatography on silica eluted with 1:19 ether–DCM afforded the α,β-unsaturated amine **22** as a white foam (35 mg, 25%).

R_f 0.70 (1:9 MeOH–$CHCl_3$); ^{1}H NMR (300 MHz) δ 2.39 (1H, dd, *J* 19.1, 5.5 Hz, one of ArCHCH_2), 2.97–3.06 (1H, m, one of ArCHCH_2), 3.08 (1H, d, *J* 15.9 Hz, one of ArCH_2CH), 3.35 (1H, dd, *J* 15.9, 5.9 Hz, one of ArCH_2CH), 3.70 (3H, s, indole NCH_3), 4.87 (1H, dd, *J* 11.4, 5.3 Hz, ArCH$_2$C*H*), 5.36 (1H, dd, *J* 10.6, 5.5 Hz, ArC*H*CH$_2$), 6.66 (1H, br d, *J* 5.3 Hz, ArCHCH$_2$C*H*), 7.14–7.53 (4H, m, Ar*H*); ^{13}C NMR (75 MHz) δ 25.7 (t), 29.7 (q), 30.9 (t), 45.2 (d), 49.6 (d), 104.9 (s), 109.2 (d), 114.1 (s), 116.5 (s), 118.5 (d), 120.0 (d), 122.6 (d), 126.0 (s), 131.7 (s), 137.0 (s), 141.4 (d); IR ν_{max}/cm^{-1} ($CHCl_3$) 2205, 1635, 1470, 1430; MS *m*/*z* 249 (M$^+$, 100%), 234 (13), 183 (82), 168 (25), 79 (56); found *m*/*z* 249.1266, calc. for $C_{16}H_{15}N_3$ 249.1266.

Debenzylation of the TBDMS enol ether 14

The TBDMS enol ether **14** (250 mg, 0.53 mmol) was dissolved in dry MeOH (30 ml) and then evaporated to dryness to ensure that traces of halogenated solvent were removed. The amorphous white solid obtained was redissolved in dry MeOH (40 ml) and stirred over catalytic 10% Pd–C for 45 min under an atmosphere of hydrogen. Filtration and evaporation afforded the free amine **26** (202 mg, 100%) which was found to be unstable and was therefore used immediately, without full characterisation.

R_f 0.13 (1:9 ether–$CHCl_3$); ^{1}H NMR (80 MHz) δ 0.11 (3H, s, one of Si(CH_3)$_2$), 0.13 (3H, s, one of Si(CH_3)$_2$), 0.88 (9H, s, SiC(CH_3)$_3$), 1.90–2.05 (1H, m, one of ArCHCH_2), 2.65–2.80 (1H, m, one of ArCHCH_2), 3.00–3.07 (2H, m, ArCH_2CH), 3.64 (3H, s, indole NCH_3), 4.18–4.29 (1H, m, ArCH$_2$C*H*), 4.49 (1H, br d, *J* 5.7 Hz, ArC*H*CH$_2$), 7.09–7.47 (4H, m, Ar*H*); IR ν_{max}/cm^{-1} ($CHCl_3$) 3320, 2210, 1730, 1630, 1470, 1415, 1365.

Formation of (6*S*,10*S*)-12-butyryl-9-cyano-8-*tert*-butyldimethylsilyloxy-5-methyl-6,7,10,11-tetrahydro-5*H*-6,10-iminocycloocta[*b*]indole 27 and the ester 28

The free amine **26** (202 mg, 0.53 mmol) was stirred over Cs_2CO_3 (326 mg, 1 mmol) in DCM (20 ml). Butyryl chloride (85 mg, 83 μl, 0.8 mmol) was added dropwise and the reaction stirred at ambient temperature for 30 min. Filtration and evaporation then afforded a yellow oil (264 mg). Flash chromatography on silica eluted with a solvent gradient (DCM to 1:19 MeOH–DCM) afforded the amide **27** (145 mg, 61%) and the ester **28** both as white foams (28 mg, 13%).

Data for the amide 27 (minor rotamer in italics). R_f 0.77 (1:9 ether–$CHCl_3$); ^{1}H NMR (90 MHz) δ 0.10 (3H, s, one of Si(CH_3)$_2$), 0.13 (3H, s, one of Si(CH_3)$_2$), 0.88 (9H, s, SiC(CH_3)$_3$), 0.85–1.08 (3H, m, NCO(CH$_2$)$_2$CH_3), 1.44–1.86 (4H, m, NCO(CH_2)$_2$CH$_3$), 2.03–2.57 (2H, m, ArCHCH_2), 2.69–3.20 (2H, m, ArCH_2CH), 3.69 (3H, s, indole NCH_3), {4.95–5.06, *5.19–5.32*} (1H, m, ArCH$_2$C*H*), {*5.77*, 6.10} (1H, d, *J* 5.0 Hz, ArC*H*CH$_2$), 7.09–7.53 (4H, m, Ar*H*); ^{13}C NMR (22.5 MHz) δ −4.0 (q), −3.8 (q), {13.9, *16.1*} (q), 18.0 (s), {*18.5*, 18.7} (t), {25.3, *25.7*} (q), 27.1 (t), {29.6, *29.7*} (q), 35.0 (t), {35.2, *36.2*} (t), {41.6, *45.1*} (d), {*46.3*, 49.7} (d), {92.6, *93.7*} (s), {104.7, *106.8*} (s), 109.1 (d), 116.7 (s), {118.4, *118.8*} (d), 119.7 (d), {122.0, *122.3*} (d), 126.4 (s), {*132.1*, 133.0} (s), 137.2 (s), {*161.5*, 164.1} (s), {*169.9*, 170.4} (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 2210, 1640, 1470, 1430, 1370; MS *m*/*z* 449 (M$^+$, 25%), 392 (26), 307 (15), 279 (5), 182 (27), 75 (100), 57 (9); found *m*/*z* 449.2491, calc. for $C_{26}H_{35}N_3O_2Si$ 449.2499.

Data for the ester 28. R_f 0.56 (1:9 ether–$CHCl_3$); ^{1}H NMR (90 MHz) δ 0.84–1.15 (6H, m, NCO(CH$_2$)$_2$CH_3 and OCO(CH$_2$)$_2$CH_3), 1.45–1.82 (4H, m, NCOCH$_2$CH_2CH$_3$ and OCOCH$_2$CH_2CH$_3$), 2.22–2.51 (5H, m, NCOCH_2CH$_2$CH$_3$, OCOCH_2CH$_2$CH$_3$ and one of ArCHCH_2), 3.07–3.39 (3H, m, ArCH_2CH and one of ArCHCH_2), 3.69 (3H, s, indole NCH_3), {5.06–5.15, *5.27–5.38*} (1H, m, ArCH$_2$C*H*), {*5.88*, 6.18} (1H, d, *J* 5.9 Hz, ArC*H*CH$_2$), 7.04–7.55 (4H, m, Ar*H*); ^{13}C NMR (22.5 MHz) δ 13.5 (q), 13.9 (q), {18.2, *18.3*} (t), 18.6 (t), {*24.7*, 26.7} (t), 29.6 (q), {33.1, *34.1*} (t), 35.2 (t), 35.9 (t), {41.4, *45.1*} (d), {*46.0*, 49.9} (d), {101.8, *102.8*} (s), {104.3, *106.8*} (s), 109.2 (d), 114.0 (s), {118.4, *118.8*} (d), 119.8 (d), {122.2, *122.4*} (d), 126.2 (s), 132.8 (s), 137.3 (s), {*158.5*, 160.8} (s), 169.7 (s), 170.4 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 2230, 1765, 1715, 1650, 1470, 1420, 1380, 1350; MS *m*/*z* 405 (M$^+$, 100%), 335 (89), 264 (29), 247 (70), 222 (17), 183 (31), 170 (37), 144 (13), 71 (70); found *m*/*z* 405.2046, calc. for $C_{24}H_{27}N_3O_3$ 405.2052.

Fluoride ion mediated desilylation of the TBDMS enol ether 27

To the amide **27** (130 mg, 0.29 mmol) stirred in MeOH (10 ml) at room temp. was added TBAF (113 mg, 0.44 mmol). After 30 min, evaporation and flash chromatography on silica eluted with 3:97 MeOH–DCM afforded the ketone **29** as a white foam (100 mg, 100%). This material displayed very broad NMR resonances and was not fully characterised.

R_f 0.46 (1:9 MeOH–$CHCl_3$); IR ν_{max}/cm^{-1} ($CHCl_3$) 2210, 1735, 1650, 1470, 1415, 1380; MS *m*/*z* 335 (M$^+$, 65%), 265 (28), 248 (11), 222 (10), 183 (100), 89 (19), 71 (96), 57 (32), 43 (83).

Sodium borohydride reduction of the ketone 29

The ketone **29** (120 mg, 0.36 mmol) was dissolved in dry MeOH (10 ml) and $NaBH_4$ (136 mg, 3.6 mmol) was added in portions. After stirring at ambient temperature for 72 h the solvent was removed by evaporation and the residue partitioned between DCM and water. The organic layer was separated and the aqueous layer was repeatedly extracted with DCM (until the extract exhibited little or no UV chromophore: *ca.* 6–9 extracts required). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to afford a pale yellow oil (100 mg). TLC indicated that at least 3 products were present and our attempts to purify this material by flash chromatography on silica eluted with a variety of systems met with little success. This mixture was therefore used directly in the subsequent step.

Formation of (6*S*,10*S*)-12-butyryl-9-cyano-5-methyl-6,7,10,11-tetrahydro-5*H*-6,10-iminocycloocta[*b*]indole 23

The mixture of products obtained above (100 mg), phosphoryl chloride (184 mg, 1.2 mmol) and pyridine (475 mg, 6 mmol) were refluxed together in dry benzene for 24 h. The solution was then cooled, treated with water and stirred for 30 min. The organic layer was separated, twice washed with saturated $NaHCO_3$ (aq) then dried over $MgSO_4$, filtered and evaporated

to afford a yellow oil (115 mg). TLC indicated that this material was composed of at least 3 products. However, careful flash chromatography on silica eluted with a solvent gradient (1 : 19 ether–DCM to 1 : 1 : 18 MeOH–ether–DCM) afforded some of the α,β-unsaturated product **23** as a white foam (27 mg, 24%) and some ketone **29** was recovered as a yellow foam (10 mg, 8%). Other lower running components could not be isolated cleanly.

R_f 0.44 (1 : 9 ether–$CHCl_3$); ^{1}H NMR (90 MHz) δ 1.00 (3H, br t, *J* 6.9 Hz, $NCO(CH_2)_2CH_3$), 1.52–1.85 (2H, m, $NCOCH_2$-CH_2CH_3), 2.13–2.51 (3H, m, $NCOCH_2CH_2CH_3$ and one of $ArCHCH_2$), 2.74–3.22 (3H, m, $ArCH_2CH$ and one of $ArCH$-CH_2), 3.70 (3H, s, indole NCH_3), {4.89–4.99, *5.20–5.31*} (1H, m, $ArCH_2CH$), {*5.74*, 6.10} (1H, d, *J* 5.7 Hz, $ArCHCH_2$), 6.58–6.69 (1H, m, $ArCHCH_2CH$), 7.09–7.54 (4H, m, Ar*H*); ^{13}C NMR (22.5 MHz) δ 14.0 (q), 18.8 (t), 26.5 (t), 29.7 (q), 30.4 (t), 35.3 (t), 40.8 (d), {*49.8*, 50.6} (d), 104.5 (s), {109.2, *109.9*} (d), 114.7 (s), 117.2 (s), 118.3 (d), 119.8 (d), 122.2 (d), 126.2 (s), 133.7 (s), 137.3 (s), 142.8 (d), 170.4 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 2225, 1650, 1470, 1430, 1420, 1385, 1350; MS *m*/*z* 319 (M^+, 100%), 279 (11), 249 (46), 248 (38), 232 (74), 221 (16), 206 (17), 183 (75), 167 (23), 157 (18), 149 (37), 71 (33), 57 (24), 43 (95); found *m*/*z* 319.1669, calc. for $C_{20}H_{21}N_3O$ 319.1685.

General procedure for attempted ring closure of 23, 27 and 29

The amides **23**, **27** and **29** (10 mg) were each dissolved in dry THF (1 ml) and cooled to −78 °C. LDA (1.1 eq. of 1.5 M solution in THF) was added and the reaction monitored by TLC. When no reaction was observed after several hours at −78 °C the reaction was allowed to warm to −20 °C and later to ambient temperature. When TLC indicated the presence of significant quantities of starting material the reaction was cooled to −78 °C, and more LDA added dropwise. This process was repeated until most of the starting material was consumed. Work-up was achieved by cooling the reaction back to −78 °C, quenching with saturated NH_4Cl (aq), extracting into EtOAc, washing with brine and drying over $MgSO_4$. Filtration and evaporation invariably gave yellow oils which were composed of several products (by TLC). Investigation of the crude NMR data indicated that little or no cyclisation had occurred, and the isolation of a single product which could be fully characterised proved impossible.

Small-scale LAH reduction of the TBDMS enol ether 14: formation of the vinylogous amide 31

The TBDMS enol ether **14** (50 mg, 0.11 mmol) was added to a suspension of LAH (7 mg, 0.18 mmol) in dry THF (4 ml) at 0 °C. The reaction was then allowed to warm to room temp. and stirred for 24 h. Water (50 μl), aqueous 2 M NaOH (150 μl) and water (50 μl) were added sequentially, then the mixture was partitioned between EtOAc and water. The organic phase was separated, dried over $MgSO_4$, filtered and evaporated to afford a yellow oil (40 mg). Flash chromatography on silica eluted with a solvent gradient (DCM to 1 : 19 MeOH–DCM) afforded the vinylogous amide **31** as a pale yellow foam (17 mg, 45%).

R_f 0.51 (1 : 9 MeOH–$CHCl_3$); ^{1}H NMR (300 MHz) δ 2.39 (1H, d, *J* 17.0 Hz, one of $ArCHCH_2$), 2.48 (1H, d, *J* 15.3 Hz, one of $ArCH_2CH$), 2.93 (1H, dd, *J* 17.0, 5.9 Hz, one of $ArCH$-CH_2), 3.34 (1H, dd, *J* 15.3, 5.3 Hz, one of $ArCH_2CH$), 3.57 (3H, s, indole NCH_3), 3.78–3.98 (2H, ABq, *J* 12.9 Hz, NCH_2Ph), 3.93 (1H, d, *J* 5.3 Hz, $ArCH_2CH$), 4.11 (1H, d, *J* 5.9 Hz, $ArCHCH_2$), 5.16 (1H, br s, one of $CHNH_2$), 6.79–6.86 (1H, m, $CHNH_2$), 7.06–7.47 (9H, m, Ar*H*), 9.30 (1H, br s, one of $CHNH_2$); ^{13}C NMR (22.5 MHz) δ 27.4 (t), 29.3 (q), 42.3 (t), 48.9 (d), 54.4 (d), 56.8 (t), 103.6 (s), 107.2 (s), 108.8 (d), 118.1 (d), 118.9 (d), 121.2 (d), 127.1 (s), 127.1 (d), 128.4 (d), 128.6 (d), 135.6 (s), 137.3 (s), 138.9 (s), 149.2 (d), 195.7 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 3500, 1650, 1585, 1470; MS *m*/*z* 357 (M^+, 100%), 340 (16), 314 (7), 273 (21), 266 (17), 250 (19), 187 (22), 170 (52), 91 (60); found *m*/*z* 357.1844, calc. for $C_{23}H_{23}N_3O$ 357.1841; $[\alpha]_D$ −102.9 (*c* 1.7, DCM).

Larger-scale LAH reductions of the TBDMS enol ether 14

The TBDMS enol ether **14** (250 mg, 0.53 mmol) was added in portions to a suspension of LAH (30 mg, 0.79 mmol) in dry THF (15 ml) at 0 °C. The reaction was then allowed to warm to room temp. and stirred for 72 h. Work-up and flash chromatography as for the previous reaction afforded the vinylogous amide **31** as a pale yellow foam (38 mg, 20%) and a higher running component **32** as a white foam (100 mg, 55%) which could only be partially characterised before dimerising to an unknown structure.

Data for 32. R_f 0.77 (1 : 9 ether–$CHCl_3$); ^{1}H NMR (80 MHz) δ 2.44–3.40 (4H, m, $ArCH_2CH$ and $ArCHCH_2$), 3.53 (3H, s, indole NCH_3), 3.86 (2H, br s, NCH_2Ph), 4.14–4.30 (2H, m, $ArCHCH_2$ and $ArCH_2CH$), 5.32 (1H, br s, one of CCH_2), 6.09 (1H, br s, one of CCH_2), 7.03–7.50 (9H, m, Ar*H*); IR ν_{max}/cm^{-1} ($CHCl_3$) 1690, 1610, 1490, 1465.

Selected data for the dimer of 32. R_f 0.57 (1 : 9 ether–$CHCl_3$); ^{1}H NMR (300 MHz) δ 1.20 (1H, t, *J* 7.0 Hz), 1.58–1.64 (1H, m), 1.96–2.00 (1H, m), 2.10 (2H, br d, *J* 15.9 Hz), 2.24 (1H, dd, *J* 12.9, 2.3 Hz), 2.56 (1H, d, *J* 16.4 Hz), 2.69 (1H, d, *J* 15.3 Hz), 2.78–2.86 (1H, m), 2.94 (1H, d, *J* 15.3 Hz), 3.01–3.08 (1H, m), 3.26 (1H, d, *J* 6.5 Hz), 3.40 (3H, s, one indole NCH_3), 3.41 (3H, s, one indole NCH_3), 3.44–3.56 (3H, m), 3.68 (1H, d, *J* 13.5 Hz, one CH_2Ph), 3. 84 (1H, d, *J* 13.5 Hz, one CH_2Ph), 4.08 (2H, d, *J* 4.7 Hz), 6.90 (1H, dd, *J* 5.9, 2.9 Hz), 7.02–7.49 (18H, m, Ar*H*); ^{13}C NMR (22.5 MHz) >50 resonances; IR ν_{max}/cm^{-1} ($CHCl_3$) 1720, 1600, 1490, 1465, 1415, 1375; FAB MS 685 ($[M + H]^+$, 14%), 663 (44), 647 (27), 341 (54), 338 (27), 281 (39), 207 (50), 154 (100); MS *m*/*z* 684 (M^+, 1%), 342 (100), 314 (12), 273 (48), 251 (21), 197 (24), 182 (31), 170 (58), 91 (70); found *m*/*z* 684.3446, calc. for $C_{46}H_{44}N_4O_2$ 684.3464.

For a second attempt, the TBDMS enol ether **14** (423 mg, 0.90 mmol) was dissolved in dry THF (15 ml) at 0 °C. LAH (60 mg, 1.58 mmol) was added in portions over 5 h until TLC of the reaction mixture indicated complete consumption of the starting material. Work-up and flash chromatography as for the previous reaction afforded the vinylogous amide **31** as a pale yellow foam (85 mg, 26%) and the desilylated ketone **8** as a white foam (216 mg, 67%).

Attempted enamine reaction with the vinylogous amide 31

The vinylogous amide **31** (15 mg, 0.04 mmol), butyraldehyde (28.8 mg, 0.40 mmol) and a trace of PTSA were stirred over activated molecular sieves in $CHCl_3$ (5 ml). After a 5 day reaction time no reaction was visible by TLC. Under reflux or with more acid present decomposition of the starting material was the only process observed.

Attempted hydrogenation of the vinylogous amide 31: formation of the ketone 33

The vinylogous amide **31** (33 mg, 0.09 mmol) was dissolved in MeOH (10 ml) and stirred over an excess of 10% Pd–C under an atmosphere of hydrogen. After 24 h the catalyst was removed by filtration and the filtrate evaporated to dryness to afford a mixture of the ketone **33** and inorganic contaminants. Extraction of the residue into DCM followed by evaporation afforded the ketone **33** as a white foam (16 mg, 66%).

R_f 0.46 (1 : 9 MeOH–$CHCl_3$); ^{1}H NMR (300 MHz) δ 1.04 (3H, d, *J* 7.0 Hz, $CHCH_3$), 2.41 (1H, dd, *J* 14.1, 2.4 Hz, one of $ArCH_2CH$), 2.64 (3H, s, N^bCH_3), 2.72 (1H, d, *J* 16.8 Hz, one of $ArCHCH_2$), 2.92 (1H, q, *J* 7.0 Hz, $CHCH_3$), 2.99 (1H, dd, *J* 16.8, 5.9, one of Ar $CHCH_2$), 3.09 (1H, dd, *J* 14.1, 4.7 Hz, one of Ar CH_2CH), 3.60 (3H, s, indole NCH_3), 3.58–3.62 (1H, m, $ArCH_2CH$), 4.26 (1H, br s, $ArCHCH_2$), 7.04–7.26 (3H, m,

Ar*H*), 7.44 (1H, d, *J* 8.2 Hz, Ar*H*); ^{13}C NMR (22.5 MHz) δ 11.3 (q), 16.6 (t), 29.2 (q), {41.0, *41.3*} (q), 46.0 (t), {*47.4*, 48.0} (d), {*53.9*, 54.9} (d), 61.2 (d), 103.2 (s), 108.8 (d), 118.3 (d), {119.0, *119.2*} (d), {121.4, *121.8*} (d), 126.6 (s), 133.9 (s), 137.4 (s), 208.8 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 1710, 1520, 1470, 1450, 1420, 1380; MS *m*/*z* 268 (M^+, 39%), 197 (100), 182 (10), 170 (24), 168 (10), 151 (13); found *m*/*z* 268.1578, calc. for $C_{17}H_{20}N_2O$ 268.1576.

LAH reduction and Boc protection of the nitrile alcohol 9: formation of the Boc-protected amine 34

The alcohol **9** (1.88 g, 5.26 mmol) was dissolved in dry THF (40 ml) and stirred at 0 °C. LAH (15 ml of 1 M solution, 15 mmol) was added dropwise and then the reaction was allowed to warm to room temperature and stirred overnight, then refluxed for 5 h. After cooling back to 0 °C, water (0.5 ml), 2 M NaOH (0.5 ml) and water (0.5 ml) were added sequentially, then the mixture was stirred and allowed to warm to room temperature then filtered to remove inorganic waste and evaporated. The organic residue was then suspended in EtOAc and washed three times with brine, dried over $MgSO_4$, filtered and evaporated to afford a pale yellow oil, homogeneous by TLC (1.8 g). This primary amine (1.8 g, 4.99 mmol) was dissolved in $CHCl_3$ (50 ml) and stirred over $NaHCO_3$ (1 g) at room temperature. Boc_2O (1.091 g, 5.0 mmol) dissolved in $CHCl_3$ (25 ml) was added dropwise over 30 min and then the reaction stirred for 1 h. Water (25 ml) was added and the mixture vigorously stirred for 5 min, then the organic phase was separated, washed with brine, dried over $MgSO_4$, filtered and evaporated to afford a yellow oil (2.39 g). Flash chromatography on silica eluted with a solvent gradient (1:2 EtOAc–hexane to 1:1 EtOAc–hexane) afforded the Boc-protected amine **34** as a white foam (1.55 g, 64% from the amine **34**).

R_f 0.25 (1:9 Et_2O–$CHCl_3$); ^{1}H NMR (400 MHz) δ 1.52 (9H, s, (C*H*$_3$)$_3$C), 2.13 (1H, d, *J* 13.9 Hz, one of ArCHC*H*$_2$), 2.27 (1H, dt, *J* 13.9, 4.4 Hz, one of ArCHC*H*$_2$), 2.43–2.53 (1H, m, C*H*CH$_2$NHBOC), 2.78 (1H, d, *J* 17.0 Hz, one of ArC*H*$_2$CH), 3.13 (1H, dd, *J* 17.0, 7.1 Hz, one of ArC*H*$_2$CH), 3.26–3.47 (3H, m, ArCH$_2$C*H* and C*H*$_2$NHBOC), 3.63 (3H, s, indole NC*H*$_3$), 3.65 (1H, d, *J* 13.5 Hz, one of C*H*$_2$Ph), 3.77 (1H, d, *J* 13.5 Hz, one of C*H*$_2$Ph), 3.89–3.97 (2H, m, ArC*H*CH$_2$ and C*H*OH), 4.85 (1H, br s, N*H*BOC), 7.14–7.43 (8H, m, Ar*H*), 7.57 (1H, d, *J* 7.8 Hz, Ar*H*); ^{13}C NMR (50 MHz) δ 17.3 (t), 28.4 (q), 29.2 (q), 37.8 (t), 40.4 (t), 45.0 (d), 47.6 (d), 52.8 (d), 57.3 (t), 65.8 (d), 79.2 (s), 103.7 (s), 109.1 (d), 118.3 (d), 119.4 (d), 121.5 (d), 126.7 (s), 127.0 (d), 128.3 (d), 128.5 (d), 137.2 (s), 137.3 (s), 139.0 (s), 156.2 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 3506, 3455, 1707, 1508, 1468, 1368; MS *m*/*z* 461 (M^+, 5%), 273 (10), 199 (10), 84 (80), 49 (100); found *m*/*z* 461.2684, calc. for $C_{28}H_{35}N_3O_3$ 461.2678.

Swern oxidation of the alcohol 34

Oxalyl chloride (70 mg, 48 µl, 0.55 mmol) was stirred in DCM at −60 °C (CO_2–$CHCl_3$ bath). DMSO (86 mg, 78 µl, 1.1 mmol) in DCM (1 ml) was added slowly and the mixture stirred for 2 min. The alcohol (46 mg, 0.1 mmol) was dissolved in DCM (1 ml) and added dropwise and the reaction stirred for 30 min at −60 °C. TEA (250 mg, 350 µl, 2.5 mmol) was then added and the reaction allowed to warm to room temperature. Water (10 ml) was added and the mixture stirred for 10 min, then the organic layer separated and the aqueous phase extracted with DCM. The combined organic extracts were washed with brine 5 times then dried over $MgSO_4$, filtered and evaporated to afford a pale yellow oil. Flash chromatography on silica eluted with 5:95 Et_2O–$CHCl_3$ gave the ketone **35** as a pale yellow foam (17 mg, 37%), along with a complex mixture (33 mg, homogeneous by TLC) which was composed of at least 3 non-indolic products (>50 resonances in ^{13}C NMR, but the characteristic quaternary resonance normally observed around 103 ppm was not present).

Data for the ketone 35. R_f 0.77 (1:9 Et_2O–$CHCl_3$); ^{1}H NMR (400 MHz) δ 1.44 (9H, s, (C*H*$_3$)$_3$C), 2.39 (1H, br d, *J* 13.7 Hz, one of ArCHC*H*$_2$), 2.55–2.64 (1H, br d, *J* 16.9 Hz, one of ArC*H*$_2$CH), 2.96–3.06 (2H, m, one of ArCHC*H*$_2$ and C*H*-CH$_2$NHBOC), 3.12 (1H, dd, *J* 16.9, 6.3 Hz, one of ArC*H*$_2$CH), 3.16–3.35 (2H, m, C*H*$_2$NHBOC), 3.51 (3H, s, indole NC*H*$_3$), 3.68–3.95 (3H, m, C*H*$_2$Ph and ArCH$_2$C*H*), 4.19–4.28 (1H, m, ArC*H*CH$_2$), 5.01 (1H, br s, N*H*BOC), 7.07–7.48 (9H, m, Ar*H*); ^{13}C NMR (50 MHz) δ 18.2 (t), 28.4 (q), 29.2 (q), 38.2 (t), 46.7 (t), 51.4 (d), 54.1 (d), 56.5 (t), 57.8 (d), 79.2 (s), 103.2 (s), 108.9 (d), 118.3 (d), 119.1 (d), 121.6 (d), 126.5 (s), 127.4 (d), 128.6 (d), 134.0 (s), 137.4 (s), 138.5 (s), 155.9 (s), 209.7 (s); MS *m*/*z* 459 (M^+, 26%), 386 (9), 342 (12), 273 (94), 91 (86); found *m*/*z* 459.2520, calc. for $C_{28}H_{33}N_3O_3$ 459.2522.

PCC oxidation of the alcohol 34

The alcohol **34** (1.33 g, 2.88 mmol) was dissolved in DCM (2 ml) and added to a suspension of PCC–Florosil (50:50, 2.5 g, 6 mmol of PCC) in DCM (10 ml) and stirred at room temperature overnight. The suspension was then filtered through a pad of Florosil and evaporated to give a yellow oil (1.19 g). This material was pre-sorbed onto silica (2 g) then subjected to flash chromatography on silica eluted with 1:2 EtOAc–hexane to afford starting material alcohol **34** (174 mg) and a 1:1.5 mixture of the Boc-protected ketone **35** and the pentacycle **36** as a white foam (539 mg, 41 or 47% based on recovered starting material).

Data for the pentacycle 36. R_f 0.77 (1:9 Et_2O–$CHCl_3$); ^{1}H NMR (400 MHz) δ 1.57 (9H, s, (C*H*$_3$)$_3$C), 2.57 (1H, dd, *J* 15.1, 2.6 Hz, one of ArCHC*H*$_2$), 3.01–3.10 (2H, m, one of ArCH-C*H*$_2$ and C*H*CH$_2$NHBOC), 3.58 (3H, s, indole NC*H*$_3$), 3.80 (1H, dd, *J* 11.6, 1.8 Hz, one of C*H*$_2$NBOC), 3.88 (1H, d, *J* 13.3 Hz, one of C*H*$_2$Ph), 3.94–4.02 (2H, m, one of C*H*$_2$Ph and one of C*H*$_2$NBOC), 4.08–4.14 (1H, m, ArCHC*H*N), 4.28–4.33 (1H, m, ArC*H*CH$_2$), 5.51 (1H, d, *J* 6.4 Hz, ArC*H*CHN), 7.14–7.46 (8H, m, Ar*H*), 8.16 (1H, d, *J* 8.0 Hz, Ar*H*); ^{13}C NMR (50 MHz) δ 28.5 (q), 28.7 (q), 43.3 (t), 44.8 (t), 48.7 (d), 49.5 (d), 50.1 (d), 57.7 (t), 60.5 (d), 79.5 (s), 107.2 (s), 108.6 (d), 119.9 (d), 121.5 (d), 121.9 (d), 126.2 (s), 127.6 (d), 128.6 (d), 134.5 (s), 137.9 (2 × s), 155.0 (s), 206.7 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 1710, 1683, 1506, 1430, 1368; MS *m*/*z* 457 (M^+, 27%), 401 (12), 342 (15), 273 (16), 91 (37); found *m*/*z* 457.2359 calc. for $C_{28}H_{31}N_3O_3$ 457.2365.

Formation of N^b-benzylsuaveoline 2c

The mixture of ketone **35** and pentacycle **36** (75 mg) was dissolved in 1:9 water–TFA and stirred at room temperature for 1 h. The solution was then evaporated to dryness, and then three times redissolved in toluene and evaporated. The residue was used directly in the next step and was dissolved in dry DCM (10 ml) and stirred over molecular sieves at room temperature while PrCHO (36 mg, 0.48 mmol) was added in DCM (1 ml). After 72 h the solution was filtered through Florosil to remove sieve dust, then evaporated to afford a yellow oil composed of at least 5 products by TLC. Flash chromatography on silica eluted with 5:95 MeOH–$CHCl_3$ afforded 6 small analytical samples, one of which had an appropriate R_f and displayed the EI mass ion and primary fragmentation expected for N^b-benzylsuaveoline **2c**: MS (EI, 70 eV) *m*/*z* 393 (M^+, 9%), 273 (30), 170 (54), 91 (100); lit.[14a] MS (EI, 15 eV) *m*/*z* 393 (M^+, 100%), 273 (67).

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