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Tetrahedron
Tetrahedron 63 (2007) 10211–10225

A synthetic strategy using Witkop's pyrroloindole for (−)-debromoflustramine B, (+)-*ent*-debromoflustramine B and (+)-*ent*-debromoflustramide B

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Received 17 June 2007; revised 22 July 2007; accepted 23 July 2007
Available online 31 July 2007

Abstract—While prenylation of (−)-Witkop's pyrroloindole (**2**), secured from L-tryptophan under standard N-alkylation conditions, led to a ca. 1:1 diastereoisomeric mixture of two C^{3a}-alkylated indolenines **3** and **4**, use of phase-transfer conditions altered this to ca. 1:2. Reduction followed by N-prenylation of the resulting secondary amines gave *C*,*N*-dialkylated products. The derived separable diastereoisomeric (−)- and (+)-Barton esters **19a** and **19b** were then converted into (−)-debromoflustramine B and (+)-*ent*-debromoflustramine B, respectively. A novel reaction involving oxygen and the carbanion derived from Barton ester **19b** led to (+)-*ent*-debromoflustramide B. Treatment of N^8-prenylated Witkop's pyrroloindole **5** with Lewis acid ($BF_3 \cdot Et_2O$) uncovered a new clean intramolecular cyclisation involving the prenyl unit.

1. Introduction

Examination of the chemical constituents of the marine bryozoan *Flustra foliacea* occurring in cold waters of the North Sea, initiated in the late '70s by Christophersen, had resulted in the isolation and characterisation of 14 alkaloids, at least 10 of which are based on the hexahydropyrrolo(2,3-*b*)indole nucleus.[1a] All of them are characterised by the presence of a prenyl group at C^3 that may or may not be inverted. An example of the former is provided by 8,8a-dihydroflustramine C[1b] (**1a**), while flustramine E[1c] (**1b**) represents the latter. In those alkaloids that contain both these sub-units a prenyl group is found invariably at N^8 as in flustramine A[1d] (**1c**). (−)-Flustramine B[1d] (**1d**) and (−)-debromoflustramine B[1e] (**1e**) are examples of natural products that contain two prenyl groups at both C^3 and N^8. Within this structural framework, substances at different oxidation levels also occur as exemplified by flustramide B[1f] (**1f**), flustramine C[1g] (**1h**) and flustraminol[1g] (**1j**) (Fig. 1). Medicinally important (−)-physostigmine[2] (**1k**) and other biologically active natural products such as amauramines[3] and *N*-acetylardeemin[4] also possess this structural element as the predominant feature.

2. Results and discussion

An efficient means of establishing two adjacent quaternary carbon atoms in a molecule is by an intramolecular reaction.[5] Alkaloids such as flustramine A (**1c**) and flustramine C (**1h**) contain such centres. Our interest in a simple synthesis of the prototype of these substances,[6] **1i** for instance, bearing an inverted prenyl group, by a pericyclic reaction led us to consider Witkop's pyrroloindole[7] **2** as the starting material (cf. Scheme 1).

The choice was dictated by the fact that (a) it is prepared readily from L-tryptophan methyl ester in high overall yield, (b) it possesses appropriate functionalities amenable, in principle, to a facile conversion into the alkaloid and (c) diastereoselection can be expected in the introduction of an alkyl group at C^{3a}. We describe herein a few preliminary unsuccessful attempts to obtain **1i**, and report the full details[8] of a synthesis[1e,9] of (−)-debromoflustramine B (**1e**), its enantiomer (+)-debromoflustramine B (*ent*-**1e**) and (+)-*ent*-debromoflustramide B (*ent*-**1g**).

2.1. Lewis acid reaction with N^8-prenylated (−)-Witkop's pyrroloindole (5)

Following the method of Witkop[7] et al., **2** was prepared from L-*N*-acetyltryptophan methyl ester in 88% yield, with an

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doi:10.1016/j.tet.2007.07.091

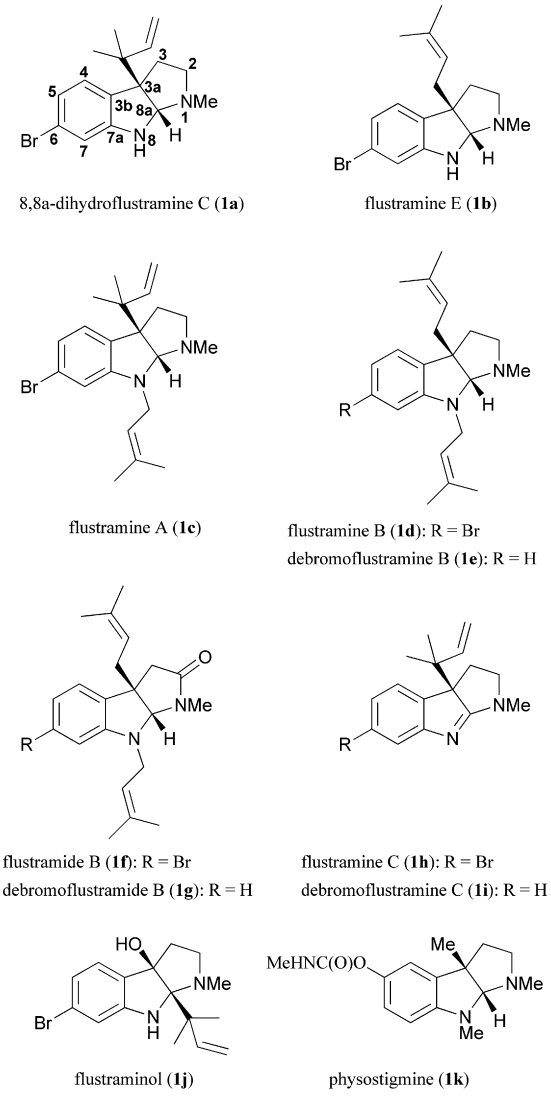
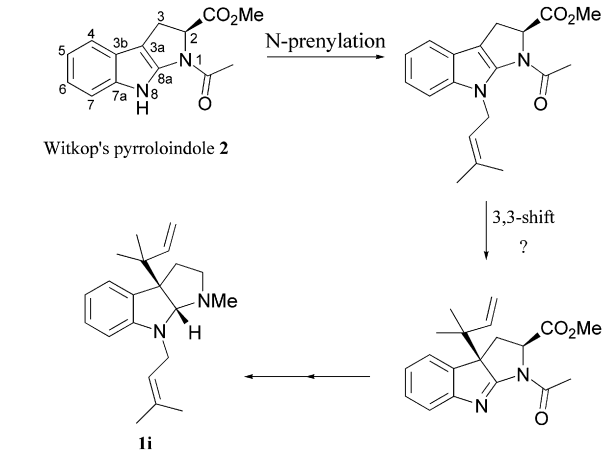


Figure 1.



Scheme 1.

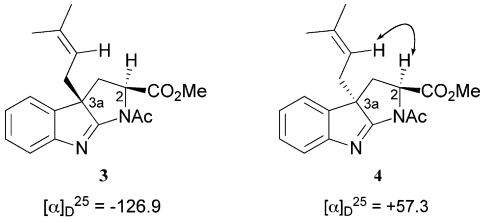
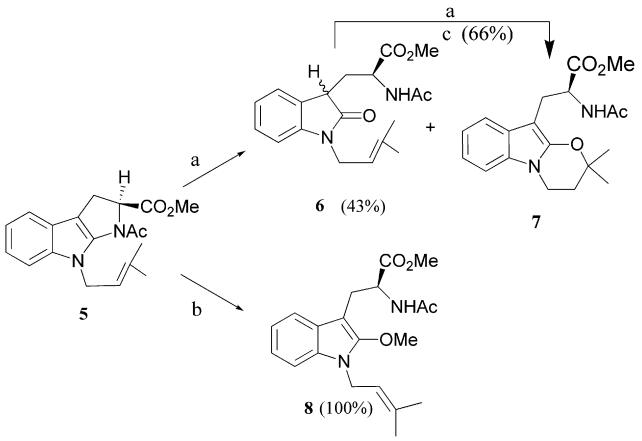


Figure 2.

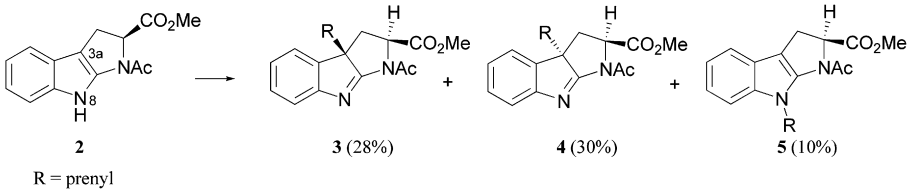


Scheme 3. Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, rt; (b) $BF_3{\cdot}MeOH$, rt; (c) aq HCl, rt.

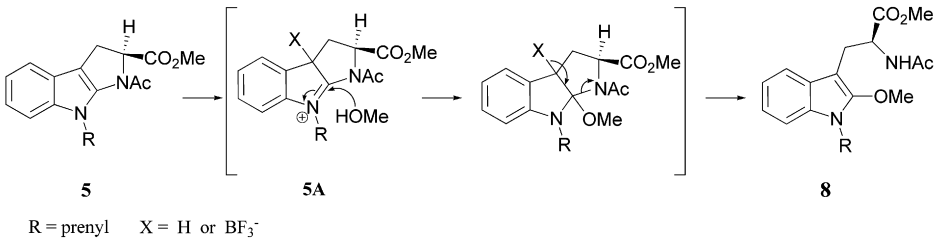
$[\alpha]_D$ −96.1, equal to that reported. The observation that the signal due to the Me group (CO_2Me) continued to remain as a sharp singlet on addition of the ^1H NMR shift reagent Eu(tfc)$_3$ dispelled any doubt regarding its optical purity.

Under conditions generally deemed to favour N-alkylation[10] prenylation of Witkop's tricycle furnished a mixture of three compounds **3**, **4** and **5** in 28%, 30% and 10% yields, respectively (Scheme 2).

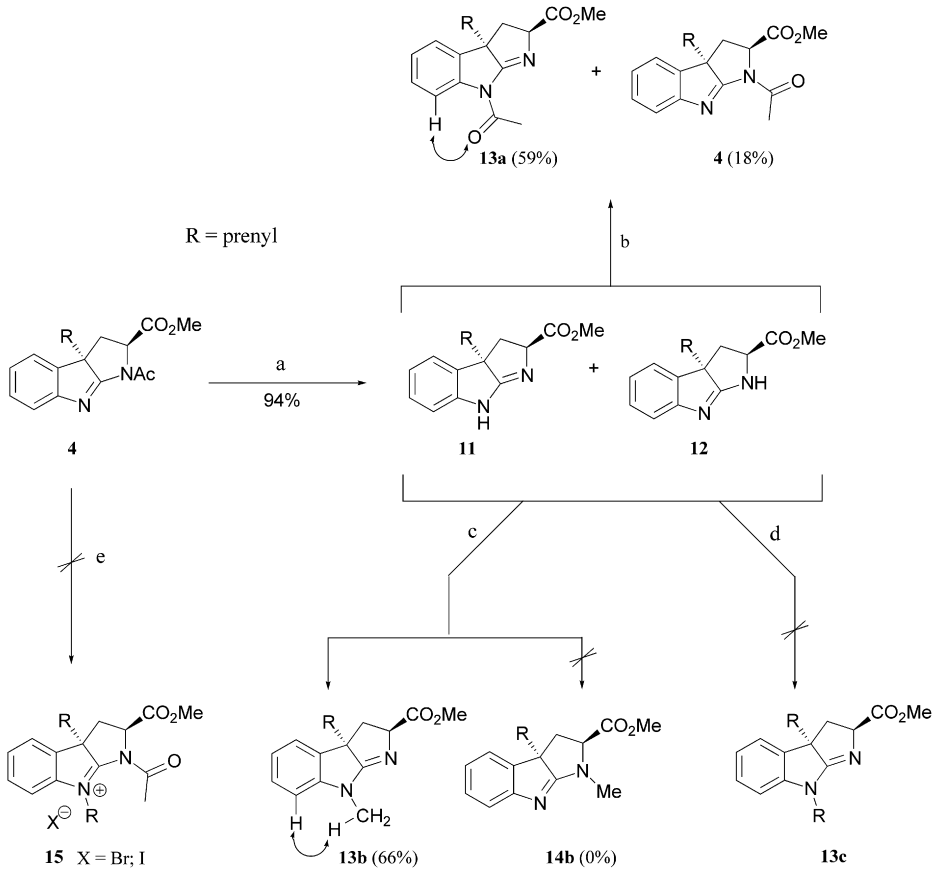
Substances **3** and **4** (Fig. 2) could be obtained in pure state by multiple PTLC, albeit with significant loss of material. Both were found to have the same molecular formula $C_{19}H_{22}N_2O_3$ as determined by accurate mass measurement and their spectral data (^1H, ^{13}C, 2D NMR, IR) were consistent with the structures assigned. They were adjudged to be optically pure by experiments with ^1H NMR shift reagent. Furthermore the spatial proximity of the C^2 hydrogen and the vinylic hydrogen of the prenyl group at C^{3a} in **4** could be



Scheme 2.



Scheme 4.

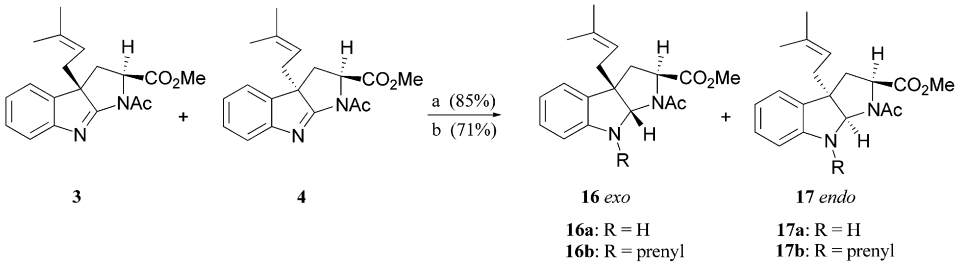


Scheme 5. Reagents and conditions: (a) NaOMe, MeOH; (b) Ac_2O, DMAP, Et_3N; (c) MeI, NaH, DMF; (d) $Me_2C{=}CHCH_2X$, NaH, DMF; (e) $Me_2C{=}CHCH_2Br$, $AgBF_4$.

established by bi-dimensional ^1H NMR and NOESY. No similar relationship was found for the corresponding hydrogens in **3**. Therefore, structure **4** was attributed to the isomer with a positive sign of rotation. Compound **5**, being the least polar, could be readily separated by column chromatography and was shown to be the requisite N^8-prenyl derivative by its accurate mass value and spectral properties (^1H NMR, IR).

Since thermolysis of **5** produced a complex array of products, Lewis acid induced 3,3-aza-Cope rearrangement of **5** was attempted. Whilst short treatment of **5** with $BF_3{\cdot}Et_2O$ in CH_2Cl_2, at rt, furnished oxindole **6**, on continued exposure it generated **7** by an intramolecular cyclisation (Scheme 3).

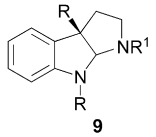
The latter was rapidly produced from **6** and $BF_3{\cdot}Et_2O$ suggesting that compound **6** is a likely precursor of **7**. $BF_3{\cdot}MeOH$ also failed to induce any rearrangement of **5**; instead product **8** was obtained virtually quantitatively. Variations in experimental condition such as temperature, time and molar ratio (substrate/Lewis acid) failed to furnish product or products arising from any shift of the allyl functionality. Structures **6**, **7** and **8** were deduced from their respective spectral data and by accurate mass measurements. In view of the care taken to exclude water from the solvent and the reagent (both distilled twice from CaH_2 before use), and the non-acidic nature of the work-up procedure (neutralisation with Et_3N or aq $NaHCO_3$), a plausible mechanism for the formation of these compounds is presented. Thus, it is proposed that the reactive imonium ion **5A** (Scheme 4), formed by interaction of the Lewis acid with the electron rich C^3-carbon[25] of the bis-enamine derivative **5**, serves as the common intermediate for **6**, **7** and **8**.



Scheme 6. Reagents and conditions: (a) $NaCNBH_3$, MeOH/AcOH; (b) prenyl bromide, K_2CO_3, THF, rt, four days.

2.2. (+)-*ent*-Debromoflustramine B and (−)-debromoflustramine B

Compounds **3** and **4** were next used in the synthesis of (+)-*ent*-debromoflustramine B and (−)-debromoflustramine B. Mindful of the previous studies[1e] that had shown the difficulties associated with the hydrolysis of *N*-acetyl group in substances of the type **9** and **10**, it was decided to remove the acetyl from the *N*-acetylamidine **4** and then introduce the prenyl group at N^8.



9

9: R = prenyl; R^1 = Ac
10: R = prenyl; R^1 = H

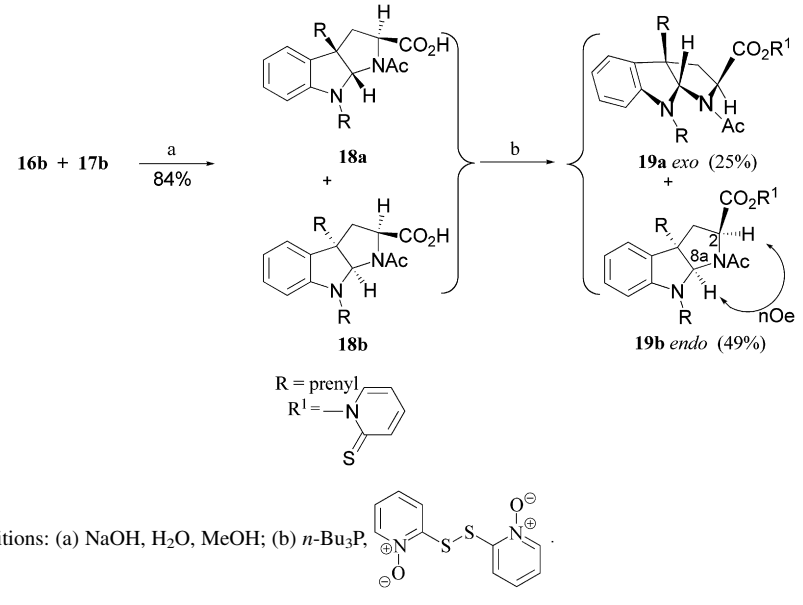
Thus, treatment of **4** with methanolic methoxide solution furnished a product in high yield. Despite possessing a well defined mp, its solution spectrum (^{1}H NMR) indicated it to be an isomeric mixture of amidines, probably **11** and **12** (Scheme 5).

Acetylation with Ac_2O, DMAP and Et_3N occurred on both nitrogen atoms to give a separable mixture of **4** and **13a** in which the latter was the major product (59%). Structure **13a** follows from its ^{1}H NMR spectrum. It contained resonances, in addition to the prenyl group, for a CO_2Me and an NCOMe functionalities at δ 3.78 (3H, s) and 2.68 (3H, s), respectively. More important was the presence of a deshielded aromatic H at δ 8.21 (1H, d, J 8.1 Hz) ascribed to the hydrogen *peri* to the N^8-acetyl group. The presence of molecular ion 284 in the mass spectrum further supported the structure assigned.

Methylation of the mixture **11** and **12** with MeI (NaH/DMF) showed high regioselectivity and furnished **13b** (66%). The isomer **14b** was not formed. Structure **13b** was based on accurate mass measurement and the NOE observed between the H^7 and the N^8-methyl. Unfortunately, a similar product **13c** with such selectivity could not be obtained with prenyl bromide or prenyl iodide[11] in an acceptable yield. Attempted alkylation of **4** with prenyl bromide/$AgBF_4$ also failed to provide satisfactory yields of **15**.

In the light of these results it was decided to reduce first the mixture of **3** and **4** and subsequently prenylate the products formed. Treatment with $NaBH_3CN$,[12] followed by alkylation (prenyl bromide; K_2CO_3/THF/rt/four days) of the resulting *sec*-amines **16a** and **17a**, furnished products **16b** and **17b**, respectively (Scheme 6).

Separation of the mixture **16b** and **17b** into pure diastereomers, although possible on a small scale PTLC, was deferred



Scheme 7. Reagents and conditions: (a) NaOH, H_2O, MeOH; (b) *n*-Bu_3P,

to a later stage of the synthesis when it became operationally simpler to do so (vide infra).

2.2.1. Preparation of Barton esters 22a and 22b: their separation, structures and reactions. Saponification of the mixture **16b** and **17b** in aq MeOH and subsequent neutralisation gave acids **18a** and **18b** (84%) which without purification were converted into the corresponding Barton esters **19a** and **19b** via the mixed anhydride method[13] in 41% yield (Scheme 7). An improved yield (74%) was obtained using 2,2′-dithiopyridine 1,1′-dioxide and (*n*-Bu)$_3$P.[14] The separation of the mixture of **19a** and **19b** by column chromatography (SiO_2/Et_2O) was cleanly effected into the *exo*-Barton ester **19a** (25%) and the *endo*-isomer **19b** (49%). An NOE was observed between H^2 and the H^{8a} only in **19b**.

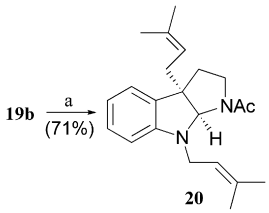
The greater availability of the *endo*-isomer **19b** led us to attempt the removal of the acetyl group in **20** obtained from **19b** after the thionoester removal (Scheme 8).

Thus in the case of **20**, a large excess of hydrazine (150 mmol) in EtOH under reflux for an extended period of time (15 days) failed to remove the acetyl group. Similarly, use of triflic anhydride[15]/$NaHCO_3$ or Al(EtO)$_3$H reduction[16] of **20** failed to give the required product.

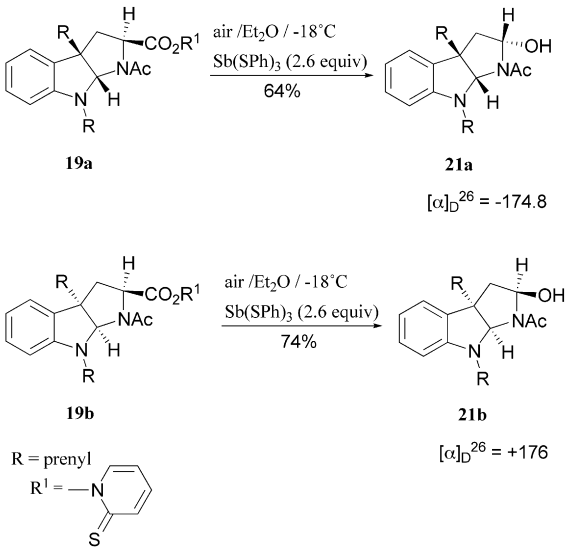
With this end in view **19b** was exposed to the combined action[17] of Sb(SPh)$_3$ and air (O_2) in wet ether. A clean and rapid reaction ensued and the β-alcohol **21b** (74%) was isolated by PTLC. The assigned stereochemistry was supported by the NOE observed between H^2 and H^{8a}. Similarly, **19a** gave the α-alcohol **21a** (64%). The enantiomeric nature of these compounds (**21a** and **21b**) was evident from the identity of their spectra [IR, NMR (^{1}H, ^{13}C)] and absolute optical rotations (equal, but of opposite signs) (Scheme 9).

The highly stereoselective reaction is best explained by assuming an attack on the carbon-centred radical **22**, derived from **19b**, by the sterically bulky Sb(SPh)$_3$ occurring exclusively from the side opposite to that of the C^{3a}-prenyl group, to give the organo antimony compound **23**. The latter reacts with oxygen to give the peroxyantimony intermediate **24**. Subsequent rearrangement with retention of configuration gives rise to **25** and thence to **21b** (Scheme 10).

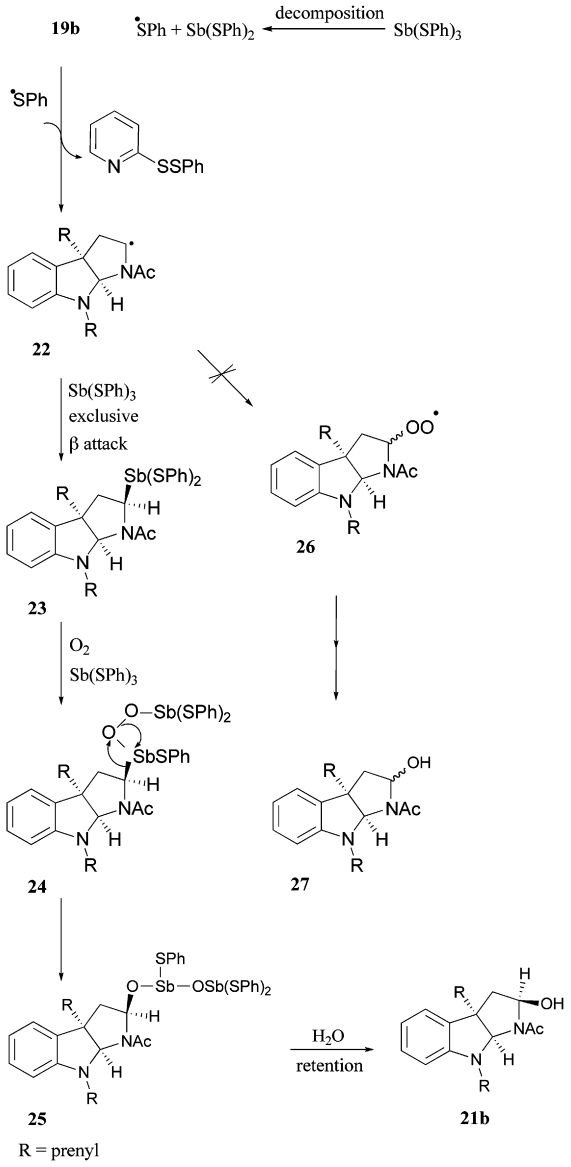
It is interesting to recall in this context the lack of such high selectivity observed in steroidal and other compounds studied by Barton et al.[17b] It was attributed by these authors to alkyl radical reacting in a competing reaction without spatial discrimination with O_2 as represented in the hypothetical conversion of **22**→**26**→**27**.



Scheme 8. Reagents and conditions: (a) *hν*, *t*-BuSH.



Scheme 9.



Scheme 10.

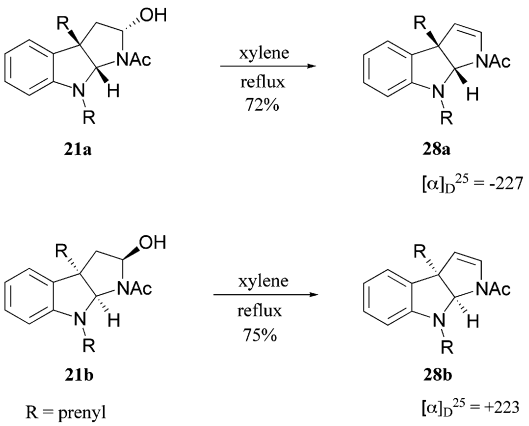
With **21b** in hand, oxidation of the OH group was attempted. However, experiments involving Dess–Martin periodinane,[18] Swern reagent,[19] Pt/O_2[20] or Pd^{+2}/O_2[21] were not successful. Either a complex mixture of products was obtained or the starting material remained largely intact. Instead, simply heating a solution of **21b** in xylene under reflux (12 h) furnished the enamide **28b** ($[\alpha]_D^{25}$ +223.0) as a colourless oil (75%) (Scheme 11). The elemental composition $C_{22}H_{28}N_2O$ as determined by accurate mass measurement taken in conjunction with ^1H NMR resonances at δ 5.20 and 6.46, each (1H) doublet with J 4.3 Hz, was fully consistent with the enamide structure. Also its IR spectrum did not contain any absorption due to NH or OH group. Similar treatment of **21a** afforded enamide **28a** possessing spectral properties (IR, ^1H and ^{13}C NMR) and R_f values (TLC plates) identical with those of **28b**. Its negative rotation ($[\alpha]_D^{25}$ −227) established its enantiomeric relationship with **28b**.

Gratifyingly, treatment of **28b** with a solution of MeOH containing $NaOMe/NH_2NH_2$ brought about hydrazinolysis to afford the imine **29b** (63%) which contained a low field resonance at δ 7.61 (1H) and δ 2.86 (2H) in its ^1H NMR spectrum (Scheme 12). LAH reduction of the latter provided **30b**.[22]

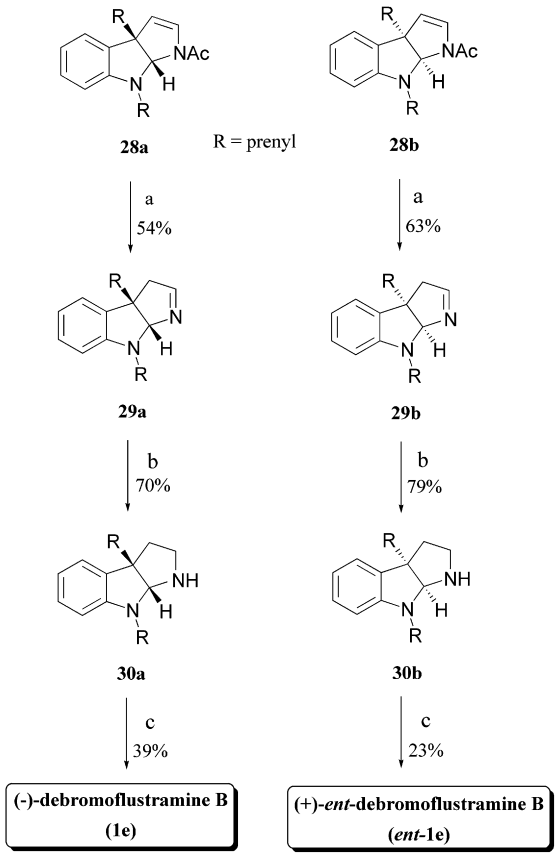
Having thus established a viable synthetic route for the conversion **28b**→**29b**→**30b** the same protocol was applied to the less readily available **28a** to furnish N^1-*nor*-debromoflustramine B **30a** (Scheme 12). The ^{13}C NMR spectra of **30a** and **30b** were coincident with those reported for racemic N^1-*nor*-debromoflustramine B.[1e]

Compound (+)-**30b** was then methylated with NaH and MeI in THF to afford (+)-*ent*-debromoflustramine B (*ent*-**1e**) (23%; 51% based on recovered starting material) possessing ^1H and ^{13}C NMR resonances and α_D identical with those reported in the literature.[9d] Similarly **30a** furnished (−)-debromoflustramine B[1b,1e] (**1e**) (18%; 46% based on recovered starting material) possessing spectral data and optical rotation ($[\alpha]_D^{25}$ −97.5; lit.[1b] $[\alpha]_D^{25}$ −98.2) identical with those described for the alkaloid[1b] (Scheme 12).

As mentioned earlier, prenylation of **2** with NaH gave very poor diastereoselection (α:β=ca. 1:1). In contrast, it is interesting that the same alkylation performed with a phase-transfer reagent, such as Adogen 464 [methyl trialkyl (C_8–C_{10}) ammonium chloride] or those derived from Cinchona alkaloids, proceeded with higher diastereoselection but in favour of the undesired α-isomer **4**, (α:β=2:1). Working on the assumption that these results are due to a greater degree of shielding of the β-face[23] (cf. Fig. 3), (+)-Witkop's pyrroloindole **2A** was prenylated.



Scheme 11.



Scheme 12. Reagents and conditions: (a) NaOMe, MeOH (5 M, 104 mmol), NH_2NH_2 (8 mmol), reflux, 3 h; (b) LAH, Et_2O, rt; (c) MeI, THF.

The reaction provided a mixture of **3A** and the required **4A** (1.0:1.70; 46%) in which the latter predominated (Scheme 13). The ^1H NMR, ^{13}C NMR and IR spectra of **4A** were identical with those of **4**. In addition its $[\alpha]_D^{25}$ −61 was numerically close to that of **4** ($[\alpha]_D^{25}$ +57.3) except for the sign of rotation, thus showing their enantiomeric relationship.

Since **4** had been converted into (+)-*ent*-debromoflustramine B, the diastereoselective preparation of **4A** constitutes, in a formal sense, a diastereoselective synthesis of the (−)-alkaloid.

2.3. (+)-*ent*-Debromoflustramide B (1g)

The relative stability of the Barton ester **19b** prompted us to examine the chemistry of its conjugate base generated at C^2

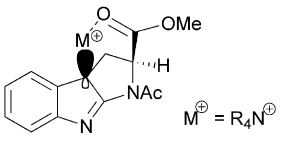
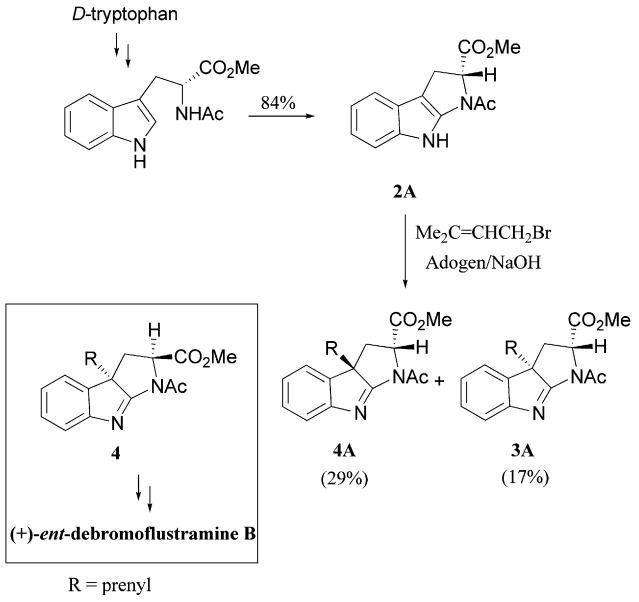


Figure 3. Preferred α-prenylation of (+)-Witkop's pyrroloindole **2**.



Scheme 13.

in the presence of air. With this end in view the above ester in THF was treated with *t*-BuOK at rt. A rapid reaction (1 h) ensued and four products could be isolated from the reaction mixture. Two of them were identified as 2-thiopyridine (**31**; 39%) and 1,3-diprenyl indole (**32**; 30%). The third compound was provisionally ascribed structure **18b** (34%) on the basis of its IR and ^{1}H NMR spectra (Fig. 4).

The fourth compound (15%), $C_{20}H_{26}N_2O$ (based on its accurate mass value), possessed IR spectrum absorptions at 3422 and 1702 cm^{-1}. Whilst containing all relevant signals due to the aromatic ring and the prenyl groups attached to C^{3a} and N^8, the presence of a 2H singlet at a relatively low δ 2.67 ppm was noteworthy. On this basis the pyrrolidone structure **33** was attributed to this product. Indeed, methylation (NaH, DMF, MeI) gave the corresponding *N*-Me compound *ent*-**1g**, the ^{1}H and ^{13}C NMR spectra of which contained all resonances with δ values coincident with those reported for the racemic[9b] substance.

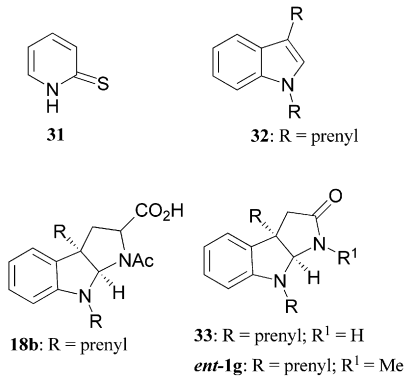
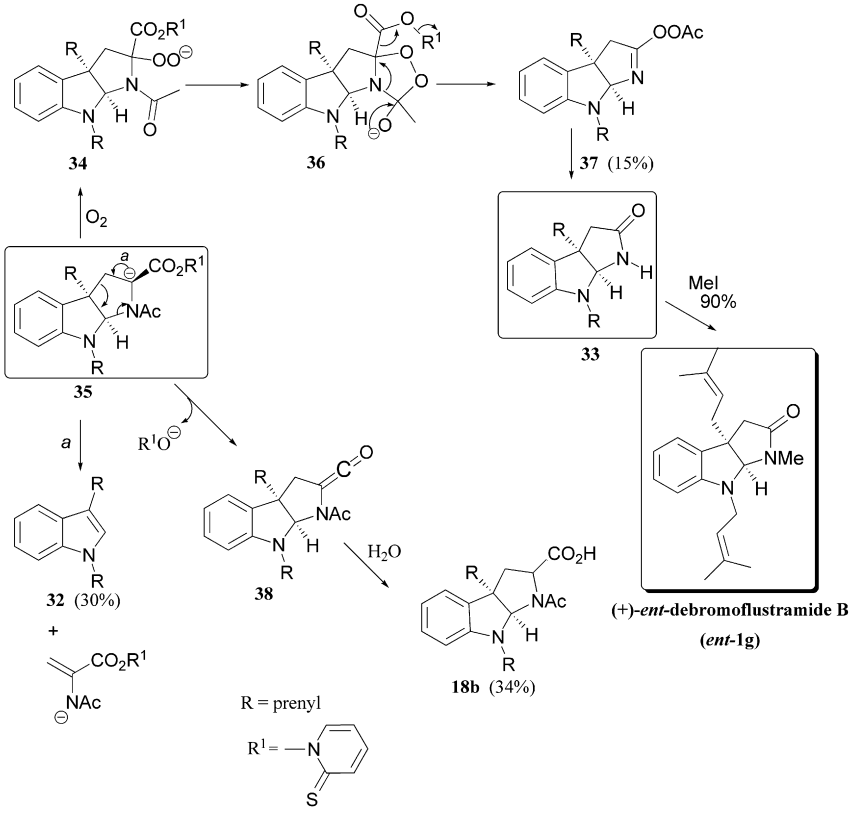


Figure 4.

Variations in experimental conditions such as temperature, prior saturation of the system with O_2, or change of solvent had only marginal effect in the relative proportions and yields of the products formed. A plausible mechanism could involve the hydroperoxide anion **34** generated from the carbanion **35** and O_2 (Scheme 14). Subsequent intramolecular attack by the nucleophile (R–OO$^-$) thus produced, on the



Scheme 14.

proximate CO group would furnish **36**. This would be followed by elimination of CO_2 and pyridine-2-thiolate anion (easily oxidisable) to give the imino-peroxy acetate **37**. An oxidation–reduction between the latter two substances would account for **33**. A fragmentation reaction occurring in parallel with oxygenation could give rise to 1,3-diprenyl indole (**32**). As for **18b**, its formation is assumed to proceed via the ketene **38**, produced from the carbanion **35**, and subsequent reaction with water during work-up.

3. Conclusions

In conclusion, Witkop's pyrroloindole **2**, readily prepared from (−)-1-acetyl-L-tryptophan methyl ester, is prenylated (NaH, DMF) to furnish a mixture of *C*-allylated compounds, (−)-(2*S*,3a*S*)-1-acetyl-3a-(3-methyl-2-butenyl)-2-methoxycarbonyl-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole (**3**) and (+)-(2*S*,3a*R*)-1-acetyl-3a-(3-methyl-2-butenyl)-2-methoxycarbonyl-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole (**4**), without diastereoselection (ca. 1:1). The two isomers are converted by selective functional group modifications into (−)-debromoflustramine B and (+)-*ent*-debromoflustramine B, respectively. Alkylation, under phase-transfer conditions, however give the undesired isomer in higher proportion (**3**:**4**, 1:2). Based on the above result methyl 1-acetyl-D-tryptophan carboxylate (**2A**) is prenylated and the major product is found to be (−)-(2*R*,3a*S*)-1-acetyl-3a-(3-methyl-2-butenyl)-2-methoxycarbonyl-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole (**4A**), the enantiomer of **4**. Since **4** is transformed to the (+)-*ent*-alkaloid, the diastereoselective preparation of **4A** constitutes, in a formal sense, a diastereoselective synthesis of the (−)-alkaloid. The carbanion derived from (+)-Barton ester **19b** and oxygen leads to (+)-*ent*-debromoflustramide B in 15% yield. A mechanism is proposed for the reaction.

4. Experimental

4.1. General

Melting points were determined on a Reichert Thermovar apparatus and are uncorrected. Optical rotations were determined in a Perkin–Elmer 241 MC polarimeter at rt, and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Ordinary mass spectra were recorded on a Fisons TRIO 2000 or AEI MS-9 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker ARX 400 spectrometer (400 MHz for ^{1}H, 100.63 MHz for ^{13}C). Chemical shifts are reported relative to tetramethylsilane as the internal reference (δ_H 0.00) for ^{1}H NMR spectra and to $CDCl_3$ (δ_C 77.00) for ^{13}C NMR spectra. High resolution mass spectra were recorded on an AutoSpecQ spectrometer. IR spectra were run on an FT Perkin–Elmer 683 instrument, with absorption frequencies expressed in reciprocal centimetres. Thin-layer chromatography was performed on Merck silica gel 60 F_{254} plates and PTLC on 0.5 mm thick plates. Column chromatography was carried out on Merck silica gel 60 (70–230 mesh). Usual work-up implies drying the water- or brine-washed organic extracts over anhydrous sodium sulfate or magnesium sulfate, followed by filtration and evaporation of the solvent from the filtrate under reduced pressure. Anhydrous solvents were dried as described[24] and freshly distilled.

4.2. Starting materials

4.2.1. Methyl (−)-1-acetyl-2,3-dihydropyrrolo[2,3-*b*]indole-2*S*-carboxylate (2). Methyl 1-acetyl-2,3-dihydropyrrolo[2,3-*b*]indole-2*S*-carboxylate (**2**) prepared from *N*-acetyl-L-tryptophan methyl ester in 88% yield as described by Witkop et al.[7] had mp 168–170 °C (lit.[7] 175–177 °C); $[\alpha]_D^{26}$ −96.1 (*c* 0.67, EtOH; lit.[7] $[\alpha]_D^{25}$ −97 (*c* 0.92, EtOH); IR (film): ν_{max}/cm^{-1} 1742 (ester C=O), 1648 (amide C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.2 (1H, s, exchangeable with D_2O, NH), 7.32–7.31 (2H, m, Ar-CH), 7.11–7.07 (2H, m, Ar-CH), 5.22 (1H, dd, *J* 10.0, 2.8 Hz, $CHCO_2CH_3$), 3.81 (3H, s, OCH_3), 3.68 (1H, dd, *J* 14.3, 10.3 Hz, 1H of CH_2), 3.31 (1H, dd, *J* 14.4, 2.8 Hz, 1H of CH_2), 2.12 (3H, s, $NCOCH_3$); ^{13}C NMR: δ_C 171.5, 167.4, 143.0, 137.2, 123.1, 121.1, 120.5, 120.2, 117.3, 98.3, 66.3, 52.9, 29.8, 21.6.

4.2.2. Methyl (+)-1-acetyl-2,3-dihydropyrrolo[2,3-*b*]indole-2*R*-carboxylate (2A). Methyl (+)-1-acetyl-2,3-dihydropyrrolo[2,3-*b*]indole-2*R*-carboxylate (**2A**) was similarly prepared from 1-acetyl-D-tryptophan methyl ester in 85% yield. It had mp 170–171 °C; $[\alpha]_D^{26}$ +96 (*c* 2, EtOH); IR (film): ν_{max}/cm^{-1} 1744 (ester C=O), 1655 (amide C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.23 (1H, s, exchangeable with D_2O, NH), 7.33–7.30 (2H, m, Ar-H), 7.11–7.06 (2H, m, Ar-H), 5.22 (1H, dd, *J* 10.0, 2.96 Hz, $CHCO_2CH_3$), 3.82 (3H, s, OCH_3), 3.68 (1H, dd, *J* 14.4, 10.2 Hz, 1H of CH_2), 3.31 (1H, dd, *J* 14.40, 2.92 Hz, 1H of CH_2), 2.13 (3H, s, $NCOCH_3$); ^{13}C NMR: δ_C 171.2, 167.2, 142.8, 136.9, 123.4, 121.1, 120.5, 120.2, 117.2, 98.2, 66.3, 52.9, 29.9, 21.6; acc. mass: 259.1080, $C_{14}H_{15}N_2O_3$ requires 258.1004.

4.2.3. Prenylation of 2 under standard conditions. Compound **2** (9 g, 35 mmol) in DMF (80 ml) was treated portionwise with NaH (60% dispersion, 1.41 g, 35.3 mmol) and the resulting mixture stirred under argon atmosphere (45 min) in an ice bath. Dimethylallyl bromide, freshly distilled (5.20 ml, 44.7 mmol), was added dropwise and the resulting solution stirred at 0 °C until the reaction was complete (2 h, TLC control). The mixture was diluted with EtOAc (300 ml) and washed repeatedly with saturated solution of sodium bicarbonate, followed by brine. Usual work-up led to an oil which was chromatographed on silica to furnish a mixture of *C*-allylated (**3**+**4**, 6.85 g, 60%) and the *N*-allyl compound *(−)-(2S)-1-acetyl-8-(3′-methyl-2′-butenyl)-2-methoxycarbonyl-1,2,3,8-tetrahydropyrrolo[2,3-b]indole (**5**)* (1.25 g, 11%), as a yellow oil; $[\alpha]_D^{23}$ −102 (*c* 1.05, CH_2Cl_2); IR (film): ν_{max}/cm^{-1} 1749 (ester C=O), 1673 (amide C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.32 (1H, d, *J* 6.4 Hz, Ar-CH), 7.26 (1H, d, *J* 7.6 Hz, Ar-CH), 7.09–7.06 (2H, m, Ar-CH), 5.29–5.25 [1H, m, C*H*=C(CH$_3$)$_2$], 5.18–5.15 (2H, m, 1H of C*H*CO$_2$CH$_3$ and 1H of NC*H*$_2$), 4.95 (1H, dd, *J* 15.6, 4.9 Hz, 1H of NCH$_2$), 3.76 (3H, s, OCH$_3$), 3.58 (1H, d, *J* 14.4, 9.3 Hz, 1H of C*H*$_2$CHCO$_2$CH$_3$), 3.22 (1H, dd, *J* 14.5, 1.3 Hz, 1H of C*H*$_2$CHCO$_2$CH$_3$), 2.22 (3H, s, NCOCH$_3$), 1.79 [3H, s, C(C*H*$_3$)$_2$], 1.68 [3H, s, C(C*H*$_3$)$_2$]; ^{13}C NMR: δ_C 171.9, 167.3, 143.4, 139.5, 134.1, 123.4, 121.2, 120.3, 120.2, 117.6, 111.1, 68.1, 52.8, 44.7, 28.5, 25.4, 22.7, 17.8; acc. mass: 326.16333, $C_{19}H_{22}N_2O_3$ requires 326.16303.

The diastereomeric mixture of C^{3a}-alkylated compounds (**3**:**4**=1:1.9 by ^{1}H NMR analysis) formed in the reaction

was difficult to separate by column chromatography. Therefore, for characterisation purposes a small quantity was purified by PTLC (Et_2O/*n*-hexane 50%) to give **3** and **4** as homogeneous compounds: *(−)-(2S,3aS)-1-acetyl-3a-(3′-methyl-2′-butenyl)-2-methoxycarbonyl-1,2,3,3a-tetrahydropyrrolo[2,3-b]indole (**3**)*, a colourless solid, mp 108–110 °C; $[\alpha]_D^{25}$ −162.9 (*c* 0.42, Et_2O); IR (film): ν_{max}/cm^{-1} 1750s (ester C=O), 1698s (amide C=O), 1625 (C=N); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.36 (1H, d, *J* 7.6 Hz, Ar-H), 7.28 (1H, t, *J* 7.7 Hz, Ar-H), 7.21 (1H, d, *J* 7.2 Hz, Ar-H), 7.05 (1H, t, *J* 7.3 Hz, Ar-H), 5.24 (1H, d, *J* 10.5 Hz, C*H*CO_2CH_3), 4.79 [1H, t, *J* 6.9 Hz, C*H*=$C(CH_3)_2$], 3.85 (3H, s, OCH_3), 2.70 (3H, s, $NCOCH_3$), 2.61 [1H, dd, *J* 13.9, 7.2 Hz, 1H of CH_2CH=$C(CH_3)_2$], 2.49 (1H, d, *J* 13.1 Hz, 1H of CH_2CHCO_2CH_3), 2.36–2.27 [2H, m, 1H of CH_2CH=$C(CH_3)_2$ and 1H of CH_2CHCO_2CH], 1.61 [3H, s, C(CH_3)$_2$], 1.44 [3H, s, C(CH_3)$_2$]; ^{13}C NMR: δ_C 181.8, 175.5, 170.1, 158.6, 139.9, 136.5, 128.7, 123.7, 122.8, 119.6, 117.1, 64.6, 61.2, 52.7, 35.1, 30.7, 25.7, 23.8, 17.7; acc. mass: 326.16302, $C_{19}H_{22}N_2O_3$ requires 326.16303, and *(+)-(2S,3aR)-1-acetyl-3a-(3′-methyl-2′-butenyl)-2-methoxycarbonyl-1,2,3,3a-tetrahydropyrrolo[2,3-b]indole (**4**)*, a colourless solid, mp 131–132 °C (from Et_2O); $[\alpha]_D^{25}$ +57.3 (*c* 0.38, Et_2O); IR (film): ν_{max}/cm^{-1} 1745s (ester C=O), 1689s (amide C=O), 1629s (C=N); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.42 (1H, d, *J* 7.7 Hz, Ar-H), 7.31 (1H, t, *J* 7.8 Hz, Ar-H), 7.24 (1H, d, *J* 7.6 Hz, Ar-H), 7.08 (1H, t, *J* 7.4 Hz, Ar-H), 5.08 (1H, dd, *J* 9.7, 6.4 Hz, C*H*CO_2CH_3), 4.92 [1H, t, *J* 7.1 Hz, C*H*=$C(CH_3)_2$], 3.73 (3H, s, OCH_3), 2.64 (4H, m, $NCOCH_3$ and 1H of CH_2CHCO_2CH_3), 2.50 [1H, dd, *J* 13.9, 7.6 Hz, 1H of CH_2CH=$C(CH_3)_2$], 2.21 [1H, dd, *J* 13.9, 7.6 Hz, 1H of CH_2CH=$C(CH_3)_2$], 1.87 (1H, dd, *J* 12.1, 10.1 Hz, 1H of CH_2CHCO_2CH_3), 1.65 [3H, s, C(CH_3)$_2$], 1.47 [3H, s, C(CH_3)$_2$]; ^{13}C NMR: δ_C 180.8, 170.6, 169.5, 158.8, 139.2, 136.9, 128.8, 124.0, 122.9, 120.0, 116.9, 65.1, 61.0, 52.4, 34.9, 30.7, 25.7, 23.2, 17.7; acc. mass: 326.16364, $C_{19}H_{22}N_2O_3$ requires 326.16303.

4.2.4. Prenylation of 2 and 2A under phase-transfer conditions. Compound **2** (100 mg, 0.388 mmol) in CH_2Cl_2 (3 ml) was stirred vigorously with Adogen 464 (0.2 ml, 0.378 mmol) and 50% aq NaOH (1 ml, 12.5 mmol) while 3,3-dimethylallyl bromide (81.0 µl) was added. The mixture, after 5 min of stirring at rt, was diluted with CH_2Cl_2 and washed with water. Work-up yielded a mixture which was separated by PTLC to give a mixture of **3** and **4** (68 mg, 54%) in a ratio of 0.47:1.0 as determined by ^1H NMR analysis, and **5** (10 mg, 8%). Essentially similar results were obtained with (−)-(8*S*,9*R*)-*N*-benzylcinchonidinium chloride and (+)-(8*R*,9*S*)-*N*-[4-(trifluoromethylbenzyl)]cinchonium bromide as phase-transfer catalysts.

4.2.4.1. (+)-(2*R*,3a*R*)-1-Acetyl-3a-(3′-methyl-2′-butenyl)-2-methoxycarbonyl-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole (3A) and (−)-(2*R*,3a*S*)-1-acetyl-3a-(3′-methyl-2′-butenyl)-2-methoxycarbonyl-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole (4A). Compound **2A** when subjected to the above conditions furnished a mixture which was purified as above to yield **3A** in 17% yield; mp 105–107 °C; $[\alpha]_D^{25}$ +160 (*c* 0.38, Et_2O); IR (film): ν_{max}/cm^{-1} 1745s (ester C=O), 1710s (amide C=O), 1659s (C=N); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.36 (1H, d, *J* 7.68 Hz, Ar-H), 7.28 (1H, t, *J* 7.7 Hz, Ar-H), 7.21 (1H, d, *J* 7.28 Hz, Ar-H), 7.05 (1H, d, *J* 7.16 Hz, Ar-H), 5.24 (1H, d, *J* 10.4 Hz, C*H*CO_2CH_3), 4.79 [1H, t, *J* 7.20 Hz, C*H*=$C(CH_3)_2$], 3.85 (3H, s, OCH_3), 2.70 (3H, s, $NCOCH_3$), 2.61 [1H, dd, *J* 13.7, 6.8 Hz, 1H of CH_2CH=$C(CH_3)_2$], 2.49 (1H, d, *J* 13.20 Hz, 1H of CH_2CHCO_2CH_3), 2.36–2.27 [2H, m, 1H of CH_2CH=$C(CH_3)_2$ and 1H of CH_2CHCO_2CH], 1.61 [3H, s, C(CH_3)$_2$], 1.44 [3H, s, C(CH_3)$_2$]; ^{13}C NMR: δ_C 181.4, 172.3, 169.7, 158.0, 140.7, 136.2, 128.4, 123.5, 122.6, 122.1, 116.5, 63.4, 52,4, 37.2, 30.2, 25.8, 22.6, 17.9; acc. mass: (MNa^+) 349.1523, $C_{19}H_{22}N_2NaO_3$ requires 349.15281, and **4A** in 29% yield; mp 130–135 °C; $[\alpha]_D^{25}$ −61 (*c* 0.2, Et_2O); IR (film): ν_{max}/cm^{-1} 1708s (ester C=O), 1664s (amide C=O), 1621s (C=N); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.41 (1H, d, *J* 7.76 Hz, Ar-H), 7.30 (1H, t, *J* 7.6 Hz, Ar-H), 7.23 (1H, d, *J* 7.12 Hz, Ar-H), 7.07 (1H, t, *J* 7.30 Hz, Ar-H), 5.08 (1H, dd, *J* 9.84, 6.36 Hz, C*H*CO_2CH_3), 4.91 [1H, t, *J* 7.4 Hz, C*H*=$C(CH_3)_2$], 3.72 (3H, s, OCH_3), 2.62 (4H, m, $NCOCH_3$ and 1H of CH_2CHCO_2CH_3), 2.50 [1H, dd, *J* 13.9, 7.6 Hz, 1H of CH_2CH=$C(CH_3)_2$], 2.21 [1H, dd, *J* 13.9, 7.5 Hz, 1H of CH_2CH=$C(CH_3)_2$], 1.87 (1H, dd, *J* 12.0, 10.0 Hz, 1H of CH_2CHCO_2CH_3), 1.65 [3H, s, C(CH_3)$_2$], 1.46 [3H, s, C(CH_3)$_2$]; ^{13}C NMR: δ_C 181.3, 172.2, 169.7, 157.5, 141.1, 136.2, 128.1, 123.9, 123.8, 119.9, 116.7, 65.3, 61.2, 52.2, 35.1, 30.3, 25.8, 23.4, 17.9; acc. mass: (MNa^+) 349.1523, $C_{19}H_{22}N_2NaO_3$ requires 349.15281.

4.3. Reaction of 5 with Lewis acid

4.3.1. Method A. Synthesis of 6 and 7. Compound **5** (52.4 mg, 0.16 mmol) in dry CH_2Cl_2 (1.5 ml) was treated with $BF_3{\cdot}Et_2O$ (freshly distilled twice from CaH_2) (102 µl, 0.79 mmol, 5 equiv), under argon atmosphere at rt and the reaction monitored by TLC (Et_2O/*n*-hexane, 1:1). The mixture was then neutralised with Et_3N at 0 °C and the products worked up in the usual manner. Purification by PTLC (silica, Et_2O, multiple elution) furnished **6** as a diastereomeric mixture (1:0.4), a yellow oil (23.3 mg, 43%); $[\alpha]_D^{20}$ +4.12 (*c* 6.3, Et_2O); IR (film): ν_{max}/cm^{-1} 1746 (ester C=O), 1709s (amide C=O), 1680s (amide C=O), 1612 (N–CO), 1538 (C=C); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.83 (1H, d, *J* 6.6 Hz, exchangeable with D_2O, NH), 7.42 (1H, d, *J* 7.3 Hz, Ar-H), 7.28–7.21 (4H, m, Ar-H and NH, exchangeable with D_2O), 7.07 (2H, t, *J* 7.4 Hz, Ar-H), 6.80 (2H, d, *J* 7.8 Hz, Ar-H), 5.13 [2H, br s, C*H*=$C(CH_3)_2$], 4.89–4.83 (1H, m, C*H*CO_2CH_3), 4.71 (1H, m, C*H*CO_2CH_3), 4.30 [4H, d, *J* 6.6 Hz, CH_2CH=$C(CH_3)_2$], 3.75 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.54–3.48 (2H, m, C*H*CO), 2.59–2.53 (1H, m, 1H of CH_2CHCO_2CH_3), 2.38–2.21 (3H, m, CH_2CHCO_2CH_3), 2.07 (3H, s, $NCOCH_3$), 2.05 (3H, s, $NCOCH_3$), 1.81 [6H, s, C(CH_3)$_2$], 1.71 [6H, s, C(CH_3)$_2$]; ^{13}C NMR: δ_C 177.6, 177.1, 172.2, 170.4, 170.1, 143.2, 136.9, 136.8, 128.4, 128.2, 127.8, 124.2, 123.6, 122.8, 122.7, 118.1, 117.9, 109.0, 108.8, 52.4, 51.0, 50.8, 43.0, 42.6, 38.2, 32.7, 31.4, 25.6, 22.9, 18.1; acc. mass: 344.172873, $C_{19}H_{24}N_2O_4$ requires 344.173608. On letting the reaction run for more than 24 h the diastereomeric ratio was found to be 1:0.90. Mineral acid hydrolysis of **5** (25 mg, 0.007 mmol) in acetone (0.9 ml) and HCl (1 M, 0.01 ml, 0.01 mmol) for 30 min at rt furnished **6** (17 mg, 66%) on work-up with $NaHCO_3$.

4.3.2. Method B. Synthesis of 7. Compound **5** (50 mg, 0.15 mmol, 1 equiv) in freshly distilled $BF_3{\cdot}Et_2O$ (169 μl, 1.8 mmol, 12 equiv) at 0 °C, under argon atmosphere, was allowed to warm to rt and held at this temperature (24 h). The mixture was neutralised with triethylamine at 0 °C, water added and the product extracted twice with ether. Usual work-up furnished a residue which was purified by PTLC (silica, Et_2O, four elutions) to give **7** as an oil (12.2 mg, 24%); $[\alpha]_D^{20}$ +25.3 (*c* 4.1, Et_2O); IR (film): ν_{max}/cm^{-1} 1732 (ester C=O), 1667 (amide C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.33 (1H, d, *J* 7.0 Hz, Ar-H), 7.13–7.03 (3H, m, Ar-H), 6.22 (1H, d, *J* 6.8 Hz, NH, exchangeable with D_2O), 4.81–4.76 (1H, m, C*H*CO_2CH_3), 4.08 (2H, t, *J* 6.4 Hz, NCH_2CH_2), 3.68 (3H, s, OCH_3), 3.16 (2H, m, CH_2CHCO_2CH_3), 2.14 (2H, t, *J* 6.3 Hz, NCH_2CH_2), 1.94 (3H, s, $NCOCH_3$), 1.45 [6H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 172.4, 169.6, 147.8, 131.0, 127.6, 120.1, 118.9, 116.5, 107.7, 85.3, 53.1, 52.1, 36.9, 32.4, 26.6, 26.4, 24.9, 23.3; acc. mass: 344.173400, $C_{19}H_{24}N_2O_4$ requires 344.173608.

4.3.3. 8-Prenyl-2-methoxy-1-acetyl-L-tryptophan methyl ester (8). Compound **5** (20 mg, 0.061 mmol) in dry CH_2Cl_2 (0.9 ml) and molecular sieves 4 Å at 0 °C, under argon, was treated with $BF_3{\cdot}MeOH$ (14% in MeOH, 216 μl, 0.36 mmol). On completion of reaction (5 min, TLC control), the mixture was neutralised with aq satd $NaHCO_3$ solution and the product extracted twice with Et_2O. Usual work-up furnished **8** as a colourless oil (23.3 mg, 100%); $[\alpha]_D^{20}$ +24.5 (*c* 1.0, Et_2O); IR (film): ν_{max}/cm^{-1} 1743 (ester C=O), 1656 (amide C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.39 (1H, d, *J* 7.6 Hz, Ar-H), 7.24–7.05 (3H, m, Ar-H), 6.12 (1H, d, *J* 7.1 Hz, exchangeable with D_2O, NH), 5.22 [1H, m, C*H*=$C(CH_3)_2$], 4.85–4.81 (1H, m, C*H*CO_2CH_3), 4.59 [2H, d, *J* 6.3 Hz, CH_2CH=$C(CH_3)_2$], 3.91 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.28–3.22 (2H, m, CH_2CHCO_2CH_3), 1.94 (3H, s, $NCOCH_3$), 1.84 [3H, s, $C(CH_3)_2$], 1.71 [3H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 172.3, 169.8, 150.4, 134.8, 131.3, 126.9, 120.7, 120.4, 119.6, 117.7, 109.3, 91.1, 62.3, 53.1, 52.3, 39.9, 25.7, 25.5, 23.2, 18.0; acc. mass: 358.188415, $C_{20}H_{26}N_2O_4$ requires 358.18926.

4.4. Alkaloid syntheses

4.4.1. (+)-(2*S*,3a*R*)-3a-(3′-Methyl-2′-butenyl)-2-methoxycarbonyl-2,3,3a,8-tetrahydropyrrolo[2,3-*b*]indole (11)/(+)-(2*S*,3a*R*)-3a-(3′-methyl-2′-butenyl)-2′-methoxycarbonyl-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole (12). Compound **4** (0.60 g, 1.84 mmol) in methanolic sodium methoxide (0.06 M, 35 ml, 2.10 mmol) was allowed to stand at rt (1 h). After concentrating the solution under reduced pressure, water was added to the resulting mixture neutralised with 1 M HCl and the product extracted with ether. Work-up furnished a yellow solid (**11** or **12**, 0.49 g, 94%) which was crystallised (Et_2O). It had mp 133–135 °C; $[\alpha]_D^{25}$ +108.5 (*c* 0.39, CH_2Cl_2); IR (film): ν_{max}/cm^{-1} 3411 (N–H), 1747s (ester C=O), 1675s; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.17 (1H, t, *J* 7.30 Hz, Ar-H), 7.10 (1H, d, *J* 7.2 Hz, Ar-H), 6.95 (1H, d, *J* 7.0 Hz, Ar-H), 6.87 (1H, t, *J* 7.4 Hz, Ar-H), 5.17 [4/5H, br s, C*H*=$C(CH_3)_2$], 5.11 [1/5H, br s, C*H*=$C(CH_3)_2$], 4.91 (1H, dd, *J* 9.7, 5.1 Hz, C*H*CO_2CH_3), 3.82 (3/5H, s, OCH_3), 3.77 (12/5H, s, OCH_3), 2.68 (1H, dd, *J* 11.9, 4.9 Hz, CH_2CHCO_2CH_3), 2.41 [1H, dd, *J* 13.7, 7.7 Hz, CH_2CH=$C(CH_3)_2$], 2.19 [1H, dd, *J* 13.9, 7.6 Hz, CH_2CH=$C(CH_3)_2$], 2.12 [1H, t, *J* 10.9 Hz, CH_2CH=$C(CH_3)_2$], 1.70 [3H, s, $C(CH_3)_2$], 1.44 [3H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 184.4, 173.4, 169.5, 149.7, 135.8, 133.6, 128.1, 124.0, 120.7, 118.5, 111.9, 70.8, 61.2, 52.2, 39.3, 34.6, 25.9, 17.7; *m/z* (EI) 284 (58%, M^+), 216 (89.5%), 155 (100%).

4.4.2. Acetylation of 11/12 to (2*S*,3a*R*)-8-acetyl-3a-(3′-methyl-2′-butenyl)-2-methoxycarbonyl-2,3,3a,8-tetrahydropyrrolo[2,3-*b*]indole (13a). The mixture **11/12** (45.0 mg, 0.158 mmol) in dry EtOAc (2 ml) was acetylated with Ac_2O (20.0 μl, 0.210 mmol), Et_3N (30.0 μl, 0.215 mmol) and 4-DMAP (13.0 mg, 0.104 mmol) at rt (0.5 h). It was then diluted with EtOAc (20 ml) and the organic phase washed with a saturated solution of $NaHCO_3$. The residue obtained on work-up was purified by PTLC (Et_2O) to give **4** (10 mg, 19%; identical ^1H NMR, ^{13}C NMR, $[\alpha]_D^{25}$ with an authentic sample) and its N^8 isomer **13a** as a colourless oil (30.4 mg, 59%); IR (film): ν_{max}/cm^{-1} 1743s (ester C=O), 1693s (amide C=O), 1667s (C=N); ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.21 (1H, d, *J* 8.1 Hz, Ar-H), 7.28 (1H, t, *J* 7.4 Hz, Ar-H), 7.15–7.09 (2H, m, Ar-H), 5.02 [2H, m, 1H of C*H*=$C(CH_3)_2$ and 1H of C*H*CO_2CH_3], 3.78 (3H, s, OCH_3), 2.68 (3H, s, $NCOCH_3$), 2.64 (1H, dd, *J* 12.2, 5.3 Hz, CH_2CHCO_2CH_3), 2.31 [2H, dd, *J* 7.5, 2.6 Hz, CH_2CH=$C(CH_3)_2$], 2.25 (1H, dd, *J* 11.9, 10.2 Hz, CH_2CHCO_2CH_3), 1.66 [3H, s, $C(CH_3)_2$], 1.39 [3H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 178.5, 172.6, 169.8, 144.3, 136.9, 132.1, 128.6, 123.5, 117.4, 117.2, 73.1, 60.1, 52.4, 38.9, 35.4, 25.8, 25.2, 17.5; *m/z* (EI) 326 (16.8%, M^+), 258 (74.4%), 215 (100%).

4.4.3. Methylation of 11/12 to (2*S*,3a*R*)-8-methyl-3a-(3′-methyl-2′-butenyl)-2-methoxycarbonyl-2,3,3a,8-tetrahydropyrrolo[2,3-*b*]indole (13b). To **11/12** (46.0 mg, 0.162 mmol) in 4 ml dry DMF was added NaH (8.0 mg, 0.200 mmol) and the mixture stirred in an ice bath (0.5 h) after which time MeI (15.0 μl, 0.240 mmol) was introduced via a syringe. On completion of reaction (0.5 h) EtOAc was added and the mixture worked up in the usual manner to give product **13b**, as a colourless oil (31.8 mg, 65.8%); IR (film): ν_{max}/cm^{-1} 1738 (ester C=O), 1664 (C=N); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.22 (1H, t, *J* 7.8 Hz, Ar-H), 7.10 (1H, d, *J* 7.2 Hz, Ar-H), 6.89 (1H, t, *J* 7.4 Hz, Ar-H), 6.73 (1H, d, *J* 7.8 Hz, Ar-H), 5.15 [1H, t, *J* 7.5 Hz, C*H*=$C(CH_3)_2$], 4.93 (1H, dd, *J* 9.7, 4.9 Hz, C*H*CO_2CH_3), 3.76 (3H, s, OCH_3), 3.23 (3H, s, NCH_3), 2.62 (1H, dd, *J* 11.9, 4.8 Hz, CH_2CHCO_2CH_3), 2.36 [1H, dd, *J* 13.7, 7.8 Hz, CH_2CH=$C(CH_3)_2$], 2.18–2.07 [2H, m, 1H of CH_2CHCO_2CH_3 and 1H of CH_2CH=$C(CH_3)_2$], 1.70 [3H, s, $C(CH_3)_2$], 1.42 [3H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 178.5, 173.4, 138.1, 128.1, 123.9, 120.6, 118.4, 108.1, 72.3, 59.0, 52.0, 39.3, 34.6, 29.5, 25.7, 17.4; acc. mass: 298.16780, $C_{18}H_{22}N_2O_2$ requires 298.16812.

4.4.4. Reduction of 3/4. A stirred mixture of **3** and **4** (5.68 g, 17.4 mmol) in dry MeOH, under N_2 atmosphere, was treated portionwise with $Na(CN)BH_3$ (1.65 g, 23.6 mmol) at rt. Acetic acid in MeOH (1:1) was added when necessary, to maintain the pH between 5 and 6. On completion of the reaction (TLC control, Et_2O) the bulk of the solvent was removed under reduced pressure and to the resulting residue aq NaOH (1 M, 70 ml) was added. Extraction with EtOAc followed by work-up gave a mixture of products which was separated by column chromatography

(Et_2O) into a mixture of the two diastereomers **16a** and **17a** (4.86 g; 85%).

4.4.5. Separation of compounds 16a and 17a. A small quantity of the mixture of **16a** and **17a** was separated by PTLC (Et_2O/*n*-hexane, 30%) into pure *(−)-(2S,3aS,8aS)-1-acetyl-3a-(3′-methyl-2′-butenyl)-2-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (**16a**)* as a colourless oil; $[\alpha]_D^{25}$ −174.5 (*c* 0.83, CH_2Cl_2); IR (film): ν_{max}/cm^{-1} 3430 (N–H), 1744s (ester C=O), 1674s (amide C=O), 1651s (amide C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.09–7.04 (2H, m, Ar-H), 6.81 (1/3H, t, *J* 7.4 Hz, Ar-H), 6.74 (2/3H, t, *J* 7.4 Hz, Ar-H), 6.63 (1/3H, d, *J* 7.8 Hz, Ar-H), 6.59 (2/3H, d, *J* 7.7 Hz, Ar-H), 5.51 (1H, s, exchangeable with D_2O, NH), 5.40 (2/3H, s, NCHN), 5.38 (1/3H, s, NCHN), 5.09–5.03 [1H, m, C*H*=$C(CH_3)_2$], 4.26–4.19 (1H, m, C*H*CO_2CH_3), 3.79 (2H, s, OCH_3), 3.73 (1H, s, OCH_3), 2.69 (2/3H, dd, *J* 13.1, 8.6 Hz, C*H*$_2$CHCO_2CH_3), 2.50–2.47 [2/3H, m, C*H*$_2$CH=$C(CH_3)_2$], 2.36–2.31 [8/3H, m, 4/3H of C*H*$_2$CHCO_2CH_3 and 4/3H of C*H*$_2$CH=$C(CH_3)_2$], 2.20 (1H, s, $NCOCH_3$), 1.87 (2H, s, $NCOCH_3$), 1.68 [3H, s, $C(CH_3)_2$], 1.55 [1H, s, $C(CH_3)_2$], 1.51 [2H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 173.3, 172.8, 171.5, 170.0, 148.5, 147.9, 135.6, 132.1, 128.8, 128.6, 123.0, 120.2, 118.8, 118.7, 110.4, 109.5, 82.1, 81.2, 60.0, 59.3, 55.1, 52.6, 52.1, 40.5, 39.2, 35.9, 35.0, 25.7, 22.4, 22.2, 17.8, 17.7; acc. mass: 328.17785, $C_{19}H_{24}N_2O_3$ requires 328.17868, and *(+)-(2S,3aR,8aR)-1-acetyl-3a-(3′-methyl-2′-butenyl)-2-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (**17a**)*; $[\alpha]_D^{25}$ +242.5 (*c* 0.99, CH_2Cl_2); IR (film): ν_{max}/cm^{-1} 3406 (N–H), 1735s (ester C=O), 1654s (amide C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.02 (1H, t, *J* 7.7 Hz, Ar-H), 6.97 (1H, d, *J* 7.5 Hz, Ar-H), 6.66 (1H, t, *J* 7.3 Hz, Ar-H), 6.56 (1H, d, *J* 7.8 Hz, Ar-H), 5.27 (1H, s, NCHN), 5.22 (1H, s, exchangeable with D_2O, NH), 5.17 [1H, t, *J* 7.2 Hz, CH=$C(CH_3)_2$], 4.41 (1H, d, *J* 8.5 Hz, $CHCO_2CH_3$), 3.17 (3H, s, OCH_3), 2.71 (1H, d, *J* 12.9 Hz, $CH_2CHCO_2CH_3$), 2.51 (1H, dd, *J* 12.9, 8.7 Hz, $CH_2CHCO_2CH_3$), 2.41–2.31 [2H, m, CH_2CH=$C(CH_3)_2$], 1.98 (3H, s, $NCOCH_3$), 1.71 [3H, s, $C(CH_3)_2$], 1.53 [3H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 171.2, 171.0, 150.0, 135.5, 130.6, 128.7, 123.7, 118.7, 118, 109.2, 80.5, 60.8, 55.5, 52.3, 38.8, 35.3, 26.0, 22.1, 17.9; acc. mass: 328.17628, $C_{19}H_{24}N_2O_3$ requires 328.17868.

4.4.6. Prenylation of 16a and 17a. The mixture **16a** and **17a** (5.45 g, 16.6 mmol) in dry THF (110 ml) containing K_2CO_3 (7.00 g, 50.7 mmol) and 3,3-dimethylallyl bromide (freshly distilled, 20.0 ml, 172 mmol) was stirred at rt (four days). Most of the solvent was then evaporated under reduced pressure and the resulting residue dissolved in EtOAc (250 ml). Work-up furnished an oil which was purified by filtration through a short column of silica (Et_2O/CH_2Cl_2 50%) to give a mixture (1:2) of the diastereomers **16b** and **17b** (4.70 g, 71%) which was used as such for the preparation of Barton esters. For characterisation purpose a small quantity of the mixture was separated by PTLC (Et_2O) into pure *(−)-(2S,3aS,8aS)-1-acetyl-3a,8-bis-(3-methyl-2-butenyl)-2-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (**16b**)*; $[\alpha]_D^{26}$ −83.5 (*c* 1.19, CH_2Cl_2); IR (film): ν_{max}/cm^{-1} 1744s (ester C=O), 1655s (amide C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.13–7.08 (1H, m, Ar-H), 7.02 (3/5H, d, *J* 7.2 Hz, Ar-H), 6.97 (2/5H, d, *J* 7.2 Hz, Ar-H), 6.76 (3/5H, t, *J* 7.3 Hz, Ar-H), 6.70 (2/5H, t, *J* 7.3 Hz, Ar-H), 6.49 (1H, d, *J* 7.8 Hz, Ar-H), 5.61 (2/5H, s, NCHN), 5.29 (3/5H, s, NCHN), 5.12 [1H, br s, CC*H*=$C(CH_3)_2$], 5.03 [3/5H, br s, NCH_2CH=$C(CH_3)_2$], 4.93 [2/5H, br s, NCH_2CH=$C(CH_3)_2$], 4.43–4.34 [1H, m, 3/5H of NCH_2CH=$C(CH_3)_2$ and 2/5H of C*H*CO_2CH_3], 4.27 (3/5H, dd, *J* 8.6, 6.7 Hz, C*H*CO_2CH_3), 4.07 [2/5H, dd, *J* 15.9, 3.9 Hz, NCH_2CH=$C(CH_3)_2$], 3.95–3.83 [1H, m, NCH_2CH=$C(CH_3)_2$], 3.80 (6/5H, s, OCH_3), 3.75 [9/5H, s, CCH_2CH=$C(CH_3)_2$], 2.70 [3/5H, dd, *J* 14.6, 9.3 Hz, CCH_2CH=$C(CH_3)_2$], 2.55 (2/5H, dd, *J* 13.3, 9.6 Hz, $CH_2CHCO_2CH_3$), 2.45–2.30 [12/5H, m, 7/5H of CCH_2CHC=$C(CH_3)_2$ and 1H of $CH_2CHCO_2CH_3$], 2.20 (9/5H, s, $NCOCH_3$), 2.11 (3/5H, dd, *J* 13.1, 6.4 Hz, $CH_2CHCO_2CH_3$), 1.95 (6/5H, s, $NCOCH_3$), 1.76, 1.70, 1.68, 1.67, 1.64, 1.61, 1.56 [12H, all s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 173.5, 172.5, 171.7, 170.1, 149.7, 149.1, 135.7, 135.0, 133.8, 133.5, 128.4, 122.2, 121.9, 121.2, 120.3, 119.8, 119.5, 119.1, 118.1, 109.2, 108.8, 86.7, 86.1, 60.4, 59.4, 57.0, 52.6, 52.1, 46.8, 45.3, 42.5, 40.4, 34.9, 34.3, 25.8, 25.6, 23.1, 22.0, 18.2, 18.1, 18.1; acc. mass: 396.24154, $C_{24}H_{32}N_2O_3$ requires 396.24128, and *(+)-(2S,3aR,8aR)-1-acetyl-3a,8-bis-(3′-methyl-2′-butenyl)-2-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (**17b**)*; $[\alpha]_D^{26}$ +133.5 (*c* 1.92, CH_2Cl_2); IR (film): ν_{max}/cm^{-1} 1737s (ester C=O), 1653s (amide C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.09–7.00 (4/3H, m, Ar-H), 6.93 (2/3H, d, *J* 7.2 Hz, Ar-H), 6.70 (1/3H, t, *J* 7.3 Hz, Ar-H), 6.58 (2/3H, t, *J* 7.3 Hz, Ar-H), 6.53 (1H, m, Ar-H), 5.57 (2/3H, s, NCHN), 5.30 (1/3H, s, NCHN), 5.23–5.20 [1H, m, NCH_2CH=$C(CH_3)_2$], 5.10–5.03 [1H, m, CCH_2CH=$C(CH_3)_2$], 5.00 (1/3H, t, *J* 7.1 Hz, C*H*CO_2CH_3), 4.44 (2/3H, d, *J* 8.2 Hz, C*H*CO_2CH_3), 4.26 [2/3H, dd, *J* 15.9, 6.9 Hz, NCH_2CH=$C(CH_3)_2$], 4.00 [2/3H, dd, *J* 16.0, 5.0 Hz, NCH_2CH=$C(CH_3)_2$], 3.93–3.92 [2/3H, m, NCH_2CH=$C(CH_3)_2$], 3.46 (1H, s, OCH_3), 3.26 (2H, s, OCH_3), 2.63 (2/3H, d, *J* 12.8 Hz, C*H*$_2$CHCO_2CH_3), 2.46–2.28 [10/3H, m, 4/3H of C*H*$_2$CHCO_2CH_3 and 2H of CCH_2CH=$C(CH_3)_2$], 2.19 (1H, s, $NCOCH_3$), 2.04 (2H, s, $NCOCH_3$), 1.76 [2H, s, $C(CH_3)_2$], 1.72 [2H, s, $C(CH_3)_2$], 1.69 [5H, s, $C(CH_3)_2$], 1.61 [1H, s, $C(CH_3)_2$], 1.54 [2H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 171.6, 170.5, 150.1, 135.2, 133.5, 131.6, 128.6, 123.0, 122.3, 121.8, 120.2, 118.9, 118.7, 117.7, 116.8, 106.8, 106.3, 86.4, 83.6, 61.0, 58.7, 55.0, 52.2, 44.1, 42.4, 40.1, 39.7, 36.3, 34.7, 25.9, 25.8, 25.6, 22.5, 21.4, 18.2, 18.0, 17.9; acc. mass: 396.24154, $C_{24}H_{32}N_2O_3$ requires 396.24128.

4.4.7. Hydrolysis of the ester mixture 16b and 17b. A mixture of **16b** and **17b** (4.46 g, 11.3 mmol) in MeOH (100 ml) and aq NaOH (5%, 11 ml) was refluxed (20 h). The solvent was removed under reduced pressure and water added to the resultant residue and extracted with EtOAc to remove non-acidic substances. Acidification of the alkaline solution with aq HCl (1 M) to pH 1 gave the mixture of acids **18a** and **18b** (3.60 g, 84%) which was used as such for the following reaction.

4.4.8. Synthesis and isolation of Barton esters 19a and 19b. The above mixture (1.10 g, 2.88 mmol) in dry CH_2Cl_2 (35 ml), protected from light and under Ar, was treated at 0 °C with 1,1′-dioxide-2,2′-dithiodipyridine (1.00 g, 3.96 mmol) and *n*-Bu_3P (freshly distilled, 1 ml, 4.01 mmol). On completion of the reaction (1 h, TLC

control) CH_2Cl_2 (15 ml) was added and the resulting solution washed twice with ice cold aq NaOH (1 M) and then water. Evaporation of solvent under reduced pressure furnished a yellow oil which was purified by column chromatography (protected from light by aluminium foil, Et_2O) to give pure **19a** (336 mg, 25%); mp (Et_2O): 28–30 °C; $[\alpha]_D^{25}$ −185.1 (*c* 0.50, CH_2Cl_2); IR (film): ν_{max}/cm^{-1} 1810 [C(O)ON], 1648s (amide C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.79 (1H, d, *J* 6.7 Hz, Ar-H), 7.66 (1H, d, *J* 8.9 Hz, Ar-H), 7.23–7.08 (3H, m, Ar-H), 6.82 (1H, t, *J* 7.4 Hz, Ar-H), 6.62 (1H, dt, *J* 6.8, 1.2 Hz, Ar-H), 6.56 (1H, d, *J* 7.8 Hz, Ar-H), 5.28 (1H, s, NCHN), 5.16 [1H, br s, NCH_2CH=$C(CH_3)_2$], 5.06 [1H, t, *J* 7.0 Hz, CCH_2CH=$C(CH_3)_2$], 4.46 (1H, t, *J* 7.9 Hz, $CHCO_2N$), 3.92 [2H, ddd, *J* 16.7, 7.1, 3.6 Hz, NCH_2CH=$C(CH_3)_2$], 2.80 (1H, dd, *J* 13.3, 7.6 Hz, CH_2CHCO_2N), 2.67 [1H, dd, *J* 15.1, 9.5 Hz, CCH_2CH=$C(CH_3)_2$], 2.61 (1H, dd, *J* 13.5, 8.6 Hz, CH_2CHCO_2N), 2.45 [1H, dd, *J* 14.6, 5.4 Hz, CCH_2CH=$C(CH_3)_2$], 2.33 (3H, s, $NCOCH_3$), 1.71 [3H, s, $C(CH_3)_2$], 1.70 [3H, s, $C(CH_3)_2$], 1.69 [3H, s, $C(CH_3)_2$], 1.56 [3H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 170.7, 149.4, 138.3, 137.2, 136.0, 135.4, 133.8, 133.5, 128.7, 122.8, 120.4, 119.9, 119.4, 112.7, 109.9, 86.8, 58.0, 57.6, 46.2, 39.3, 34.7, 25.7, 25.5, 21.8, 18.0, 17.9, and **19b**, (671 mg, 49%) as a yellow solid; mp (Et_2O): 30–32 °C; $[\alpha]_D^{25}$ +248.2 (*c* 0.83, CH_2Cl_2); IR (film): ν_{max}/cm^{-1} 1801 [C(O)ON], 1660s (amide C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.55 (1H, d, *J* 8.8 Hz, Ar-H), 7.13–7.07 (2H, m, Ar-H), 7.04 (1H, d, *J* 7.1 Hz, Ar-H), 6.64 (1H, t, *J* 7.3 Hz, Ar-H), 6.42–6.36 (2H, m, Ar-H), 6.31 (1H, br s, Ar-H), 5.62 (1H, s, NCHN), 5.20 [1H, br s, NCH_2CH=$C(CH_3)_2$], 5.09 [1H, br s, CCH_2CH=$C(CH_3)_2$], 4.99 (1H, d, *J* 8.2 Hz, $CHCO_2N$), 4.31 [1H, dd, *J* 16.0, 7.1 Hz, NCH_2CH=$C(CH_3)_2$], 4.02 [1H, dd, *J* 16.0, 5.1 Hz, NCH_2CH=$C(CH_3)_2$], 2.84 (1H, d, *J* 13.0 Hz, CH_2CHCO_2N), 2.54 (1H, dd, *J* 13.1, 8.5 Hz, CH_2CHCO_2N), 2.43–2.37 [2H, m, CCH_2CH=$C(CH_3)_2$], 2.36 (3H, s, $NCOCH_3$), 1.75 [3H, s, $C(CH_3)_2$], 1.71 [3H, s, $C(CH_3)_2$], 1.65 [3H, s, $C(CH_3)_2$], 1.54 [3H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 171.2, 150.6, 137.8, 136.9, 135.9, 134.1, 133.6, 131.2, 129.0, 124.0, 121.2, 118.2, 116.8, 112.4, 106.3, 83.2, 60.3, 55.7, 43.9, 39.4, 36.8, 25.9, 25.7, 23.1, 18.0, 17.9.

4.4.9. Decarboxylation of Barton ester 19b to 20. Barton ester **19b** (200 mg, 0.52 mmol) in CH_2Cl_2 (10 ml) on UV irradiation (HP, 125 W) for 30 min in the presence of excess of *t*-BuSH (0.6 ml, 5.32 mmol) furnished on purification (PTLC; Et_2O/*n*-hexane, 25%) compound **20** (124.7 mg, 71%) as a yellow oil; $[\alpha]_D^{25}$ +237.9 (*c* 0.63, CH_2Cl_2); IR (film): ν_{max}/cm^{-1} 1643s (amide C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.11–7.05 (1H, m, Ar-H), 7.03 (1/4H, d, *J* 7.7 Hz, Ar-H), 6.98 (3/4H, d, *J* 7.1 Hz, Ar-H), 6.69 (1/4H, t, *J* 7.3 Hz, Ar-H), 6.64 (3/4H, t, *J* 7.2 Hz), 6.38 (1H, d, *J* 7.7 Hz), 5.54 (3/4H, s, NCHN), 5.23 (1/4H, s, NCHN), 5.15 [1H, br s, NCH_2CH=$C(CH_3)_2$], 5.05 [1H, t, *J* 7.2 Hz, CCH_2CH=$C(CH_3)_2$], 4.22 [1H, dd, *J* 15.6, 7.0 Hz, NCH_2CH=$C(CH_3)_2$], 3.99 [1H, dd, *J* 15.7, 4.4 Hz, NCH_2CH=$C(CH_3)_2$], 3.61–3.57 (1H, m, NCH_2CH_2), 3.25 (1H, dd, *J* 17.0, 10.3 Hz, NCH_2CH_2), 2.45 [1/2H, d, *J* 6.9 Hz, CCH_2CH=$C(CH_3)_2$], 2.37 [3/2H, d, *J* 6.8 Hz, CCH_2CH=$C(CH_3)_2$], 2.09–2.07 (2H, m, NCH_2CH_2), 2.05 (3H, s, $NCOCH_3$), 1.76 [3H, s, $C(CH_3)_2$], 1.67 [6H, s, $C(CH_3)_2$], 1.54 [3H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 169.7, 150.4, 134.8, 134.1, 133.1, 128.3, 122.7, 121.2, 120.4, 117.8, 117.1, 106.6, 106.4, 85.1, 82.6, 55.7, 46.9, 44.5, 37.1, 25.9, 25.8, 22.9, 18.0, 17.8; acc. mass: 382.23162, $C_{22}H_{30}N_2O$ requires 382.23580.

4.4.10. *N*-Acetylcarbinolamine 21a from Barton ester 19a and $Sb(SPh)_3$. Compound **19a** (130 mg, 0.265 mmol) in Et_2O (25 ml) was treated with $Sb(SPh)_3$ (304.0 mg, 0.677 mmol) in ice–salt bath (−18 °C) with vigorous stirring (1/2 h). The yellow solid (Sb_2O_3) that formed was filtered and the filtrate taken to dryness under reduced pressure. The resulting residue was purified by PTLC (Et_2O) to furnish **21a** (60.2 mg, 64%); $[\alpha]_D^{26}$ −174.8 (*c* 0.85, CH_2Cl_2); IR (film): ν_{max}/cm^{-1} 3320 (O–H), 1661s (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.12 (1H, t, *J* 7.5 Hz, Ar-H), 7.06 (1H, d, *J* 7.2 Hz, Ar-H), 6.70 (1H, t, *J* 7.3 Hz, Ar-H), 6.47 (1H, d, *J* 7.8 Hz, Ar-H), 5.47 (1H, s, NCHN), 5.36 (1H, br s, C*H*OH), 5.19 [1H, br s, NCH_2CH=$C(CH_3)_2$], 5.01 [1H, t, *J* 6.7 Hz, CCH_2CH=$C(CH_3)_2$], 4.28 [1H, dd, *J* 16.0, 7.3 Hz, NCH_2CH=$C(CH_3)_2$], 4.04 [1H, dd, *J* 16.1, 5.1 Hz, NCH_2CH=$C(CH_3)_2$], 2.33–2.28 [4H, m, 2H of CCH_2CH=$C(CH_3)_2$ and 2H of CH_2CHOH], 2.19 (3H, s, $NCOCH_3$), 1.77 [3H, s, $C(CH_3)_2$], 1.68 [6H, s, $C(CH_3)_2$], 1.53 [3H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 170.9, 148.5, 135.3, 134.3, 133.6, 128.9, 122.9, 121.2, 118.6, 117.9, 108.0, 83.8, 83.3, 54.1, 45.1, 45.0, 37.1, 26.0, 25.8, 22.4, 18.2, 18.1; acc. mass: 354.23170, $C_{22}H_{28}N_2O$ requires 354.23071.

4.4.11. *N*-Acetylcarbinolamine 21b from Barton ester 19b and $Sb(SPh)_3$. Compound **19b** similarly furnished **21b** (36.4 mg, 74%); $[\alpha]_D^{26}$ +176.0 (*c* 0.48, CH_2Cl_2); IR (film): ν_{max}/cm^{-1} 3318 (O–H), 1660s (C=O), 1634s; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.12 (1H, t, *J* 7.5 Hz, Ar-H), 7.06 (1H, d, *J* 7.2 Hz, Ar-H), 6.70 (1H, t, *J* 7.3 Hz, Ar-H), 6.47 (1H, d, *J* 7.8 Hz, Ar-H), 5.47 (1H, s, NCHN), 5.36 (1H, br s, C*H*OH), 5.19 [1H, br s, NCH_2CH=$C(CH_3)_2$], 5.01 [1H, t, *J* 6.7 Hz, CCH_2CH=$C(CH_3)_2$], 4.28 [1H, dd, *J* 16.0, 7.3 Hz, NCH_2CH=$C(CH_3)_2$], 4.04 [1H, dd, *J* 16.1, 5.1 Hz, NCH_2CH=$C(CH_3)_2$], 2.33–2.28 [4H, m, 2H of CCH_2CH=$C(CH_3)_2$ and 2H of CH_2CHOH], 2.19 (3H, s, $NCOCH_3$), 1.77 [3H, s, $C(CH_3)_2$], 1.68 [6H, s, $C(CH_3)_2$], 1.53 [3H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 170.9, 148.5, 135.3, 134.3, 133.6, 128.9, 122.9, 121.2, 118.6, 117.9, 108.0, 83.8, 83.3, 54.1, 45.1, 45.0, 37.1, 26.0, 25.8, 22.4, 18.2, 18.1; acc. mass: 354.23170, $C_{22}H_{28}N_2O$ requires 354.23071.

4.4.12. Enamide 28b. Compound **21b** (60 mg, 0.17 mmol) in xylene (3 ml) was heated under reflux (10 h). The solvent was evaporated and the residue obtained was purified by PTLC (Et_2O/*n*-hexane 20%) to give **28b** (42.6 mg, 75%) as a colourless oil; $[\alpha]_D^{25}$ +223.0 (*c* 0.83, CH_2Cl_2); IR (film): ν_{max}/cm^{-1} 3049 (O–H), 1662s (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.07 (1H, t, *J* 7.5 Hz, Ar-H), 7.01 (1H, d, *J* 7.2 Hz, Ar-H), 6.68 (1H, t, *J* 7.3 Hz, Ar-H), 6.48 (1H, d, *J* 7.9 Hz, Ar-H), 6.46 (1H, d, *J* 4.3 Hz, NC*H*=CH), 5.75 (1H, s, NCHN), 5.20 (1H, d, *J* 4.3 Hz, NCH=C*H*), 5.13 [1H, br s, NCH_2CH=$C(CH_3)_2$], 4.96 [1H, t, *J* 6.7 Hz, CCH_2CH=$C(CH_3)_2$], 4.34 [1H, dd, *J* 15.9, 8.1 Hz, NCH_2CH=$C(CH_3)_2$], 4.04 [1H, dd, *J* 15.9, 3.7 Hz, NCH_2CH=$C(CH_3)_2$], 2.50 [1H, dd, *J* 14.9, 7.5 Hz, CCH_2CH=$C(CH_3)_2$], 2.44 [1H, dd, *J* 15.0, 7.6 Hz, CCH_2CH=$C(CH_3)_2$], 2.15 (3H, s, $NCOCH_3$), 1.79 [3H, s, $C(CH_3)_2$], 1.68 [3H, s, $C(CH_3)_2$], 1.66 [3H, s, $C(CH_3)_2$], 1.59 [3H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 168.0, 150.3, 135.1,

135.0, 132.3, 128.3, 128.0, 122.5, 120.3, 118.5, 118.1, 117.5, 108.3, 84.2, 60.4, 45.8, 36.0, 25.9, 25.8, 22.3, 18.1; acc. mass: 336.22004, $C_{22}H_{28}N_2O$ requires 336.22015.

4.4.13. Enamide 28a. Compound **28a** (117.0 mg, 72%) was similarly obtained from **21a** (180 mg, 0.50 mmol, 12 h reflux); $[\alpha]_D^{27}$ −227.7 (*c* 0.43, CH_2Cl_2), identical in all other aspects with **28b**.

4.4.14. (+)-(3a*R*,8a*R*)-3a,8-Bis-(3′-methyl-2′-butenyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole (29b). Compound **28b** (250 mg, 0.089 mmol) in a solution of sodium methoxide in methanol (5 M, 21 ml, 12.7 mmol) containing hydrazine hydrate (370 μl, 104 mmol) was heated under reflux (3 h). The mixture was concentrated under reduced pressure and diluted with water. Usual work-up furnished a residue which was purified by PTLC (Et_2O/*n*-hexane 20%) to give **29b** (119 mg, 63%) as a yellow oil; $[\alpha]_D^{27}$ +89.6 (*c* 2.07, CH_2Cl_2); IR (film): ν_{max}/cm^{-1} 1605 (C=N); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.61 (1H, s, CH=N), 7.06 (1H, t, *J* 7.6 Hz, Ar-H), 7.00 (1H, d, *J* 7.1 Hz, Ar-H), 6.62 (1H, t, *J* 7.3 Hz, Ar-H), 6.40 (1H, d, *J* 7.8 Hz, Ar-H), 5.36 [1H, br s, $NCH_2CH{=}C(CH_3)_2$], 5.31 (1H, s, NCHN), 5.07 [1H, br s, $CCH_2CH{=}C(CH_3)_2$], 4.03 [2H, ddd, *J* 15.3, 7.0, 5.3 Hz, $NCH_2CH{=}C(CH_3)_2$], 2.86 (2H, s, $CH_2CH{=}N$), 2.46–2.36 [2H, m, $CCH_2CH{=}C(CH_3)_2$], 1.77 [3H, s, $C(CH_3)_2$], 1.75 [3H, s, $C(CH_3)_2$], 1.69 [3H, s, $C(CH_3)_2$], 1.55 [3H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 167.6, 149.1, 134.9, 134.8, 128.4, 123.5, 121.3, 119.7, 117.1, 106.5, 99.0, 52.2, 49.6, 43.4, 35.9, 25.8, 25.6, 17.9; acc. mass: 294.20992, $C_{20}H_{26}N_2$ requires 294.20959.

4.4.15. (−)-(3a*S*,8a*S*)-3a,8-Bis-(3′-methyl-2′-butenyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole (29a). Compound **29a** was similarly obtained from **28a** in 54% yield (140 mg) as a yellow oil; $[\alpha]_D^{26}$ −88.0 (*c* 0.25, CH_2Cl_2), identical in all other aspects with **29b**.

4.4.16. (−)-*N*^{1}-*nor*-Debromoflustramine B (30a). Compound **29a** in dry Et_2O (1 ml) was stirred with LAH (2 mg, 0.05 mmol) at rt (1.5 h). Aq NaOH (0.1 M, 2 ml) was then added followed by EtOAc. Usual work-up gave *(−)-(3aS,8aR)-3a,8-bis-(3′-methyl-2′-butenyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (**30a**)* (9.2 mg, 70%) as a colourless oil; $[\alpha]_D^{25}$ −95.0 (*c* 0.25, CH_2Cl_2); IR (film): ν_{max}/cm^{-1} 3357 (N–H); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.03 (1H, t, *J* 7.7 Hz, Ar-H), 6.99 (1H, d, *J* 7.2 Hz, Ar-H), 6.60 (1H, t, *J* 7.4 Hz, Ar-H), 6.32 (1H, d, *J* 7.8 Hz, Ar-H), 5.21 [1H, br s, $NCH_2CH{=}C(CH_3)_2$], 5.06 [1H, br s, $CCH_2CH{=}C(CH_3)_2$], 4.63 (1H, s, NCHN), 3.82 [2H, d, *J* 5.9 Hz, $NCH_2CH{=}C(CH_3)_2$], 3.01–2.98 (1H, m, NCH_2CH_2), 2.75–2.69 (1H, m, NCH_2CH_2), 2.43 [2H, d, *J* 7.0 Hz, $CCH_2CH{=}C(CH_3)_2$], 1.98–1.86 (3H, m, 1H of NH, exchangeable with D_2O and 2H of NCH_2CH_2), 1.73 [3H, s, $C(CH_3)_2$], 1.72 [3H, s, $C(CH_3)_2$], 1.67 [3H, s, $C(CH_3)_2$], 1.58 [3H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 151.2, 134.9, 134.8, 133.9, 127.8, 123.2, 121.2, 120.6, 116.7, 105.3, 87.0, 56.4, 45.5, 43.0, 40.8, 37.6, 25.8, 25.6, 18.0, 17.8.

4.4.17. (+)-*ent*-*N*^{1}-*nor*-Debromoflustramine B (30b) from 29b. Compound **29b** (14 mg, 0.042 mmol) in dry Et_2O (1 ml) was stirred with LAH (2 mg, 0.05 mmol) at rt (1.5 h). Aq NaOH (0.1 M, 2 ml) was then added followed by EtOAc. Usual work-up gave **30b** (11.2 mg, 79%) as a colourless oil; $[\alpha]_D^{25}$ +94.3 (*c* 0.30, CH_2Cl_2); identical in all other aspects with **30a**.

4.4.18. (+)-*ent*-*N*^{1}-*nor*-Debromoflustramine B (30b) from alcohol 21b. Compound **21b** (18.0 mg, 0.051 mmol) in a mixture of dry methanol (2 ml) and 3.0 ml (6.10 mmol) solution of NaOMe/methanol (2.0 M) was treated with hydrazine hydrate (25.0 μl, 0.514 mmol). The resulting solution was stirred at rt (24 h) after which time water was added and the product worked up (EtOAc) in the usual manner. The *sec*-amine thus secured was purified by PTLC (Et_2O) to give **30b** (5.9 mg, 39%) identical with that obtained by LAH reduction as described above.

4.4.19. (+)-*ent*-Debromoflustramine B (*ent*-1e). Compound **30b** (11 mg, 0.037 mmol) in dry THF (1 ml) was stirred in the presence of NaH (1.7 mg, 0.057 mmol) for 0.5 h in an ice–salt bath. MeI (3.0 μl, 0.048 mmol) was added and the mixture stirred at rt (2.5 h). Usual work-up afforded a residue which was purified by PTLC (Et_2O) to give the starting material (6.1 mg, 56%) and (+)-*ent*-debromoflustramine B (*ent*-**1e**) (2.6 mg, 23%) as a colourless oil; $[\alpha]_D^{25}$ +96.4 (*c* 0.06, CH_2Cl_2); IR (film): ν_{max}/cm^{-1} 1488 (C=C); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.04 (1H, t, *J* 7.3 Hz, Ar-H), 6.97 (1H, d, *J* 7.2 Hz, Ar-H), 6.66 (1H, t, *J* 7.3 Hz, Ar-H), 6.42 (1H, d, *J* 7.8 Hz, Ar-H), 5.17 [1H, br s, $NCH_2CH{=}C(CH_3)_2$], 4.97 [1H, br s, $CCH_2CH{=}C(CH_3)_2$], 4.29 (1H, s, NCHN), 3.93 [1H, dd, *J* 16.0, 5.5 Hz, $NCH_2CH{=}C(CH_3)_2$], 3.80 [1H, dd, *J* 16.1, 7.0 Hz, $NCH_2CH{=}C(CH_3)_2$], 2.72–2.69 (1H, m, NCH_2CH_2), 2.56 (1H, ddd, *J* 12.2, 9.3, 6.0 Hz, NCH_2CH_2), 2.49 (3H, s, NCH_3), 2.42 [2H, d, *J* 7.1 Hz, $CCH_2CH{=}C(CH_3)_2$], 2.10–2.02 (1H, m, NCH_2CH_2), 1.92 (1H, ddd, *J* 11.7, 5.6, 3.2 Hz, NCH_2CH_2), 1.71 [3H, s, $C(CH_3)_2$], 1.70 [3H, s, $C(CH_3)_2$], 1.65 [3H, s, $C(CH_3)_2$], 1.58 [3H, s, $C(CH_3)_2$]; ^{13}C NMR: δ_C 152.0, 135.8, 134.3, 133.7, 127.7, 122.9, 121.5, 120.9, 117.6, 107.4, 91.4, 57.0, 46.8, 38.8, 38.3, 25.8, 25.6, 18.0, 17.9.

4.4.20. (−)-Debromoflustramine B (1e). From **30a** (12.0 mg, 0.041 mmol) and MeI (12.0 mg, 0.041 mmol) in dry THF (1 ml) were obtained the starting material (7.2 mg) and (**1e**) (2.3 mg, 18.3%, based on recovered starting material); $[\alpha]_D^{25}$ −97.5 (*c* 0.06, $CHCl_3$) [lit.[1e] $[\alpha]_D^{20}$ −98.2 (*c* 0.02, $CHCl_3$)], identical in all other aspects with *ent*-**1e**.

4.4.21. 1,3-Bis(3′-methyl-2′-butenyl)-1*H*-indole (32) and (+)-*ent*-*N*^{1}-*nor*-debromoflustramide B (33). To compound **19b** (45.0 mg, 0.092 mmol) in dry THF (10 ml) was added *t*-BuOK (32.2 mg, 0.273 mmol) and the mixture stirred at rt (1–2 h). It was then evaporated to dryness under reduced pressure, the resulting residue dissolved in EtOAc, washed once with water and the products worked up as usual to furnish a mixture of compounds. Purification (PTLC, Et_2O) afforded 1*H*-pyridine-2-thione (**31**), **32** and the amide **33**. Acidification of the aqueous extract with HCl (0.1 M) yielded (2*R*/*S*)-**18b** (31.4 mg, 34%). *Data for compound **32***: yellow oil (13.9 mg, 30%); IR (film): ν_{max}/cm^{-1} 1466 (C=C); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.56 (1H, d, *J* 7.8 Hz, Ar-H), 7.27 (1H, d, *J* 7.8 Hz, Ar-H), 7.18 (1H, t, *J* 7.4 Hz, Ar-H), 7.07 (1H, t, *J* 7.2 Hz, Ar-H), 6.84 (1H, s, NCH=C), 5.41 [1H, br s, $NCH_2CH{=}C(CH_3)_2$], 5.36 [1H,

br s, $CCH_2CH{=}C(CH_3)_2$], 4.63 [2H, d, *J* 6.6 Hz, $NCH_2CH{=}C(CH_3)_2$], 3.44 [2H, d, *J* 6.8 Hz, $CCH_2CH{=}C(CH_3)_2$], 1.81 [3H, s, $C(CH_3)_2$], 1.77 [3H, s, $C(CH_3)_2$], 1.74 [6H, s, $C(CH_3)_2$]; acc. mass: 253.18216, $C_{18}H_{23}N$ requires 253.18305, and for *(+)-ent-N*^{1}*-nor-debromoflustramide B* (***33***): colourless oil (5.2 mg, 15%); $[\alpha]_D^{25}$ +36.1 (*c* 0.04, EtOH); IR (film): ν_{max}/cm^{-1} 3422s (N–H), 1702s (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.14–7.11 (1H, m, Ar-H), 7.03 (1H, d, *J* 7.4 Hz, Ar-H), 6.73 (1H, t, *J* 7.4 Hz, Ar-H), 6.47 (1H, d, *J* 7.8 Hz, Ar-H), 5.97 (1H, br s, NH, exchangeable with D_2O), 5.35 [1H, br s, $NCH_2CH{=}C(CH_3)_2$], 5.08 [1H, br s, $CCH_2CH{=}C(CH_3)_2$], 4.92 (1H, s, NCHN), 3.85–3.71 [1H, m, $NCH_2CH{=}C(CH_3)_2$], 3.61–3.57 [1H, m, $NCH_2CH{=}C(CH_3)_2$], 2.62 (2H, d, *J* 2.6 Hz, $COCH_2$), 2.40 [2H, t, *J* 8.5 Hz, $CCH_2CH{=}C(CH_3)_2$], 1.77 [3H, s, $C(CH_3)_2$], 1.74 [3H, s, $C(CH_3CH_3)_2$], 1.71 [3H, s, $C(CH_3)_2$], 1.54 [3H, s, $C(CH_3)_2$]; acc. mass: 310.20437, $C_{20}H_{26}N_2O$ requires 310.20450.

4.4.22. (+)-*ent*-Debromoflustramide B (*ent*-1g). Methylation of **33** (14 mg, 0.044 mmol) in dry DMF (1.5 ml) with MeI (8.5 μl, 0.13 mmol, freshly distilled) at 0 °C in the presence of NaH (2.1 mg, 0.053 mmol) was complete in 1 h (TLC control, Et_2O). The product, worked up as described for **1e**, provided the title compound *ent*-**1g** (13 mg, 90%) in a virtually pure state. Traces of impurities were removed by PTLC (Et_2O) furnishing *ent*-**1g** with $[\alpha]_D^{25}$ +35 (*c* 0.04, CH_2Cl_2).

Acknowledgements

We thank the Foundation for Science and Technology for partial financial support and for fellowships (to A.S.P.C. and N.S.). It is a pleasure to record our gratitude to Ms. Luz Fernandes and Ms. Carla Rodrigues of REQUIMTE Analytical Services Laboratories for mass spectra and elemental analyses, respectively.

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22. Interestingly exposure of **21b** to a solution of NaOMe/MeOH (2 M, 6.10 mmol) containing hydrazine (0.51 mmol) for a day, at rt, also gave **30b** in a comparable yield (39%).
23. Dipolar solvents such as DMF are known to favour solvent separated ion pairs. Thus the C^3 carbanion, generated from **2** and NaH, becomes susceptible to attack from both sides, the CO_2Me group offering little, if any, steric hindrance to the approaching electrophile. Under phase-transfer conditions involving CH_2Cl_2 as the solvent, the ion pair is likely to have more covalent character. If some electrostatic attraction between the bulky cation and the ester group is invoked (Fig. 3), then the β-face becomes more shielded and diastereoselection during alkylation becomes possible. Such an attraction, among other factors, is believed to be important in explaining the origin of the enantioselectivity in the alkylation of prochiral ketones catalysed by chiral quaternary salts of Cinchona alkaloids. For the mechanism of chiral induction, see: *Chiral Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, NY, 2000; pp 585, 736.
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