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A formal synthesis of (±)-physostigmine via 3,3-rearrangement of a bis-enamine☆

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Abstract—A new flexible approach to hexahydropyrrolo[2,3-*b*]indole system via the [3,3]-sigmatropic rearrangement of 1-(2′-methoxycarbonyl-*N*-methylvinylamino)skatole, culminating in the synthesis of (±)-desoxyeseroline, is described.

1. Introduction

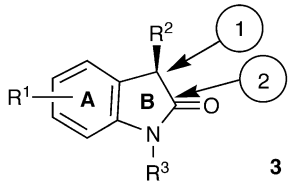
(−)-Physostigmine (**1a**) (Fig. 1), the major alkaloid of *Physostigma venenosum* (Balf.) seeds (Calabar beans)[2] is a member of a class of natural products incorporating the hexahydropyrrolo[2,3-*b*]indole nucleus. Some representative natural products, excluding those containing a diketopiperazine ring,[3] are (−)-debromoflustramine B (**2a**),[4] (−)-flustramine A (**2b**)[5] and (−)-pseudophrynaminol (**2c**).[6] (−)-Physostigmine shows wide biological activity[7] and the finding that suitably altering its carbamate side chain, for example, **1d**, afforded a derivative of much improved pharmacological profile in the fight against Alzheimer disease[8] has stimulated, during the last decade, studies aimed at constructing the skeleton of the alkaloid by expeditious and novel routes.

Amongst many syntheses[9] of alkaloid **1a** and related substances reported to date, a number of them involve an appropriate 1,3-dimethyloxindole (**3**, $R^2=R^3=Me$) playing a central role[10] (Scheme 1).

Introduction of the aminoethyl side chain or its synthetic equivalent with chiral induction,[9a–n] or otherwise,[9o–w] achieved in a variety of interesting ways, still necessitated a number of trivial, but nonetheless, obligatory functional group transformations to construct ring C.

During our studies on pericyclic reactions over a period of years, we have reported their applications to the synthesis of a variety of heterocycles.[11] It was shown that the rearranging system **5** (Scheme 2), generated from an aromatic hydroxamic acid derivative **4** containing a SPh functionality acting as an anion stabilising group,[12] underwent smooth rearrangement to the substituted *o*-aminophenylacetic acid derivative **6**, which was subsequently elaborated, via **7**, to **1c**.[9u]

It was anticipated that the aminoethyl side chain equivalent could be directly introduced by a similar sigmatropic process involving cleavage of the N–N bond of an



3

1 *chiral or non-chiral introduction of* **C—C—NR⁴** *or equivalent*

2 *cyclisation to ring* **C**

Scheme 1.

☆ Part of this work has been published as a communication, see Ref. 1.

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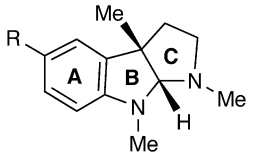


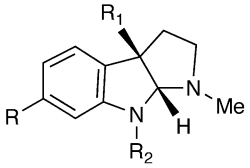
1

a: R = OCONHMe; (-)-physostigmine

b: R = OH; (-)-eseroline

c: R = H; (-)-desoxyeseroline

d: R = OCONHPh; (-)-phenserine



2

a: R = H; $R^1 = R^2 = CH_2CH{=}CMe_2$; (-)-debromoflustramine B

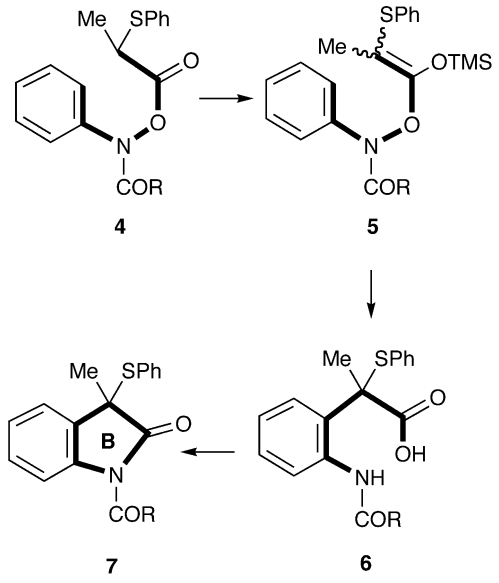
b: R = Br; $R^1 = R^2 = CH_2CH{=}CMe_2$; (-)-flustramine A

c: R = H ; $R^1 = CH_2CH{=}C(Me)CH_2OH$; R^2 = H; (-)-pseudophrynaminol

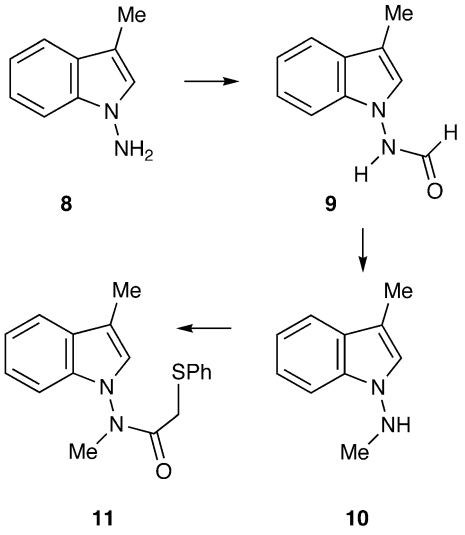
Figure 1. Molecules related to physostigmine, containing the hexahydropyrrolo[2,3-*b*]indole nucleus.

appropriate indole derivative. It was further expected that, should such a reaction occur, the appositely generated electrophilic and nucleophilic centres would cyclise[13] to install rings B and C in cis fusion in one step.[14]

The requisite starting material for the contemplated synthesis, the phenylthioacetamide **11** (Scheme 3) was secured by *N*-amination of skatole[15] followed by conversion



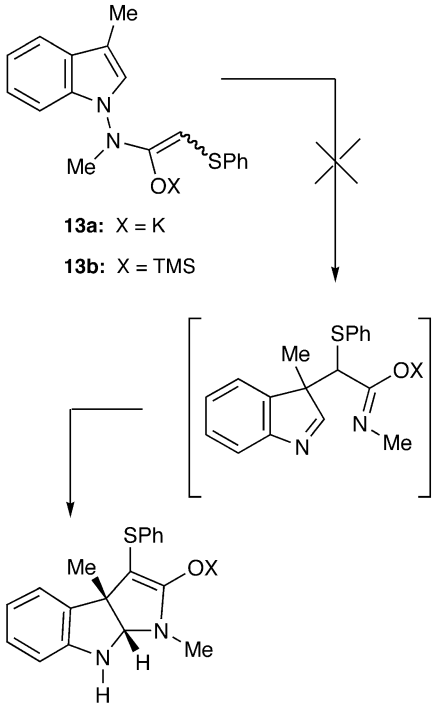
Scheme 2.



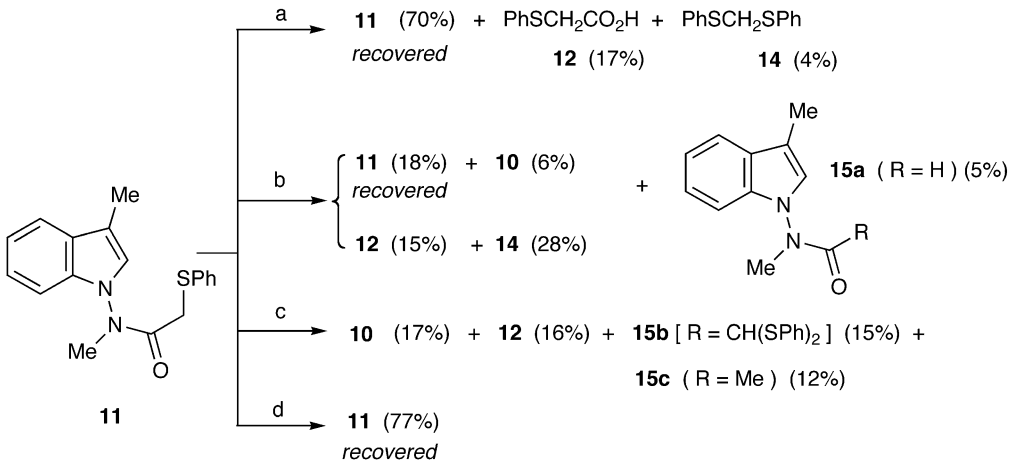
Scheme 3.

of the resulting hydrazine **8** (40% yield), into the formamide **9**[16] with formic acid under reflux. Its ^{1}H NMR spectrum disclosed the presence of two rotamers (1:2) with the major isomer attributed the trans structure on the basis of the coupling constant (J = 10.4 Hz) of the formamide protons NH–C(O)H. LAH reduction of formamide **9** yielded **10**,[16] which on reaction with 2-(phenylsulfanyl)acetic acid (**12**) in the presence of DCC and 4-DMAP, provided **11** in 70% yield.

However, all efforts to induce the desired rearrangement of the derived enolate **13a** (Scheme 4) or the corresponding silyl ether **13b** generated in situ, under a variety of conditions, only met with failure; either the starting material



Scheme 4.



Scheme 5. Reagents and conditions: (a) KHMDS (1.1 equiv), THF, −80 °C to rt, 1 h, rt, 2 h, 45 °C, 2 h, reflux, 50 h; (b) KH (1.1 equiv), THF, −80 °C to rt, 2 h, reflux 30 h; (c) KHMDS (1.1 equiv), $(MeOCH_2CH_2)_2O$, 120–130 °C, 3 h (d) KHMDS (1.1 equiv), TMSCl (2.0 equiv), $(MeOCH_2CH_2)_2O$, −80 °C to rt, 1 h, 120–130 °C, 32 h, reflux, 27 h.

was largely returned or a complex mixture of products obtained.

Scheme 5 summarises the results obtained under different experimental conditions and indicates that radical processes are most probably involved in the formation of some of the products, especially **14** and those of type **15**.

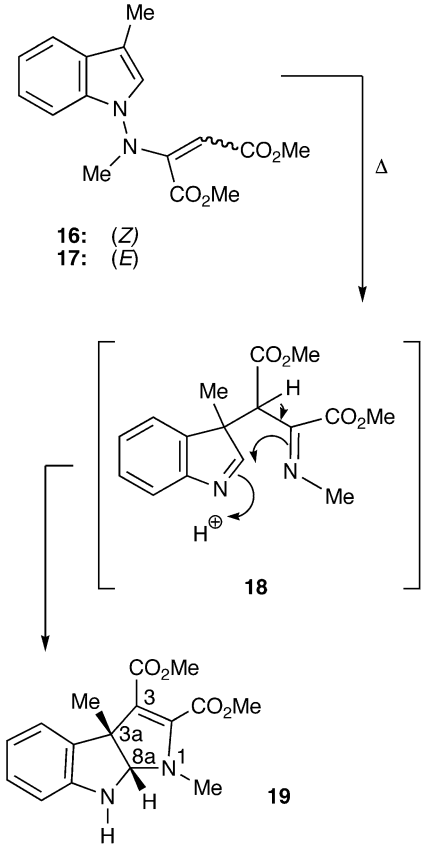
It was thought that the failure of **11** to undergo a 3,3-shift could be overcome if the relatively weak N–N bond is further weakened by incorporation of an EWG at the terminal position in the pendant *N*-vinyl group. In the event this minor structural modification led to a successful synthesis of (±)-desoxyeseroline (**1c**), which we had earlier reported in a preliminary communication.[1] Full details of the work are described herein.

Dimethyl acetylenedicarboxylate was initially chosen for the study. Addition of **10** to the diester in methanol at rt, cleanly provided in a near quantitative yield a mixture of **16** (*Z*-isomer, 32%) and **17** (*E*-isomer, 63%) (Scheme 6).

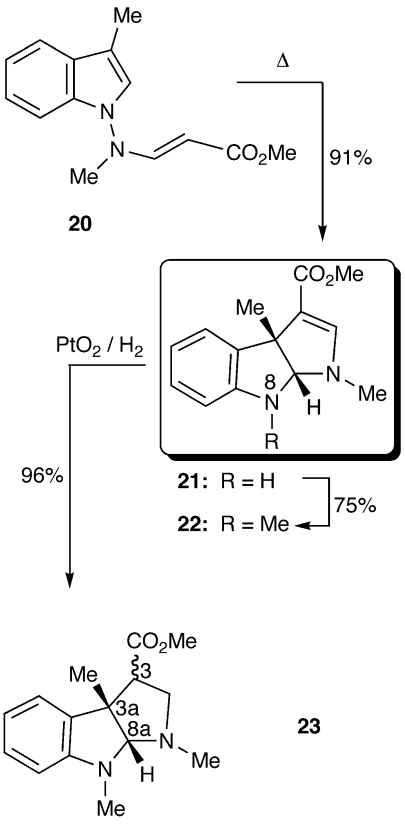
Their olefinic hydrogens resonated at δ 5.48 and 4.73, respectively. The attribution of the *E*-geometry for the isomer with lower δ value was based on the comparison of its chemical shift with that of similar olefinic hydrogen δ (4.60) in the ^{1}H NMR spectra of dimethyl 2-(methylamino) maleate.[17] The olefinic mixture on thermolysis in diphenyl ether at 180–200 °C (ca. 8 h) afforded, probably via **18**, the tricyclic compound **19** (45%) as a yellow oil. Its molecular formula as determined by accurate mass measurement and IR spectrum were fully consistent with the proposed structure. More importantly, the resonance signals (^{1}H NMR) at δ 1.67 (C_{3a}–CH_3) and δ 5.12 (C_{8a}–*H*) uniquely defined its structure.

A similar addition to methyl propiolate, a less reactive Michael acceptor, required a higher temperature and extended reaction time (MeOH, reflux, 14 h) to give the enaminoester **20**. Thermolysis of finely ground **20** in diphenyl ether at 210–220 °C (3 h) furnished the tricycle **21** in 51% yield (Scheme 7). Significant improvement in yield (91%) was achieved when the rearrangement was carried out in *o*-dichlorobenzene under reflux (35 h).

As in **19**, the C_{8a}–*H* in **21** resonated at δ 5.05 as a singlet indicating that ring C of hexahydropyrrolo[2,3-*b*]indole ring system had been established in one step. Although in principle the synthesis of DL-desoxyeseroline (**1c**) from the tricycle **21** involved four simple steps, namely N^8-methylation, saturation of the double bond and removal of the ester functionality, in actual practice the last step in this sequence could not be realised. Thus, the *N*-methyl



Scheme 6.



Scheme 7.

compound **22** secured in 75% yield (NaH, DMF, 15-crown-5, THF, MeI, 92%), on reduction (PtO_2–H_2; rt) furnished the corresponding dihydro compound **23** of undetermined stereochemistry in high yield.

Although the Na salt of the acid was readily formed by base hydrolysis of the ester **23**, the corresponding Barton ester could not be obtained in any synthetically meaningful yield via the activated carboxylic acid derivatives with the usual coupling agents, such as isobutylchloroformate[18] or $(EtO)_2$-P(O)CN[19] and the anion of *N*-hyroxypyridine-2-thione.

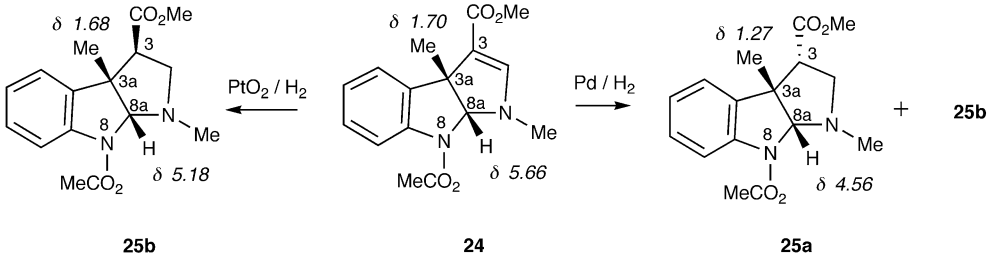
On the assumption that the nucleophilicity of N^8 could be responsible for the observed failure, **21** was first converted into its methylcarbamate derivative **24** (81%) (Scheme 8). Whilst saturation of the double bond of **24** with Pt°–H_2 provided **25b** (β-ester: C_{3a}–CH_3, δ 1.68; C_{8a}–*H*, δ 5.18) as the exclusive product (98%), the use of Pd produced a diastereomeric mixture of **25a** (α-ester: 58%: C_{3a}–CH_3, δ 1.27; C_{8a}–*H*, δ 4.56) and **25b** (35%). In view of the lower δ values of the C_{3a}–CH_3 and C_{8a}–*H* resonances for **25a** vis à vis **25b** the β configuration is assigned to the latter. Consistent with this attribution, is the observation that a pure sample of **25b** on exposure to a methanolic sodium methoxide solution epimerises to the more stable **25a**.

Selective hydrolysis of the ester group in **25a** or in **25a**, **25b** mixture with aqueous methanolic NaOH (1 N; 1 equiv) followed by evaporation of the solvents gave the corresponding salt **26a** (Scheme 9), which was thoroughly dried in high vacuum prior to use. The derived acid chloride **26b**, formed in situ with oxalyl chloride, on reaction with the anion of *N*-hydroxypyridine-2-thione yielded the Barton ester **27** that on decarboxylation in the usual manner (AIBN, TBSH)[20] afforded the product **28** in poor yield (24%). Compound **27**, obtained via the mixed anhydride **26c**, on photolysis in the presence of *tert*-butylthiol as the hydrogen donor[21] underwent decarboxylation to afford an improved yield of **28** (51%). A considerable improvement in this yield (92%) was achieved on irradiating[22] the benzophenone oxime ester **29** secured in 75% yield via the mixed anhydride **26c**, in a THF–isopropanol mixture containing a large excess of *tert*-butylthiol (10 mmol).

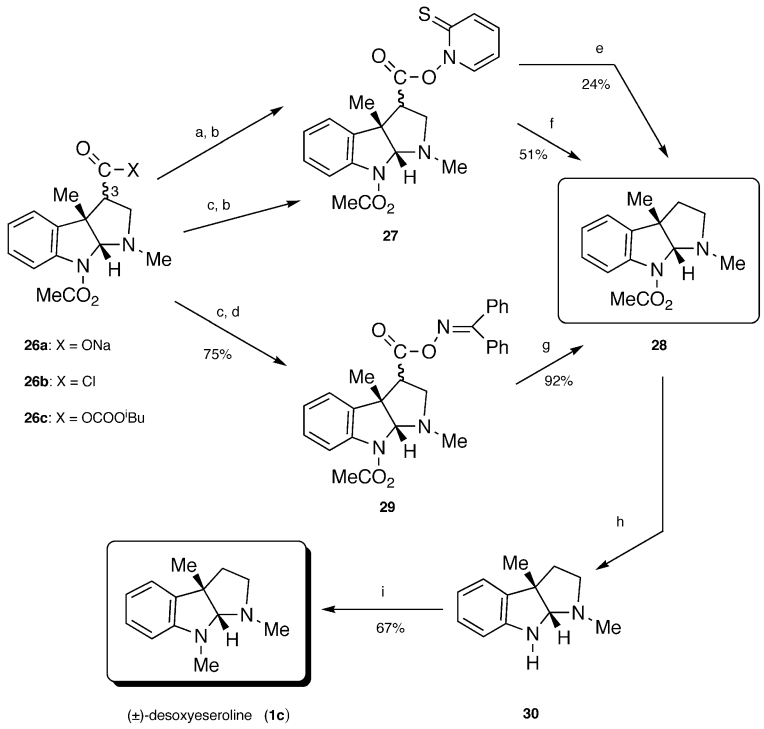
The presence of a 2H triplet centred at δ 2.04 (C_3–*H*) in its ^{1}H NMR spectrum and a single CO absorption (IR) taken in conjunction with the elemental analysis confirmed the structure assigned to **28**. Although LAH reduction of *N*,*N*-disubstituted carbamates in general provides the corresponding tertiary amines,[23] such a reduction of **28** yielded N^8-nordesoxyeseroline (**30**) (mp 110–112 °C; 69% lit.[24] 111–112 °C) with δ values in its ^{13}C NMR spectrum coincident with those reported for such compound.[25] *N*-methylation, carried out at pH≈6, with aqueous formalin and $NaBH_3CN$,[26] furnished (±)-desoxyeseroline (**1c**) as a pale yellow oil (PTLC; 67% yield). It formed a picrate, mp 183–184 °C (from EtOH), lit.[10] mp 179–180 °C, and the δ values of the various hydrogens in its ^{1}H NMR spectrum were in full accordance with those reported.[14b]

Since (−)-desoxyeseroline (**1c**) had been previously converted into (−)-eseroline (**1b**) and hence to (−)-physostigmine (**1a**)[27] this work constitutes also a formal synthesis of (±)-physostigmine.

In summary, a novel route to 3a-methyl hexahydropyrrolo[2,3-*b*]indole nucleus involving a pericyclic reaction of a *N*-aminoskatole derivative as the starting material is described. The protocol employed above is applicable, in principle, to the diastereoselective synthesis of alkaloids by using chiral Michael acceptors (e.g., a chiral acetylene sulphoxide or a chiral propiolic ester).



Scheme 8.



Scheme 9. Reagents and conditions: (a) oxalyl chloride, C_6H_6, reflux; (b) *N*-hydroxpyridine-2-thione sodium salt, reflux; (c) $ClCO_2CH_2CH(CH_3)_2$, THF, −20 °C; (d) $Ph_2C{=}NOH/Et_3N$; (e) AIBN, $^nBu_3SnH$; (f) hν, THF, ^{t}ButSH; (g) hv, Me_2CHOH, THF, ^{t}BuSH; (h) LAH, THF, reflux, (69%) or aqueous NaOH 5 N MeOH, reflux, (66%); (i) aqueous formalin, $NaBH_3CN$; pH 6.

2. Experimental

2.1. General

Melting points were determined on a Reichert Thermovar apparatus and are uncorrected. IR spectra were measured on a Buck Scientific 500 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Brucker ARX 400 spectrometer unless otherwise stated. Chemical shifts are reported relative to tetramethylsilane as internal reference (δ 0.00) for ^1H spectra and to $CDCl_3$ (δ 77.00) for ^{13}C spectra. The solvent used was $CDCl_3$, unless stated otherwise. Ordinary mass spectra were recorded on a Fisons TRIO 2000 or AEI MS-9 spectrometer. High resolution mass spectra were recorded on a AutoSpecQ spectrometer. Elemental analyses were performed by the National Institute of Engineering and Industrial Technology, Lisbon. Thin-layer chromatography was performed on Merck silica gel 60 F_{254} plates. Column chromatography was carried out on Merck silica gel 60 (70–230 mesh). Hydrogenation reactions were carried out in a Parr 3911 hydrogenator, at rt. Usual work up implies drying the water or brine washed organic extracts over anhydrous sodium sulphate or magnesium sulphate, followed by filtration and evaporation of the solvent from the filtrate under reduced pressure. Anhydrous solvents were dried[28] and freshly distilled.

2.1.1. 1-[*N*-Methyl-2′-(phenylsulfanyl)acetamido]-3-methylindole (11). To a solution of 3-methyl-1-(methylamino)indole (**10**) (2.45 g, 15.3 mmol), 2-(phenylsulfanyl)-acetic acid (**12**) (2.85 g, 16.9 mmol) and 4-DMAP (0.38 g, 3.1 mmol) in anhydrous CH_2Cl_2 (80 mL), under vigorous stirring at rt, was added dropwise a solution of DCC (3.32 g, 16.1 mmol) in the same solvent (50 mL). After being stirred for 3 h 30 min, the reaction mixture was filtered at reduced pressure and the filtrate evaporated to dryness. To the residue was added Et_2O and the resulting mixture again filtered to remove the residual *N*,*N*-dicyclohexylurea. The filtrate was then washed sequentially with 5% aqueous $NaHCO_3$, 5% aqueous HCl and water. The oil obtained on usual work-up was purified by preparative TLC (silica, CH_2Cl_2/*n*-hexane 1:1) to give, after recrystallization from Et_2O/*n*-hexane, **11** (3.32 g, 70%), as colourless needles: mp 75.0–75.5 °C; IR (KBr) ν_{max} 1686 (s, C=O) cm^{-1}; ^1H NMR δ 7.58 (1H, d, J=7.8 Hz, Ar*H*), 7.36–7.14 (8H, m, Ar*H*), 6.73 (1H, s, NC*H*=C), 3.50/3.47 (2H, *AB* system, J=14.9 Hz, CH_2SPh), 3.30 (3H, s, NCH_3), 2.30 (3H, d, J= 1.2 Hz, CCH_3); MS (EI) *m/z* 310 (M^+, 93.6), 160 (32.0), 159 (100.0). Anal. Calcd for $C_{18}H_{18}N_2OS$: C 69.65; H 5.85; N 9.03. Found: C 69.76; H 5.97; N 9.00.

2.2. Reaction of 11 with base

2.2.1. KHMDS in THF. To a stirred suspension of KH (0.78 mmol, 89 mg of a 35% dispersion, washed free of mineral oil with anhydrous THF), in anhydrous THF (8 mL), at rt under N_2 atmosphere, was added bis(trimethylsilyl)amine (0.15 mL, 0.71 mmol). After further stirring for 2 h, the suspension was cooled to −80 °C and a solution of **11** (200 mg, 0.65 mmol) in the same solvent (5 mL) was added dropwise. The reaction mixture was stirred for 1 h, while the temperature was allowed to rise slowly to rt. After being stirred for 2 h at rt, 2 h at 45 °C and 50 h under reflux, the reaction mixture was cooled, diluted with water, neutralized with 5% aqueous HCl and extracted with ethyl acetate. The combined organic layers were washed with 5% aqueous $NaHCO_3$ and water and dried. After removal of the solvent at reduced pressure, the resulting brown oil was

subjected to preparative TLC (silica, Et_2O/*n*-hexane 1:1) to give, in increasing order of polarity: bis(phenylsulfanyl)-methane (**14**) (6 mg, 4%), as a yellow solid: mp 33–37 °C (from *n*-hexane) (lit.[29] mp 36–38 °C); IR (film) ν_{max} 1588, 1484, 1442, 1268, 1204, 1092, 1028, 744 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.47–7.44 (4H, m, Ar*H*), 7.37–7.33 (4H, m, Ar*H*), 7.29–7.25 (2H, m, Ar*H*), 4.56 (2H, s, CH_2); MS (EI) *m*/*z* 232 (M^+, 74.3), 123 (85.3), 109 (13.8), 51 (38.5), 45 (100.0); and recovered **11** (74 mg, 37%). From the original base extract 2-(phenylsulfanyl)acetic acid (**12**) was obtained (after neutralisation with 5% aqueous HCl) in 17% yield (19 mg).

2.2.2. KH in THF. To a stirred suspension of KH (0.76 mmol, 87 mg of a 35% dispersion, washed free of mineral oil with anhydrous THF) in anhydrous THF (8 mL), cooled to −80 °C, under N_2 atmosphere, was added dropwise a solution of **11** (202 mg, 0.65 mmol) in the same solvent (5 mL). The reaction mixture was stirred for 2 h, while the temperature was left to rise slowly to rt. After being stirred for 2 h at rt and 30 h under reflux, the reaction mixture was worked-up as above. Evaporation of the combined ethyl acetate extracts, left an oil, which was subjected to preparative TLC (silica, Et_2O/*n*-hexane 1:1) to give, **14** (21 mg, 28%), as a pale-yellow solid, which was identical with a sample previously isolated; recovered **11** (36 mg, 18%), 3-methyl-1-(*N*-methylformamido)indole (**15a**) (6 mg, 5%), as a white solid: mp 83–85 °C, on recrystallization from Et_2O/*n*-hexane; IR (KBr) ν_{max} 1692 (f, C=O) cm^{-1}; ^1H NMR δ 8.42 (1H, s, C*H*O), 7.60 (1H, d, J=8.1 Hz, Ar*H*), 7.3–7.20 (3H, m, Ar*H*), 6.88 (1H, s, NC*H*=C), 3.29 (3H, s, NCH_3), 2.32 (3H, s, CCH_3); MS (EI) *m*/*z* 188 (M^+, 91.3), 159 (45.0), 130 (100.0); exact mass calcd for $C_{11}H_{12}N_2O$: 188.094963. Found: 188.095597; and 3-methyl-1-(methylamino)indole (**10**) (6 mg, 6%), as a yellowish oil: IR (film) ν_{max} 3310 (br, NH) cm^{-1}; ^1H NMR δ 7.54 (1H, d, J=7.6 Hz, Ar*H*), 7.39 (1H, d, J=7.6 Hz, Ar*H*), 7.21 (1H, *t*, J=7.6 Hz, Ar*H*), 7.10 (1H, *t*, J=7.6 Hz, Ar*H*), 6.96 (1H, s, NC*H*=C), 4.23 (1H, br s, N*H*, D_2O exchangeable), 2.92 (3H, s, NCH_3), 2.30 (3H, d, J=1.0 Hz, CCH_3); MS (EI) *m*/*z* 160 (M^+, 100.0). From the aqueous $NaHCO_3$ extracts was isolated 2-(phenylsulfanyl)acetic acid (**12**) (16 mg, 15%).

2.2.3. KHMDS in bis(2-methoxyethyl) ether. To a suspension of KHMDS (0.71 mmol) in anhydrous bis(2-methoxyethyl) ether (8 mL), prepared as previously described, stirred at rt under N_2 atmosphere, was added dropwise a solution of **11** (200 mg, 0.65 mmol) in the same solvent (5 mL). After the addition was complete, the reaction mixture was heated at 120–130 °C for 3 h and then worked-up as in procedure (a). Removal of the solvent from the ethyl acetate extracts left an oil, which was purified by preparative TLC (silica, Et_2O/*n*-hexane 1:1) to give, 1-[bis(2′-phenylsulfanyl)-*N*-methylacetamido]-3-methylindole (**15b**) (20 mg, 15%), as a yellowish oil: IR (film) ν_{max} 1692 (C=O) cm^{-1}; ^1H NMR (acetone-d_6) δ 7.54 (1H, d, J=7.5 Hz, Ar*H*), 7.40–7.14 (10H, m, Ar*H*), 7.09–7.03 (3H, m, Ar*H*), 6.56 (1H, s, NC*H*=C), 4.50 (1H, s, COC*H*), 3.31 (3H, s, NCH_3), 2.15 (3H, d, J=0.8 Hz, CCH_3); MS (EI) *m*/*z* 418 (M^+, 38.5), 309 (100.0); exact mass calcd for $C_{24}H_{22}N_2OS_2$: 418.117357. Found: 418.116225; **10** (18 mg, 17%), 3-methyl-1-(*N*-methylacetamido)indole (**15c**) (16 mg, 12%), as a colourless solid: mp 140–141 °C, after recrystallization form Et_2O/*n*-hexane (lit.[30] mp 140.5–141.0 °C); IR (KBr) ν_{max} 1684 (C=O) cm^{-1}; ^1H NMR δ 7.60 (1H, d, J=7.8 Hz, Ar*H*), 7.31–7.18 (3H, m, Ar*H*), 6.84 (1H, s, NC*H*=C), 3.33 (3H, s, NCH_3), 2.33 (3H, J=1.0 Hz, CCH_3), 1.85 (3H, s, $COCH_3$); MS (EI) *m*/*z* 202 (M^+, 100.0). From the aqueous $NaHCO_3$ extracts was isolated, as in procedure (a), 2-(phenylsulfanyl)acetic acid (**12**) (17 mg, 16%), as a colourless solid, which was identical with an authentic sample.

2.2.4. KHMDS and TMSCl in bis(2-methoxyethyl) ether. To a stirred suspension of KHMDS (0.71 mmol) in anhydrous bis(2-methoxyethyl) ether (8 mL), prepared as described above, cooled to −80 °C, under N_2 atmosphere, were added a solution of **11** (199 mg, 0.64 mmol) in the same solvent (5 mL) and TMSCl (0.16 mL, 1.25 mmol). The reaction mixture was stirred for 1 h, while the temperature was left to rise slowly to rt. After being stirred for 1 h at rt, 32 h at 120–130 °C and 27 h under reflux, the reaction mixture was cooled, neutralized with 5% aqueous HCl and the organic layer, separated by decantation, washed with water and dried. Removal of the solvent at reduced pressure and purification of the resulting residue by preparative TLC (silica, Et_2O/*n*-hexane 1:1), furnished **11** (157 mg, 77%).

2.2.5. 1-[1′,2′-Bis(methoxycarbonyl)-*N*-methylvinylamino]-3-methylindole (16,17). To a stirred solution of 3-methyl-1-(methylamino)indole (**10**) (117 mg, 0.73 mmol) in MeOH (8 mL), at rt, was added dropwise dimethyl acetylenedicarboxylate (0.1 mL, 0.82 mmol). After being stirred for 3 h 10 min, the reaction mixture was evaporated to dryness and the resulting residue subjected to preparative TLC (silica, CH_2Cl_2), to give two isomers: *Z* isomer **16** (71 mg, 32%), as a yellow solid: mp 89.5–90.5 °C, after recrystallization from Et_2O/*n*-hexane; IR (KBr) ν_{max} 1732 (s, C=O), 1708 (s, C=O) cm^{-1}; ^1H NMR δ 7.50 (1H, d, J=7.5 Hz, Ar*H*), 7.45 (1H, d, J=7.5 Hz, Ar*H*), 7.25 (1H, *t*, J=7.5 Hz, Ar*H*), 7.14 (1H, *t*, J=7.5 Hz, Ar*H*), 6.99 (1H, s, NC*H*=C), 5.48 (1H, s, NC=C*H*), 3.76 (3H, s, OCH_3), 3.55 (3H, s, OCH_3), 3.29 (3H, s, NCH_3), 2.27 (3H, d, J=0.8 Hz, CCH_3); MS (EI) *m*/*z* 302 (M^+, 100.0). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C 63.55; H 6.00; N.9.27. Found: C 63.78; H 6.14; N 9.29; *E* isomer 17 (139 mg, 63%), as a colourless solid: mp 93.0–94.5 °C, after recrystallization from Et_2O/*n*-hexane; IR (KBr) ν_{max} 1744 (s, C=O), 1704 (s, C=O) cm^{-1}; ^1H NMR δ 7.53 (1H, d, J=7.8 Hz, Ar*H*), 7.29–7.15 (3H, m, Ar*H*), 6.84 (1H, s, NC*H*=C), 4.73 (1H, br s, NC=C*H*), 3.71 (3H, br s, OCH_3), 3.64 (3H, s, OCH_3), 3.16 (3H, s, NCH_3), 2.27 (3H, d, J=0.7 Hz, CCH_3); MS (EI) *m*/*z* 302 (M^+, 100.0). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C 63.55; H 6.00; N 9.27. Found: C 64.05; H 6.11; N 9.35.

2.2.6. 2,3-Bis(methoxycarbonyl)-1,3a-dimethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole (19). A solution containing the two isomers **16** and **17** (1/1.8 mixture, 322 mg, 0,11 mmol) in diphenyl ether (15 mL) was heated at 180–200 °C in an oil bath, for 7 h 45 min. The solvent was removed at reduced pressure and the resulting dark residue purified by preparative TLC (silica, CH_2Cl_2/*n*-hexane 2:1) to give 19 (145 mg, 45%), as a yellowish oil: IR (KBr) ν_{max} 3365 (br, NH), 1748 (s, 2-*CO*OMe), 1684 (s, 3-*CO*OMe)

cm^{-1}; ^1H NMR δ 7.56 (1H, d, $J=7.6$ Hz, Ar*H*), 7.05 (1H, *t*, $J=7.6$ Hz, Ar*H*), 6.80 (1H, *t*, $J=7.6$ Hz, Ar*H*), 6.68 (1H, d, $J=7.6$ Hz, Ar*H*), 5.12 (1H, s, NC*H*N), 4.46 (1H, br s, N*H*, D_2O exchangeable), 3.88 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 2.83 (3H, s, NCH_3), 1.67 (3H, s, CCH_3); MS (EI) *m/z* 302 (M^+, 100.0); exact mass calcd for $C_{16}H_{18}N_2O_4$: 302.126657. Found: 302.125918.

2.2.7. 1-(2′-Methoxycarbonyl-*N*-methylvinylamino)-3-methylindole (20). Methyl propiolate (1.5 mL, 16.86 mmol) was added to a solution of 3-methyl-1-(methylamino)indole (**10**) (0.75 g, 4.69 mmol) in MeOH (20 mL), at rt. The reaction mixture was heated under reflux for 14 h and then evaporated to dryness at reduced pressure to give **20** (1.08 g, 94%), as colourless needles: mp 112.0–112.5 °C, after recrystallization from Et_2O/*n*-hexane; IR (KBr) ν_{max} 1698 (s, C=O) cm^{-1}; ^1H NMR δ 7.65 (1H, d, $J=13.2$ Hz, NC*H*=CH), 7.57 (1H, d, $J=7.8$ Hz, Ar*H*), 7.26–7.15 (3H, m, Ar*H*), 6.86 (1H, s, NC*H*=CMe), 4.61 (1H, br d, $J=13.2$ Hz, NCH=C*H*), 3.64 (3H, s, OCH_3), 3.31 (3H, s, NCH_3), 2.30 (3H, d, $J=0.8$ Hz, CCH_3); MS (EI) *m/z* 244 (M^+, 100.0). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C 68.82, H 6.61, N 11.47. Found C 68.96, H 6.66, N 11.48.

2.2.8. 3-Methoxycarbonyl-1,3a-dimethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole (21). To diphenyl ether (8 mL) at 210–220 °C was added finely powdered 20 (625 mg, 2.56 mmol) and the mixture while being stirred was kept at that temperature, for 2 h 50 min. The solvent was then removed at reduced pressure and the dark residue subjected to column chromatography (Et_2O/*n*-hexane 1:1) to give **21** (319 mg, 51%), as a yellowish oil: IR (film) ν_{max} 3355 (br, NH), 1674 (s, C=O) cm^{-1}; ^1H NMR δ 7.62 (1H, d, $J=$ 7.5 Hz, Ar*H*), 7.05–7.01 (2H, m, Ar*H* and NC*H*=C), 6.79 (1H, *t*, $J=7.5$ Hz, Ar*H*), 6.67 (1H, d, $J=7.5$ Hz, Ar*H*), 5.05 (1H, s, NC*H*N), 4.48 (1H, br s, N*H*, D_2O exchangeable), 3.66 (3H, s, OCH_3), 2.90 (3H, s, NCH_3), 1.65 (3H, s, CCH_3); MS (EI) *m/z* 244 (M^+, 100.0); exact mass calcd for $C_{14}H_{16}N_2O_2$: 244.121178. Found: 244.121673.

Compound **20** (1.61 g, 6.6 mmol) in *o*-dichlorobenzene (distilled, 30 mL) was heated under reflux in an argon atmosphere (35 h). Evaporation of the solvent under reduced pressure followed by chromatographic purification of the resulting residue (EtOAc/*n*-hexane 3:7) furnished **21** (1.47 g, 91%) as a colourless solid mp 120–122 °C, identical in all respects with the sample above.

2.2.9. 3-Methoxycarbonyl-1,3a,8-trimethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole (22). *Compound* **21** (240 mg, 0.98 mmol) in anhydrous dichloromethane (15 mL) containing 15-crown-5-ether (2 mg) and NaH (80%; 87 mg, 3 mmol) was treated with an excess of MeI (5 mmol) and the mixture heated under reflux (15 h). Evaporation of the solvent followed by purification of the resulting residue by column chromatography (EtOAc/*n*-hexane 1:6) gave the *N*-alkylated product **22** (190 mg, 75%) as a colourless solid, mp 52–53 °C; IR (KBr) ν_{max} 1722, 1671 cm^{-1}; ^1H NMR δ 7.58 (1H, d, $J=8.0$ Hz, Ar*H*), 7.08 (2H, m, Ar-*H* and NC*H*=C), 6.73 (1H, *t*, $J=8.0$ Hz, Ar-*H*), 6.47 (1H, d, $J=$ 8.0 Hz, Ar*H*), 4.71 (1H, s, NC*H*N), 3.65 (3H, s, OCH_3), 3.02 (3H, s, NCH_3), 3.00 (3H, s, NCH_3), 1.63 (3H, s, CCH_3); exact mass calcd for $C_{15}H_{18}N_2O_2$: 258.12682. Found: 258.13674.

2.2.10. 3-Methoxycarbonyl-1,3a,8-trimethyl-2,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (23). *Compound* **22** (264 mg, 1.02 mmol) in MeOH (10 mL), was hydrogenated in the presence of PtO_2 (26 mg) at 25 psi (8 h). After removal of the catalyst by filtration, the solvent was evaporated at reduced pressure and the resulting residue purified by column chromatography (EtOAc/*n*-hexane 1:4) to give the title compound **23** (255 mg; 96%) as a colourless solid, mp 48–50 °C; IR (KBr) ν_{max} 1743 (s, C=O) cm^{-1}; ^1H NMR δ 7.14 (1H, *t*, $J=8.0$ Hz/br s, Ar*H*), 6.86 (1H, d, $J=8.0$ Hz, Ar*H*), 6.62 (1H, *t*, $J=8.0$ Hz, Ar*H*), 6.44 (1H, d, $J=8.0$ Hz, Ar-*H*), 4.33 (1H, br s, NC*H*N), 3.54 (3H, s, OCH_3), 2.90 (3H, s, NCH_3), 2.55 (3H, s, NCH_3), 1.65 (3H, s, CCH_3); exact mass calcd for $C_{15}H_{20}N_2O_2$: 260.15247. Found: 260.15228.

2.2.11. 3,8-Bis(methoxycarbonyl)-1,3a-dimethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole (24). A solution of methyl chloroformate (0.09 mL, 1.16 mmol) in anhydrous Et_2O (2 mL) was added dropwise to an ice-cooled solution of **21** (283 mg, 1.16 mmol) and 4-DMAP (142 mg, 1.16 mmol), in the same solvent (10 mL). The mixture was stirred at rt for 2 h 30 m and then washed with water and dried. The solvent was evaporated at reduced pressure and the residue purified by preparative TLC (Et_2O/*n*-hexane 2:1) to give **24** (284 mg, 81%), as a white solid: mp 180.0–180.5 °C, after recrystallization from acetone/Et_2O; IR (KBr) ν_{max} 1722 (s, N*CO*OMe), 1678 (s, 3-*CO*OMe) cm^{-1}; ^1H NMR δ 7.74–750 (2H, d, $J=7.5$ Hz/br s, Ar*H*), 7.20 (1H, *t*, $J=7.5$ Hz, Ar*H*), 7.03 (1H, *t*, $J=7.5$ Hz, Ar*H*), 6.99 (1H, s, NC*H*=C), 5.66 (1H, br s, NC*H*N), 3.90 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.02 (3H, s, NCH_3), 1.70 (3H, s, CCH_3); MS (EI) *m/z* 302 (M^+, 100.0). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C 63.55, H 6.00, N 9.27. Found: C 63.56, H 5.97, N 9.21.

2.2.12. 3,8-Bis(methoxycarbonyl)-1,3a-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (25a+25b). A solution of **24** (583 mg, 1.93 mmol) in MeOH (180 mL), containing 10% palladium on carbon (179 mg, 0.17 mmol), was shaken under hydrogen pressure (45 Psi) for 16 h. After removal of the catalyst by filtration over Celite, the solvent was evaporated at reduced pressure and the residue subjected to preparative TLC (Et_2O/*n*-hexane 2:1) to give the less polar diastereoisomer **25a** (340 mg, 58%), as a colourless solid: mp 154.0–154.5 °C, after recrystallization from *n*-hexane; IR (KBr) ν_{max} 1740 (s, 3-*CO*OMe), 1712 (s, N*CO*OMe) cm^{-1}; ^1H NMR δ 7.66 (1H, br s, Ar*H*), 7.37 (1H, d, $J=7.6$ Hz, Ar*H*), 7.23 (1H, *t*, $J=7.6$ Hz, Ar*H*), 7.06 (1H, *t*, $J=7.6$ Hz, Ar*H*), 4.56 (1H, br s, NC*H*N), 3.87 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.23–3.18 (1H, m, NCH_2CH), 3.08–3.04 (1H, m, NCH_2CH), 2.94 (1H, *t*, $J=9.8$ Hz, NCH_2CH), 2.59 (3H, br s, NCH_3), 1.27 (3H, s, CCH_3); MS (EI) *m/z* 304 (M^+, 32.9), 273 (8.2), 245 (7.3), 189 (50.7), 158 (23.4), 144 (14.2), 130 (23.4), 115 (100.0). Anal. Calcd for $C_{16}H_{20}N_2O_4$: C 63.13; H 6.63; N 9.21. Found: C 63.07; H 6.33; N 9.22; and the more polar diastereoisomer **25b** (205 mg, 35%), as a colourless solid: mp 73.5–75.0 °C, after recrystallization from acetone/Et_2O; IR (KBr) ν_{max} 1734 (s, 3-*CO*OMe), 1720 (s, N*CO*OMe) cm^{-1}; ^1H NMR δ 7.70 (1H, br s, Ar*H*), 7.24–7.20 (1H, m, Ar*H*), 6.98–6.94 (2H, m,

Ar*H*), 5.18 (1H, s, NC*H*N), 3.86 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.20–3.16 (1H, m, NCH_2CH), 2.90–2.82 (2H, m, NCH_2CH and NCH$_2$C*H*), 2.56 (3H, s, NCH_3), 1.68 (3H, s, CCH_3); MS (EI) *m*/*z* 304 (M^+, 27.4), 273 (14.6), 245 (7.8), 189 (81.3), 158 (25.1), 144 (34.7), 130 (19.1), 115 (100.0). Anal. Calcd for $C_{16}H_{20}N_2O_4$: C 63.13; H 6.63; N 9.21. Found: C 63.23; H 6.70; N 9.21.

The diastereomer **25b**, obtained as the exclusive product with Pt° as the hydrogenating catalyst in anhydrous MeOH, was found to isomerise to **25a** on exposure to 1 N methanolic sodium methoxide.

2.3. Sodium salt of 8-methoxycarbonyl-1,3a-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-3-carboxylic acid (26a)

To a mixture of the diastereoisomers **25a** and **25b** (144 mg, 0.47 mmol) in MeOH (6 mL), was added 1 N aqueous NaOH (0.48 mL, 0.48 mmol) and the mixture heated under reflux for 5 h. The solvents were removed at reduced pressure, benzene was added to the residue and the resulting mixture evaporated to dryness at reduced pressure. The process was repeated several times. The resulting solid, presumably a mixture of the sodium salts **26a** was dried over phosphorous pentoxide in vacuo.

2.3.1. 8-Methoxycarbonyl-1,3a-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (28). *Method a*. A suspension of the above sodium salts **26a** (49.9 mg, 0.16 mmol) in benzene was treated with oxalyl chloride (0.015 mL, 0.18 mmol) in benzene (3 mL) and the mixture refluxed (2 h). Subsequent to the addition of the sodium salt of *N*-hydroxythiopyridine-2-thione (28.6 mg, 0.19 mmol) to the above mixture at rt, reflux was continued for 30 min. To the resulting yellow solution, under reflux, was added a mixture of AIBN (4 mg, 0.024 mmol) and *n*-Bu_3SnH (0.13 mL, 0.48 mmol) in benzene (2 mL). On completion of the reaction (1 h 30 m), the mixture was taken to dryness and the residue obtained was purified by preparative TLC (Et_2O/*n*-hexane 1:1) to give **28** as an oil (9.4 mg, 24%); IR (film) ν_{max} 1712 (s, C=O) cm^{-1}; ^1H NMR δ 7.66 (1H, br s, Ar*H*), 7.19 (1H, *t*, *J*=7.3 Hz, Ar*H*), 7.12 (1H, d, *J*=7.3 Hz, Ar*H*), 7.02 (1H, *t*, *J*=7.3 Hz, Ar*H*), 4.89 (1H, s, NC*H*N), 3.86 (3H, s, OCH_3), 2.71–2.60 (2H, m, NCH_2CH$_2$), 2.56 (3H, s, NCH_3), 2.04 (2H, *t*, *J*=6.2 Hz, NCH$_2$CH_2), 1.43 (3H, s, CCH_3); MS (EI) *m*/*z* 246 (M^+, 100.0). exact mass calcd for $C_{14}H_{18}N_2O_2$: 246.136828. Found 246.136829.

Method b. To a mixture of sodium salts **26a** (488 mg, 1.56 mmol) in anhydrous THF (6 mL), cooled to −20 °C and under N_2 atmosphere, was added isobutyl chloroformate (0.2 mL, 1.56 mmol). After stirring for 2 h, finely powdered sodium salt of *N*-hydroxypyridine-2-thione (280 mg, 1.88 mmol) was added and the suspension stirred at −20 °C, sheltered from light, for 1 h 30 min. The resulting yellow mixture was irradiated in the presence of *tert*-butylthiol (1 mL) with a 125 W high-pressure mercury lamp at rt, under N_2 atmosphere, until the yellow color disappeared (2 h). The reaction mixture was then diluted with Et_2O and washed sequentially with 0.1 N aqueous $NaHCO_3$, water and brine. The organic phase was dried, the solvent removed at reduced pressure and the residue subjected to preparative TLC (Et_2O/*n*-hexane 1:1) to afford **28** (196 mg, 51%), identical with that obtained by Method a.

Method c. Via oxime ester **29**. To a mixture of sodium salts **26a** (64 mg, 0.21 mmol) in DMF (3 mL) containing a catalytic amount of 15-crown-5-ether cooled to 0 °C, was added with stirring freshly distilled isobutyl chloroformate (0.026 mL, 0.20 mmol) under N_2 atmosphere. After stirring for 1 h, the mixture was treated with benzophenone oxime (38 mg, 0.2 mmole) and Et_3N (0.12 mL, 0.6 mmol) and the reaction allowed to stand at rt overnight. It was then diluted with EtOAc (25 mL) and washed with water. Usual work up led to a solid residue which was purified by preparative TLC (EtOAc/*n*-hexane 1:1) to afford the oxime ester **29** as a pale yellow solid (72 mg, 75%), mp 38–40 °C; IR (KBr) ν_{max} 1766 (s, C=O), 1711 (NC*O*OMe) cm^{-1}; ^1H NMR δ 7.66–7.36 (11H, m, Ar*H*), 7.15 (1H, *t*, *J*=7.6 Hz, Ar*H*), 6.77 (1H, *t*, *J*=7.6 Hz, Ar*H*), 6.43 (1H, d, *J*=7.6 Hz, Ar*H*), 4.44 (1H, s, NC*H*N), 3.84 (3H, s, OCH_3), 3.14 (1H, d, *J*=10.2, 6.6 Hz, NCH$_2$C*H*), 3.04 (1H, d, *J*=9.4, 6.6 Hz), 2.95 (1H, t, CHCOO, *J*=10 Hz), 2.52 (3H, s, NCH_3), 1.21 (3H, s, CCH_3). exact mass calcd for $C_{28}H_{27}N_3O_4$: 469.20014 46. Found 469.2002452.

The above oxime-ester **29** (50 mg, 1.07 mmol) and *t*-BuSH (0.2 mL,10 mmol) in a mixture of iso-propanol/THF (2:1, 3 mL) was irradiated (Philips HPR 125 W HG) at 25 °C for 20 h. Evaporation of solvents and excess reagent under reduced pressure gave a residue, which was taken up in EtOAc and washed with ice-cold 1 N aqueous NaOH and then with water and dried (Na_2SO_4). The yellow solid obtained on removal of the solvent and after purification by column chromatography (EtOAc/*n*-hexane 1:50) gave **28** (23 mg, 92%) identical with that obtained by Method a.

2.3.2. 1,3a-Dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole [(±)-N^8-nordesoxyeseroline] (30). *By reduction of* **28**. To a solution of **28** (53.0 mg, 0.22 mmol) in anhydrous THF (8 mL) was added $LiAlH_4$ (15.1 mg, 0.40 mmol) and the resulting suspension heated under reflux for 50 min. The reaction mixture was cooled in an ice-bath and 5 N aqueous NaOH was added. The mixture was heated under reflux for 1 h, extracted with boiling AcOEt and the combined organic layers were dried and concentrated under reduced pressure. Purification of the resulting residue by preparative TLC (AcOEt/MeOH 20/1) afforded **30** (28.1 mg, 69%), as a colourless solid: mp 110–112 °C (lit.[24] mp 111–112 °C), after recrystallization from *n*-hexane; IR (KBr) ν_{max} 3180 (br, NH), 1620 cm^{-1}; ^1H NMR δ 7.05–6.99 (2H, m, Ar*H*), 6.73 (1H, *t*, *J*=7.6 Hz, Ar*H*), 6.58 (1H, d, *J*=7.6 Hz, Ar*H*), 4.36 (1H, s, NC*H*N), 4.18 (1H, br s, N*H*, D_2O exchangeable), 2.71–2.60 (2H, m, NCH_2CH$_2$), 2.45 (3H, s, NCH_3), 2.01–1.98 (2H, m, NCH$_2$CH_2), 1.45 (3H, s, CCH_3); ^{13}C NMR δ 149.5 (C-7a), 137.0 (C-3b), 127.5 (C-6), 122.8 (C-4), 118.8 (C-5), 109.0 (C-7), 89.7 (C-8a), 53.5 (C-3a), 52.5 (C-2), 40.9 (C-3), 37.0 (1-*C*H$_3$), 27.0 (3a-*C*H$_3$); MS (FAB, glycerol) *m*/*z* 189 ([M+H]$^+$, 100.0).

By hydrolysis of **28**. To a solution of **28** (31.0 mg, 0.13 mmol) in MeOH (3 mL) was added 5 N aqueous NaOH (0.1 mL, 0.5 mmol) and the resulting suspension heated under reflux for 3 h. The reaction mixture was

cooled, diluted with water and extracted with Et_2O. The combined organic layers were washed with brine and dried. After removal of the solvent at reduced pressure, the resulting residue was subjected to preparative TLC (AcOEt/MeOH 20/1) to give **30** (15.7 mg, 66%), which was identical with a sample prepared by method a.

2.3.3. 1,3a,8-Trimethyl-1,2,3,3a,8,8a-hexahydro-pyrrolo[2,3-*b*]indole [(±)-desoxyeseroline] (1c). To an ice-cooled solution of **30** (13.5 mg, 0.07 mmol) in MeOH (3 mL) was added $NaBH_3CN$ (9.1 mg, 0.14 mmol). The mixture was then adjusted to pH≈6 with 1% aqueous HCl and 35% aqueous formalin (2.1 mL, 24.5 mmol) added. After being stirred at rt for 1 h 10 min, the reaction mixture was evaporated to dryness under reduced pressure and the residue basified with 25% aqueous NH_4OH. The resulting mixture was extracted with AcOEt, the combined organic extracts washed with brine, dried and the solvent removed under reduced pressure. Purification of the residue by preparative TLC (alumina, Et_2O/*n*-hexane 1.5:9), afforded **1c** (9.7 mg, 67%), as a yellowish oil: IR (film) ν_{max} 1605, 1495, 1450, 1345, 1300, 1255, 1120, 1035, 1020, 955, 735 cm^{-1}; ^1H NMR (300 MHz) δ 7.08 (1H, *td*, $J=1.1$, 7.5 Hz, Ar*H*), 7.00 (1H, d, $J=1.1$, 7.5 Hz, Ar*H*), 6.68 (1H, dt, $J=1.1$, 7.5 Hz, Ar*H*), 6.42 (1H, d, $J=7.5$ Hz, Ar*H*), 4.12 (1H, s, NC*H*N), 2.95 (3H, s, NCH_3), 2.77–2.59 (2H, m, NCH_2CH_2), 2.55 (3H, s, NCH_3), 1.99–1.95 (2H, m, NCH_2CH_2), 1.44 (3H, s, CCH_3); ^{13}C NMR (75 MHz) δ 151.9, 136.6, 127.7, 122.2, 117.5, 106.6, 97.5 (C-8a), 53.2 (C-2), 52.7 (C-3a), 40.8 (C-3), 38.4 (8-CH_3), 36.5 (1-CH_3), 27.3 (3a-CH_3); MS (EI) *m*/*z* 202 (M^+, 100.0); exact mass calcd for $C_{13}H_{18}N_2$: 202.146999. Found: 202.147656.

The picrate of **1c**, obtained as yellow crystals, had: mp 182.5–184 °C (lit.[10] mp 179–180 °C), on recrystallization from EtOH; IR (KBr) ν_{max} 1635, 1615, 1565 (s, NO_2), 1490, 1430, 1360, 1320 (s, NO_2), 1275, 1165, 1075, 1005, 910, 785, 740 cm^{-1}; ^1H NMR (300 MHz) δ 11.30 (1H, br s, N*H*), 8.93 (2H, s, Ar*H*), 7.24 (1H, t, $J=7.2$ Hz, Ar*H*), 7.11 (1H, d, $J=7.2$ Hz, Ar*H*), 6.92 (1H, t, $J=7.2$ Hz, Ar*H*), 6.66 (1H, d, $J=7.2$ Hz, Ar*H*), 5.16 (1H, d, $J=3.0$ Hz, NC*H*N),3.71–3.65 (1H, m, NCH_2CH_2), 3.19 (3H, s, NCH_3), 2.83 (3H, d, $J=4.5$ Hz, NCH_3), 2.71–2.61 (1H, m, NCH_2CH_2), 2.57–2.47 (1H, m, NCH_2CH_2), 2.35–2.30 (1H, m, NCH_2CH_2), 1.55 (3H, s, CCH_3).

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