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Preparation of 3-hydroxyoxindoles with dimethyldioxirane and their use for the synthesis of natural products

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Abstract—This work describes a general protocol for the oxidation of indole and oxindole derivatives with dimethyldioxirane to give 3-hydroxyoxindoles present in many natural products. This strategy allowed us to synthesize the natural product **1**, to carry out the first total synthesis of **4**, a formal total synthesis of donaxaridine (**5**) and to achieve the synthesis of pyrroloindoline **8**, a debromo analogue of the natural product flustraminol B (**7**).
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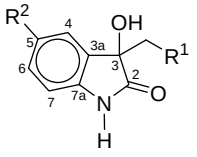
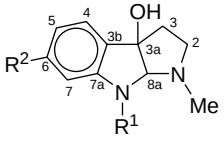
1. Introduction

A number of oxindole, pyrroloindole and furoindole alkaloids possessing a 3- and/or 3a-hydroxyl substituent, some of which possess interesting biological activities,[1] have been isolated from natural sources. Examples of these are metabolites **1**–**3** (Scheme 1) isolated from rice bran,[1a,b] which are putative intermediates in the oxidation of 3-indolylacetic acid. Particularly, **1** has also been isolated from *Hibiscus moscheutos* L.[1c] In addition, dioxindole **4** was isolated from cabbage inoculated with *Pseudomonas cichorii*,[1d] donaxaridine (**5**) was isolated from the giant reed *Arundo donax*,[1e] allina (**6**) was isolated from the epigeal part of *Allium odorum* L.,[1f] and flustraminol B (**7**) was isolated from the marine bryozoan *Flustra foliacea*.[1g] The tricyclic compounds **6**–**8** possess a physostigmine-like skeleton.



1: $R^1 = CO_2Me$, $R_2 = H$
2: $R^1 = CO_2H$, $R_2 = OH$
3: $R^1 = CO_2Me$, $R_2 = OH$
4: $R^1 = CN$, $R_2 = H$
5: $R^1 = CH_2NHMe$, $R_2 = H$



6: $R^1 = R^2 = H$
7: R^1 =  ; $R^2 = Br$
8: R^1 =  ; $R^2 = H$

Scheme 1.

The biological activity of oxindole derivatives and their structural relationship to indoles make these compounds important targets in medicinal and synthetic organic chemistry, as is reflected in the number of synthetic approaches hitherto. 3-Hydroxyoxindoles and 3a-hydroxypyrrolo- or furo-indole derivatives have been synthesized starting from isatins,[2] indoles,[1b,h,3] oxindoles,[4] 3-hydroxy-2,4-quinolinediones[5] and 2-allyloxyindolin-3-ones,[6] using different oxidating agents such as *m*-CPBA, H_2O_2/chloroperoxidase, *t*-BuOOH, NBS/SeO_2, DMSO, and $FeCl_3$/MeOH/H_2O. The use of oxone as the oxidant to prepare DMD in buffered acetone[7] has become popular due in part to its stability and cost-effectiveness.[8] Zhang et al. have demonstrated that indole derivatives with an *N*-electron withdrawing group can be oxidized to oxindoles with DMD via putative epoxide intermediates. Under these experimental conditions they reported that only minor amounts of 3-hydroxyindole derivatives were obtained.[9] On the other hand, Danishefsky et al. also successfully oxidized trytophan and dihydropyrroloindole derivatives with DMD in order to obtain 3a-hydroxypyrroloindoles.[10]

We report herein a general approach to 3-hydroxyoxindole derivatives based on the dimethyldioxirane (DMD)

Keywords: 3-Hydroxyoxindoles; 3-Hydroxyfuroindole; Donaxaridine; Dimethyldioxirane.
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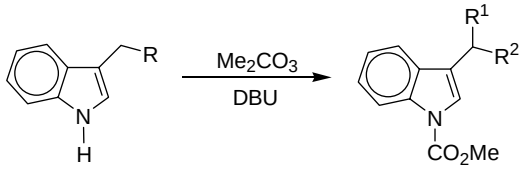
oxidation of *N*-substituted indoles and oxindoles and its application to the synthesis of natural product **1**, the first total synthesis of **4**, the formal total synthesis of donaxaridine (**5**) and the synthesis of pyrroloindoline **8**, a debromo analogue of the natural product flustraminol B (**7**).

2. Results and discussion

In order to improve the yield of 3-hydroxyoxindole derivatives using a DMD protocol, we oxidized the indole 2,3-double bond of *N*-carbomethoxy compounds **13–16** (Scheme 2) and oxindoles **23–29** (Scheme 3) with DMD prepared according to Corey.[7] These compounds were selected as starting materials in concordance to the functionality present in synthetic targets **1**, **4**, **5** and **8**.



9 : R = CO_2Me
10: R = CH_2OH
11: R = CONHMe
12: R = CN

13: R^1 = H, R^2 = CO_2Me
14: R^1 = H, R^2 = CH_2OCO_2Me
15: R^1 = H, R^2 = CONHMe
16: R^1 = H, R^2 = CN
17: R^1 = CO_2Me, R^2 = CN

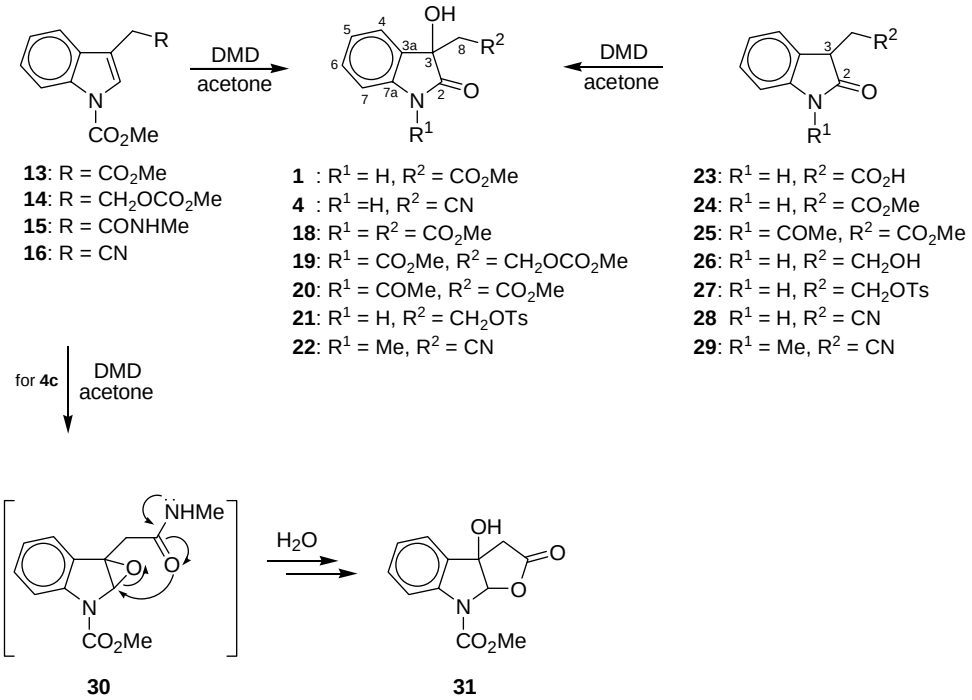
Scheme 2.

Compounds **13–15** were prepared from **9–11**[11] according to Scheme 2. When **9–11** were treated with Me_2CO_3, containing 0.1 equiv of 1,8-diazabicyclo[5.4.0]undecen-7-ene[12] (DBU) as the base, compounds **13–15** were obtained in 63–82% yield. When indole **12** was treated with DBU/Me_2CO_3 or Na/Me_2CO_3 compound **16** was obtained in low yields (15–21%) together with **17** (57–60%).[13] However, when compound **12** was treated with NaH/$ClCO_2Me$, then **16** was obtained in 73% yield and no traces of **17** were observed.

Oxidation of **13** with 2.5 equiv of DMD, generated in situ from oxone in acetone, afforded 3-hydroxyoxindole **18** in 63% yield (Scheme 3). The ^{1}H NMR spectrum of **18**, obtained in $(CD_3)_2SO$, showed an AB pattern at δ 3.25 and 3.19 (J_{AB} = 16.5 Hz) for the C8 methylene group and a singlet for the proton of the OH group at δ 6.60, which exchanged with D_2O. The structure of **18** was confirmed by X-ray crystallography (Fig. 1, Table 1).

Similarly, oxidation of **14** with 5 equiv of DMD afforded **19** in 94% yield. When **15** was oxidized with 2.5 equiv of DMD, the expected hydroxyoxindole was not formed, instead compound **31** was obtained in 96% yield. The formation of **31** can be rationalized by amide oxygen assisted cleavage of the intermediate epoxide in **30**, followed by hydrolysis of the intermediate iminolactone. Oxidation of indole **16** with DMD did not produced the corresponding oxindole, instead a complex mixture of products, as judged from ^{1}H NMR spectrum of the crude reaction product, was obtained.

We then turned our attention to synthesize the series of oxindole derivatives **23–29** (Scheme 3). Thus, oxidation of indole-3-acetic acid with DMSO/HCl[14] at room temperature gave oxindole **23**, which after treatment with MeOH/H^+ at reflux afforded ester **24**[15a] in 77% overall yield. Compound **24** was converted into the *N*-acetyl derivative **25** in 92% yield by acetylation with boiling acetic anhydride.[15b] Similarly, oxidation of indole **10** with DMSO/HCl afforded **26**[2a] (72%), which upon reaction with TsCl gave **27**[16]



13: R = CO_2Me
14: R = CH_2OCO_2Me
15: R = CONHMe
16: R = CN

1 : R^1 = H, R^2 = CO_2Me
4 : R^1 =H, R^2 = CN
18: R^1 = R^2 = CO_2Me
19: R^1 = CO_2Me, R^2 = CH_2OCO_2Me
20: R^1 = COMe, R^2 = CO_2Me
21: R^1 = H, R^2 = CH_2OTs
22: R^1 = Me, R^2 = CN

23: R^1 = H, R^2 = CO_2H
24: R^1 = H, R^2 = CO_2Me
25: R^1 = COMe, R^2 = CO_2Me
26: R^1 = H, R^2 = CH_2OH
27: R^1 = H, R^2 = CH_2OTs
28 R^1 = H, R^2 = CN
29: R^1 = Me, R^2 = CN

Scheme 3.

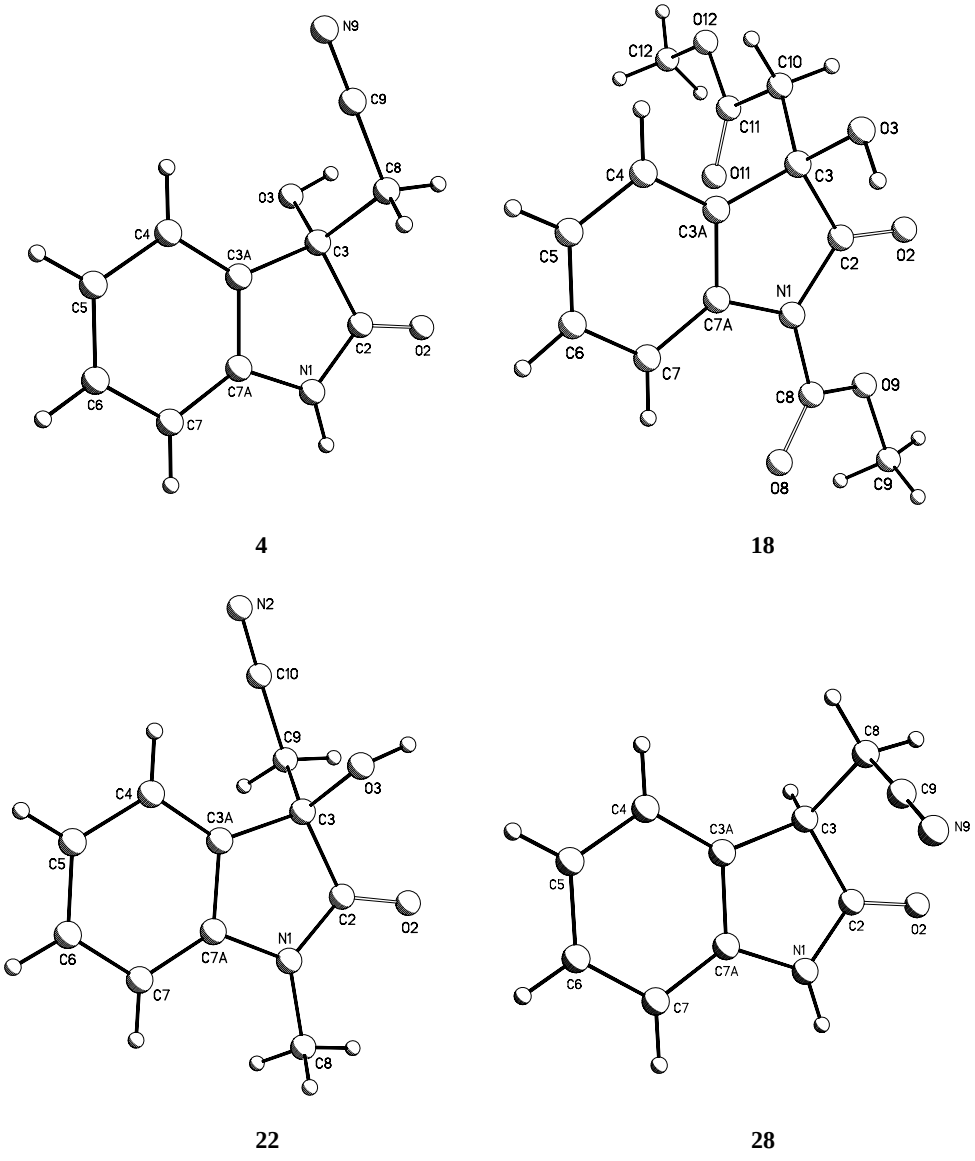


Figure 1.

(87%). Finally, treatment of **12** with DMSO/HCl afforded oxindole **28** in 78% yield. The X-ray structure of **28** is shown in Figure 1 (Table 1). The reaction of these oxindoles with DMD was then examined in order to gain more information about the oxidation process. Thus, **23** failed to oxidized with DMD even after prolonged reaction times. In contrast, reaction of **24** with 5 equiv of DMD at room temperature for 8 h afforded the natural product **1** in good yield (80%). This compound was carefully identified since some spectroscopic properties are ambiguous in the literature.[1a,1h]

The *N*-acylated oxindole **25** reacted much more rapidly (0.75 h) and with less oxidant (2.5 equiv) than **24**, to produce the dioxindole derivative **20** in 69% yield, a fact consistent with the expected easier enolization of the imide system present in **25**. These results suggest that the generation of **18** and **19** from **13** and **14**, respectively, involves two successive oxidations, where the hydroxyl group at C-3 is introduced via the enol derivative of an intermediate oxindole.[17]

When oxindole **26** was reacted with DMD no hydroxylated product was obtained even after 24 h. However, the *N*-tosyl derivative **27** smoothly gave the dioxindole derivative **21** in 65% yield. Since donaxaridine (**5**) has been previously prepared from **21**,[2b] the above procedure constitutes a formal total synthesis of **5**. Thus, the natural product **5** was obtained from **26** in 50% overall yield. Oxidation of **28** with 2.5 equiv of DMD completed the first total synthesis of the natural product **4** in 94% yield. Finally, oxidation of **29**[18] with 2.5 equiv of DMD yielded the analog **22** in 83% yield. The X-ray structures of **4** and **22** are shown in Figure 1 (Table 1).

In order to evaluate if oxidation of compounds **24**, **25**, **27**–**29** with DMD occurs either as a benzylic oxidation[19] or as an α-keto oxidation, *N*-carbomethoxy-2,3-dihydroindole was treated with DMD under the same reaction conditions used for the oxidation of **24**, after which no traces of the benzylic oxidated products could be detected even after 24 h, these results being consistent with the above proposed reaction

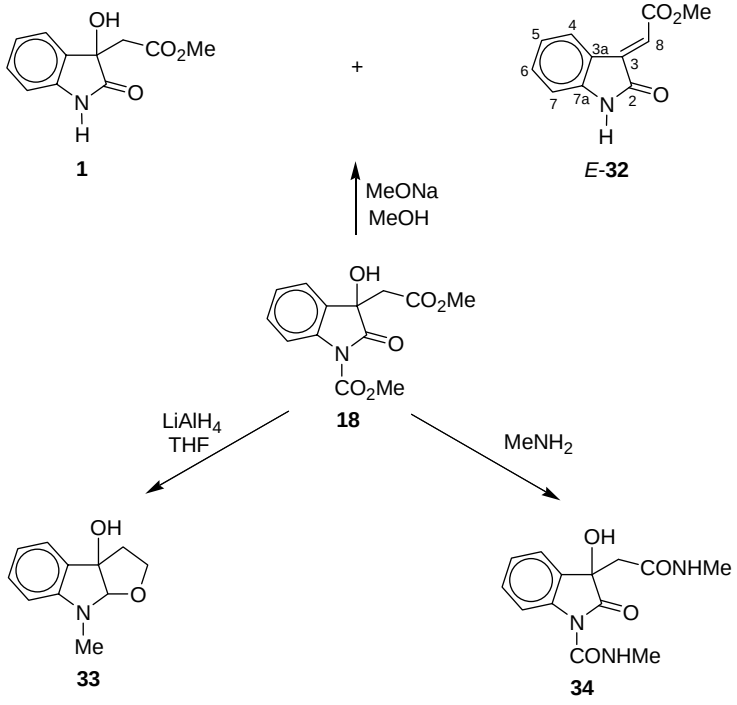
Table 1. X-ray data collection and processing parameters for **4**, **18**, **22**, **28**, **35** and **39**

Compound	**4**	**18**	**22**	**28**	**35**	**39**
Formula	$C_{10}H_8O_2N_2$	$C_{13}H_{13}O_6N$	$C_{11}H_{10}O_2N_2$	$C_{10}H_8O_1N_2$	$C_{16}H_{19}O_4N$	$C_{11}H_{14}ON_2$
Size (mm^3)	0.53×0.49×0.39	0.42×0.41×0.22	0.40×0.35×0.35	0.51×0.50×0.30	0.49×0.40×0.34	0.30×0.20×0.20
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/n$	$P2_1$	$P2_1/n$	$P2_1/c$	$P2_1/n$
a (Å)	5.839(1)	10.9983(5)	8.207(2)	7.292(1)	8.767(3)	8.530(2)
b (Å)	12.119(2)	8.1492(4)	4.857(1)	15.958(2)	22.314(7)	6.319(1)
c (Å)	12.566(3)	14.7280(6)	12.615(1)	7.612(1)	8.942(3)	19.197(4)
β (°)	92.06(3)	102.555(1)	93.10(3)	101.208(4)	114.168(8)	95.33(2)
V ($Å^3$)	888.5(3)	1288.47(10)	502.2(1)	869.0(2)	1595.9(9)	1030.4(3)
D_{calcd} (g cm^{-3})	1.41	1.44	1.34	1.19	1.20	1.23
Z	4	4	2	4	4	4
M (mm^{-1})	0.10 (Mo Kα)	0.12 (Mo Kα)	0.78 (Cu Kα)	0.07 (Mo Kα)	0.09 (Mo Kα)	0.64 (Cu Kα)
T (K)	293	293	293	293	293	293
$2\theta_{range}$ (°)	2.34–26.12	2.11–26.01	3.51–54.97	2.55–26.02	1.83–26.02	4.63–54.92
Total reflections	5706	8136	1339	5830	10,376	1595
Unique reflections	1751	2521	1337	1701	3116	1286
R_{int} (%)	0.05	0.03	0.001	0.001	0.08	0.03
Observed reflections	1351 $I\geq 4\sigma(I)$	1976 $I\geq 4\sigma(I)$	1266 $I\geq 4\sigma(I)$	1066 $I\geq 4\sigma(I)$	1367 $I\geq 4\sigma(I)$	1263 $I\geq 4\sigma(I)$
Parameters	160	234	141	126	198	140
R (%), R_w (%)	4.2, 11.4	3.8, 10	2.8, 7.5	3.7, 7.6	5.9, 15.2	3.8, 9.8
e_{max} (e $Å^{-3}$)	0.20	0.20	0.13	0.16	0.32	0.20
CCDC no.	295377	295378	295379	295380	295381	295382

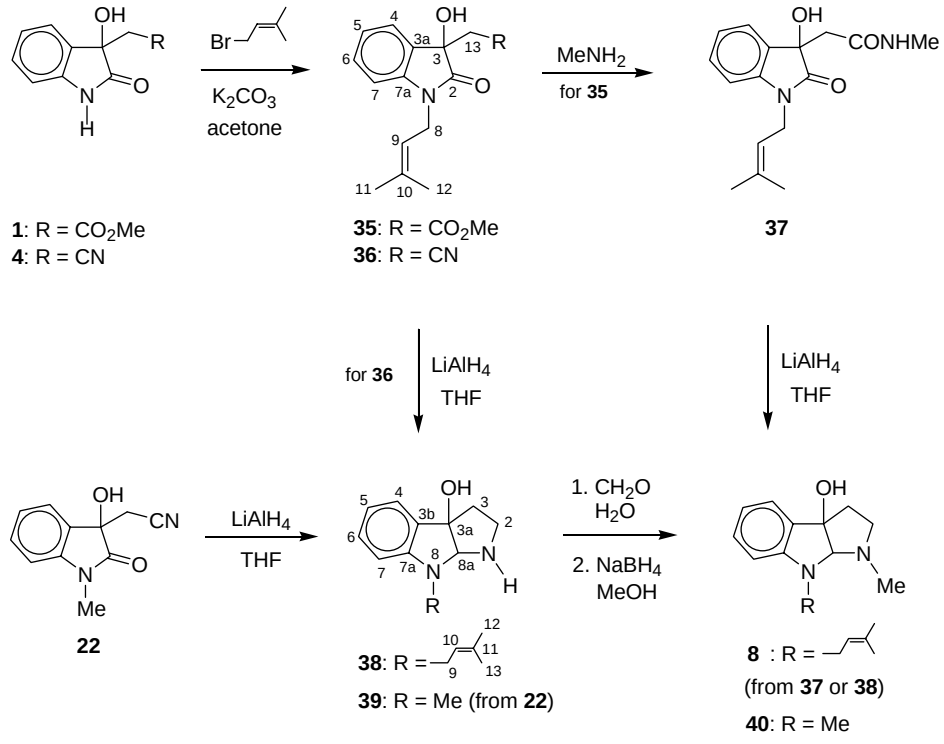
mechanism for the oxidation of **13** and **14** involving two successive oxidations to give **18** and **19**, respectively.

On the other hand, dioxindole **18** could also be used to produce **1**. The later was generated in modest yield (42%) by removal of the *N*-methoxycarbonyl group with methanolic sodium methoxide (reflux, 0.25 h, Scheme 4), which also afforded undesired dehydration product **32** (47%) as only the *E* isomer. The stereochemistry around the C3=C8 double bond in **32** was established on the basis of the marked deshielding of the H4 signal (8.54 ppm in $CDCl_3$ solution) caused by the proximity of the carbonyl ester group.[20]

In order to construct a trycyclic 3-hydroxyindole skeleton, dioxindole **18** was reduced with $LiAlH_4$ (THF/reflux/3 h) to afford 3-hydroxyfuroindole **33** in 21% yield, which has the furoindole skeleton found in natural occurring madindolines A and B.[21] In addition, compound **18** was quantitatively converted into the urea derivative **34**, however, it was insoluble for further chemical transformations (e.g., for $LiAlH_4$ reduction). The obtention of **33** from **18** suggested



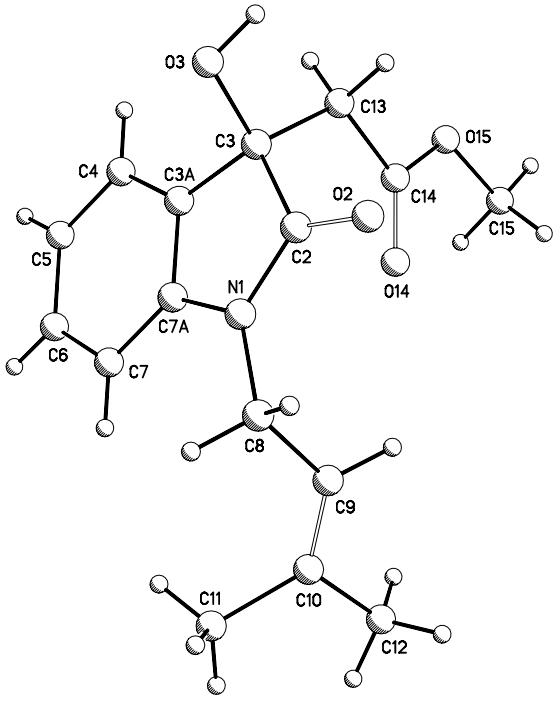
Scheme 4.



Scheme 5.

that the corresponding *N*-demethyl analog should likewise be available from **1**. However, tryptophol (**10**), was obtained instead, in quantitative yield.[22]

With **1** and **4** now being readily available, their conversion into **8**, containing a physostigmine-like skeleton, was examined (Scheme 5). Thus, N-alkylation of **1** and **4** with prenyl bromide (K_2CO_3/acetone/reflux 4 h) gave **35** and **36** in 97 and 96% yield, respectively. The X-ray structure of **35** is shown in Figure 2 (Table 1). Compound **35** reacted with $MeNH_2$ (room temperature/16 h) to give the oxindole **37** in 98% yield. Reduction of **37** with $LiAlH_4$ in refluxing THF



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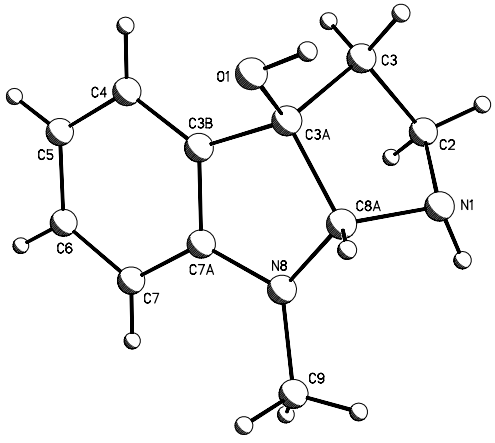

39

Figure 2.

gave debromoflustraminol **8** (55%) in 52% overall yield from **1**. On the other hand, reduction of **36** with $LiAlH_4$ in refluxing THF afforded **38** in 47% yield. Reductive alkylation of **38** was carried out with CH_2O/H_2O and $NaBH_4$/MeOH to give **8** (47%) in 21% overall yield from **4**. On the other hand, the synthesis of the *N*-methylated analog **40** of the natural product **6**, was undertaken from **22**. Thus, reduction of **22** with $LiAlH_4$/THF afforded the pyrroloindole **39**[3d] in 67% yield. The X-ray structure of **39** is shown in Figure 2 (Table 1). Reductive alkylation of **39** with CH_2O/H_2O and then with $NaBH_4$/MeOH afforded **40**[23] in 89% yield.

3. Conclusion

In summary, we have developed a general and practical protocol for the synthesis of 3-hydroxyoxindoles starting from indole or oxindole derivatives. This methodology has allowed us to achieve the syntheses of natural products **1**, **4**, **5** and of unnatural **8**.

4. Experimental

4.1. General experimental procedures

Melting points were determined on a Büchi B-540 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 2000 FT-IR spectrophotometer. The 400 and 100 MHz ^1H and ^{13}C NMR spectra were obtained on a JEOL Eclipse 400 spectrometer and the 300 and 75 MHz ^1H and ^{13}C NMR spectra were obtained on a Varian Mercury-300 spectrometer, using $CDCl_3$, CD_3OD, acetone-d_6 or DMSO-d_6 as the solvent and TMS as the internal reference. For the complete assignments 2D NMR spectra, HMQC and HMBC were used. Chemical shifts are reported in ppm from TMS. Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz) and assignment. Low-resolution mass spectra were recorded at an ionizing voltage of 70 eV on a Hewlett Packard 5989-A spectrometer. High-resolution (HR) mass spectra were measured on a JEOL JMS-SX 102A mass spectrometer at Instituto de Química, UNAM-Mexico. Microanalytical determinations were performed on a Perkin Elmer 2400 Series PCII apparatus. Analytical thin-layer chromatography (TLC) was done on silica gel 60 F_{254} coated aluminum sheets (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with UV light (254 nm). Flash chromatography[24] was done using silica gel 60 (230–400 mesh) from Aldrich.

4.2. General procedure for the preparation of indole carbamates 13–15

A solution of the appropriate indole **9**–**11** (16.4 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) 246 μL (0.250 g, 0.1 equiv) in Me_2CO_3 (50 mL) was stirred at reflux for a specified period of time as follows: **9** (26 h), **10** (33 h) and **11** (26 h). After cooling to room temperature, EtOAc (50 mL) was added to the mixture and the organic phase was washed with a saturated solution of NH_4Cl (2×30 mL) and brine (2×30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant crude products **13**–**15** were purified by flash chromatography on silica gel (using EtOAc/hexane 2:3 for **13** and **14**, and EtOAc for **15**, as the eluant).

4.2.1. Methyl(1-carbomethoxy-1*H*-indol-3-yl)acetate (13). Prepared from 3.10 g of **9** as a yellow oil (3.3 g, 82%); ^1H NMR ($CDCl_3$), δ 8.17 (1H, br d, J=7.8 Hz, H7); 7.60 (1H, s, H2); 7.53 (1H, d, J=7.3 Hz, H4); 7.35 (1H, td, J=7.8, 1.1 Hz, H6); 7.27 (1H, td, J=7.9, 1.1 Hz, H5); 4.02 (3H, s, NCO_2CH_3); 3.72 (2H, s, H8); 3.71 (3H, s, CO_2CH_3). ^{13}C NMR ($CDCl_3$), δ 171.3 (CO_2Me); 151.3 (NCO_2Me); 135.4 (C7a); 130.0 (C3a); 124.9 (C6); 124.0 (C2); 123.0 (C5); 119.0 (C4); 115.2 (C7); 114.0 (C3); 53.8 (NCO_2CH_3); 52.2 (CO_2CH_3); 30.8 (C8). IR (film) ν_{max} 3029, 2954, 1738, 1612, 1455, 1259 cm^{-1}. EIMS *m/z* (relative intensity) 247 (M^+, 41), 188 (100), 144 (49). Anal. Calcd for $C_{13}H_{11}NO_4$: C 63.15; H 5.30; N 5.66. Found: C 62.77; H 5.35; N 5.75.

4.2.2. 3-(2-Carbomethoxyethoxyl)-1-carbomethoxy-1*H*-indole (14). Prepared from 2.64 g of **10** as a yellow oil (3.27 g, 72%). ^1H NMR (DMSO-d_6), δ 8.08 (1H, d, J=7.5 Hz, H7); 7.64 (1H, d, J=7.7 Hz, H4); 7.56 (1H, s, H2); 7.34 (1H, td, J=7.3, 1.5 Hz, H6); 7.26 (1H, td, J=7.7, 1.3 Hz, H5); 4.36 (2H, t, J=7.0 Hz, H9); 3.97 (3H, s, NCO_2CH_3); 3.67 (3H, s, OCO_2CH_3); 3.02 (2H, td, J=6.9, 1.1 Hz, H8). ^{13}C NMR (DMSO-d_6), δ 155.1 (OCO_2Me); 150.8 (NCO_2Me); 134.8 (C7a); 130.0 (C3a); 124.6 (C6); 123.1 (C2); 122.7 (C5); 119.2 (C4); 117.1 (C3); 114.6 (C7); 66.6 (C9); 54.5 (OCO_2CH_3); 53.9 (NCO_2CH_3); 23.8 (C8). IR (film) ν_{max} 2958, 1747, 1457, 1381, 1264 cm^{-1}. EIMS *m/z* (relative intensity) 277 (M^+, 12), 201 (100), 144 (22), 115 (39), 59 (32). Anal. Calcd for $C_{14}H_{15}NO_5$: C 60.64; H 5.45; N 5.05. Found: C 60.86; H 5.68; N 4.46.

4.2.3. Methyl(1-carbomethoxy-1*H*-indol-3-yl)acetamide (15). Prepared from 3.09 g of **11** as colorless crystals (2.55 g, 63%), mp 147–148 °C (Et_2O). ^1H NMR ($CDCl_3$), δ 8.16 (1H, br d, H7); 7.55 (1H, s, H2); 7.51 (1H, d, J=8.1 Hz, H4); 7.36 (1H, td, J=7.0, 1.1 Hz, H6); 7.27 (1H, td, J=8.0, 1.1 Hz, H5); 5.92 (1H, br s, NH), 3.98 (3H, s, CO_2CH_3); 3.63 (2H, s, H8); 2.74 (3H, d, J=5.1 Hz, NCH_3). ^{13}C NMR ($CDCl_3$), δ 170.6 (*C*ONHMe); 151.2 (NCO_2Me); 135.6 (C7a); 129.8 (C3a); 125.2 (C6); 124.4 (C2); 123.3 (C5); 119.1 (C4); 115.3 (C7); 114.9 (C3); 53.8 (NCO_2CH_3); 33.0 (C8); 26.4 (NCH_3). IR (KBr) ν_{max} 3437, 3275, 3126, 1745, 1650, 1555, 1456 cm^{-1}. EIMS *m/z* (relative intensity) 246 (M^+, 55), 188 (100), 144 (59), 102 (20), 58 (17). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C 63.40; H 5.73; N 11.38. Found: C 63.51; H 5.93; N 11.41.

4.2.4. Preparation of (1-carbomethoxy-1*H*-indol-3-yl)-acetonitrile (16). To a solution of 1.5 g of **12** (9.62 mmol) in $ClCO_2Me$ (15 mL) was added NaH (1.73 g, 72.1 mmol) and heated under reflux for 24 h. After cooling to room temperature, EtOAc (150 mL) was added. The mixture was washed with a saturated solution of NH_4Cl (4×50 mL) and brine (2×30 mL), dried over Na_2SO_4, filtrated and concentrated in vacuum. The resultant crude product was purified by crystallization with EtOAc/hexane to obtain **16** as a white solid (1.51 g, 73%), mp 121–123 °C. Lit.[13] 119–120 °C.

4.3. General procedure for the preparation of 3-hydroxyoxindoles 1, 4, 18–22 and furoindole 31

To a solution of the appropriate indole **13** (0.494 g, 2 mmol), **14** (0.195 g, 0.7 mmol), **15** (0.50 g, 2.03 mmol) or oxindole **24** (0.51 g, 2.49 mmol), **25** (0.765 g, 3.1 mmol), **27** (0.239 g, 0.72 mmol), **28** (0.20 mg, 1.16 mmol), **29** (0.153 g, 0.82 mmol) in acetone (10–15 mL) was added $NaHCO_3$ (3.5 equiv for **13**, **15**, **25**, **28** and **29**, 5.25 equiv for **27**, and 7.0 equiv for **14** and **24**). The resulting thick mixture was treated dropwise, over 10 min at room temperature, with a solution of oxone monopersulfate complex (2.5 equiv of $KHSO_5$ for **13**, **15**, **25**, **28** and **29**, 3.75 equiv for **27**, and 5.0 equiv for **14**, **24**) and 5 mg of disodium EDTA in water (5–10 mL). After addition was complete, the mixture was stirred at room temperature for additional 1.3 h for **29**, 3 h for **13**, 5 h for **14**, 8 h for **24**, 0.75 h for **25**, 30 h for **27**, 3.5 h for **28**, and under reflux for 2 h for **15**. After cooling to room temperature the acetone was evaporated under reduce pressure and the residue was dissolved in EtOAc (50 mL). The separated organic phase was washed with brine (2×20 mL), dried over $NaSO_4$ and concentrated in vacuo. The resultant crude products were purified by flash column chromatography with EtOAc/hexane 2:3 for **1**, **4**, **18** and **20**, EtOAc/hexane 1:4 for **19**, EtOAc/hexane 1:1 for **21** and **22**, and EtOAc/MeOH 97:3 for **31**.

4.3.1. Methyl(3-hydroxy-2-oxo-2,3-dihydroindol-3-yl)-acetate (1). Prepared from **24** as colorless crystals (0.440 g, 80%), mp 132–133 °C (EtOAc/hexane). ^{1}H NMR (CD_3OD), δ 7.39 (1H, d, J=7.3 Hz, H4); 7.28 (1H, td, J=7.7, 1.1 Hz, H6); 7.05 (1H, td, J=7.7, 1.1 Hz, H5); 6.92 (1H, d, J=7.7 Hz, H7); 4.91 (2H, s, NH and OH); 3.50 (3H, s, CO_2Me); 3.12 and 3.10 (2H, AB system, J=15.3 Hz, H8). ^{13}C NMR (CD_3OD), δ 180.9 (C=O lactam); 171.0 (CO_2Me); 143.6 (C7a); 131.7 (C3a); 131.0 (C6); 125.2 (C4); 123.6 (C5); 111.3 (C7); 74.8 (C3); 52.1 (CO_2CH_3); 42.6 (C8). IR (KBr) ν_{max} 3388, 3322, 3042, 2964, 1718, 1622 cm^{-1}. EIMS m/z (relative intensity) 221 (M^+, 42), 161 (82), 148 (100), 133 (34), 120 (60), 92 (50), 65 (40). Anal. Calcd for $C_{11}H_{11}NO_4$: C 59.73; H 5.01; N 6.33. Found: C 59.58; H 4.94; N 5.91.

4.3.2. (3-Hydroxy-2-oxo-2,3-dihydroindol-3-yl)acetonitrile (4). Prepared from **28** as pale yellow crystals (0.206 g, 94%), mp 162–164 °C (EtOAc/hexane). Lit.[1d] 162–163 °C. Although compound **4** is known,[1d] it is spectroscopically not yet fully characterized. Thus, NMR data follow: ^{1}H NMR (acetone-d_6), δ 9.76 (1H, br s, NH); 7.62 (1H, d, J=7.3 Hz, H4); 7.36 (1H, t, J=7.7 Hz, H6); 7.13 (1H, t, J=7.7 Hz, H5); 7.02 (1H, d, J=8.1 Hz, H7); 5.88 (1H, s, OH); 3.19 and 2.98 (2H, AB system, J=16.6 Hz, H8). ^{13}C NMR (acetone-d_6) δ 178.1 (C=O lactam); 143.1 (C7a); 131.8 (C6); 130.8 (C3a); 125.9 (C4); 124.0 (C5); 117.7 (CN); 111.9 (C7); 74.0 (C3); 27.8 (C8). IR (KBr) ν_{max} 3352, 2964, 2850, 2254, 1726, 1244, 1619 cm^{-1}. EIMS m/z (relative intensity) 188 (M^+, 17), 170 (100), 148 (90), 115 (58). Anal. Calcd for $C_{10}H_8N_2O_2$: C 63.83; H 4.28; N 14.89. Found: C 63.81; H 4.35; N 14.65.

4.3.3. Methyl(1-carbomethoxy-3-hydroxy-2-oxo-2,3-dihydroindol-3-yl)acetate (18). Prepared from **13** as colorless crystals (0.350 g, 63%), mp 127–129 °C (EtOAc/hexane). ^{1}H NMR (DMSO-d_6), δ 7.84 (1H, d, J=8.0 Hz, H7); 7.52 (1H, dd, J=7.5, 1.1 Hz, H4); 7.41 (1H, td, J=8.0, 1.4 Hz, H6); 7.22 (1H, td, J=7.7, 1.1 Hz, H5); 6.60 (1H, s, OH); 3.94 (3H, s, NCO_2CH_3); 3.39 (3H, s, CO_2CH_3); 3.25 and 3.19 (2H, AB system, J=16.5 Hz, H8). ^{13}C NMR (DMSO-d_6), δ 174.7 (C=O lactam); 169.3 (CO_2Me); 151.0 (NCO_2Me); 139.5 (C7a); 129.8 (C3a); 129.7 (C6); 124.7 (C5); 123.9 (C4); 114.5 (C7); 72.1 (C3); 53.7 (NCO_2CH_3); 51.5 (CO_2CH_3); 41.8 (C8). IR (KBr) ν_{max} 3458, 3003, 2957, 1783, 1740, 1711, 1610 cm^{-1}. EIMS m/z (relative intensity) 279 (M^+, 15), 219 (24), 146 (100), 90 (22), 59 (15). Anal. Calcd for $C_{13}H_{13}NO_6$: C 55.92; H 4.69; N 5.02. Found: C 56.40; H 4.84; N 4.73.

4.3.4. 1-Carbomethoxy-1*H*-3-hydroxy-3-(2-carbomethoxyethoxyl)-2-indolinone (19). Prepared from **14** as a pale yellow oil (0.204 g, 94%). ^{1}H NMR ($CDCl_3$), δ 7.22 (1H, d, J=8.0 Hz, H7); 7.42 (1H, dd, J=6.6, 1.0 Hz, H4); 7.40 (1H, td, J=6.2, 1.5 Hz, H6); 7.24 (1H, td, J=7.7, 1.1 Hz, H5); 4.24 (1H, ddd, J=11.3, 6.3, 4.8 Hz, H9A), 3.40 (1H, ddd, J=11.3, 8.8, 5.9 Hz, H9B), 3.99 (3H, s, NCO_2CH_3), 3.69 (3H, s, CO_2CH_3); 3.57 (1H, br s, OH); 2.48 (1H, ddd, J=14.3, 8.4, 6.3 Hz, H8A); 2.28 (1H, ddd, J=14.3, 5.9, 5.1 Hz, H8B). ^{13}C NMR ($CDCl_3$), δ 176.2 (C=O lactam); 155.3 (OCO_2Me); 151.3 (NCO_2Me); 139.0 (C7a); 130.5 (C3a); 128.3 (C6); 125.5 (C5); 124.1 (C4); 115.6 (C7); 74.8 (C3); 63.2 (C9); 55.0 (OCO_2CH_3); 54.1 (NCO_2CH_3); 37.7 (C8). IR ($CHCl_3$) ν_{max} 3550, 3030, 3022, 3010, 2356, 1802, 1748, 1440, 1276 cm^{-1}. EIMS m/z (relative intensity) 309 (M^+, 25), 281 (7), 205 (40), 178 (26), 146 (100), 83 (11). Anal. Calcd for $C_{14}H_{15}NO_7$: C 54.37; H 4.89; N 4.53. Found: C 54.69; H 4.69; N 4.55.

4.3.5. Methyl(1-acetyl-3-hydroxy-2-oxo-2,3-dihydroindol-3-yl)acetate (20). Prepared from **25** as a white solid (0.562 g, 69%), mp 111–112 °C (AcOEt/hexane). ^{1}H NMR ($CDCl_3$), δ 8.21 (1H, d, J=8.0 Hz, H7); 7.42 (1H, d, J=7.4 Hz, H4); 7.39 (1H, td, J=8.5, 1.1 Hz, H6); 7.24 (1H, t, J=7.3 Hz, H5); 4.41 (1H, br s, OH); 3.61 (3H, s, CO_2CH_3); 3.12 and 2.99 (2H, AB system, J=16.2 Hz, H8); 2.61 (3H, s, $NCOCH_3$). ^{13}C NMR ($CDCl_3$), δ 177.5 (C=O lactam); 171.1 (C=O amide); 170.5 (CO_2Me); 140.4 (C7a); 131.0 (C6); 128.4 (C3a); 126.0 (C5); 123.7 (C4); 117.2 (C7); 73.6 (C3); 52.5 (CO_2CH_3); 42.0 (C8); 26.7 ($NCOCH_3$). IR (KBr) ν_{max} 3429, 2958, 2939, 1776, 1731, 1683, 1607, 1479 cm^{-1}. EIMS m/z (relative intensity) 263 (M^+, 35), 221 (94), 161 (100), 146 (96), 120 (23), 90 (38). Anal. Calcd for $C_{13}H_{13}NO_5$: C 59.31; H 4.98; N 5.32. Found: C 59.40; H 5.00; N 5.23.

4.3.6. 3-Hydroxy-3-[2-(tosyloxy)ethyl]-2-indolinone (21). Prepared from **27** as a white solid (0.162 g, 65%), mp 142–143 °C (decomp.) (EtOAc/hexane). Lit.[2b] 144–145 °C. The later referred work contains ^{1}H NMR data where the H5 and H6 signals are reversed, while the ^{13}C NMR signals are unassigned. ^{13}C NMR (acetone-d_6), δ 179.1 (C=O lactam); 145.7 (C4′); 142.2 (C7a); 133.8 (C1′); 131.5 (C3a); 130.8 (C3′, C5′); 130.2 (C6); 128.5 (C2′, C6′); 124.9 (C4); 122.9 (C5); 110.8 (C7); 74.8 (C3); 67.0 (C9); 37.4 (C8); 21.5 (CH_3).

4.3.7. (1-Methyl-3-hydroxy-2-oxo-2,3-dihydroindol-3-yl)acetonitrile (22). Prepared from **29** as colorless crystals (0.138 g, 83%), mp 130–131 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.64 (1H, ddd, J=7.5, 1.3, 0.7 Hz,

H4), 7.41 (1H, td, J=7.5, 1.3 Hz, H6); 7.17 (1H, td, J=7.5, 0.9 Hz, H5); 6.91 (1H, br d, J=7.7 Hz, H7); 4.62 (1H, s, OH); 3.20 (3H, s, CH_3); 2.97 and 2.65 (2H, AB system, J=16.5 Hz, H8). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 175.5 (C=O lactam); 142.6 (C7a); 130.8 (C6); 127.6 (C3a); 124.1 (C4); 123.8 (C5); 115.4 (CN); 109.1 (C7); 72.6 (C3); 27.3 (C8); 26.6 (CH_3). IR ($CHCl_3$) ν_{max} 3362, 2258, 1724 cm^{-1}. EIMS m/z (relative intensity) 202 (M^+, 23), 162 (100). FABHRMS m/z 202.0744 (M^+, $C_{11}H_{10}N_2O_2$ requires 202.0742).

4.3.8. Methyl(3a-hydroxy-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo-[2,3-*b*]indole)-8-carboxylate (31). Prepared from **15** as a white solid (0.486 g, 96%), mp 150–152 °C (Et_2O). ^{1}H NMR (DMSO-d_6), δ 7.74 (1H, br s, H7); 7.54 (1H, d, J=7.7 Hz, H4); 7.43 (1H, t, J=7.8 Hz, H6); 7.19 (1H, t, J=7.3 Hz, H5); 6.56 (1H, s, OH); 6.17 (1H, s, H8a); 3.86 (3H, s, OMe); 3.29 and 3.23 (2H, AB system, J=18 Hz, H3). ^{13}C NMR (DMSO-d_6), δ 172.6 (C=O lactone); 152.3 (NCO_2Me); 140.2 (C7a); 132.6 (C3b); 130.6 (C6); 125.3 (C4); 124.3 (C5); 114.9 (C7); 96.2 (C8a); 79.8 (C3a); 35.4 (OMe); 40.6 (C3). IR (KBr) ν_{max} 3408, 3018, 1792, 1706, 1604, 1488, 1450, 1396 cm^{-1}. EIMS m/z (relative intensity) 249 (M^+, 82), 221 (18), 204 (30), 193 (32), 176 (30), 161 (26), 146 (100), 132 (33), 77 (52), 59 (56). Anal. Calcd for $C_{12}H_{11}NO_5$: C 57.83; H 4.45; N 5.62. Found: C 58.02; H 4.44; N 5.27.

4.3.9. Methyl oxindole-3-acetate (24). To a stirred solution of **23** (1.45 g, 7.58 mmol) in MeOH (20 mL) was added *p*-toluensulfonic acid (43 mg) and heated under reflux for 7 h. After cooling to room temperature, the MeOH was evaporated under reduced pressure and the residue was dissolved with EtOAc (50 mL). The organic phase was washed with a saturated solution of $NaHCO_3$ (2×20 mL) and brine (2×20 mL), dried over Na_2SO_4 and evaporated to dryness in vacuo. The residue was purified by flash column chromatography eluting with EtOAc/hexane 2:3 to give **24** as colorless crystals (1.20 g, 77%), mp 168–170 °C (EtOAc/hexane). Lit.[1a] 170–172 °C. Lit.[15a] 164–167 °C. Although **24** is known,[1a,15a] it is spectroscopically not yet fully characterized. Thus, NMR data follow: ^{1}H NMR (DMSO-d_6), δ 10.44 (1H, br s, NH); 7.19 (1H, d, J=7.7 Hz, H4); 7.16 (1H, t, J=7.7 Hz, H6); 6.91 (1H, t, J=7.3 Hz, H5); 6.83 (1H, d, J=7.7 Hz, H7); 3.67 (1H, t, J=5.9 Hz, H3); 3.55 (3H, s, CO_2CH_3); 2.98 (1H, dd, J=16.9, 5.1 Hz, H8A); 2.82 (1H, dd, J=16.8, 7.0 Hz, H8B). ^{13}C NMR (DMSO-d_6), δ 178.0 (C=O lactam); 171.2 (CO_2Me); 142.9 (C7a); 129.0 (C3a); 127.9 (C6); 123.6 (C4); 121.3 (C5); 109.3 (C7); 51.6 (CO_2CH_3); 41.8 (C3); 33.6 (C8). IR (KBr) ν_{max} 3150, 3026, 2947, 2880, 2821, 2731, 1726, 1702, 1622, 1488 cm^{-1}. EIMS m/z (relative intensity) 205 (M^+, 30), 173 (34), 145 (100), 128 (35), 117 (52), 90 (26), 77 (26). FABHRMS m/z 206.0822 (MH^+, $C_{11}H_{11}NO_3$ requires 206.0817).

4.3.10. Methyl(1-acetyl-2-oxo-2,3-dihydroindol-3-yl)-acetate (25). To a stirred solution of **24** (0.239 g, 1.16 mmol) in Ac_2O (20 mL) was added pyridine (2 mL), heated at reflux for 9 h, cooled to room temperature and diluted with EtOAc (30 mL). The organic phase was washed with 10% aqueous HCl (2×20 mL) and brine (2×20 mL), dried over Na_2SO_4 and evaporated to dryness in vacuo. The resultant crude product was purified by flash column chromatography eluting with EtOAc/hexane 3:1 to give **24** as a yellow oil (0.264 g, 92%). ^{1}H NMR ($CDCl_3$), δ 8.22 (1H, d, J=7.7 Hz, H7); 7.31 (1H, t, J=6.9 Hz, H6); 7.23 (1H, d, J=7.4 Hz, H4); 7.17 (1H, td, J=7.3, 1.1 Hz, H5); 3.91 (1H, t, J=5.5 Hz, H3); 3.64 (3H, s, CO_2CH_3); 3.09 (1H, dd, J=17.2, 4.8 Hz, H8A); 3.00 (1H, dd, J=17.2, 6.5 Hz, H8B); 2.67 (3H, s, $NCOCH_3$). ^{13}C NMR ($CDCl_3$), δ 178.2 (C=O lactam); 171.0 (C=O amide); 170.9 (CO_2Me); 140.9 (C7a); 128.4 (C6); 127.2 (C3a); 125.2 (C5); 123.2 (C4); 116.8 (C7); 52.3 (CO_2CH_3); 42.7 (C3); 35.1 (C5); 26.7 ($NCOCH_3$). IR (KBr) ν_{max} 2958, 2939, 1776, 1732, 1684, 1569, cm^{-1}. EIMS m/z (relative intensity) 247 (M^+, 23), 205 (29), 173 (19), 145 (100), 117 (34), 90 (12). Anal. Calcd for $C_{13}H_{13}NO_4$: C 63.15; H 5.30; N 5.66. Found: C 63.26; H 5.49; N 5.24.

4.3.11. 3-(2-Hydroxyethyl)-2-indolinone (26). To a solution of **10** (0.250 g, 1.55 mmol) in dimethyl sulfoxide (DMSO) (0.120 mL, 1.55 mmol) were added 0.31 mL (3.1 mmol) of 36% aqueous HCl and the mixture was stirred at room temperature for 6 h, diluted with EtOAc (30 mL) and neutralized with saturated solution of $NaHCO_3$. The aqueous layer was separated and extracted with EtOAc (2×30 mL), the combined organic layers were washed with brine (2×30 mL), dried over Na_2SO_4 and evaporated to dryness in vacuo. The resultant crude product was purified by flash column chromatography eluting with EtOAc/hexane 1:4 to give **26** as white crystals (0.197 g, 72%), mp 109–111 °C (EtOAc/hexane). Lit.[2a] 111–112. Lit.[2b] 112–114 °C.

4.3.12. 3-[2-(Tosyloxy)ethyl]-2-indolinone (27). To a solution of **26** (0.322 g, 1.8 mmol) in pyridine (7 mL) was added *p*-toluenesulfonyl chloride (0.416 g, 2.2 mmol) and the mixture stirred for 3 h at room temperature. The reaction mixture was poured onto a cold 10% aqueous HCl solution and extracted with EtOAc (4×30 mL). The combined organic layers were washed with brine (2×30 mL), dried and evaporated to dryness in vacuo. The resultant crude product was purified by flash column chromatography eluting with EtOAc/hexane 1:1 to give **27** as colorless crystals (0.516 g, 86%), mp 111–114 °C (EtOAc/hexane). Lit.[16] 115–116 °C. ^{1}H NMR ($CDCl_3$), δ 9.40 (1H, br s, NH); 7.73 (2H, d, J=8.0 Hz, H2′, H6′); 7.31 (2H, d, J=8.1 Hz, H3′, H5′); 7.18 (1H, t, J=7.6, Hz, H6); 7.09 (1H, d, J=7.3 Hz, H4); 6.97 (1H, t, J=7.7 Hz, H5); 6.89 (1H, d, J=7.7 Hz, H7); 4.26 (2H, t, J=6.6 Hz, H9); 3.50 (1H, t, J=6.6 Hz, H3); 2.41 (3H, s, CH_3); 2.24 (2H, m, H8). ^{13}C NMR ($CDCl_3$), δ 179.9 (C=O lactam); 144.9 (C4′); 141.7 (C7a); 132.6 (C1′); 129.9 (C3′, C5′); 128.3 (C6); 128.1 (C3a); 127.8 (C2′, C6′); 124.1 (C4); 122.4 (C5); 110.2 (C7); 67.3 (C9); 42.3 (C3); 29.7 (C8); 21.6 (CH_3). IR ($CHCl_3$) ν_{max} 3185, 3084, 1702, 1622, 1430, 1358, 1227 cm^{-1}. EIMS m/z (relative intensity) 160 ($M^+ - C_7H_7SO_3$, 14), 159 (100), 144 (99), 130 (74), 77 (21), 51 (14).

4.3.13. (2-Oxo-2,3-dihydroindol-3-yl)acetonitrile (28). To a solution of **12** (1.5 g, 9.6 mmol) in neat DMSO (0.687 mL, 9.6 mmol) were added 1.9 mL (19.2 mmol) of 36% aqueous HCl and the mixture was stirred for 10 h at room temperature, diluted with water (100 mL), neutralized with $NaHCO_3$, and extracted with EtOAc (4×25 mL). The organic layer was washed with brine (2×20 mL), dried

and evaporated to dryness in vacuo. The resultant crude product was crystallized to give **28** as pale yellow crystals (1.3 g, 78%), mp 163–165 °C (EtOAc/hexane). ^{1}H NMR (DMSO-d_6), δ 10.62 (1H, s, NH); 7.39 (1H, d, J=7.4 Hz, H4); 7.24 (1H, t, J=7.7 Hz, H6); 7.01 (1H, t, J=7.5 Hz, H5); 6.88 (1H, d, J=7.7 Hz, H7); 3.82 (1H, t, J=5.9 Hz, H3), 3.20 (1H, dd, J=17.2, 5.8 Hz, H8A), 3.06 (1H, dd, J=17.2, 5.9 Hz, H8B). ^{13}C NMR (DMSO-d_6), δ 176.4 (C=O lactam); 142.8 (C7a); 128.6 (C6), 127.1 (C3a), 124.2 (C4), 121.6 (C5); 118.2 (CN); 109.6 (C7); 41.3 (C3); 17.6 (C8). IR (KBr) ν_{max} 3137, 2966, 2897, 2249, 1708, 1247 cm^{-1}. EIMS *m/z* (relative intensity) 172 (M^+, 65), 132 (100), 77 (33), 51 (37). Anal. Calcd for $C_{10}H_8N_2O$: C 69.76; H 4.68; N 16.27. Found: C 69.87; H 4.74; N 15.91.

4.3.14. Methyl 3-isatylideneacetate (32). To a stirred solution of **18** (0.250 g, 0.895 mmol) in MeOH (20 mL) was added NaH (5.4 mg, 0.23 mmol) and heated under reflux for 15 min. After cooling to room temperature the MeOH was evaporated under reduced pressure and the residue was dissolved with EtOAc (30 mL). The organic phase was washed with saturated solution of NH_4Cl (2×20 mL) and brine (2×20 mL), dried over Na_2SO_4 and evaporated to dryness in vacuo. The resultant crude product was purified by flash column chromatography eluting with EtOAc/hexane 2:3 to give **1** (82 mg, 42%) and **32** as an orange solid (0.086 g, 47%), mp 181–182 °C (EtOAc/hexane). Lit.[20b] 178–180 °C. ^{13}C NMR ($CDCl_3$), δ 169.4 (C=O lactam); 166.2 (CO_2Me); 143.5 (C7a); 138.6 (C3); 132.9 (C6); 129.2 (C4); 123.1 (C5); 122.2 (C8); 120.5 (C3a); 110.4 (C7); 52.4 (CO_2CH_3).

4.3.15. 3a-Hydroxy-8-methyl-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole (33). To a cooled solution of **18** (0.2 g, 0.72 mmol) in dry THF (20 mL) was added $LiAlH_4$ (0.2 g, 5.26 mmol). The resulting mixture was stirred under reflux for 3 h, then quenched with EtOAc (25 mL) and with cold water (40 mL). The solids were filtered off and the organic layer was separated. The aqueous phase was extracted with EtOAc (3×20 mL) and the combined organic layers were washed with brine (3×20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography eluting with EtOAc/hexane 2:3 to give **33** as a brown oil (0.029 g, 21%). ^{1}H NMR ($CDCl_3$), δ 7.25 (1H, dd, J=7.3, 1.1 Hz, H4); 7.19 (1H, td, J=7.6, 1.1 Hz, H6); 6.72 (1H, td, J=7.5, 1.1 Hz, H5); 6.41 (1H, d, J=8.1 Hz, H7); 5.11 (1H, s, H8a); 4.01 (1H, ddd, J=9.2, 7.7, 2.2 Hz, H2A); 3.56 (1H, ddd, J=11.0, 9.2, 5.5 Hz, H2B); 2.88 (3H, s, CH_3); 2.60 (1H, br s, OH); 2.39 (1H, ddd, J=12.1, 11.0, 7.7 Hz, H3A); 2.27 (1H, ddd, J=5.5, 2.2 Hz, H3B). ^{13}C NMR ($CDCl_3$), δ 151.1 (C7a); 130.5 (C6); 130.4 (C3b); 123.7 (C4); 117.9 (C5); 106.1 (C7); 105.0 (C8a); 88.0 (C3a); 67.5 (C2); 41.3 (C3); 31.4 (CH_3). IR (KBr) ν_{max} 3399, 3052, 2929, 1610, 1481 cm^{-1}. EIMS *m/z* (relative intensity) 191 (M^+, 100), 160 (82), 146 (32), 118 (26), 106 (29), 91 (26), 77 (41), 51 (20). FABHRMS *m/z* 190.0867 (M−1, $C_{11}H_{13}NO_2$ requires 190.0868).

4.3.16. Methyl(3-hydroxy-1-carbomethylamin-2-oxo-2,3-dihydroindol-3-yl)acetamide (34). Excess methylamine (4 mL) was condensed at −78 °C in a flask containing **18** (0.2 g, 0.72 mmol). The cooling bath was removed and the reaction mixture was stirred until the excess methylamine was evaporated. The solid residue was washed with Et_2O to afford **34** as a white solid (0.195 g, 98%), mp 217–218 °C (decomp.). ^{1}H NMR ($CDCl_3$), δ 10.08 (1H, br s, OH); 7.97, 7.76 (2H, 2c, J=4.4 Hz, 2N*H*Me); 7.35 (1H, dd, J=7.7, 1.1 Hz, H7); 7.21 (1H, td, J=7.7, 1.1 Hz, H5); 6.95 (1H, td, J=7.1, 1.1 Hz, H6); 6.81 (1H, dd, J=7.6, 0.6 Hz, H4); 3.00 (2H, s, H8); 2.59, 2.48 (6H, 2d, J=4.8 Hz, NHCH_3). ^{13}C NMR ($CDCl_3$), δ 169.3 (C=O urea); 167.3 (C=O amide); 148.7 (C=O lactam); 134.9 (C7a); 129.1 (C5); 124.7 (C7); 122.2 (C6); 119.6 (C3a); 113.9 (C4); 84.1 (C3); 43.6 (C8); 26.2, 25.3 (2NHCH_3). IR (KBr) ν_{max} 3358, 3313, 2999, 2945, 1745, 1649, 1600 cm^{-1}. EIMS *m/z* (relative intensity) 277 (M^+, 3.4), 220 (100), 202 (62), 162 (54), 144 (71), 118 (40), 58 (40), 44 (60). FABHRMS *m/z* 278.1140 (MH^+, $C_{13}H_{15}N_3O_4$ requires 278.1141).

4.4. General procedure for the prenylation of 35 and 36

To a solution of **1** (0.205 g, 0.93 mmol) or **4** (0.100 g, 0.57 mmol) in acetone (15 mL) were added 268 μL of prenyl bromide (2.3 mmol) and 321 mg of K_2CO_3 (2.3 mmol) or 193 μL (1.44 mmol) and 199 mg of K_2CO_3 (1.44 mmol), respectively, and the mixture was heated under reflux for 4 h. After cooling to room temperature, the solid was filtered off and washed with acetone (2×10 mL), the volatiles were evaporated under reduced pressure and the residue was dissolved with EtOAc (100 mL). The organic layer was washed with brine (2×20 mL), dried over Na_2SO_4 and evaporated to dryness in vacuo. The crude product was purified by flash column chromatography eluting with EtOAc/hexane 2:3.

4.4.1. Methyl[3-hydroxy-1-(3-methyl-2-buten-1-yl)-2-oxo-2,3-dihydroindol-3-yl]acetate (35). Prepared from **1** as colorless crystals (0.261 g, 97%), mp 172–174 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$), δ 7.39 (1H, dd, J=7.2, 0.7 Hz, H4); 7.30 (1H, td, J=7.6, 1.1 Hz, H6); 7.06 (1H, td, J=7.7, 0.7 Hz, H5); 6.80 (1H, d, J=7.2 Hz, H7); 5.18 (1H, br t, J=6.6 Hz, H9); 4.55 (1H, br s, OH); 4.32 (1H, dd, J=16.9, 6.6 Hz, H8A); 4.27 (1H, dd, J=16.5, 6.6 Hz, H8B); 3.64 (3H, s, OCH_3); 2.99 and 2.93 (2H, AB system, J=16.1 Hz, H13); 1.82, 1.72 (6H, 2s, Me11, Me12). ^{13}C NMR ($CDCl_3$), δ 175.8 (C=O lactam); 170.7 (CO_2CH_3); 142.9 (C7a); 136.9 (C10); 130.0 (C6); 129.3 (C3a); 123.9 (C4); 123.0 (C5); 118.0 (C9); 109.3 (C7); 73.5 (C3); 52.0 (OMe); 41.4 (C13); 38.2 (C8); 25.6, 18.2 (Me11, Me12). IR ($CHCl_3$) ν_{max} 3278, 3010, 2918, 1737, 1694, 1616, 1433, 1407 cm^{-1}. EIMS *m/z* (relative intensity) 289 (M^+, 43), 271 (21), 221 (28), 212 (30), 161 (81), 146 (100), 69 (38). Anal. Calcd for $C_{16}H_{19}NO_4$: C 66.42; H 6.62; N 4.84. Found: C 66.39; H 6.67; N 4.44.

4.4.2. [3-Hydroxy-1-(3-methyl-2-buten-1-yl)-2-oxo-2,3-dihydroindol-3-yl]acetonitrile (36). Prepared from **4** as colorless crystals (0.141 g, 96%), mp 116–118 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$), δ 7.64 (1H, d, J=7.3 Hz, H4); 7.37 (1H, td, J=7.7, 1.1 Hz, H6); 7.15 (1H, td, J=7.7, 0.8 Hz, H5); 6.86 (1H, d, J=8.0 Hz, H7); 5.13 (1H, br t, J=6.9 Hz, H9), 4.82 (1H, s, OH); 4.33 (1H, dd, J=15.4, 6.6 Hz, H8A) 4.23 (1H, dd, J=15.4, 6.6 Hz, H8B) 3.02 and 2.68 (2H, AB system, J=16.8, 16.4 Hz, H13); 1.80, 1.71 (6H, s, Me11, Me12); 1.71 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$),

δ 175.3 (s, C=O lactam); 142.1 (C7a); 137.7 (C10); 130.7 (C6); 127.9 (C3a); 124.3 (C4); 123.8 (C5); 117.3 (C9); 115.5 (CN); 109.9 (C7); 72.7 (C3); 38.3 (C8); 27.4 (C13); 25.6, 18.2 (Me11, Me12). IR (KBr) ν_{max} cm^{-1} 3282, 2968, 2850, 2251, 1702, 1243, 1617, 1107, 825. EIMS *m/z* (relative intensity) 256 (M^+, 26), 238 (7), 188 (29), 170 (20), 148 (85), 69 (100). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C 70.29; H 6.29; N 10.93. Found: C 69.88; H 6.28; N 10.55.

4.4.3. Methyl(3-hydroxy-1-(3-methyl-2-buten-1-yl)-2-oxo-2,3-dihydroindol-3-yl)acetamide (37). To a solution of **35** (0.5 g, 1.73 mmol) in MeOH (10 mL) was added 40% aqueous $MeNH_2$ (3.3 mL). The mixture was stirred at room temperature for 16 h, then diluted with EtOAc (100 mL) and washed with saturated solution of NH_4Cl (3×20 mL) and brine (2×20 mL), dried over Na_2SO_4 and evaporated to dryness in vacuo. The resultant crude product was purified by flash column chromatography with EtOAc/hexane 4:1 to give **37** as a yellow oil (0.490 g, 98%). ^1H NMR ($CDCl_3$), δ 7.39 (1H, dd, *J*=7.7, 1.1 Hz, H4); 7.28 (1H, td, *J*=7.7, 1.1 Hz, H6); 7.05 (1H, td, *J*=7.3, 0.7 Hz, H5); 6.78 (1H, d, *J*=8.0 Hz, H7); 6.22 (1H, br s, NH); 5.82 (1H, br s, OH); 5.13 (1H, br t, *J*=6.6 Hz, H9); 4.28 (1H, dd, *J*=16.4, 6.9 Hz, H8A); 4.23 (1H, dd, *J*=16.9, 6.6 Hz, H8B); 2.85 (3H, d, *J*=5.1 Hz, NMe); 2.74, 2.50 (2H, AB system, *J*=15.0 Hz, H13); 1.80, 1.70 (6H, 2s, Me11, Me12). ^{13}C NMR ($CDCl_3$), δ 176.1 (C=O lactam); 170.9 (C=O amide); 142.2 (C7a); 137.1 (C10); 130.2 (C3a); 129.7 (C6); 124.1 (C4); 123.2 (C5); 118.0 (C9); 109.3 (C7); 74.4 (C3); 41.9 (C13); 38.2 (C8); 26.3 (NMe); 25.6, 18.15 (Me11, Me12). IR (KBr) ν_{max} 3330, 2972, 2933, 1714, 1650, 1614, 1557, 1488, 1469 cm^{-1}. EIMS *m/z* (relative intensity) 288 (M^+, 50), 270 (63), 212 (95), 192 (24), 161 (100), 146 (53), 69 (29). FABHRMS *m/z* 289.1537 (MH^+, $C_{16}H_{20}N_2O_3$ requires 289.1552).

4.5. General procedure for the $LiAlH_4$ reduction of 36 and 22

To a solution of **36** (0.5 g, 1.95 mmol) or **22** (0.48 g, 2.37 mmol) in anhydrous THF (20 mL), cooled at 5 °C, was added $LiAlH_4$ (0.297 g, 7.8 mmol for **36** and 0.087 g, 2.30 mmol for **22**). The resulting mixture was stirred under reflux for 0.25 h for **36** and at room temperature for 3 h for **22**, cooled and quenched dropwise with cold H_2O (25 mL) and EtOAc (25 mL). The solids were filtered off through a Celite pad, washed with EtOAc (80 mL) and the organic phase was washed with brine (2×20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resultant crude product **38** was crystallized from EtOAc/hexane and **39** was purified by flash chromatography eluting with CH_2Cl_2/MeOH 19:1.

4.5.1. 3a-Hydroxy-8-(3-methyl-2-buten-1-yl)-1,2,3,3a,8a-hexahydropyrrolo[2,3-*b*]indole (38). Prepared from **36** as colorless crystals (0.222 g, 47%), mp 164–166 °C. ^1H NMR ($CDCl_3$), δ 7.23 (1H, dd, *J*=7.3, 1.1 Hz, H4); 7.12 (1H, td, *J*=7.7, 1.1 Hz, H6); 6.68 (1H, t, *J*=7.3 Hz, H5); 6.41 (1H, d, *J*=8.0 Hz, H7); 5.19 (1H, br t, H10); 4.63 (1H, s, H8a); 3.82 (1H, dd, *J*=15.7, 7.3 Hz, H9A); 3.75 (1H, dd, *J*=15.8, 6.2 Hz, H9B); 3.07 (2H, br s, OH, NH); 3.03 (1H, ddd, *J*=13.6, 7.0, 2.6 Hz, H2A); 2.76 (1H, ddd, *J*=14.6, 10.6, 6.3 Hz, H2B); 2.14 (2H, m, H3); 1.73, 1.70 (6H, 2s, Me12, Me13). ^{13}C NMR ($CDCl_3$), δ 150.6 (C7a); 135.7 (C11); 131.8 (C3b); 129.9 (C6); 123.8 (C4); 120.1 (C10); 117.6 (C5); 106.8 (C7); 90.6 (C8a); 88.4 (C3a); 45.7 (C3); 43.4 (C9); 42.4 (C2); 29.9, 18.2 (Me12, Me13). IR (KBr) ν_{max} 3435, 3245, 3052, 3029, 2971, 2929, 2902, 2636, 1610, 1489, 1467 cm^{-1}. EIMS *m/z* (relative intensity) 244 (M^+, 50), 226 (22), 224 (22), 211 (26), 158 (100), 157 (96), 130 (39), 129 (24), 69 (43). Anal. Calcd for $C_{15}H_{20}N_2O$: C 73.74; H 8.25; N 11.47. Found: C 73.65; H 8.58; N 11.13.

4.5.2. 3a-Hydroxy-8-methyl-1,2,3,3a,8a-hexahydropyrrolo[2,3-*b*]indole (39). Prepared from **22** as colorless crystals (0.226 g, 50%), mp 127–128 °C (acetone/CH_2Cl_2). Lit., [3d] mp 126–128 °C. Although compound **39** is known,[3d] no spectral characterization has been given. Thus, NMR data follow. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25 (1H, dd, *J*=7.4, 1.4 Hz, H4); 7.17 (1H, td, *J*=7.4, 1.4 Hz, H6); 6.70 (1H, td, *J*=7.4, 1.1 Hz, H5); 6.41 (1H, br d, *J*=8.0 Hz, H7); 4.59 (1H, s, H8a); 3.17 (1H, m, H2A); 2.83 (3H, s, NCH_3); 2.82 (1H, m, H2B), 2.20 (2H, m, H3A, H3B); ^{13}C NMR ($CDCl_3$) δ 151.0 (C7a); 131.3 (C3b); 129.7 (C6); 123.4 (C4); 117.4 (C5); 106.2 (C7); 92.8 (C8a); 88.3 (C3a); 45.9 (C2); 42.2 (C3); 32.3 (NCH_3).

4.5.3. 3a-Hydroxy-1,8-dimethyl-1,2,3,3a,8a-hexahydropyrrolo[2,3-*b*]indole (40). To a solution of pyrroloindole **39** (0.30 g, 1.8 mmol) in MeOH (11 mL) at room temperature was added 37% aqueous CH_2O (1 mL, 12.3 mmol). The resulting mixture was stirred at this temperature for 3 h, then cooled to 0 °C, and $NaBH_4$ (0.261 g, 6.9 mmol) was added portionwise over 5 min. After stirring the mixture for 1 h at room temperature, the solvent was removed under reduced pressure, the residue was treated dropwise with H_2O (18 mL) and Et_2O (40 mL). The aqueous layer was extracted with Et_2O (2×40 mL) and the combined organic layers were washed with brine (1×60 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with acetone/EtOAc 9:1, yielding 0.287 g (89%) of the title compound as colorless crystals, mp 68–69 °C (CH_2Cl_2/MeOH 4:1). Although compound **40** is known,[23] it is spectroscopically not yet fully characterized. Thus, NMR data follows: ^1H NMR ($CDCl_3$, 300 MHz), δ 7.23 (1H, dd, *J*=7.5, 1.3 Hz, H4); 7.19 (1H, td, *J*=7.5, 1.3 Hz, H6); 6.74 (1H, td, *J*=7.5, 0.7 Hz, H5); 6.49 (1H, br d, *J*=7.9 Hz, H7); 4.21 (1H, s, H8a); 2.94 (3H, s, CH_3); 2.82 (1H, m, H2A); 2.63 (1H, m, H2B); 2.55 (3H, s, CH_3); 2.29 (1H, m, H3A); 2.16 (1H, m, H3B). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 152.0 (C7a); 131.8 (C3b); 130.0 (C6); 123.3 (C4); 118.5 (C5); 108.0 (C7); 97.9 (C8a); 88.2 (C3a); 53.1 (C2); 40.2 (C3); 38.3 (N1 CH_3); 36.9 (N8 CH_3).

4.5.4. 3a-Hydroxy-1-methyl-8-(3-methyl-2-buten-1-yl)-1,2,3,3a,8a-hexahydropyrrolo[2,3-*b*]indole (8). *Method A*. To a cool solution of **37** (0.362 g, 1.3 mmol) in dry THF (20 mL) was added $LiAlH_4$ (0.143 mg, 3.8 mmol). The resulting mixture was stirred under reflux for 5 h, quenched with EtOAc (50 mL) and with cold water (120 mL). The mixture was filtrated and the organic layer was separated and washed with saturated solution of NH_4Cl (3×30 mL) and brine (2×20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column

chromatography eluting with EtOAc/hexane 4:1 to give **8** (0.179 mg, 55%) as a pale yellow oil.

Method B. To a solution of **38** (0.255 g, 1.0 mmol) in MeOH (10 mL) was added CH_2O (0.665 mL, 8.8 mmol) and the mixture was stirred at room temperature for 5 h. The mixture was cooled and $NaBH_4$ (173.0 mg, 4.54 mmol) was added, then warmed to room temperature and stirred for 2 h. The volatiles were evaporated, water (50 mL) was added and extracted with Et_2O (4×20 mL). The organic phase was washed with brine (2×25 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography eluting with EtOAc/hexane 4:1 to give **8** (0.127 g, 47%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$), δ 7.24 (1H, dd, J=7.3, 0.7 Hz, H4); 7.14 (1H, td, J=8.1, 1.5 Hz, H6); 6.73 (1H, td, J=7.3, 0.7 Hz, H5); 6.51 (1H, d, J=8.0 Hz, H7); 5.22 (1H, br t, J=6.0 Hz, H10); 4.32 (1H, s, H8a); 3.88 (1H, dd, J=16.0, 8.4 Hz, H9A); 3.82 (1H, dd, J=16.1, 8.4 Hz, H9B); 3.02 (1H, br s, OH); 2.79 (1H, ddd, J=9.2, 6.8, 4.8 Hz, H2A); 2.62 (1H, ddd, J=8.6, 8.5, 6.9 Hz, H2B); 2.50 (3H, s, NCH_3); 2.28 (1H, ddd, J=12.4, 8.1, 6.9 Hz, H3A); 2.16 (1H, ddd, J=12.4, 5.9, 4.8 Hz, H3B); 1.72, 1.70 (6H, 2s, Me12, Me13). ^{13}C NMR ($CDCl_3$), δ 151.4 (C7a); 134.7 (C11); 132.5 (C3b); 129.7 (C6); 123.3 (C4); 120.7 (C10); 118.2 (C5); 108.5 (C7); 95.5 (C8a); 88.3 (C3a); 53.0 (C2); 47.1 (C9); 40.4 (C3); 38.5 (NCH_3); 25.7, 18.2 (Me12, Me13). IR (KBr) ν_{max} 3354, 3050, 2964, 2928, 2856, 1673, 1608, 1488, 1465 cm^{-1}. EIMS *m/z* (relative intensity) 258 (M^+, 25), 238 (41), 169 (100), 146 (20), 69 (34). FABHRMS *m/z* 259.1816 (MH^+, $C_{16}H_{22}N_2O$ requires 259.1810).

4.6. X-ray diffraction analysis of 4, 18, 22, 28, 35 and 39

Single crystal X-ray diffraction studies were done on a Bruker Smart 6000 CCD diffractometer for **4**, **18**, **28** and **35** using Mo radiation (λ=0.7073 Å). A total of 1321 frames were collected at a scan width of 0.3° and an exposure time of 10 s/frame. These data were processed with the SAINT software package, provided by the diffractometer manufacturer, by using a narrow-frame integration algorithm. An empirical absorption correction was applied. Data collections for **22** and **39** were done on a Bruker-Nonius CAD4 diffractometer using Cu radiation (λ=1.5418 Å). The structures were solved by direct methods using the SHELXS-97[25] program included in the WINGX VI.6.[26] The structural refinement was carried out by full-matrix least squares on F^2. The non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. Atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, hydrogen coordinates, calculated and observed structure factors and torsion angles are in deposit at the Cambridge Crystallographic Data Center.

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