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Preparation of *O*-Methyl Substituted 2-Oxofuro- and 2-Oxopyrrolidinoindolines by Reductive Lactonization of Oxindol-3-ylacetic Acids

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A practical procedure for the preparation of *O*-methyl substituted 3a,8-dialkyl-2-oxofuroindolines is described. Reductive lactonization of the corresponding oxindol-3-ylacetic acids provides a route for the formation of this class of compounds. Further transformation of 2-oxofuroindolines into 2-oxopyrrolidinoindolines, and then to pyrrolidinoindolines demonstrates their versatility as key intermediates in natural products synthesis. The results of single-crystal X-ray crystallographic analyses are given for five of the studied compounds.

Keywords: 2-Oxofuroindolines, 2-Oxopyrrolidinoindolines, Synthesis, Rearrangement.

Compounds bearing an *O*-methyl group on the oxindole moiety are found in a number of natural products which often display interesting biological and pharmacological activities. Representative examples include the anticancer pyrrolidinylspirooxindole alkaloids horsfiline [1], isolated from *Horsfieldia superba*, and spirotryprostatin A [2], isolated from the fermentation broth of *Aspergillus fumigatus*, as well as the *Gelsemium* alkaloids humantenirine [3], gelsemicine [4], and gelegamines A-E [5]. In addition, 3,3-disubstituted oxindoles constitute attractive targets in pharmaceutical and fine chemistry because of their potential role as key intermediates in drug research [6]. Particularly, 3,3-disubstituted oxindoles are valuable functional handles for the synthesis of pyrrolidinoindoline structures, which are common among indole alkaloids [7].

As part of our ongoing research into pyrrolidinoindoline alkaloids of chemical and pharmacological significance [8], in this study we investigated the alkylation of methyl esters **9a** and **9b** of 2-(5-methoxy-2-oxo-3-indolyl) acetic acids **7a** and **7b** employing electron-rich alkylating agents [9] in order to provide a convenient approach to functionalized 2-oxofuroindolines **1a-c** and 2-oxopyrrolidinoindolines **2a-c** (Figure 1). Compounds **2a-c** were further reduced to known pyrrolidinoindolines **3a-c** [8b].

Starting with 5-methoxyindol-3-ylacetonitrile **4a** and its *N*-benzylated derivative **4b**, the corresponding 2-(5-methoxy-2-oxo-3-indolyl)- and 2-(1-benzyl-5-methoxy-2-oxo-3-indolyl)acetic acids, **7a** and **7b**, were obtained through exploration of alternative reaction sequences, which include oxidation and hydrolysis (Scheme 1, and Table 1).

Thus, oxidation of **4a** and **4b** with DMSO/aqueous HCl at room temperature afforded **5a** and **5b** (entries 1 and 3). Oxidized products

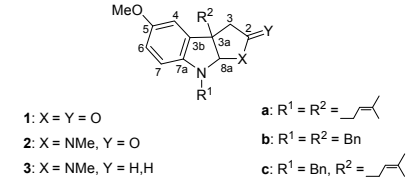
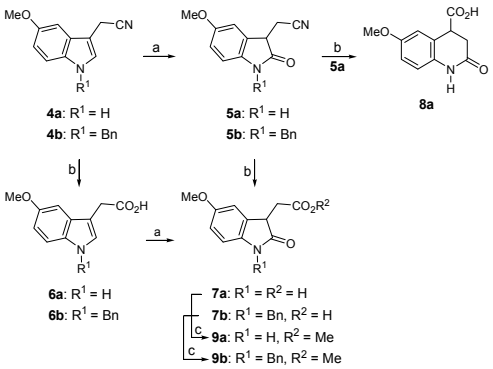


Figure 1: Structures of 2-oxofuroindolines **1a-c**, 2-oxopyrrolidinoindolines **2a-c**, and pyrrolidinoindolines **3a-c**.



Scheme 1: Preparation of methyl oxindol-3-ylacetates **9a** and **9b**. (a) DMSO, 37% aqueous HCl (1:1, v/v), rt, 1-3 h; (b) 35% aqueous KOH, MeOH, reflux, 4-8 h; (c) CH_2N_2/diethylether, rt, 20 min.

5a and **5b** were then hydrolyzed by treatment with aqueous KOH in refluxing MeOH, followed by acidic work-up to provide carboxylic acids **7a** and **7b** (entries 5 and 6). Nevertheless, it was observed that after 4 h of reaction in the manner defined above, **5a** furnished a 6:1 mixture of **7a** (59%) and quinolone **8a** (10%). Besides, starting material **5a** was recovered in 13% (entry 5). Prolonging the reaction time resulted in the formation of a higher amount of **8a** (entry 7).

The formation of **8a** appears to result from intramolecular rearrangement of **7a** arising from the basic lactone ring opening. In fact, this ring enlargement was not surprising as a similar type of transformations has been previously observed [10].

Table 1: Products and yields.

Entry	Substrate	Time (h)	Product	Yield (%)
1	**4a**[a]	1	**5a**	77
2	**4a**[b]	7	**6a**	76
3	**4b**[a]	2	**5b**	62
4	**4b**[b]	7	**6b**	74
5	**5a**[b]	4	**7a/8a**[c]	69[e]
6	**5b**[b]	6	**7b**	76
7	**5a**[b]	8	**7a/8a**[d]	75[e]
8	**6a**[a]	3	**7a**	80
9	**6b**[a]	2	**7b**	57

[a]Oxidation procedure. [b]Hydrolysis procedure. [c]In 6:1 mixture; 13% of starting material was also recovered. [d]In 4:1 mixture. [e]Global yield.

The ^{1}H NMR spectra (CD_3OD) of compounds **7a** and **8a** share structural features which seriously impede their recognition. Of particular interest was the observation that, in the case of **7a**, the CH signal of the ABX system is exchangeable. The exact structure of the structural isomers **7a** and **8a** was confirmed by means of ^{1}H,^{13}C heteronuclear couplings. Especially relevant was the splitting pattern of the CH_2 carbon, which appears as a triplet signal (δ = 36.1 ppm, J = 131 Hz) in the coupled ^{13}C spectrum of **7a**-d_1, while the CH_2 carbon in **8a** is split into a doublet of doublet of doublets centered at δ 34.5 ppm, whose values were found to be $^1J_{C,H}$ = 136 and 129 Hz, and $^2J_{C,H}$ = 4 Hz, in agreement with a conformational restricted system (Figure 2).

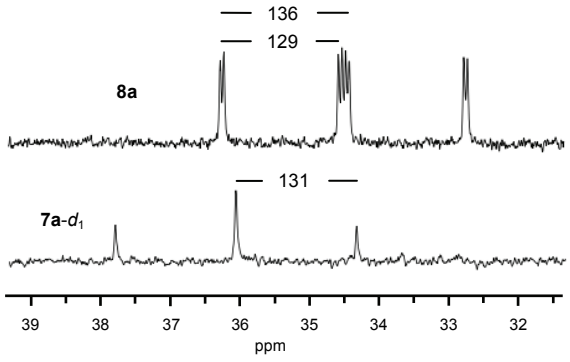


Figure 2: Coupled ^{1}H,^{13}C NMR spectra of **7a**-d_1 and **8a** (75.4 MHz, CD_3OD) illustrating the distinct heteronuclear coupling patterns (in Hz) observed for the CH_2 carbon signal.

We next examined the feasibility of preparing compounds **7a** and **7b** by initial hydrolysis of **4a** and **4b**, followed by oxidation (Scheme 1). Thus, alkaline hydrolysis of **4a** and **4b** under the same conditions described above furnished carboxylic acids **6a** and **6b** (entries 2 and 4, Table 1), which by subsequent oxidation with DMSO/aqueous HCl at room temperature for 2-3 h gave **7a** and **7b** (entries 8 and 9, Table 1). Formation of the quinolone product was detected in either case. In terms of achieving good yields, the hydrolysis and oxidation reaction sequence to transform **4a** into **7a** was more advantageous than the alternative pathway involving initial oxidation followed by hydrolysis, whereas the yield of **7b** depends little on such reaction sequence. Reaction of **7a** and **7b** with a freshly prepared solution of diazomethane in diethylether furnished the corresponding oxindol-3-ylacetates **9a** and **9b** in good yields. The structures of **7a**, **7b**, **9a** and **9b** were consistent with NMR spectroscopic and mass spectrometric data and were confirmed for **7b** and **9a** by X-ray diffraction analysis (Figure 3, Table 2 in experimental).

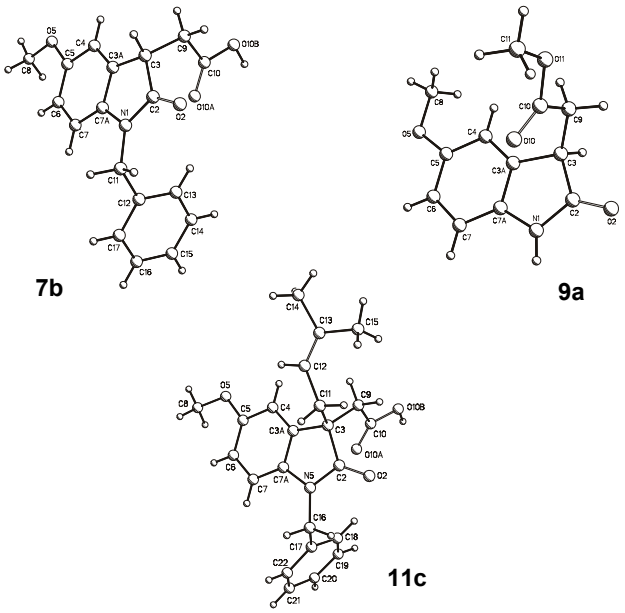
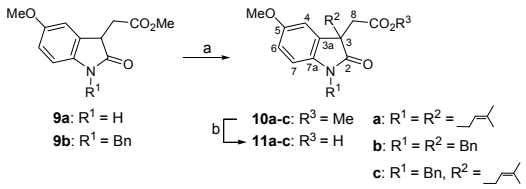


Figure 3: X-ray crystal structure of **7b**, **9a** and **11c**. The methyl groups C14 and C15 in **11c** are disordered, but only one representation is shown.

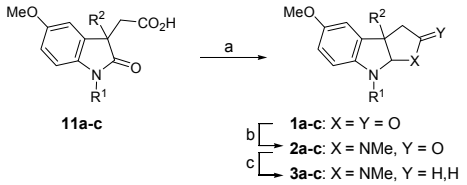


Scheme 2: Preparation of 2-(1,3-dialkyl-5-methoxy-2-oxo-3-indolyl)acetic acids **11a-c**. (a) 15% aqueous KOH, $(t\text{-Bu})_4NHSO_4$, prenylbromide or BnBr, CH_2Cl_2, rt, 4 h; (b) 15% aqueous KOH, MeOH, 40-45°C, 1.5 h.

N- and/or *C*-alkylations of **9a** and **9b** were carried out using the appropriate electron-rich alkyl halides (1.1-2.5 equiv) in mild reaction conditions, using a phase-transfer reagent, and in expected convenient chemical yields (84-88%) to give **10a-c** (Scheme 2). The yields reflect a combination of the stability of the intermediate carbonium ion arising by a simple S_N1-type nucleophilic substitution mechanism and the electron-donating substrate. The methyl 1,3-alkyloxindol-3-ylacetates **10a-c** were then subjected to alkaline hydrolysis with 15% aqueous NaOH/MeOH, followed by acidic work-up to afford the corresponding carboxylic acids **11a-c** in 73-88% yield.

The structures of 2-(1,3-dialkyl-2-oxo-3-indolyl)acetic acids **11a-c** and their esters **10a-c** were supported by analysis of the NMR and mass spectra, and confirmed for **11c** by X-ray crystallographic analysis (Figure 3, Table 2 in experimental).

The preparation of novel 2-oxopyrrolidinoindolines **2a-c** was achieved in two steps from the sodium salt of 2-(1,3-dialkyl-2-oxo-3-indolyl)acetic acids **11a-c** by reductive cyclization with $LiBHEt_3$ to produce the corresponding 2-oxofuroindolines **1a-c**, followed by treatment with methylamine in MeOH at room temperature in 55-65% global yield (Scheme 3). The structures of 2-oxofuroindolines **1a-c** and 2-oxopyrrolidinoindolines **2a-c** were supported by analysis of the NMR and mass spectra, and confirmed for **1b** and **2b** by X-ray crystallographic analysis (Figure 4, Table 2 in experimental). The 2-oxopyrrolidinoindolines **2a-c** were further reduced to the known pyrrolidinoindolines **3a-c** [8b] in nearly quantitative yields with $LiAlH_4$ in refluxing THF (Scheme 3).



Scheme 3: Preparation of 2-oxofuroindolines **1a-c**, 2-oxopyrrolidinoindolines (**2a-c**) and pyrrolidinoindolines **3a-c** (for R^1 and R^2 see Figure 1). (a) NaH/THF, rt, 10 min, then $LiBHEt_3$/THF, rt, 6 h; (b) 40% aqueous $MeNH_2$/MeOH, rt, 2-24 h; (c) $LiAlH_4$/THF, 0°C then reflux, 3 h.

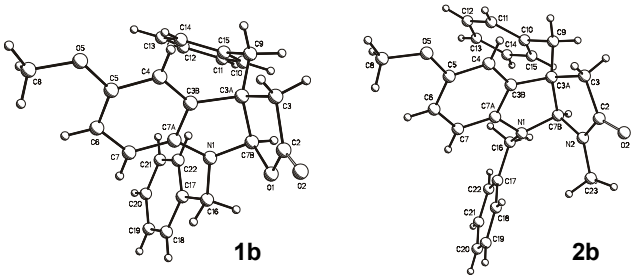


Figure 4: X-Ray crystal structure of **1b** and **2b**. The methyl group C23 in **2b** is disordered, but only one representation is shown.

In conclusion, a simple route for the synthesis of functionalized and sterically encumbered 2-oxofuroindolines **1a-c** and 2-oxopyrrolidinoindolines **2a-c** is reported, based on the alkylation of methyl oxindol-3-ylacetates **9a** and **9b**, followed by intramolecular cyclization. Compounds **2a-c** can be further reduced to pyrrolidinoindolines **3a-c**.

Experimental

General: All reagents were of commercial quality and obtained from Sigma-Aldrich (St. Louis, MO). Solvents were dried, where necessary, using standard procedures. Melting points (mp) were determined using a Fisher-Johns apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on precoated aluminum sheets (Merck TLC, silica gel 60 F254) with detection by UV light or with ceric ammonium sulfate in H_2SO_4, followed by heating. Flash chromatography was performed on silica gel 60 (230-400 mesh). IR spectra were obtained using a Perkin-Elmer 16 FPC FT spectrophotometer. NMR spectra were recorded on Mercury spectrometers working at 300 and 75.4 MHz for ^1H and ^{13}C, respectively; chemical shifts were measured in ppm (δ) relative to internal tetramethylsilane (TMS) and coupling constants (*J*) are in Hz. The spectral assignments were confirmed by standard procedures (gHMBC, gHSQC, NOESY). Signals, when declared, are expressed as s (singlet), d (doublet), t (triplet), m (multiplet), or br (broad). LRMS were recorded on a Varian Saturn 2000 spectrometer working at 70 eV. HRMS were recorded at the University of California, Riverside CA. Indoles **4a** [13], **4b** [8b], **6a** [11], and **6b** [12], oxindoles **5a** [8b], **5b** [8b], and **7a** [14], as well as pyrrolidinoindolines **3a** [8b], **3b** [8b], and **3c** [8b], are known and were synthesized using procedures described from this laboratory.

Typical hydrolysis procedure, method A: Preparation of (1-benzyl 5-methoxy-1H-indol-3-yl)acetic acid (6b): A solution of (1-benzyl-5-methoxy-1*H*-indol-3-yl)acetonitrile (**4b**) (200 mg, 0.72 mmol) in MeOH (15 mL) was treated with 35% aq KOH (8 mL) and the resulting mixture stirred for 7 h at reflux under argon. The reaction mixture was cooled in an ice/water bath prior to quenching by the addition of 1 M HCl until pH ca. 1, followed by extraction with EtOAc (2 x 30 mL). The combined organic phases were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc) to give **6b** as colorless crystals (158 mg, 74%).

MP: 124-126°C (acetone-*n*-hexane). (Lit. [12] 122-123°C).

^1H NMR (300 MHz, $CDCl_3$). Although compound **6b** is known, it is not yet spectroscopically fully characterized. Thus, NMR data follows: δ 10.49 (1H, very broad, OH), 7.29-7.19 (3H, m, H_m, H_p), 7.10 (1H, d, J = 8.9 Hz, H7), 7.07 (2H, overlapped, H_o), 7.05 (1H, overlapped, H2), 7.04 (1H, d, partially overlapped, J = 2.5 Hz, H4), 6.82 (1H, dd, J = 8.9, 2.5 Hz, H6), 5.18 (2H, s, N-CH_2), 3.81 (3H, s, Me), 3.74 (2H, s, C-CH_2).

^{13}C NMR (75.4 MHz, $CDCl_3$): 178.3 (CO_2H), 154.1 (C5), 137.3 (C_i), 131.7 (C7a), 128.7 ($2C_m$), 128.1 (C3a), 127.9 (C2), 127.5 (C_p), 126.7 ($2C_o$), 112.3 (C6), 110.7 (C7), 106.2 (C3), 100.7 (C4), 55.8 (OMe), 50.1(N-CH_2), 31.1 (C-*C*H_2).

(5-Methoxy-2-oxo-2,3-dihydro-1H-indol-3-yl)acetic acid (7a) and 1,2,3,4-Tetrahydro-6-methoxy-2-oxo-4-quinolinecarboxylic acid (8a): Prepared by stirring (5-methoxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl) acetonitrile (**5a**) (202 mg, 1.0 mmol) for 4 h, according to the typical hydrolysis procedure, method A. Upon workup, the crude product was evaporated under reduced pressure. ^1H NMR (AcOD-d_4) of the crude showed a mixture consisting of **5a**, **7a**, and **8a** (1:6:1 ratio). Flash chromatography, eluted with *n*-hexane/acetone (4:1), gave **5a** (26 mg, recovered); further elution with EtOAc/MeOH (9:1–7:3) afforded **7a** (131 mg, 59%) and **8a** (23 mg, 10%).

For **7a**

MP: 181-182°C (acetone); slightly yellow needles. (Lit. [14] unreported).

Rf: 0.37 (EtOAc/MeOH, 7:3).

^1H NMR (300 MHz, CD_3OD). Although compound **7a** is known [15], it is not yet spectroscopically fully characterized. Thus, NMR data follows: δ 6.95 (1H, m, H4), 6.82 (2H, m, H6, H7), 3.73 (1H, ABX, J = 7.6, 4.6 Hz, H3, CD_3OD exchangeable), 3.78 (3H, s, Me), 3.06 and 2.80 (1H, ABX, J = 17.0, 7.6, 4.6 Hz, CH_2).

^{13}C NMR (75.4 MHz, CD_3OD): δ 182.2 (C2), 175.4 (CO_2H), 158.1 (C5), 137.9 (7a), 132.8 (C3a), 114.7 (C6), 113.0 (C4), 112.0 (C7), 57.0 (OMe), 44.7 (br t, $^1J_{C,D}$ = 21 Hz, C3) [15] 36.1 (CH_2).

For **8a**

MP: 205-208°C (MeOH); white amorphous solid.

Rf: 0.23 (EtOAc/MeOH, 7:3).

IR (KBr): 3226, 1704, 1652 cm^{-1}.

^1H NMR (300 MHz, CD_3OD). Although **8a** is commercially available, it is not yet spectroscopically characterized. Thus, NMR data follows: δ 6.91 (1H, br s, H5), 6.81 (2H, m, H7, H8), 3.89 (1H, ABX, J = 6.5, 3.5 Hz, H4), 3.76 (3H, s, Me), 2.82 and 2.71 (2H, ABX, J = 16.4, 6.5, 3.5 Hz, CH_2).

^{13}C NMR (75.4 MHz, CD_3OD): δ 175.9 (CO_2H), 172.8 (C2), 158.1 (C6), 132.9 (8a), 124.4 (C4a), 118.7 (C8), 116.6 (C5), 115.9 (C7), 56.9 (OMe), 44.4 (C4), 34.5 (C3).

MS (EI, 70 eV): m/z (%) = 221 [$M^{+\cdot}$] (94), 176 (100), 104 (16). HRMS (ESI/APCIMS): [M + H^+] calcd for $C_{11}H_{12}NO_4$: 222.0766; found: 222.0765.

(1-Benzyl-5-methoxy-2-oxo-2,3-dihydro-1H-indol-3-yl)acetic acid (7b): Prepared by stirring (1-benzyl-5-methoxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetonitrile (**5b**) (875 mg, 3 mmol) for 6 h according to the typical hydrolysis procedure A. Upon workup, the crude product was purified by flash chromatography (1:1 *n*-hexane/EtOAc) to give **7b** (709 mg, 76%).

MP: 180-181°C (acetone/CH_2Cl_2); colorless crystals.

Rf: 0.14 (*n*-hexane/EtOAc, 1:1).

IR ($CHCl_3$): 3524, 3024, 2942, 1710, 1602, 1494 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.24 (5H, m, Ar), 6.92 (1H, dd, J = 2.2, 0.8 Hz, H4), 6.70 (1H, ddd, J = 8.5, 2.5, 0.6 Hz, H6), 6.62

(1H, d, *J* = 8.5 Hz, H7), 4.96 and 4.87 (2H, AB, *J* = 15.7 Hz, N-CH_2), 3.88 (1H, ABX, *J* = 6.9, 6.1 Hz, H3), 3.74 (3H, s, Me), 3.12 and 2.96 (2H, ABX, *J* = 17.1, 6.9, 6.1 Hz, C-CH_2).
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 177.0 (C2), 174.0 (CO_2H), 156.2 (C5), 136.6 (7a), 135.5 (C_i), 129.0 (C3a), 128.8 ($2C_m$), 127.7 (C_p), 127.3 ($2C_o$), 112.7 (C6), 111.5 (C4), 109.8 (C7), 55.8 (OMe), 44.1(N-CH_2), 41.9 (C3), 34.8 (C-*C*H_2).
MS (EI, 70 eV): *m/z* (%): 311 [M^+] (55), 265 (100), 91 (47).
HRMS (ESI/APCIMS): [M + H^+] calcd for $C_{18}H_{18}NO_4$: 312.1236; found: 312.1231.

Typical oxidation procedure: Preparation of (5-methoxy-2-oxo-2,3-dihydro-1H-indol-3-yl)acetic acid (7a): To a solution of **6a** (100 mg, 0.49 mmol) in DMSO (2.5 mL) was added dropwise and under stirring 37% aq HCl (2.5 mL). The resulting mixture was stirred at rt until TLC analysis showed complete loss of starting material. After completion (3 h), the resulting mixture was cooled to 5°C, diluted with water (15 mL) and extracted with EtOAc (5 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried, and concentrated under reduced pressure. The crude product was purified by flash chromatography (1:1 CH_2Cl_2/EtOAc) to give **7a** as colorless crystals (87 mg, 81%). MP and spectroscopic data were consistent with those described above for the same compound prepared from oxindole **5a**.

Typical esterification procedure: Preparation of methyl (5-methoxy-2-oxo-2,3-dihydro-1H-indol-3-yl)acetate (9a): To a solution of **7a** (135 mg, 0.61 mmol) in a mixture of THF/diethylether/MeOH (1:1:1, 30 mL) was added an excess of freshly prepared ethereal solution of diazomethane [16] (20 mL, ca 13.6 mg CH_2N_2/mL, 6.5 mmol). The reaction mixture was stirred at rt for 20 min and evaporated at rt under atmospheric pressure with a stream of nitrogen, which was bubbled into a solution containing 5% acetic acid in ethanol. The crude product was purified by flash chromatography (3:2 *n*-hexane/EtOAc) to give **9a** (128 mg, 89%).
MP: 138-140°C (acetone/CH_2Cl_2); colorless crystals.
Rf: 0.29 (*n*-hexane/EtOAc, 1:1).
IR ($CHCl_3$): 3016, 2915, 1736, 1602 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.03 (1H, br s, NH), 6.85 (1H, m, H4), 6.82 (1H, d, *J* = 8.4 Hz, H7), 6.75 (1H, ddd, *J* = 8.4, 2.3, 0.7 Hz, H6), 3.81 (1H, ABX, *J* = 8.4, 4.6 Hz, H3), 3.77 (3H, s, OMe), 3.71 (3H, s, CO_2Me), 3.09 and 2.82 (2H, ABX, *J* = 17.0, 8.4, 4.6 Hz, CH_2).
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 179.2 (C2), 171.5 (*C*O_2Me), 155.7 (C5), 135.0 (7a), 130.1 (C3a), 112.6 (C6), 111.4 (C4), 110.2 (C7), 55.7 (OMe), 52.0 (CO_2*Me*), 42.7 (C3), 34.5 (CH_2).
MS (EI, 70 eV): *m/z* (%) = 235 [M^+] (100), 175 (45), 160 (15).
HRMS (ESI/APCIMS): [M + H^+] calcd for $C_{12}H_{14}NO_4$: 236.0923; found: 236. 0918.

Typical alkylation procedure: Preparation of methyl 2-[5-methoxy-1,3-bis(3-methyl-2-buten-1-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]acetate (10a): To a solution of **9a** (1.18 g, 5.0 mmol) in CH_2Cl_2 (30 mL) were added 15% aq NaOH (15 mL), TBAHS (70 mg, 0.21 mmol) and prenyl bromide (1.5 mL, 2.5 equiv). The resulting mixture was stirred at rt for 4 h, the organic layer separated and the aqueous phase extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (4:1 *n*-hexane/EtOAc) to give **10a** as pale yellow oil (1.62 g, 87%).
Rf: 0.54 (*n*-hexane/EtOAc, 7:3).
IR ($CHCl_3$): 3012, 2975, 1735, 1708, 1605 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.79 (1H, d, *J* = 2.5 Hz, H4), 6.75 (1H, dd, *J* = 8.4, 2.5 Hz, H6), 6.68 (1H, d, *J* = 8.4 Hz, H7), 3.77 (3H, s, OMe), 3.44 (3H, s, CO_2Me), 3.02 and 2.86 (2H, AB, *J* = 16.5 Hz, CH_2), *C*-prenyl: 4.84 (1H, tm, *J* = 7.7 Hz, CH=), 2.43 (2H, m, CH_2), 1.59 (3H, br s, Me), 1.49 (3H, br s, Me), *N*-prenyl: 5.13 (1H, ABX, tm, *J* = 6.6 Hz, CH=), 4.41 and 4.23 (2H, ABX, *J* = 15.5, 7.4, 6.6 Hz, CH_2), 1.82 (3H, br s, Me) 1.72 (3H, br s, Me).
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 178.3 (C2), 170.3 (*C*O_2Me), 155.4 (C5), 137.0 (C7a), 132.6 (C3a), 111.8 (C4), 110.6 (C6), 108.6 (C7), 55.7 (OMe), 51.5 (CO_2*Me*), 50.0 (C3), 39.8 (CH_2), *C*-prenyl: 135.9 (C=), 117.0 (CH=), 36.4 (CH_2), 25.7 (Me), 17.9 (Me), *N*-prenyl: 135.8 (C=), 118.9 (CH=), 38.1 (CH_2), 25.6 (Me), 18.0 (Me).
MS (EI, 70 eV): *m/z* (%) = 371 [M^+] (100), 303 (54), 247 (26), 234 (31), 192 (56) 175 (65).
HRMS (ESI/APCIMS): [M + Na^+] calcd for $C_{22}H_{29}NO_4Na$: 394.1994; found: 394.1996.

Methyl 2-(1,3-dibenzyl-5-methoxy-2-oxo-2,3-dihydro-1H-indol-3-yl)acetate (10b): Prepared from **9b** (1.63 g, 5.0 mmol) and benzyl bromide (221 mg, 1.3 equiv) for 4 h according to the typical alkylation procedure. The crude product was purified by flash chromatography (1:1 *n*-hexane/EtOAc) to give **10b** (1.75 g, 84%).
MP: 116-118ºC; pale yellow crystals.
Rf: 0.27 (*n*-hexane/EtOAc, 1:1).
IR ($CHCl_3$): 3024, 2954, 1738, 1708, 1602 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83 (1H, d, *J* = 2.5 Hz, H4), 6.58 (1H, dd, *J* = 8.5, 2.7 Hz, H6), 6.28 (1H, d, *J* = 8.5 Hz, H7), 3.74 (3H, s, OMe), 3.45 (3H, s, CO_2Me), 3.22 and 2.99 (2H, AB, *J* = 16.2 Hz, CH_2), *C*-Bn: 7.20 -7.04(3H, m, $2H_m$, H_p), 6.86 (2H, m, $2H_o$), 3.12 (2H, unresolved AB, CH_2), *N*-Bn: 7.20-7.04 (3H, m, $2H_m$, H_p), 6.78 (2H, m, $2H_o$), 4.86 and 4.56 (2H, AB, *J* = 15.9 Hz, CH_2).
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 178.0 (C2), 170.0 (*C*O_2Me), 155.4 (C5), 137.0 (C7a), 131.4 (C3a), 112.2 (C6), 110.7 (C4), 109.4 (C7), 55.6 (OMe), 51.6 (CO_2*Me*), 41.0 (CH_2), *C*-Bn: 134.8 (C_i), 130.2 ($2C_o$), 127.8 ($2C_m$), 126.8 (C_p), 43.8 (CH_2), *N*-Bn: 135.6 (C_i), 128.4 ($2C_m$), 127.0 (C_p), 126.7 ($2C_o$), 43.8 (CH_2).
MS (EI, 70 eV): *m/z* (%) = [M^+] 415 (100), 325 (15), 283 (24), 91 (41).
HRMS (ESI/APCIMS): [M + H^+] calcd for $C_{26}H_{26}NO_4$: 416.1862; found: 416.1860.

Methyl 2-[1-benzyl-5-methoxy-3-(3-methyl-2-buten-1-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]acetate (10c): Prepared from **9b** (1.63 g, 5.0 mmol) and prenyl bromide (0.75 mL, 1.3 equiv) for 3 h according to the typical alkylation procedure. The crude product was purified by flash chromatography (3:2 *n*-hexane/EtOAc) to give **10c** (1.73 g, 88%).
MP: 83-85ºC; colorless crystals.
Rf: 0.42 (*n*-hexane/EtOAc, 1:1).
IR ($CHCl_3$): 3026, 2916, 1738, 1708, 1602 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.80 (1H, d, *J* = 2.5 Hz, H4), 6.65 (1H, dd, *J* = 8.5, 2.7 Hz, H6), 6.55 (1H, d, *J* = 8.5 Hz, H7), 3.74 (3H, s, OMe), 3.43 (3H, s, CO_2Me), 3.08 and 2.91 (AB, *J* = 16.5 Hz, CH_2), *C*-prenyl: 4.85 (tm, *J* = 7.4 Hz, 1H, CH=), 2.51 (2H, m, 2H, CH_2), 1.60 (3H, br s, Me), 1.52 (3H, br s, Me), *N*-Bn: 7.34-7.22 (5H, m, Ph), 5.11 and 4.73 (AB, *J* = 15.9 Hz, 2H, CH_2).
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 178.8 (C2), 170.2 (*C*O_2Me), 155.5 (C5), 136.9 (C7a), 132.4 (C3a), 111.8 (C6), 110.6 (C4), 109.1 (C7), 55.6 (OMe), 51.5 (CO_2*Me*), 50.1 (C3), 40.2 (C8), *C*-prenyl: 136.3 (C=), 117.1 (CH=), 36.7 (CH_2), 25.9 (Me), 18.0 (Me), *N*-Bn: 136.3 (C_i), 128.6 ($2C_o$), 127.3 ($2C_m$), 127.2 (C_p), 44.0 (CH_2).
MS (EI, 70 eV): *m/z* (%) = [M^+] 393 (100), 325 (9), 283 (8), 266 (16), 91 (8).
HRMS (ESI/APCIMS): [M + H^+] calcd for $C_{24}H_{28}NO_4$: 394.2018; found: 394.2015.

Typical hydrolysis procedure, method B: Preparation of 2-[5-methoxy-1,3-bis(3-methyl-2-buten-1-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]acetic acid (11a): A precooled (0ºC) solution of **10a** (965 mg, 2.6 mmol) in MeOH (15 mL) was treated with 15% aq NaOH (3 mL) and the resulting mixture stirred for 1.5 h at 40-50ºC. The reaction mixture was cooled in an ice/water bath prior to quenching by the addition of 1 M HCl until pH ca. 1, followed by extraction with EtOAc (2 x 30 mL). The combined organic phases were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (7:3 *n*-hexane/EtOAc) to give **11a** as pale yellow oil (817 mg, 88%).
Rf: 0.25 (*n*-hexane/EtOAc, 7:3).
IR ($CHCl_3$): 3510, 3018, 2918, 2638, 1710, 1602 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$): δ 7.81 (1H, very br s, CO_2H), 6.78 (1H, partially overlapped, H4), 6.76 (1H, dd, partially overlapped *J* = 8.3, 2.4 Hz, H6), 6.67 (1H, d, *J* = 8.2 Hz, H7), 3.77 (3H, s, OMe), 2.98 and 2.80 (2H, AB, *J* = 16.6 Hz, CH_2), *C*-prenyl: 4.74 (1H, tm, *J* = 7.5 Hz, CH=), 2.44 (2H, m, CH_2), 1.56 (3H, br s, Me), 1.46 (br 3H, s, Me), *N*-prenyl: 5.06 (ABX, tm, *J* = 6.5 Hz, 1H, CH=), 4.36 and 4.17 (2H, ABX, *J* = 15.6, 6.4, 6.4 Hz, CH_2) 1.80 (3H, br s, Me), 1.70 (3H, br s, Me).
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 178.9 (C2), 173.9 (CO_2H), 155.7 (C5), 136.5 (C7a), 132.4 (C3a), 110.4 (C4), 112.1 (C6), 109.0 (C7), 55.6 (OMe), 49.8 (C3), 39.9 (CH_2), *C*-prenyl: 136.2 (C=), 116.6 (CH=), 36.1 (CH_2), 25.7 (Me), 17.9 (Me), *N*-prenyl: 136.1 (C=), 118.4 (CH=), 38.2 (CH_2), 25.5 (Me), 18.0 (Me).
MS (EI, 70 eV): *m*/*z* (%) = [$M^{+\cdot}$] 357 (100), 289 (52), 233 (51), 188 (78), 175 (64).
HRMS (ESI/APCIMS): [M + Na^+] calcd for $C_{21}H_{27}NO_4Na$: 380.1838; found: 380.1831.

2-(1,3-Dibenzy-5-methoxy-2-oxo-2,3-dihydro-1H-indol-3-yl]acetic acid (11b): Prepared from **10b** (1.08 g, 2.6 mmol) according to the typical hydrolysis procedure B. The crude product was purified by flash chromatography (1:1 *n*-hexane/EtOAc) to give **11b** (762 mg, 73%).
MP: 63-64ºC; pale yellow crystals.
Rf: 0.16 (*n*-hexane/EtOAc, 1:1).
IR ($CHCl_3$): 3510, 3018, 2918, 2638, 1710, 1602 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$): δ 7.85 (1H, very br s, CO_2H), 6.81 (1H, d, *J* = 2.6 Hz, H4), 6.56 (1H, dd, *J* = 8.6, 2.6 Hz, H6), 6.24 (1H, d, *J* = 8.6 Hz, H7), 3.72 (3H, s, OMe), 3.21 and 2.96 (2H, AB, *J* = 16.6 Hz, CH_2), *C*-Bn: 7.18-7.03 (3H, m, $2H_m$, H_p), 6.80 (2H, m, $2H_o$), 3.10 (2H, unresolved AB, CH_2), *N*-Bn: 7.18-7.03 (3H, m, $2H_m$, H_p), 6.75 (2H, m, $2H_o$), 4.70 and 4.56 (2H, AB, *J* = 16.0 Hz, CH_2).
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 178.3 (C2), 174.4 (CO_2H), 155.6 (C5), 136.7 (C7a), 131.2 (C3a), 112.5 (C6), 110.6 (C4), 109.8 (C7), 55.7 (OMe), 51.5 (C3), 40.8 (CH_2), *C*-Bn: 134.6 (C_i), 130.1 ($2C_o$), 127.8 ($2C_m$), 127.1 (C_p), 43.7 (CH_2), *N*-Bn: 135.2 (C_i), 128.5 ($2C_m$), 126.9 (C_p), 126.6 ($2C_o$), 43.8 (CH_2).
MS (EI, 70 eV): *m*/*z* (%) = [$M^{+\cdot}$] 401 (91), 311 (13), 266 (100), 188 (37), 91 (45).
HRMS (ESI/APCIMS): [M + Na^+] calcd for $C_{25}H_{23}NO_4Na$: 424.1525; found: 424.1518.

2-[1-Benzyl-5-methoxy-3-(3-methyl-2-buten-1-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]acetic acid (11c): Prepared from **10c** (1.02 g, 2.6 mmol) according to the typical hydrolysis procedure B. The crude product was purified by flash chromatography (2:3 *n*-hexane/EtOAc) to give **11c** (867 mg, 88%).
MP: 174-176ºC; colorless crystals.
Rf: 0.17 (*n*-hexane/EtOAc, 1:1).
IR ($CHCl_3$): 3586, 3018, 2836, 1710, 1602, 1498 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$): δ 6.80 (1H, d, *J* = 2.5 Hz, H4), 6.66 (1H, dd, *J* = 8.5, 2.5 Hz, H6), 6.55 (1H, d, *J* = 8.5 Hz, H7), 3.07 and 2.87 (2H, AB, *J* = 16.6 Hz, CH_2), 3.74 (3H, s, OMe), *C*-prenyl: 4.80 (ABX, tm, *J* = 7.2 Hz, 1H, CH=), 2.60 and 2.51 (2H, ABX, *J* = 13.7, 8.3, 6.9 Hz, CH_2), 1.58 (3H, br s, Me), 1.50 (3H, br s, Me), *N*-Bn: 7.30-7.24 (5H, m, Ph), 5.04 and 4.74 (2H, AB, *J* = 15.7 Hz, CH_2).
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 179.6 (C2), 173.2 (CO_2H), 156.0 (C5), 135.7 (C7a), 132.2 (C3a), 112.3 (C6), 110.4 (C4), 109.7 (C7), 55.7 (OMe), 50.0 (C3), 40.3 (CH_2), *C*-prenyl: 136.8 (C=), 116.6 (CH=), 36.2 (CH_2), 25.9 (Me), 18.0 (Me), *N*-Bn: 136.2 (C_i), 128.7 ($2C_m$), 127.5 (C_p), 127.1 ($2C_o$), 44.1 (CH_2).
MS (EI, 70 eV): *m*/*z* (%) = [$M^{+\cdot}$] 379 (48), 311 (68), 265 (100), 188 (19), 91 (36).
HRMS (ESI/APCIMS): [M + Na^+] calcd for $C_{23}H_{25}NO_4Na$: 402.1681; found: 402.1673.

Typical lactonization procedure: Preparation of 5-methoxy-3a,8-bis(3-methyl-2-buten-1-yl)-2-oxo-2,3,3a,8a-tetrahydro-8H-furo[2,3-b]indole (1a): To a precooled (0°C) solution of **11a** (893 mg, 2.5 mmol) in dry THF (25 mL) was added NaH (71.0 mg, 2.96 mmol), and the reaction mixture stirred for 10 min at rt. After cooling at 0°C, $LiBHEt_3$ (1.3 eq, 0.41 mL) was added, dropwise, and stirring continued at 60ºC for 5 h. The reaction mixture was cooled in an ice/water bath prior to quenching by adding brine, dropwise (5-10 mL). The organic layer was evaporated under reduced pressure and the residue treated with 5% aq HCl until pH ca. 7, followed by extraction with EtOAc (4 x 20 mL). The combined organic phases were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (4:1 *n*-hexane/EtOAc) to give **1a** as pale yellow oil (486 mg, 57%).
Rf: 0.68 (*n*-hexane/EtOAc, 7:3).
IR (CCl_3): 3028, 2934, 1768, 1600 cm^{-1}.
^1H NMR (300 MHz, CD_2Cl_2): δ 6.71 (1H, dd, *J* = 7.3, 2.7 Hz, H6), 6.70 (1H, overlapped, H4), 6.46 (1H, m, H7), 5.60 (1H, s, H8a), 3.73 (3H, s, OMe), 2.87 and 2.76 (2H, AB, *J* = 17.6 Hz, H3), *C*-prenyl: 5.12 (1H, tm, *J* = 7.3 Hz, CH=), 2.37 (m, 2H, CH_2), 1.76 (br s, 3H, Me), 1.72 (br s, 3H, Me), *N*-prenyl: 5.31 (1H, overlapped, CH=), 3.88 (2H, m, CH_2), 1.78 (3H, br s, Me), 1.56 (3H, br s, Me).
^{13}C NMR (75.4 MHz, CD_2Cl_2): δ 175.2 (C2), 154.2 (C5), 142.3 (C7a), 134.9 (C3b), 113.7 (C6), 111.3 (C4), 108.2 (C7), 103.0 (C8a), 56.3 (OMe), 53.2 (C3a), 39.8 (C3), *C*-prenyl: 136.8 (C=), 118.4 (CH=), 34.8 (CH_2), 26.1 (Me), 18.1 (Me), *N*-prenyl: 137.1 (C=), 119.9 (CH=), 43.3 (CH_2), 25.9 (Me), 18.3 (Me).
MS (EI, 70 eV): *m*/*z* (%) = [$M^{+\cdot}$] 341 (100), 295 (54), 273 (57), 228 (67), 197 (21), 160 (74).
HRMS (ESI/APCIMS): [M + H^+] calcd for $C_{21}H_{28}NO_3$: 342.2069; found: 342.2064.

3a,8-Dibenzyl-5-methoxy-2-oxo-2,3,3a,8a-tetrahydro-8H-furo[2,3-b]indole (1b): Prepared from **11b** (1.0 g, 2.5 mmol) according to the typical lactonization procedure. The crude product was purified by flash chromatography (7:3 *n*-hexane/EtOAc) to give **1b** (615 mg, 64%).
MP: 144-146ºC; pale brown crystals.
Rf: 0.33 (*n*-hexane/EtOAc, 7:3).
IR ($CHCl_3$): 3010, 2938, 1764, 1602, 1496 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$): **δ** 6.67 (1H, dd, *J* = 8.5, 2.5 Hz, H6), 6.58 (1H, d, *J* = 2.5 Hz, H4), 6.29 (1H, d, *J* = 8.5 Hz, H7), 5.60 (1H, s, H8a), 3.71 (3H, s, OMe), 2.97 and 2.89 (2H, AB, *J* = 17.3 Hz, H3), *C*-Bn: 7.32-7.19 (3H, m, $2H_m$, H_p), 6.90 (2H, m, $2H_o$), 3.07 and 2.92 (2H, AB, *J* = 13.7 Hz, CH_2), *N*-Bn: 7.32-7.19 (3H, m,

2H$_m$, H$_p$), 7.11 (2H, m, 2H$_o$), 4.39 and 4.32 (2H, AB, J = 15.1 Hz, CH$_2$).
^{13}C NMR (75.4 MHz, CDCl$_3$): δ 174.3 (C2), 153.9 (C5), 142.0 (C7a), 133.1 (C3b), 113.9 (C6), 111.1 (C4), 108.5 (C7), 102.2 (C8a), 55.9 (OMe), 53.4 (C3a), 40.3 (C3), *C*-Bn: 135.6 (C$_i$), 129.9 (2C$_o$), 128.4 (2C$_m$), 127.1 (C$_p$), 42.5 (C-*C*H$_2$), *N*-Bn: 136.7 (C$_i$), 128.5 (2C$_m$), 127.7 (2C$_o$), 127.4 (C$_p$), 49.1 (CH$_2$).
MS (EI, 70 eV): *m*/*z* (%) = [M$^+$] 385 (100), 340 (66), 250 (88), 91 (96).
HRMS (ESI/APCIMS): [M + H$^+$] calcd for $C_{25}H_{24}NO_3$: 386.1756; found: 386.1750.

8-Benzyl-5-methoxy-3a-(3-methyl-2-buten-1-yl)-2-oxo-2,3,3a,8a-tetrahydro-8H-furo[2,3-b]indole (1c): Prepared from **11c** (948 mg, 2.5 mmol) according to the typical lactonization procedure. The crude product was purified by flash chromatography (4:1 *n*-hexane/EtOAc) to give **1c** (681 mg, 75%) as pale brown oil.
Rf: 0.62 (*n*-hexane/EtOAc, 7:3).
IR (CHCl$_3$): 3010, 2936, 1766, 1670 cm^{-1}.
^{1}H NMR (300 MHz, CDCl$_3$): δ 6.71 (1H, d, J = 2.2 Hz, H4), 6.67 (1H, dd, J = 8.4, 2.6 Hz, H6), 6.40 (1H, d, J = 8.3 Hz, H7), 5.53 (1H, s, H8a), 3.74 (3H, s, OMe), 2.87 (2H, unresolved AB, H3), *C*-prenyl: 5.07 (1H, tm, J = 7.2 Hz, CH=), 2.42 (2H, m, CH$_2$), 1.71 (3H, br s, Me), 1.51 (3H, br s, Me), *N*-Bn: 7.38-7.27 (5H, m, Ph), 4.53 and 4.44 (2H, AB, J = 15.4 Hz, CH$_2$).
^{13}C NMR (75.4 MHz, CDCl$_3$): δ 175.0 (C2), 154.0 (C5), 141.9 (C7a), 134.1 (C3b), 113.3 (C6), 111.0 (C4), 108.1 (C7), 102.6 (C8a), 56.0 (OMe), 52.9 (C3a), 39.9 (C3), *C*-prenyl: 136.4 (C=), 117.8 (CH=), 34.7 (CH$_2$), 25.9 (Me), 18.0 (Me), *N*-Bn: 136.9 (C$_i$), 128.6 (2C$_m$), 127.5 (C$_p$), 127.7 (2C$_o$), 49.2 (CH$_2$).
MS (EI, 70 eV): *m*/*z* (%) = [M$^+$] 363 (100), 318 (72), 304 (62), 250 (14), 212 (36), 91 (83).
HRMS (ESI/APCIMS): [M + H$^+$] calcd for $C_{23}H_{26}NO_3$: 364.1913; found: 364.1913.

Typical lactamization procedure: Preparation of 1-methyl-5-methoxy-3a,8-bis(3-methyl-2-buten-1-yl)-2-oxo-2,3,3a,8a-tetrahydro-8H-furo[2,3-b]indole (2a): To a solution of **1a** (213 mg, 0.6 mmol) in MeOH (20 mL) was added NH$_2$Me (3 mL of a 2 M solution in MeOH, 4 mmol). The reaction mixture was stirred for 2 h at rt. The mixture was evaporated under reduced pressure, and the residue was suspended in EtOAc (30 mL). The suspension was washed successively with 5% aq HCl (2 x10 mL) and brine (2 x 10 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (1:1 *n*-hexane/EtOAc) to give **2a** as pale yellow oil (215 mg, 97%).
Rf: 0.20 (*n*-hexane/EtOAc, 1:1).
IR (CHCl$_3$): 3006, 2972, 1676, 1596, 1494 cm^{-1}.
^{1}H NMR (300 MHz, CDCl$_3$): δ 6.70 (1H, dd, J = 8.4, 2.8 Hz, H6), 6.64 (1H, d, J = 2.6 Hz, H4), 6.50 (1H, d, J = 8.3 Hz, H7), 4.64 (1H, s, H8a), 3.75 (3H, s, OMe), 2.86 (3H, s, NMe), 2.64 (2H, br s, H3), *C*-prenyl: 4.99 (1H, AB<u>X</u>, tm, J = 7.5 Hz, CH=), 2.41 and 2.33 (2H, <u>AB</u>X, J = 14.6, 8.1, 6.6 Hz, CH$_2$), 1.71 (3H, s, Me), 1.58 (3H, s, Me), *N*-prenyl: 5.26 (1H, AB<u>X</u>, tm, J = 7.0 Hz, CH=), 3.89 and 3.81 (2H, <u>AB</u>X, J = 15.4, 7.0, 6.6 Hz, CH$_2$), 1.74 (3H, s, Me), 1.72 (3H, s, Me).
^{13}C NMR (75.4 MHz, CDCl$_3$): δ 172.7 (C2), 154.0 (C5), 143.6 (C7a), 137.1 (C3b), 113.6 (C6), 110.6 (C7), 110.1 (C4), 88.2 (C8a), 56.0 (OMe), 50.3 (C3a), 41.8 (C3), 27.6 (NMe), *C*-prenyl: 135.7 (C=), 118.7 (CH=), 37.6 (CH$_2$), 26.0 (Me), 18.1 (Me), *N*-prenyl: 135.2 (C=), 121.2 (CH=), 48.7 (CH$_2$), 25.7 (Me), 18.0 (Me).
MS (EI, 70 eV): *m*/*z* (%) = [M$^+$] 354 (91), 285 (16), 217 (100), 160 (25), 69 (22).
HRMS (ESI/APCIMS): [M + Na$^+$] calcd for $C_{22}H_{30}N_2O_2Na$: 377.2205; found: 377.2203.

1-Methyl-3a,8-dibenzyl-5-methoxy-2-oxo-2,3,3a,8a-tetrahydro-8H-pyrrolo[2,3-b]indole (2b): Prepared from **1b** (231 mg, 0.6 mmol) for 3 h according to the typical lactamization procedure. The crude product was purified by flash chromatography (1:1 *n*-hexane/EtOAc) to give **2b** (220 mg, 92%).
MP: 186-187ºC; colorless crystals.
Rf: 0.15 (*n*-hexane/EtOAc, 1:1).
IR (CHCl$_3$): 3010, 2920, 1682, 1602, 1496 cm^{-1}.
^{1}H NMR (300 MHz, CDCl$_3$): δ 6.67 (1H, dd, J = 8.3, 2.5 Hz, H6), 6.61 (1H, d, J = 2.8 Hz, H4), 6.33 (1H, d, J = 8.5 Hz, H7), 4.80 (1H, s, H8a), 3.74 (3H, s, OMe), 2.79 (2H, s, H3), 2.58 (3H, s, NMe), *C*-Bn: 7.30-7.21 (m, 3H, 2H$_m$, H$_p$), 6.82 (m, 2H, 2H$_o$), 3.08 and 2.77 (2H, AB, J = 13.2 Hz, CH$_2$), *N*-Bn: 7.30-7.21 (3H, m, 2H$_m$, H$_p$), 7.17 (2H, m, 2H$_o$), 3.91 and 3.84 (2H, AB, J = 15.7 Hz, CH$_2$).
^{13}C NMR (75.4 MHz, CDCl$_3$): δ 172.1 (C2), 154.2 (C5), 144.1 (C7a), 136.1 (C3b), 114.2 (C6), 110.9 (C7), 110.3 (C4), 88.3 (C8a), 56.0 (OMe), 51.6 (C3a), 42.6 (C3), 27.5 (NMe), *C*-Bn: 136.5 (C$_i$), 130.0 (2C$_o$), 128.2 (2C$_m$), 127.0 (C$_p$), 42.3 (CH$_2$), *N*-Bn: 136.7 (C$_i$), 128.6 (2C$_m$), 127.7 (2C$_o$), 127.4 (C$_p$), 55.0 (CH$_2$).
MS (EI, 70 eV): *m*/*z* (%) = [M$^+$] 398 (100), 308 (46), 91 (43).
HRMS (ESI/APCIMS): [M + H$^+$] calcd for $C_{26}H_{27}N_2O_2$: 399.2073; found: 399.2065.

8-Benzyl-1-methyl-5-methoxy-3a-(3-methyl-2-buten-1-yl)-2-oxo-2,3,3a,8a-tetrahydro-8H-pyrrolo[2,3-b]indole (2c): Prepared from **1c** (218 mg, 0.6 mmol) for 24 h according to the typical lactamization procedure. The crude product was purified by flash chromatography (2:3 *n*-hexane/EtOAc) to give **2c** (197 mg, 87%) as pale yellow oil.
Rf: 0.18 (*n*-hexane/EtOAc, 1:1).
IR (CHCl$_3$): 3020, 2932, 1682, 1598, 1496 cm^{-1}.
^{1}H NMR (300 MHz, CDCl$_3$): δ 6.67 (1H, overlapped, H4), 6.65 (1H, dd, J = 9.0, 2.6 Hz, H6), 6.39 (1H, br d, J = 7.7 Hz, H7), 4.74 (1H, s, H8a), 3.74 (3H, s, OMe), 2.71 and 2.64 (AB, J = 17.3 Hz, 2H, H3), 2.71 (s, 3H, NMe), *C*-prenyl: 4.96 (1H, AB<u>X</u>, tm, J = 7.3 Hz, CH=), 2.38 and 2.29 (2H, <u>AB</u>X, J = 15.9, 8.1, 6.6 Hz, CH$_2$), 1.70 (3H, br s, Me), 1.56 (3H, br s, Me), *N*-Bn: 7.37-7.24 (5H, m, Ph), 4.49 and 4.42 (2H, AB, J = 15.8 Hz, CH$_2$).
^{13}C NMR (75.4 MHz, CDCl$_3$): δ 172.8 (C2), 154.0 (C5), 143.7 (C7a), 136.6 (C3b), 113.4 (C6), 110.2 (C4), 110.0 (C7), 89.2 (C8a), 55.9 (OMe), 50.3 (C3a), 41.9 (C3), 27.9 (NMe), *C*-prenyl: 135.8 (C=), 118.5 (CH=), 37.5 (CH$_2$), 26.0 (Me), 18.1 (Me), *N*-Bn: 138.6 (C$_i$), 128.6 (2C$_m$), 127.5 (2C$_o$), 127.4 (C$_p$), 55.2 (CH$_2$).
MS (EI, 70 eV): *m*/*z* (%) = [M$^+$] 376 (100), 308 (78), 91 (67).
HRMS (ESI/APCIMS): [M + H$^+$] calcd for $C_{24}H_{29}N_2O_2$: 377.2229; found: 377.2224.

X-ray diffraction analysis of 1b, 2b, 7b, 9a and 11c: An Enraf-Nonius CAD4 diffractometer was used with Cu Kα radiation (λ = 1.54184 Å). The data were collected in the ω-2θ scan mode. Unit cell refinements were achieved using CAD4 Express v 2.0 software and structures were solved by direct methods using the SHELXS-97 program included in the WINGX v 1.64.05 package. The non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. The X-ray data collection and processing parameters are presented in Table 2. Complete X-ray data are in deposit at the Cambridge Crystallographic Data Center (CCDC No., see Table 2).

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Table 2: X-ray data collection and processing parameters for oxofuroindoline **1b**, oxopyrrolidinoindoline **2b**, and oxindoles **7b**, **9a** and **11c**.

Compound	**1b**	**2b**	**7b**	**9a**	**11c**
Formula	$C_{25}H_{23}NO_3$	$C_{26}H_{26}N_2O_2$	$C_{18}H_{17}NO_4$	$C_{12}H_{13}NO_4$	$C_{23}H_{25}NO_4$
T (K)	298(2)	293(2)	298(2)	298(2)	298(2)
Size (mm)	0.40x0.34x 0.34	0.32x0.32x 0.28	0.38x0.38x 0.32	0.36x0.30x 0.30	0.36x0.34x 0.28
Crystal system	monoclinic	tetragonal	monoclinic	monoclinic	monoclinic
Space group	$P2_1/n$	$P4_1$	$P2_1/c$	$P2_1/c$	$P2_1/a$
a (Å)	14.159(4)	11.417(1)	9.510(1)	8.522(5)	11.366(2)
b (Å)	10.319(1)	11.417(1)	14.943(2)	14.236(3)	14.148(3)
c (Å)	14.178(2)	16.009(4)	11.128(2)	9.707(2)	12.370(1)
β (°)	96.56(2)	90	101.20(2)	91.36(3)	96.866(8)
V (Å^3)	2058.0(7)	2086.7(6)	1551.2(4)	1177.3(8)	1974.9(6)
D_{calcd} (g cm^{-3})	1.24	1.27	1.33	1.33	1.28
Z	4	4	4	4	4
μ (mm^{-1})	0.651	0.634	0.778	0.841	0.703
θ_{range} (°)	4.18 – 59.95	6.75 – 59.91	4.74 – 59.97	5.19 - 59.92	3.60 – 59.93
Refl. total	3498	1578	2492	2027	3331
Refl. unique	3036	1350	2178	1739	2921
R_{int} (%)	0.01	0.01	4.1	1.7	3.8
Refl. observ.	2754	1292	2001	1676	2722
Param. refined	266	275	217	163	262
R (%), R_w (%)	5.4, 17.5	2.4, 6.1	3.8, 9.9	3.9, 10.0	4.5, 12.3
e_{max} (eÅ^{-3})	0.227	0.070	0.152	0.222	0.203
CCDC No.	898834	898835	898836	898837	898838

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