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Synthesis of Pyrrolidinoindolines from 2-(2-Oxo-3-indolyl)acetates: Scope and Limitations

Martha S. Morales-Ríos[a,b,*], Ernesto Rivera-Becerril[a,b], Daphne E. González-Juárez[a,b], Juan Benjamín García-Vázquez[a,b], Joel J. Trujillo-Serrato[a], Angelina Hernández-Barragán[a], and Pedro Joseph-Nathan[a,b]

[a]*Departamento de Química and* [b]*Programa de Posgrado en Farmacología*, *Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional*, *Apartado 14-740*, *México*, *D. F., 07000 México*

smorales@cinvestav.mx

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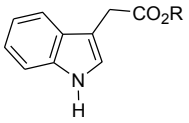
A series of 1,3a,8-alkylpyrrolidinoindolines have been synthesized. The scope and limitations of the alkylation of starting methyl oxindol-3-acetates are explored employing electron-rich and electron-poor alkylating agents. Hydrolysis and reductive lactonization of the resulting carboxylic γ-oxindolic acid derivatives proceeds with good yields to afford 2-oxofuroindolines providing ready access to the pyrrolidinoindoline derivatives.

Keywords: Pyrrolidinoindolines, 2-oxofuroindolines, 3,3-dialkyloxindoles, electron-rich and electron poor alkylating agents.

The bryozoan *Flustra foliacea* has been a rich source of prenylated pyrrolidinoindoline alkaloids, structurally related to terrestrial acetylcholinesterase inhibitor physostigmine. The potential relevance of these naturally occurring marine alkaloids to medicinal chemistry [1-3] has contributed to an extended development of synthetic strategies, as evidenced from the growing amount of work published in the past few years, compiled in earlier publications [4,5].

Our group already reported a convenient procedure for the efficient preparation of (1,3-dialkyl-2-oxo-3-indolyl)aceto-nitriles from commercially available 3-acetonitrilindole in good yields. This method was applied to the synthesis of isotope labeled Me(3a)-^{13}C-physostigmine [6] and extended to the synthesis of a series of pyrrolidino-indolines **1a**-**g**, including the marine alkaloid debromoflustramine B (**1a**) [1]. Nevertheless, this approach presents a drawback in the relatively pricey starting 3-acetonitrylindole. For this reason, an alternative method to form the fore-mentioned pyrrolidinoindolines could be the use of cheaper plant hormone 3-indolyl acetic acid (**2a**) [7] as starting material coupled with further synthetic transformations.

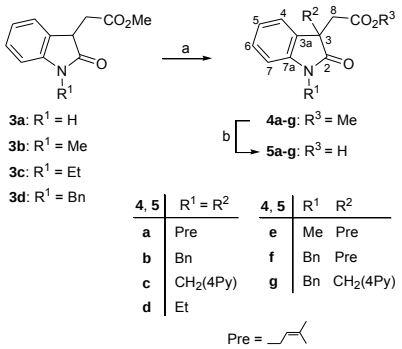
Particularly promising γ-lactones were envisaged as intermediates. In this regard, the recently published synthesis of 2-(1,3-dialkyl-2-oxo-3-inolyl)acetic acids starting from methyl ester **2b** [8] offers a valuable route to 2-oxofuro[2,3-*b*]indoles. Herein we describe an alternative synthetic route of pyrrolidinoindoline derivatives **1b**-**g**



2a: R = H
2b: R = Me

based on the reductive lactonization of the sodium salt of carboxylic γ-oxindolic acid derivatives [9].

First, we decided to investigate the synthetic scope and limitations of the *N*- and *C*-alkylation of methyl 2-(2-oxo-3-indolyl)acetates **3a**-**d** (Scheme 1). The influence of the alkyl halide and oxindole substrate on the yield of methyl 2-(1,3-dialkyl-2-oxo-3-indolyl)acetates **4a**-**g** was studied for this aim. A full range of 1,3-substituted aliphatic, allyl, benzyl and heterobenzyl oxindol-3-acetates **4a**-**g** were prepared by mono- or di-alkylation of the corresponding oxindoles **3a**-**d** with the proper alkyl halide under phase-transfer conditions in the presence of 15% aq KOH. The results are presented in Table 1. Good yields were obtained for symmetrical *N*- and *C*-alkyloxindoles **4a** and **4b** prepared by reaction of **3a** with 2.5 equiv of allyl and benzyl bromides (entries 1 and 2), whereas, similar reaction conditions with **3a** as the substrate and the electron-poor pyridin-4-ylmethyl bromide or ethyl bromide as alkylating agents afforded much lower yields of the desired products **4c** and **4d** (entries 3 and 4). This disparity in yields reflects a combination of the stability of the intermediate carbonium ion arising by a simple S_N1-type nucleophilic substitution mechanism and the nucleophilicity of the nitrogen and carbon atoms of the ambient oxindole.



4, 5	$R^1 = R^2$	4, 5	R^1	R^2
a	Pre	**e**	Me	Pre
b	Bn	**f**	Bn	Pre
c	CH_2(4Py)	**g**	Bn	CH_2(4Py)
d	Et			

Scheme 1: Preparation of 2-(1,3-dialkyl-2-oxo-3-indolyl)acetic acids **5a-g**. (a) 15% aq KOH/CH_2Cl_2, RBr (see Table 1), rt; (b) 15% aq NaOH, 40-45°C, average yield 80%.

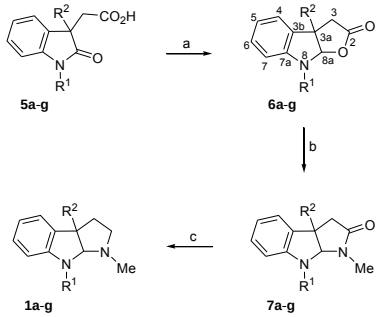
Table 1: Alkylation of methyl 2-(2-oxo-3-indolyl)acetates **3a-d**.

Entry		RBr(equiv)	Time	Product	Yield(%)
1	**3a**	PreBr (2.5)	5 h	**4a**	76 [9]
2	**3a**	BnBr (2.5)	5 h	**4b**	68
3	**3a**	(4Py)CH_2Br (2.5)	5 h	**4c**	27
4	**3a**	EtBr (2.5)	5 h	**4d**	15
5	**3b**	PreBr (1.3)	4 h	**4e**	93
6	**3d**	PreBr (1.3)	4 h	**4f**	86
7	**3d**	(4Py)CH_2Br (1.3)	4 h	**4g**	88
8	**3c**	EtBr (1.3)	4 h	**4d**	50

To confirm the above finding, we have also examined the *C*-alkylation of protected *N*-alkyloxindoles **3b** and **3d** carrying methyl and benzyl groups, respectively. As shown in Table 1, the reaction occurs cleanly to give the corresponding 3,3-alkyloxindoles **4e-g** in good to excellent yields (entries 5-7). It should also be noted that an improved yield of **4d** was obtained starting from **3c** (entry 8).

With methyl 1,3-alkyloxindol-3-acetates **4a-g** in hand, we subjected them to alkaline hydrolysis with 15% aq NaOH, affording the corresponding carboxylic acids **5a-g** in 82-88% yield. It should be noted that ring enlargement of methyl oxindole-3-acetates to structural isomer quinolones could occur under acidic conditions [10]. Finally, the carboxylic acids **5a-g** were transformed by a three steps sequence into pyrrolidinoindolines **1a-g** (Scheme 2). The reductive lactonization of the sodium salt of carboxylic γ-oxindolic acid derivatives **5a-g** with $LiBHEt_3$ produce the corresponding 2-oxofuroindolines **6a-g** (Scheme 2), which were transformed into 2-oxopyrroloindolines **7a-g** by reaction with methylamine in MeOH at room temperature. Further reduction of **7a-g** with $LiAlH_4$ in refluxing THF gave pyrrolidinoindoline derivatives **1a-g** in yields of 37% [9], 55%, 74%, 56%, 58%, 62%, and 56%, respectively, for the three-step sequence. Interestingly, compared with the global chemical yields previously reported [1], which were carried out starting from (1,3-dialkyl-2-oxo-3-indolyl)acetonitriles in two steps, pyrrolidinoindolines **1b-d** gave significant better global yields.

In general, the current method constitutes a valuable alternative to obtain pyrrolidinoindolines functionalized at C-3a and N-8 with different aliphatic, allyl, benzyl and heterobenzyl substituents starting from plant hormone 3-indolyl acetic acid.



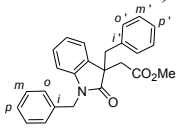
Scheme 2: Synthesis of pyrrolidinoindolines **1a-g** (for R^1 and R^2 see Scheme 1). (a) NaH/THF, rt, 10 min, then $LiBHEt_3$/THF, rt, 6 h; (b) 40% aq $MeNH_2$/MeOH, rt, 2-3 h; (c) $LiAlH_4$/THF, reflux, 3 h.

Experimental

Melting points (uncorrected), Fisher-Johns apparatus; IR, Perkin-Elmer 16 FPC FT infrared spectrophotometer; ^1H (300 MHz) and ^{13}C (75 MHz) NMR, Varian Mercury spectrometer; MS, Varian Saturn 2000 spectrometer (70 eV ion source); High-resolution MS, Agilent LCTOF spectrometer at the UCR Mass Spectrometry Facility, University of California, Riverside. Flash chromatography was performed using silica gel 60 (230-400 mesh). The methyl oxindole-3-acetates **3a-3d** used in this study were prepared as previously described [8,11]. Compounds **4a**, **5a**, **6a**, **7a**, and **5f** were synthesized [9,12] as indicated in Schemes 1 and 2.

General alkylation procedure: To a solution of the corresponding methyl oxindole-3-acetate **3a-d** (5.0 mmol) in CH_2Cl_2 (30 mL) were added 15% aq. KOH (15 mL), TBAHS (0.07 g, 0.21 mol) and the corresponding alkyl halide (1.3 or 2.5 equiv, see Table 1). The resulting mixture was stirred at rt for 4-5 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 hexane-EtOAc) to afford the corresponding dialkylated methyl oxindole-3-acetates **4b-g**.

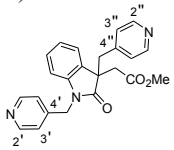
Methyl 2(1,3-dibenzyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (4b): Prepared from **3a** (1.0 g, 5.0 mmol) as a pale yellow oil. The crude product was purified by flash chromatography (hexane/EtOAc 4:1) (1.3 g, 68%).



Rf: 0.26 (hexane/EtOAc 7:3).
IR ($CHCl_3$): 3010, 2918, 1738, 1710, 1614 cm^{-1}.
^1H NMR ($CDCl_3$): 7.19 (1H, dd, J = 6.9, 1.5 Hz, H-4), 7.16-7.11 (4H, m, Ph), 7.07-7.01 (2H, m, Ph), 7.01 (1H, m, H-6), 6.83 (1H, td, J = 7.2, 1.3 Hz, H-5), 6.78-6.74 (4H, m, Ph), 6.37 (1H, dd, J = 7.3, 1.3 Hz, H-7), 4.86 and 4.56 (2H, AB, J = 16.1 Hz, N-CH_2), 3.4 (3H, s, OCH_3), 3.21 and 3.01 (2H, AB, J = 16.1 Hz, H-8), 3.13 (2H, s, C-CH_2).

^{13}C NMR ($CDCl_3$): 178 (s, C-2), 169.7 (s, C=O), 143.2 (s, C-7a), 135.2 (s, C_i), 134.6 (s, $C_{i'}$), 130.0 (d, $2C_{o'}$), 129.8 (s, C-3a), 128.3 (d, $2C_m$), 128.0 (d, C-6), 127.6 (d, $2C_{m'}$), 126.8 (d, $C_{p'}$), 126.6 (d, C_p), 126.5 (d, $2C_o$), 122.9 (d, C-4), 121.8 (d, C-5), 109.0 (d, C-7), 51.6 (q, OCH_3), 51.4 (s, C-3), 43.9 (t, C-*C*H_2), 43.8 (t, N-CH_2), 41.2 (t, C-8).
MS (EI, 70 eV): *m/z* (%) = 385 [M^+] (88), 325 (15), 294 (100), 252 (67), 158 (8), 91 (74); HRESI/APCIMS: *m/z* calcd for $C_{25}H_{23}NO_3$: 385.1678; found: 385.1664.

Methyl 2[2-oxo-1,3-bis(pyridin-4-ylmethyl)-2,3-dihydro-1*H*-indol-3-yl]acetate (4c): Prepared from **3a** (1.00 g, 5 mmol) as a pale yellow oil. The crude product was purified by flash chromatography (Me_2CO/MeOH 9:1) (0.51 g, 27% yield).



Rf: 0.12 (CH_2Cl_2/MeOH 19:1).
IR ($CHCl_3$): 3034, 2994, 1736, 1716, 1604 cm^{-1}.
^{1}H NMR ($CDCl_3$): 8.44 (2H, dm, *J* = 3.9 Hz, H-2‘), 8.28 (2H, dm, *J* = 4.4 Hz, H-2‘‘), 7.33 (1H, td, *J* = 6.2, 1.9 Hz, H-5), 7.12 (1H, d, *J* = 6.0 Hz, H-6), 7.11 (1H, d, *J* = 5.8 Hz, H-4), 6.73-6.70 (4H, m, H-3‘, H-3‘‘), 6.35 (1H, dd, *J* = 6.6, 1.6 Hz, H-7), 4.68 (2H, AB, *J* = 16.8 Hz, N-CH_2), 3.49 (3H, s, OCH_3), 3.22 and 3.08 (2H, AB, *J* = 16.6 Hz, H-8), 3.15 (2H, br s, C-CH_2).
^{13}C NMR ($CDCl_3$): 177.6 (s, C-2), 169.6 (s, C=O), 150.0 (d, 2C-2‘), 149.2 (d, 2C-2‘‘), 144.4 (s, C-4‘), 143.6 (s, C-4‘‘), 142.8 (s, C-7a), 129.2 (d, C-6), 128.8 (s, C-3a), 125.1 (d, 2C-3‘‘), 122.9 (d, C-5), 122.8 (d, C-4), 121.4 (d, 2C-3‘), 108.9 (d, C-7), 52.1 (q, OCH_3), 50.9 (s, C-3), 43.0 (t, C-*C*H_2), 42.6 (t, N-CH_2), 41.0 (t, C-8).
MS (EI, 70 eV): *m/z* (%) = 387 [M^+] (100), 295 (10), 253 (33), 65 (8); HRESI/APCIMS: *m/z* calcd for $C_{23}H_{21}N_3O_3$ + H: 388.1661; found: 388.1660.

Methyl 2(1,3-diethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (4d): Prepared from **3a** (1.00 g, 5 mmol) as a pale yellow oil. The crude product was purified by flash chromatography (hexane/EtOAc 4:1) (0.19 g, 15 % yield). Compound **4d** was also prepared from **3c** (1.17 g, 5 mmol) using the general alkylation procedure described above in 50% yield (0.65 g).

Rf: 0.16 (hexane/EtOAc 4:1).
IR ($CHCl_3$): 3012, 2929, 1737, 1705, 1613 cm^{-1}.
^{1}H NMR ($CDCl_3$): 7.25 (1H, td, *J* = 7.8, 1.1 Hz, H-6), 7.14 (1H, dd, *J* = 7.3, 0.8 Hz, H-4)), 7.01 (1H, td, *J* = 7.4, 0.9 Hz, H-5), 6.85 (1H, br d, *J* = 7.9 Hz, H-7), 3.78 (2H, m, N-CH_2), 3.39 (3H, s, OCH_3), 2.99 and 2.83 (2H, AB, *J* = 16.3 Hz, H-8), 1.82 (2H, m, C-CH_2), 1.26 (3H, m, CH_3), 0.56 (3H, t, *J* = 7.4 Hz, CH_3).
^{13}C NMR ($CDCl_3$): 178.6 (s, C-2), 170.1 (s, C=O), 143.4 (s, C-7a), 130.9 (s, C-3a), 128.0 (d, C-6), 122.6 (d, C-4), 122.0 (d, C-5), 107.9 (d, C-7), 51.3 (q, OCH_3), 49.9 (s, C-3), 40.8 (t, C-8), 34.5 (N-CH_2), 31.2 (C-*C*H_2), 12.4 (CH_3), 7.86 (CH_3).
MS (EI, 70 eV): *m/z* (%) = 261 [M^+] (100), 247 (25), 190 (46), 173 (33), 160 (37). HRESI/APCIMS: *m/z* calcd for $C_{15}H_{19}NO_3$: 261.1365; found 261.1368.

Methyl 2[1-methyl-3-(3-methylbut-2-enyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]acetate (4e): Prepared from **3b** (1.10 g, 5.0 mmol) as a pale yellow oil. The crude product was purified by flash chromatography (hexane/EtOAc 19:1) (1.34 g, 93% yield).
Rf: 0.54 (hexane/EtOAc 3:2).
IR ($CHCl_3$): 3005, 2931, 1737, 1710, 1613 cm^{-1}.
^{1}H NMR ($CDCl_3$): 7.13 (1H, td, *J* = 7.7, 1.2 Hz, H-6), 7.06 (1H, dd, *J* = 7.3, 0.9 Hz, H-4), 6.90 (1H, td, *J* = 7.5, 1.2 Hz, H-5), 6.72 (1H, br d, *J* = 7.9 Hz, H-7), 4.80 (1H, tm, *J* = 7.6 Hz, CH=), 3.30 (3H, s, OCH_3), 3.10 (3H, s, N-CH_3), 2.90 and 2.80 (2H, AB, *J* = 16.4 Hz, H-8), 2.33 (2H, m, C-CH_2), 1.50 (3H, s, =CCH_3), 1.40 (3H, s, =CCH_3).
^{13}C NMR ($CDCl_3$): 178.7 (s, C-2), 169.8 (s, C=O), 143.7 (s, C-7a), 135.5 (s, C=), 130.7 (s, C-3a), 127.6 (d, C-6), 122.3 (d, C-4), 121.6 (d, C-5), 116.6 (d, CH=), 107.4 (d, C-7), 50.9 (q, OCH_3), 49.2 (s, C-3), 39.4 (t, C-8), 35.8 (t, C-*C*H_2), 25.7 (q, N-CH_3), 25.4 (q, =C*C*H_3), 17.5 (q, =C*C*H_3).
MS (EI, 70 eV): *m/z* (%) = 287 [M^+] (3), 219 (100), 159 (13). HRESI/APCIMS: *m/z* calcd for $C_{17}H_{21}NO_3$: 287.1521; found 287.1524.

Methyl 2[1-benzyl-3-(3-methylbut-2-enyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]acetate (4f): Prepared from **3d** (1.48 g, 5.0 mmol) as a pale yellow oil. The crude product was purified by flash chromatography (hexane/EtOAc 4:1) (1.56 g, 86% yield).
Rf: 0.33 (hexane/EtOAc 4:1).
IR ($CHCl_3$): 3028, 2972, 2254, 1705, 1602, 1436 cm^{-1}.
^{1}H NMR ($CDCl_3$): 7.34-7.22 (5H, m, Ph), 7.18 (1H, dd, *J* = 7.9, 1.3 Hz, H-4), 7.13 (1H, td, *J* = 7.6, 1.3 Hz, H-6), 6.99 (1H, td, *J* = 7.5, 0.6 Hz, H-5), 6.67 (1H, br d, *J* = 7.7 Hz, H-7), 5.14 and 4.75 (2H, AB, *J* = 15.8 Hz, N-CH_2), 4.84 (1H, tm, *J* =7.6 Hz, CH=), 3.4 (3H, s, OCH_3), 3.09 and 2.93 (2H, AB, *J* = 16.3 Hz, H-8), 2.52 (2H, m, C-CH_2), 1.58 (3H, s, =CCH_3), 1.50 (3H, s, =CCH_3)
^{13}C NMR ($CDCl_3$): 179.2 (s, C-2), 170.3 (s, C=O), 143.4 (s, C-7a), 136.3 (s, C=), 136.1 (s, C_i), 131.0 (s, C-3a), 128.6 (d, $2C_m$), 128.0 (d, C-6), 127.4 (d, C_p), 127.3 (d, $2C_o$), 122.8 (d, C-4), 122.1 (d, C-5), 117.1 (d, CH=), 108.9 (d, C-7), 51.5 (q, OCH_3), 49.9 (s, C-3), 43.9 (t, N-CH_2), 40.3 (t, C-8), 36.7 (t, C-*C*H_2), 25.9 (q, =C*C*H_3), 18.0 (q, =C*C*H_3).
MS (EI, 70 eV): *m/z* (%) = 363 [M^+] (8), 295 (99), 235 (100), 91 (87); HRESI/APCIMS: *m/z* calcd for $C_{23}H_{25}NO_3$: 363.1834; found: 363.1839.

Methyl 2[1-benzyl-2-oxo-3-(pyridin-4-ylmethyl)-2,3-dihydro-1*H*-indol-3-yl]acetate (4g): Prepared from **3d** (1.48 g, 5.0 mmol) as a pale yellow oil. The crude product was purified by flash chromatography (hexane/EtOAc 9:1) (1.70 g, 88% yield).
Rf: 0.41 (EtOAc).
IR ($CHCl_3$): 3019, 1738, 1711, 1613 cm^{-1}.
^{1}H NMR ($CDCl_3$): 8.25 (2H, br d, *J* = 6.0 Hz, H-2‘‘), 7.30 (1H, dd, *J* = 7.5, 1.4 Hz, H-4), 7.21-7.18 (3H, m, H_m, H_p),

7.10 (1H, td, *J* = 7.6, 1.4 Hz, H-5), 7.04 (1H, td, *J* = 1.2, 7.5 Hz, H-6), 6.8 (2H, dm, *J* = 6.7 Hz, H_o), 6.71 (2H, br d, *J* = 6.0 Hz, H-3‘‘), 6.45 (1H, br d, *J* = 8.3 Hz, H-7), 4.8 and 4.6 (2H, AB, *J* = 16.0 Hz, N-CH_2), 3.44 (3H, s, OCH_3), 3.19 and 3.04 (2H, AB, *J* = 16.2 Hz, H-8), 3.15 (2H, br s, C-CH_2).
^{13}C NMR ($CDCl_3$): 177.4 (s, C-2), 169.6 (s, C=O), 149.1 (d, 2C-2‘‘), 143.6 (s, C-4‘‘), 143.3 (s, C-7a), 135.2 (s, C_i), 129.1 (s, C-3a), 128.6 (d, C-5), 128.5 (d, 2C_m), 127.2 (d, C_p), 126.6 (d, 2C_o), 125.0 (d, 2C-3‘‘), 122.9 (d, C-4), 122.2 (d, C-6), 109.2 (d, C-7), 51.6 (q, OCH_3), 50.7 (s, C-3), 43.7 (t, N-CH_2), 42.7 (t, C-*C*H_2), 41.1 (t, C-8).
MS (EI, 70 eV): *m/z* (%) = 386 [M^+] (100), 295 (38), 252 (39), 91 (57). HRESI/APCIMS: *m/z* calcd for $C_{24}H_{22}N_2O_3$: 386.1631; found 386.1631.

General hydrolysis procedure: A precooled (0°C) solution of the corresponding dialkylated methyl oxindole-3-acetate **4b-g** (2.0 mmol) in MeOH (10 mL) was treated with 15% aq NaOH (2.3 mL) and the resulting mixture stirred for 1.5 h at 40-50°C. 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.

2(1,3-Dibenzyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetic acid (5b): Prepared from **4b** (0.77 g, 2.0 mmol) as colorless crystals. The crude product was purified by flash chromatography (hexane/EtOAc 7:3) (645 mg, 87% yield).
MP: 174-175°C (CH_2Cl_2/Me_2CO).
Rf: 0.22 (hexane/EtOAc 1:1).
IR ($CHCl_3$): 3664, 3012, 2934, 1714, 1614 cm^{-1}.
^{1}H NMR ($CDCl_3$): 9.00 (1H, br s, COOH), 7.17 (1H, dd, *J* = 6.2, 1.5 Hz, H-4), 7.14-7.06 (4H, m, H_m, H_p, $H_{p'}$), 7.04-6.98 (4H, m, H-5, H-6, $H_{m'}$), 6.97 (1H, td obscured, *J* = 7.7, 1.3 Hz, H-5), 6.78-6.70 (4H, m, H_o, $H_{o'}$), 6.32 (1H, dd, *J* = 6.7, 1.8 Hz, H-7), 4.68 and 4.57 (2H, AB, *J* = 16.0 Hz, N-CH_2), 3.20 and 2.97 (2H, AB, *J* = 16.5 Hz, H-8), 3.09 (2H, br s, C-CH_2).
^{13}C NMR ($CDCl_3$): 178.2 (C-2), 174.3 (COOH), 143.0 (s, C-7a), 135.0 (s, C_i), 134.4 (s, $C_{i'}$), 129.9 (d, 2$C_{o'}$), 129.6 (s, C-3a), 128.3 (d, 2C_m), 128.1 (d, 2$C_{m'}$), 127.6 (d, C-6), 126.9 (d, $C_{p'}$), 126.6 (d, C_p), 126.4 (d, 2C_o), 122.9 (d, C-4), 122.1 (d, C-5), 109.2 (d, C-7), 51.2 (s, C-3), 43.9 (t, C-*C*H_2), 43.8 (t, N-CH_2), 40.9 (t, C-8).
MS (EI, 70 eV): *m/z* (%) = 371 [M^+] (100), 325 (14), 236 (66), 158 (22); HRESI/APCIMS: *m/z* calcd for $C_{24}H_{21}NO_3$: 371.1521; found: 371.1534.

2[2-Oxo-1,3-bis(pyridin-4-ylmethyl)-2,3-dihydro-1*H*-indol-3-yl]acetic acid (5c): Prepared from **4c** (0.77 g, 2.0 mmol) as colorless crystals. The crude product was purified by flash chromatography (CH_2Cl_2/Me_2OH 19:1) (600 mg, 81% yield).
MP: 267-268°C (CH_2Cl_2/MeOH).
Rf: 0.25 (CH_2Cl_2/MeOH 19:1).
IR ($CHCl_3$): 3510, 3012, 2918, 1714, 1614 cm^{-1}.
^{1}H NMR ($CDCl_3$): 9.70 (1H, br s, COOH), 8.45 (2H, dm, *J* = 6.3 Hz, H-3‘), 8.25 (2H, dm, *J* = 4.4 Hz, H-3‘‘), 7.43 (2H, dm, *J* = 6.1 Hz, H-2‘), 7.23 (1H, dd, *J* = 8.9, 4.9 Hz, H-4), 7.02 (2H, m, H-5, H-6), 6.73 (2H, dm, *J* = 4.4 Hz, H-2‘‘), 6.19 (1H, m, H-7), 5.19 and 4.02 (2H, AB, *J* = 17.0 Hz, N-CH_2), 3.37 and 3.13 (2H, AB, *J* = 17.0 Hz, H-8), 3.11 and 3.00 (2H, AB, *J* = 12.6 Hz, C-CH_2).
^{13}C NMR ($CDCl_3$): 178.3 (s, C-2), 172.0 (s, COOH), 147.8 (d, 2C-3‘‘), 147.5 (d, 2C-3‘), 147.3 (s, C-4‘), 144.6 (s, C-4‘‘), 142.4 (s, C-7a), 129.9 (s, C-3a), 128.5 (d, C-6), 125.3 (d, 2C-2‘‘), 122.7 (d, C-4, d C-5, d 2C-2‘), 108.5 (d, C-7), 51.2 (s, C-3), 43.8 (t, C-*C*H_2), 42.0 (t, N-CH_2), 41.0 (t, C-8).
MS (EI, 70 eV): *m/z* (%) = 373 [M^+] (90), 237 (100), 93 (54); HRESI/APCIMS: *m/z* calcd for $C_{22}H_{19}N_3O_3$: 373.11426; found: 373.11412.

2(1,3-Diethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetic acid (5d): Prepared from **4d** (0.52 g, 2.0 mmol) as a pale yellow oil. The crude product was purified by flash chromatography (AcOEt) (394 mg, 80% yield).
Rf: 0.12 (AcOEt).
IR ($CHCl_3$): 3502, 3014, 2880, 2646, 1712, 1612 cm^{-1}.
^{1}H NMR ($CDCl_3$): 7.90 (1H, br s, COOH), 7.26 (1H, td, *J* = 7.6, 1.4 Hz, H-6), 7.13 (1H, dd, *J* = 7.4, 0.5 Hz, H-4), 7.03 (1H, td, *J* = 7.5, 0.9 Hz, H-5), 6.83 (1H, br d, *J* = 7.8 Hz, H-7), 3.74 (2H, m N-CH_2), 2.97 and 2.78 (2H, AB, *J* = 16.5 Hz, H-8), 1.80 (2H, m C-CH_2), 1.19 (3H, t, *J* = 7.3 Hz, CH_3), 0.54 (3H, t, *J* = 7.4 Hz, CH_3).
^{13}C NMR ($CDCl_3$): 179.1 (s, C-2), 174.3 (s, COOH), 143.2 (s, C-7a), 130.9 (s, C-3a), 128.1 (d, C-6), 122.6 (d, C-4), 122.4 (d, C-5), 108.2 (d, C-7), 49.9 (s, C-3), 40.7 (t, C-8), 34.6 (t, N-CH_2), 31.0 (t, C-*C*H_2), 12.1 (q, CH_3), 7.8 (q, CH_3).
MS (EI, 70 eV): *m/z* (%) = 247 [M^+] (100), 231 (21), 202 (28), 174 (76), 160 (25); HRESI/APCIMS: *m/z* calcd for $C_{14}H_{17}NO_3$: 247.1208; found: 247.1206.

2[1-Methyl-3-(3-methylbut-2-enyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]acetic acid (5e): Prepared from **4e** (0.57 g, 2.0 mmol) as colorless crystals. The crude product was purified by flash chromatography (hexane/EtOAc 1:1) (423 mg, 78% yield).
MP: 111-113°C (hexane/EtOAc).
Rf: 0.12 (hexane/EtOAc 7:3).
IR ($CHCl_3$): 3502, 3012, 2916, 1712, 1614 cm^{-1}.
^{1}H NMR ($CDCl_3$): 9.40 (1H, br s, COOH), 7.27 (1H, td, *J* = 7.7, 1.4 Hz, H-6), 7.16 (1H, dd, *J* = 7.4, 1.4 Hz, H-4), 7.04 (1H, td, *J* = 7.6, 0.8 Hz, H-5), 6.83 (1H, br d, *J* = 7.4 Hz, H-7), 4.83 (1H, tm, *J* = 7.7 Hz, CH=), 3.20 (3H, s, N-CH_3), 3.01 and 2.83 (2H, AB, *J* = 16.5 Hz, H-8), 2.45 (2H, m, CH_2), 1.58 (3H, s, =CCH_3), 1.45 (3H, s, =CCH_3).
^{13}C NMR ($CDCl_3$): 179.9 (s, C-2), 173.5 (s, COOH), 143.6 (s, C-7a), 136.6 (s, C=), 130.9 (s, C-3a), 128.3 (d, C-6), 122.9 (d, C-4), 122.6 (d, C-5), 116.5 (d, CH=), 108.2 (d, C-7), 49.6 (s, C-3), 39.8 (t, C-8), 35.9 (t, C-*C*H_2), 26.4 (t, N-CH_3), 25.8 (q, =C*C*H_3), 17.9 (q, =C*C*H_3).
MS (EI, 70 eV): *m/z* (%) = 273 [M^+] (22), 205 (86), 187 (15), 159 (100); HRESI/APCIMS: *m/z* calcd for $C_{16}H_{19}NO_3$: 273.1365; found: 273.1364.

2[1-Benzyl-3-(3-methylbut-2-enyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]acetic acid (5f): Prepared from **4f** (0.73 g, 2.0 mmol) as a pale yellow oil. The crude product was purified by flash chromatography (hexane/EtOAc 1:1) (533 mg, 76% yield). Compound **5f** displayed analytical data in accordance with the published values [12].

2[1-Benzyl-2-oxo-3-(pyridin-4-ylmethyl)-2,3-dihydro-1*H*-indol-3-yl]acetic acid (5g): Prepared from **4g** (0.77 g, 2.0 mmol) as colorless crystals. The crude product was purified by flash chromatography (EtOAc) (594 mg, 80% yield).

MP: 222-223°C (CH_2Cl_2/MeOH).
Rf: 0.26 (CH_2Cl_2/Me_2OH 19:1).
IR ($CHCl_3$): 3517, 3005, 2258, 1718, 1615, 1495 cm^{-1}.
^1H NMR (DMSO-d_6): 8.16 (2H, br d, J = 5.7 Hz, H2‘‘), 7.46 (1H, br d, J = 7.5 Hz, H-4), 7.14 (1H, m, H_p), 7.12 (2H, m, H_m), 6.97 (1H, td obscured, J = 7.1 Hz, H-6), 6.96 (1H, td obscured, J = 7.0 Hz, H-5), 6.87 (2H, m, H_o), 6.39 (1H, d, J = 7.3 Hz, H-7), 6.65 (2H, br d, J = 5.7 Hz, H-3‘‘), 4.61 (2H, br s, N-CH_2), 3.18 and 2.98 (2H, AB, J = 12.5 Hz, C-CH_2), 3.05 and 2.93 (2H, AB, J = 16.3 Hz, H-8).
^{13}C NMR ($CDCl_3$): 177.6 (s, C-2), 171.0 (s, COOH), 148.4 (d, 2C-2‘‘), 144.1 (s, C-4‘‘), 143.0 (s, C-7a), 135.8 (s, C_i), 130.3 (s, C-3a), 128.0 (d, 2C_m), 127.5 (d, C-6), 126.6 (d, C_p), 126.4 (d, 2C_o), 124.8 (d, 2C-3‘‘), 123.1 (d, C-4), 121.4 (d, C-5), 108.2 (d, C-7), 50.8 (s, C-3), 42.7 (t, C-8, t, N-CH_2), 42.4 (t, C-*C*H_2).
MS (EI, 70 eV): *m/z* (%) = 372 [M^+] (100), 236 (32), 158 (43), 91 (70); HRESI/APCIMS: *m/z* calcd for $C_{23}H_{20}N_2O_3$ + H: 373.1552; found: 373.1548.

General reductive cyclization procedure: To a precooled (0°C) solution of corresponding dialkylated oxindole-3-acetic acid **5b-g** (2.0 mmol) in dry THF (20 mL) was added NaH (57 mg, 2.4 mmol), and the reaction mixture stirred for 10 min at rt. After cooling at 0°C, $LiBHEt_3$ (1 M in THF, 2.5 mL, 2.5 mmol) was added dropwise and stirring continued at rt for 6 h. The reaction mixture was cooled in an ice/water bath prior to quenching by adding brine dropwise (5 mL). The organic layer was evaporated under reduced pressure and the residue treated with 5% HCl in brine until pH ca. 6, followed by extraction with EtOAc (3 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.

3a,8-Dibenzyl-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole (6b): Prepared from **5b** (742 mg, 2.0 mmol) as pale yellow needles. The crude product was purified by flash chromatography (hexane/EtOAc 4:1). (405 mg, 57% yield).

MP: 136-138°C ($CHCl_3$/Et_2O).
Rf: 0.72 (hexane/EtOAc 7:3).
IR ($CHCl_3$): 3010, 2980, 1766, 1608, 1494 cm^{-1}.
^1H NMR ($CDCl_3$): 7.28-7.17 (6H, m, H_m, $H_{m'}$, H_p, $H_{p'}$), 7.10 (1H, td, J = 7.8, 1.3 Hz, H-6), 7.06 (2H, m, H_o), 6.97 (1H, dd, J = 7.4, 0.9 Hz, H-4), 6.85 (2H, m, $H_{o'}$), 6.81 (1H, td, J = 7.4, 0.9 Hz, H-5), 6.38 (1H, br d, J = 7.9 Hz, H-7), 5.60 (1H, s, H-8a), 4.45 and 4.35 (2H, AB, J = 15.2 Hz, N-CH_2), 3.08 and 2.94 (2H, AB, J = 14.6 Hz, C-CH_2), 2.99 and 2.92 (2H, AB, J = 16.0 Hz, H-3).
^{13}C NMR ($CDCl_3$): 174.2 (s, C-2), 147.9 (s, C-7a), 136.3 (s, C_i), 135.4 (s, $C_{i'}$), 131.7 (s, C-3b), 129.7 (d, 2$C_{o'}$), 129.2 (d, C-6), 128.5 (d, 2C_m), 128.3 (d, 2$C_{m'}$), 127.5 (d, 2C_o), 127.3 (d, C_p), 126.9 (d, $C_{p'}$), 123.7 (d, C-4), 119.5 (d, C-5), 107.9 (d, C-7), 101.2 (d, C-8a), 53.3 (s, C-3a), 48.8 (t, N-CH_2), 43.0 (t, C-*C*H_2), 40.6 (t, C-3).
MS (EI, 70 eV): *m/z* (%) = 355 [M^+] (100), 310 (71), 220 (60), 91 (95); HRESI/APCIMS: *m/z* calcd for $C_{24}H_{21}NO_2$: 355.1572; found: 355.1571.

2-Oxo-3a,8-bis(pyridin-4-ylmethyl)-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole (6c): Prepared from **5c** (746 mg, 2.0 mmol) as a pale yellow oil. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH 95:5) (543 mg, 76% yield).

Rf: 0.34 (CH_2Cl_2/MeOH 95:5).
IR ($CHCl_3$): 3022, 2964, 1780, 1604, 1560 cm^{-1}.
^1H NMR ($CDCl_3$): 8.50 (2H, d, J = 5.2 Hz, H-2‘), 8.43 (2H, d, J = 5.2 Hz, H-2‘‘), 7.15 (1H, td, J = 7.6, 1.4 Hz, H-6), 7.10 (1H, br d, J = 7.0 Hz, H-4), 6.91 (1H, td, J = 7.4, 0.8 Hz, H-5), 6.77 (2H, dm, J = 5.2 Hz, H-3‘), 6.75 (2H, dm, J = 5.2 Hz, H-3‘‘), 6.23 (1H, br d, J = 8.0 Hz, H-7), 5.62 (1H, s, H-8a), 4.34 (2H, br s, N-CH_2), 3.23 and 2.99 (2H, AB, J = 13.2 Hz, C-CH_2), 3.09 and 3.00 (2H, AB, J = 16.2 Hz, H-3).
^{13}C NMR ($CDCl_3$): 173.5 (s, C-2), 150.0 (d, 2C-2‘), 149.7 (d, 2C-2‘‘), 147.7 (s, C-7a), 145.8 (s, C-4‘), 144.4 (s, C-4‘‘), 130.4 (s, C-3b), 130.0 (d, C-6), 124.8 (d, 2C-3‘‘), 123.9 (d, C-4), 122.0 (d, 2C-3‘), 120.4 (d, C-5), 108.2 (d, C-7), 101.2 (d, C-8a), 52.8 (s, C-3a), 48.0 (t, N-CH_2), 42.9 (t, C-*C*H_2), 41.4 (t, C-3).
MS (EI, 70 eV): *m/z* (%) = 357 [M^+] (70), 312 (97), 221 (100), 92 (44); HRESI/APCIMS: *m/z* calcd for $C_{22}H_{19}N_3O_2$: 357.1477; found: 357.1481.

3a,8-Diethyl-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole (6d): Prepared from **5d** (494 mg, 2.0 mmol) as a pale yellow oil. The crude product was purified by flash chromatography (hexane/EtOAc 4:1) (273 mg, 59% yield).

Rf: 0.47 (hexane/EtOAc 7:3).
IR ($CHCl_3$): 3030, 2974, 1764, 1608, 1490 cm^{-1}.
^1H NMR ($CDCl_3$): 7.17 (1H, td, J = 7.7, 1.3 Hz, H-6), 7.05 (1H, ddd, J = 7.4, 1.3, 0.6 Hz, H-4), 6.80 (1H, td, J = 7.4, 0.9 Hz, H-5), 6.53 (1H, br d, J = 7.8 Hz, H-7), 5.66 (1H, s, H-8a), 3.45 (2H, m, N-CH_2), 2.80, 2.91 (2H, AB, J = 17.6 Hz, H-3), 1.80 (2H, m, C-CH_2), 1.31 (3H, t, J = 7.2 Hz, CH_3), 0.88 (3H, t, J =7.4 Hz, CH_3).
^{13}C NMR ($CDCl_3$): 175.2 (s, C-2), 147.9 (s, C-7a), 132.0 (s, C-3b), 129.0 (d, C-6), 123.5 (d, C-4), 118.9 (d, C-5), 107.0 (d, C-7), 102.6 (d, C-8a), 52.6 (s, C-3a), 40.4 (t, C-3), 39.2 (t, N-CH_2), 30.3 (t, C-*C*H_2), 12.8 (q, CH_3), 8.8 (q, CH_3).
MS (EI, 70 eV): *m/z* (%) = 231 [M^+] (91), 186 (100), 158 (87), 130 (21); HRESI/APCIMS: *m/z* calcd for $C_{14}H_{17}NO_2$: 231.1259; found: 231.1252.

8-Methyl-3a-(3-methylbut-2-enyl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole (6e): Prepared from **5e** (546 mg, 2.0 mmol) as a pale yellow oil. The crude product was purified by flash chromatography (hexane/EtOAc 4:1) (309 mg, 60% yield).

Rf: 0.71 (hexane/EtOAc 7:3).
IR ($CHCl_3$): 3018, 2934, 1762, 1610, 1490 cm^{-1}.
^1H NMR ($CDCl_3$): 7.19 (1H, td, J = 7.6, 1.3 Hz, H-6), 7.06 (1H, ddd, J = 7.4, 1.3, 0.5 Hz, H-4), 6.79 (1H, td, J = 7.5, 1.0 Hz, H-5), 6.52 (1H, br d, J = 7.8 Hz, H-7), 5.58 (1H, s, H-8a), 5.14 (1H, tm, J = 7.5 Hz, CH=), 3.0 (3H, s, N-CH_3), 2.92 and 2.82 (2H, AB, J = 17.8 Hz, H-3), 2.39 (2H, m, C-CH_2), 1.74 (3H, br s, =CCH_3), 1.56 (3H, br s, =CCH_3).
^{13}C NMR ($CDCl_3$): 175.2 (s, C-2), 148.3 (s, C-7a), 136.7 (s, C=), 132.8 (s, C-3b), 129.1 (d, C-6), 123.3 (d, C-4), 119.2 (d, C-5), 117.8 (d, CH=), 107.2 (d, C-7), 103.7 (d, C-8a), 52.7 (s, C-3a), 39.4 (t, C-3), 34.5 (t, C-*C*H_2), 31.3 (q, N-CH_3), 25.9 (q, =C*C*H_3), 18.1 (q, =C*C*H_3).
MS (EI, 70 eV): *m/z* (%) = 257 [M^+] (53), 212 (30), 160 (51), 144 (100); HRESI/APCIMS: *m/z* calcd for $C_{16}H_{19}NO_2$: 257.1415; found: 257.1412.

8-Benzyl-3a-(3-methylbut-2-enyl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole (6f) Prepared from **5f** (698 mg, 2.0 mmol) as a pale yellow oil. The crude product was purified by flash chromatography (hexane/EtOAc 7:3) (433 mg, 65% yield).

Rf: 0.60 (hexane/EtOAc 7:3).
IR ($CHCl_3$): 3022, 2928, 1768, 1670, 1608 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$): 7.34-7.22 (5H, m, Ph), 7.10 (1H, td, J = 7.6, 1.1 Hz, H-6), 7.07 (1H, br d, J = 6.6 Hz, H-4), 6.79 (1H, td, J = 7.4, 0.8 Hz, H-5), 6.46 (1H, br d, J = 7.7 Hz, H-7), 5.52 (1H, s, H-8a), 5.03 (1H, tm, J = 7.4 Hz, CH=), 4.58 and 4.46 (2H, AB, J = 15.4 Hz, N-CH_2), 2.91, 2.85 (2H, s, H-3), 2.42 (2H, m, C-CH_2), 1.69 (3H, s, =CCH_3), 1.49 (3H, s, =CCH_3).
^{13}C NMR ($CDCl_3$): 174.8 (s, C-2), 147.7 (s, C-7a), 136.5 (s, C_i), 136.2 (s, C=), 132.5 (s, C-3b), 128.9 (d, C-6), 128.5 (d, 2C_m), 127.5 (d, 2C_o), 127.3 (d, C*p*), 123.2 (d, C-4), 119.4 (d, C-5), 117.6 (d, CH=), 107.6 (d, C-7), 101.7 (d, C-8a), 52.7 (s, C-3a), 48.8 (t, N-CH_2), 40.1 (t, C-3), 35.2 (t, C-CH_2), 26.1 (q, =C*C*H_3), 18.2 (q, =CCH_3).
MS (EI, 70 eV): *m/z* (%) = 333 [M+] (84), 288 (65), 220 (89), 91 (100); HRESI/APCIMS: *m/z* calcd for $C_{22}H_{23}NO_2$: 333.1728; found: 333.1719.

8-Benzyl-2-oxo-3a-(pyridin-4-ylmethyl)-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole (6g): Prepared from **5g** (744 mg, 2.0 mmol) as colorless crystals. The crude product was purified by flash chromatography (EtOAc) (413 mg, 58% yield).

MP: 183-184°C (CH_2Cl_2/MeOH).
Rf: 0.59 (EtOAc/Me_2CO 1:1).
IR ($CHCl_3$): 3022, 2956, 1774, 1606, 1560 cm^{-1}.
^1H NMR ($CDCl_3$): 8.41 (2H, br d, J = 5.8 Hz, H-2‘‘), 7.34-7.28 (3H, m, H_m, H_p), 7.16 (1H, td, J = 7.8, 1.4 Hz, H-6), 7.03 (1H, dd, J = 7.4, 1.4 Hz, H-4), 6.97 (2H, br d, J = 6.5 Hz, H_o), 6.86 (1H, td, J = 7.4, 0.8 Hz, H-5), 6.72 (2H, dd, J = 4.5, 1.4 Hz, H-3‘‘), 6.40 (1H, br d, J = 8.0 Hz, H-7), 5.55 (1H, s, H-8a), 4.41 and 4.30 (2H, AB, J = 14.8 Hz, N-CH_2), 3.14 and 2.93 (2H, AB, J = 13.2 Hz, C-CH_2), 3.04 and 2.95 (2H, AB, J = 17.6 Hz, H-3).
^{13}C NMR ($CDCl_3$): 173.8 (s, C-2), 149.7 (d, 2C-2‘‘), 148.2 (s, C-7a), 144.4 (s, C-4‘‘), 136.0 (s, C_i), 130.6 (s, C-3b), 129.9 (d, C-6), 128.7 (d, 2C_m), 127.7 (d, 2C_o), 127.6 (d, C_p), 124.9 (d, 2C-3‘‘), 123.8 (d, C-4), 119.9 (d, C-5), 108.2 (d, C-7), 101.0 (d, C-8a), 52.6 (s, C-3a), 48.6 (t, N-CH_2), 42.7 (t, C-*C*H_2), 41.2 (t, C-3).
MS (EI, 70 eV): *m/z* (%) = 356 [M+] (58), 311 (45), 220 (36), 91 (100); HRESI/APCIMS: *m/z* calcd for $C_{23}H_{20}N_2O_2$ + H: 357.1603; found: 357.1607.

General lactamization procedure: Using a procedure described previously [13], to a solution of the appropriate lactone **6b-g** (0.6 mmol) in MeOH (20 mL) was added NH_2Me (3 mL of a 2.0 M solution in MeOH, 4 mmol). The reaction mixture was stirred for 2-3 h at rt. Afterward, methanol was removed under reduced pressure, and the residue was suspended in EtOAc (30 mL). The suspension was washed successively with a 5% aq HCl solution (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure.

3a,8-Dibenzyl-1-methyl-2-oxo-2,3,3a,8a-tetrahydro-8*H*-pyrrolo[2,3-*b*]indole (7b): Prepared from **6b** (213 mg, 0.6 mmol) as pale yellow needles. The crude product was purified by flash chromatography (hexane/EtOAc 1:1) (217 mg, 98% yield).

MP: 142-143°C ($CHCl_3$/Et_2O).
Rf: 0.21 (hexane/EtOAc 1:1).
IR ($CHCl_3$): 3014, 2922, 1682, 1604, 1492 cm^{-1}.
^1H NMR ($CDCl_3$): 7.27 (3H, m, $H_{m'}$), 7.26 (1H, t obscured, J = 7.1 Hz, H_p), 7.19 (3H, m, H_m, $H_{p'}$), 7.13 (2H, m, H_o), 7.09 (1H, td, J = 7.7, 1.4 Hz, H-6), 7.03 (1H, dd, J = 7.4, H-4), 6.81 (1H, td, J = 7.4, 1.1 Hz, H-5), 6.79 (2H, m, $H_{o'}$), 6.37 (1H, br d, J = 7.7 Hz, H-7), 4.85 (1H, s, H-8a), 4.08 (2H, s, N8-CH_2), 3.08, 2.83 (2H, AB, J = 13.4 Hz, C-CH_2), 2.86 and 2.80 (2H, AB, J = 17.5 Hz, H-3), 2.62 (3H, s, N1-CH_3).
^{13}C NMR ($CDCl_3$): 172.1 (s, C-2), 149.5 (s, C-7a), 138.1 (s, $C_{i'}$), 136.2 (s, C_i), 134.3 (s, C-3b), 129.8 (d, 2$C_{o'}$), 128.8 (d, C-6), 128.5 (d, C_p), 128.1 (d, 2C_m), 127.3 (d, 2$C_{m'}$), 127.2 (d, 2C_o), 126.8 (d, $C_{p'}$), 123.6 (d, C-4), 119.3 (d, C-5), 109.2 (d, C-7), 87.5 (d, C-8a), 53.6 (t, N8-CH_2), 51.2 (s, C-3a), 45.4 (t, C-*C*H_2), 42.6 (t, C-3), 28.2 (q, N1-CH_3).
MS (EI, 70 eV): *m/z* (%) = 368 [M^+] (100), 277 (96), 220 (9), 91 (83); HRESI/APCIMS: *m/z* calcd for $C_{25}H_{24}N_2O$: 368.1888; found: 368.1892.

1-Methyl-2-oxo-3a,8-bis(pyridin-4-ylmethyl)-2,3,3a,8a-tetrahydro-8*H*-pyrrolo[2,3-*b*]indole (7c): Prepared from **6c** (214 mg, 0.6 mmol) as colorless crystals. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH 19:1) (220 mg, 99% yield).

MP: 200-202°C (CH_2Cl_2/MeOH).
Rf: 0.21 (CH_2Cl_2/MeOH 19:1).
IR ($CHCl_3$): 3010, 2926, 1690, 1602, 1558 cm^{-1}.

^{1}H NMR ($CDCl_3$): 8.52 (2H, dd, *J* = 4.4, 1.7 Hz, H-2‘), 8.44 (2H, dd, *J* = 4.4, 1.7 Hz, H-2‘‘), 7.13 (1H, dm, *J* = 7.1 Hz, H-4), 7.11 (1H, m, H-6), 6.97 (2H, dm, *J* = 4.4 Hz, H-3‘), 6.90 (1H, td, *J* = 7.3, 1.1 Hz, H-5), 6.72 (2H, dm, *J* = 4.4 Hz, H-3‘‘), 6.15 (1H, br d, *J* = 8.4 Hz, H-7), 4.82 (1H, s, H-8a), 4.08 and 3.95 (2H, AB, *J* = 17.4 Hz, N8-CH_2), 3.21 and 2.89 (2H, AB, *J* = 13.2 Hz, C-CH_2), 2.82, 2.96 (2H, AB, *J* = 17.3 Hz, H-3), 2.71 (3H, s, N1-CH_3).
^{13}C NMR ($CDCl_3$): 172.0 (s, C-2), 150.2 (d, 2C-2‘), 149.6 (d, 2C-2‘‘), 149.1 (s, C-7a), 147.2 (s, C-4‘), 145.1 (s, C-4‘‘), 133.0 (s, C-3b), 129.6 (d, C-6), 124.9 (d, C-3‘‘), 123.7 (d, C-4), 121.6 (d, C-3‘), 120.2 (d, C-5), 108.9 (d, C-7), 88.6 (d, C-8a), 52.1 (t, N8-CH_2), 50.7 (s, C-3a), 45.0 (t, C-*C*H_2), 43.1 (t, C-3), 28.3 (q, N1-CH_3).
MS (EI, 70 eV): *m/z* (%) = 370 [M^+] (100), 278 (97), 221 (55), 92 (21), 93 (38); HRESI/APCIMS: *m/z* calcd for $C_{23}H_{22}N_4O$: 370.1794; found: 370.1784.

3a,8-Diethyl-1-methyl-2-oxo-2,3,3a,8a-tetrahydro-8*H*-pyrrolo[2,3-*b*]indole (7d): Prepared from **6d** (139 mg, 0.6 mmol) as colorless crystals. The crude product was purified by flash chromatography (hexane/EtOAc 1:1) (143 mg, 97% yield).
MP: 96-97°C (hexane/EtOAc).
Rf: 0.11 (hexane/EtOAc 1:1).
IR ($CHCl_3$): 3006, 2932, 1680, 1606, 1490 cm^{-1}.
^{1}H NMR ($CDCl_3$): 7.13 (1H, td, *J* = 7.5, 1.4 Hz, H-6), 7.0 (1H, ddd, *J* = 7.4, 1.3, 0.4 Hz, H-4), 6.74 (1H, td, *J* = 7.4, 1.0 Hz, H-5), 6.52 (1H, br d, *J* = 7.9 Hz, H-7), 4.75 (1H, s, H-8a), 3.53 and 3.37 (2H, ABX$_3$, *J* = 14.5 Hz, N8-CH_2), 2.90 (3H, s, N1-CH_3), 2.73 and 2.60 (2H, AB, *J* = 17.2 Hz, H-3), 1.73 (2H, m, C-CH_2), 1.22 (3H, t, *J* = 7.2 Hz, CH_3), 0.85 (3H, t, *J* = 7.5 Hz, CH_3).
^{13}C NMR ($CDCl_3$): 173.0 (s, C-2), 148.7 (s, C-7a), 134.6 (s, C-3b), 128.5 (d, C-6), 123.3 (d, C-4), 118.6 (d, C-5), 108.4 (d, C-7), 87.6 (d, C-8a), 50.1 (s, C-3a), 43.2 (t, N8-CH_2), 42.1 (t, C-3), 32.3 (t, C-*C*H_2), 27.7 (q, N1-CH_3), 13.3 (q, CH_3), 8.7 (q, CH_3).
MS (EI, 70 eV): *m/z* (%) = 244 [M^+] (100), 229 (25), 202 (24), 186 (24); 172 (39); HRESI/APCIMS: *m/z* calcd for $C_{15}H_{20}N_2O$: 244.1576; found: 244.1580.

1,8-Dimethyl-3a-(3-methylbut-2-enyl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-pyrrolo[2,3-*b*]indole (7e): Prepared from **6e** (154 mg, 0.6 mmol) as a pale yellow oil. The crude product was purified by flash chromatography (hexane/EtOAc 1:1) (157 mg, 97% yield).
Rf: 0.13 (hexane/EtOAc 3:2).
IR ($CHCl_3$): 3006, 2928, 1682, 1608, 1494 cm^{-1}.
^{1}H NMR ($CDCl_3$): 7.14 (1H, td, *J* = 7.6, 1.3 Hz, H-6), 7.03 (1H, dd, *J* = 7.4, 0.6 Hz, H-4), 6.75 (1H, td, *J* = 7.4, 1.0 Hz, H-5), 6.47 (1H, br d, *J* = 7.7 Hz, H-7), 4.97 (1H, tm, *J* = 7.4 Hz, CH=), 4.63 (1H, s, H-8a), 3.05 (3H, s, N8-CH_3), 2.91 (3H, *s*, N1-CH_3), 2.71 and 2.65 (2H, AB, *J* = 18.1 Hz, H-3), 2.39 (2H, m, C-CH_2), 1.69, (3H, s, =CCH_3), 1.57 (3H, s, =CCH_3).
^{13}C NMR ($CDCl_3$): 173.2 (s, C-2), 149.7 (s, C-7a), 134.7 (s, C-3b), 134.6 (s, C=), 128.7 (d, C-6), 123.1 (d, C-4), 118.7 (d, C-5), 118.5 (d, CH=), 107.7 (d, C-7), 89.6 (d, C-8a), 49.9 (s, C-3a), 41.8 (t, C-3), 37.4 (t, C-*C*H_2), 35.7 (q, N8-CH_3), 28.2 (q, N1-CH_3), 25.9 (q, =C*C*H_3), 18.1 (q, =C*C*H_3).
MS (EI, 70 eV): *m/z* (%) = 270 [M^+] (75), 201 (100), 144 (83); HRESI/APCIMS: *m/z* calcd for $C_{17}H_{22}N_2O$: 270.1732; found: 270.1735.

8-Benzyl-1-methyl-3a-(3-methylbut-2-enyl)-2-oxo-2,3,3a,8a-tetrahydro-8*H*-pyrrolo[2,3-*b*]indole (7f): Prepared from **6f** (200 mg, 0.6 mmol) as a pale yellow oil. The crude product was purified by flash chromatography (hexane/EtOAc 1:1) (202 mg, 97% yield). Compound **7f** displayed analytical data in accordance with the published values [14].

8-Benzyl-1-methyl-2-oxo-3a-(pyridin-4-ylmethyl)-2,3,3a,8a-tetrahydro-8*H*-pyrrolo[2,3-*b*]indole (7g): Prepared from **6g** (214 mg) as a pale yellow oil. The crude product was purified by flash chromatography (EtOAc/Me_2CO 7:3) (215 mg, 97% yield).
Rf: 0.34 (Me_2CO).
IR ($CHCl_3$): 3006, 2932, 1686, 1604, 1560 cm^{-1}.
^{1}H NMR ($CDCl_3$): 8.38 (2H, br s, H-2‘‘), 7.22-7.20 (3H, m, H_m, H_p), 7.09 (1H, td, *J* = 7.8, 1.1 Hz, H-6), 7.03 (2H, dm, *J* = 7.6 Hz, H_o), 7.00 (1H, dd, *J* = 7.4, 0.8 Hz, H-4), 6.80 (1H, td, *J* = 7.4, 0.8 Hz, H-5), 6.67 (2H, br d, *J* = 5.7 Hz, H-3‘‘), 6.35 (1H, br d, *J* = 7.7 Hz, H-7), 4.79 (1H, s, H-8a), 4.14 and 4.05 (2H, AB, *J* = 15.9 Hz, N8-CH_2), 3.06 and 2.79 (2H, AB, *J* = 13.2 Hz, C-CH_2), 2.88 and 2.76 (2H, AB, *J* = 16.8 Hz, H-3), 2.66 (3H, s, N1-CH_3).
^{13}C NMR ($CDCl_3$): 171.6 (s, C-2), 149.2 (d, 2C-2‘‘), 149.1 (s, C-7a), 145.0 (s, C-4‘‘), 137.6 (s, C_i), 132.9 (s, C-3b), 129.1 (d, C-6), 128.5 (d, 2C_m), 127.3 (d, C_p), 126.9 (d, 2C_o), 124.8 (d, 2C-3‘‘), 123.4 (d, C-4), 119.3 (d, C-5), 109.0 (d, C-7), 87.3 (d, C-8a), 53.1 (t, N8-CH_2), 50.6 (s, C-3a), 44.6 (t, C-*C*H_2), 42.7 (t, C-3), 28.2 (q, N1-CH_3).
MS (EI, 70 eV): *m/z* (%) = 369 [M^+] (100), 277 (56), 91 (82); HRESI/APCIMS: *m/z* calcd for $C_{24}H_{23}N_3O$: 369.1841; found: 369.1851.

General reduction procedure: To a precooled (0°C) stirred suspension of $LiAlH_4$ (100 mg, 2.6 mmol) in dry THF (20 mL) was added the appropriate lactam **7b-g** (0.23 mmol) in dry THF (15 mL), and the mixture was heated at reflux for 3 h. After cooling the solution in an ice/water bath, the reaction was quenched by adding, in sequence, EtOAc (2 x 15 mL) and water (10 mL). The solids were removed by filtration and washed with EtOAc (2 x 15 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc 1:1) to afford **1b-g** in 97-99% yield. Compounds **1b-g** have spectroscopic data, which closely matches those previously reported [9].

X-Ray diffraction analysis of 5b, 5c, 5e, 5g, 6b, 6g and 7c. The studies were done on a Bruker-Nonius CAD4 diffractometer using Cu Kα radiation (λ = 1.54184 Å). The data were collected in the ω-2θ scan mode. Unit cell

refinements were done 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.

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Table 2: X-ray data collection and processing parameters for oxindole-3-acetic acids **5b**, **5c**, **5e**, and **5g**, oxofuroindolines **6b** and **6g**, and pyrrolidinoindoline **7c**.

Compound	**5b**	**5c**	**5e**	**5g**	**6b**	**6g**	**7c**
Formula	$C_{24}H_{21}NO_3$	$C_{22}H_{19}N_3O_3$	$C_{16}H_{19}NO_3$	$C_{23}H_{20}N_2O_3$	$C_{24}H_{21}NO_2$	$C_{23}H_{20}N_2O_2$	$C_{23}H_{22}N_4O$
T (K)	293(2)	298(2)	298(2)	298(2)	298(2)	298(2)	298(2)
Size (mm^3)	0.44 x 0.32 x 0.32	0.40 x 0.38 x 0.32	0.42 x 0.40 x 0.32	0.42 x 0.37 x 0.21	0.38 x 0.32 x 0.32	0.40 x 0.38 x 0.34	0.42 x 0.34 x 0.34
System	orthorhombic	triclinic	triclinic	triclinic	monoclinic	monoclinic	monoclinic
Space group	$P2_12_12_1$	P-1	P-1	P-1	$P2_1/n$	$P2_1/c$	$P2_1/a$
a (Å)	8.646(2)	8.663(1)	9.337(2)	8.773(2)	12.686(1)	12.523(2)	14.894(5)
b (Å)	14.785(2)	10.258(1)	13.035(2)	10.230(1)	10.670(1)	8.255(1)	8.861(2)
c (Å)	15.621(2)	10.900(1)	14.315(2)	10.954(1)	13.753(4)	17.970(2)	15.490(8)
α (°)	90	90.49(1)	109.62(1)	87.45(1)	90	90	90
β (°)	90	104.17(1)	101.63(2)	74.82(2)	92.21(1)	96.74(1)	111.27(4)
γ (°)	90	104.06(2)	106.08(2)	75.46(2)	90	90	90
V ($Å^3$)	1996.7(7)	908.6(2)	1491.0(4)	918.2(2)	1860.2(6)	1844.7(4)	1905(1)
D_{calcd} (g cm^{-3})	1.236	1.365	1.218	1.347	1.269	1.283	1.292
Z	4	2	4	2	4	4	4
M (mm^{-1})	0.652	0.753	0.680	0.727	0.635	0.658	0.646
$2\theta_{range}$ (°)	5.6 - 59.9	4.2 - 59.9	3.5 - 59.9	4.2 - 59.9	4.8 - 59.9	4.9 - 59.9	3.1 - 59.9
Refl. total	1501	2799	4534	2876	2875	2729	2693
Refl. unique	1436	2630	4343	2714	2737	2634	2577
R_{int} (%)	0.01	0.03	0.03	0.02	0.05	0.03	0.06
Refl. observ.	1395	2549	3888	2520	2417	2252	2291
Parameters	258	306	377	258	249	248	258
R (%), R_w (%)	3.3, 8.8	4.5, 12.3	5.9, 17.3	4.2, 11.5	3.7, 10.2	4.2, 11.0	5.2, 14.5
e_{max} ($eÅ^{-3}$)	0.11	0.20	0.28	0.23	0.15	0.14	0.29
CCDC No.	807967	807968	807969	807970	807971	807972	807973

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