Tetrahedron 65 (2009) 3465–3472

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Intramolecular *N*-acyliminium ion versus Friedel–Crafts cyclization onto 3-indoles: synthesis of the novel rings pyrrolizino[2,1-*b*]indole and homologues

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ARTICLE INFO

Article history:
Received 21 November 2008
Received in revised form 25 January 2009
Accepted 13 February 2009
Available online 24 February 2009

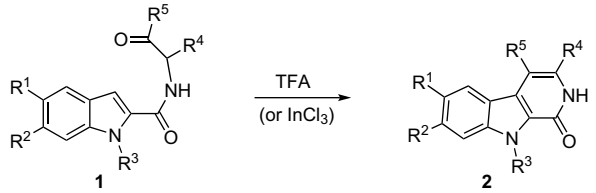
Keywords:
Friedel–Crafts
Acyliminium ion
Indole-fused heterocycles
Synthesis

ABSTRACT

Acid treatment of indole-2-carboxylic acid β- and γ-oxoamides causes Friedel–Crafts intramolecular cyclization to β-carbolinones and dihydro-2*H*-azepino[3,4-*b*]indol-1-ones, in contrast to secondary δ-,ε-, and ζ-oxoamides, which cyclize to the novel heterocyclic rings pyrrolizino[2,1-*b*]indole, indolizino[2,1-*b*]indole, and 9a,11-diaza-indeno[1,2-*a*]azulene, via an intermediate *N*-acyliminium ion. Tertiary amides lead only the Friedel–Crafts ring closure, thus allowing the synthesis of larger fused rings.

1. Introduction

In a recent paper[1] we reported that the intramolecular Friedel–Crafts cyclization of indole-2-carboxylic acids β-oxoamides (**1**), catalyzed by trifluoroacetic acid (TFA) or $InCl_3$, represents a simple, straightforward synthesis of β-carbolin-1-ones (**2**) (Scheme 1).



Scheme 1.

Due to the simplicity and efficiency of the synthesis, we decided to extend its scope to the preparation of indole-fused larger rings, such as azepino[3,4-*b*]indol-1-ones and higher homologues.

To this purpose, indole-2-carboxylic acid γ-oxoamides were synthesized by condensation of the acids (**3**) with the appropriate 3-aminoalcohols (**4**), followed by oxidation of the hydroxyl with IBX, and cyclization with TFA to the expected 3,10-dihydroazepino[3,4-*b*]indol-1-ones (**7**) in good yields (Scheme 2).[2]

Compared to the syntheses of the azepino[3,4]indole scaffold reported in the literature,[3–5] our procedure required simpler reagents and conditions, and could give easy access to aryl and alkyl substituted azepino[3,4-*b*]indol-1-ones.

In this paper we report the results of the application of the intramolecular Friedel–Crafts cyclization to the synthesis of higher homologues.

2. Results and discussion

To investigate the scope and aim of the TFA catalyzed annulation process, indole-2-carboxylic acid oxoamides with increasing chain length were subjected to intramolecular Friedel–Crafts cyclization.

Interestingly, when the ring-closure reaction was attempted on a δ-oxoamide (**8**), a compound with the mass expected for an azocino[3,4-*b*]indol-1-one (**9**) was obtained in good yield (75%). However, careful analysis of the ^1H and ^{13}C NMR spectra of this product indicated that they were more consistent with a tetracyclic pyrrolizino[2,1-*b*]indol-9-one structure (**10a**) (Scheme 3).

The disappearance of the proton in position 3b of the indole nucleus, together with H-10/C-8a, H-10/C-3c, and H-3/C-8a long range correlations, clearly demonstrated the occurrence of a cyclization process (Table 1). However, in the ^{13}C spectra, no further olefinic carbon was present, apart from those of the indole ring, suggesting that the condensation did not give the expected azocino[3,4-*b*]indol-1-one nucleus. The ^1H NMR spectrum revealed the presence of well-separated protons belonging to the three CH_2 groups, as clearly demonstrated by the ^1H-COSY, DEPT, and HSQC experiments. The different chemical shifts of the protons of each

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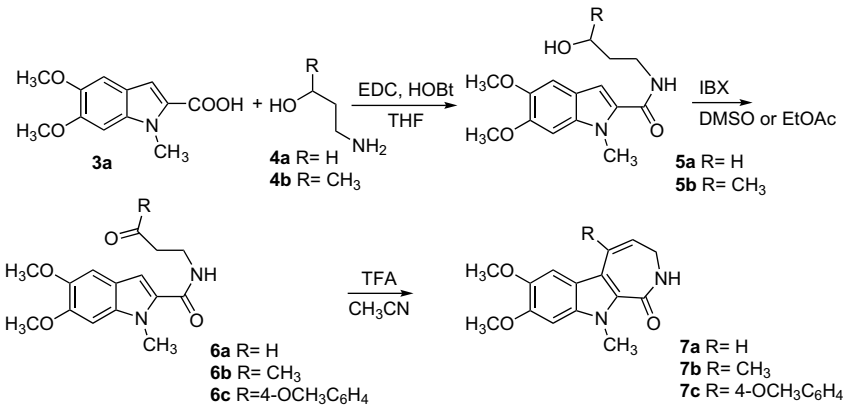
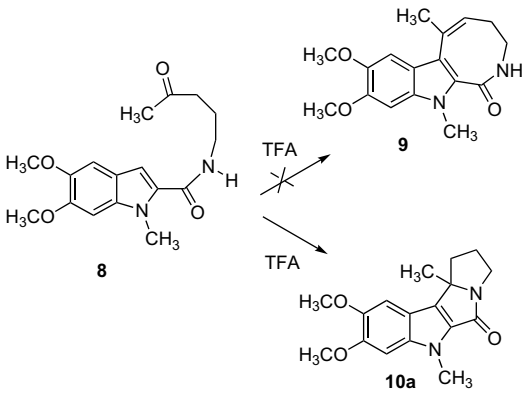
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.02.036

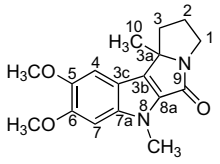


Scheme 2.



Scheme 3.

Table 1
^{1}H, ^{13}C, and HMBC NMR data for compound **10a** (DMSO-d_6)



10a

C	δ_C	δ_H	HMBC
1	41.56	3.48–3.20	C-2; C-3; C-3a; C-9
2	28.86	2.38–2.25	C-3; C-3a
3	35.03	2.12–1.40	C-10; C-2; C-1; C-3a; C-8a
3a	67.08		
3b	113.55		
3c	130.91		
4	94.78	7.10	C-3a; C-7; C-3b; C-8a; C-7a; C-5; C-6
5	145.86		
6	149.24		
7	101.93	7.19	C-4; C-8a; C-7a; C-5; C-6; NCH_3; C-3c
7a	137.87		
8a	136.34		
9	166.11		
10	24.00	1.54	C-3; C-3a; C-3c; C-8a
NMe	30.29	3.81	C-3c; C-7a; C-9
5-OMe	56.21	3.85	C-4; C-6
6-OMe	56.39	3.80	C-7; C-5

methylene group and the coupling constants were an evidence of a small-size ring system. Moreover, the amidic NH proton was absent, and H-3 showed a coupling only with the adjacent H-2. The ^{13}C and DEPT spectra showed the presence of two methyl groups, one linked to a nitrogen atom (δ 30.29 ppm) and the other (δ 24.00 ppm) attached to a sp^3 quaternary carbon.

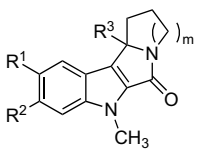
All this information, together with the value of 67.08 ppm for the chemical shift of the quaternary carbon C-3a, most likely due to the linkage to a nitrogen atom, clearly support the proposed tetracyclic structure.

As the reaction appeared a useful method for the synthesis of novel heterocyclic rings, its scope was explored by extending the study to the preparation of compounds with six- and seven-membered distal rings, differently substituted on the ring junction (Table 2).

To the best of our knowledge, only two examples of indolizidino[2,1-*b*]indoles, both with a distal aromatic ring, and obtained via Fischer indole synthesis[6] or Nazarov reaction,[7] have been reported recently, whereas no examples of pyrrolizidino[2,1-*b*]indoles or of 9a,11-diaza-indeno[1,2-*a*]azulenes have been reported so far.

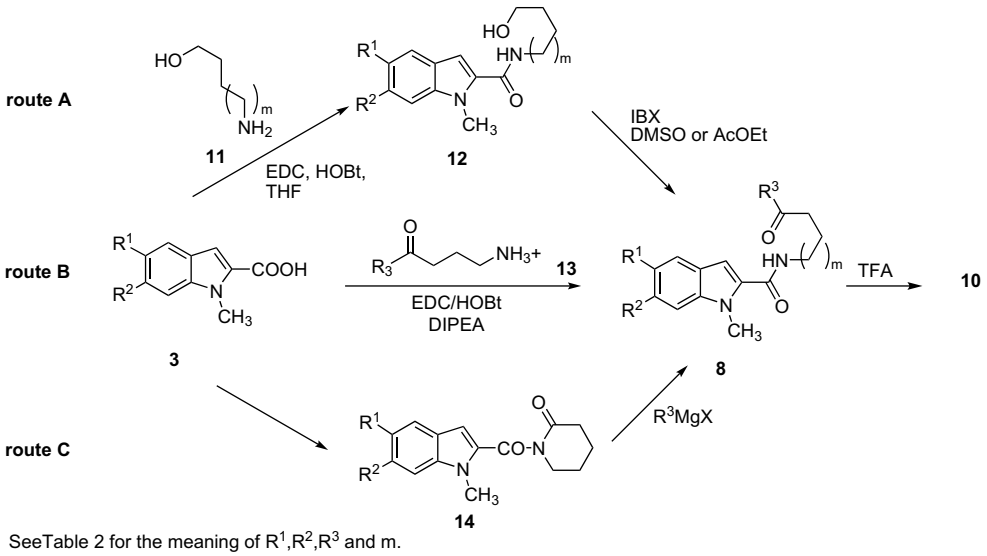
The amides **8** were prepared by condensing the appropriate indole-2-carboxylic acid **3** with the corresponding aminoalcohols or aminoketone hydrochlorides or toluenesulfonates in the presence of EDC and HOBt (Scheme 4, routes A and B). In the former case, the alcohols **12** were oxidized to the corresponding aldehydes with IBX in DMSO. Alternatively, amide **8g** was obtained by acylation of valerolactam with 2-indolecarboxylic acid chloride,

Table 2

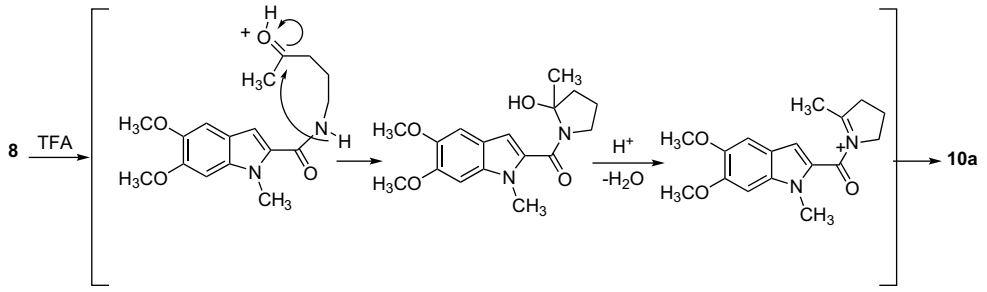


10

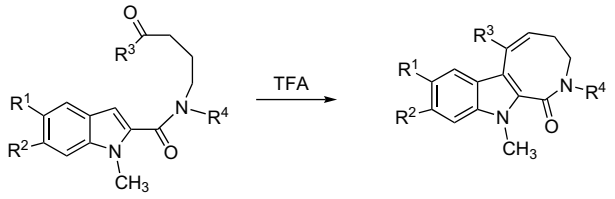
Entry	m	R_1	R_2	R_3	Method	Yield (%)
a	1	OCH_3	OCH_3	CH_3	B	76
b	1	OCH_3	OCH_3	H	A	10
c	1	H	H	H	A	10
d	1	H	H	4-CH_3O-Ph	B	75
e	1	OCH_3	OCH_3	4-CH_3O-Ph	B	93
f	2	OCH_3	OCH_3	H	A	20
g	2	H	H	CH_3	C	57
h	3	OCH_3	OCH_3	H	A	40



Scheme 4.



Scheme 5.



8i R^1, R^2 = OMe R^3 = H, R^4 = *n*Bu
8l R^1, R^2 = H R^3 = *p*OMePh R^4 = Me
9a R^1, R^2 = OMe R^3 = H, R^4 = *n*Bu
9b R^1, R^2 = H, R^3 = *p*OMePh R^4 = Me

Scheme 6.

followed by preferential lactam ring-opening with a Grignard reagent[8] (Scheme 4, route C).

The cyclization was performed with TFA in acetonitrile to obtain compounds **10**. The results are reported in Table 2.

The yields of the cyclization range from good to excellent in the case of ketones, especially when activating groups are present on the indole ring. The low yields of ring closure by aldehydes are most probably due to the lower stability of the intermediates, or to competitive reactions, such as the easier formation of intermolecular products.[9]

The formation of the tetracyclic compound can be explained by an acid-catalyzed activation of the carbonyl group, which undergoes a nucleophilic attack by the amide nitrogen, to give a hydroxylactam. This latter can be readily converted to the *N*-acyliminium ion by protonation. The intramolecular cyclization of this ion onto the indole nucleus gives rise to the final product (Scheme 5).[10]

Intramolecular *N*-acyliminium cyclizations of indoles are well-known, and a large number of examples of their use in the synthesis of alkaloids have been reported.[11] However, almost all of them involve the cyclization onto the 2-position of indole of a *N*-acyliminium ion tethered to position 3. In some cases, attack at position 3 gave a spirocyclization. The exhaustive survey of Maryanoff et al.[11] reports only one case[12] where the reaction has been exploited in the reverse sense, to cyclize onto position 3 a *N*-acyliminium ion tethered at position 2.

Support to the mechanism proposed for the formation of the tetracyclic compounds comes from the restoration of the Friedel–Crafts product, when the cyclization conditions were applied to a tertiary amide, which would not give an iminium ion. In fact, with tertiary amides, azocino[3,4-*b*]indol-1-ones **9** were obtained (Scheme 6).

3. Conclusion

In conclusion, the acid-catalyzed intramolecular reaction of indole-2-carboxylic acid secondary oxoamides takes place with two different mechanisms, depending on the length of the chain between the amide and the oxo group. One pathway, which follows a Friedel–Crafts mechanism, gives rise to β-carbolinones and dihydro-2*H*-azepino[3,4-*b*]indol-1-ones; the other one leads to a tetracyclic pyrrolizino[2,1-*b*]-indole and homologues with larger rings via a *N*-acylium ion. Both pathways represent a simple and straightforward method for the synthesis of these classes of heterocycles. Tertiary amides give only the Friedel–Crafts ring closure, thus allowing the synthesis of larger rings.

4. Experimental

4.1. General

All reagents and solvents were reagent grade or were purified by standard methods before use. Melting points were determined in open capillaries on a melting point apparatus and are uncorrected. Column chromatography was carried out on flash silica gel (Merck 230–400 mesh). TLC analysis was conducted on silica gel plates (Merck 60F_{254}). ^{1}H and ^{13}C NMR spectra were recorded, respectively, at 300 MHz and 75 MHz. Chemical shifts (δ values) and coupling constants (J values) are given in parts per million and hertz, respectively. High-resolution mass spectra were recorded on an APEX II ICR-FTMS spectrometer using electrospray ionization (ESI). The IR spectra were measured on a Perkin–Elmer 177 spectrophotometer. Solvents were routinely distilled prior to use; anhydrous tetrahydrofuran (THF) was obtained by distillation from sodium-benzophenone ketyl; dry methylene chloride was obtained by distillation from phosphorus pentoxide; DMF was dried over 4 Å molecular sieves. All reactions requiring anhydrous conditions were performed under a positive nitrogen flow, and all glassware was oven-dried and/or flame dried. The synthesis of compounds **7a–c** was performed as described in Ref. 2.

4.2. General procedure for the synthesis of indole-2-carboxylic acid hydroxyalkylamides (route A)

The appropriate aminoalcohol (1.59 mmol) was dissolved in dry THF (5.8 mL), then EDC (1.59 mmol), HOBt (1.59 mmol), and the appropriate indole-2-carboxylic acid (1.06 mmol) were added sequentially at room temperature. After the resulting mixture was stirred overnight, the solvent was removed and the crude product was poured into saturated aqueous $NaHCO_3$ (30 mL) and extracted with ethyl acetate (20×2 mL). The combined organic layers were washed with 1 N HCl, saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated in vacuo to give the product.

*4.2.1. 5,6-Dimethoxy-1-methyl-1H-indole-2-carboxylic acid (4-hydroxybutyl)-amide (**12b**)*

Yield 85%, mp 170–171 °C; R_f (20% hexane/ethyl acetate) 0.14; ν_{max} (KBr) 3600, 3350, 3300, 3050, 2900, 1640, 1560, 1460, 1410, 1390, 1250, 1230 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.27 (t, 1H, J=5.6 Hz, NH), 7.06 (s, 1H, ArH), 7.02 (s, 1H, ArH), 6.93 (s, 1H, ArH), 4.42 (t, 1H, J=5.2 Hz, OH), 3.93 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.75 (s, 3H, NMe), 3.42 (m, 2H, CH_2OH), 3.22 (m, 2H, NHCH_2), 1.62–1.40 (m, 4H, NHCH_2(CH_2)$_2$). δ_C (75 MHz, DMSO-d_6) 166.8, 153.4, 150.4, 138.5, 135.5, 123.1, 109.2, 107.6, 98.3, 65.5, 60.9, 60.5, one peak missing due to the overlapping with solvent signal, 36.3, 35.0, 31.0. HRMS (ESI$^+$): [M+Na]$^+$ found 329.1476, $C_{16}H_{22}N_2NaO_4$ requires 329.1472.

*4.2.2. 1-Methyl-1H-indole-2-carboxylic acid (4-hydroxybutyl)-amide (**12c**)*

Yield 74%, mp 99 °C; R_f (20% hexane/ethyl acetate) 0.36; ν_{max} (KBr): 3600, 3400, 3300, 3050, 2900, 1650, 1540, 1470, 1440, 1390, 1040 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.47 (t, J=5.95 Hz, 1H, NH), 7.63 (d, J=8.6 Hz, 1H, ArH), 7.52 (d, J=8.6 Hz, 1H, ArH), 7.25 (dd, J=8.6, 7.4 Hz, 1H, ArH), 7.08 (dd, J=8.6, 7.4 Hz, 1H, ArH), 7.04 (s, 1H, ArH), 4.45 (t, J=5.2 Hz, 1H, OH), 3.98 (s, 3H, NMe), 3.43 (dt, J=6.3, 5.2 Hz, 2H, CH_2OH), 3.26 (m, 2H, NHCH_2), 1.63–1.40 (m, 4H, NHCH_2(CH_2)$_2$). δ_C (75 MHz, DMSO-d_6) 161.9, 138.5, 132.7, 125.9, 123.6, 121.7, 120.3, 110.7, 104.2, 60.7, one peak missing due to the overlapping with solvent signal, 31.5, 30.3, 26.1. HRMS (ESI$^+$): [M+Na]$^+$ found 268.1265, $C_{14}H_{18}N_2NaO_2$ requires 269.1261.

*4.2.3. 5,6-Dimethoxy-1-methyl-1H-indole-2-carboxylic acid (5-hydroxypentyl)-amide (**12f**)*

Yield 81%, mp 155–157 °C; R_f (30% hexane/ethyl acetate) 0.21; ν_{max} (KBr) 3600, 3300, 3060, 2900, 1630, 1560, 1470, 1460, 1250, 1210, 1100 cm^{-1}; UV (methanol) λ_{max} nm (log ε) 316 (4.29). δ_H (300 MHz, DMSO-d_6) 8.26 (t, J=5.5 Hz, 1H, NH), 7.07 (s, 1H, ArH), 7.03 (s, 1H, ArH), 6.93 (s, 1H, ArH), 4.35 (t, J=5.3 Hz, 1H, OH), 3.94 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.76 (s, 3H, NMe), 3.44–3.35 (m, 2H, CH_2OH), 3.27–3.15 (m, 2H, NHCH_2), 1.61–1.26 (m, 6H, NHCH_2(CH_2)$_3$). δ_C (75 MHz, DMSO-d_6) 162.2, 148.8, 145.8, 133.9, 130.9, 118.5, 104.5, 103.0, 93.8, 61.1, 56.2, 56.1, one peak missing due to the overlapping with solvent signal, 32.7, 31.9, 29.6, 23.5. HRMS (ESI$^+$): [M+Na]$^+$ found 343.1633, $C_{17}H_{24}N_2NaO_4$ requires 343.1629.

*4.2.4. 5,6-Dimethoxy-1-methyl-1H-indole-2-carboxylic acid (6-hydroxyhexyl)-amide (**12h**)*

Yield 87%, mp 160–161 °C; R_f (20% hexane/ethyl acetate) 0.8; ν_{max} (KBr) 3350, 3250, 3080, 2850, 1690, 1580, 1480, 1410, 1380, 1230, 930 cm^{-1}; UV (methanol) λ_{max} nm (log ε) 212 (4.48), 316 (4.23). δ_H (300 MHz, DMSO-d_6) 8.27 (t, 1H, J=5.6 Hz, NH), 7.07 (s, 1H, ArH), 7.02 (s, 1H, ArH), 6.93 (s, 1H, ArH), 4.35 (t, 1H, J=5.2 Hz, OH), 3.94 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.76 (s, 3H, NMe), 3.44–3.35 (m, 2H, CH_2OH), 3.27–3.13 (m, 2H, NHCH_2), 1.59–1.23 (m, 8H, NHCH_2(CH_2)$_4$). δ_C (75 MHz, DMSO-d_6) 162.1, 148.8, 145.8, 133.8, 130.8, 118.5, 104.4, 103.0, 93.8, 61.0, 56.1 (2C), 32.9, 31.9, 29.7, 26.8, 25.7, one peak missing due to overlapping with solvent signal. HRMS (ESI$^+$): [M+Na]$^+$ found 357.1790, $C_{18}H_{26}N_2NaO_4$ requires 357.1785.

4.3. General procedure for the oxidation of hydroxyalkylamides (route A)

To a solution of IBX (1.37 mmol) in DMSO (1.85 mL) was added the hydroxyalkylamide (0.684 mmol) and the solution was stirred 2 h at room temperature under nitrogen. The solution was diluted with water (20 mL) and extracted with ethyl acetate (25×2 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (30×2 mL), water (50 mL), dried over Na_2SO_4, and evaporated. The compounds were purified by crystallization from ethyl acetate or by flash chromatography (hexane/ethyl acetate).

*4.3.1. 5,6-Dimethoxy-1-methyl-1H-indole-2-carboxylic acid (6-oxohexyl)-amide (**8f**)*

Yield 40%, mp 85 °C; R_f (20% hexane/ethyl acetate) 0.57; ν_{max} (KBr) 3350, 3080, 2995, 1735, 1680, 1630, 1240 cm^{-1}; δ_H (300 MHz, acetone-d_6) 9.76 (s, 1H, CHO), 7.60 (br s, 1H, NH), 7.06 (s, 1H, ArH),

7.02 (s, 1H, ArH), 6.93 (s, 1H, ArH), 4.02 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.80 (s, 3H, NMe), 3.20 (dd, J=7.1, 5.9 Hz, 2H, NHCH_2), 2.52 (t, J=7.0 Hz, 2H, CH_2CHO), 1.80–1.50 (m, 4H, NHCH$_2$(CH_2)$_2$). HRMS (ESI$^+$): [M+Na]$^+$ found 341.1477, $C_{17}H_{22}N_2NaO_4$ requires 341.1472.

4.3.2. 5,6-Dimethoxy-1-methyl-1H-indole-2-carboxylic acid (6-oxo-hexyl)-amide (**8h**)

Yield 37%, mp 124–125 °C; R_f (20% hexane/ethyl acetate) 0.53; ν_{max} (KBr) 3340, 3080, 2990, 1730, 1680, 1630, 1540, 1230 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 9.66 (s, 1H, CHO), 8.27 (t, 1H, J=5.6 Hz, NH), 7.06 (s, 1H, ArH), 7.02 (s, 1H, ArH), 6.92 (s, 1H, ArH), 3.93 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.75 (s, 3H, NMe), 3.26–3.15 (m, 2H, NHCH_2), 2.42 (t, 2H, J=7.07 Hz, CH_2CHO), 1.64–1.24 (m, 6H, NHCH$_2$(CH_2)$_3$). δ_C (75 MHz, DMSO-d_6) 203.9, 162.2, 148.8, 145.8, 133.8, 130.8, 118.5, 104.4, 103.0, 93.8, 56.1 (2C), 43.4, 38.8, 31.9, 29.4, 26.4, 21.7. HRMS (ESI$^+$): [M+Na]$^+$ found 355.1633, $C_{18}H_{24}N_2NaO_4$ requires 355.1629.

4.3.3. 5,6-Dimethoxy-1-methyl-1H-indole carboxylic acid butyl-(4-oxobutyl)amide (**8i**)

To a stirred mixture of n-butanol (1.471 g, 20.4 mmol), 4-aminobutanol (2 g, 22.4 mmol), and crushed/dried 4 Å molecular sieves in methanol (10 mL) at room temperature under nitrogen was added pyridine-borane complex (1.580 g, 17.0 mmol). After being stirred overnight, the mixture was filtered and the solvent evaporated in vacuo. The residue was purified by flash chromatography using CH_2Cl_2/MeOH/Et_3N 90:10:0.5 to give 890 mg (30%) of 4-butylaminobutan-1-ol (yellow oil); R_f (95% CH_2Cl_2/MeOH) 0.32; ν_{max} (liquid film) 3320, 2900, 1540, 1480, 1390, 1310, 1080 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.95–3.74 (br s, 2H, OH+NH), 3.65–3.53 (m, 2H, CH_2OH), 2.80–2.60 (m, 4H, CH_2NHCH_2), 1.80–1.25 (m, 8H, (CH_2)$_2$CH$_2$NHCH$_2$(CH_2)$_2$), 0.92 (t, J=7.1 Hz, 3H, Me). δ_C (75 MHz, $CDCl_3$) 62.0, 49.0, 48.7, 31.8, 30.8, 27.5, 20.14, 13.7. HRMS (ESI$^+$): [M+Na]$^+$ found 168.1354, $C_8H_{19}NNaO$ requires 168.1359. This compound was reacted as described in the general procedure to give 5,6-dimethoxy-1-methyl-1H-indole carboxylic acid butyl-(4-hydroxybutyl)amide, yield 54%, oil; R_f (5% hexane/ethyl acetate) 0.45; ν_{max} (liquid film) 3610, 3450, 3080, 2990, 2900, 1630, 1540, 1470, 1430, 1390, 1220, 1100 cm^{-1}; δ_H (300 MHz, acetone-d_6) 7.10 (s, 1H, ArH), 7.00 (s, 1H, ArH), 6.50 (s, 1H, ArH), 3.88 (s, 3HOMe), 3.80 (s, 3H, NMe), 3.72 (s, 3H, NMe), 3.65–3.45 (m, 6H, CH_2NCH_2+OCH_2), 1.80–1.22 (m, 8H, (CH_2)$_2$CH$_2$NCH$_2$(CH_2)$_2$), 0.89 (t, J=6.7 Hz, 3H, Me). δ_C (75 MHz, acetone-d_6) 163.9, 148.6, 145.9, 132.6, 131.7, 119.2, 103.2, 101.6, 93.4, 61.0, 55.6, 55.4, 30.5, 29.7, two peaks missing due to the overlapping with solvent signal, 28.2, 24.6, 19.8, 13.2. HRMS (ESI$^+$): [M+Na]$^+$ found 385.2096, $C_{20}H_{30}N_2NaO_4$ requires 385.2098.

Oxidation of 5,6-dimethoxy-1-methyl-1H-indole carboxylic acid butyl-(4-hydroxybutyl)amide with IBX, as described in the general procedure, afforded the title compound as a yellow oil, yield 93%; R_f (5% hexane/ethyl acetate) 0.37; ν_{max} (liquid film) 3080, 2990, 1730, 1660, 1630, 1540, 1270 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.80 (s, 1H, CHO), 7.05 (s, 1H, ArH), 6.77 (s, 1H, ArH), 6.49 (s, 1H, ArH), 3.89 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.78 (s, 3H, NMe), 3.60–3.46 (m, 4H, CH_2NCH_2), 2.60–2.41 (m, 2H, CH_2CHO), 2.04–1.25 (m, 8H, (CH_2)$_2$CH$_2$NCH$_2$(CH_2)$_2$), 0.90 (t, J=6.75 Hz, 3H, Me). δ_C (75 MHz, $CDCl_3$) 202.3, 162.3, 149.0, 145.7, 134.2, 130.9, 118.7, 104.6, 103.2, 94.2, 56.2, 56.1, 47.5 (2C), 42.5, 33.9, 31.8, 21.6, 20.5, 14.2. HRMS (ESI$^+$): [M+Na]$^+$ found 383.1947, $C_{20}H_{28}N_2NaO_4$ requires 383.1942.

4.4. General procedure for the synthesis of indole-2-carboxylic acid oxoamides by condensation with the appropriate aminoketone (route B)

To a suspension of the appropriate carboxylic acid (0.20 mmol) in dry THF (1.09 mL) were added EDC (0.30 mmol) and HOBt (0.30 mmol). The mixture was stirred at room temperature, under nitrogen, for 3 h. The appropriate aminoketone trifluoromethanesulfonate[13] or hydrochloride[14] (0.404 mmol) was added, followed by N-ethyldiisopropylamine (0.404 mmol). After the mixture was stirred 1 h at room temperature, the solvent was evaporated and the crude product was poured into saturated $NaHCO_3$ (25 mL) and extracted with ethyl acetate (25×2 mL). The combined extracts were then washed with 1 N HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography (hexane/ethyl acetate) to give the product.

4.4.1. 5,6-Dimethoxy-1-methyl-1H-indole-2-carboxylic acid (4-oxopentyl)-amide (**8a**)

Yield 69%, mp 143–144 °C; R_f (30% hexane/ethyl acetate) 0.23; ν_{max} (KBr) 3450, 3350, 3080, 2990, 2900, 1720, 1660, 1540, 1470, 1410, 1390, 1260, 1220, 1160, 1110, 1010 cm^{-1}; UV (methanol) λ_{max} nm (log ε) 212 (4.45), 315 (4.15). δ_H (300 MHz, DMSO-d_6) 8.28 (t, 1H, J=5.58 Hz, NH), 7.07 (s, 1H, ArH), 7.02 (s, 1H, ArH), 6.94 (s, 1H, ArH), 3.94 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.76 (s, 3H, NMe), 3.26–3.14 (m, 2H, NHCH_2), 2.49 (t, 2H, J=7.1 Hz, COCH$_2$), 2.09 (s, 3H, COMe), 1.76–1.62 (m, 2H, COCH$_2$CH_2). δ_C (75 MHz, DMSO-d_6) 208.5, 162.3, 148.8, 145.8, 133.9, 130.7, 118.5, 104.5, 103.0, 93.7, 56.1 (2C), 38.3, 31.9, 30.2, 23.8, one peak missing due to overlapping with solvent signal. HRMS (ESI$^+$): [M+Na]$^+$ found 341.1476, $C_{17}H_{22}N_2NaO_4$ requires 341.1472.

4.4.2. 1-Methyl-1H-indole-2-carboxylic acid [4-(4-methoxyphenyl)-4-oxo-butyl]-amide (**8d**)

Yield 76%, mp 115 °C; R_f (60% hexane/ethyl acetate) 0.22; ν_{max} (KBr) 3450, 3340, 3080, 2990, 2900, 1680, 1640, 1540, 1290, 1270, 1180 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.51 (t, 1H, J=5.0 Hz, NH), 7.94 (d, 2H, J=8.3 Hz, 2ArH), 7.61 (d, 1H, J=7.8 Hz, ArH), 7.50 (d, 1H, J=7.8 Hz, ArH), 7.25 (t, 1H, J=7.8 Hz, ArH), 7.13–6.97 (m, 4H, 4ArH), 3.95 (s, 3H, OMe), 3.82 (s, 3H, NMe), 3.39–3.27 (m, 2H, NHCH_2), 3.05 (t, 2H, J=7.2 Hz, COCH$_2$), 1.96–1.89 (m, 2H, COCH$_2$CH_2). δ_C (75 MHz, DMSO-d_6) 198.4, 163.4, 162.3, 138.7, 132.8, 130.5 (2C), 130.1, 126.0, 123.7, 121.8, 120.4, 114.2 (2C), 110.8, 104.4, 55.9, 38.7, 35.4, 31.6, 24.3. HRMS (ESI$^+$): [M+Na]$^+$ found 373.1528, $C_{21}H_{22}N_2NaO_3$ requires 373.1523.

4.4.3. 5,6-Dimethoxy-1-methyl-1H-indole-2-carboxylic acid [4-(4-methoxyphenyl)-4-oxobutyl]-amide (**8e**)

Yield 43%, mp 182 °C; R_f (20% hexane/ethyl acetate) 0.37; ν_{max} (KBr) 3340, 3080, 2990, 1680, 1630, 1540, 1270 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.34 (t, 1H, J=5.6 Hz, NH), 7.95 (d, 2H, J=8.9 Hz, ArH), 7.07 (s, 1H, ArH), 7.04 (d, 2H, J=8.9 Hz, 2ArH), 7.03 (s, 1H, ArH), 6.95 (s, 1H, ArH), 3.92 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.32–3.25 (m, 2H, NCH_2), 3.04 (t, 2H, J=7.1 Hz, COCH$_2$), 1.90–1.82 (m, 2H, COCH$_2$CH_2). δ_C (75 MHz, DMSO-d_6) 163.4, 162.3, 156.7, 148.8, 145.8, 133.9, 133.9, 131.7, 130.5, 128.5, 127.4, 118.5, 114.2, 104.6, 103.0, 93.8, 56.1 (2C), 55.9, 55.8, 38.6, 35.4, 31.9, 24.4. HRMS (ESI$^+$): [M+Na]$^+$ found 433.1738, $C_{23}H_{26}N_2NaO_5$ requires 433.1734.

4.4.4. 1H-Indole-2-carboxylic acid butyl-[4-(4-methoxyphenyl)-4-oxo-butyl]-amide (**8l**)

Trifluoromethanesulfonic acid (4 mL) was ice-cooled and 4-(methylamino)butyric acid hydrochloride (1.62 g, 10.53 mmol) and anisole (1 g, 9.25 mmol) were added. The mixture was heated and stirred at 80 °C for 50 min. The mixture was cooled to room temperature, water (16 mL) was added under ice-cooling and the aqueous phase was extracted with ethyl acetate (25 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to give 1-(4-methoxyphenyl)-4-methylaminobutan-1-one trifluoromethanesulfonate as a sticky solid (2.49 g, 79%); ν_{max} (film) 2800, 1680, 1630, 1230 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.45 (br s, 2H, NH_2^+), 7.95 (d, J=8.6 Hz, 2H, 2ArH), 7.06 (d, J=8.6 Hz, 2H, 2ArH), 3.85

(s, 3H, OMe), 3.12 (s, 3H, NMe), 3.12 (t, J=7.06 Hz, 2H, NCH_2), 2.94 (t, J=7.6 Hz, 2H, $COCH_2$), 1.98–1.84 (m, 2H, NCH_2CH_2). This compound was reacted as described in the general procedure (route B) to give the title compound: yield 72%, mp 125 °C; R_f (30% hexane/ethyl acetate) 0.17; ν_{max} (KBr) 3080, 2990, 1680, 1640, 1530, 1230 cm^{-1}; δ_H (300 MHz, acetone-d_6) 7.97 (m, 2H, 2ArH), 7.59 (d, J=8.0 Hz, 1H, ArH), 7.43 (d, J=8.4 Hz, 1H, ArH), 7.25 (dd, J=8.0, 8.2 Hz, 1H, ArH), 7.14–6.95 (m, 4H, 4ArH), 6.66 (s, 1H, ArH), 3.89 (s, 3H, OMe), 3.78 (s, 3H, NMe), 3.67 (t, J=7.2 Hz, 2H, NCH_2), 3.20 (s, 3H, NMe), 3.19 (m, 2H, $COCH_2$), 2.05 (m, 2H, $COCH_2CH_2$). δ_C (75 MHz, acetone-d_6) 197.2, 163.3, 137.4, 132.9, 129.9 (2C), 126.5, 122.7, 122.3, 121.1, 120.9, 119.8, 119.4, 113.7, 113.2, 109.5, 54.8, 34.5, 30.1, two peaks missing due to the overlapping with signal solvent, 21.5. HRMS (ESI^+): $[M+Na]^+$ found 387.1685, $C_{22}H_{24}N_2NaO_3$ requires 387.1680.

4.5. Synthesis of indole-2-carboxylic acid oxoamides by Grignard reaction on *N*-acyllactams (route C)

4.5.1. 1-(1-Methyl-1H-indole-2-carbonyl)-piperidin-2-one (**14**)

To a solution of *n*-BuLi (0.6 mL, 1.6 mmol, 2.7 M in heptane) at −78 °C was added a solution of δ-valerolactam (139 mg, 1.4 mmol) in THF (4 mL). After 20 min at −78 °C, 1-methyl-1*H*-indole-2-carbonyl chloride[15] (271 mg, 1.4 mmol) was added and the solution was slowly warmed to room temperature and stirred for 48 h. The reaction was then quenched with aq NH_4Cl (10 mL) and extracted with ethyl acetate (10×2 mL). The organic phase was washed with satd aq $NaHCO_3$ (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give **14** (127 mg, 35%) as a brown oil. Yield 35%; R_f (20% hexane/ethyl acetate) 0.52; ν_{max} (liquid film) 3300, 2900, 2800, 1680, 1520, 1470, 1390, 1270, 1220, 1190, 1150, 980 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.60 (d, 1H, J=7.5 Hz, ArH), 7.42–7.30 (m, 2H, 2ArH), 7.15–7.05 (m, 1H, ArH), 6.85 (s, 1H, ArH), 3.95 (s, 3H, NMe), 3.82–3.70 (m, 2H, NCH_2), 2.70–2.55 (m, 2H, $COCH_2$), 2.02–1.90 (m, 4H, $NCH_2(CH_2)_2$). δ_C (75 MHz, $CDCl_3$) 174.0, 163.2, 139.4, 138.8, 134.0, 125.6, 123.6, 120.5, 110.8, 107.4, 46.1, 34.3, 31.7, 31.2, 22.2. HRMS (ESI^+): $[M+Na]^+$ found 279.1108, $C_{15}H_{16}N_2NaO_2$ requires 279.1104.

4.5.2. 1-Methyl-1H-indole-2-carboxylic acid (6-oxohexyl)-amide (**8g**)

In a three-necked round bottomed flask equipped with an nitrogen inlet and a thermometer, compound **14** (100 mg, 0.390 mmol) was dissolved in dry THF (1.37 mL). To this solution cooled at −78 °C was added dropwise CH_3MgI (0.546 mL of a 1 M solution in isoamyl ether, 0.546 mmol). The mixture was warmed to room temperature and 2 M HCl was added until pH was 1–3. The organic phase was extracted with diethyl ether (15×2 mL), dried over Na_2SO_4, and concentrated in vacuo. The product **8g** was isolated by flash chromatography eluting with hexane/ethyl acetate 65:35 (14 mg, 14%, yellow oil); R_f (40% hexane/ethyl acetate) 0.32; ν_{max} (liquid film) 3350, 3080, 2990, 1710, 1650, 1530, 1470, 1230, 1100 cm^{-1}; δ_H (300 MHz, acetone-d_6) 7.76 (br s, 1H, CONH), 7.59 (d, J=8.0 Hz, 1H, ArH), 7.48 (d, J=8.4 Hz, 1H, ArH), 7.28 (dd, J=8.0, 8.2 Hz, 1H, ArH), 7.09 (dd, J=8.2, 8.4 Hz, 1H, ArH), 7.04 (s, 1H, ArH), 4.06 (s, 3H, NMe), 3.40 (m, 2H, $NHCH_2$), 2.53 (t, J=7.1 Hz, 2H, $COCH_2$), 2.10 (s, 3H, COMe), 1.70–1.50 (m, 4H, $COCH_2(CH_2)_2$). δ_C (75 MHz, acetone-d_6) 207.3, 162.1, 138.8, 126.3, 123.4, 121.4, 120.0, 110.0, 103.5, 42.3, 38.6, 38.5, 30.73, one peak missing due to the overlapping with solvent signal, 20.8. HRMS (ESI^+): $[M+Na]^+$ found 295.1422, $C_{16}H_{20}N_2NaO_2$ requires 295.1417.

4.6. General procedure for the cyclization of indole-2-carboxylic acid oxoamides

Trifluoroacetic acid (0.258 mmol) was added to a solution of the appropriate oxoalkylamide (0.172 mmol) in CH_3CN (3.2 mL) and the mixture was refluxed until the starting material disappeared (TLC). The solvent was evaporated and the crude product was purified by flash column or preparative layer chromatography (hexane/ethyl acetate).

4.6.1. 2-Butyl-8,9-dimethoxy-11-methyl-2,3,4,6a,11,11a-hexahydroazocino[3,4-b]indol-1-one (**9a**)

Yield 10%, yellow oil, R_f (95% ethyl acetate/hexane) 0.27; ν_{max} (liquid film) 3080, 2900, 1660, 1460, 1430, 1380, 1260 cm^{-1}; δ_H (300 MHz, acetone-d_6) 7.08 (s, 1H, ArH), 7.02 (s, 1H, ArH), 6.57 (dt, J=12.6, 2.1 Hz, 1H, CH=), 5.71 (dt, J=12.6, 4.2 Hz, 1H, CH=), 3.90 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.79 (s, 3H, NMe), 3.22–3.00 (m, 4H, $NCH_2+NCH_2CH_2$), 2.78–2.50 (m, 2H, NCH_2), 1.80–1.61 (m, 2H, $CH_2CH_2CH_3$), 1.52–1.34 (m, 2H, CH_2CH_3), 0.98 (t, J=7.44 Hz, 3H, Me). δ_C (75 MHz, acetone-d_6) 166.1, 149.8, 146.1, 133.8, 129.6, 125.7, 117.7, 117.0, 101.8, 101.1, 97.3, 56.5, 56.4, 47.7, 47.6, 34.5, 32.1, 26.3, 20.4, 13.6. HRMS (ESI^+): $[M+Na]^+$ found 365.1832, $C_{20}H_{26}N_2NaO_3$ requires 365.1836.

4.6.2. 6-(4-Methoxyphenyl)-2,11-dimethyl-2,3,4,6a,11,11a-hexahydroazocino[3,4-b]indol-1-one (**9b**)

Yield 21%, mp 85 °C; R_f (60% ethyl aceatate/hexane) 0.23; ν_{max} (KBr) 3080, 2995, 1690, 1620, 1570, 1520, 1470, 1260 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.32 (d, J=8.4 Hz, 1H, ArH), 7.22–7.14 (m, 1H, ArH), 7.10 (d, J=8.6 Hz, 2H, 2ArH), 6.90–6.81 (m, 1H, ArH), 6.73 (d, J=8.6 Hz, 2H, 2ArH), 5.89 (dd, J=6.3, 2.8 Hz, 1H, CH=), 4.33 (dt, J=13.9, 2.8 Hz, 1H, $NCH_2CH_aCH_b$), 3.87 (s, 3H, OMe), 3.76 (s, 3H, NMe), 3.18 (s, 3H, NMe), 3.14–3.03 (m, 1H, $NCH_2CH_aCH_b$), 2.98–2.79 (m, 1H, NCH_aCH_b), 2.61–2.48 (m, 1H, NCH_aCH_b). δ_C (75 MHz, $CDCl_3$) 163.8, 159.8, 148.3, 140.5, 140.1, 132.1, 125.2 (3C), 122.1, 121.5, 121.1 (2C), 116.3, 114.2 (2C), 110.3, 56.0, 50.2, 34.3, 33.0, 25.2. HRMS (ESI^+): $[M+Na]^+$ found 369.1571, $C_{22}H_{22}N_2NaO_2$ requires 369.1574.

4.6.3. 3a-Methyl-5,6-dimethoxy-1,2,3,3a,9,9a-hexahydropyrrolizino[1,2-b]indol-9-one (**10a**)

Yield 76%, mp 152–153 °C; R_f (20% hexane/ethyl acetate) 0.42; ν_{max} (KBr) 3000, 2930, 1680, 1560, 1510, 1480, 1430, 1340, 1280, 1220, 1040 cm^{-1}; UV (methanol) λ_{max} nm (log ε) 321 (4.38); δ_H (300 MHz, DMSO-d_6) 7.19 (s, 1H, ArH), 7.10 (s, 1H, ArH), 3.85 (s, 3H, OMe), 3.81 (s, 3H, NMe), 3.80 (s, 3H, OMe), 3.48–3.20 (m, 2H, NCH_2–), 2.38–2.25 (m, 2H, NCH_2CH_2), 2.12–1.40 (m, 2H, $NCH_2CH_2CH_2$), 1.54 (s, 3H, Me). δ_C (75 MHz, DMSO-d_6) 166.1, 149.2, 145.8, 137.8, 136.3, 130.9, 113.5, 101.9, 94.7, 67.0, 56.3, 56.2, 41.5, 35.0, 30.2, 28.8, 24.0. HRMS (ESI^+): $[M+Na]^+$ found 323.1366, $C_{17}H_{20}O_3N_2Na$ requires 323.1363; $[2M+Na]^+$ found 623.2838, $C_{34}H_{40}O_6N_4Na$ requires 623.2840; $[3M+Na]^+$ found 923.4332, $C_{51}H_{60}O_9N_6Na$ requires 923.4314.

4.6.4. 5,6-Dimethoxy-1,2,3,3a,9,9a-hexahydropyrrolizino-[1,2-b]indol-9-one (**10b**)

Under a stream of nitrogen, 2-iodoxybenzoic acid (298 mg, 1.1 mmol) was dissolved in DMSO (1.55 mL), and then the alcohol **12b** (168 mg, 0.55 mmol) was added. The mixture was stirred at room temperature for 4 h. Water (10 mL) was added and the product was extracted with ethyl acetate (10×2 mL). The organic phase was washed with water (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude aldehyde **8b** (150 mg) was dissolved in 2.5 mL of CH_3CN, and then TFA (56 μL, 0.73 mmol) was added. The solution was refluxed for 1 h. The solid formed was filtered and dried under vacuum to give 16 mg of the desired product. Yield 10%, mp >300 °C; R_f (20% hexane/ethyl acetate) 0.45; ν_{max} (KBr) 3080, 2800, 1650, 1460, 1430, 1380, 1340, 1260, 900 cm^{-1}; δ_H (300 MHz, TFA) 7.60 (s, 1H, ArH), 7.44 (s, 1H, ArH), 6.43 (d, J=8.0 Hz, 1H, NCH), 4.47 (s, 3H, OMe), 4.46 (s, 3H, OMe), 4.17 (s, 3H, NMe), 4.11–4.06 (m, 1H, NCH_aCH_b), 3.91–3.85 (m, 1H, NCH_aCH_b), 3.02–2.95 (m, 1H, $NCH_2CH_aCH_b$), 2.81–2.76 (m, 1H,

$NCH_2CH_aCH_b$), 2.64–2.56 (m, 1H, $NCH_2CH_2CH_aCH_b$), 2.45–2.39 (m, 1H, $NCH_2CH_2CH_aCH_b$). δ_C (75 MHz, TFA) 169.9, 151.9, 147.8, 137.5, 135.4, 128.1, 115.1, 104.6, 95.7, 62.6, 58.5, 57.5, 52.7, 34.8, 31.7, 23.8. HRMS (ESI$^+$): $[M+Na]^+$ found 309.1207, $C_{16}H_{18}O_3N_2Na$ requires 309.1210.

4.6.5. 8-Methylpyrrolizino[2,1-b]indol-9-one (**10c**)

Under a stream of nitrogen, 2-iodoxybenzoic acid (145 mg, 0.536 mmol) was dissolved in DMSO, and then alcohol **12c** (66 mg, 0.268 mmol) was added. The mixture was stirred at room temperature for 1 h. Water was added and the product was extracted with ethyl acetate. The organic phase was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The crude aldehyde **8c** (55 mg) was dissolved in 1.6 mL of CH_3CN, and then TFA (36 μL, 0.47 mmol) was added. The solution was refluxed for1 h. The solid formed was filtered and dried under vacuum to give 8 mg of the desired product. Yield 10%, mp >300 °C; R_f (10% hexane/ethyl acetate) 0.55; ν_{max} (KBr) 3060, 2980, 1650, 1460, 1430, 1400, 920 cm^{-1}; δ_H (300 MHz, TFA) 8.03 (d, J=7.8 Hz, 1H, ArH), 7.83–7.-75 (m, 2H, 2ArH), 7.69–7.-60 (m, 1H, ArH), 6.49 (d, J=5.2 Hz, 1H, NCH), 4.20 (s, 3H, NMe), 4.10–4.05 (m, 1H, NCH_aCH_b), 3.95–3.83 (m, 1H, NCH_aCH_b), 3.08–2.90 (m, 1H, $NCH_2CH_aCH_b$), 2.86–2.76 (m, 1H, $NCH_2CH_aCH_b$), 2.70–2.51 (m, 1H, $NCH_2CH_2CH_aCH_b$), 2.47–2.34 (m, 1H $NCH_2CH_2CH_aCH_b$). HRMS (ESI$^+$): $[M+H]^+$ found 227.1181, $C_{14}H_{15}N_2O$ requires 227.1186; $[2M+H]^+$ found 453.2284, $C_{28}H_{29}N_4O_2$ requires 453.2281; $[2M+Na]^+$ found 475.2104, $C_{28}H_{28}N_4NaO_2$ requires 475.2110; $[4M+H]^+$ found 905.4463, $C_{56}H_{57}N_8O_4$ requires 905.4483; $[4M+Na]^+$ found 927.4302, $C_{56}H_{56}N_8NaO_4$ requires 927.4284.

4.6.6. 4-Methoxyphenyl-1,2,3,3a,9,9a-hexahydropyrrolizino-[1,2-b]indol-9-one (**10d**)

Yield 75%, mp 130 °C; R_f (65% hexane/ethyl acetate) 0.41; ν_{max} (KBr) 3080, 2995, 1700, 1620, 1570, 1520, 1470, 1340, 1260, 1190, 1050, 905, 840 cm^{-1}; UV (methanol) λ_{max} nm (log ε) 230 (4.52), 302 (4.17); δ_H (300 MHz, $CDCl_3$) 7.65 (d, 1H, J=7.8 Hz, ArH), 7.56 (d, 2H, J=8.6 Hz, 2ArH), 7.41–7.25 (m, 2H, 2ArH), 7.14 (t, 1H, J=7.8 Hz, ArH), 6.90 (d, 2H, J=8.6 Hz, ArH), 3.96 (s, 3H, OMe), 3.88–3.73 (m, 4H, OMe+NCH_aCH_b), 3.46–3.34 (m, 1H, NCH_aCH_b), 2.84–2.72 (m, 1H, $NCH_2CH_aCH_b$), 2.45–2.30 (m, 1H, $NCH_2CH_aCH_b$), 2.24–2.07 (m, 1H, $NCH_2CH_2CH_aCH_b$), 1.86–1.70 (m, 1H, $NCH_2CH_2CH_aCH_b$). δ_C (75 MHz, $CDCl_3$) 166.7, 158.8, 142.48, 135.3, 132.9, 126.3 (3C), 124.2, 120.7, 120.3, 120.0, 114.1 (2C), 110.9, 73.0, 55.2, 41.2, 36.2, 29.9, 28.7. HRMS (ESI$^+$): $[M+Na]^+$ found 355.1410, $C_{21}H_{20}N_2NaO_2$ requires 355.1417.

4.6.7. 4-Methoxyphenyl-5,6-dimethoxy-1,2,3,3a,9,9a-hexahydropyrrolizino[1,2-b]indol-9-one (**10e**)

Yield 93%, mp 88 °C; R_f (35% hexane/ethyl acetate) 0.33; ν_{max} (KBr) 3050, 2930, 1685, 1510, 1470, 1430, 1320, 1240, 1030, 900 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.59 (d, 2H, J=8.93 Hz, 2ArH), 7.11 (s, 1H, ArH), 7.07 (s, 1H, ArH), 6.91 (d, 2H, J=8.9 Hz, ArH), 3.82 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.71 (s, 3H, NMe), 3.65–3.51 (m, 1H, NCH_aCH_b), 3.27–3.15 (m, 1H, NCH_aCH_b), 2.83–2.69 (m, 1H, $NCH_2CH_aCH_b$), 2.36–2.21 (m, 1H, $NCH_2CH_aCH_b$), 1.98–1.79 (m, 1H, $NCH_2CH_2CH_aCH_b$), 1.71–1.56 (m, 1H, $NCH_2CH_2CH_aCH_b$). δ_C (75 MHz, DMSO-d_6) 166.2, 158.5, 149.2, 145.8, 137.8, 136.0, 133.7, 130.0, 126.7 (2C), 114.3 (2C), 113.27, 102.0, 94.7, 72.7, 56.4, 56.1, 55.4, 41.6, 36.4, 30.3, 28.8. HRMS (ESI$^+$): $[M+Na]^+$ found 415.1625, $C_{23}H_{24}N_2NaO_4$ requires 415.1629.

4.6.8. 6,7-Dimethoxy-1,2,3,4,4a,9,10,10a-octahydro-9H-indolizino[1,2-b]indol-10-one (**10f**)

Under a stream of nitrogen, 2-iodoxybenzoic acid (330 mg, 1.22 mmol) was dissolved in DMSO (1.7 mL), and then alcohol **12f** (196 mg, 0.61 mmol) was added. The mixture was stirred at room temperature for 4 h. Water was added and the product was extracted with ethyl acetate. The organic phase was washed twice with water, dried over Na_2SO_4, and concentrated in vacuo. To give a crude product (115 mg), that was dissolved in 6.6 mL of CH_3CN, then TFA (42 μL, 0.542 mmol) was added. The solution was refluxed for 5 h. The solvent was evaporated in vacuo and the crude product was purified by flash chromatography (hexane/ethyl acetate 20:80) to give 22 mg (20%) of **10f** as a yellow solid. Mp 162–163 °C; R_f (20% hexane/ethyl acetate) 0.47; ν_{max} (KBr) 3080, 2850, 1650, 1465, 1430, 1380, 1320, 1250 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.18 (s, 1H, ArH), 7.11 (s, 1H, ArH), 4.33 (dd, J=3.8, 12.0 Hz, 1H, NCH), 4.16 (dd, J=13.0, 5.0 Hz, 1H, NCH_aCH_b), 3.86 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.78 (s, 3H, NMe), 2.96 (td, J=13.0, 13.0, 3.6 Hz, 1H, NCH_aCH_b), 2.60–2.56 (m, 1H, $NCH_2CH_aCH_b$), 1.89–1.85 (m, 1H, $NCH_2CH_aCH_b$), 1.79–172 (m, 1H, $NCH_2CH_2CH_aCH_b$), 1.65–1.59 (m, 1H, $NCH_2CH_2CH_aCH_b$), 1.23–1.29 (m, 1H, $N(CH_2)_3CH_aCH_b$), 0.90–1.09 (m, 1H, $N(CH_2)_3CH_aCH_b$). δ_C (75 MHz, DMSO-d_6) 159.3, 148.1, 145.0, 136.5, 131.9, 128.1, 113.2, 101.5, 55.7, 55.5, 54.4, 38.9, 32.2, 29.6, 25.5, 22.6. HRMS (ESI$^+$): $[M+Na]^+$ found 323.1363, $C_{17}H_{20}O_3N_2Na$ requires 323.1366; $[2M+Na]^+$ found 623.2838, $C_{34}H_{40}O_6N_4Na$ requires 623.2840; $[3M+Na]^+$ found 923.4326, $C_{51}H_{60}O_9N_6Na$ requires 923.4314.

4.6.9. 4a-Methyl-1,2,3,4,4a,4b,4c-hexahydro-9H-indolizino-[1,2-b]indol-10-one (**10g**)

Yield 57%, mp 118 °C; R_f (50% hexane/ethyl acetate) 0.41; ν_{max} (KBr) 3050, 2900, 1680, 1460, 1430, 1380 cm^{-1}; δ_H (300 MHz, acetone-d_6) 7.72 (d, J=8.4 Hz, 1H, ArH), 7.54 (d, J=8.4 Hz, 1H, ArH), 7.33 (dd, J=8.0, 8.4 Hz, 1H, ArH), 7.16 (dd, J=8.0, 8.4 Hz, 1H, ArH), 4.25 (m, 1H, NCH_aCH_b), 3.97 (s, 3H, NMe), 2.99 (m, 1H, NCH_aCH_b), 2.39 (m, 1H, $NCH_2CH_aCH_b$), 1.80–1.67 (m, 2H, $NCH_2CH_aCH_b$+$NCH_2CH_2CH_aCH_b$), 1.59 (s, 3H, Me), 1.43–1.21 (m, 3H, $NCH_2CH_2CH_aCH_b$+$N(CH_2)_3CH_2$). δ_C (75 MHz, acetone-d_6) 165.4, 143.4, 141.8, 135.4, 123.3, 120.9, 119.8, 119.6, 110.8, 57.9, 36.9, 35.9, one peak missing due to the overlapping with solvent signal, 25.9, 20.4, 19.7. HRMS (ESI$^+$): $[M+Na]^+$ found 277.1309, $C_{16}H_{18}N_2NaO$ requires 277.1312.

4.6.10. 2,3-Dimethoxy-11-methyl-4c,6,7,8,9,11-hexahydro-5H-9a,11-diaza-indeno[1,2-a]azulen-10-one (**10h**)

Yield 40%, mp 156–157 °C; R_f (30% hexane/ethyl acetate) 0.28; ν_{max} (KBr) 3060, 2980, 1660, 1460, 1420, 1380, 1350, 1260 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.15 (s, 1H, ArH), 7.10 (s, 1H, ArH), 4.67 (t, 1H, J=5.2 Hz, NCH), 3.84 (s, 6H, 2 OMe), 3.78 (s, 3H, NMe), 3.73–3.65 (m, 1H, NCH_aCH_b), 3.35–3.20 (m, 1H, NCH_aCH_b), 2.40–2.24 (m, 1H, $NCH_2CH_aCH_b$), 1.84–1.40 (m, 6H, $NCH_2CH_aCH_b$+$N(CH_2)_2CH_2CH_2$ +$N(CH_2)_4CH_aCH_b$), 1.39–1.19 (m, 1H, $N(CH_2)_4CH_aCH_b$). δ_C (75 MHz, DMSO-d_6) 162.6, 148.7, 145.7, 137.5, 132.7, 128.9, 113.9, 101.7, 94.8, 57.3, 56.2, 56.1, 43.5, 33.7, 30.3, 29.2, 27.1. HRMS (ESI$^+$): $[M+Na]^+$ found 337.1519, $C_{18}H_{22}O_3N_2Na$ requires 337.1522; $[2M+Na]^+$ found 651.3146, $C_{36}H_{44}O_6N_4Na$ requires 651.3153; $[3M+Na]^+$ found 965.4765, $C_{54}H_{66}O_9N_6Na$ requires 965.4783.

Acknowledgements

This work was supported by the University of Milano (FIRST funds).

References and notes

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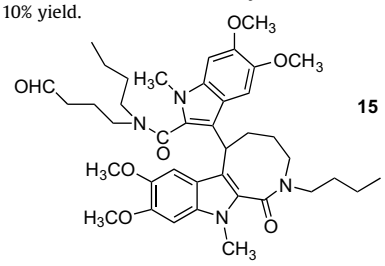
9. From the reaction of **8i**, the bis-indole **15**, apparently deriving from both intra and intermolecular reaction of the aldehyde with two indole nuclei, was isolated in a 10% yield.



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10. A referee (whom we thank) has suggested an alternative mechanism, i.e., that the Friedel–Crafts might take place first, followed by the transannular attack of the poorly nucleophilic amide nitrogen onto the alcohol (or its protonated state) to give **10**.
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