A Versatile Synthesis of 3-Substituted 4-Cyano-1,2,3,4-tetrahydro-1-oxo-β-carbolines

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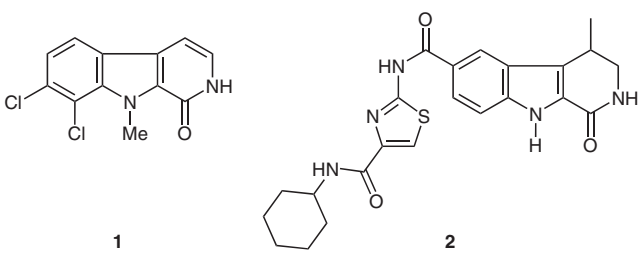
Received 28 June 2010; revised 19 August 2010

Abstract: In a project aimed at the synthesis of analogues of the cytotoxic β-carboline alkaloid bauerine C with more advantageous solubility properties, a 3-amino analogue was prepared by treating ethyl 3-(cyanomethyl)indole-2-carboxylate with ammonia. Upon addition of aldehydes or ketones to the reaction mixture, 3-substituted 4-cyano-1,2,3,4-tetrahydro-1-oxo-β-carbolines were obtained in a one-pot condensation. When cyclic ketones are used, the procedure allows a convenient synthesis of tetracyclic spiro compounds.

Key words: β-carbolines, cyclizations, multicomponent reactions, indoles, lactams

Natural products are a vital source of material for the discovery and development of novel drugs enabling the treatment of major diseases, e.g. cancer.[1] Moreover, the broad variety of heterocyclic ring systems provided by alkaloids permits the structure-based design of new enhanced bioactive compounds.

Bauerine C (**1**, Figure 1), a 1,2-dihydro-1-oxo-β-carboline isolated from the blue-green alga *Dichotrix baueriana*, has been reported to have strong cytotoxic as well as antiviral activity.[2] In previous studies, we presented the first total synthesis of this alkaloid,[3] and prepared hybrids between **1** and the quinazolinocarboline alkaloid rutaecarpine which exhibited cytotoxic activity superior to those of both parent alkaloids.[4] Recently, we successfully combined the unique 6,7-dichloroindole substructure of alkaloid **1** with a common kinase inhibitor scaffold to prepare a new class of sirtuin (class III histone deacetylase) inhibitors.[5] Recently 1-oxo-β-carboline-derived compounds, such as **2**, have been shown to exert antitumoral activity and to be potent inhibitors of protein kinases implicated in the pathogenesis of various diseases.[6]



1 2

Figure 1 Lead structures

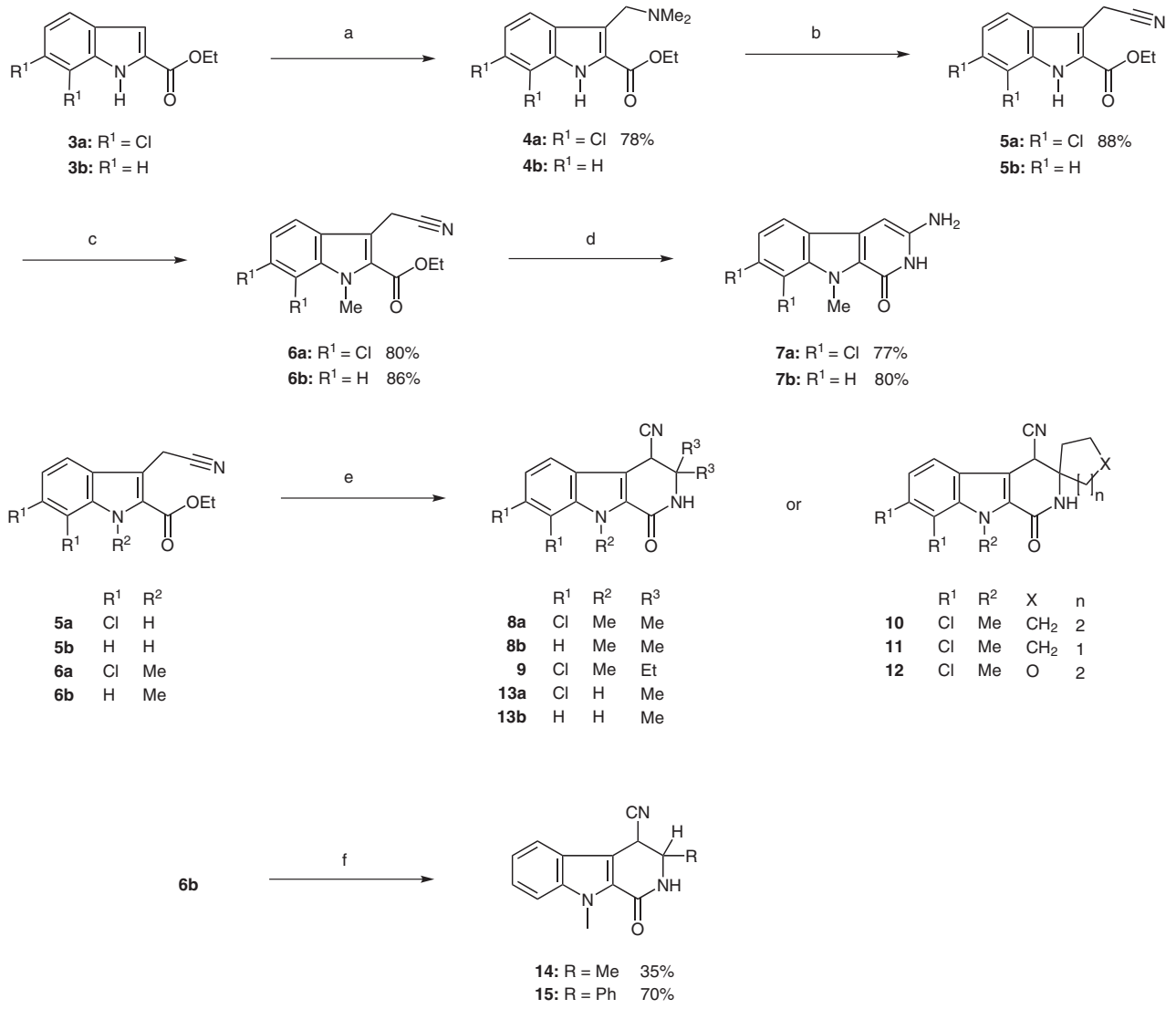
SYNTHESIS 2010, No. 22, pp 3849–3854
Advanced online publication: 01.10.2010
DOI: 10.1055/s-0030-1258282; Art ID: T14010SS

Encouraged by these results, we decided to further explore bauerine C type 1-oxo-β-carbolines as scaffolds for novel bioactive compounds. A number of synthetic approaches to 1-oxo-β-carbolines have been published in literature; representative examples are discussed here. For our total synthesis of bauerine C (**1**) we employed a Japp–Klingemann synthesis starting from diazotized 2,3-dichloroaniline and ethyl 2-oxopiperidine-3-carboxylate, followed by Fischer cyclization to afford the 1,2,3,4-tetrahydro-1-oxo-β-carboline in good yield.[3] We have also established other efficient routes towards this ring system using tryptamines as versatile building blocks;[7] isocyanates and carbamoyl chlorides prepared from tryptamines and triphosgene are conveniently cyclized using acid catalysis to give 1,2,3,4-tetrahydro-1-oxo-β-carbolines. Recently, the palladium-catalyzed intramolecular olefination of alkenyl-substituted indoles has been reported for the preparation of 4-substituted 1-oxo-β-carbolines.[8]

Due to the very poor solubility of bauerine C (**1**) in water, our first intention was to prepare a derivative with superior physico-chemical properties. We selected a 3-amino analogue of **1**, which would hopefully provide better solubility, and, in addition, include an additional functional group susceptible to hydrogen bonding.

The central building block ethyl 6,7-dichloro-1*H*-indole-2-carboxylate (**3a**) was prepared starting from 2,3-dichlorophenylhydrazine and ethyl pyruvate in a Fischer cyclization with polyphosphoric acid.[9] Subsequent aminomethylation at C3 using Eschenmoser's salt[10] gave the gramine derivative **4a**. This amine was converted into nitrile **5a** under standard conditions upon quaternization with dimethyl sulfate,[11] followed by nucleophilic substitution with potassium cyanide. N-Methylation at the indole nitrogen to give **6a** was performed using sodium hydride and methyl iodide in anhydrous *N*,*N*-dimethylformamide. Analogous to previously published procedures,[12] cyano ester **6a** was converted into the target aminopyridone **7a** by heating with liquid ammonia and ammonium chloride in a sealed tube. The chlorine-free analogue **7b** was prepared in an analogous manner starting from phenylhydrazine (Scheme 1).

Having the intermediate **6a** in hand, we worked out a completely new approach towards highly substituted 1,2,3,4-tetrahydro-1-oxo-β-carbolines. Thus, upon heating the 3-(cyanomethyl)indole ester **6a** with acetone, liquid ammonia, and ammonium chloride in a sealed tube,



Scheme 1 *Reagents and conditions*: (a) *N*,*N*-dimethylmethyleneiminium chloride, DMF, 100 °C, 2 h; (b) $(MeO)_2SO_2$, KCN, DMSO, r.t., 7 h; (c) NaH, MeI, DMF, r.t., 5 h; (d) NH_4Cl, NH_3, 120 °C, 16 h, sealed tube; (e) ketone $R^3{}_2CO$, NH_4Cl, NH_3, 100 °C, 16 h, sealed tube, yields see Table 1; (f) aldehyde RCHO, NH_4Cl, NH_3, 100 °C, 16 h, sealed tube.

Table 1 Synthesized Oxo-β-carbolines

Entry	Starting materials	Product	Yield (%)
1	**6a**, acetone	**8a**	87
2	**6b**, acetone	**8b**	87
3	**6a**, pentan-3-one	**9**	39
4	**6a**, cyclohexanone	**10**	21
5	**6a**, cyclopentanone	**11**	22
6	**6a**, tetrahydropyran-4-one	**12**	62
7	**5a**, acetone	**13a**	95
8	**5b**, acetone	**13b**	65
9	**6b**, acetaldehyde	**14**	35
10	**6b**, benzaldehyde	**15**	70

7,8-dichloro-4-cyano-1,2,3,4-tetrahydro-3,3,9-trimethyl-1-oxo-β-carboline (**8a**) was obtained in high yield (87%). The formation of this product may be explained by various mechanisms. Most likely, acetone condenses with the acidic methylene group of the (cyanomethyl)indole to give an α,β-unsaturated nitrile. Michael-type addition of ammonia to this system might yield a primary amine, which in turn forms the lactam upon nucleophilic attack at the ester group. However, alternative pathways, e.g. aminolysis of the ester prior to the Michael addition, or initial formation of a ketimine and subsequent Mannich-type reaction with the (cyanomethyl)indole cannot be excluded.

Excited by this smooth conversion, we investigated the scope and limitations of this novel approach (Table 1). Not surprisingly, pentan-3-one reacted in an analogous manner giving the 3,3-diethyl analogue **9** (entry 3), and cyclic ketones (cyclohexanone, cyclopentanone, tetrahydropyran-4-one; entries 4–6) gave the corresponding spiro derivatives **10**, **11**, and **12** in moderate to good

yields. Further we found that this cyclization also takes place with 3-(cyanomethyl)indole-2-carboxylates **5a**,**b** lacking an alkyl substituent at the indole nitrogen (entries 7 and 8) and non-chlorinated indoles **5b** and **6b** (entries 2 and 8).

Replacing the ketones with aldehydes (acetaldehyde, benzaldehyde; entries 9 and 10) in this cyclocondensation with **6b** led to 3-monosubstituted products **14** and **15**. Due to the generation of two stereogenic centers, the products were obtained as racemic mixtures of diastereoisomers. These mixtures could not be separated by column chromatography, but in the case of the 3-methyl derivative **14**, a single diastereoisomer was obtained upon crystallization from ethyl acetate. However, the coupling constants recorded for H4 (**14**, J = 4.1 Hz; mixture of diastereoisomers **15**, J = 4.6 and 5.1 Hz) do not allow the stereochemistry (*cis*/*trans*) at C3 and C4 to be assigned.

Among all of the carbonyl compounds investigated so far, only formaldehyde and hexafluoroacetone failed to give the desired cyclization products.

In conclusion, our new procedure constitutes a feasible and efficient approach towards 3-substituted 4-cyano-1,2,3,4-tetrahydro-1-oxo-β-carbolines starting from readily available starting materials. Furthermore, these compounds have the potential for further functionalization at C4 using standard operations (hydrolysis or reduction of the nitrile; deprotonation/alkylation). Thus, additional efforts are being undertaken to expand this synthetic procedure and apply it to the preparation of more complex systems.

NMR spectra were recorded using a Jeol JNMR-GSX 400 or Jeol JNMR-GSX 500 (Jeol, Peabody, USA). Mass spectra (EI, 70 eV) were recorded using a Hewlett Packard 5989 A Mass Spectrometer with a 59980 B Particle Beam LC/MS-interface (Agilent Technologies, Palo Alto, USA). HRMS were obtained using a Jeol Mstation 700 (Jeol, Peabody, USA). IR spectra were recorded as KBr discs on a Perkin Elmer FT-IR Paragon 1000 (Perkin Elmer, Waltham, USA) or Jasco FT/IR-410 (Jasco, Easton, USA). Melting points were determined with a Büchi B-540 apparatus (Büchi, Flawil, Switzerland) and are uncorrected. Elemental analyses were performed using a CHN-Elementaranalysator Rapid (Heraeus, Hanau, Germany) or Elementaranalysator Vario EL (Elementar, Hanau, Germany). Purification by flash column chromatography (FCC) was performed using Silica gel 60 (Merck, Darmstadt, Germany); petroleum ether = PE. All chemicals were purchased from Sigma-Aldrich, Fluka and Acros.

Ethyl 6,7-Dichloro-3-[(dimethylamino)methyl]-1*H*-indole-2-carboxylate (4a)

Ethyl 6,7-dichloro-1*H*-indole-2-carboxylate (**3a**)[9] (3.10 g, 12.0 mmol) and *N*,*N*-dimethylmethyleneiminium chloride (1.46 g, 15.6 mmol) were dissolved in DMF (10 mL) and heated to 100 °C for 2 h. The mixture was diluted with H_2O (50 mL), brought to pH >10 using 6 M NaOH and extracted with Et_2O (3 × 50 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was evaporated. The residue was recrystallized (MeCN) to give **4a** (2.95 g, 78%) as white needles; mp 132 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.92 (br s, 1 H, NH), 7.74 (d, J = 8.7 Hz, 1 H, H4), 7.21 (d, J = 8.7 Hz, 1 H, H5), 4.45 (q, J = 7.1 Hz, 2 H, OCH_2), 3.92 (s, 2 H, Ar-CH_2), 2.29 (s, 6 H, NCH_3), 1.45 (t, J = 7.1 Hz, 3 H, CH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.5 (C=O), 133.8 (C7a), 129.0 (C6), 128.1 (C3a), 125.8 (C2), 122.6 (C5), 122.0 (C3), 121.1 (C4), 115.4 (C7), 61.3 (OCH_2), 53.2 (Ar-CH_2), 45.7 (NCH_3), 14.4 (CH_2CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 318 (3) [M$^+$], 316 (15) [M$^+$], 314 (23) [M$^+$], 299 (100).

Anal. Calcd for $C_{14}H_{16}Cl_2N_2O_2$: C, 53.35; H, 5.12; N, 8.89. Found: C, 53.47; H, 5.07; N, 8.92.

Ethyl 6,7-Dichloro-3-(cyanomethyl)-1*H*-indole-2-carboxylate (5a)

Under N_2, to a soln of **4a** (2.30 g, 7.30 mmol) and KCN (950 mg, 14.6 mmol) in anhyd DMSO (50 mL), $(MeO)_2SO_2$ (1.84 g, 14.6 mmol) was added dropwise over 15 min. The mixture was stirred at r.t. for 7 h, then diluted with H_2O (250 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with 2 M HCl (2 × 100 mL) and brine (100 mL), dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue was recrystallized (EtOH) to give **5a** (1.90 g, 88%) as white needles; mp 177 °C.

IR (KBr): 2247 (CN) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.07 (br s, 1 H, NH), 7.65 (d, J = 8.7 Hz, 1 H, H4), 7.30 (d, J = 8.7 Hz, 1 H, H5), 4.50 (q, J = 7.1 Hz, 2 H, OCH_2), 4.23 (s, 2 H, Ar-CH_2), 1.48 (t, J = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.6 (C=O), 133.7 (C7a), 130.0 (C6), 126.1 (C3a), 125.5 (C2), 123.6 (C5), 119.2 (C4), 117.0 (CN), 116.1 (C7), 112.0 (C3), 62.0 (OCH_2), 14.4 (CH_3) 13.7 (Ar-CH_2).

MS (EI, 70 eV): *m*/*z* (%) = 300 (5) [M$^+$], 298 (29) [M$^+$], 296 (41) [M$^+$], 270 (12), 250 (100).

Anal. Calcd for $C_{13}H_{10}Cl_2N_2O_2$: C, 52.55; H, 3.39; N, 9.43. Found: C, 52.43; H, 3.35; N, 9.44.

Ethyl 6,7-Dichloro-3-(cyanomethyl)-1-methyl-1*H*-indole-2-carboxylate (6a); Typical Procedure

Under N_2, to a suspension of NaH (77 mg, 1.91 mmol) in anhyd DMF (15 mL), a soln of **5a** (520 mg, 1.75 mmol) in anhyd DMF (5 mL) was added and the mixture stirred at 40 °C for 1 h. After cooling to r.t., MeI (248 mg, 1.75 mmol) was added dropwise and the mixture was stirred for 5 h, then poured into H_2O (50 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (2 × 100 mL), dried ($MgSO_4$), and filtered, and the solvent was evaporated. The residue was recrystallized (EtOH) to give **6a** (434 mg, 80%) as white needles; mp 178 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.56 (d, J = 8.6 Hz, 1 H, H4), 7.30 (d, J = 8.6 Hz, 1 H, H5), 4.47 (q, J = 7.1 Hz, 2 H, OCH_2), 4.38 (s, 3 H, NCH_3), 4.10 (s, 2 H, Ar-CH_2), 1.47 (t, J = 7.1 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 160.9 (C=O), 134.9 (C7a), 131.1 (C6), 128.8 (C2), 126.6 (C3a), 123.1 (C5), 118.8 (C4), 117.4 (CN), 116.6 (C7), 111.8 (C3), 61.8 (OCH_2), 35.2 (NCH_3), 14.2 (Ar-CH_2), 14.0 (CH_2CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 314 (7) [M$^+$], 312 (40) [M$^+$], 310 (65) [M$^+$], 281 (100).

Anal. Calcd for $C_{14}H_{12}Cl_2N_2O_2$: C, 54.04; H, 3.89; N, 9.00. Found: C, 53.76; H, 3.93; N, 8.92.

Ethyl 3-(Cyanomethyl)-1-methyl-1*H*-indole-2-carboxylate (6b)

Following the typical procedure for **6a** using **5b**[13] (400 mg, 1.75 mmol) gave **6b** (365 mg, 86%) as white crystals (PE); mp 89 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.86 (d, J = 8.1 Hz, 1 H, H4), 7.62 (d, J = 8.6 Hz, 1 H, H7), 7.38–7.42 (m, 1 H, H6), 7.16–7.24 (m, 1 H, H5), 4.36 (q, J = 7.2 Hz, 2 H, OCH_2), 4.31 (s, 2 H, Ar-CH_2), 3.99 (s, 3 H, NCH_3), 1.39 (t, J = 7.2 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.7 (C=O), 138.5 (C7a), 126.2 (C6), 126.0 (C2), 125.6 (C3a), 121.4 (C5), 120.7 (C4), 119.4 (CN), 112.1 (C3), 111.7 (C7), 61.6 (OCH_2), 32.7 (NCH_3), 14.5 (CH_2CH_3), 14.3 (Ar-CH_2).

MS (EI, 70 eV): m/z (%) = 242 (64) [M$^+$], 213 (100).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.31; H, 5.64; N, 11.62.

3-Amino-2,9-dihydro-1-oxo-β-carbolines 7a,b; General Procedure

At –80 °C, gaseous NH_3 was introduced into a glass tube containing **6a**,**b** (3.21 mmol) and NH_4Cl (6.42 mmol) until approx. 10 mL were condensed. The tube was closed tightly and heated to 120 °C for 16 h in an autoclave. The mixture was allowed to reach r.t. and after evaporation of excess NH_3 extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed. The crude product was purified by flash column chromatography.

3-Amino-7,8-dichloro-9-methyl-2,9-dihydro-1*H*-pyrido[3,4-*b*]indol-1-one (7a)

Following the general procedure using **6a** (1.00 g, 3.21 mmol) with FCC (EtOAc–MeOH–concd NH_3, 90:5:5) gave **7a** as green crystals (EtOH); yield: 700 mg (77%); mp 256 °C.

^{1}H NMR (400 MHz, DMSO-d_6, 40 °C): δ = 10.74 (br s, 1 H, 2-NH), 7.81 (d, J = 8.5 Hz, 1 H, H5), 7.25 (d, J = 8.5 Hz, 1 H, H6), 5.85 (s, 1 H, H4), 5.37 (br s, 2 H, 3-NH_2), 4.46 (s, 3 H, NCH_3).

^{13}C NMR (100 MHz, DMSO-d_6, 40 °C): δ = 155.5 (C=O), 145.7 (C3), 137.9 (C8a), 131.1 (C7), 129.8 (C4a), 123.3 (C4b), 121.8 (C5), 121.3 (C9a), 121.0 (C6), 115.2 (C8), 76.7 (C4), 34.3 (NCH_3).

MS (EI, 70 eV): m/z (%) = 285 (12) [M$^+$], 283 (66) [M$^+$], 281 (100) [M$^+$].

Anal. Calcd for $C_{12}H_9Cl_2N_3O$: C, 51.09; H, 3.22; N, 14.89. Found: C, 50.00; H, 3.18; N, 14.03.

3-Amino-9-methyl-2,9-dihydro-1*H*-pyrido[3,4-*b*]indol-1-one (7b)

Following the general procedure using **6b** (778 mg, 3.21 mmol) with FCC (EtOAc–MeOH–concd NH_3, 90:5:5) gave **7b** as a yellow solid; yield: 548 mg (80%); mp 184 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.64 (s, 1 H, NH), 7.83 (d, J = 7.9 Hz, 1 H, H5), 7.45 (d, J = 8.4 Hz, 1 H, H8), 7.39–7.43 (m, 1 H, H7), 7.06–7.10 (m, 1 H, H6), 5.88 (s, 1 H, H4), 5.25 (s, 2 H, NH_2), 3.39 (s, 3 H, NCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.7 (C1), 144.8 (C3), 141.6 (C8a), 129.4 (C4a), 127.0 (C7), 121.9 (C5), 121.3 (C4b), 120.1 (C9a), 118.9 (C6), 110.5 (C8), 77.5 (C4), 31.3 (NCH_3).

MS (CI): m/z (%) = 214 (100) [M + H]$^+$.

Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 66.88; H, 5.30; N, 19.14.

Cyclization of Ethyl 3-(Cyanomethyl)indole-2-carboxylates 5a,b and 6a,b; General Procedure

Compound **5a**,**b** and **6a**,**b** (3.21 mmol) and NH_4Cl (6.42 mmol) were suspended in the given amount of aldehyde or ketone in a glass tube. After cooling to –80 °C, gaseous NH_3 was introduced into the tube until approx. 10 mL were condensed. The tube was closed tightly and heated to 100 °C for 16 h in an autoclave. The mixture was allowed to reach r.t., excess NH_3 was evaporated, and it was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent removed. The crude product was purified by flash column chromatography.

(4*RS*)-7,8-Dichloro-3,3,9-trimethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carbonitrile (8a)

Following the general procedure using **6a** (1.00 g, 3.21 mmol) and acetone (5 mL) with FCC (PE–EtOAc, 1:1) gave **8a** as white needles (EtOH); yield: 900 mg (87%); mp 235 °C.

IR (KBr): 2245 cm^{-1} (CN).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.69 (d, J = 8.5 Hz, 1 H, H5), 7.31 (d, J = 8.5 Hz, 1 H, H6), 6.01 (br s, 1 H, NH), 4.55 (s, 3 H, NCH_3), 4.18 (s, 1 H, H4), 1.61 (s, 3 H, 3-CH_3), 1.51 (s, 3 H, 3-CH_3).

^{13}C NMR (125 MHz, CD_2Cl_2): δ = 159.8 (C=O), 135.4 (C8a), 130.6 (C7), 126.8 (C9a), 124.7 (C4b), 123.2 (C6), 118.7 (C5), 116.9 (C8), 116.8 (CN), 111.8 (C4a), 55.7 (C3), 36.2 (C4), 34.5 (NCH_3), 27.8 (3-CH_3), 25.9 (3-CH_3).

MS (EI, 70 eV): m/z (%) = 325 (5) [M$^+$], 323 (32) [M$^+$], 321 (47) [M$^+$], 264 (73), 236 (100).

Anal. Calcd for $C_{15}H_{13}Cl_2N_3O$: C, 55.92; H, 4.07; N, 13.04. Found: C, 55.70; H, 4.13; N, 12.94.

(4*RS*)-3,3,9-Trimethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carbonitrile (8b)

Following the general procedure using **6b** (778 mg, 3.21 mmol) and acetone (5 mL) with FCC (PE–EtOAc, 1:1) gave **8b** as white crystals (EtOAc); yield: 707 mg (87%); mp 218 °C (dec).

IR (KBr): 2240 cm^{-1} (CN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02 (s, 1 H, NH), 7.73 (d, J = 8.0 Hz, 1 H, H5), 7.57 (d, J = 8.5 Hz, 1 H, H8), 7.32–7.38 (m, 1 H, H7), 7.15–7.23 (m, 1 H, H6), 4.72 (s, 1 H, H4), 4.02 (s, 3 H, NCH_3), 1.45 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.0 (C1), 143.4 (C8a), 130.2 (C9a), 129.7 (C7), 128.0 (C4b), 125.7 (C6), 124.5 (C5), 123.4 (C4a), 116.0 (C8), 59.8 (C3), 39.5 (C4), 35.9 (NCH_3), 32.0 (CH_3), 30.9 (CH_3).

MS (CI): m/z (%) = 214 (100) [M + H]$^+$.

Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 70.67; H, 5.83; N, 16.71.

(4*RS*)-7,8-Dichloro-3,3-diethyl-9-methyl-1-oxo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carbonitrile (9)

Following the general procedure using **6a** (1.00 g, 3.21 mmol) and pentan-3-one (5 mL) with FCC (PE–EtOAc, 1:1) gave **9** as white crystals (EtOH); yield: 436 mg (39%); mp 245 °C.

IR (KBr): 2241 cm^{-1} (CN).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.29 (br s, 1 H, NH), 7.87 (d, J = 8.5 Hz, 1 H, H5), 7.45 (d, J = 8.5 Hz, 1 H, H6), 4.90 (s, 1 H, H4), 4.47 (s, 3 H, NCH_3), 1.93 (dq, J = 14.4, 7.6 Hz, 1 H, CH_2), 1.76 (dq, J = 14.4, 7.6 Hz, 1 H, CH_2), 1.63 (dq, J = 14.4, 7.4 Hz, 1 H, CH_2), 1.47 (dq, J = 14.4, 7.4 Hz, 1 H, CH_2), 0.96 (t, J = 7.6 Hz, 3 H, CH_2CH_3), 0.81 (t, J = 7.4 Hz, 3 H, CH_2CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 159.2 (C=O), 134.4 (C8a), 129.0 (C7), 127.5 (C9a), 124.9 (C4b), 122.8 (C6), 119.9 (C5), 117.8 (CN), 115.7 (C8), 112.3 (C4a), 59.9 (C3), 34.1 (NCH_3), 31.5 (C4), 27.4 (CH_2), 26.3 (CH_2), 7.7 (CH_2CH_3), 7.1 (CH_2CH_3).

MS (EI, 70 eV): m/z (%) = 353 (7) [M$^+$], 351 (34) [M$^+$], 349 (50) [M$^+$], 264 (100).

Anal. Calcd for $C_{17}H_{17}Cl_2N_3O$: C, 58.30; H, 4.89; N, 12.00. Found: C, 58.04; H, 4.75; N, 11.84.

(4′*RS*)-7′,8′-Dichloro-9′-methyl-1′-oxo-1′,2′,4′,9′-tetrahydrospiro[cyclohexane-1,3′-pyrido[3,4-*b*]indole]-4′-carbonitrile (10)
Following the general procedure using **6a** (1.00 g, 3.21 mmol) and cyclohexanone (5 mL) with FCC (PE–EtOAc, 1:1) gave **10** as white crystals (EtOH); yield: 244 mg (21%); mp 290 °C.

IR (KBr): 2238 cm^{-1} (CN).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.22 (br s, 1 H, H2′), 7.91 (d, *J* = 8.5 Hz, 1 H, H5′), 7.44 (d, *J* = 8.5 Hz, 1 H, H6′), 5.06 (s, 1 H, H4′), 4.46 (s, 3 H, NCH_3), 1.99–1.33 (m, 10 H, H2/H3/H4/H5/H6).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 159.3 (C=O), 134.4 (C8a′), 129.0 (C7′), 127.6 (C9a′), 125.0 (C4b′), 122.9 (C6′), 119.9 (C5′), 117.9 (CN), 115.7 (C8′), 112.0 (C4a′), 56.6 (spiro C), 34.55 (C2 or C6), 34.59 (C2 or C6), 34.1 (NCH_3), 30.8 (C4′), 24.7 (C4), 21.3 (C3 or C5), 20.5 (C3 or C5).

MS (EI, 70 eV): *m*/*z* (%) = 365 (9) [M^+], 363 (42) [M^+], 361 (79) [M^+], 264 (93), 236 (100).

Anal. Calcd for $C_{18}H_{17}Cl_2N_3O$: C, 59.68; H, 4.73; N, 11.60. Found: C, 59.34; H, 4.78; N, 11.41.

(4′*RS*)-7′,8′-Dichloro-9′-methyl-1′-oxo-1′,2′,4′,9′-tetrahydrospiro[cyclopentane-1,3′-pyrido[3,4-*b*]indole]-4′-carbonitrile (11)
Following the general procedure using **6a** (1.00 g, 3.21 mmol) and cyclopentanone (5 mL) with FCC (PE–EtOAc, 1:1) gave **11** as white crystals (EtOH); yield: 250 mg (22%); mp 253 °C.

IR (KBr): 2239 cm^{-1} (CN).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.5 Hz, 1 H, H5′), 7.30 (d, *J* = 8.5 Hz, 1 H, H6′), 6.34 (br s, 1 H, NH), 4.56 (s, 3 H, NCH_3), 4.17 (s, 1 H, H4′), 2.16–2.24 (m, 1 H, H2 or H5), 2.01–2.08 (m, 1 H, H2 or H5), 1.80–1.96 (m, 6 H, H2, 2 H3, 2 H4, H5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.6 (C=O), 135.5 (C8a′), 131.2 (C7′), 127.3 (C9a′), 124.5 (C4b′), 123.6 (C6′), 118.6 (C5′), 117.2 (C8′), 117.1 (CN), 112.8 (C4a′), 66.3 (spiro C), 39.2 (C2 or C5), 37.8 (C2 or C5), 34.8 (NCH_3), 34.5 (C4′), 23.6 (C3 or C4), 23.3 (C3 or C4).

MS (EI, 70 eV): *m*/*z* (%) = 351 (11) [M^+], 349 (61) [M^+], 347 (100) [M^+].

Anal. Calcd for $C_{17}H_{15}Cl_2N_3O$: C, 58.63; H, 4.34; N, 12.07. Found: C, 58.46; H, 4.41; N, 11.93.

(4′*RS*)-7′,8′-Dichloro-9′-methyl-1′-oxo-1′,2,2′,3,4′,5,6,9′-octahydrospiro[pyran-4,3′-pyrido[3,4-*b*]indole]-4′-carbonitrile (12)
Following the general procedure using **6a** (1.00 g, 3.21 mmol) and tetrahydropyran-4-one (5 mL) with FCC (PE–EtOAc, 1:1) gave **12** as white crystals (EtOH); yield: 720 mg (62%); mp 316 °C.

IR (KBr): 2239 cm^{-1} (CN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.51 (br s, 1 H, NH), 7.83 (d, *J* = 8.6 Hz, 1 H, H5′), 7.46 (d, *J* = 8.6 Hz, 1 H, H6′), 5.11 (s, 1 H, H4′), 4.46 (s, 3 H, NCH_3), 3.88–3.96 (m, 1 H, H2 or H6), 3.70–3.78 (m, 1 H, H2 or H6), 3.58–3.66 (m, 1 H, H2 or H6), 3.50–3.58 (m, 1 H, H2 or H6), 1.90–2.05 (m, 2 H, H3 or H5), 1.62–1.74 (m, 2 H, H3 or H5).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.3 (C=O), 134.5 (C8a′), 129.1 (C7′), 127.7 (C9a′), 124.9 (C4b′), 123.0 (C6′), 119.8 (C5′), 117.5 (CN), 115.8 (C8′), 111.6 (C4a′), 62.5 (C2 or C6), 61.8 (C2 or C6), 54.2 (spiro C), 35.0 (C3 or C5), 34.3 (C3 or C5), 34.2 (NCH_3), 32.1 (C4′).

MS (EI, 70 eV): *m*/*z* (%) = 367 (8) [M^+], 365 (46) [M^+], 363 (66) [M^+], 264 (100).

Anal. Calcd for $C_{17}H_{15}Cl_2N_3O_2$: C, 56.06; H, 4.15; N, 11.54. Found: C, 55.82; H, 4.24; N, 11.34.

(4*RS*)-7,8-Dichloro-3,3-dimethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carbonitrile (13a)
Following the general procedure using **5a** (954 mg, 3.21 mmol) and acetone (5 mL) with FCC (PE–EtOAc, 1:1) gave **13a** as white needles (EtOH); yield: 996 mg (95%); mp 248 °C.

IR (KBr): 2239 cm^{-1} (CN).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.72 (br s, 1 H, 9-NH), 8.21 (br s, 1 H, 2-NH), 7.75 (d, *J* = 8.5 Hz, 1 H, H5), 7.41 (d, *J* = 8.5 Hz, 1 H, H6), 4.83 (s, 1 H, H4), 1.51 (s, 3 H, 3-CH_3), 1.35 (s, 3 H, 3-CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 159.5 (C=O), 135.6 (C8a), 129.2 (C9a), 127.9 (C7), 125.0 (C4b), 123.0 (C6), 119.9 (C5), 118.7 (CN), 116.4 (C8), 112.6 (C4a), 55.9 (C3), 34.9 (C4), 27.8 (3-CH_3), 26.5 (3-CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 311 (11) [M^+], 309 (66) [M^+], 307 (100) [M^+].

Anal. Calcd for $C_{14}H_{11}Cl_2N_3O$: C, 54.57; H, 3.60; N, 13.64. Found: C, 54.39; H, 3.51; N, 13.61.

(4*RS*)-3,3-Dimethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carbonitrile (13b)
Following the general procedure using **5b** (733 mg, 3.21 mmol) and acetone (5 mL) with FCC (PE–EtOAc, 1:1) gave **13b** as white crystals (EtOAc); yield: 499 mg (65%); mp 267 °C.

IR (KBr): 2243 cm^{-1} (CN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.08 (s, 1 H, 9-NH), 8.02 (s, 1 H, 2-NH), 7.74 (d, *J* = 8.1 Hz, 1 H, H5), 7.48 (d, *J* = 8.2 Hz, 1 H, H8), 7.27–7.35 (m, 1 H, H7), 7.08–7.15 (m, 1 H, H6), 4.76 (s, 1 H, H4), 1.52 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.9 (C1), 137.2 (C8a), 126.6 (C9a), 124.6 (C7), 124.1 (C4b), 120.4 (C6), 119.5 (C4), 118.6 (CN), 113.0 (C8), 110.4 (C4a), 55.5 (C3), 34.6 (C4), 27.4 (CH_3), 26.1 (CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 239 (48) [M^+], 154 (96), 127 (100).

Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 69.79; H, 5.80; N, 17.39.

(3*RS*,4*RS*)-3,9-Dimethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carbonitrile (14)
Following the general procedure using **6b** (778 mg, 3.21 mmol) and acetaldehyde (5 mL) with FCC (PE–EtOAc, 1:1). Crystallization (EtOAc) gave a single diastereoisomer as white crystals; yield: 269 mg (35%); mp 245 °C.

IR (KBr): 2233 cm^{-1} (CN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.04 (s, 1 H, NH), 7.74 (d, *J* = 8.2 Hz, 1 H, H5), 7.59 (d, *J* = 8.8 Hz, 1 H, H8), 7.36–7.42 (m, 1 H, H7), 7.18–7.24 (m, 1 H, H6), 4.71 (d, *J* = 4.1 Hz, 1 H, H4), 4.04 (s, 3 H, NCH_3), 4.03–4.10 (m, 1 H, H3), 1.39 (d, *J* = 6.6 Hz, 3 H, 3-CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.1 (C1), 138.5 (C8a), 126.9 (C9a), 125.1 (C7), 122.5 (C4b), 120.9 (C6), 119.9 (C5), 117.9 (CN), 112.9 (C4a), 111.1 (C8), 49.3 (C3), 31.1 (NCH_3), 29.7 (C4), 17.7 (3-CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 239 (54) [M^+], 196 (53), 168 (100).

Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 69.78; H, 5.48; N, 17.49.

(3*RS*,4*RS*)-9-Methyl-1-oxo-3-phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-4-carbonitrile (15)
Following the general procedure using **6b** (778 mg, 3.21 mmol) and benzaldehyde (5 mL) with FCC (PE–EtOAc, 2:1) gave **15** as ~1:1 mixture of diastereoisomers as white crystals (EtOAc); yield: 677 mg (70%); mp 255 °C.

IR (KBr): 2236 cm^{-1} (CN).

^1H NMR (400 MHz, DMSO-d_6): δ = 8.54 (d, *J* = 3.3 Hz, 1 H, NH), 8.39 (s, 1 H, NH), 7.78 (d, *J* = 8.0 Hz, 1 H, H5), 7.74 (d, *J* = 8.0 Hz, 1 H, H5), 7.61–7.12 (m, 16 H), 5.25 (d, *J* = 4.6 Hz, 1 H, H3), 5.18–5.21 (m, 1 H, H3), 5.05 (d, *J* = 5.1 Hz, 1 H, H4), 4.98 (d, *J* = 4.6 Hz, 1 H, H4), 4.09 (s, 3 H, NCH_3), 4.07 (s, 3 H, NCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.0 (C1), 161.7 (C1), 140.0, 139.6, 139.4, 138.0, 129.5, 129.4, 129.3, 129.0, 128.4, 127.8, 127.0, 126.8, 126.2, 126.0, 123.6, 123.4, 121.8, 121.1, 120.8, 120.2, 118.7, 113.6, 112.10, 112.07, 111.2, 58.6 (C3), 58.4 (C3), 33.0 (C4), 32.1 (NCH_3), 31.8 (C4).

MS (EI, 70 eV): *m*/*z* (%) = 301 (52) [M^+], 196 (54), 168 (100).

Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.66; H, 5.09; N, 14.00.

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