γ-Carboline Synthesis by Heterocyclization of TosMIC Derivatives

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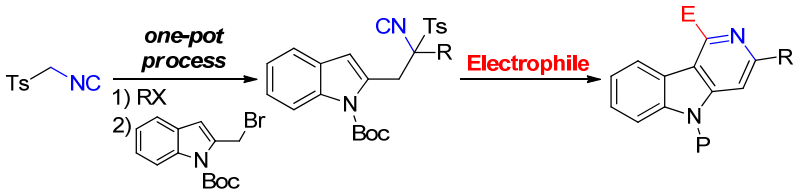
GRAPHICAL ABSTRACT:



ABSTRACT: A new method for the synthesis of γ-carbolines by a heterocyclization that involves α-indol-2-ylmethyl TosMIC derivatives and different electrophiles has been developed. This methodology has been successfully applied to the synthesis of several highly substituted γ-carbolines.

KEYWORDS: γ-Carbolines; Heterocyclization; TosMIC; *N*-Heterocycles

Introduction

Carbolines (pyrido[x,y-*b*]indoles) are important *N*-heterocycles found in many naturally occurring and pharmaceutically active compounds.[1] Among the four different possible isomers, the β-carboline nucleus is the most prominent in nature and therefore it is the most widely studied.[2] Less attention has been paid to γ-carbolines, even though this heterocyclic motif is present in several compounds that have shown a broad spectrum of biological properties.[3] For instance, this unit has been reported very recently in derivatives that act as inhibitors of bromodomain and extra terminal proteins (BET),[4] DNA intercalators[5] and potential anti-Alzheimer agents.[6] Moreover, pyrimidine-γ-carboline alkaloid ingenine B was isolated from an Indonesian sponge and it exhibited pronounced cytotoxicity against the murine lymphoma L5178Y cancer cell line.[7] Isocanthines are another family of alkaloids with significant properties[8] (Figure 1).

The medicinal importance of γ-carboline-containing compounds make them interesting synthetic targets, and several methods have been reported for their synthesis. Classically, these derivatives have been synthesized by the Graebe–Ullmann method,[9] which involves thermal cleavage of benzotriazoles, or the Fischer indole synthesis.[10] Nevertheless, these methods are often limited due to the use of harsh reaction conditions and the development of newer and more efficient approaches is still of great interest.[3] Thus, several preparations of these *N*-heterocycles have been reported very recently.[11] The most noteworthy are the hetero-annulation reactions of indoles catalyzed by transition metal-salts, although most of the examples of this methodology involve the use of toxic and expensive metals.[12]

As part of a research program aimed at expanding tosylmethyl isocyanide (TosMIC) chemistry[13,14] to the preparation of six-membered heterocycles,[15] our group very

recently developed a new method for the synthesis of isoquinolines through a heterocyclization that involves α-benzyl TosMIC derivatives and different electrophiles.[16] This cyclization takes advantage of the tendency of isocyanides to act both as nucleophiles and electrophiles, which means that cyclization of a TosMIC derivative by electrophilic aromatic substitution and attack of the isocyanide to the corresponding electrophile would occur as a tandem process. As a consequence, this methodology works efficiently when electron-donating substituents are present in the benzene ring and it was applied to the synthesis of the natural products mansouramycin B and cassiarin A.

Due to the electron-rich nature of indole derivatives, which typically undergo electrophilic aromatic substitution reactions that allow the introduction of functionalized side-chains at C3,[17] we envisaged this structural motif to be a good candidate to enhance the scope of our methodology. Thus, we devised its application to different α-indol-2-ylmethyl TosMIC intermediates with the aim of obtaining substituted γ-carbolines.

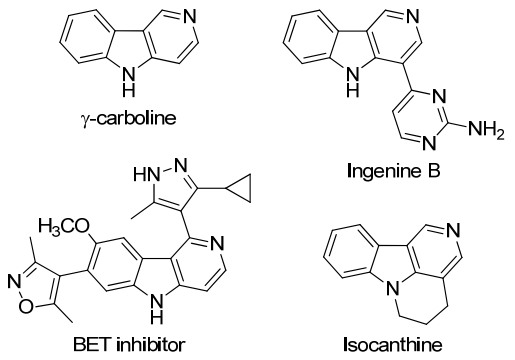


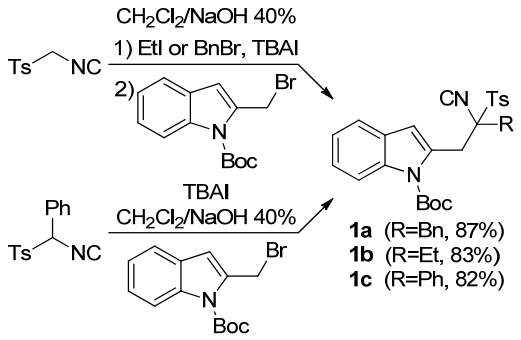
Figure 1. Significant γ-carboline-containing compounds

Results and discussion

In order to synthesize suitable TosMIC derivatives to explore the different heterocyclization reactions, the preparation of the corresponding α-indol-2-ylmethyl α-alkyl TosMIC derivatives **1a**–**1b** was achieved by the addition of two different alkyl

groups in a single one-pot phase transfer catalyst (PTC) process.[16] TosMIC reacted sequentially with two different alkyl halides in a single two-phase medium [CH_2Cl_2/NaOH (40%)] in the presence of tetrabutylammonium iodide (TBAI) as catalyst, with the first addition involving a simple alkyl halide and the second the 2-bromomethyl-1-(*tert*-butoxycarbonyl)indole.[18] This process gave isonitriles **1a**–**1b** in high yields (Scheme 1).

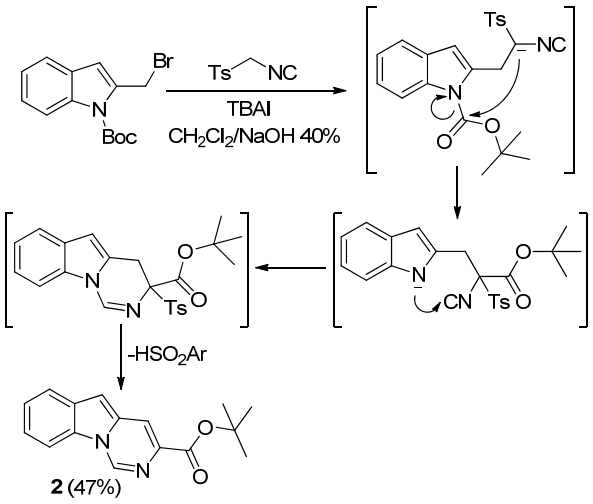
Scheme 1. Synthesis of α-Indol-2-ylmethyl α-Alkyl TosMIC Derivatives **1a**–**1c**



Interestingly, when 2-bromomethyl-1-(*tert*-butoxycarbonyl)indole was added to TosMIC, a side reaction occurred that afforded undesired azolopyrimidine **2** in 47% yield. This result can be explained by a mechanism that involves initial nucleophilic substitution of TosMIC to the bromomethylindole followed by intramolecular transfer of the *tert*-butoxycarbonyl protecting group. Subsequent cyclization and 1,2-elimination of toluenesulfonate would afford the azolopyrimidine derivative (Scheme 2).[15a]

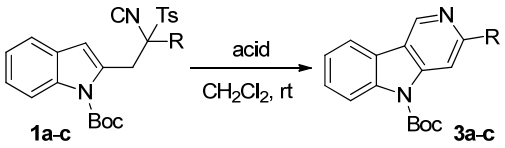
Additionally, α-indol-2-ylmethyl α-phenyl TosMIC derivative **1c** was obtained in 82% yield by addition of 2-bromomethyl-1-(*tert*-butoxycarbonyl)indole to tosylbenzyl isocyanide[19] in a two-phase medium [CH_2Cl_2/NaOH (40%)] in the presence of tetrabutylammonium iodide (TBAI) as catalyst.

Scheme 2. Mechanistic Hypothesis for the Formation of **2**



Acid-mediated cyclization was tested with the best reaction conditions achieved previously in our group for the synthesis of isoquinolines.[16a] Thus, TosMIC derivative **1a** was treated at room temperature with catalytic amounts of trifluoroacetic acid or aluminium trichloride, using CH_2Cl_2 as solvent. Nevertheless, the addition of at least one equivalent of acid was necessary to achieve full conversion (Table 1), with the best conditions identified as treatment with 2.5 equivalents of trifluoroacetic acid, which afforded γ-carbolines **3a**, **3b** and **3c** in 87%, 61% and 67% yield, respectively.

Table 1. Optimization of the Reaction Conditions for Acid-mediated Cyclization



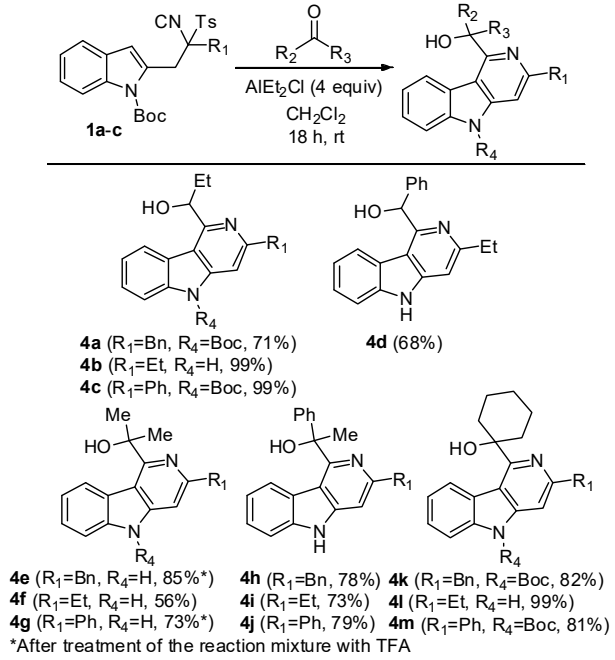
	acid	R	equiv	time (h)	yield (%)
1	$AlCl_3$	Bn	0.3	18	49
2	$AlCl_3$	Bn	0.5	18	66
3	$AlCl_3$	Bn	1	22	69
4	CF_3CO_2H	Bn	0.1	18	0*
5	CF_3CO_2H	Bn	1.1	18	41
6	CF_3CO_2H	Bn	1.5	18	65
7	CF_3CO_2H	Bn	2.5	22	87
8	CF_3CO_2H	Et	2.5	22	61
9	CF_3CO_2H	Ph	2.5	22	67

* Starting material was recovered.

With the aim of obtaining different 1-substituted γ-carbolines, we also explored the heterocyclization reaction with several types of electrophiles. The first attempts were made using different aldehydes and ketones in the presence of the Lewis acid $AlEt_2Cl$. This acid medium is necessary as it enhances the electrophilicity of the carbonyl group[16b] but it does lead as a side effect to the partial deprotection of the *tert*-butyloxycarbonyl group of the indole. We partially solved this problem by increasing the number of equivalents of $AlEt_2Cl$, although only reactions with α-ethyl TosMIC derivative **1b** took place with total deprotection of the Boc group. When TosMIC derivatives **1a** and **1c** were used, the resulting carbolines either contained this carbamate or not depending on the electrophile used, although in general good yields of a single reaction product were obtained. Only when acetone was used did the heterocyclization afford a mixture of the carbolines with and without the Boc group, which can be treated with trifluoroacetic acid to get **4e** and **4g** as single compounds (Scheme 3). These results were rationalized through a plausible mechanistic hypothesis that involves cyclization of the TosMIC derivative, by an electrophilic aromatic substitution, and attack of the isocyanide to the aldehyde in a single process. The subsequent elimination of *p*-toluenesulfonic acid would afford the final product.

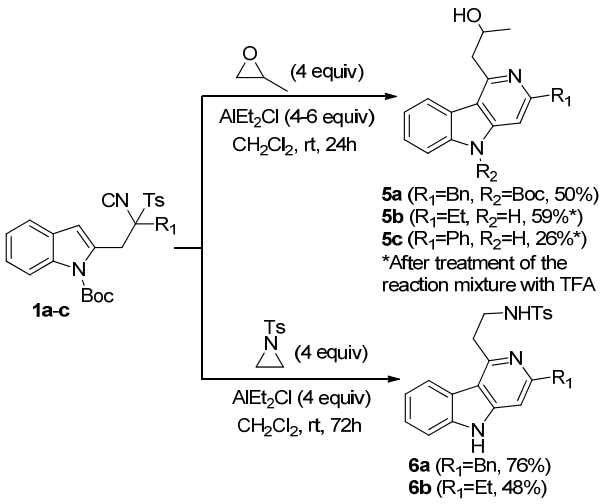
In order to determine the scope of this new γ-carboline synthesis, we studied the cyclization using other kinds of electrophiles, including Michael acceptors, epoxides, aziridines, iminium salts and halogenating agents. Attempts with the first type of reagent were unsuccessful. The addition to α-indol-2-ylmethyl TosMIC derivative **1a** of $AlEt_2Cl$ and *tert*-butyl acrylate or *β*-nitrostyrene only led to the recovery of starting material.

Scheme 3. Synthesis of 1-Substituted γ-Carbolines **4a**–**4m**



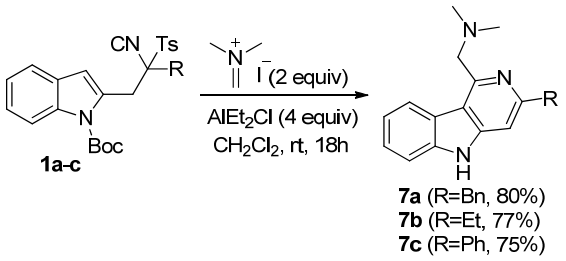
However, the reaction of **1a** with propylene oxide and $AlEt_2Cl$ yielded the Boc-protected carboline **5a** in 50% yield. Cyclization of **1b** and **1c** in the presence of this electrophile also took place but required the addition of six equivalents of $AlEt_2Cl$. Although partial deprotection of the Boc group was found in these two examples, **5b** and **5c** were obtained as single compounds after treatment with trifluoroacetic acid. It is worth noting that in all of these attempts the isocyanide group only attacked the less substituted carbon of the epoxide. On the other hand, when *N*-tosyl aziridine was used as the electrophile, carbolines **6a** and **6b** were obtained in 76 and 48% yield, respectively, but the reaction did not work when the α-phenyl TosMIC derivative **1c** was tested (Scheme 4).

Scheme 4. Synthesis of 1-Substituted γ-Carbolines **5a**–**5c** and **6a**–**6b**



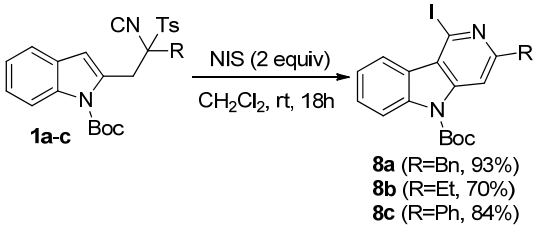
The use of the Eschenmoser's salt as the electrophile also led to the desired heterocyclization. In this way, the addition of two equivalents of this strong dimethylaminomethylating agent over TosMIC derivatives **1a–1c** in the presence of four equivalents of $AlEt_2Cl$ afforded γ-carbolines **7a–7c** in 80, 77 and 75% yield, respectively (Scheme 5).

Scheme 5. Synthesis of 1-Substituted γ-Carbolines **7a**–**7c**



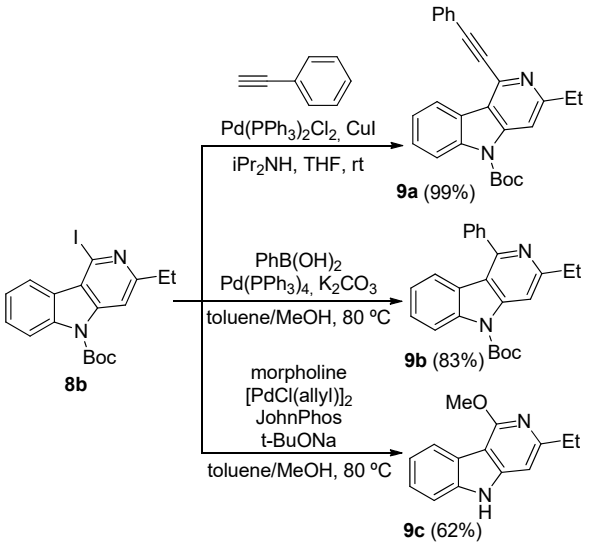
Finally, the heterocyclization of α-indol-2-ylmethyl TosMIC derivatives **1a**–**1c** also took place when *N*-iodosuccinimide was used as the electrophile. Moreover, the addition of a Lewis acid was not necessary in this case and Boc-protected carbolines **8a**–**8c** were obtained in excellent yields (Scheme 6).

Scheme 6. Synthesis of 1-Substituted γ-Carbolines **8a**–**8c**



Interestingly, 1-iodo γ-carbolines are suitable for further functionalization by palladium-catalyzed cross-coupling reactions. Suzuki and Sonogashira reactions afforded good yields under standard conditions. A Buchwald–Hartwig coupling was also tested, but in this case compound **9c** was obtained instead of the expected amination product. Further experiments showed the need for the presence of the palladium catalyst for the formation of this carboline derivative (Scheme 7).

Scheme 7. Synthesis of 1-Substituted γ-Carbolines **9a**–**9c**



Conclusions

A new synthesis of γ-carbolines involving a heterocyclization of α-indol-2-ylmethyl TosMIC derivatives is reported. This methodology has been successfully applied using protons, aldehydes, ketones, epoxides, aziridines, iminium salts and halogenating agents

as electrophiles. In this way, several highly substituted γ-carbolines have been synthesized in a straightforward manner under mild reaction conditions.

Experimental Section

General information. Reagents of the highest commercial quality were purchased and used without further purification, unless stated otherwise. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60FS-254) using UV light for visualization. Column chromatography was performed using silica gel (60 F254, 70–200 mm) as the stationary phase. All melting points were determined in open capillary tubes, on a Stuart Scientific SMP3 melting point apparatus. IR spectra were obtained on a Perkin–Elmer FTIR spectrum 2000 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with either Varian Mercury VX-300, Varian Unity 300 or Varian Unity 500 MHz spectrometer at room temperature. Chemical shifts are given in ppm (δ) downfield from TMS. Coupling constants (*J*) are in hertz (Hz), and signals are described as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; br, broad; ap, apparent. High-resolution analysis (HRMS) were performed on an Agilent 6210 time-of-flight LC/MS. Microwave reactions were performed using a Biotage Initiator and a Biotage 5 mL vial. This is a single mode operating system, working at 2.45 GHz, with a programmable power level from 0–400 W. Sealed reaction vessels were used, the reaction temperature was monitored by an external surface sensor and stirring was performed at 400 rpm with the magnetic stirrer included in the apparatus. Compound **3c**[12i] has been previously described.

tert-*Butyl 2-(2-isocyano-3-phenyl-2-tosylpropyl)-1*H-*indole-1-carboxylate (**1a**)*. To a stirred solution of TosMIC (195 mg, 1 mmol), benzyl bromide (171 mg, 0.12 mL, 1 mmol) and TBAI (74 mg, 0.2 mmol) in CH_2Cl_2 (2 mL), was added, at 0 ºC, a solution of NaOH (40% in H_2O, 2 mL) and the reaction mixture was vigorously stirred at room

temperature for 2h. Then, a solution of 2-bromomethyl-1-(*tert*-butoxycarbonyl)indole[18] (403 mg, 1.3 mmol) in CH_2Cl_2 (3 mL) was added, the reaction mixture was cooled to 0 ºC and a solution of NaOH (40% in H_2O, 4 mL) was added. The reaction mixture was warmed to room temperature and stirring was maintained at the same temperature for 24 h. Then, water (5 mL) was added, the two layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (1:9 EtOAc/hexanes) to supply TosMIC derivative **1a** as white needles (448 mg, 0.87 mmol, 87%). This derivative is only fairly stable and must be stored at -10 – -20 ºC. M.p.: 52-54 ºC. IR (KBr) υ_{max} (cm^{-1}) 2978, 2122, 1734, 1453, 1328, 1150, 1119, 1087, 749. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.01 (d, *J* = 8.4, Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.31-7.24 (m, 8H), 7.20 (td, *J* = 7.4, 1.1 Hz, 1H), 6.59 (s, 1H), 4.01 (d, *J* = 2.2 Hz, 2H), 3.58 (d, *J* = 14.2 Hz, 1H), 3.34 (d, *J* = 14.2 Hz, 1H), 2.43 (s, 3H), 1.72 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 166.7, 150.5, 146.1, 136.5, 132.4, 131.5, 131.1 (2C), 131.0 (2C), 130.7, 129.6 (2C), 128.5, 128.2 (2C), 127.9, 124.3, 122.8, 120.5, 115.7, 112.3, 84.9, 81.9, 39.4, 33.1, 28.4 (3C), 21.9. HRMS (ESI-TOF) m/z calcd. for $C_{30}H_{31}N_2O_4S$ $[M+H]^+$ 515.1999 found: 515.1996.

tert-*Butyl 2-(2-isocyano-2-tosylbutyl)-1*H-*indole-1-carboxylate (**1b**).* To a stirred solution of TosMIC (195 mg, 1 mmol), ethyl iodide (312 mg, 0.16 mL, 2 mmol) and TBAI (74 mg, 0.2 mmol) in CH_2Cl_2 (2 mL), was added, at 0 ºC, a solution of NaOH (40% in H_2O, 2 mL) and the reaction mixture was vigorously stirred at room temperature for 18h. Then, a solution of 2-bromomethyl-1-(*tert*-butoxycarbonyl)indole[18] (403 mg, 1.3 mmol) in CH_2Cl_2 (3 mL) was added, the reaction mixture was cooled to 0 ºC and a solution of NaOH (40% in H_2O, 4 mL) was added.

The reaction mixture was warmed to room temperature and stirring was maintained at the same temperature for 24 h. Then, water (5 mL) was added, the two layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (1:9 EtOAc/hexanes) to supply TosMIC derivative **1b** as a colorless oil (376 mg, 0.83 mmol, 83%). This derivative is only fairly stable and must be stored at -10 – -20 ºC. IR (NaCl) υ_{max} (cm^{-1}) 2980, 2943, 2123, 1733, 1453, 1329, 1157, 1121, 1082. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.05 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.30 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H), 7.22 (td, *J* = 7.7, 1.0 Hz, 1H), 6.64 (s, 1H), 4.14 (d, *J* = 14.9 Hz, 1H), 3.77 (d, *J* = 14.9 Hz, 1H), 2.49 (s, 3H), 2.27 (dq, *J* = 14.9, 7.5 Hz, 1H), 2.07 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.69 (s, 9H), 1.01 (t, *J* = 7.5 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) 166.5, 150.6, 146.4, 136.8, 131.7 (2C), 131.4, 130.6, 129.9 (2C), 128.5, 124.5, 123.0, 120.6, 115.8, 112.4, 84.9, 82.1, 32.5, 28.2 (3C), 26.4, 21.8, 8.8. HRMS (ESI-TOF) m/z calcd. for $C_{25}H_{29}N_2O_4S$ $[M+H]^+$ 453.1843 found: 453.1855.

tert-*Butyl 2-(2-isocyano-2-phenyl-2-tosylethyl)-1*H-*indole-1-carboxylate (**1c**).* To a stirred solution of tosylbenzylisocyanide[19] (272 mg, 1 mmol), 2-bromomethyl-1-(*tert*-butoxycarbonyl)indole[18] (403 mg, 1.3 mmol) and TBAI (74 mg, 0.2 mmol) in CH_2Cl_2 (5 mL), was added, at 0 ºC, a solution of NaOH (40% in H_2O, 5 mL) and the reaction mixture was vigorously stirred at room temperature for 24h. Then, water (5 mL) was added, the two layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (1:9 EtOAc/hexanes) to supply TosMIC derivative **1c** as

pale-yellow needles (410 mg, 0.82 mmol, 82%). This derivative is only fairly stable and must be stored at -10 – -20 ºC. M.p.: 144-145 ºC. IR (KBr) υ_{max} (cm^{-1}) 2979, 2931, 2126, 1732, 1454, 1329, 1152, 1084, 751. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.02 (d, *J* = 8.3 Hz, 1H), 7.48-7.36 (m, 4H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.29-7.25 (m, 2H), 7.24-7.17 (m, 3H), 7.10 (td, *J* = 7.4, 1.0 Hz, 1H), 6.03 (s, 1H), 4.62 (s, 2H), 2.43 (s, 3H), 1.76 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 167.1, 150.4, 146.3, 136.4, 131.8, 131.4 (2C), 130.7, 130.1, 129.3 (2C), 129.3, 129.0, 128.6 (2C), 128.5, 127.8 (2C), 124.2, 122.7, 120.4, 115.6, 110.9, 85.0, 32.7, 28.6 (3C), 22.0. HRMS (ESI-TOF) m/z calcd. for $C_{29}H_{29}N_2O_4S$ $[M+H]^+$ 501.1843 found: 501.1847.

tert-*Butyl pyrimido[1,6-*a*]indole-3-carboxylate (**2**).* To a stirred solution of TosMIC (195 mg, 1 mmol), 2-bromomethyl-1-(*tert*-butoxycarbonyl)indole[18] (403 mg, 1.3 mmol) and TBAI (74 mg, 0.2 mmol) in CH_2Cl_2 (5 mL), was added, at 0 ºC, a solution of NaOH (40% in H_2O, 5 mL) and the reaction mixture was vigorously stirred at room temperature for 24h. Then, water (5 mL) was added, the two layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (3:7 EtOAc/hexanes) to supply tricycle **2** as a yellow oil (126 mg, 0.47 mmol, 47%). IR (NaCl) υ_{max} (cm^{-1}) 2975, 2932, 1713, 1531, 1456, 1368, 1246, 1137, 1089. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 9.19 (s, 1H), 8.09 (d, *J* = 1.4 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.46 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.41 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 6.86 (s, 1H), 1.64 (s, 9H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) 163.9, 138.4, 135.4, 133.1, 130.3, 128.8, 125.0, 123.0, 121.5, 117.3, 110.8, 97.7, 82.1, 28.3 (3C). HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{17}N_2O_2$ $[M+H]^+$ 269.1285 found: 269.1311.

*General procedure for the synthesis of γ-carbolines **3a-3c**.* To a stirred solution of the corresponding α-(2-indolylmethyl) TosMIC derivative (0.20 mmol) in dry CH_2Cl_2 (2 mL), under argon atmosphere, TFA (57 mg, 37 μL, 0.50 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 22 h. Then, saturated aq. $NaHCO_3$ solution (4 mL) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to supply the corresponding γ-carboline.

tert-*Butyl 3-benzyl-5*H-*pyrido[4,3-*b*]indole-5-carboxylate (**3a**).* Following the general procedure, starting from TosMIC derivative **1a** (106 mg, 0.20 mmol), and after purification by flash column chromatography on silica gel (3:7 EtOAc/hexanes), γ-carboline **3a** was obtained as a yellow oil (62 mg, 0.17 mmol, 87%). IR (NaCl) υ_{max} (cm^{-1}) 2978, 2930, 1734, 1596, 1452, 1352, 1220, 1151, 701. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 9.18 (s, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 8.02 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.92 (s, 1H), 7.49 (ddd, *J* = 8.5, 7.3, 1.3 Hz, 1H), 7.39 (td, *J* = 7.5, 1.0 Hz, 1H), 7.36-7.30 (m, 4H), 7.23 (ddd, *J* = 8.7, 7.4, 1.9 Hz, 1H), 4.34 (s, 2H), 1.65 (s, 9H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) 159.1, 150.6, 144.5, 141.7, 139.9, 138.8, 129.4 (2C), 128.8 (2C), 127.9, 126.5, 123.9, 123.7, 120.4, 119.9, 116.4, 110.3, 85.0, 45.3, 28.3 (3C). HRMS (ESI-TOF) m/z calcd. for $C_{23}H_{23}N_2O_2$ $[M+H]^+$ 359.1754 found: 359.1747.

tert-*Butyl 3-ethyl-5*H-*pyrido[4,3-*b*]indole-5-carboxylate (**3b**).* Following the general procedure, starting from TosMIC derivative **1b** (90 mg, 0.20 mmol), and after purification by flash column chromatography on silica gel (3:7 EtOAc/hexanes), γ-carboline **3b** was obtained as an orange oil (36 mg, 0.12 mmol, 61%). IR (NaCl) υ_{max} (cm^{-1}) 2973, 2933, 1734, 1600, 1460, 1351, 1152, 748. ^{1}H-NMR (500 MHz, $CDCl_3$) δ

(ppm) 9.14 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.05 (s, 1H), 8.00 (d, *J* = 7.7 Hz, 1H), 7.47 (ddd, *J* = 8.4, 7.3, 1.1 Hz 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 3.00 (q, *J* = 7.6 Hz, 2H), 1.77 (s, 9H), 1.40 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) 161.7, 150.8, 144.6, 141.6, 138.5, 127.6, 123.9, 123.8, 120.1, 119.9, 116.3, 109.0, 84.9, 32.2, 28.4 (3C), 14.4. HRMS (ESI-TOF) m/z calcd. for $C_{18}H_{21}N_2O_2$ $[M+H]^+$ 297.1598 found: 297.1603.

tert-*Butyl 3-phenyl-5*H-*pyrido[4,3-*b*]indole-5-carboxylate (**3c**).* Following the general procedure, starting from TosMIC derivative **1c** (100 mg, 0.20 mmol), and after purification by flash column chromatography on silica gel (3:7 EtOAc/hexanes), γ-carboline **3c** was obtained as a yellow oil (46 mg, 0.13 mmol, 67%). IR (NaCl) υ_{max} (cm^{-1}) 2977, 2929, 1733, 1596, 1450, 1351, 1152, 766. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 9.30 (s, 1H), 8.64 (s, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 8.11 (dd, *J* = 8.3, 1.3 Hz, 2H), 8.07 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.56-7.48 (m, 3H), 7.46-7.39 (m, 2H), 1.82 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 155.6, 150.7, 144.8, 142.1, 140.3, 139.0, 128.9 (2C), 128.8, 128.0, 127.3 (2C), 124.0, 123.7, 121.0, 120.1, 116.4, 108.0, 85.1, 28.5 (3C). HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{21}N_2O_2$ $[M+H]^+$ 345.1598 found: 345.1609.

*General procedure for the synthesis of γ-carbolines **4a-4o**.* To a stirred solution of the corresponding α-(2-indolylmethyl) TosMIC derivative (0.20 mmol) and the aldehyde or ketone (0.40 mmol) in dry CH_2Cl_2 (2 mL), under argon atmosphere, at 0ºC was added dropwise a solution of $AlEt_2Cl$ (1 M in hexanes, 0.80 mmol, 0.80 mL) and the reaction mixture was stirred at the same temperature for additional 15 min. The reaction mixture was warmed to room temperature and stirred for 18 h at the same temperature. Then, saturated aq. $NaHCO_3$ solution (4 mL) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with CH_2Cl_2, and the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under

reduced pressure. The crude product was purified by flash column chromatography on silica gel to supply the corresponding γ-carboline.

tert-*Butyl 3-benzyl-1-(1-hydroxypropyl)-5*H-*pyrido[4,3-*b*]indole-5-carboxylate (**4a**).* Following the general procedure, starting from TosMIC derivative **1a** (106 mg, 0.20 mmol), and propionaldehyde (23 mg, 29 μL, 0.40 mmol), after purification by flash column chromatography on silica gel (2:8 EtOAc/hexanes), γ-carboline **4a** was obtained as a white solid (59 mg, 0.14 mmol, 71%). M.p.: 124-125 ºC. IR (KBr) υ_{max} (cm^{-1}) 3400, 2976, 2931, 1735, 1592, 1448, 1331, 1155, 1125, 995, 748. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.38 (d, *J* = 8.3 Hz, 1H), 7.93 (s, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.51 (td, *J* = 7.4 Hz, 1.2 Hz, 1H), 7.43 (td, *J* = 7.3, 1.0 Hz, 1H), 7.37-7.29 (m, 4H), 7.25-7.19 (m, 1H), 5.39 (dd, *J* = 7.7, 2.6 Hz, 1H), 5.41 (br, 1H), 4.32 (s, 2H), 2.09 (dqd, *J* = 14.6, 7.3, 2.3 Hz, 1H), 1.76-1.59 (m, 1H), 1.65 (s, 9H), 1.10 (t, *J* = 7.3 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 156.8, 156.0, 150.5, 145.3, 139.7, 138.9, 129.4 (2C), 128.8 (2C), 127.4, 126.6, 124.1, 123.3, 122.4, 116.4, 115.7, 109.1, 85.2, 71.7, 45.0, 30.2, 28.3 (3C), 10.0. HRMS (ESI-TOF) m/z calcd. for $C_{26}H_{29}N_2O_3$ $[M+H]^+$ 417.2173 found: 417.2168.

*1-(3-Ethyl-5*H-*pyrido[4,3-*b*]indol-1-yl)propan-1-ol (**4b**).* Following the general procedure, starting from TosMIC derivative **1b** (90 mg, 0.20 mmol), and propionaldehyde (23 mg, 29 μL, 0.40 mmol), after purification by flash column chromatography on silica gel (3:7 EtOAc/hexanes), γ-carboline **4b** was obtained as a pale yellow solid (50 mg, 0.20 mmol, 99%). M.p.: 141-143 ºC. IR (KBr) υ_{max} (cm^{-1}) 3257, 2970, 2932, 2873, 1608, 1576, 1457, 1260, 969, 738. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.39 (brs, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.50-7.43 (m, 2H), 7.33 (ddd, *J* = 8.1, 6.7, 1.6 Hz, 1H), 7.11 (s, 1H), 5.39 (dd, *J* = 7.8, 3.2 Hz, 1H), 2.95 (q, *J* = 7.6 Hz, 2H), 2.16 (dqd, *J* = 14.8, 7.4, 3.2 Hz, 1H), 1.73 (tt, *J* = 14.8, 7.3 Hz, 1H), 1.38 (t, *J* = 7.6 Hz, 3H), 1.11 (t, *J* = 7.4 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 156.8, 155.4,

145.8, 139.6, 126.1, 122.4, 121.0, 120.9, 113.5, 111.2, 102.8, 72.0, 31.3, 30.2, 14.2, 10.2. HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{19}N_2O$ $[M+H]^+$ 255.1492 found: 255.1494.

*1-(3-Phenyl-5*H*-pyrido[4,3-*b*]indol-1-yl)propan-1-ol (**4c**).* Following the general procedure, starting from TosMIC derivative **1c** (100 mg, 0.20 mmol), and propionaldehyde (23 mg, 29 μL, 0.40 mmol), after purification by flash column chromatography on silica gel (3:7 EtOAc/hexanes), γ-carboline **4c** was obtained as a white solid (60 mg, 0.20 mmol, 99%). M.p.: 197-198 ºC. IR (KBr) υ_{max} (cm^{-1}) 3409, 3247, 2966, 2929, 1605, 1455, 1427, 1329, 1263, 973, 739, 695. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.79 (brs, 1H), 8.07 (d, *J* = 7.4 Hz, 2H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.67 (s, 1H), 7.54-7.46 (m, 4H), 7.42 (tt, *J* = 7.3, 1.8 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 5.74 (s, 1H), 5.49 (dd, *J* = 7.8, 3.2 Hz, 1H), 2.21 (dqd, *J* = 14.7, 7.4, 3.2 Hz, 1H), 1.80 (tt, *J* = 14.8, 7.4 Hz, 1H), 1.16 (t, *J* = 7.3 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 156.4, 151.0, 145.8, 139.9, 139.4, 128.9 (2C), 127.1 (2C), 126.7, 122.9, 121.5, 121.0, 114.7, 111.3, 101.7, 72.1, 30.3, 10.1. HRMS (ESI-TOF) m/z calcd. for $C_{20}H_{19}N_2O$ $[M+H]^+$ 303.1492 found: 303.1494.

*(3-Ethyl-5*H*-pyrido[4,3-*b*]indol-1-yl)(phenyl)methanol (**4d**).* Following the general procedure, starting from TosMIC derivative **1b** (90 mg, 0.20 mmol), and benzaldehyde (42 mg, 41 μL, 0.40 mmol), after purification by flash column chromatography on silica gel (3:7 EtOAc/hexanes), γ-carboline **4d** was obtained as a white solid (41 mg, 0.14 mmol, 68%). M.p.: 198-200 ºC. IR (KBr) υ_{max} (cm^{-1}) 3250, 2964, 1607, 1459, 1263, 1244, 996, 737. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.30 (brs, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.43-7.36 (m, 4H), 7.28-7.25 (m, 2H), 7.23-7.15 (m, 3H), 6.37 (s, 1H), 3.02 (q, *J* = 7.6 Hz, 2H), 1.44 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 157.1, 153.4, 153.4, 145.7, 142.5, 139.4, 128.7 (2C), 127.9 (2C), 127.8, 126.2, 122.8, 120.8, 114.6,

110.9, 103.2, 73.2, 31.5, 14.3. HRMS (ESI-TOF) m/z calcd. for $C_{20}H_{19}N_2O$ $[M+H]^+$ 303.1492 found: 303.1493.

*2-(3-Benzyl-5*H*-pyrido[4,3-*b*]indol-1-yl)propan-2-ol (**4e**) and* tert*-butyl 3-benzyl-1-(2-hydroxypropan-2-yl)-5*H*-pyrido[4,3-*b*]indole-5-carboxylate (**4n**).* The general procedure, starting from TosMIC derivative **1a** (106 mg, 0.20 mmol) and acetone (23 mg, 29 μL, 0.40 mmol), after purification by flash column chromatography on silica gel (2:8 EtOAc/hexanes), supplied *N*-deprotected γ-carboline **4e** as a white solid (35 mg, 0.11 mmol, 56%) and *N*-Boc protected γ-carboline **4n** as a yellow solid (27 mg, 0.07 mmol, 33%). Alternatively, the mixture of **4e** and **4n** was treated with a mixture of CH_2Cl_2 (3.0 mL) and TFA (1.0 mL) at room temperature for 5 h. Then, saturated aq. $NaHCO_3$ solution (5 mL) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (2:8 EtOAc/hexanes) to supply γ-carboline **4e** as a white solid (53 mg, 0.17 mmol, 85%). *2-(3-Benzyl-5*H*-pyrido[4,3-*b*]indol-1-yl)propan-2-ol (**4e**).* M.p.: Decomp. 251 ºC. IR (KBr) υ_{max} (cm^{-1}) 3400, 3159, 2971, 2925, 1611, 1410, 1324, 1251, 1149, 738, 697. ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm) 11.63 (brs, 1H), 8.73 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.40-7.37 (m, 3H), 7.31 (t, J = 7.6 Hz, 2H), 7.20 (t, J = 7.4 Hz, 2H), 7.17 (s, 1H), 5.69 (brs, 1H), 4.18 (s, 2H), 1.70 (s, 6H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ (ppm) 160.8, 153.0, 146.3, 140.4, 139.7, 129.1 (2C), 128.3 (2C), 126.4, 126.0, 125.4, 120.8, 119.3, 113.7, 110.7, 103.8, 73.2, 44.0, 29.1 (2C). HRMS (ESI-TOF) m/z calcd. for $C_{21}H_{21}N_2O$ $[M+H]^+$ 317.1648 found: 317.1644. tert*-Butyl 3-benzyl-1-(2-hydroxypropan-2-yl)-5*H*-pyrido[4,3-*b*]indole-5-carboxylate (**4n**).* M.p.: 139-140 ºC. IR (KBr) υ_{max} (cm^{-1}) 3401, 2978, 2932, 1734, 1588, 1461, 1371, 1327, 1256, 1152, 753.

^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.43 (d, *J* = 8.5 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 8.04 (s, 1H), 7.51 (ddd, *J* = 8.4, 7.3, 1.2 Hz, 1H), 7.43 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H), 7.38-7.31 (m, 4H), 7.24 (tt, *J* = 7.0, 1.8 Hz, 1H), 6.85 (brs, 1H), 4.33 (s, 2H), 1.88 (s, 6H), 1.64 (s, 9H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) 159.1, 155.4, 150.4, 146.6, 139.5, 139.1, 129.5 (2C), 128.8 (2C), 127.3, 126.6, 124.8, 123.6, 122.9, 116.2, 115.7, 109.2, 85.3, 71.6, 44.8, 28.3 (3C), 28.2 (2C). HRMS (ESI-TOF) m/z calcd. for $C_{26}H_{29}N_2O_3$ $[M+H]^+$ 417.2173 found: 417.2178.

*2-(3-Ethyl-5*H*-pyrido[4,3-*b*]indol-1-yl)propan-2-ol* ***(4f)***. Following the general procedure, starting from TosMIC derivative **1b** (90 mg, 0.20 mmol), and acetone (23 mg, 29 μL, 0.40 mmol), after purification by flash column chromatography on silica gel (3:7 EtOAc/hexanes), γ-carboline **4f** was obtained as a white solid (28 mg, 0.11 mmol, 56%). M.p.: 202-204 ºC. IR (KBr) υ_{max} (cm^{-1}) 3196, 2965, 1610, 1402, 1325, 1183, 957, 742. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.92 (brs, 1H), 8.25 (d, *J* = 8.1 Hz, 1H), 7.55 (brs, 1H), 7.51 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.46 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H), 7.34 (ddd, *J* = 8.3, 6.8, 1.6 Hz, 1H), 7.18 (s, 1H), 2.97 (q, *J* = 7.6 Hz, 2H), 1.92 (s, 6H), 1.40 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 159.1, 155.9, 146.9, 139.6, 126.1, 124.6, 120.8, 120.7, 112.9, 111.2, 103.0, 71.3, 31.1, 28.2 (2C), 13.9. HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{18}N_2O$ $[M+H]^+$ 255.1492 found: 255.1494.

*2-(3-Phenyl-5*H*-pyrido[4,3-*b*]indol-1-yl)propan-2-ol* ***(4g)*** *and* tert*-butyl 1-(2-hydroxypropan-2-yl)-3-phenyl-5*H*-pyrido[4,3-*b*]indole-5-carboxylate* ***(4o)***. The general procedure, starting from TosMIC derivative **1c** (100 mg, 0.20 mmol) and acetone (23 mg, 29 μL, 0.40 mmol), after purification by flash column chromatography on silica gel (3:7 EtOAc/hexanes), supplied *N*-deprotected γ-carboline **4g** as a white solid (30 mg, 0.10 mmol, 50%) and *N*-Boc protected γ-carboline **4o** as a yellow solid (22 mg, 0.05 mmol, 27%). Alternatively, the mixture of **4g** and **4o** was treated with a mixture of

CH_2Cl_2 (3.0 mL) and TFA (1.0 mL) at room temperature for 5 h. Then, saturated aq. $NaHCO_3$ solution (5 mL) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (3:7 EtOAc/hexanes) to supply γ-carboline **4g** as a white solid (44 mg, 0.15 mmol, 73%). *2-(3-Phenyl-5*H*-pyrido[4,3-*b*]indol-1-yl)propan-2-ol (**4g**).* M.p.: Decomp. 285 ºC. IR (KBr) υ_{max} (cm^{-1}) 3152, 3091, 2961, 1608, 1395, 1324, 1175, 956, 770, 699. ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm) 11.80 (brs, 1H), 8.84 (d, *J* = 8.0 Hz, 1H), 8.22 (d, *J* = 7.8 Hz, 2H), 7.90 (s, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 5.61 (brs, 1H), 1.77 (s, 6H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ (ppm) 161.1, 148.5, 146.6, 140.2, 139.7, 128.6 (2C), 128.2, 126.8, 126.4 (2C), 125.7, 120.8, 119.5, 115.0, 110.8, 101.1, 73.8, 29.1 (2C). HRMS (ESI-TOF) m/z calcd. for $C_{20}H_{19}N_2O$ $[M+H]^+$ 303.1492 found: 303.1501. *tert-Butyl 1-(2-hydroxypropan-2-yl)-3-phenyl-5*H*-pyrido[4,3-*b*]indole-5-carboxylate (**4o**).* M.p.: 162-164 ºC. IR (KBr) υ_{max} (cm^{-1}) 3344, 2976, 1732, 1587, 1370, 1394, 1255, 1151, 1127, 771. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.83 (s, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.41 (d, *J* = 8.1 Hz, 1H), 8.17 (d, *J* = 7.7 Hz, 2H), 7.58-7.50 (m, 3H), 7.49-7.43 (m, 2H), 6.44 (brs, 1H), 1.94 (s, 6H), 1.82 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 159.5, 151.5, 150.6, 147.0, 139.3, 131.3, 129.2, 129.0 (2C), 127.5, 127.2 (2C), 125.2, 123.8, 123.0, 116.7, 116.3, 106.8, 85.5, 72.4, 28.5 (3C), 28.4 (2C). HRMS (ESI-TOF) m/z calcd. for $C_{25}H_{27}N_2O_3$ $[M+H]^+$ 403.2016 found: 403.2022.

*1-(3-Benzyl-5*H*-pyrido[4,3-*b*]indol-1-yl)-1-phenylethanol (**4h**).* Following the general procedure, starting from TosMIC derivative **1a** (106 mg, 0.20 mmol), and acetophenone (48 mg, 46 μL, 0.40 mmol), after purification by flash column chromatography on silica

gel (2:8 EtOAc/hexanes), γ-carboline **4h** was obtained as a pale orange solid (59 mg, 0.16 mmol, 78%). M.p.: 106-107 ºC. IR (KBr) υ_{max} (cm^{-1}) 3406, 3238, 3027, 2980, 1608, 1452, 1326, 1266, 1029, 908, 729, 699. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.96 (brs, 1H), 8.05 (brs, 1H), 7.43 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.37 (d, *J* = 6.9 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.32-7.19 (m, 6H), 7.13 (d, *J* = 8.1 Hz, 1H), 7.05 (s, 1H), 6.93 (ddd, *J* = 8.2, 6.8, 1.4 Hz, 1H), 4.35 (s, 2H), 2.14 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 157.2, 153.0, 146.5, 144.4, 139.6, 139.5, 129.3 (2C), 128.6 (4C), 127.6, 126.9 (2C), 126.5, 126.0, 124.2, 120.4, 120.3, 114.0, 110.8, 104.8, 75.0, 44.5, 26.0. HRMS (ESI-TOF) m/z calcd. for $C_{26}H_{23}N_2O$ $[M+H]^+$ 379.1805 found: 379.1808.

*1-(3-Ethyl-5*H*-pyrido[4,3-*b*]indol-1-yl)-1-phenylethanol (**4i**).* Following the general procedure, starting from TosMIC derivative **1b** (90 mg, 0.20 mmol), and acetophenone (48 mg, 46 µL, 0.40 mmol), after purification by flash column chromatography on silica gel (3:7 EtOAc/hexanes), γ-carboline **4i** was obtained as an orange solid (46 mg, 0.15 mmol, 73%). M.p.: 185-186 ºC. IR (KBr) υ_{max} (cm^{-1}) 3402, 3234, 2973, 1608, 1461, 1401, 1266, 1032, 911, 734, 699. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 9.02 (brs, 1H), 7.47 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.32-7.27 (m, 3H), 7.27-7.23 (m, 1H), 7.18 (s, 1H), 7.16 (d, *J* = 8.1 Hz, 1H), 6.96 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 3.04 (q, *J* = 7.6 Hz, 2H), 2.17 (s, 3H), 1.46 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) 156.9, 155.4, 146.8, 144.6, 139.7, 128.7 (2C), 127.7, 127.1 (2C), 125.9, 124.1, 120.5, 120.3, 113.8, 111.0, 103.7, 75.0, 31.0, 25.8, 14.0. HRMS (ESI-TOF) m/z calcd. for $C_{21}H_{21}N_2O$ $[M+H]^+$ 317.1648 found: 317.1651.

*1-Phenyl-1-(3-phenyl-5*H*-pyrido[4,3-*b*]indol-1-yl)ethanol (**4j**).* Following the general procedure, starting from TosMIC derivative **1c** (100 mg, 0.20 mmol), and acetophenone (48 mg, 46 µL, 0.40 mmol), after purification by flash column chromatography on silica gel (2:8 EtOAc/hexanes), γ-carboline **4j** was obtained as a pale yellow solid (58 mg,

0.16 mmol, 79%). M.p.: Decomp. 195 ºC. IR (KBr) υ_{max} (cm^{-1}) 3401, 3244, 3059, 2919, 1605, 1450, 1395, 1227, 909, 771, 695. ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm) 11.77 (s, 1H), 8.31 (t, *J* = 7.8 Hz, 3H), 7.98 (s, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.46-7.40 (m, 4H), 7.29 (dd, *J* = 8.0, 7.2 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.33 (s, 1H), 2.10 (s, 3H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ (ppm) 159.6, 148.3, 147.6, 146.6, 140.0, 139.7, 128.7 (2C), 128.3, 127.7 (2C), 126.6, 126.5 (2C), 126.1, 125.6, 125.3 (2C), 120.5, 119.1, 115.9, 110.5, 101.4, 77.7, 32.6. HRMS (ESI-TOF) m/z calcd. for $C_{25}H_{21}N_2O$ $[M+H]^+$ 365.1648 found: 365.1638.

tert-*Butyl 3-benzyl-1-(1-hydroxycyclohexyl)-5*H-*pyrido[4,3-*b*]indole-5-carboxylate (**4k**).* Following the general procedure, starting from TosMIC derivative **1a** (106 mg, 0.20 mmol), and cyclohexanone (39 mg, 41 μL, 0.40 mmol), after purification by flash column chromatography on silica gel (1:9 EtOAc/hexanes), γ-carboline **4k** was obtained as a white solid (75 mg, 0.16 mmol, 82%). M.p.: 129-130 ºC. IR (KBr) υ_{max} (cm^{-1}) 3297, 2930, 2857, 1734, 1587, 1327, 1255, 1152, 1126, 975, 743. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.57 (d, *J* = 8.0 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.05 (s, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.37-7.30 (m, 4H), 7.23 (td, *J* = 7.2, 1.3 Hz, 1H), 4.30 (s, 2H), 2.62 (td, *J* = 13.4, 4.0 Hz, 2H), 2.01 (qt, *J* = 13.0, 3.0 Hz, 2H), 1.93-1.83 (m, 4H), 1.71-1.61 (m, 2H), 1.64 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 159.7, 155.3, 150.4, 146.6, 139.5, 139.0, 129.5 (2C), 128.8 (2C), 127.1, 126.6, 125.7, 123.4, 123.0, 116.2, 109.1, 85.3, 73.3, 44.9, 42.1, 34.2 (2C), 28.3 (3C), 25.1, 22.3 (2C). HRMS (ESI-TOF) m/z calcd. for $C_{29}H_{33}N_2O_3$ $[M+H]^+$ 457.2486 found: 457.2486.

*1-(3-Ethyl-5*H-*pyrido[4,3-*b*]indol-1-yl)cyclohexanol (**4l**).* Following the general procedure, starting from TosMIC derivative **1b** (90 mg, 0.20 mmol), and cyclohexanone (39 mg, 41 μL, 0.40 mmol), after purification by flash column chromatography on silica gel (3:7 EtOAc/hexanes), γ-carboline **4l** was obtained as a white solid (58 mg, 0.20

mmol, 99%). M.p.: 203-204 ºC. IR (KBr) υ_{max} (cm^{-1}) 3146, 2927, 2857, 1609, 1462, 1416, 1323, 1263, 1148, 963, 751. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.93 (brs, 1H), 8.50 (d, *J* = 8.1 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.47 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.36 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.16 (s, 1H), 2.93 (q, *J* = 7.6 Hz, 2H), 2.73 (td, *J* = 13.6, 4.5 Hz, 2H), 2.11-2.00 (m, 2H), 1.96 (d, *J* = 13.1 Hz, 1H), 1.89 (d, *J* = 12.8 Hz, 2H), 1.80-1.69 (m, 1H), 1.65 (d, *J* = 12.8 Hz, 2H), 1.37 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 159.7, 155.6, 147.0, 139.7, 126.1, 125.4, 120.8, 120.7, 113.2, 111.3, 103.1, 73.0, 34.3 (2C), 30.9, 25.2, 22.5 (2C), 13.7. HRMS (ESI-TOF) m/z calcd. for $C_{19}H_{23}N_2O$ $[M+H]^+$ 295.1805 found: 295.1810.

tert-*Butyl 1-(1-hydroxycyclohexyl)-3-phenyl-5*H-*pyrido[4,3-*b*]indole-5-carboxylate (**4m**).* Following the general procedure, starting from TosMIC derivative **1c** (100 mg, 0.20 mmol), and cyclohexanone (39 mg, 41 µL, 0.40 mmol), after purification by flash column chromatography on silica gel (1:9 EtOAc/hexanes), γ-carboline **4m** was obtained as a white solid (72 mg, 0.16 mmol, 81%). M.p.: Decomp. 281 ºC. IR (KBr) υ_{max} (cm^{-1}) 3306, 2931, 2856, 1733, 1587, 1393, 1257, 1152, 769. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.83 (s, 1H), 8.68 (d, *J* = 7.9 Hz, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 7.3 Hz, 2H), 7.57-7.41 (m, 5H), 2.63 (td, *J* = 13.2, 3.6 Hz, 2H), 2.09-1.98 (m, 2H), 1.95-1.78 (m, 5H), 1.81 (s, 9H), 1.72-1.61 (m, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) 160.1, 151.4, 150.6, 147.0, 139.3, 131.0, 129.1, 128.9 (2C), 127.4, 127.1 (2C), 126.1, 123.6, 123.2, 117.2, 116.2, 106.6, 85.4, 74.1, 34.6 (2C), 28.5 (3C), 25.2, 22.4 (2C). HRMS (ESI-TOF) m/z calcd. for $C_{28}H_{31}N_2O_3$ $[M+H]^+$ 443.2329 found: 443.2321.

*General procedure for the synthesis of γ-carbolines **5a-5e**.* To a stirred solution of the corresponding α-(2-indolylmethyl) TosMIC derivative (0.20 mmol) and propylene oxide in dry CH_2Cl_2 (2 mL), under argon atmosphere, at 0ºC was added dropwise a solution of $AlEt_2Cl$ (1 M in hexanes) and the reaction mixture was stirred at the same

temperature for additional 15 min. The reaction mixture was warmed to room temperature and stirred for 24 h at the same temperature. Then, saturated aq. $NaHCO_3$ solution (4 mL) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with CH_2Cl_2, and the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to supply the corresponding γ-carboline.

tert-*Butyl 3-benzyl-1-(2-hydroxypropyl)-5*H-*pyrido[4,3-*b*]indole-5-carboxylate (**5a**).* Following the general procedure, starting from TosMIC derivative **1a** (106 mg, 0.20 mmol), propylene oxide (46 mg, 56 µL, 0.80 mmol) and $AlEt_2Cl$ (1 M in hexanes, 0.80 mmol, 0.80 mL), after purification by flash column chromatography on silica gel (3:7 EtOAc/hexanes), γ-carboline **5a** was obtained as a colorless oil (42 mg, 0.10 mmol, 50%). IR (NaCl) υ_{max} (cm^{-1}) 3401, 2970, 2927, 1733, 1589, 1442, 1371, 1155, 1126, 747, 702. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.35 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 7.7 Hz, 1H), 7.94 (s, 1H), 7.50 (ddd, *J* = 8.5, 7.5, 1.2 Hz, 1H), 7.41 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 7.35-7.30 (m, 4H), 7.22 (ddd, *J* = 8.6, 5.6, 2.6 Hz, 1H), 4.60-4.50 (m, 1H), 4.28 (s, 2H), 3.47 (dd, *J* = 16.1, 1.6 Hz, 1H), 3.24 (dd, *J* = 16.6, 8.4 Hz, 1H), 1.67 (s, 9H), 1.43 (d, *J* = 6.3 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 157.3, 154.7, 150.6, 145.0, 139.7, 138.7, 129.4 (2C), 128.8 (2C), 127.3, 126.6, 124.1, 123.9, 122.1, 118.0, 116.3, 108.3, 85.2, 65.9, 45.2, 42.9, 28.3 (3C), 23.0. HRMS (ESI-TOF) m/z calcd. for $C_{26}H_{29}N_2O_3$ $[M+H]^+$ 417.2173 found: 417.2175.

*1-(3-Ethyl-5*H-*pyrido[4,3-*b*]indol-1-yl)propan-2-ol (**5b**) and* tert-*butyl 3-ethyl-1-(2-hydroxypropyl)-5*H-*pyrido[4,3-*b*]indole-5-carboxylate (**5d**).* The general procedure, starting from TosMIC derivative **1b** (90 mg, 0.20 mmol), propylene oxide (46 mg, 56 µL, 0.80 mmol) and $AlEt_2Cl$ (1 M in hexanes, 1.20 mmol, 1.20 mL), after purification

by flash column chromatography on silica gel (1:1 EtOAc/hexanes), supplied *N*-deprotected γ-carboline **5b** as a pale yellow solid (23 mg, 0.09 mmol, 46%) and *N*-Boc protected γ-carboline **5d** as a pale orange solid (16 mg, 0.04 mmol, 22%). Alternatively, the mixture of **5b** and **5d** was treated with a mixture of CH_2Cl_2 (3.0 mL) and TFA (1.0 mL) at room temperature for 5 h. Then, saturated aq. $NaHCO_3$ solution (5 mL) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (1:1 EtOAc/hexanes) to supply γ-carboline **5b** as a pale yellow solid (30 mg, 0.12 mmol, 59%). *1-(3-Ethyl-5*H*-pyrido[4,3-*b*]indol-1-yl)propan-2-ol (**5b**).* M.p.: 162-163 ºC. IR (KBr) υ_{max} (cm^{-1}) 3252, 3970, 1609, 1575, 1456, 1326, 1262, 1120, 849, 741. ^{1}H-NMR (300 MHz, CD_3OD) δ (ppm) 8.18 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.40-7.32 (m, 2H), 4.44-4.31 (m, 1H), 3.50 (d, *J* = 6.6 Hz, 2H), 2.98 (q, *J* = 7.6 Hz, 2H), 1.39 (t, *J* = 7.6 Hz, 3H), 1.33 (d, *J* = 6.2 Hz, 3H). ^{13}C-NMR (75 MHz, CD_3OD) δ (ppm) 156.3, 152.8, 148.2, 142.1, 128.3, 123.5, 122.4, 118.0, 112.8, 104.2, 67.9, 44.1, 30.1, 23.4, 14.6. HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{19}N_2O$ $[M+H]^+$ 255.1492 found: 255.1492. tert-*Butyl 3-ethyl-1-(2-hydroxypropyl)-5*H*-pyrido[4,3-*b*]indole-5-carboxylate (**5d**).* M.p.: 97-98 ºC. IR (KBr) υ_{max} (cm^{-1}) 3370, 2973, 2932, 1734, 1592, 1408, 1370, 1155, 1127, 865, 747. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.34 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 8.03 (s, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 6.22 (brs, 1H), 4.66-4.51 (m, 1H), 3.49 (d, *J* = 16.1 Hz, 1H), 3.26 (br, 1H), 2.97 (q, *J* = 7.6 Hz, 2H), 1.77 (s, 9H), 1.45 (d, *J* = 6.3 Hz, 3H), 1.39 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) 159.7, 154.4, 150.7, 145.1, 138.6, 127.1, 124.3, 123.8, 122.0, 117.8, 116.2, 107.2, 85.1, 66.1,

42.7, 31.8, 28.4 (3C), 23.1, 14.1. HRMS (ESI-TOF) m/z calcd. for $C_{21}H_{27}N_2O_3$ $[M+H]^+$ 355.2016 found: 355.2020.

*1-(3-Phenyl-5*H*-pyrido[4,3-*b*]indol-1-yl)propan-2-ol (**5c**) and* tert*-butyl 1-(2-hydroxypropyl)-3-phenyl-5*H*-pyrido[4,3-*b*]indole-5-carboxylate (**5e**).* The general procedure, starting from TosMIC derivative **1c** (100 mg, 0.20 mmol), propylene oxide (23 mg, 28 μL, 0.40 mmol) and $AlEt_2Cl$ (1 M in hexanes, 0.80 mmol, 0.80 mL), after purification by flash column chromatography on silica gel (3:7 EtOAc/hexanes), supplied *N*-deprotected γ-carboline **5c** as a pale yellow solid (13 mg, 0.04 mmol, 21%) and *N*-Boc protected γ-carboline **5e** as a pale yellow solid (36 mg, 0.09 mmol, 45%). Alternatively, the mixture of **5c** and **5e** was treated with a mixture of CH_2Cl_2 (3.0 mL) and TFA (1.0 mL) at room temperature for 5 h. Then, saturated aq. $NaHCO_3$ solution (5 mL) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (3:7 EtOAc/hexanes) to supply γ-carboline **5c** as a pale yellow solid (35 mg, 0.11 mmol, 56%). *1-(3-Phenyl-5*H*-pyrido[4,3-*b*]indol-1-yl)propan-2-ol (**5c**).* M.p.: 190-192 ºC. IR (KBr) υ_{max} (cm^{-1}) 3233, 2963, 2914, 2850, 1261, 1156, 1096, 1017, 799. ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm) 11.80 (s, 1H), 8.22 (d, J = 7.9 Hz, 1H), 8.15 (d, J = 7.5 Hz, 2H), 7.83 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.47 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 5.11 (s, 1H), 4.44-4.36 (m, 1H), 3.53 (dd, J = 13.6, 6.4 Hz, 1H), 3.36 (dd, J = 13.5, 6.5 Hz, 1H), 1.22 (d, J = 6.1 Hz, 3H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ (ppm) 153.7, 150.4, 145.2, 140.0, 139.6, 128.5 (2C), 128.1, 126.5 (2C), 125.9, 122.1, 120.7, 120.0, 116.5, 111.3, 100.5, 65.8, 45.7, 23.3. HRMS (ESI-TOF) m/z calcd. for $C_{20}H_{19}N_2O$ $[M+H]^+$ 303.1492 found: 303.1493. tert*-Butyl 1-(2-hydroxypropyl)-3-*

*phenyl-5*H-*pyrido[4,3-*b*]indole-5-carboxylate (**5e**).* M.p.: 146-147 ºC. IR (KBr) υ_{max} (cm^{-1}) 3401, 2975, 1733, 1589, 1438, 1397, 1259, 1154, 1127, 769. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.63 (s, 1H), 8.38 (d, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 3H), 7.57-7.39 (m, 5H), 5.99 (brs, 1H), 4.79-4.64 (m, 1H), 3.55 (dd, *J* = 16.6, 2.3 Hz, 1H), 3.35 (dd, *J* = 16.6, 9.5 Hz, 1H), 1.81 (s, 9H), 1.50 (d, *J* = 6.3 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 154.8, 153.7, 150.7, 145.3, 139.7, 139.0, 131.3, 129.0 (2C), 127.6, 127.2 (2C), 124.1, 124.1, 122.3, 118.9, 116.4, 106.2, 85.3, 66.0, 43.2, 28.5 (3C), 23.0. HRMS (ESI-TOF) m/z calcd. for $C_{25}H_{27}N_2O_3$ $[M+H]^+$ 403.2016 found: 403.2022.

*General procedure for the synthesis of γ-carbolines **6a-6b**.* To a stirred solution of the corresponding α-(2-indolylmethyl) TosMIC derivative (0.20 mmol) and *N*-tosylaziridine (158 mg, 0.80 mmol) in dry CH_2Cl_2 (2 mL), under argon atmosphere, at 0ºC was added dropwise a solution of $AlEt_2Cl$ (1 M in hexanes, 0.80 mmol, 0.80 mL) and the reaction mixture was stirred at the same temperature for additional 15 min. The reaction mixture was warmed to room temperature and stirred for 72 h at the same temperature. Then, saturated aq. $NaHCO_3$ solution (4 mL) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with CH_2Cl_2, and the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to supply the corresponding γ-carboline.

N-*(2-(3-Benzyl-5*H-*pyrido[4,3-*b*]indol-1-yl)ethyl)-4-methylbenzenesulfonamide (**6a**).* Following the general procedure, starting from TosMIC derivative **1a** (106 mg, 0.20 mmol), after purification by flash column chromatography on silica gel (1:1 EtOAc/hexanes), γ-carboline **6a** was obtained as an orange oil (69 mg, 0.15 mmol, 76%). IR (NaCl) υ_{max} (cm^{-1}) 3347, 3061, 2924, 1602, 1455, 1328, 1157, 1092, 814, 739. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.57 (brs, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J*

= 8.3 Hz, 2H), 7.43-7.38 (m, 2H), 7.32-7.28 (m, 2H), 7.26-7.19 (m, 4H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.95 (s, 1H), 6.73 (brs, 1H), 4.06 (s, 2H), 3.56 (t, *J* = 5.7 Hz, 2H), 3.36 (t, *J* = 5.7 Hz, 2H), 2.30 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) 155.3, 153.1, 145.1, 143.1, 140.2, 139.3, 137.4, 129.6 (2C), 129.1 (2C), 128.8 (2C), 127.0 (2C), 126.5, 126.3, 122.2, 121.5, 120.9, 116.1, 111.1, 103.5, 44.8, 41.0, 34.0, 21.5. HRMS (ESI-TOF) m/z calcd. for $C_{27}H_{26}N_3O_2S$ $[M+H]^+$ 456.1740 found: 456.1740.

N-*(2-(3-Ethyl-5*H*-pyrido[4,3-*b*]indol-1-yl)ethyl)-4-methylbenzenesulfonamide* ***(6b)***. Following the general procedure, starting from TosMIC derivative **1b** (80 mg, 0.20 mmol), after purification by flash column chromatography on silica gel (1:1 EtOAc/hexanes), γ-carboline **6b** was obtained as a yellow oil (38 mg, 0.10 mmol, 48%). IR (NaCl) υ_{max} (cm^{-1}) 3349, 2968, 2931, 1608, 1457, 1328, 1157, 1093, 738. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.89 (brs, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 2H), 6.98 (s, 1H), 3.58 (t, *J* = 5.6 Hz, 2H), 3.43 (t, *J* = 5.6 Hz, 2H), 2.74 (q, *J* = 7.5 Hz, 2H), 2.35 (s, 3H), 1.27 (t, *J* = 7.5 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 157.6, 152.5, 145.2, 143.1, 139.3, 137.0, 129.6 (2C), 127.0 (2C), 126.1, 121.9, 121.4, 120.7, 115.9, 111.1, 102.2, 41.3, 33.8, 31.4, 21.7, 14.3. HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{24}N_3O_2S$ $[M+H]^+$ 394.1584 found: 394.1591.

General procedure for the synthesis of γ-carbolines ***7a-7c***. To a stirred solution of the corresponding α-(2-indolylmethyl) TosMIC derivative (0.20 mmol) and dimethylmethylideneammonium iodide (74 mg, 0.40 mmol) in dry CH_2Cl_2 (2 mL), under argon atmosphere, at 0ºC was added dropwise a solution of $AlEt_2Cl$ (1 M in hexanes, 0.80 mmol, 0.80 mL) and the reaction mixture was stirred at the same temperature for additional 15 min. The reaction mixture was warmed to room temperature and stirred for 18 h at the same temperature. Then, saturated aq. $NaHCO_3$

solution (4 mL) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with CH_2Cl_2, and the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to supply the corresponding γ-carboline.

*1-(3-Benzyl-5*H*-pyrido[4,3-*b*]indol-1-yl)*-N,N-*dimethylmethanamine (**7a**).* Following the general procedure, starting from TosMIC derivative **1a** (106 mg, 0.20 mmol), after purification by flash column chromatography on silica gel (1:9 MeOH/CH_2Cl_2), γ-carboline **7a** was obtained as a colorless oil (50 mg, 0.16 mmol, 80%). IR (NaCl) υ_{max} (cm^{-1}) 3177, 3058, 2945, 1603, 1453, 1327, 1264, 850, 736. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.03 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.36 (td, *J* = 8.1, 1.1 Hz, 1H), 7.24 (td, *J* = 7.9, 0.9 Hz, 1H), 7.22-7.17 (m, 4H), 7.17-7.13 (m, 1H), 6.97 (s, 1H), 4.17 (s, 2H), 4.14 (s, 2H), 2.43 (s, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 154.0, 150.5, 145.9, 140.0, 139.4, 129.2 (2C), 128.5 (2C), 126.5, 126.4, 123.2, 121.1, 120.9, 116.9, 111.4, 104.8, 62.9, 45.7 (2C), 43.7. HRMS (ESI-TOF) m/z calcd. for $C_{21}H_{22}N_3$ $[M+H]^+$ 316.1808 found: 316.1813.

*1-(3-Ethyl-5*H*-pyrido[4,3-*b*]indol-1-yl)*-N,N-*dimethylmethanamine (**7b**).* Following the general procedure, starting from TosMIC derivative **1b** (90 mg, 0.20 mmol), after purification by flash column chromatography on silica gel (1:9 MeOH/CH_2Cl_2), γ-carboline **7b** was obtained as a pale yellow solid (39 mg, 0.15 mmol, 77%). M.p.: 86-87 ºC. IR (KBr) υ_{max} (cm^{-1}) 3157, 2926, 2854, 2776, 1609, 1456, 1330, 1267, 1173, 739. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.03 (d, *J* = 7.9 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.40 (td, *J* = 8.1, 1.0 Hz, 1H), 7.36 (s, 1H), 7.27 (t, *J* = 8.0 Hz, 1H), 4.27 (s, 2H), 2.95 (q, *J* = 7.6 Hz, 2H), 2.48 (s, 6H), 1.25 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 153.8, 148.3, 147.0, 140.8, 127.4, 123.2, 121.5, 120.7, 117.1, 112.4, 104.5, 60.5,

45.7 (2C), 28.9, 14.1. HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{20}N_3$ $[M+H]^+$ 254.1652 found: 254.1663.

N,N-*Dimethyl-1-(3-phenyl-5*H*-pyrido[4,3-*b*]indol-1-yl)methanamine (**7c**).* Following the general procedure, starting from TosMIC derivative **1c** (100 mg, 0.20 mmol), after purification by flash column chromatography on silica gel (1:9 MeOH/CH_2Cl_2), γ-carboline **7c** was obtained as a yellow oil (45 mg, 0.15 mmol, 75%). IR (NaCl) υ_{max} (cm^{-1}) 3222, 3063, 2819, 1605, 1452, 1326, 1266, 1154, 771, 697. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 7.76 (d, *J* = 8.1 Hz, 1H), 7.74 (dd, *J* = 6.7, 3.1 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.28 (td, *J* = 8.1, 1.1 Hz, 1H), 7.24-7.21 (m, 3H), 7.19 (s, 1H), 7.13 (t, *J* = 8.0, 1H), 4.12 (s, 2H), 2.65 (s, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) 151.0, 149.0, 145.5, 140.1, 139.2, 128.6 (2C), 128.4, 126.9 (2C), 126.5, 122.9, 120.7, 120.7, 116.8, 111.4, 101.9, 62.7, 45.7 (2C). HRMS (ESI-TOF) m/z calcd. for $C_{20}H_{20}N_3$ $[M+H]^+$ 302.1652 found: 302.1639.

*General procedure for the synthesis of γ-carbolines **8a-8c**.* A solution of the corresponding α-(2-indolylmethyl) TosMIC derivative (0.20 mmol) and NIS (90 mg, 0.40 mmol) in dry CH_2Cl_2 (5 mL), under argon atmosphere, was vigorously stirred at room temperature for 18 h. Then, water (5 mL) was added, the reaction mixture was extracted with CH_2Cl_2, and the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to supply the corresponding iodinated γ-carboline.

tert-*Butyl 3-benzyl-1-iodo-5*H*-pyrido[4,3-*b*]indole-5-carboxylate (**8a**).* The general procedure, starting from TosMIC derivative **1a** (106 mg, 0.20 mmol), after purification by flash column chromatography on silica gel (1:9 EtOAc/hexanes), supplied iodinated γ-carboline **8a** as a yellow oil (90 mg, 0.19 mmol, 93%). IR (NaCl) υ_{max} (cm^{-1}) 2979 1742, 1587, 1528, 1386, 1321, 1150, 751. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.93

(dd, *J* = 8.0, 1.3 Hz, 1H), 8.36 (t, *J* = 8.4 Hz, 1H), 7.89 (s, 1H), 7.56 (ddd, *J* = 8.5, 7.3, 1.3 Hz, 1H), 7.47 (ddd, *J* = 8.2, 7.2, 1.0 Hz, 1H), 7.35-7.33 (m, 4H), 7.26-7.23 (m, 1H), 4.32 (s, 2H), 1.59 (s, 9H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) 159.8, 150.0, 144.6, 139.2, 139.1, 129.6 (2C), 128.9 (2C), 128.6, 126.7, 123.5, 123.3, 120.9, 116.0, 110.0, 109.8, 85.5, 44.8, 28.3 (3C). HRMS (ESI-TOF) m/z calcd. for $C_{23}H_{22}IN_2O_2$ $[M+H]^+$ 485.0720 found: 485.0720.

tert-*Butyl 3-ethyl-1-iodo-5*H-*pyrido[4,3-*b*]indole-5-carboxylate (**8b**)*. The general procedure, starting from TosMIC derivative **1b** (90 mg, 0.20 mmol), after purification by flash column chromatography on silica gel (3:7 EtOAc/hexanes), supplied iodinated γ-carboline **8b** as a white powder (59 mg, 0.14 mmol, 70%). M.p.: 113-115 ºC. IR (KBr) υ_{max} (cm^{-1}) 2979, 2967, 1744, 1638, 1591, 1460, 1388, 1320, 1150, 744. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.93 (d, *J* = 8.0 Hz, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 8.13 (s, 1H), 7.56 (ddd, *J* = 8.5, 7.3, 1.3 Hz, 1H), 7.47 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 2.97 (q, *J* = 7.6 Hz, 2H), 1.77 (s, 9H), 1.38 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) 162.4, 150.2, 145.0, 138.8, 128.4, 123.7, 123.2, 123.0, 120.9, 116.0, 109.9, 108.5, 85.5, 31.7, 28.4 (3C), 14.3. HRMS (ESI-TOF) m/z calcd. for $C_{18}H_{20}IN_2O_2$ $[M+H]^+$ 423.0564 found: 423.0570.

tert-*Butyl 1-iodo-3-phenyl-5*H-*pyrido[4,3-*b*]indole-5-carboxylate (**8c**)*. The general procedure, starting from TosMIC derivative **1c** (100 mg, 0.20 mmol), after purification by flash column chromatography on silica gel (5:95 EtOAc/hexanes), supplied iodinated γ-carboline **8c** as a white solid (79 mg, 0.17 mmol, 84%). M.p.: 192-193 ºC. IR (KBr) υ_{max} (cm^{-1}) 2973, 1736, 1586, 1431, 1382, 1199, 1152, 763, 683. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.94 (d, *J* = 7.9 Hz, 1H), 8.71 (s, 1H), 8.33 (d, *J* = 8.3 Hz, 1H), 8.11 (d, *J* = 7.2 Hz, 2H), 7.58 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.52-7.39 (m, 4H), 1.83 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 155.5, 150.2, 145.0, 139.2, 138.5, 129.3, 128.9

(2C), 128.7, 127.3 (2C), 123.8, 123.6, 123.3, 121.0, 116.0, 110.5, 107.1, 85.7, 28.5 (3C). HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{20}IN_2O_2$ $[M+H]^+$ 471.0564 found: 471.0564.

tert-*Butyl 3-ethyl-1-(phenylethynyl)-5*H-*pyrido[4,3-*b*]indole-5-carboxylate (**9a**).* To a round-bottom flask charged with iodinated γ-carboline **8b** (84 mg, 0.20 mmol), $Pd(PPh_3)_2Cl_2$ (7 mg, 0.01 mmol, 5 mol%) and CuI (4 mg, 0.02 mmol, 10 mol%), under argon atmosphere, dry THF (3 mL) and *i*-Pr_2NH (1 mL) were added, and the resulting mixture was stirred at room temperature for 24 h. Then, the reaction was quenched by addition of saturated aq. NH_4Cl solution (6 mL), and the layers were separated. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified flash column chromatography on silica gel (5:95 EtOAc/hexanes), supplying alkyne **9a** as a brown oil (78 mg, 0.20 mmol, 99%). IR (NaCl) υ_{max} (cm^{-1}) 2975, 2933, 2214, 1734, 1589, 1397, 1314, 1154, 755. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.67 (d, *J* = 7.8 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.10 (s, 1H), 7.78-7.75 (m, 2H), 7.52 (ddd, *J* = 8.5, 7.3, 1.3 Hz, 1H), 7.45-7.41 (m, 4H), 3.04 (q, *J* = 7.6 Hz, 2H), 1.78 (s, 9H), 1.43 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) 161.9, 150.6, 145.0, 138.8, 135.4, 132.2 (2C), 129.2, 128.6 (2C), 128.0, 123.9, 123.7, 122.6, 121.9, 121.0, 116.0, 108.7, 93.4, 88.5, 85.2, 32.3, 28.4 (3C), 14.6. HRMS (ESI-TOF) m/z calcd. for $C_{26}H_{25}N_2O_2$ $[M+H]^+$ 397.1911 found: 397.1907.

tert-*Butyl 3-ethyl-1-phenyl-5*H-*pyrido[4,3-*b*]indole-5-carboxylate (**9b**).* A Biotage microwave vial was charged with iodinated γ-carboline **8b** (42 mg, 0.10 mmol), phenylboronic acid (17 mg, 0.14 mmol), $Pd(PPh_3)_4$ (6 mg, 0.005 mmol, 5 mol%) and K_2CO_3 (19 mg, 0.14 mmol). Then, a mixture of toluene/methanol (4:1, 2.5 mL) was added, and the vial was placed in a Biotage Initiator system. The reaction mixture was stirred and irradiated with MW at 80 ºC for 20 minutes. The reaction was quenched by

addition of water (2 mL), and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (5:95 EtOAc/hexanes), supplying γ-carboline **9b** as a pale yellow solid (31 mg, 0.08 mmol, 83%). M.p.: 124-125 ºC. IR (KBr) υ_{max} (cm^{-1}) 2975, 1733, 1590, 1370, 1319, 1146, 1126, 861, 751. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.31 (d, *J* = 8.4 Hz, 1H), 8.14 (s, 1H), 7.70 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.57-7.52 (m, 3H), 7.41 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.12 (ddd, *J* = 8.2, 7.3, 1.0 Hz, 1H), 3.06 (q, *J* = 7.6 Hz, 2H), 1.80 (s, 9H), 1.44 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) 161.1, 154.1, 150.8, 145.6, 140.5, 138.7, 129.1 (2C), 128.8, 128.8 (2C), 127.3, 124.2, 123.3, 121.9, 117.5, 116.0, 107.6, 85.0, 32.2, 28.5 (3C), 14.6. HRMS (ESI-TOF) m/z calcd. for $C_{24}H_{25}N_2O_2$ $[M+H]^+$ 373.1911 found: 373.1914.

*3-Ethyl-1-methoxy-5*H-*pyrido[4,3-*b*]indole (**9c**).* An oven-dried Biotage microwave vial was charged with iodinated γ-carboline **8b** (42 mg, 0.10 mmol), $PdCl(allyl)_2$ (1.1 mg, 0.0025 mmol, 2.5 mol%), JohnPhos (1.5 mg, 0.005 mmol, 5 mol%), morpholine (10 mg, 11μL, 0.12 mmol) and *t*-BuONa (13 mg, 0.14 mmol). Under argon atmosphere, a mixture of dry toluene/methanol (4:1, 2.5 mL) was added, and the vial was placed in a Biotage Initiator system. The reaction mixture was stirred and irradiated with MW at 80 ºC for 30 minutes. The residue was diluted with Et_2O and filtered over celite, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (5:95 EtOAc/hexanes), supplying γ-carboline **9c** as a white solid (14 mg, 0.06 mmol, 62%). M.p.: 103-104 ºC. IR (KBr) υ_{max} (cm^{-1}) 3167, 2968, 1609, 1576, 1452, 1359, 1125, 741. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 8.19 (d, *J* = 8.0 Hz, 1H), 8.18 (brs, 1H), 7.40-7.35 (m, 2H), 7.28 (ddd, *J* = 7.9, 5.8, 2.2 Hz, 1H), 6.80 (s, 1H), 4.21 (s, 3H), 2.85 (q, *J* = 7.6 Hz, 2H), 1.36 (t, *J* =

7.6 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) 159.3, 157.7, 146.9, 138.4, 125.0, 122.4, 121.9, 120.8, 110.4, 104.5, 98.4, 53.2, 31.6, 14.1. HRMS (ESI-TOF) m/z calcd. for $C_{14}H_{15}N_2O$ $[M+H]^+$ 227.1179 found: 227.1182.

Supporting Information

^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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References

(1) (a) Cao, R.; Peng, W.; Wang, Z.; Xung, A. Beta-Carboline Alkaloids: Biochemical and Pharmacological Functions. *Curr. Med. Chem*. **2007**, *14*, 479–500. (b) Gupta, A.; Kamble, B.; Nanjan, M. J.; Nanjan, C. M. J. Synthetic Strategies for the Construction of δ-Carbolines: A Chemical Ladder in Search of Novel Drugs. *Curr. Org. Synth.* **2012**, *9*, 377–396. (c) Wadsworth, A. D.; Naysmith, B. J.; Brimble, M. A. A Review of the Synthesis of α-Carbolines. *Eur. J. Med. Chem.* **2015**, *97*, 816–829. (d) Devi, N.; Singh, D.; Kaur, G.; Mor, S.; Putta, V. P. R. K.; Polina, S.; Malakar, C. C.; Singh, V. $In(OTf)_3$ Assisted Synthesis of β-Carboline C-3 Tethered Imidazo[1,2-*a*]azine Derivatives. *New J. Chem.* **2017**, *41*, 1082–1093.

(2) (a) González-Gómez, A.; Domínguez, G.; Pérez-Castells, J. Novel Chemistry of β-Carbolines. Expedient Synthesis of Polycyclic Scaffolds. *Tetrahedron* **2009**, *65*, 3378–

3391. (b) Milen, M.; Ábrányi-Balogh, P. Synthesis of β-Carbolines. *Chem. Heterocycl. Compd.* **2016**, *52*, 996–998.

(3) Alekseyev, R. S.; Kurkin, A. V.; Yurovskaya, M. A. γ-Carbolines and their Hydrogenated Derivatives. 1. Aromatic γ-Carbolines: Methods of Synthesis, Chemical and Biological Properties. *Chem. Heterocycl. Compd.* **2009**, *45*, 889–925.

(4) Ran, X.; Zhao, Y.; Liu, L.; Bai, L.; Yang, C.-Y.; Zhou, B.; Meagher, J. L.; Chinnaswamy, K.; Stuckey, J. A.; Wang, S. Structure-Based Design of γ-Carboline Analogues as Potent and Specific BET Bromodomain Inhibitors. *J. Med. Chem.* **2015**, *58*, 4927−4939.

(5) Jia, T.; Wang, J.; Guo, P.; Yu, J. Characterizations of Cationic γ-Carbolines Binding with Double-Stranded DNA by Spectroscopic Methods and AFM Imaging. *Org. Biomol. Chem.* **2015**, *13*, 1234–1242.

(6) (a) Otto, R.; Penzis, R.; Gaube, F.; Winckler, T.; Appenroth, D.; Fleck, C.; Tränkle, C.; Lehmann, J.; Enzensperger, C. Beta and Gamma Carboline Derivatives as Potential anti-Alzheimer Agents: A Comparison. *Eur. J. Med. Chem.* **2014**, *87*, 63–70. (b) Otto, R.; Penzis, R.; Gaube, F.; Adolph, O.; Föhr, K. J.; Warncke, P.; Robaa, D.; Appenroth, D.; Fleck, C.; Enzensperger, C.; Lehmann, J.; Winckler, T. Evaluation of Homobivalent Carbolines as Designed Multiple Ligands for the Treatment of Neurodegenerative Disorders. *J. Med. Chem.* **2015**, *58*, 6710−6715.

(7) Ibrahim, S. R. M.; Mohamed, G. A.; Zayed, M. F.; Sayed, H. M. Ingenines A and B, Two New Alkaloids from the Indonesian Sponge *Acanthostrongylophora ingens*. *Drug Res.* **2015**, *65*, 361–365.

(8) Naik, P. N.; Khan, A.; Kusurkar, R. S. Intramolecular Diels–Alder Reaction for the Synthesis of Tetracyclic Carbazoles and Isocanthines. *Tetrahedron* **2013**, *69*, 10733–10738.

(9) Mehta, L. K.; Parrick, J.; Payne, F. The elimination of an alkoxy group in the photo-Graebe–Ullmann conversion of 1-(2,5-dialkoxyphenyl)triazolopyridines into carbolines, and the preparation of α-, γ- and δ-carboline quinines. *J. Chem. Soc., Perkin Trans 1* **1993**, 1261–1267.

(10) Humphrey, G. R.; Kuethe, J. T. Practical Methodologies for the Synthesis of Indoles. *Chem. Rev.* **2006**, *106*, 2875–2911.

(11) (a) Pilipenko, A. S.; Uchuskin, M. G.; Trushkov, I. V.; Butin, A. V. A Simple Route to γ-Carbolines and Indolizino[7,6-*b*]indoles. *Tetrahedron* **2015**, *71*, 8786–8790. (b) Dagar, A.; Biswas, S.; Samanta, S. A Catalyst-free, Efficient Green MCR Protocol for Access to Functionalized γ-Carbolines in Water. *RSC Adv.* **2015**, *5*, 52497–52507. (c) Hingane, D. G.; Parekh, N. P.; Khan, A.; Kusurkar, R. S. Efficient Synthetic Route Toward Biologically Active γ-Carboline Derivatives. *Synth. Commun.* **2016**, *46*, 160–164. (d) Chepyshev, S. V.; Lujan-Montelongo, J. A.; Chao, A.; Fleming, F. F. Alkenyl Isocyanide Conjugate Additions: A Rapid Route to γ-Carbolines. *Angew. Chem. Int. Ed.* **2017**, *56*, 4310–4313. (e) Rubio-Presa, R.; Pedrosa, M. R.; Fernández-Rodríguez, M. A.; Arnáiz, F. J.; Sanz, R. Molybdenum-Catalyzed Synthesis of Nitrogenated Polyheterocycles from Nitroarenes and Glycols with Reuse of Waste Reduction Byproduct. *Org. Lett.* **2017**, *19*, 5470−5473.

(12) (a) Zhu, Y.; Shen, X.-R.; Tang, H.-T.; Lin, M.; Zhan, Z.-P. Silver(I)-catalyzed Annulation for the Regioselective Synthesis of *N*-Imino-γ-carbolinium Ylides from Hydrazones of Indole-3-carbonyl Derivatives and Propargylic Alcohols. *Org. Biomol.*

Chem. **2014**, *12*, 9514–9518. (b) Zheng, L.; Bin, Y.; Wang, Y.; Hua, R. Synthesis of Natural Product-like Polyheterocycles via One-Pot Cascade Oximation, C–H Activation, and Alkyne Annulation. *J. Org. Chem.* **2016**, *81*, 8911−8919. (c) Muralirajan, K.; Kuppusamy, R.; Prakash, S.; Cheng, C.-H. Easy Access to 1-Amino and 1-Carbon Substituted Isoquinolines via Cobalt-Catalyzed C−H/N−O Bond Activation. *Adv. Synth. Catal.* **2016**, *358*, 774–783. (d) Rodrigues, N.; Boiaryna, L.; Vercouillie, J.; Guilloteau, D.; Suzenet, F.; Buron, F.; Routier, S. Tandem Silver-Catalyzed Cyclization/Nucleophilic Functionalization of 2-Alkynylindole-3-carbaldehyde Oximes to Afford New 2,4-Disubstituted γ-Carbolines. *Eur. J. Org. Chem.* **2016**, 5024–5036. (e) Chen, A. Y.; Lu, Q.; Fu, Y.; Sarpong, R.; Stoltz, B. M.; Zhang, H. Isocanthine Synthesis via Rh(III)-Catalyzed Intramolecular C–H Functionalization. *J. Org. Chem.* **2018**, *83*, 330–337.

(13) For reviews, see: (a) van Leusen, D.; van Leusen, A. M. Synthetic Uses of Tosylmethyl Isocyanide (TosMIC). *Org. React.* **2001**, *57*, 417–666. (b) Lygin, A. V.; de Meijere, A. Isocyanides in the Synthesis of Nitrogen Heterocycles. *Angew. Chem. Int. Ed.* **2010**, *49*, 9094–9124. (c) Kaur, T.; Wadhwa, P.; Sharma, A. Arylsulfonylmethyl Isocyanides: a Novel Paradigm in Organic Synthesis. *RSC Adv.* **2015**, *5*, 52769–52787.

(14) For recent representative examples, see: (a) Liu, J.; Liu, Z.; Liao, P.; Bi, X. Modular Synthesis of Sulfonyl Benzoheteroles by Silver-Catalyzed Heteroaromatization of Propargylic Alcohols with *p*-Toluenesulfonylmethyl Isocyanide (TosMIC): Dual Roles of TosMIC. *Org. Lett*. **2014**, *16*, 6204-6207. (b) Zhang, X.; Feng, C.; Jiang, T.; Li, Y.; Pan, L.; Xu, X. Expedient and Divergent Tandem One-Pot Synthesis of Benz[*e*]indole and Spiro[indene-1,3′-pyrrole] Derivatives from Alkyne-Tethered Chalcones/Cinnamates and TosMIC. *Org. Lett*. **2015**, *17*, 3576-3579. (c) Lu, S.; Zhu, X.; Li, K.; Guo, Y.-J; Wang, M.-D.; Zhao, X.-M.; Hao, X.-Q; Song, M.-P. Reactivity of

p-Toluenesulfonylmethyl Isocyanide: Iron-Involved C–H Tosylmethylation of Imidazopyridines in Nontoxic Media. *J. Org. Chem*. **2016**, *81*, 8370-8377. (d) Kadari, L.; Palakodety, R. K.; Yallapragada, L. P. Iodine-Catalyzed Facile Approach to Sulfones Employing TosMIC as a Sulfonylating Agent. *Org. Lett*., **2017**, *19*, 2580-2583. (e) Wang, L.; Studer, A. 1-Trifluoromethylisoquinolines from α-Benzylated Tosylmethyl Isocyanide Derivatives in a Modular Approach. *Org. Lett*., **2017**, *19*, 5701–5704.

(15) (a) Mendiola, J.; Minguez, J. M.; Alvarez-Builla, J.; Vaquero, J. J. Reaction of 2-Bromomethylazoles and TosMIC: A Domino Process to Azolopyrimidines. Synthesis of Core Tricycle of the Variolins Alkaloids. *Org. Lett*. **2000**, *2*, 3253–3256. (b) Baeza, A.; Mendiola, J.; Burgos, C.; Alvarez-Builla, J.; Vaquero, J. J. Heterocyclizations with Tosylmethyl Isocyanide Derivatives. A New Approach to Substituted Azolopyrimidines. *J. Org. Chem.* **2005**, *70*, 4879–4882. (c) Coppola, A.; Sánchez-Alonso, P.; Sucunza, D.; Burgos, C.; Alajarín, R.; Alvarez-Builla, J.; Mosquera, M. E. G.; Vaquero, J. J. Remote Aryl Cyanation via Isocyanide–Cyanide Rearrangement on Tosylmethyl Isocyanide Derivatives. *Org. Lett*. **2013**, *15*, 3388–3391.

(16) (a) Coppola, A.; Sucunza, D.; Burgos; C.; Vaquero, J. J. Isoquinoline Synthesis by Heterocyclization of Tosylmethyl Isocyanide Derivatives: Total Synthesis of Mansouramycin B. *Org. Lett.* **2015**, *17*, 78−81. (b) Gutiérrez, S.; Coppola, A.; Sucunza, D.; Burgos; C.; Vaquero, J. J. Synthesis of 1-Substituted Isoquinolines by Heterocyclization of TosMIC Derivatives: Total Synthesis of Cassiarin A. *Org. Lett.* **2016**, *18*, 3378−3381.

(17) Barluenga, J.; Valdés, C. Five-Membered Heterocycles: Indole and Related Systems. In *Modern Heterocyclic Chemistry*; Alvarez-Builla, J.; Vaquero, J. J.; Barluenga, J., Eds.; Wiley-VCH: Weinheim, Germany, 2011; Vol. 1, pp 377−531.

(18) Freed, J. D.; Hart, D. J.; Magomedov, N. A. Trapping of the Putative Cationic Intermediate in the Morin Rearrangement with Carbon Nucleophiles. *J. Org. Chem.* **2001**, *66*, 839–852.

(19) Sisko, J.; Mellinger, M.; Sheldrake, P. W.; Baine, N. H. α-Tosylbenzyl Isocyanide. *Org. Synth.* **2000**, *77*, 198–205.