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A convenient synthesis of 3,4-difunctionalized δ-carbolines

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Abstract—An efficient and direct preparation of functionalized δ-carbolines, via a ring closure reaction between the appropriate indole amine and a masked 1,3-dicarbonyl compound is described. This method afforded new 3-substituted δ-carbolines and these products were subjected to *ortho*-lithiation experiments. Various 3,4-disubstituted δ-carbolines were obtained in acceptable yields.

1. Introduction

A lot of natural alkaloids belong to the carboline series (mainly β-carboline) and represent a pharmacologically important class of compounds displaying a wide range of activities.[1] In connection with our studies of the synthesis and functionalization of α- and γ-carboline rings,[2] we found it interesting to synthesize 3-substituted δ-carbolines designed for a study of the lithiation reaction with the view to obtain 3,4-disubstituted products in this series.

2. Results and discussion

2.1. Synthesis of 3-substituted δ-carbolines

Although some synthetic approaches have been reported,[3] there is still need of new and efficient routes to the functionalized δ-carboline ring. We report here our results concerning a new synthetic method affording the 3-functionalized pyrido[3,2-*b*]indole system starting from readily available compounds.

In a previous paper, we described the synthesis of α-carbolines via reaction of 2-tosylaminoindole with a protected 1,3-dicarbonyl compound.[4] A valuable strategy would consist in applying the same method to 3-aminoindole derivatives. The gram-scale synthesis of 3-aminoindole derivatives is rather difficult because the indole amines are known to be unstable.[5] Moreover, convenient syntheses of 3-acetylaminoindole are scarce.[5] For this reason, we initiated the synthesis of δ-carboline **4** from oximes **1a**–**b** obtained from the corresponding ketones and NH_2OH, HCl according to the procedure previously described.[6] In our hands, very good yields (79% for **1b**) were obtained after a crystallization from $MeOH/H_2O$ instead of diisopropyl ether. The rearrangement of the oximes in refluxing acetic acid provided the 3-acylaminoindoles **2a**–**b** (Scheme 1)[6] which were used after crystallization or short filtration on silica gel with no further purification. The so-obtained amine derivatives **2a**–**b** were reacted with the masked 1,3-dicarbonyl compound **3**[7] in an easy one pot process. The new 3-substituted δ-carboline **4** was thus obtained in a 66% yield from the indole amine derivative **2b**. The intermediate tricyclic structure obtained with **2a** was reacted with CH_3I/NaH in anhydrous THF at 0°C to provide the 3-functionalized pyrido[3,2-*b*]indole system **4** in a 20% overall yield.

Starting from δ-carboline **4**, the nitrile group was converted into an amide moiety. This transformation was achieved by classical hydrolysis in alkaline medium containing hydrogen peroxide, leading to carboxamide **5** in a 70% yield. We also synthesized carboxylic acid **6** in a 64% yield by alkaline hydrolysis. Carboxylic acid **6** was reacted with thionyl chloride and subsequent treatment with diisopropylamine led to compound **7a** possessing as *ortho*-directing metalation group a *N*,*N*-diisopropylcarboxamide moiety in a 70% yield. Compound **7b** was isolated as a side-product of the reaction with thionyl chloride (ca. 15% by ^1H NMR analysis of the crude product). To avoid this undesired side-reaction, we used oxalyl chloride instead of thionyl chloride during the synthesis of compound **8**. Thus, the acyl chloride was obtained and reacted with *tert*-butylamine to give compound **8** in a 33% overall yield. Finally, to obtain amino derivatives as *ortho*-directing metalation groups, we reacted the carboxylic acid **6** with diphenylphosphoryl azide leading to the intermediate carbonyl azide which was then heated to reflux of *tert*-butyl alcohol. These reactions afforded carbamate **9** in a 32% yield.

Keywords: indoles; cyclization; polycyclic heterocyclic compounds; polycyclic aromatic compounds; nitrogen heterocycles; regioselection; lithiation.

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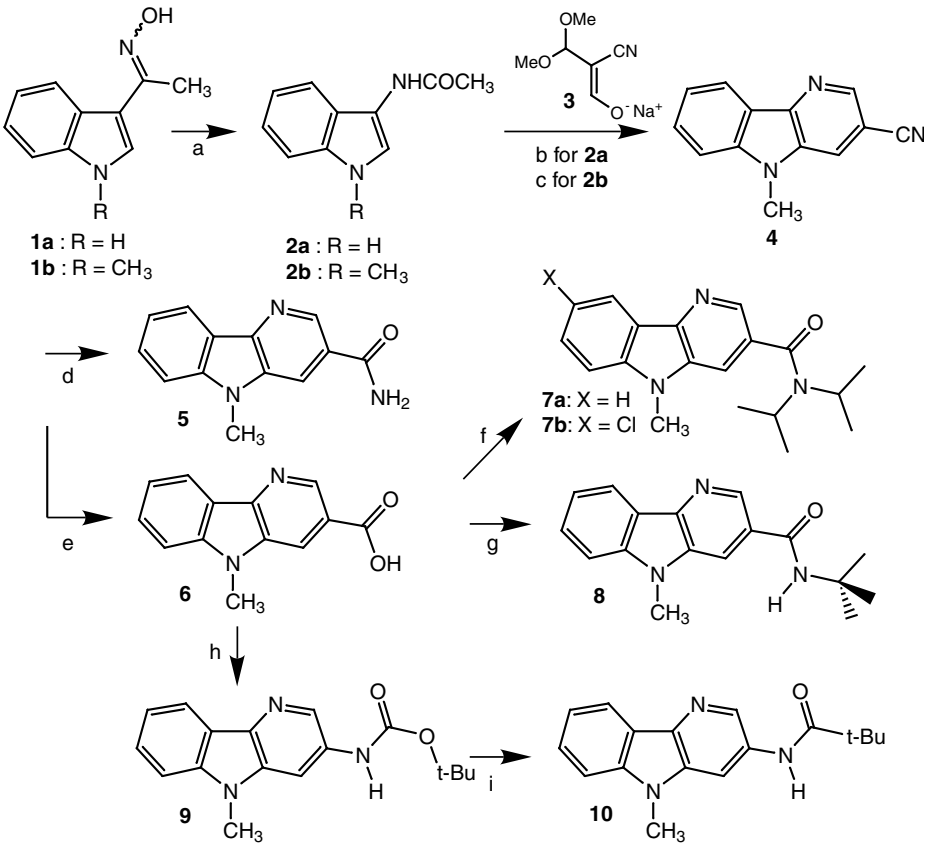


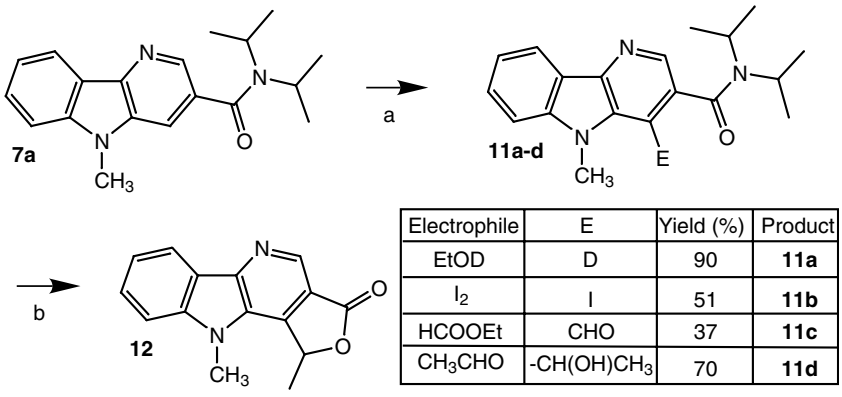
Scheme 1. (a) CH_3COOH, reflux, 2 h; (b) HCl, MeOH, 70°C, 20 h; NaH, CH_3I, 0°C, 1 h, anhydrous THF (20%); (c) HCl, MeOH, 70°C, 20 h (66%); (d) NaOH, H_2O_2, EtOH, 30°C, 18 h (70%); (e) NaOH, EtOH, reflux, 20 h (64%); (f) $SOCl_2$, reflux, 3 h; *i*-Pr_2NH, CH_2Cl_2, rt, 24 h (70%); (g) $(COCl)_2$, cat. DMF, CH_2Cl_2, rt, 90 min; *t*-$BuNH_2$, CH_2Cl_2, rt, 24 h (33%); (h) DPPA, Et_3N, *t*-BuOH, reflux, 24 h (32%); (i) H_2SO_4 20%, reflux, 4 h; $(CH_3)_3CCOCl$, Et_3N, THF, rt, 4 h (61%).

Hydrolysis of **9** under acidic conditions proceeded smoothly in good yield and the resulting amine was quenched with pivaloyl chloride leading to the pivalamide **10**.

2.2. Lithiation reaction with carboxamides 7a and 8

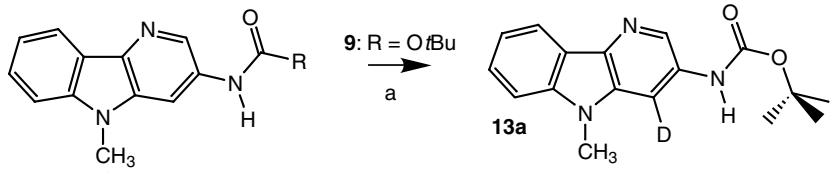
We first studied the metalation reaction of carboxamide **7a** (Scheme 2), with lithium 2,2,6,6-tetramethylpiperidide (LTMP) under the conditions used in the pyridine series.[8] This compound was cleanly lithiated and quenching of the intermediate lithio species with ethanol-*d* afforded the 4-deutero compound **11a**. As expected, analysis of the ^1H NMR spectra of **11a** compared to that of **7a** showed that deuterium incorporation had occurred in the 4-position of the pyridine ring of the δ-carboline system (the chemical shifts of H_2 and H_4 of compound **7a** were assigned with a NOE experiment: NOE observed between H_4 and NCH_3). In order to confirm the synthetic interest of this new lithiation reaction, we quenched the reaction medium with several electrophiles to obtain δ-carbolines **11b–d** in moderate to good yields. Acid hydrolysis of the carboxamide **11d** gave the lactone **12** with a non-optimized yield of 66%.

For the *tert*-butylcarboxamide δ-carboline **8**, we used *tert*-butyllithium as a metalation reagent in order to avoid any addition reaction.[9] But, whatever the conditions (−70 or



Electrophile	E	Yield (%)	Product
EtOD	D	90	**11a**
I_2	I	51	**11b**
HCOOEt	CHO	37	**11c**
CH_3CHO	-CH(OH)CH_3	70	**11d**

Scheme 2. (a) LTMP, anhydrous THF, −70°C, 2 h; Electrophile; H_2O/EtOH (37–90%); (b) EtOH, CH_3COOH, reflux, 4 h (66%).



Electrophile	E	Yield (%)	Product
EtOD	D	74	**14a**
I_2	I	17	**14b**
HCOOEt	CHO CH=CH	35	**14c**
DMF	CHO	25	**14d**

Scheme 3. (a) 2.5 equiv. *tert*-BuLi, TMEDA, anhydrous THF, −10°C, 2 h; EtOD; H_2O/EtOH (70%); (b) 9 equiv. *tert*-BuLi, TMEDA, anhydrous THF, −40°C, 6 h; Electrophile; H_2O/EtOH (17–74%).

−40 or −10°C, 2 h) with 2.5 equiv. of *tert*-butyllithium in anhydrous THF and quenching with ethanol-*d*, we recovered only δ-carboline **8**.

2.3. Lithiation reaction with amine derivatives 9 and 10

For carbamate **9**, our experience in the α- and γ-carboline series[2a,c] led us to use *tert*-butyllithium as a metalation reagent.[10] We were first pleased to isolate the 4-deutero compound **13a** (Scheme 3) in a good yield (70% of deuterium incorporation). The ^{1}H NMR spectrum of **13a** displayed no signal for the H-4 proton as confirmed by a NOE experiment performed on carbamate **9** (NOE observed between H-4 and NCH_3). But quenching of the lithio intermediate with other electrophiles (I_2 or DMF) was disappointing since no expected compounds (<10%) were observed by ^{1}H NMR of the crude products. We mainly recovered the unreacted carbamate **9** after hydrolysis of the reaction mixture.

In the case of pivalamide **10**, the metalation reaction was first carried out under the same conditions as those used in the α-carboline series[2a] (5 equiv. *tert*-BuLi, TMEDA, −70°C, 6 h). But, quenching of the lithio species with ethanol-*d* did not afford the expected 4-deutero compound **14a** since only unreacted pivalamide **10** was recovered. However, at −40°C instead of −70°C, under the same conditions of reaction, we obtained 56% of deuterium incorporation at the 4-position. This last result was interesting but the yield of the lithiation reaction was unfortunately too low to have a real synthetic interest. In order to improve this yield, we decided to use these last conditions of reaction (5 equiv. *tert*-BuLi, TMEDA, −40°C) but by adding now 4 more equivalents of *tert*-butyllithium and TMEDA after 4 h of reaction. The mixture was stirred for an additional 2 h and ethanol-*d* was introduced to give 74% of deuterium incorporation. We used other electrophiles to obtain various 3,4-disubstituted δ-carbolines (Scheme 3). Reaction of the lithio species gave the expected iodo derivative **14b** whilst ethyl formate gave surprisingly **14c** instead of the expected aldehyde **14d**. We are now performing other experiments in order to explain this amazing reaction. Finally, the initially expected aldehyde **14d** was obtained in a 25% yield by using DMF as the electrophile.

3. Conclusion

In summary, a novel synthetic pathway has been developed to obtain new 3-substituted δ-carbolines. Compounds **7**–**10** are interesting compounds since they possess different *ortho*-directing metalation groups. Studies on the lithiation reaction afforded various 3,4-disubstituted derivatives in this series with the *N*,*N*-diisopropylcarboxamide and the pivalamido *ortho*-directing lithiation groups. With the pivalamido directing metalation group, an unusual reaction with ethyl formate as electrophile leading to a *trans*-α,β-unsaturated aldehyde moiety is reported.

4. Experimental

4.1. General

All reagents were purchased from commercial sources and used as received. Solvents were generally dried and distilled prior to use. Reactions were monitored by thin-layer chromatography on E. Merck silica gel $60F_{254}$ (0.2 mm) precoated aluminum foils. Column chromatography: E. Merck silica gel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or in DMSO-d_6. Chemical shifts (δ) are given in ppm relative to Me_4Si as internal standard, *J* values in Hz. IR spectra were recorded on a Perkin-Elmer 1750 FT-IR instrument. Low resolution mass spectrometry was carried out on Micromass Platform, Masslab 20-250 using the atmospheric pressure chemical ionization method ($APCI^-$ and $APCI^+$).

4.1.1. 5-Methyl-[5*H*]-pyrido[3,2-*b*]indole-3-carbonitrile (4). A mixture of acetylated amine **2b**[6] (200 mg, 1.06 mmol), 3,3-dimethoxy-2-formyl propionitrile sodium salt **3**[7] (376 mg, 2.28 mmol) and concentrated hydrochloric acid (0.24 mL) in methanol (1.5 mL) was heated at 70°C for 20 h. The solvent was then removed under reduced pressure and a small amount of water was added. The product was filtered, dried and purified by flash chromatography (silica gel, CH_2Cl_2 to CH_2Cl_2/AcOEt 9:1) to yield 144.5 mg (66%) of **4**. Mp=220°C. ^{1}H NMR (360.14 MHz, $CDCl_3$) δ 3.89 (s, 3H, NCH_3), 7.39 (ddd, *J*=7.8, 7.2, 0.9 Hz, 1H, H-8), 7.49 (m, 1H, H-6), 7.68 (ddd, *J*=8.4, 7.2, 1.2 Hz, 1H, H-7), 7.90 (d, *J*=1.8 Hz, 1H, H-4), 8.39 (m, 1H, H-9), 8.76 (d,

J=1.8 Hz, 1H, H-2). ^{1}H NMR (360.14 MHz, DMSO-d_6) δ 3.95 (s, 3H, NCH_3), 7.37 (m, 1H, H-8), 7.71 (m, 1H, H-7), 7.77 (m, 1H, H-6), 8.28 (m, 1H, H-9), 8.68 (d, J=1.8 Hz, 1H, H-4), 8.82 (d, J=1.8 Hz, 1H, H-2). ^{13}C NMR (50.30 MHz, $CDCl_3$) δ 29.2, 104.4, 109.3, 118.1, 118.3, 121.0, 121.7, 129.9, 132.4, 143.2, 143.5, 144.1. IR (KBr): 2226, 1627 cm^{-1}. LRMS APCI$^+$ m/z 208.1 ([M+H]$^+$, 100). Anal. Calcd for $C_{13}H_9N_3$ (207.22): C, 75.35; H, 4.38; N, 20.28. Found: C, 75.33; H, 4.41; N, 20.02.

4.1.2. 5-Methyl-[5*H*]-pyrido[3,2-*b*]indole-3-carboxamide (5). A mixture of nitrile **4** (258.9 mg, 1.25 mmol), 30% hydrogen peroxide (0.64 mL, 6.3 mmol), aqueous 3N sodium hydroxide (0.167 mL, 0.5 mmol) in ethanol (13 mL) was stirred at 30°C for 18 h. The resulting mixture was acidified with 1N sulphuric acid, the precipitated material was filtered and dried to afford the crude amide **5**. This compound was purified by recrystallization from ethanol/water (1:1) to yield 197 mg (70%) of **5**. Mp=281–282°C. ^{1}H NMR (360.14 MHz, DMSO-d_6) δ 4.00 (s, 3H, NCH_3), 7.38 (m, 1H, H-8), 7.71 (m, 1H, H-7), 7.74 (broad s, 1H, NH), 7.80 (m, 1H, H-6), 8.33 (m, 2H, H-4 and NH), 8.73 (broad s, 1H, H-4), 9.06 (broad s, 1H, H-2). ^{13}C NMR (50.30 MHz, DMSO-d_6) δ 29.0, 110.2, 116.9, 119.1, 120.4, 121.0, 126.1, 129.7, 133.9, 136.7, 137.2, 142.6, 165.4. IR (KBr): 1675, 1625 cm^{-1}. LRMS APCI$^+$ m/z 226.1 ([M+H]$^+$, 100). Anal. Calcd for $C_{13}H_{11}N_3O$ (225.25): C, 69.32; H, 4.92; N, 18.65. Found: C, 69.31; H, 4.88; N, 18.52.

4.1.3. 5-Methyl-[5*H*]-pyrido[3,2-*b*]indole-3-carboxylic acid (6). A mixture of nitrile **4** (143 mg, 0.69 mmol), 25% aqueous sodium hydroxide (0.34 mL) in ethanol (1.5 mL) was refluxed with stirring for 20 h. After cooling, the reaction mixture was acidified with diluted hydrochloric acid. The precipitate was filtered, dried and purified by recrystallization from EtOH/water (9:1) to yield 100.3 mg (64%) of **6**. Mp=309–310°C. ^{1}H NMR (360.14 MHz, DMSO-d_6) δ 3.97 (s, 3H, NCH_3), 7.33 (m, 1H, H-8), 7.66 (ddd, J=8.2, 7.6, 1.2 Hz, 1H, H-7), 7.74 (m, 1H, H-6), 8.26 (m, 1H, H-9), 8.51 (d, J=1.8 Hz, 1H, H-4), 9.00 (d, J=1.8 Hz, 1H, H-2). ^{13}C NMR (50.30 MHz, DMSO-d_6) δ 28.6, 109.7, 117.0, 119.5, 120.0, 120.2, 122.1, 128.4, 132.7, 141.7, 142.4, 142.9, 166.7. IR (KBr): 3058, 2933, 2564, 1715, 1626 cm^{-1}. LRMS APCI$^+$ m/z 227.1 ([M+H]$^+$, 100). Anal. Calcd for $C_{13}H_{10}N_2O_2$ (226.23): C, 69.01; H, 4.46; N, 12.39. Found: C, 68.71; H, 4.40; N, 12.12.

4.1.4. *N*,*N*-Diisopropyl-5-methyl-[5*H*]-pyrido[3,2-*b*]indole-3-carboxamide (7a). A mixture of freshly distilled thionyl chloride (2 mL, 27.5 mmol) and 5-methyl-[5*H*]-pyrido[3,2-*b*]indole-3-carboxylic acid **6** (90 mg, 0.4 mmol) was heated to reflux for 3 h. The excess of thionyl chloride was removed under reduced pressure and then co-distilled with toluene (4 mL). The residue was dissolved in dichloromethane (5 mL) and diisopropylamine (0.7 mL, 9.6 mmol) was added at 0°C. The mixture was stirred at rt for 24 h and hydrolyzed with water (5 mL). The aqueous layer was extracted with dichloromethane. The organic layers were collected, dried on magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography (silica gel, hexane/AcOEt: gradient from 3:2 to 1:1) afforded 86 mg (70%) of carboxamide **7a**. Mp=202°C. ^{1}H NMR (360.14 MHz, $CDCl_3$) δ 1.0–1.9 (m, 12H, CH_3 *i*-Pr), 3.5–4.1 (m, 5H, CH *i*-Pr and NCH_3), 7.34 (ddd, J=7.7, 7.1, 0.9 Hz, 1H, H-8), 7.46 (m, 1H, H-6), 7.60 (ddd, J=8.3, 7.1, 1.1 Hz, 1H, H-7), 7.73 (d, J=1.7 Hz, 1H, H-4), 8.37 (m, 1H, H-9), 8.51 (d, J=1.7 Hz, 1H, H-2). The chemical shifts of H_2 and H_4 were assigned with a NOE experiment (NOE=6.3% between H_4 and NCH_3). ^{13}C NMR (50.30 MHz, $CDCl_3$) δ 20.8, 29.0, 108.9, 113.6, 120.2, 121.0, 121.5, 128.2, 130.8, 133.9, 138.3, 141.9, 142.4, 169.4. IR (KBr): 1618 cm^{-1}. LRMS APCI$^+$ m/z 310.2 ([M+H]$^+$, 100). Anal. Calcd for $C_{19}H_{23}N_3O$ (309.41): C, 73.76; H, 7.49; N, 13.58. Found: C, 74.01; H, 7.41; N, 13.70. Compound **7b** was isolated for analysis as a white solid. Mp=254°C. ^{1}H NMR (200.00 MHz, $CDCl_3$) δ 1.1–1.9 (m, 12H, CH_3 *i*-Pr), 3.5–4.1 (m, 5H, CH *i*-Pr and NCH_3), 7.40 (d, J=8.6 Hz, 1H, H-6), 7.56 (dd, J=8.6, 2.0 Hz, 1H, H-7), 7.75 (d, J=1.6 Hz, 1H, H-4), 8.35 (d, J=2.0 Hz, 1H, H-9), 8.52 (d, J=1.6 Hz, 1H, H-2). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.2, 29.7, 110.5, 114.6, 121.1, 123.0, 126.4, 128.8, 131.9, 134.9, 139.1, 141.1, 141.2, 169.5. IR (KBr): 1619 cm^{-1}. LRMS APCI$^+$ m/z 346.2 ([M+H]$^+$, 28), 344.2 ([M+H]$^+$, 92). Anal. Calcd for $C_{19}H_{22}ClN_3O$ (343.85): C, 66.37; H, 6.45; N, 12.22. Found: C, 66.41; H, 6.41; N, 12.56.

4.1.5. 3-(*N*-*tert*-Butylcarboxamido)-5-methyl-[5*H*]-pyrido-[3,2-*b*]indole-3-carboxamide (8). A mixture of carboxylic acid **6** (250 mg, 1.1 mmol) and oxalyl chloride (240 μL, 2.76 mmol) in 6 mL dichloromethane with two drops of DMF was stirred at rt for 90 min. The solvent was removed under reduced pressure and the residue was dissolved in 12 mL of dichloromethane. The resulting solution was cooled at 0°C and *tert*-butylamine (465 μL, 4.4 mmol) was added. After 24 h stirring at rt, the solvent was evaporated. Water and ethyl acetate were added and the precipitate was filtered. The organic layer was dried on magnesium sulfate, filtered and evaporated. Purification by flash chromatography (silica gel, hexane/AcOEt 3:2) afforded 102 mg (33%) of **8** as a white solid. Mp=214°C. ^{1}H NMR (250.00 MHz, $CDCl_3$) δ 1.58 (s, 9H, CH_3 *t*-Bu), 3.93 (s, 3H, NCH_3), 6.18 (br s, 1H, NH), 7.39 (ddd, J=8.0, 7.1, 0.9 Hz, 1H, H-8), 7.51 (m, 1H, H-6), 7.66 (ddd, J=8.4, 7.1, 1.2 Hz, 1H, H-7), 8.25 (d, J=1.8 Hz, 1H, H-4), 8.43 (m, 1H, H-9), 8.81 (d, J=1.8 Hz, 1H, H-2). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.3, 29.5, 52.5, 109.4, 115.3, 120.5, 121.5, 121.6, 128.3, 129.0, 134.0, 139.5, 143.1, 143.6, 166.5. IR (KBr): 3430, 3349, 1631, 1534 cm^{-1}. LRMS APCI$^+$ m/z 282.3 ([M+H]$^+$, 100). Anal. Calcd for $C_{17}H_{19}N_3O$ (281.34): C, 72.57; H, 6.81; N, 14.94. Found: C, 72.47; H, 6.95; N, 14.88.

4.1.6. 3-(*tert*-Butyloxycarbonylamino)-5-methyl-[5*H*]-pyrido[3,2-*b*]indole (9). A mixture of 5-methyl-[5*H*]-pyrido[3,2-*b*]indole-3-carboxylic acid **6** (0.8 g, 3.54 mmol), triethylamine (1.25 mL, 9.0 mmol), diphenylphosphoryl azide (1.61 mL, 7.45 mmol) and *tert*-butyl alcohol (14 mL) was heated to reflux for 24 h. The solvent was removed and water was added. The aqueous layer was extracted with ethyl acetate. The organic layers were collected, washed with water, with diluted $NaHCO_3$, dried on magnesium sulfate, filtered and concentrated. Purification by flash chromatography (silica gel, hexane/AcOEt 13:7) afforded 341 mg (32%) of **9** as a white solid. Mp=199–201°C. ^{1}H NMR (360.14 MHz, $CDCl_3$) δ 1.55

(s, 9H, *t*-Bu), 3.79 (s, 3H, NCH_3), 7.12 (broad s, 1H, NH), 7.28 (ddd, *J*=7.7, 7.1, 1.1 Hz, 1H, H-8), 7.37 (m, 1H, H-6), 7.50 (ddd, *J*=8.2, 7.1, 1.4 Hz, 1H, H-7), 8.18 (d, *J*=2.0 Hz, 1H, H-2), 8.22–8.32 (m, 2H, H-9 and H-4). The chemical shifts of H_2 and H_4 were assigned with a NOE experiment (NOE=2.5% between H_4 and NCH_3). ^{13}C NMR (50.30 MHz, $CDCl_3$) δ 28.3, 28.9, 29.0, 105.2, 108.6, 119.8, 120.1, 121.8, 126.7, 132.7, 132.8, 134.7, 137.2, 141.9, 153.0. IR (KBr): 1721 cm^{-1}. LRMS APCI$^+$ *m/z* 298.2 ($[M+H]^+$, 15), 242.1 ($[M-tBu]^+$, 60). Anal. Calcd for $C_{17}H_{19}N_3O_2$ (297.36): C, 68.67; H, 6.44; N, 14.13. Found: C, 69.02; H, 6.41; N, 14.45.

4.1.7. 3-(*tert*-Butylcarbonylamino)-5-methyl-[5*H*]-pyrido-[3,2-*b*]indole (10). A mixture of compound **9** (367 mg, 1.24 mmol) and 20% sulfuric acid (19 mL) was heated to reflux for 4 h. After cooling to rt, the mixture was poured on crushed ice and 20% aqueous ammonia solution (15 mL). The pH was adjusted to 8 with 20% aqueous ammonia solution and the solution was extracted with dichloromethane. Standard workup afforded 180 mg of the crude amine. ^1H NMR (250.00 MHz, $CDCl_3$) δ 3.59 (s, 3H, NCH_3), 3.85 (broad s, 2H, NH_2), 6.76 (d, *J*=2.3 Hz, 1H, H-4), 7.23–7.29 (m, 2H, H-6 and H-8), 7.44 (m, 1H, H-7), 8.04 (d, *J*=2.3 Hz, 1H, H-2), 8.24 (m, 1H, H-9). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 29.1, 100.9, 108.8, 119.8, 120.0, 122.8, 126.1, 131.8, 134.6, 136.1, 141.3, 141.7. LRMS APCI$^+$ *m/z* 198.0 ($[M+H]^+$, 100). The crude amine was dissolved in 2.5 mL of anhydrous THF and triethylamine (191 μL, 1.37 mmol). The mixture was cooled (0°C) and pivaloyl chloride (169 μL, 1.37 mmol) was slowly added. After 4 h stirring at rt, water was added and the solution was extracted three times with ethyl acetate. The organic layer was dried on magnesium sulfate, filtered and evaporated under reduced pressure. Purification by flash chromatography (silica gel, hexane/AcOEt 1:1) afforded 211 mg (61%) of **10** as a white solid. Mp=239°C. ^1H NMR (250.00 MHz, $CDCl_3$) δ 1.41 (s, 9H, *t*-Bu), 3.75 (s, 3H, NCH_3), 7.28 (m, 1H, H-8), 7.37 (m, 1H, H-6), 7.53 (m, 1H, H-7), 7.96 (br s, 1H, NH), 8.27 (d, *J*=2.1 Hz, 1H, H-2), 8.28 (m, 1H, H-9), 8.55 (d, *J*=2.1 Hz, 1H, H-4). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 28.0, 29.3, 40.3, 107.7, 109.2, 120.3, 120.6, 122.1, 127.4, 132.6, 134.2, 134.8, 138.3, 142.5, 178.0. IR (KBr): 3436, 1654 cm^{-1}. LRMS APCI$^+$ *m/z* 282.1 ($[M+H]^+$, 15), 226.3 ($[M-tBu]^+$, 5). Anal. Calcd for $C_{17}H_{19}N_3O$ (281.34): C, 72.57; H, 6.81; N, 14.94. Found: C, 72.37; H, 7.02; N, 14.95.

4.2. General procedure for the metalation reaction of diisopropylcarboxamido-δ-carboline (7a) and quenching with various electrophiles

A solution of LTMP was prepared in a 5 mL flask flushed with argon from *n*-butyllithium (1.6 M solution in hexanes, 0.98 mL, 1.3 mmol), and 2,2,6,6-tetramethylpiperidine (0.22 mL, 1.3 mmol) in anhydrous THF (2 mL) at −70°C. The resulting solution was stirred at −20°C for 15 min before use. To a solution of **7a** (0.1 g, 0.33 mmol) in anhydrous THF (8 mL) previously cooled to −70°C, the solution of LTMP was added slowly at −70°C. After 2 h stirring at this temperature, the electrophile was added and stirring was continued at −70°C for 2 h. After hydrolysis with ethanol/water (1/1 mixture, 5 mL), the aqueous layer was extracted three times with dichloromethane. The organic layer was dried on magnesium sulfate, filtered and evaporated.

4.2.1. 4-Deutero-3-(*N*,*N*-diisopropylcarboxamido)-5-methyl-[5*H*]-pyrido[3,2-*b*]indole (11a). According to the general procedure, the electrophile was EtOD (0.5 mL, 8.5 mmol). The product was purified by flash chromatography on silica gel (hexane/AcOEt: gradient from 3:2 to 1:1). The spectral characteristics were identical to those of compound **7a** but no signal (90% of deuterium incorporation by integration) was observed for H-4 in the ^1H NMR spectrum. LRMS APCI$^+$ *m/z* 311.2 ($[M+H]^+$, 100).

4.2.2. 3-(*N*,*N*-Diisopropylcarboxamido)-4-iodo-5-methyl-[5*H*]-pyrido[3,2-*b*]indole (11b). According to the general procedure, the electrophile was iodine (0.33 g, 1.3 mmol) dissolved in THF (2.5 mL) at −20°C. Hydrolysis was carried out with a 10% aqueous solution of sodium thiosulfate. The product was purified by flash chromatography on silica gel (cyclohexane/AcOEt 7:3) to yield 72.1 mg (51%) of **11b** as a white solid. Mp=206–207°C. ^1H NMR (200.00 MHz, $CDCl_3$) δ 1.10, 1.20, 1.62 and 1.65 (4×d, *J*=6.6 Hz, 4×3H, CH_3 *i*-Pr), 3.5–3.7 (m, 2H, CH *i*-Pr), 4.20 (s, 3H, NCH_3), 7.32 (m, 1H, H-8), 7.40 (m, 1H, H-6), 7.56 (m, 1H, H-7), 8.15 (s, 1H, H-2), 8.30 (m, 1H, H-9). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.5, 21.2, 32.3, 46.8, 52.1, 82.4, 109.8, 120.9, 121.3 (×2), 129.0, 134.7, 137.6, 138.4, 141.9, 143.7, 169.3. IR (KBr): 1630 cm^{-1}. LRMS APCI$^+$ *m/z* 436.3 ($[M+H]^+$, 8), 308.3 ($[M-I]^+$, 93). Anal. Calcd for $C_{19}H_{22}IN_3O$ (435.29): C, 52.42; H, 5.10; N, 9.65. Found: C, 52.63; H, 4.95; N, 9.65.

4.2.3. 3-(*N*,*N*-Diisopropylcarboxamido)-5-methyl-[5*H*]-pyrido[3,2-*b*]indole-4-carboxaldehyde (11c). According to the general procedure, the electrophile was ethyl formate (106 μL, 1.3 mmol). The product was purified by flash chromatography on silica gel (cyclohexane/AcOEt 7:3) to yield 40.2 mg (37%) of **11c** as a yellow solid. Mp=152°C. ^1H NMR (200.00 MHz, $CDCl_3$) δ 1.16 and 1.63 (2×d, *J*=6.6 Hz, 2×6H, CH_3 *i*-Pr), 3.5–3.8 (m, 2H, CH *i*-Pr), 4.03 (s, 3H, NCH_3), 7.39 (m, 1H, H-8), 7.50 (m, 1H, H-6), 7.64 (m, 1H, H-7), 8.35 (m, 1H, H-9), 8.45 (s, 1H, H-2), 10.6 (s, 1H, CHO). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 21.0, 34.7, 46.9, 52.2, 110.1, 121.4, 121.7, 121.8, 122.8, 129.6, 131.0, 132.2, 138.0, 144.2, 145.6, 167.6, 190.6. IR (KBr): 1684, 1627 cm^{-1}. LRMS APCI$^+$ *m/z* 338.2 ($[M+H]^+$, 100). Anal. Calcd for $C_{20}H_{23}N_3O_2$ (337.40): C, 71.19; H, 6.87; N, 12.45. Found: C, 70.88; H, 6.78; N, 12.59.

4.2.4. 3-(*N*,*N*-Diisopropylcarboxamido)-4-(1-hydroxyethyl)-5-methyl-[5*H*]-pyrido[3,2-*b*]indole (11d). According to the general procedure, the electrophile was acetaldehyde (0.75 mL, 13.4 mmol). The product was purified by two successive flash chromatography on silica gel (cyclohexane/AcOEt: gradient from 7:3 to 3:2). The solid was washed several times with pentane to yield 80 mg (70%) of **11d** as a white solid. Mp=115°C. ^1H NMR (200.00 MHz, $CDCl_3$) δ 0.89–0.93, 1.13–1.30 and 1.59–1.75 (m, 15H, CH_3 *i*-Pr and CH_3), 3.51–4.24 (m, 5H, CH *i*-Pr and NCH_3), 5.53–5.72 (m, 1H, CH), 7.27–7.43 (m, 2H, H-8 and H-6), 7.55–7.61 (m, 1H, H-7), 8.23–8.34 (m, 2H, H-2 and H-9). IR (KBr): 3420, 1608 cm^{-1}. LRMS APCI$^+$

m/z 354.3.3 ([M+H]$^+$, 20), 336.2 ([M+H−H_2O]$^+$, 100). Anal. Calcd for $C_{21}H_{27}N_3O_2$ (353.45): C, 71.36; H, 7.70; N, 11.89. Found: C, 71.01; H, 7.77; N, 11.61.

4.2.5. (*R*,*S*)-10-Methylfuro[3,4-*c*]-(5-methyl-[5*H*]-pyrido-[3,2-*b*]indole)-2[10*H*]-one (12). A solution of compound **11d** (75 mg, 0.21 mmol) and acetic acid (0.4 mL, 7 mmol) in 10 mL of EtOH was heated to reflux for 4 h. The solvent was evaporated and 10 mL of toluene was added. The solvent was again evaporated under reduced pressure. Purification by flash chromatography (silica gel, hexane/AcOEt 11:9) afforded 35.3 mg (66%) of lactone **12**. Mp=227°C. ^{1}H NMR (250.00 MHz, $CDCl_3$) δ 1.85 (d, *J*=6.6 Hz, 3H, CH_3), 4.00 (s, 3H, NCH_3), 6.00 (q, *J*=6.6 Hz, 1H, CH), 7.42 (ddd, *J*=7.9, 7.1, 0.8 Hz, 1H, H-8), 7.49 (m, 1H, H-6), 7.69 (ddd, *J*=8.3, 7.1, 1.2 Hz, 1H, H-7), 8.43 (m, 1H, H-9), 9.03 (s, 1H, H-2). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 22.7, 32.6, 76.2, 109.8, 118.5, 121.7, 122.1, 122.2, 128.0, 130.0, 139.9, 140.6, 143.5, 145.1, 169.8. IR (KBr): 1751 cm^{-1}. LRMS APCI$^+$ *m/z* 253.1 ([M+H]$^+$, 100). Anal. Calcd for $C_{15}H_{12}N_2O_2$ (252.27): C, 71.41; H, 4.80; N, 11.11. Found: C, 71.01; H, 4.92; N, 11.45.

4.2.6. 4-Deutero-3-(*tert*-butyloxycarbonylamino)-5-methyl-[5*H*]-pyrido[3,2-*b*]indole (13a). A mixture of 3-(*tert*-butyloxycarbonylamino)-5-methyl-[5*H*]-pyrido[3,2-*b*]indole **9** (0.1 g, 0.34 mmol) and TMEDA (127 μL, 0.84 mmol) in 7 mL of anhydrous THF under an atmosphere of argon was cooled at −70°C. A solution of *tert*-butyllithium (1.5 M in pentane, 0.56 mL, 0.84 mmol) was added dropwise. After 2 h stirring at −10°C, the solution was cooled at −70°C and EtOD (0.5 mL, 8.5 mmol) was added and the resulting mixture was stirred at −10°C for 2 h. Hydrolysis was carried out with 1 mL of water and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried on magnesium sulfate, filtered and evaporated. The product was purified by flash chromatography on silica gel (hexane/AcOEt 13:7). The spectral characteristics were identical to those of compound **9** but no signal (70% of deuterium incorporation by integration) was observed for H-4 in the ^{1}H NMR spectrum. LRMS APCI$^+$ *m/z* 299.1 ([M+H]$^+$, 8), 243.1 ([M−*t*Bu]$^+$, 27).

4.3. General procedure for the metalation reaction of *tert*-butylcarbonylamino-δ-carboline (10) and quenching with various electrophiles

A mixture of 3-(*tert*-butylcarbonylamino)-5-methyl-[5*H*]-pyrido[3,2-*b*]indole **10** (0.1 g, 0.36 mmol) and TMEDA (268 μL, 1.8 mmol) in 7 mL of anhydrous THF under an atmosphere of argon was cooled at −70°C. A solution of *tert*-butyllithium (1.5 M in pentane, 1.2 mL, 1.8 mmol) was added dropwise. After 4 h stirring at −40°C, the solution was cooled at −70°C. Then, a solution of *tert*-butyllithium (1.5 M in pentane, 0.95 mL, 1.4 mmol) and TMEDA (215 μL, 1.4 mmol) were added again. After 2 h stirring at −40°C, the solution was cooled at −70°C and the electrophile (see amounts for each compound) was added dropwise and the resulting mixture stirred for 1 h at −70°C and 1 h at −40°C. After hydrolysis of the reaction mixture with ethanol/water (1:1, 5 mL) and warming to rt, the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried on magnesium sulfate, filtered and evaporated.

4.3.1. 3-(*tert*-Butylcarbonylamino)-4-deutero-5-methyl-[5*H*]-pyrido[3,2-*b*]indole (14a). According to the general procedure, the electrophile was EtOD (1 mL, 17 mmol). The product was purified by flash chromatography on silica gel (hexane/AcOEt 1:1). The spectral characteristics were identical to those of compound **10** but no signal (74% of deuterium incorporation by integration) was observed for H-4 in the ^{1}H NMR spectrum. LRMS APCI$^-$ *m/z* 281.4 ([M−H]$^-$, 100).

4.3.2. 3-(*tert*-Butylcarbonylamino)-4-iodo-5-methyl-[5*H*]-pyrido[3,2-*b*]indole (14b). According to the general procedure, the electrophile was iodine (0.86 g, 3.4 mmol) dissolved in THF (3 mL) at −20°C. Hydrolysis was carried out with a 10% aqueous solution of sodium thiosulfate. The product was purified by flash chromatography on silica gel (hexane/AcOEt 7:3) followed by HPLC purification (silica normal phase, particle 5μ, λ=254 nm, hexane/AcOEt 7:3) to yield 24.5 mg (17%) of **14b** as a white solid. Mp=223–225°C. ^{1}H NMR (250.00 MHz, DMSO-d_6) δ 1.33 (s, 9H, *t*-Bu), 4.27 (s, 3H, NCH_3), 7.35 (m, 1H, H-8), 7.63 (m, 1H, H-7), 7.75 (m, 1H, H-6), 8.18 (s, 1H, H-2), 8.22 (m, 1H, H-9). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 28.3, 32.9, 92.5, 111.3, 120.9, 121.0, 121.4, 128.8, 135.8 (×2), 140.1, 141.6, 143.8, 177.9. IR (KBr): 1640 cm^{-1}. LRMS APCI$^+$ *m/z* 408.0 ([M+H]$^+$, 100), 280.1 ([M−I]$^+$, 75). Anal. Calcd for $C_{17}H_{18}IN_3O$ (407.05): C, 50.16; H, 4.46; N, 10.32. Found: C, 50.25; H, 4.49; N, 10.61.

4.3.3. 3-[(*tert*-Butylcarbonylamino)-5-methyl-[5*H*]-pyrido-[3,2-*b*]indol]-4-yl-acroleine (14c). According to the general procedure, the electrophile was ethyl formate (260 μL, 3.2 mmol). The product was purified by flash chromatography on silica gel (hexane/AcOEt 1:1) to yield 42 mg (35%) of **14c** as a yellow solid. Mp=165–167°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 9H, *t*-Bu), 3.45 (s, 3H, NCH_3), 6.40 (dd, *J*=16.3, 7.7 Hz, 1H, =CHCO), 7.12 (d, *J*=8.3 Hz, 1H, H-6), 7.31 (m, 1H, H-8), 7.53 (m, 1H, H-7), 7.78 (d, *J*=16.3 Hz, 1H, Py−CH=), 7.88 (s, 1H, NH), 8.20 (d, *J*=7.7 Hz, 1H, H-9), 8.27 (s, 1H, H-2), 9.79 (d, *J*=7.7 Hz, 1H, CHO). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 27.3, 32.1, 39.3, 109.0, 120.4, 120.9 (×2), 121.7, 126.9, 127.9, 130.4, 135.6, 138.8, 140.2, 142.2, 145.4, 177.3, 192.6. The structure of **14c** was confirmed by COSY, HMBC, HMQC, DEPT and NOE experiments. IR (KBr): 3431, 1688, 1642, 1616 cm^{-1}. HRMS Calcd for $C_{20}H_{22}N_3O_2$ ([M+H]$^+$) 336.1712. Found: 336.1708. Anal. Calcd for $C_{20}H_{21}N_3O_2$ (335.40): C, 71.62; H, 6.31; N, 12.53. Found: C, 71.63; H, 6.49; N, 12.35.

4.3.4. 3-(*tert*-Butylcarbonylamino)-5-methyl-[5*H*]-pyrido-[3,2-*b*]indole-4-carboxaldehyde (14d). According to the general procedure, the electrophile was DMF (280 μL, 3.6 mmol). Hydrolysis was carried out with EtOH/water (1:1, 5 mL) and 4 mL of HCl 2 M were added at rt. The mixture was stirred 15 min and potassium carbonate was added to pH=7. The work up is similar as that described for the general procedure. The product was purified by flash chromatography on silica gel (hexane/AcOEt 3:2) to yield 28 mg (25%) of **14d** as a yellow solid. Mp=266°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (s, 9H, *t*-Bu), 4.08 (s, 3H, NCH_3), 7.33–7.41 (m, 2H, H-6 and H-8), 7.56 (m, 1H, H-7), 8.28 (m, 1H, H-9), 9.92 (s, 1H, H-2), 10.89 (s, 1H, CHO), 11.43

(br s, 1H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 28.0, 34.5, 40.9, 109.6, 111.8, 120.8, 121.9, 122.3, 128.2, 133.3, 133.6, 135.2, 140.2, 143.0, 178.4, 192.0. IR (KBr): 3435, 1690, 1655 cm^{-1}. LRMS APCI$^+$ *m/z* 310.2 ($[M+H]^+$, 100). Anal. Calcd for $C_{18}H_{19}N_3O_2$ (309.15): C, 69.88; H, 6.19; N, 13.59. Found: C, 70.14; H, 6.39; N, 13.31.

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9. We performed some MNDO calculations with δ-carboline **8** (E_{LUMO}=2.1 eV) and with the corresponding pyridine analogue (E_{LUMO}=3.3 eV).[2] The geometries were first determined after minimization with PCMODEL and MNDO calculations were then performed with MOPAC 6.00 on a PC pentium 133 computer. The computed structures were intermediates resulting from N–H abstraction by the first equivalent of alkyllithium. The LUMO energy of carboline derivative is lower than for the pyridine derivative. The addition reaction of the metalation reagent might be easier with δ-carboline **8** than with the pyridine analogue.
10. For details see Ref. 9. δ-carboline **9**: E_{LUMO}=2.9 eV; pyridine analogue: E_{LUMO}=4.3 eV.[2]