REGIOSELECTIVE METALATION OF γ-CARBOLINES

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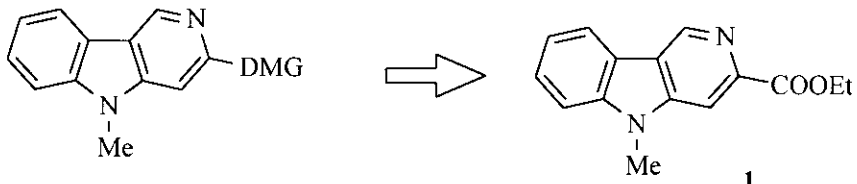
Abstract-The synthesis of new 3-substituted γ-carbolines is described and these products were subjected to *ortho*-lithiation experiments. Whereas 3-carboxamido derivatives (**5a,b**) were cleanly lithiated at 4-position, the 3-amino derivatives (**6a,b**) gave only small amounts of addition products. The results obtained are compared to those previously published in the α-carboline series and semi-empirical calculations were performed. Various 3,4-disubstituted γ-carbolines were obtained in acceptable yields.

INTRODUCTION

The structure of γ-carbolines (*5H*-pyrido[4,3-*b*]indoles) is very rarely encountered in natural products. However, synthetic analogues are interesting owing to their potential mutagenic activity.[1] Various methods leading to γ-carbolines have been described in the literature[2] but they rarely afforded disubstituted derivatives on the pyridine ring. The pyridine substituents are usually introduced before the elaboration of the indole part[2a-e,j] or the pyridine moiety is built starting from appropriate indole derivatives.[2k-q] We were interested in the synthesis of 3,4-disubstituted γ-carbolines because they could be used as starting materials for the obtention of analogues of β-carbolines alkaloids.[3] In previous papers,[4] we achieved the synthesis of some 3,4-disubstituted α-carbolines *via* regioselective metalation reaction of 3-substituted α-carbolines followed by quenching with various electrophiles. The aim of this paper is to describe the same type of approach for the γ-carboline series and to compare the results obtained in these two series. The carboxamido and aminocarbonyl moieties were selected as *ortho*-directing groups.



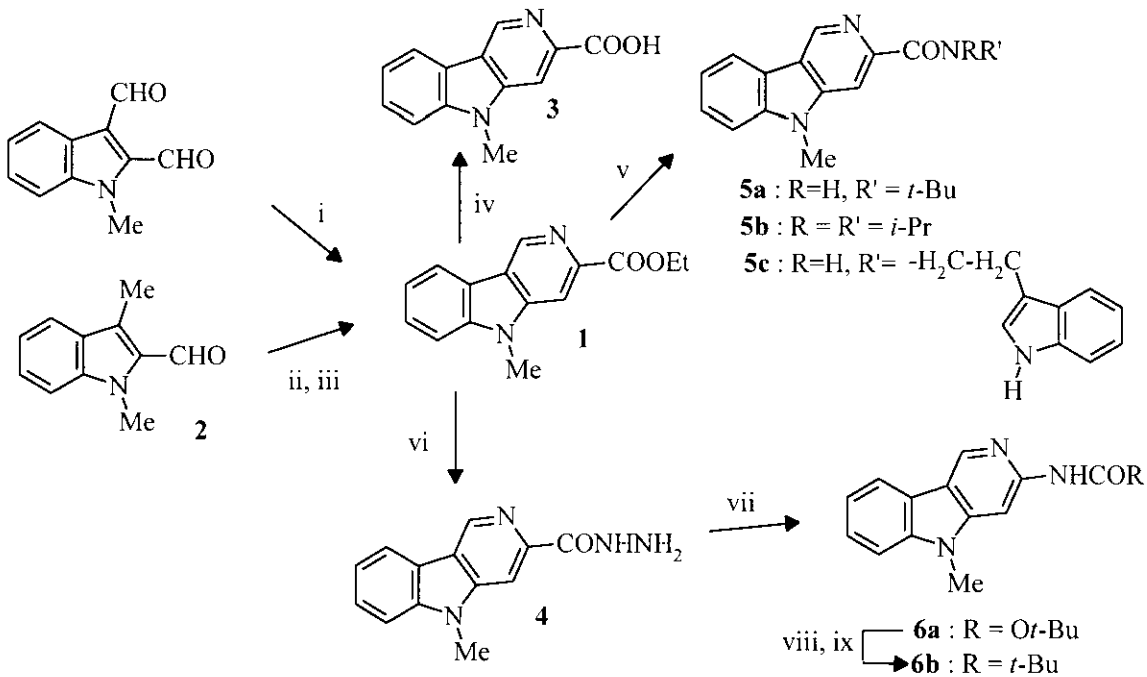
DMG = CONRR', NHCORR'

Scheme 1

RESULTS AND DISCUSSION

1) Synthesis of 3-substituted γ-carbolines

In order to obtain various compounds possessing an *ortho*-directing group for the lithiation reaction, we needed large amounts of ethyl *5H*-pyrido[4,3-*b*]indole-3-carboxylate (**1**) (Scheme 1). Two methods affording the required ester were tested. The first one used 1-methylindole-2,3-dicarboxaldehyde[21] as a key compound whereas the second one involved condensation of ethyl azidoacetate with 1,3-dimethylindole-2-carboxaldehyde (**2**).[5] The latter method was preferred because it afforded the γ-carboline ester more rapidly and on a large scale .



i) H_2N-CH_2-COOEt, cat. Et_2NH, EtOH. ii) N_3-CH_2-COOEt, EtONa in EtOH. iii) toluene, reflux. iv) LiOH, THF, H_2O, reflux. v) $AlMe_3$, RR'NH. vi) H_2N-NH_2, EtOH, reflux. vii) $NaNO_2$, MeCOOH viii) 20 % H_2SO_4, reflux, 5 h. ix) pivaloyl chloride, NEt_3, THF.

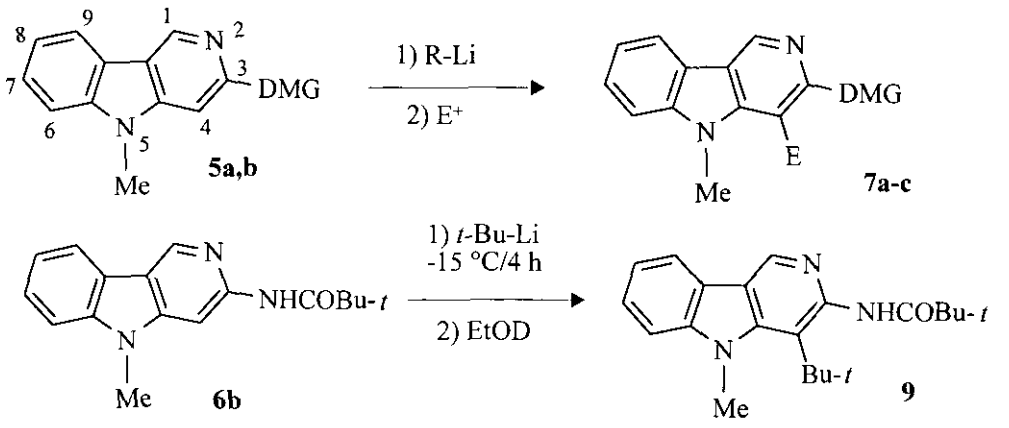
Scheme 2

Hence, the aldehyde (**2**) reacted with ethyl azidoacetate under sodium ethoxide catalysis and the intermediate azido acrylate was heated in toluene to afford the γ-carboline ester (**1**) in a 38 % overall yield. The conversion into the carboxylic acid was rather tedious: with sodium or potassium hydroxides in ethyl alcohol the yields in carboxylic acid were always low. The better results were obtained with lithium hydroxide in THF containing a small amount of water but the yield was only 60 %. However, the resulting carboxylic acid was rather unsoluble in classical organic solvents. For this reason, it was quite impossible to convert this compound neither into the amides (**5a,b**) *via* the acid chloride nor into the carbamate (**6a**) under the classical conditions used in the α-carboline series (diphenylphosphoryl azide in *tert*-butanol).[4] Alternatively, the carboxamides (**5a,b**) were obtained *via* the ester (**1**) with trimethylaluminum and the appropriate amine.[6] The compound (**5c**) was also synthesized as an analogue of the β-carboline alkaloid alangiobussinine extracted from leaves of *Alangium bussyanum*.[7] We decided to synthesize the carbamate (**6a**) *via* the readily available carbonyl hydrazide (**4**).[21] Diazotization of **4** and subsequent Curtius reactions of the intermediate carbonyl azide in refluxing *tert*-butanol led to the carbamate (**6a**). Hydrolysis of **6a** under acidic conditions proceeded smoothly in nice yield and the resulting amine was quenched with pivaloyl chloride leading to the pivalamide (**6b**).

2) Metalation reactions and quenching with electrophiles

In the case of carboxamide (**5b**), the metalation reaction was carried out under the same conditions that those used in the α-carboline series (Table 1, entry 1).[4] Quenching of the intermediate lithio species with ethanol-*d* afforded the 4-deutero compound (**7a**). The ^{1}H NMR spectrum of **7a** displayed no signal for the H_4 proton and a signal at 9.24 ppm corresponding to H_1 as confirmed by a NOE experiment (NOE observed between H_1 and H_9). The intermediate 4-lithio species reacted with some electrophiles and compounds (**7b,c**) were isolated in good yields (Table 1, entries 2,3). Substitution of the 4-position resulted in a substantial deshielding of the signal corresponding to the *N*-methyl group (4.11 ppm for **7b** and 4.28 ppm for **7c** compared with 3.90 ppm for **5b**).

For the *tert*-butylcarboxamide (**5a**), our experience in the α-carboline series[4] (no reaction with alkylamides and only addition reaction with alkyllithiums) led us to use first *tert*-BuLi as a metalation reagent in order to avoid any addition reaction. We were very happy to isolate the 4-deutero compound (**8a**) in good yield (Table 1, entry 4) after quenching of the lithio species with ethanol-*d* (NOE was observed between H_1 and H_9 and the signal of H_4 disappeared). Quenching with other electrophiles led to compounds (**8b-c**) but the yields were significantly lower and seemed to decrease with the bulkiness of the electrophile (Table 1, entries 5, 6). The same deshielding of the *N*-Me signal was observed in the ^{1}H NMR spectra of **8b** and **8c** (4.06 ppm for **8b** and 4.13 ppm for **8c** compared to 3.85 ppm for **5a**). A large number of attempts with ethyl formate were unsuccessful (entry 7).



Scheme 3

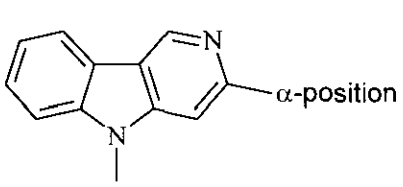
entry	DMG (starting material)	R-Li	Conditions	Electrophile	E	Yield (%) (product)
1	CON(Pr-*i*)$_2$ (**5b**)	LTMP(4 eq)	-70 °C/2 h	EtOD	D	87 (**7a**)
2	CON(Pr-*i*)$_2$ (**5b**)	LTMP(4 eq)	-70 °C/2 h	HCOOEt	CHO	74 (**7b**)
3	CON(Pr-*i*)$_2$ (**5b**)	LTMP(4 eq)	-70 °C/2 h	I_2	I	68 (**7c**)
4	CONHBu-*t* (**5a**)	*t*-BuLi (2.2 eq)	-70 °C/2 h	EtOD	D	95 (**8a**)
5	CONHBu-*t* (**5a**)	*t*-BuLi (2.2 eq)	-70 °C/2 h	PhCHO	CH(OH)Ph	35 (**8b**)
6	CONHBu-*t* (**5a**)	*t*-BuLi (2.2 eq)	-20 °C/2 h	I_2	I	22 (**8c**)
7	CONHBu-*t* (**5a**)	*t*-BuLi (2.2 eq)	-15 °C/2 h	HCOOEt	CHO	-
8	NHCOBu-*t* (**6b**)	*t*-BuLi (5 eq)	-15 °C/4 h	EtOD	D	15 (**9**)

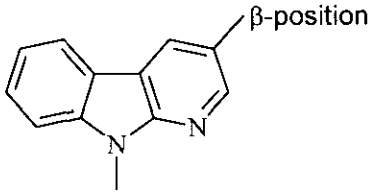
Table 1 : Results of the metalation reactions on compounds (**5a,b** and **6a,b**)

Whatever the conditions, reaction of the carbamate (**6a**) with various metalation reagents afforded always the starting material besides a very small amount of addition products. At low temperature, the absence of any metalation product was also observed with the pivalamide (**6b**) whereas above –15 °C the competitive addition reaction began to occur leading after aromatisation of the intermediate product to the 4-*tert*-butyl substituted γ-carboline (**9**) in low yield (Scheme 3 and Table 1, entry 8, the yield was calculated by integration of the ^{1}H NMR spectrum of the crude product). The position of the *tert*-butyl group was confirmed by a NOE experiment (NOE between H_1 and H_9) and the deshielding of the *N*-Me signal in the vicinity of this bulky moiety (4.25 ppm for the *N*-Me protons). This latter product was not purified.

3) Comparison between the results obtained in the two series

As in our previous paper,[4a] we performed MO calculations on structures (**5a,b**) and (**6a,b**) in order to evaluate the facility of the competitive addition reaction. If the LUMO energy is low, the addition reaction may occur. The structures were first minimized with MM2 force field[8] as implemented in PCMODEL® and then MO calculations were performed at the semi-empirical MNDO level using the package MOPAC 6.0.[9] The LUMO energies of these γ-carbolines are compared to those obtained with the corresponding α-carbolines and pyridines analogues (Table 2). As can be seen, the LUMO energies of the carbolines are always lower than those of their pyridine analogues but the difference in not very important in the case of the diisopropylcarboxamides which did not undergo addition reactions whatever the series. The case of *tert*-butylcarboxamides is more surprising. Under the same conditions, no addition reaction was observed in the γ-carboline series whereas only addition reaction occurred in the α-carboline series. However, the computed LUMO energies are similar (2.1 and 2.2 eV) . This apparent discrepancy could be explained by the different position of the secondary carboxamide group with respect to the pyridine nitrogen: α-position for the γ-series and β-position for the α series. In the case of pyridine, the addition reaction occurred only when the secondary carboxamide was in the β-position.[10]





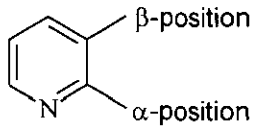


Table 2: LUMO energies of the γ-carbolines compared with those in α-carboline and pyridine series

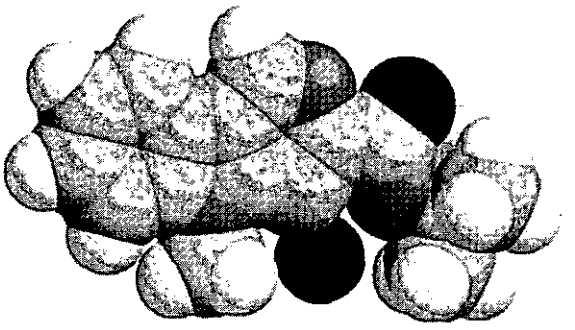
DMG	E_{LUMO}(eV) [b,c] γ-carboline	E_{LUMO}(eV) [b,c] α-carboline	E_{LUMO}(eV) [b,c] Pyridine (α and β)
CON(Pr-*i*)$_2$	-0.8 (-)	-0.56 (-)	-0.4 (-) -0.47 (-)
CONHBu-*t* [a]	2.2 (-)	2.1 (+)	3.4 (-) 3.3 (+)
NHCOOBu-*t* [a]	3.0 (+)	1.7 (+)	4.4 (-) 4.3 (-)
NHCOBu-*t* [a]	3.0 (+)	2.7 (-)	4.6 (-) 4.3 (-)

(a) : The computed structures are intermediates resulting from N-H abstraction by the first equivalent of alkyllithium.

(b) : The LUMO energies were computed for various conformations of the 3-substituent (including *s-cis* and *s-trans*). As a consequence, average values are given in this Table.

(c) : (+) addition reaction. (-) no addition reaction.

We found it interesting to explain the low yields oberved in the reaction of the lithio species resulting from **5a** with bulky electrophiles (Table 1, entries 5-7). For this purpose, we performed a geometry optimization at the semi-empirical PM3 level (Scheme 4).[11]



Scheme 4: Structure of the lithio species issued from **5a**[11]

The CPK model depicted on Scheme 4 shows very clearly the steric hindrance caused by the substituents in the vicinity of the carbon-lithium bond and may explain the low reactivity observed. It must be emphasized that this approach is only approximative because the lithiated species is probably aggregated. The computed values for carbamates are in good agreement with the experimental results because the LUMO energies are significantly lower than those of the pyridine series. The same discrepancy as above is observed for the pivalamides in the two series. The LUMO energy of the γ-series is higher but only addition reaction occurs in a small extent whereas metalation is possible without any addition in the α-series. These facts show that the prevision of this kind of reaction is impossible when the differences between the LUMO energies are too small.

The results described in this paper show that the metalation reaction is a good alternative for the functionalization of γ-carbolines when the *ortho*-directing group is a secondary or a tertiary carboxamide. However, the reaction did not work with amine derivatives. Nevertheless, interesting results were obtained in recent years concerning the lithiation experiments in the α, β,[14] γ-carboline series.

EXPERIMENTAL

The IR spectra were recorded on a Beckman IR 4250 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 device. Spectra were recorded in deuterochloroform or in hexadeuterodimethyl sulfoxide (DMSO-d_6). Chemicals were purchased from Aldrich Co or Janssen Co and, unless otherwise stated, were used without further purification. Tetrahydrofuran was distilled from sodium-benzophenone ketyl. Unless otherwise stated, the final products were not recrystallized after

purification by flash chromatography. Standard work-up means drying of the solvent on MgSO4, filtration and subsequent removal of the solvent under reduced pressure. 3-Methylindole-2-carboxaldehyde was synthezised according to the procedure described by Katritzky *et al.*[13]

1,3-Dimethylindole-2-carboxaldehyde (2)

To a cooled solution (0-5 °C) of 3-methylindole-2-carboxaldehyde[13] (1 g, 6.3 mmol) in dry THF (15 mL), sodium hydride (95 %, 0.384 g, 15.2 mmol) was added in small portions. The mixture was stirred at rt for 20 min and then treated with methyl iodide (2.3 mL, 37 mmol). After 1 h stirring at rt, the mixture was poured on crushed ice (20 g). The solvent was removed under reduced pressure and the aqueous layer extracted with dichloromethane (3 x 10 mL). Classical work-up afforded a viscous orange oil. This compound was used without further purification. The yield of crude product was 1.05 g (97 %). An analytical sample could be obtained after recrystallization from ethanol. ^{1}H NMR ($CDCl_3$): 10.18 (s, 1H); 7.71 (m, 1H); 7.14-7.46 (m, 3H); 4.06 (s, 3H); 2.65 (s, 3H). IR (cm^{-1}): 1659 (C=O). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.08. Found: C, 75.9; H, 6.3; N, 7.8.

Ethyl 5-methyl-*5H*-pyrido[4,3-*b*]indole-3-carboxylate (1)

To a cooled solution (-15°C) of sodium ethoxide (8.7 mL prepared from 0.2 g of sodium and 20 mL of ethanol), a solution of ethyl azidoacetate[15] (5.16 g, 40 mmol) and the above compound (**2**) (1.4 g, 8 mmol) in ethanol (6 mL) was slowly added. The mixture was stirred at -15°C for 7 h. After warming to rt, a saturated aqueous solution of ammonium chloride (15 mL) was added. The mixture was extracted twice with ether and the mixed organic layer washed twice with water. Classical work-up afforded an oil which was taken in toluene (70 mL). The resulting solution was heated to reflux for 14 h and the solvent removed under reduced pressure. This compound was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 60/40, $R_f \sim 0.4$). Yield 0.78 g (38 %) of a pale yellow solid. mp 195°C. IR (cm^{-1}) : 1728 (C=O). ^{1}H NMR ($CDCl_3$): 9.36 (d, J = 0.8 Hz, 1H); 8.23 (d, J = 0.8 Hz, 1H); 8.19 (m, 1H); 7.60 (s, 1H); 7.47 (m, 1H); 7.36 (m, 1H); 4.54 (q, J = 7.1 Hz, 2H); 3.90 (s, 3H); 1.50 (t, J = 7.1 Hz, 3H). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 71.0; H, 5.6; N, 11.0.

5-Methyl-*5H*-pyrido[4,3-*b*]indole-3-carboxylic acid (3)

A mixture of compound (**1**) (0.5 g, 2 mmol), lithium hydroxide monohydrate (0.215 g, 5.1 mmol) and water (2 mL) in THF (8 mL) was stirred at 50 °C for 24 h. After cooling to rt, the mixture was acidified to pH = 4 with aqueous 1 M hydrochloric acid. The solid material was collected by filtration, washed with cold water and dried under reduced pressure. The product was recrystallized from ethanol. Yield 0.27 g

(60 %) of a white solid. mp > 250°C. IR (cm^{-1}); 1660 (C=O). ^1H NMR (DMSO - d_6): 9.45 (s, 1H); 8.41 (m, 1H); 8.35 (s, 1H); 7.77 (m, 1H); 7.65 (m, 1H); 7.40 (m, 1H); 4.00 (s, 3H). Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46; N, 12.39. Found: C, 68.9; H, 4.3; N, 12.2.

5-Methyl-5*H*-pyrido[4,3-*b*]indole-3-carbonyl hydrazide (4)

This compound was prepared according to the procedure already published by us.[21]

3-(*N*-*tert*-Butylcarboxamido)-5-methyl-*5H*-pyrido[4,3-*b*]indole (5a)

A solution of trimethylaluminium in hexane (2 M solution, 1.3 mL, 2.6 mmol) was added dropwise to a stirred solution of *tert*-butylamine (0.273 mL, 2.6 mmol) in dry THF (1.5 mL). After two hours stirring, a solution of ester (**1**) (0.2 g, 0.79 mmol) in dry THF (2 mL) was slowly added (dissolution of the ester in THF was achieved by heating). The resulting mixture was heated to reflux for 96 h. After cooling, 1 M aqueous hydrochloric acid (2.8 mL, 2.8 mmol) was added carefully. After 3 h stirring at rt, the solution was extracted with dichloromethane. Standard work up afforded a solid which was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 60/40 R_f = 0.35). The yield was 0.16 g (73 %) of a pale yellow-solid. mp 155°C. IR (cm^{-1}): 1670 (C=O). ^1H NMR ($CDCl_3$): 9.09 (d, J = 0.9 Hz, 1H); 8.30 (br s, 1H); 8.23 (d, J = 0.9 Hz, 1H); 8.10 (m, 1H); 7.60 (m, 1H); 7.49 (m, 1H); 7.38 (m, 1H); 3.85 (s, 3H); 1.59 (s, 3H). The assignment of H_1 and H_4 protons was achieved by a NOE experiment (7.4 % NOE between H_1 and H_9). Anal. Calcd for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.94. Found : C, 72.9; H, 6.6; N, 14.6.

3-(*N,N*-Diisopropylcarboxamido)-5-methyl-*5H*-pyrido[4,3-*b*]indole (5b)

A mixture of the carboxylic acid (**3**) (0.5 g, 2.2 mmol) and freshly distilled thionyl chloride (13 mL, 178 mmol) was heated to reflux for 3 h. The excess of thionyl chloride was removed by distillation followed by co-distillation with toluene. The residue was dissolved in dichloromethane (10 mL), the resulting solution cooled at 0°C and *N,N*-diisopropylamine (4.0 mL, 28.5 mmol) was added. After 24 h stirring at rt, water (15 mL) was added and the solution extracted with dichloromethane. Standard work-up afforded a solid which was purified by flash chromatography (silica gel, cyclohexene/ethyl acetate 50/50, R_f = 0.4). The yield was 0.6 g (88 %) of a white solid. mp 206°C. IR (cm^{-1}) : 1625 (C=O). ^1H NMR ($CDCl_3$) ; 9.23 (d, J = 0.9 Hz, 1H) ; 8.16 (m, 1H) ; 7.53-7.60 (m, 2H) ; 7.45 (m, 1H) ; 7.34 (m, 1H) ; 3.60-4.00 (m, 5H) ; 1.22-1.61 (m, 12 H). Assignment of H_1 and H_4 was confirmed by a NOE experiment (1.8 % NOE between H_1 and H_9). Anal. Calcd for $C_{19}H_{23}N_3O$: C, 73.75; H, 7.49; N, 13.58. found : C, 73.8; H, 7.2; N, 13.2.

3-(*N*-3-Indolylethylcarboxamido)-5-methyl-*5H*-pyrido[4,3-*b*]indole: *N*-Methylisoalangiobussinine (5c)

A solution of trimethylaluminium in hexane (2 M solution, 2.4 mL, 4.8 mmol) was added dropwise to a stirred solution of tryptamine (0.39 g, 1.93 mmol) in dry THF (2 mL). After two hours stirring, a solution of ester (**1**) (0.2g, 0.79 mmol) in dry THF (3 mL) was slowly added (dissolution of the ester in THF was achieved by heating). The resulting mixture was heated to reflux for 96 h. After cooling, 1 M aqueous hydrochloric acid (4.8 mL, 4.8 mmol) was added carefully. After 24 h stirring at rt, the solution was extracted with dichloromethane. Standard work up afforded a solid which was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 60/40 R_f = 0.2). The yield was 0.09 g (31 %) of a white solid. mp 196 °C. IR (cm^{-1}): 1653 (C=O). ^1H NMR ($CDCl_3$): 9.12 (s, 1H); 8.51 (s, 1H); 8.32 (s, 1H); 8.22 (s, 1H); 8.14 (s, 1H); 7.13-7.70 (m, 8H); 3.90 (m, 5H); 3.17 (s, 2H). Anal. Calcd for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21. Found: C, 74.6; H, 5.2; N, 15.2.

3-(*tert*-Butyloxycarbonylamino)-5-methyl-*5H*-pyrido[4,3-*b*]indole (6a).

A cooled solution (10 °C) of the hydrazide (**4**) (0.317 g, 1.32 mmol) in anhydrous acetic acid (4 mL) was treated dropwise by a solution of sodium nitrite (0.66 g, 9.56 mmol) in water (10 mL). The mixture was stirred at a temperature below 10 °C for 30 min. An aqueous solution of hydrochloric acid (5 % solution, 16 mL) was then added. After one hour stirring at rt, the solid material was filtered and washed with water, aqueous sodium hydrogencarbonate (10 % solution) and then water. After careful drying, the solid was dissolved in *tert*-butanol (5 mL) and the solution heated to reflux, under an argon atmosphere for 12 h. The solvent was removed under reduced pressure. The residue was treated in hot THF, the resulting suspension was filtered and the filtrate evaporated to dryness. The resulting solid was washed with cold dichloromethane. The yield was 0.235 g (60 %). mp 230 °C (decomp, from ethanol). IR (cm^{-1}): 1705 (C=O). ^1H NMR ($CDCl_3$): 9.17 (s, 1H); 8.95 (br s, 1H); 8.02 (m, 2H); 7.51-7.27 (m, 3H); 3.85 (s, 3H); 1.60 (m, 9H). A 3 % NOE was observed between H_1 and H_9. Anal. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 69.1; H, 6.45; N,13.7.

3-(*tert*-Butylcarbonylamino)-5-methyl-*5H*-pyrido[4,3-*b*]indole (6b).

A mixture of the above compound (**6a**) (0.2 g, 0.67 mmol) and 20 % sulfuric acid (10 mL) was heated to reflux for 5 h. After cooling to rt, the mixture was poured on crushed ice (20 g) and 20 % aqueous ammonia solution (10 mL). The pH was adjusted to 8 with 20 % aqueous ammonia solution and the solution extracted with dichloromethane. Standard workup afforded the crude amine which was dissolved

and triethylamine (0.205 mL, 1.47 mmol). The mixture was cooled (0°C) and pivolyl chloride (0.180 mL, 1.46 mmol) was slowly added. After 5 h stirring at rt, water (5 mL) was added and the solution was extracted with dichloromethane (3 x 10 mL). Standard work up afforded 0.14 g (75 %) of a brown solid. mp 145 °C. IR (cm^{-1}): 1686 (C=O). ^1H NMR ($CDCl_3$): 8.89 (s, 1H); 8.36 (s, 1H); 8.32 (br s, 1H); 8.04 (m, 1H); 7.48 (m, 1H); 7.37 (m, 1H); 7.27 (m, 1H); 3.80 (s, 3H); 1.39 (s, 9H). A 3.5 % NOE was observed between H_1 and H_9. HRMS: Calcd for $C_{17}H_{19}N_3O$ 282.1606. Found: 282.1613.

General procedure for the metalation reaction of diisopropylcarboxamide (5b) and quenching with various electrophiles.

A solution of LTMP was prepared in a 10 mL flask flushed with argon from *n*-butyllithium (1.6 M solution in hexanes, 1.62 mL, 2.6 mmol), and 2,2,6,6-tetramethylpiperidine (0.44 mL, 2.6 mmol) in anhydrous THF (2 mL) at -20 °C. The resulting solution was stirred at -20 °C for 30 min before use. To a solution of **5b** (0.2 g, 0.65 mmol) in anhydrous THF (15 mL) prealably 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 the appropriate temperature for 2 h. After hydrolysis with ethanol/water (1/1 mixture, 10 mL), the aqueous layer was extracted with dichloromethane and the standard work-up was applied.

4-Deutero-3-[*N,N*-diisopropylcarboxamido]-5-methyl-*5H*-pyrido[4,3-*b*]indole (7a).

The electrophile was EtOD (1 mL, 17 mmol). The product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 60/40, R_f = 0.4). The yield was 0.17 g (87 %). The spectral characteristics were identical to those of compound (**5b**) but no signal was observed for H_4 in the ^1H NMR spectrum.

3-(*N,N*-Diisopropylcarboxamido)-5-methyl-*5H*-pyrido[4.3-*b*]indole-4-carboxaldehyde (7b).

The electrophile was ethyl formate (0.27 mL, 3.3 mmol). The product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 60/40, R_f = 0.45). The yield was 0.16 g (74 %) of a white solid. mp 215 °C. IR (cm^{-1}) : 1630 (C=O amide) ; 1685 (C=O aldehyde). ^1H NMR ($CDCl_3$): 10.45 (s, 1H); 9.33 (s, 1H); 8.15 (m, 1H); 7.48-7.66 (m, 2H); 7.41 (m, 1H); 4.11 (s, 3H); 3.57 (m, 2H); 1.17-1.66 (m, 12H). Anal. Calcd for $C_{28}H_{23}N_3O_2$: C, 71.19; H, 6.87; N, 12.45. Found: C, 71.2; H, 6.7; N, 12.2.

3-(*N,N*-Diisopropylcarboxamido)-4-iodo-5-methyl-*5H*-pyrido[4,3-*b*]indole (7c).

The electrophile was iodine (0.71 g, 2.8 mmol) in dry THF (5 mL) and the hydrolysis was carried out with a saturated aqueous solution of sodium thiosulfate. The product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 60/40 R_f = 0.30). The yield was 0.19 g of a pale

yellow solid (68 %). mp 205°C. IR (cm^{-1}) : 1630 (C=O). ^1H NMR ($CDCl_3$): 9.14 (s, 1H); 8.11 (m, 1H); 7.57 (m, 1H); 7.47 (m, 1H); 7.37 (m, 1H); 4.28 (s, 3H); 3.53 (m, 2H); 1.67-1.25 (m, 12H). Anal. Calcd for $C_{19}H_{22}N_3OI$: C, 52.42; H 5.10; N, 9.65. Found: C, 52.5; H, 5.1; N, 9.5.

General procedure for the metalation reaction of the *tert*-butylcarboxamide (5a)

A two-necked flask, under an argon atmosphere is charged with the carboxamide (**5a**) (0.1 g, 0.36 mmol), TMEDA (0.12 mL, 0.78 mmol) and anhydrous THF (2.5 mL). The solution was cooled at –70°C and maintained at this temperature during the addition of *tert*-butyllithium (1.5 M solution in hexane, 0.52 mL, 0.78 mmol). After 2 h stirring at –70 °C, the electrophile (see below for the amount of each compound) was added and the resulting mixture was stirred for two hours at a temperature depending on the electrophile concerned. Hydrolysis was carried out with ethanol/water (1/1 mixture, 10 mL). The aqueous layer was extracted with dichloromethane and standard work-up was applied.

3-(*N-tert*-Butylcarboxamido)-4-deutero-5-methyl-*5H*-pyrido[4,3-*b*]indole (8a)

According to general procedure, with EtOD (1mL, 17 mmol) at -70°C, compound (**8a**) was purifed by flash chromatography (sillica gel, cyclohexane/ethyl acetate 60/40, $R_f = 0.35$). The yield was 0.095 g (95 %). The physical and spectral data were the same as those described for **5a** but not signal was observed for H_4 in the ^1H NMR spectrum.

3-(*N-tert*-Butylcarboxamido)-4-(1-hydroxyphenyl)-5-methyl-*5H*-pyrido[4,3-*b*]indole (8b)

The electrophile was benzaldehyde (0.1 mL, 0.98 mmol) at –70 °C. Purification was achieved by flash chromatography (silica gel, cyclohexane/ethyl acetate 80/20 $R_f = 0.45$). The yield was 0.048 g (35 %) of a yellow solid. mp 120 °C (decomp). ^1H NMR ($CDCl_3$): 9.13 (s, 1H); 8.19 (m, 1H); 7.67 (s, 1H); 7.61 (m, 1H); 7.36–7.48 (m, 2H); 7.22 (m, 5H); 6.86 (m, 1H); 4.06 (s, 3H); 1.9 (s, 1H); 1.25 (s, 9H). HRMS: Calcd for $C_{24}H_{25}N_3O_2$: 387.1947. Found: 387.953.

3-(*N-tert*-Butylcarboxamido)-4-iodo-5-methyl-*5H*-pyrido[4,3-*b*]indole (8c)

The electrophile was iodine (0.2 g, 0.79 mmol) dissolved in THF (2 mL) at –20°C. Hydrolysis was carried out with a saturated aqueous solution of sodium thiosulfate. Flash chromatography on silica gel (cyclohexane / ethyl acetate 70/30 $R_f = 0.25$) afforded 0.032g (22 %) of a pale yellow solid. mp 210 °C. ^1H NMR ($CDCl_3$): 8.98 (s, 1H); 8.12 (m, 1H); 7.59 (m, 1H); 7.34-7.45 (m, 3H); 4.13 (s, 3H); 1.58 (s, 9H). Anal. Calcd for $C_{17}H_{18}NO_3I$: C, 50.14; H, 4.45; N, 10.32. Found: C, 50.5; H, 4.3; N, 10.3

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11. The AM1 hamiltonian implemented in MOPAC 6.0 is not suitable for the calculations of lithium containing structures and lithium parameters for PM3 are not available in this version. We have introduced in the text sources of MOPAC 6.0 provided by QCPE,[9] the lithium parameters published by Anders *et al.* (see reference 12). After compilation with a FORTRAN 94 compiler, we obtained an executable code working on a PC computer. Dr Ren Fang from the LESP of Mont Saint Aignan is greatly acknowledged for the delicate compilation of the FORTRAN text sources. The so-obtained executable code was checked on some known lithium containing structures and the results obtained were similar to those described by Anders *et al.*[12]

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15. Ethyl azidoacetate was obtained by reaction of sodium azide with ethyl chloroacetate in a 1/1 mixture of water and acetone. This compound is potentially explosive and must be handled carefully. It was not distilled before using, even under reduced pressure.

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