SOME APPLICATIONS OF THE REGIOSELECTIVE LITHIATION OF α-CARBOLINES

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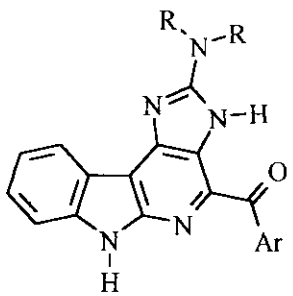
Abstract- Regioselective metallation of the 3-carboxamido-α-carboline (**1**) afforded various 4-substituted-3-carboxamido-α-carbolines. Subsequent cross-coupling methodology applied to the 4-iodo-3-carboxamido-α-carboline (**2e**) led to 4-aryl-3-carboxamido-α-carbolines. Regioselective lithiation of 3-pivalamido-α-carboline led to 3,4-diaminopyrido[2,3-*b*]indole (**7**). Condensation of this diamine with (dichloromethylene)dimethylammonium chloride was then studied and an unusual reaction was observed. Some derivatives of imidazopyrido[2,3-*b*]indole were thus obtained.

INTRODUCTION

Some heterocyclic fused systems possessing a pyrido[2,3-*b*]indole structure (α-carboline) have received an attention because they were found to exhibit pharmacological activities.[1]



R = CH_3, Ar = 3-indolyl : grossularine-1

R = CH_3, Ar = 4-hydroxyphenyl: grossularine-2

R = H, Ar = 3-indolyl : *N,N*-didesmethylgrossularine-1

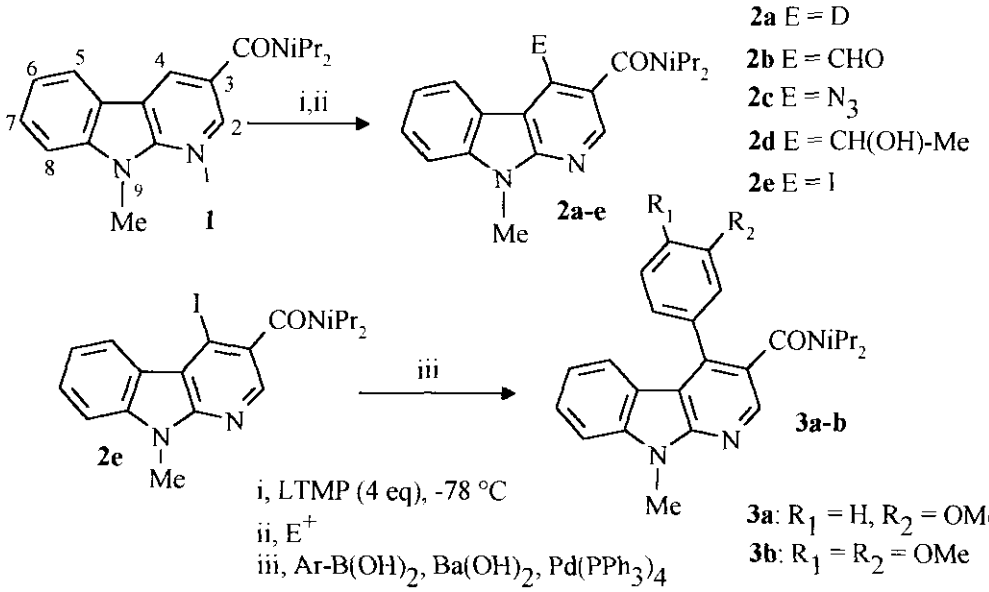
Scheme 1

Among them, the synthesis of the tetracyclic structures of grossularines (isolated from *Dendrodoa grossularia*)[2] and didesmethylgrossularine-1 (isolated from *Polycarpa aurata*)[3] represents a challenging problem (Scheme 1). Several syntheses involving ring closure of the indole part from appropriate substituted pyridine derivatives were reported by Guyot *et al.*[4] and Hibino *et al.*[5]

In a previous paper, we reported the synthesis of 3-substituted α-carbolines and their regioselective lithiation at 4-position.[6] These reactions were performed through the *ortho*-directed effect of the pivalamido and diisopropylcarboxamido groups. In connection with our study of the functionnalization of α-carbolines, we prepared intermediates in the synthesis of grossularines using this methodology as a key-step. Moreover, application of the association metalation cross-coupling methodology would allow the synthesis of 4-aryl-α-carbolines. The aim of this paper is to provide full details concerning the above mentioned regioselective lithiations and subsequent quenching with various electrophiles, to describe some cross-coupling reactions of 4-iodo-substituted α-carbolines and to open a new route leading to the tetracyclic structure of grossularines.

RESULTS

1) Synthesis of 4-aryl-α-carbolines



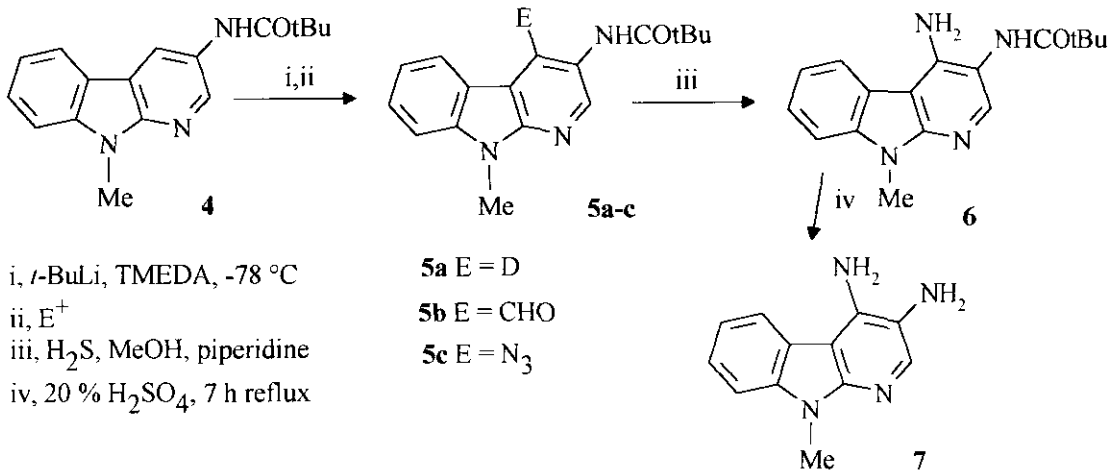
Scheme 2

In order to obtain polycyclic structures containing the α-carboline moiety, we synthesized 4-aryl derivatives *via* cross-coupling methodology. The *N,N*-diisopropylcarboxamide (**1**) was lithiated at C-4 under the previously described conditions[6] and quenching with electrophiles afforded the 3,4-disubstituted carbolines (**2a-e**). We first tried to prepare the organozinc derivative *via* reaction of the

lithiated species with zinc dichloride and to trap this intermediate with 3-bromoanisole under Pd catalysis. Whatever the conditions, no coupling product was observed. However, cross-coupling of the 4-iodocarboline (**2e**) with 3-methoxyphenylboronic acid under classical Suzuki's conditions led to a mixture of 4-aryl derivative (**3a**) and deiodinated compound (**1**). The coupling reaction was probably difficult because the large steric hindrance of C-4 due to the presence of both the diisopropylcarboxamido group and the peri proton at C-5 of the carboline ring. As a consequence, we performed the cross-coupling reaction under modified Suzuki's conditions[7] known to give satisfactory results in case of steric hindrance (barium hydroxide as a base and DME as a solvent). The 4-aryl-α-carbolines (**3a-b**) were thus obtained in good yields.

2) Synthesis of precursors of *N*-methylgrossularines

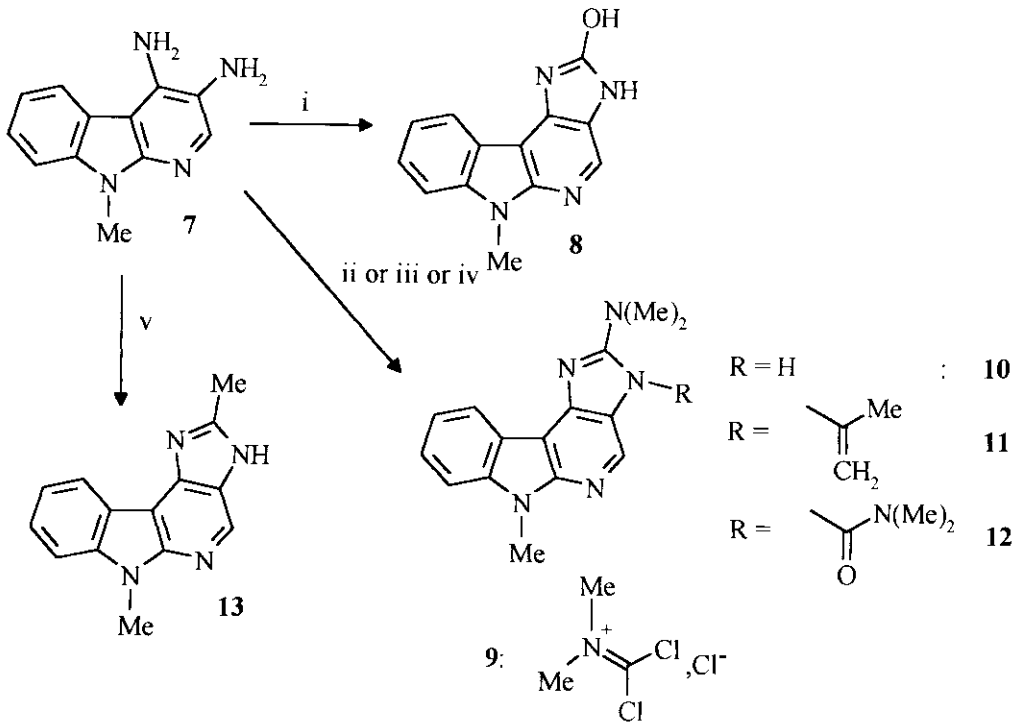
Starting from 9-methylpyrido[2,3-*b*]indole-3-carboxylic acid[8], compound (**4**) possessing an *ortho*-directing pivalamido group was synthesized.[6] Under the conditions defined before,[6] this compound was cleanly lithiated at the 4-position and quenching with electrophiles afforded the carbolines (**5a-c**) in moderate yields (Scheme 3). The azido derivative (**5c**) obtained with tosyl azide as an electrophile was particularly interesting since it could be a precursor or the grossularines tetracyclic structure.[4,5] So, the azido group was reduced with hydrogen sulfide in methanol containing a small amount of piperidine [9] leading to the amine (**6**) in a 88 % yield. Hydrolysis of **6** with 20 % aqueous sulfuric acid afforded the diamine (**7**) in a good yield (Scheme 3).



Scheme 3

Various reagent may be used in order to convert an ortho-diamino aromatic compound into a fused imidazole ring. We first tried cyanogen bromide[10] but only degradation products were observed. However, reaction of **7** with 1,1'-carbonyldiimidazole in tetrahydrofuran[11] gave the hydroxy derivative

(**8**) (or its tautomer) in a 75 % yield whereas our attempts with 1,1'-thiocarbonyldiimidazole were unsuccessful (Scheme 4).

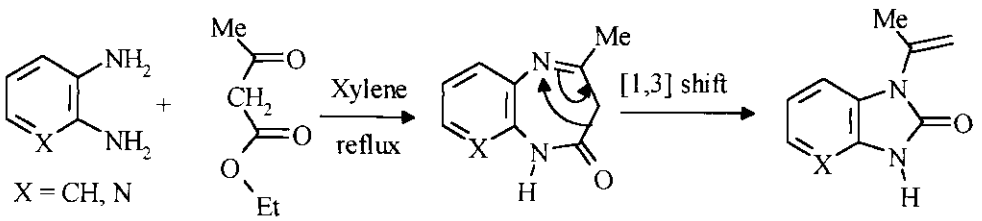


i: 1,1'-carbonyldiimidazole, THF, Δ, 4 h. ii: **9**, MeCN, 3 h reflux.
iii: **9**, MeCN, NEt_3, 24 h reflux. iv: **9**, MeCN, pyridine, reflux.
v: ethylacetimidate hydrochloride, EtOH, Δ, 24 h.

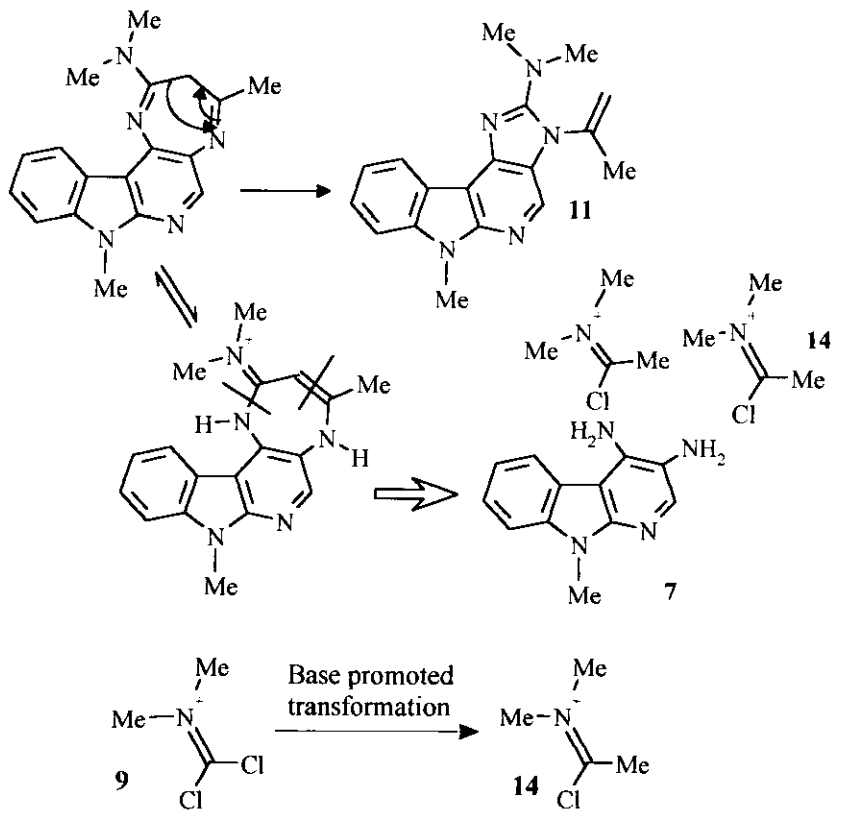
Scheme 4

In order to build the imidazole ring, Achab *et al.* [4] used condensation of phosgene iminium chloride (**9**) with the 3,4-diamino-2,6-dichloropyridine hydrochloride in refluxing chloroform. This reagent (**9**) is described as a stable dichloromethylenammonium salt and has been widely used as reactive building block for synthesis as demonstrated and reviewed by Viehe and Janousek.[12] Unfortunatly, the results obtained with **9** during the condensation reaction with the diamine (**7**) depended on the sample purchased. With the first sample, only degradation products were observed under the classical conditions (reflux in chloroform or other halogenated solvents, without base). So, we decided to carry out the reaction in the presence of a base in order to trap the hydrochloric acid generated by the condensation of the 3,4-diamino compound (**7**) with hydrochoride (**9**). With triethylamine in acetonitrile or THF and pyridine in acetonitrile, compound (**11**) was isolated in 30 % yield instead of the targeted product (**10**). The structure of **11** was elucidated by MS spectrometry (M = 305 instead of 265 for **10**) and ^1H and ^{13}C NMR spectroscopies. These spectra showed the presence of both a dimethylamino group (protons at 3.27

ppm and carbon at 20.2 ppm) and a methylvinyl group (protons at 2.12, 5.47 ppm and carbons at 40.4 and 114.6 ppm). The chemical shifts observed are similar to those reported for *N*-vinylimidazole structures.[13] On the other hand, the chemical shifts of the junction carbons C-3a and C-4a between the pyridine ring and the imidazole ring showed that the alkenyl moiety is connected to the nitrogen atom 1.[14] The formation of **11** is surprising and the mechanism involved may be of interest. A carefull survey of the literature showed that formation of *N*-isoprenylimidazolones has already been observed as by-products in the condensation reactions of *o*-phenylenediamine or 2,3-diaminopyridine with ethyl acetoacetate (Scheme 5).[15]



Scheme 5



Scheme 6

The occurrence of the *N*-isoprenylimidazolone was explained *via* a [1,3]-sigmatropic shift from carbon to nitrogen of the diazepinone, main product of the reaction. A similar sigmatropic shift could be

postulated in the case of **11** (Scheme 6). It could be thought that phosgeneiminium chloride (**9**) (in large excess) undergoes a base catalyzed transformation leading to the intermediate (**14**). This base-promoted rearrangement could be of the Stevens or Sommelet-Hauser types and might involve a methyle transfer between two molecules of **9**.[16] Various mechanisms concerning this methyle group shift could be postulated but it was impossible to trap or isolate any corresponding intermediate species. The seven-membered ring might then be obtained *via* the condensation reaction of two molecules of **14** with the diamine. However and up to now, we didn't try the direct reaction between **7** and **14**. The same reaction occurred with pyridine as a base in acetonitrile and with triethylamine in tetrahydrofuran.

Nevertheless, in the absence of a base, and with a good sample of phosgeneiminium chloride (**9**), the target product (**10**) was isolated in a 30 % yield. When the reaction was carried out with two equivalents of phosgeneiminium chloride (**9**) and six equivalents of pyridine in acetonitrile, the urea derivative (**12**) was obtained in variable yield. The latter compound resulted probably from the reaction of **10** with carbamoyl chloride generated by the hydrolysis of **9**. Alternatively, classical condensation[17] of ethyl acetimidate with **7** afforded the imidazocarboline (**13**) (Scheme 4).

These results clearly show that the above described strategy is an alternative for obtaining the grossularine backbone, the main problem being the quality of the sample of **9** purchased.[18]

EXPERIMENTAL

The IR spectra were recorded on a Beckman IR 4250 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded either on a 200 MHz or a 400 MHz Bruker device. Spectra were recorded in deuteriochloroform or in hexadeuteriodimethyl 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.

3-(*N,N*-Diisopropylcarboxamido)-9-methyl-9*H*-pyrido[2,3-*b*]indole (1). A mixture of freshly distilled thionyl chloride (5 mL, 68.8 mmol) and 9-methyl-9*H*-pyrido[2,3-*b*]indole-3-carboxylic acid[8] (1.2 g, 53 mmol) was heated to reflux for 3 h. The excess of thionyl chloride was removed under reduced pressure and then co-distilled with toluene (8 mL). The residue was dissolved in dichloromethane (8 mL) and diisopropylamine (3 mL, 21.4 mmol) was added at 0 °C. The mixture was stirred at rt for 24 h and hydrolyzed with water (15 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, ethyl acetate/cyclohexane 30/70, $R_f = 0.4$) afforded 1.44 g (88 %) of

a white solid. mp 139 °C. IR : 1618 (C=O). ^{1}H NMR ($CDCl_3$, 200 MHz) : 8.51 (d, 1H, J = 2.0 Hz) ; 8.36 (d, 1H, J = 2.0 Hz) ; 8.08 (m, 1H) ; 7.50 (m, 2H) ; 7.30 (m, 1H) ; 3.85 (m, 5H) ; 1.43 (m, 12 H). The chemical shifts of H_2 and H_4 were assigned with a NOE experiment (NOE = 5.0 % between H_4 and H_5). Anal. Calcd for $C_{19}H_{23}N_3O$: C, 73.7 ; H, 7.4 ; N, 13.6. Found : C, 73.6 ; H, 7.4 ; N, 13.5.

General procedure for the metalation reaction of diisopropylcarboxamide 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 **1** (0.2 g, 0.65 mmol) in anhydrous THF (15 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 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 organic layers dried on $MgSO_4$ and the solvent removed under reduced pressure.

4-Deuterio-3-*N,N*-diisopropylcarboxamido-9-methyl-9*H*-pyrido[2,3-*b*]indole (2a). The electrophile was EtOD (1 mL, 17 mmol) at -70 °C. The physical and spectral properties are similar to those of 1, but no signal corresponding to H_4 was observed.

3-*N,N*-Diisopropylcarboxamido-9-methyl-9*H*-pyrido[2,3-*b*]indole-4-carboxaldehyde (2b). The electrophile was ethyl formate (0.21 mL, 2.6 mmol) at -70 °C. Purification by flash chromatography (silica gel, cyclohexane/ethyl acetate 70/30, R_f = 0.3). Yield 72 %. mp 211 °C (decomp). ^{1}H NMR ($CDCl_3$, 200 MHz) : 10.45 (s, 1H) ; 8.90 (m, 1H) ; 8.50 (s, 1H) ; 5.67-7.73 (m, 3H) ; 3.48-4.00 (m, 5H) ; 1.00-1.85 (m, 12H). Anal. Calcd for $C_{20}H_{23}N_3O_2$: C, 71.2 ; H, 6.8 ; N, 12.4. Found : C, 71.1 ; H, 7.0 ; N, 12.4.

4-Azido-3-*N,N*-diisopropylcarboxamido-9-methyl-9*H*-pyrido[2,3-*b*]indole (2c). The electrophile was tosyl azide (0.63 g, 3.25 mmol) in THF (2 mL) at -20 °C. Purification by flash chromatography (silica gel, cyclohexane/ethyl acetate 70/30, R_f = 0.3). Yellow solid. Yield 89 %. No mp could be taken. ^{1}H NMR ($CDCl_3$, 60 MHz) : 8.35 (m, 1H) ; 8.3 (s, 1H) ; 7.7 - 7.1 (m, 3H) ; 4.2 - 3.5 (m, 5H) ; 2.0 - 1.0 (m, 12H).

4-(1-Hydroxyethyl)-3-*N,N*-diisopropylcarboxamido-9-methyl-9*H*-pyrido[2,3-*b*]indole (2d). The electrophile was acetaldehyde (1.5 mL, 26.8 mmol) at -70 °C. Purification with two consecutive flash chromatographies (silica gel, cyclohexane/ethyl acetate 70/30, R_f = 0.2). Yield 70 %. mp 205 °C. ^1H NMR ($CDCl_3$, 200 MHz) : 8.27 (s, 1H); 8.23 (m, 1H); 7.27 - 7.57 (m, 3H); 5.72 (q, 1H, J = 7 Hz); 3.50-3.97 (m, 5H) ; 0.85 - 2.00 (m, 15H). Anal. Calcd for $C_{21}H_{27}N_3O_2$: C, 71.4 ; H, 7.6 ; N, 11.9. Found : C, 71.0 ; H, 7.7 ; N, 11.6.

4-Iodo-3-*N,N*-diisopropylcarboxamido-9-methyl-9*H*-pyrido[2,3-*b*]indole (2e). The electrophile was iodine (0.66 g, 2.6 mmol) in THF (5mL) at -20 °C. The hydrolysis was carried out with a saturated solution of sodium thiosulfate (10 mL). Purification by flash chromatography (silica gel, cyclohexane/ethyl acetate, 70/30, R_f = 0.4). Yield 74 %. mp 244 °C. ^1H NMR ($CDCl_3$, 200 MHz) : 8.95 (m, 1H) ; 8.10 (s, 1H) ; 7.20-7.75 (m, 3H) ; 3.35-4.20 (m, 5H) ; 1.00-2.00 (m, 12H). Anal. Calcd for $C_{20}H_{23}N_3O_2I$: C, 52.4 ; H, 5.1 ; N, 9.6. Found : C, 52.6 ; H, 5.0 ; N, 9.31.

*General procedure for the coupling reactions of the iodo compound (**2e**) with arylboronic acids.*

A mixture of the iodo compound **(2e)** (0.09 g, 0.205 mmol), the appropriate arylboronic acid[19] (0.23 mmol) and barium hydroxide (0.147 g, 0.47 mmol of 8 H_2O salt) in dimethyl ether (1.2 mL) and water (0.23 mL) was degassed with an argon stream for 15 min. The catalyst (0.012 g, 0.01 mmol of tetrakis[triphenylphosphine]palladium[0]) was then added and the mixture heated to reflux for 48 h. Water (2 mL) was added and the solution extracted three times with dichloromethane. The organic layers were dried on $MgSO_4$ and the solvent removed.

3-*N,N*-Diisopropylcarboxamido-4-(3-methoxyphenyl)-9-methyl-9*H*-pyrido[2,3-*b*]indole (3a). Purification by flash chromatography (silica gel, cyclohexane/ethyl acetate 60/40, Rf = 0.45). mp 153 °C. Yield 80 %. ^1H NMR ($CDCl_3$, 200 MHz) : 8.44 (s, 1H); 7.60-7.05 (m, 8H); 4.05-3.30 (m, 8H); 1.60-0.60 (m, 18H). Anal. Calcd for $C_{26}H_{29}N_3O_2$: C, 75.15; H, 7.03; N, 10.11. Found : C, 75.1; H, 7.0; N, 9.8.

3-*N,N*-Diisopropylcarboxamido-4-(3,4-dimethoxyphenyl)-9-methyl-9*H*-pyrido[2,3-*b*]indole (3b). Purification by flash chromatography (silica gel, cyclohexane/ethyl acetate 60/40, R_f = 0.35). mp 197 °C. Yield 70 %. ^1H NMR ($CDCl_3$, 200 MHz) : 8.38 and 8.40 (2s, 1H); 7.60-7.36 (m, 11H). Anal. Calcd for $C_{27}H_{31}N_3O_3$: C, 72.8; H, 7.0; , 9.45. Found : C, 72.8; H, 7.4; N, 9.0.

3-*tert*-Butylcarbonylamino-9-methyl-9*H*-pyrido[2,3-*b*]indole (4). To a cooled mixture (5 °C) of 9-methyl-9*H*-pyrido[2,3-*b*]indole-3-carboxylic acid[8] (1.8 g, 7.95 mmol) and triethylamine (1.2 mL, 8.6

mmol) in acetone (90 mL), diphenylphosphoryl azide (1.8 mL, 8.4 mmol) was slowly added. After 5 h stirring at rt, the solvent was removed under reduced pressure. Water (250 mL) acidified with hydrochloric acid (pH = 2) was then added and the resulting mixture heated to reflux for 48 h. The mixture was basified (pH = 8) with sodium hydrogencarbonate and the solid collected by filtration. The solid was dried and the filtrate extracted with dichloromethane. The organic layer was dried on magnesium sulfate and removal of the solvent afforded an orange oil. This oil was mixed with the dried solid and anhydrous THF (90 mL) and triethylamine (2.4 mL, 17.2 mmol) were added. The mixture was cooled to 0 °C and pivaloyl chloride (2.1 mL, 17.2 mmol) was added dropwise. After 30 h stirring, water (15 mL) was added and the mixture was filtered. The solid was washed with dichloromethane and the aqueous layer was neutralized with sodium hydrogencarbonate and extracted with dichloromethane. The organic layers were collected, dried on magnesium sulfate, filtered and concentrated. Purification by flash chromatography (silica gel, cyclohexane/ethyl acetate 60/40, R_f = 0.3) afforded 1.7 g (72 %) of a white solid. mp 193 °C. IR : 3281 (NH) ; 1640 (C=O). ^{1}H NMR ($CDCl_3$, 200 MHz) : 8.77 (d, 1H, J = 2.4 Hz, H_4) ; 8.32 (d, 1H, J = 2.4 Hz, H_2) ; 8.00 (m, 1H, H_5) ; 7.54 (m, 2H, H_7 and NH) ; 7.39 (m, 1H, H_8) ; 7.26 (m, 1H, H_6) ; 3.89 (s, 3H, N-CH_3) ; 1.40 (s, 9H, *t*Bu). The chemical shifts of H_2 and H_4 were confirmed by a NOE experiment (5.4 % NOE between H_4 and H_5). Anal. Calcd for C_{17} $H_{19}N_3O$: C, 72.6 ; H, 6.8 ; N, 14.9 . Found : C, 72.2 ; H, 6.7 ; N, 14.7.

General procedure for the metalation reaction of protected amines and quenching with various electrophiles :

A two-necked flask, under an argon atmosphere is charged with the *N*-protected amine (**4**), TMEDA (0.54 mL, 3.6 mmol) and anhydrous THF (15 mL). The solution was cooled to -70°C and maintained at this temperature during the addition of *tert*-butyllithium (1.5 M solution in hexane, 2.4 mL, 3.6 mmol). After 6 h stirring at -70 °C, the electrophile (see amounts for each compound) was added and the resulting mixture stirred for 2 h at -70 °C. After careful hydrolysis of the reaction mixture with ethanol/water (50/50, 10 mL) and warming to rt, the aqueous layer was extracted with dichloromethane. The organic layers were collected, dried on magnesium sulfate and concentrated under reduced pressure.

3-*tert*-Butylcarbonylamino-4-deuterio-9-methyl-9*H*-pyrido[2,3-*b*]indole (5a). According to general procedure, with EtOD (1 mL, 17 mmol) as electrophile, compound (**5a**) was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 60/40, R_f = 0.3). Yield 80 %. mp 193 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) : 8.32 (s, 1H) ; 8.03 (s, 1H) ; 7.54 (m, 2H) ; 7.40 (m, 1H) ; 7.26 (m, 1H) ; 3.89 (s, 3H) ; 1.40 (s, 9H).

3-*tert*-Butylcarbonylamino-9-methyl-9*H*-pyrido[2,3-*b*]indole-4-carboxaldehyde (5b). According to general procedure, with ethyl formate (0.29 mL, 3.6 mmol) as electrophile, compound (**5b**) was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 70/30, R_f= 0.5). Yield 48 %. mp 199 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) : 11.16 (s, 1H) ; 10.97 (br s, 1H) ; 9.91 (s, 1H) ; 8.07 (m, 1H) ; 7.59 (m, 1H) ; 7.46 (m, 1H) ; 7.28 (m, 1H) ; 3.94 (s, 3H) ; 1.44 (s, 9H). Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.9 ; H, 6.2 ; N, 13.6. Found : C, 69.1 ; H, 6.3 ; N, 12.3.

4-Azido-3-*tert*-butylcarbonylamino-9-methyl-9*H*-pyrido[2,3-*b*]indole (5c). According to the general procedure with tosyl azide (0.7 g, 3.6 mmol) as electrophile, compound (**5c**) was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 60/40, R_f = 0.25). Yellow solid. Yield 50 %. No mp could be taken owing to quick decomposition by heating. ^{1}H NMR ($CDCl_3$, 200 MHz): 8.23 (s, 1H) ; 8.80 (m, 1H) ; 7.51 (m, 1H) ; 7.41 (s, 1H) ; 7.34 (m, 1H) ; 7.27 (m, 1H) ; 3.85 (s, 3H) ; 1.40 (s, 9H).

3-*tert*-Butylcarbonylamino-4-iodo-9-methyl-9*H*-pyrido[2,3-*b*]indole (5d). According to general procedure, with iodine (crystals, 0.92 g, 3.6 mmol) as electrophile, compound (**5d**) was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate, 70/30, R_f = 0.3). Yield 22 %. mp 173 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) : 8.79 (s, 1H) ; 8.82 (m, 1H) ; 7.60 (m, 1H) ; 7.44 (m, 1H) ; 7.36 (m, 1H) ; 3.94 (s, 3H) ; 1.46 (s, 9H). Anal. Calcd for $C_{17}H_{18}N_3OI$: C, 50.19; H, 4.45; N, 10.30. Found : C, 51.4; H, 4.6; N, 10.1.

4-Amino-3-*tert*-butylcarbonylamino-9-methyl-9*H*-pyrido[2,3-*b*]indole (6). A mixture of the azide (**5c**) (0.5 g, 1.55 mmol) and a few drops of piperidine in methanol (100 mL) was cooled to 0 °C. Hydrogen sulfide was bubbled into this solution for 1 h. The solution was stirred at rt for 12 h, under a slow bubbling of hydrogen sulfide. The excess of hydrogen sulfide was removed with a stream of compressed air. The solution was filtered and the solvent removed. The compound was purified by flash chromatography (neutral aluminium oxide, elution with cyclohexane/ethyl acetate 55/45, R_f = 0.4). Yield 0.4 g (88 %). mp 241 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) : 7.99 (s, 1H) ; 7.77 (m, 1H); 7.35 (m, 4H) ; 4.93 (s, 2H) ; 3.80 (s, 3H) ; 1.41 (s, 9H). ^{13}C NMR ($CDCl_3$) : 178.7 (C=O) ; 151.5 (C_{1a}) ; 145.1 (C_4) ; 144.4 (C_2) ; 139.3 (C_{8a}) ; 124.9, 120.6 and 119.7 (C_5, C_6, C_7, no attribution) ; 119.8 (C_{5a}) ; 112.3 (C_{4a}) ; 39.4 (tBu) ; 27.9 (CH_3) ; 27.7 (N-CH_3). Anal. Calcd for $C_{17}H_{20}N_4O$: C, 68.9; H, 6.8; N, 18.9. Found : C, 68.4; H, 6.8; N, 18.3.

3,4-Diamino-9-methyl-9*H*-pyrido[2,3-*b*]indole (7).

A solution of **6** (0.1 g, 0.34 mmol) in aqueous sulfuric acid (20 % solution, 10 mL) was heated to reflux for 7 h. After cooling, the mixture was poured in crushed ice (20 g) containing aqueous ammonia (20 % solution, 10 mL). The pH was adjusted to 8 and the aqueous layer extracted with dichloromethane. After drying on magnesium sulfate, the solvent was removed. Owing to quick decomposition, this compound was not purified before the cyclisation reactions. ^{1}H NMR ($CDCl_3$, 200 MHz) : 7.98 (s, 1H) ; 7.85 (m, 1H) ; 7.35-7.45 (m, 2H) ; 7.23 (m, 1H) ; 5.29 (s, 2H) ; 3.85 (s, 3H) ; 2.91 (s, 2H).

11-Hydroxy-9-methyl-9*H*-imidazo[4',5':3,4]pyrido[2,3-*b*]indole (8).

A mixture of the diamine (7) (0.065 g, 0.307 mmol) and 1,1'-carbonyldiimidazole (0.073 g, 0.45 mmol) in THF (1.5 mL) was heated to reflux for 4 h. After cooling, the solid material was collected by filtration, washed with cyclohexane and dried affording pure **8**. Yield 0.055 g (75 %). mp > 250 °C. ^{1}H NMR (DMSO-d_6, 200 MHz) : 10.92 (s, 2H) ; 8.43 (m, 1H) ; 8.09 (s, 1H) ; 7.63 - 7.18 (m, 2H) ; 7.22 (m, 1H) ; 3.85 (s, 3H). ^{13}C NMR (DMSO-d_6) : 155.9 (C_{11}) ; 148.0 (C_{1a}) ; 139.6 (C_{8a}) ; 130.4 (C_4) ; 126.1 (C_2) ; 126.1 (C_8) ; 122.5 (C_5); 121.5 (C_{5a}); 119.5 (C_6); 118.0 (C_3); 109.3 (C_8); 98.0 (C_{4a}) ; 27.9 (N-Me). Anal. Calcd for $C_{13}H_{10}N_4O$: C, 65.5; H, 4.2; N, 23.5. Found : C, 65.5; H, 4.0; N, 23.4.

11-*N*,*N*-Dimethylamino-9-methyl-9*H*-imidazo[4', 5' : 3,4]pyrido[2,3-*b*]indole (10).

A mixture of the diamine (7) (0.049 g, 0.23 mmol) and pyridine (0.065 mL, 0.76 mmol) in dry acetonitrile (2 mL) was cooled to 0 °C. A solution of phosgene iminium chloride (0.041g, 0.25 mmol) in dry acetonitrile (1 mL) was then added. The resulting mixture was heated to reflux for 24 h. After cooling, hydrolysis was carried out with sodium hydrogencarbonate (aqueous saturated solution, 6 mL) under ice-cooling. After 45 min stirring, the aqueous layer was separated and extracted with dichloromethane. The combined organic layers was dried on $MgSO_4$ and the solvent removed. Purification by flash chromatography (silica gel, progressive elution from cyclohexane/ethyl acetate 60/40 to pure ethyl acetate and finally ethyl acetate/methanol 90/10 in which $R_f = 0.5$). Yield 0.031 g (52 %). mp > 250°C. HRMS Calcd for $C_{15}H_{15}N_5$: 265.1328. Found : 265.1320. ^{1}H NMR ($CDCl_3$, 200 MHz) : 8.42 (s, 1H) ; 8.35 (m, 1H) ; 7.11-7.52 (m, 4H) ; 3.97 (s, 3H) ; 3.27 (s, 6H).

10-*N*-(1-Methylethenyl)-9-methyl-11-*N*,*N*-dimethylamino-9*H*-imidazo[4',5':3,4]pyrido[2,3-*b*]indole (11).

The procedure is similar as that described for **10** and **12** with the diamine (7) (0.07 g, 0.33 mmol), triethylamine (0.158 mL, 1.13 mmol) dissolved in acetonitrile (2 mL) and phosgene iminium chloride

(0.061 g, 0.37 mmol) dissolved in acetonitrile (1 mL). The compound was purified by flash chromatography (silica gel, elution with cyclohexane/ethyl acetate 60/40, R_f = 0.25). mp 189 °C. Yield 0.03 g (30 %). HRMS Calcd for $C_{18}H_{19}N_5$: 305.1641. Found : 305.1640. ^{1}H NMR ($CDCl_3$, 200 MHz) : 8.45 (m, 1H); 8.32 (s, 1H); 7.43-7.55 (m, 2H); 7.32 (m, 1H); 5.49 and 5.44 (m, 2H); 4.00 (m, 3H); 3.27 (s, 6H); 2.12 (s, 3H). ^{13}C NMR ($CDCl_3$) : 159.0 (C_{11}); 149.1 (C_4); 144.1 (C_{1a}); 140.9(C_{8a}); 139.7 (C of N-isoprenyle); 128.8 (C_{5a}); 126.6 (C_2); 124.9 (C_7); 122.9 (C_5); 119.8 (C_3); 119.1 (C_6) ; 114.6 (CH_2 isoprenyle); 108.2 (C_8); 103.7 (C_{4a}); 40.4 (CH_3 isoprenyle); 28.0 (N-CH_3); 20.2 (N(CH_3)$_2$).

9-Methyl-11-*N,N*-dimethylamino-10-*N,N*-dimethylcarboxamido-9*H*-imidazo[4',5':3,4]pyrido[2,3-*b*]indole (12).

A mixture of diamine (7) (0.06 g, 0.28 mmol) and pyridine (0.16 mL, 1.86 mmol) in dry acetonitrile (2 mL) was cooled to 0 °C. A solution of phosgene iminium chloride (0.1 g, 0.62 mmol) in dry acetonitrile (1 mL) was then added. The mixture was heated to reflux for 24 h. After cooling, and hydrolysis under ice-cooling with sodium hydrogencarbonate (saturated aqueous solution, 6 mL) the mixture was stirred for 45 min. The work up and the purification are similar as that described for **10**. TLC : R_f = 0.2 in ethyl acetate. Yield 0.028 g (30 %). mp 204 °C (decomp). HRMS. Calcd for $C_{18}H_{20}N_6O$: 336.1698. Found : 336.1684. ^{1}H NMR ($CDCl_3$, 200 MHz) : 8.45 (m, 1H); 8.22 (s, 1H); 7.45-7.6 (m, 2H); 7.33 (m, 1H); 4.01 (m, 3H); 3.27 (m, 12H). ^{13}C NMR ($CDCl_3$) : 159.1 (C=O); 153.0 (C_{11}); 149.6 (C_{1a}); 145.2 (C_4); 139.6 (C_{8a}); 126.5 (C_3); 126.3 (C_2); 125.2, 123.0 and 119.3 (C_5, C_6, C_7); 119.8 (C_{5a}); 108.3 (C_8); 103.8 (C_{4a}); 40.0 (N-Me_2); 38.6 (NMe_2 urea); 28.0 (N-CH_3).

9,11-Dimethyl-9*H*-imidazo[4',5':3,4]pyrido[2,3-*b*]indole (13).

A mixture of the diamine (7) (0.071g, 0.035 mmol), ethylacetimidate hydrochloride (0.083 g, 0.67 mmol) in ethanol (2 mL) was heated to reflux for 24 h. Ethyl acetimidate hydrochloride (0.083 g, 0.67 mmol) was added again and the reflux maintained for two additionnal hours. After removal of the solvent, sodium hydroxide (2M aqueous solution, 3 mL) was added under ice-cooling. The aqueous layer was extracted with dichloromethane. After drying with $MgSO_4$, the solvent was removed. The residue was purified by flash chromatography (silica gel, progressive elution from pure ethyl acetate to ethyl acetate/methanol 95/5 in which R_f = 0.15). Yield 0.0124 g (15 %). mp > 250 °C. HRMS : Calcd for $C_{14}H_{12}N_4$: 236.1062. Found : 236.1068. ^{1}H NMR ($CDCl_3$, 200 MHz) : 8.84 (s, 1H) ; 8.24 (m, 1H) ; 7.49 (m, 2H) ; 7.21-7.27 (m, 2H) ; 4.04 (s, 3H) ; 2.73 (s, 3H).

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Received, 8th May, 1997