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A NEW CONVERGENT SYNTHESIS OF alpha - SUBSTITUTED - beta - CARBOLINES

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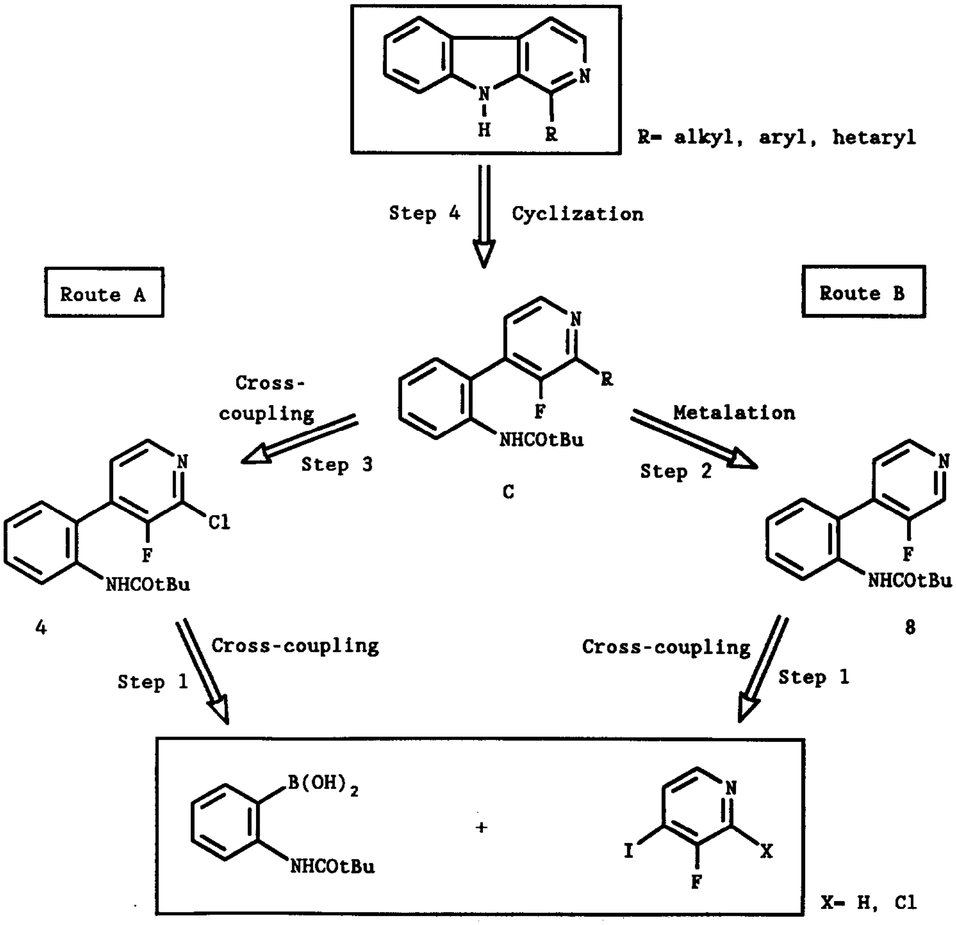
Abstract: New convergent synthesis of natural α-substituted-β-carbolines through metalations, cross-couplings and intramolecular substitution via (2-aminobenzene)-boronic acid, arylstannanes and ortho-fluoroiodopyridines.

INTRODUCTION.

Numerous alkaloids of the β-carboline series with various substituents at the alpha-position display interesting biological properties.[1] Most syntheses of such molecules are based on condensation reactions[2] between tryptophan or tryptamine and aldehydes. Some derivatives are prepared from available β-carboline reagents such as Norharman or Harmane[3] through specific reactions. In a previous paper,[4] we described a general and convergent route to the four parent carbolines based on metalation[5] and cross-coupling[6a,b] reactions. So, it was interesting to fit this methodology to the synthesis of natural α-substituted β-carbolines.

RETROSYNTHETIC ANALYSIS.

From a retrosynthetic analysis (scheme I) α-substituted β-carbolines could be prepared by cyclization of conveniently functionnalized phenylpyridines (step 4). These phenylpyridines could be obtained either by a cross-coupling reaction (step 3 - route A) or by a directed metalation of the heterobiaryl 8 taking advantage of the ortho-directing effect of the fluoro group (step 2 - route B). Heterobiaryls (4 and 8) could be prepared through a coupling reaction between the required benzene and pyridine building blocks (steps 1 - route A or B).



Scheme I

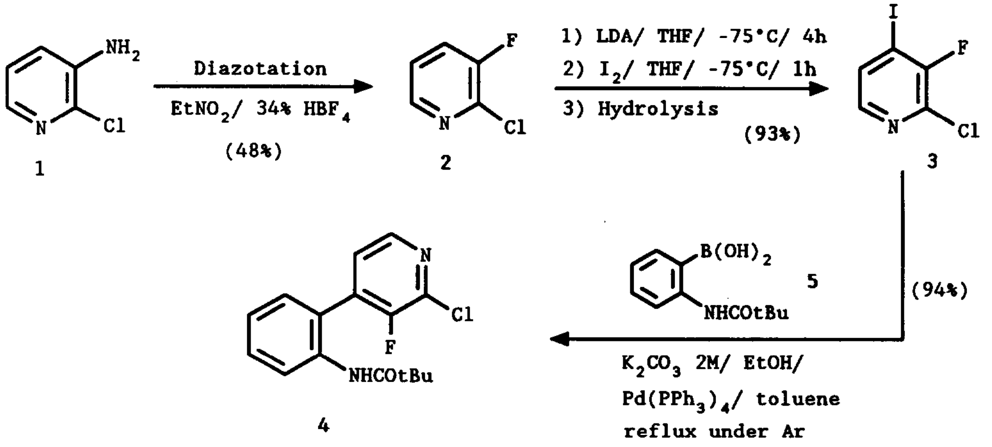
These two pathways (A and B) will be discussed in the present paper.

RESULTS AND DISCUSSION.

Route A.

a) Synthesis of 2,2-dimethyl-N-(2-(2-chloro-3-fluoro-4-pyridyl)phenyl) propanamide (4).

Diazotation of 3-amino-2-chloropyridine (**1**) according to the Talik's procedure[7] afforded 2-chloro-3-fluoropyridine (**2**). Directed metalation of this pyridine (**2**) by LDA in THF at -75°C followed by reaction of the resulting lithio derivative with iodine gave the expected 4-iodopyridine (**3**) in high yield. The heteroring cross-coupling between **3** and (2-pivaloylamino)benzeneboronic acid (**5**)[4] using the Suzuki's procedure almost quantitatively gave the corresponding 4-phenylpyridine (**4**) (scheme II).

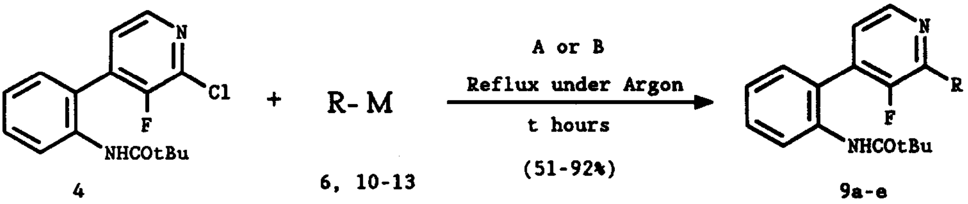


Scheme II

The foregoing cross-coupling is fully regioselective at the C-4 iodo position. This is in good agreement with the reactivity scale of halogens towards cross-coupling.[6a]

*b) Cross-coupling reactions between **4** and arylboronic acids or arylstannanes.*

The palladium catalyzed cross-coupling reaction between phenylboronic acid (**6**) and the 4-phenyl-2-chloropyridine (**4**) gave the corresponding heterotriaryl (**9a**) in good yield. This procedure could not be extended to other arylboronic acids due to dechloration of the starting material. Nevertheless, good results were obtained by coupling the same chloropyridine (**4**) with arylstannanes (**10-13**) (these stannanes were prepared by transmetalation on the corresponding lithio derivatives) (scheme III and table I).



A (phenylboronic acid): $Pd(PPh_3)_4$/ K_2CO_3 2M/ EtOH/ toluene (t= 60 h)

B (arylstannane): $Pd(PPh_3)_4$/toluene (t= 48h)

Scheme III

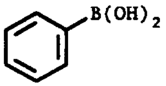
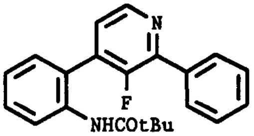
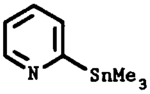
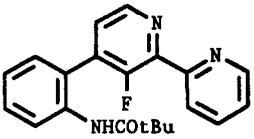
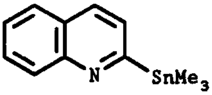
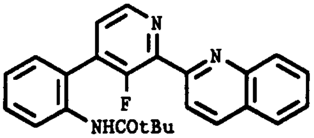
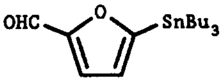
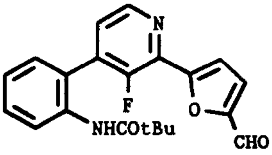
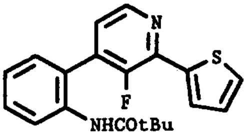
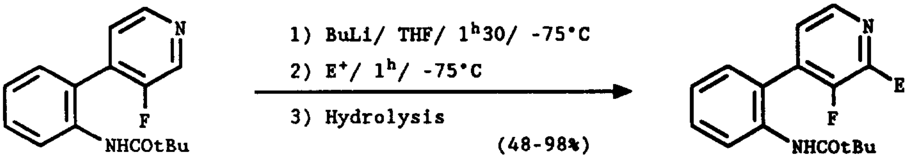
Entry	R-M	Product	Yields (%)
1	 (6)	 (9a)	89
2	 (10)	 (9b)	92
3	 (11)	 (9c)	78
4	 (12)	 (9d)	51
5	 (13)	 (9e)	89

Table I

These results show that the chloro group can induce a cross-coupling with phenylboronic acid. This reaction was however better achieved using arylstannanes instead of boronic acids likely due to the softer coupling conditions of the stannanes.

Route B.

The 4-phenyl-3-fluoropyridine (8) was subjected to lithiation with n-butyllithium at low temperature. Metallation occur almost quantitatively and regioselectively at the C-2 position as shown by deuterium incorporation (D_2O) and reaction with electrophiles (scheme IV and table II).



8

Scheme IV

14a-1

Electrophile	E	(Product)	Yield (%)
D_2O	D	(14a)	> 98
I_2	I	(14b)	89
CH_3I	CH_3	(14c)	70
C_2H_5I	C_2H_5	(14d)	48
HCOOEt	CHO	(14e)	81
CH_3CHO	CH_3CHOH	(14f)	78
PhCHO	PhCHOH	(14g)	83
$ClSiMe_3$	$SiMe_3$	(14h)	83
$ClSnMe_3$	$SnMe_3$	(14i)	91*
$ClSnBu_3$	$SnBu_3$	(14j)	78
MeO-BBN	BBN	(14k)	73
TsCN	CN	(141)	42**

Table II

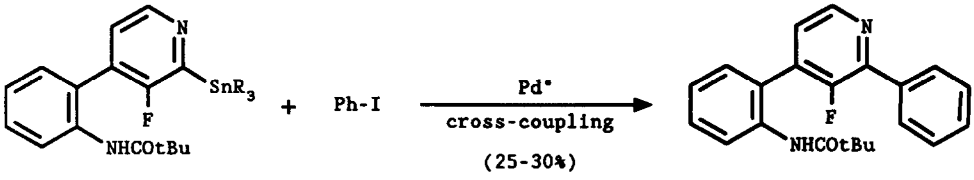
*: ^{1}H NMR integration.

**: The same nitrile 141 was obtained in good yield (79%) from aldehyde 14e according to the Vowinkel and Bartel's procedure.[8]

Metalation of 3-fluoro-4-(2-pivaloylaminophenyl)pyridine (8) is regioselectively directed by the fluoro group at the most acidic C-2 position of the pyridine ring. No reaction can be observed on the benzene ring due to the ortho-directing effect of the pivaloylamino moiety.

Synthesis of iodo compound 14b allows another access to the heterotriaryl 9a after coupling with phenylboronic acid by the Suzuki's procedure in a 77% yield. The overall sequence requires a more simple pyridine reagent than 2-chloro-3-fluoropyridine (2).

Synthesis of stannanes 14i and 14j by metalation of fluoropyridine 8 was succesfull (scheme IV and table II). However, the use of these intermediates as coupling reagents with iodobenzene failed and only low yields of triaryl derivative 9a were observed (scheme V).



R= Me (14i), Bu (14j)

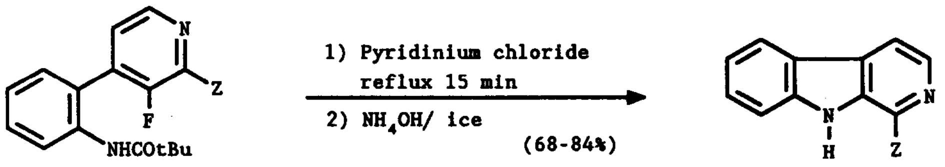
Scheme V

9a

It seems that the fluoro atom in position ortho to the trialkylstannyl or dialkylboranyl group reduces the reactivity of these moieties towards cross-coupling. Similar molecules without the fluoro group like 2-trimethylstannylpyridine (10) and 2-trimethylstannylquinoline (11) show a good reactivity under the same conditions (table I). A possible explanation for this lack of reactivity can be the stabilization of the C_2-Metal bond (LUMO of the metal) by the electron donating effect of the fluoro atom through the pyridine ring.

Cyclization.

The (o-pivaloylamino)phenyl-o'-fluoropyridines (9a-c,e; 14c-d,f,l) (previously obtained according to route A or B) were cyclized by treatment with boiling pyridinium chloride (210°C). The corresponding α-substituted-β-carbolines (15a-h) were thus isolated in good yields (scheme VI and table III).



9a-c,e; 14c-d,f,1 **15a-h**

Scheme VI

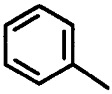
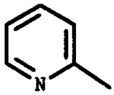
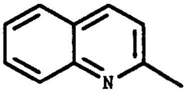
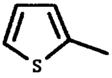
Z	Yield (%)	Product
	80	15a
	75	15b
	83	15c
	68	15d
CH_3-	84	15e
CH_3CH_2-	79	15f
CH_2=CH-*	76	15g
NC-	78	15h

Table III

*: Before cyclization, Z group is $CH_3CH(OH)$-.

Cyclization of aldehyde **14e** and trimethylsilylpyridine **14h** could not be performed without decarbonylation and desilylation giving rise to Norharman in 50% and 73% yields respectively. Cyclization of **14f** occurs simultaneously with dehydratation of the hydroxyethyl group to give pavettine,[1,9] a natural alkaloid of the *Pavetta Lanceolata*.

CONCLUSION.

The link between the metalation[5] and the cross-coupling[6a,b] provides a new convenient and simple way to α-substituted β-carbolines. α-Substituted β-carbolines are prepared in three steps from (2-pivaloylamino)benzeneboronic (5) acid and 2-chloro-3-fluoro-4-iodopyridine (3) (route A) or 3-fluoro-4-iodopyridine (7) (route B). The overall strategy shows a complete regioselectivity as well as a good convergence. Moreover, this general pathway allows good overall yields (37-67%) in few steps.

Among the synthesized β-carbolines, harmane (15e), 1-éthyl-β-carboline (15f), pavettine (15g) and nitramarine (15c)[10] are biologically active alkaloids. The easily prepared cyano compound (15h) is a key intermediate in the synthesis of various eudistomins.[12]

Nitramarine (15c)[10] possesses the carbocyclic skeleton of Lavendamycine[11], an highly active antimicrobial and antitumor alkaloid produced by the *Streptomyces Lavendulae*. Thus, the present work on the synthesis of natural α-substituted β-carbolines is currently being extended to the preparation of more complex structures.

Acknowledgments. Financial support of this research by the Centre National de la Recherche Scientifique and the Ministère de la Recherche et de la Technologie (Aide MRT n°8917) is gratefully acknowledged.

EXPERIMENTAL SECTION.

General data. The ^1H NMR spectra were obtained on a Varian T60 (60 MHz) spectrometer (and were recorded in ppm downfield from internal standard, TMS in $CDCl_3$ or HMDS in DMSO-d_6) or on a 200 MHz Brücker spectrometer. ^{13}C NMR spectra were recorded on a 200 MHz Brücker spectrometer. IR spectra were taken on a Beckman IR 4250 spectrometer, and main absorption frequencies (NH, CH, C=O, C=C, C=N) are given in cm^{-1}. Mass spectra were obtained on a JEOL D700 instrument, and elemental analyses were performed on a Carlo Erba CHN apparatus.

Solvent. Tetrahydrofuran (THF) was distilled from benzophenone/sodium and stored over 3Å molecular sieves under argon atmosphere. The water content of the solvent was estimated by the modified Karl-Fischer method:[13] < 45 ppm.

Starting materials. Commercial diisopropylamine was distilled from CaH_2 and stored over CaH_2 under a dry argon atmosphere. 3-Amino-2-chloropyridine (1) and phenylboronic acid (6) were commercial origin. 2,2-Dimethyl-N-(2-(3-fluoro-4-pyridyl)phenyl)propanamide (8) was prepared by cross-coupling reaction between 3-fluoro-4-iodopyridine (7) and (2-pivaloylamino)phenylboronic acid (5) according to the procedure described in our previous paper.[4] Commercial 2.5 M solution of n-butyllithium in hexane was stored and transfered under a deoxygenated and dehydrated argon atmosphere.

2-Chloro-3-fluoropyridine (2). This molecule was prepared by diazotation of the commercial 3-amino-2-chloropyridine (1) according to the Talik's procedure.[7] The yield was 48% after distillation at reduced pressure, bp: 80°C/80 mmHg (lit[17] bp: 84-85°C/ 55 mmHg); ^{1}H NMR ($CDCl_3$) δ 7.25 (dd, 1H, H_5), 7.60 (dd, 1H, H_4), 8.20 (dd, 1H, H_6), J_{4-5}= 5.0 Hz, J_{5-6}= 5.0 Hz, J_{4-6}= 2.0 Hz, J_{H-F}= 5.0 Hz; IR (film) 3060, 1590, 1490, 1425, 1275, 1225, 1090, 805, 725, 680; η_D= 1.5110 (lit[17] η_D= 1.5022). Anal. Calcd for C_5H_3ClFN (131.54): C, 45.66; H, 2.30; N, 10.65. Found: C, 45.45; H, 2.24; N, 10.50.

2-chloro-3-fluoro-4-iodopyridine (3). 2-Chloro-3-fluoropyridine (2) (6.58 g, 0.050 mol) was slowly added to a cold (-75°C) solution of lithium diisopropylamide in THF (previously prepared by reaction of diisopropylamine (7.0 mL, 0.050 mol) in dry THF (200 mL) and n-butyllithium (2.5 M, 20 mL, 0.050 mol) at -75°C for 15 minutes). The resulting mixture was stirred for 4 h at -75°C, before addition of iodine (12,7g, 0.050 mmol) in THF (40 mL). Stirring was continued for 1h at -75°C, before hydrolysis by a mixture of H_2O/THF (10 mL/50 mL) at -75°C, furthur addition of water (50 mL) at 0°C and reductive workup with solid sodium thiosulfate. Extraction by Et_2O, drying over $MgSO_4$ and solvent removal afforded a crude solid, which was purified by sublimation (80°C/1 mmHg). The yield was 93%: mp 104°C; ^{1}H NMR ($CDCl_3$) δ 7.64 (dd, 1H, H_5), 7.84 (d, 1H, H_6), J_{5-6}= 5.1 Hz, J_{F-H5}= 5.0 Hz; ^{13}C NMR ($CDCl_3$) δ 93.26 (d, C_4, J_{C4-F}= 24.0 Hz), 133.38 (s, C_5, J_{C5-F}= 1.2 Hz), 138.22 (d, C_2, J_{C2-F}= 21.6 Hz), 144.74 (d, C_6, J_{C6-F}= 7.2 Hz), 154.92 (d, C_3, J_{C3-F}= 258.7 Hz); IR (KBr) 1560, 1440, 1400, 825, 745. Anal. Calcd for C_5H_2ClFIN (257.43): C, 23.33; H, 0.78; N, 5.44. Found: C, 23.17; H, 0.76; N, 5.32.

2,2-Dimethyl-N-(2-(2-chloro-3-fluoro-4-pyridyl)phenyl)propanamide (4). 2-Chloro-3-fluoro-4-iodopyridine (3) (10.0 mmol) was added to a solution of potassium carbonate (2M, 10.0 mL) and ethanol (5.0 mL) in deoxygenated toluene (100 mL). The resulting mixture was stirred 0.5h under argon atmosphere. (2-Pivaloylamino)benzeneboronic (5) acid (10.0 mmol) and tetrakis (triphenylphosphine)palladium[0] (350 mg, 0.30 mmol) were added and this mixture was refluxed for 48h. Cooling, filtration, decantation, extraction by toluene, drying over $MgSO_4$ and solvent removal afforded a crude oil, which was purified by preparative flash chromatography on silica (ethyl acetate/hexane: 5/5). The yield was 94% of 4: mp 169-170°C; ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 9H, tBu), 7.22 (d, 1H, H_5), 7.26 to 7.34 (m, 3H, NH + H_5+ H_6 phenyl), 7.46 (comp, 1H, H_4 phenyl), 7.78 (d, 1H, H_3 phenyl), 8.25 (d, 1H, H_6), J_{5-6}= 4.9 Hz, J_{3-4}= 8.0 Hz; ^{13}C NMR ($CDCl_3$) δ 176.44

(C=O), 151.40 (d, C_3, J_{C3-F}= 260.5 Hz), 144.65 (d, C_6, J_{C6-F}= 7.0 Hz), 139.53 (d, C_2, J_{C2-F}= 20.1 Hz), 136.05 (d, C_4, J_{C4-F}= 14.24 Hz), 134.86, 130.30, 129.76, 126.41, 125.76, 125.39, 125.07, 39.23, 27.10; IR (KBr) 3280, 2960, 1655, 1490, 1400, 770, 700, 650. Mass Calcd for $C_{16}H_{16}ClFN_2O$ (306.77), found ($MS^{+\cdot}$): 306/308 ($^{35}Cl/^{37}Cl$). Anal. Calcd for $C_{16}H_{16}ClFN_2O$ (306.77): C, 62.65; H, 5.26; N, 9.13. Found: C, 62.83; H, 5.38; N, 9.12.

2,2-Dimethyl-N-(2-(3-fluoro-2-phenyl-4-pyridyl)phenyl)propanamide (9a). 2,2-Dimethyl-N-(2-(2-chloro-3-fluoro-4-pyridyl)phenyl)propanamide (4) (2.0 mmol) was added to a solution of potassium carbonate (2M, 2.0 mL) and ethanol (1.0 mL) in deoxygenated toluene (20 mL). The resulting mixture was stirred 0.5h under argon atmosphere. Phenylboronic acid (2.0 mmol) and tetrakis (triphenylphosphine)palladium[0] (0.06 mmol) were added and this mixture was refluxed for 48 h. Cooling, filtration, decantation, extraction by toluene, drying over $MgSO_4$ and solvent removal afforded a crude product, which was purified by preparative flash chromatography on silica (ethyl acetate/hexane: 2/8). The yield was 89% of 9: mp 102°C; ^1H NMR ($CDCl_3$) δ 1.05 (s, 9H, tBu), 7.05 to 7.65 (m, 8H, $7H_{arom.}$+ NH), 7.75 to 8.15 (m, $3H_{arom.}$), 8.50 (d, 1H, H_6), J_{5-6}= 5.0 Hz; IR (KBr) 3280, 3050, 2980, 2950, 1650, 1520, 1490, 1210, 790, 750, 695. Anal. Calcd for $C_{22}H_{21}FN_2O$ (348.42): C, 75.84; H, 6.08; N, 8.04. Found: C, 75.93; H, 6.00; N, 8.04.

2-Trimethylstannylpyridine (10). n-Butyllithium (6.0 mmol) was slowly added to a cold (-75°C) solution of 2-bromopyridine (950 mg; 6.0 mmol) in dry THF (100 mL). The resulting solution was reacted for 1h at -75°C. A solution of trimethyltin chloride (1,20g; 6.0 mmol in 20 mL of THF) was slowly added. Stirring was continued for 1h before hydrolysis at 0°C by water. Extraction by diethyl ether, drying over $MgSO_4$ and solvent removal afforded a crude oil, which was purified by distillation at reduced pressure. The yield was 85 % of 10: bp 40°C/ 0.3 mmHg (lit[14] bp: 81-83°C/ 10 mmHg); ^1H NMR ($CDCl_3$) δ 0.35 (s, 9H, $SnMe_3$), 6.95 to 7.65 (m, 3H, H_3 + H_4 + H_5), 8.70 (dd, 1H, H_6), $^2J(^1H-^{119}Sn)$= 56.0 Hz; IR (film): 3060, 2980, 1570, 1560, 1450, 1420, 770, 750, 530. Anal. Calcd dor $C_8H_{13}NSn$ (241.89): C, 39.72; H, 5.42; N, 5.79. Found: C, 39.92; H, 5.28; 5.69.

2-Trimethylstannylquinoline (11). The foregoing procedure, with 2-bromoquinoline, gave 83% of 11 as an oil. This molecule can also be prepared according to the Yamamoto's procedure[14] by action of $NaSnMe_3$ on 2-chloroquinoline. The 2-trimethylstannylquinoline was purified by distillation at reduced pressure: bp 125°C/ 0.3 mmHg (lit[14] bp: 124-126/ 1.0 mmHg); ^1H NMR ($CDCl_3$) δ 0.46 (s, 9H, $SnMe_3$), 7.48 (dd, 1H, H_6), 7.56 (d, 1H, H_3), 7.69 (dd, 1H, H_7), 7.77 (d, 1H, H_5), 7.98 (d, 1H, H_4), 8.18 (d, 1H, H_8), J_{3-4}= 8.0 Hz, J_{5-6}= 8.2 Hz, J_{6-7}= 7.0 Hz, J_{7-8}= 8.4 Hz, $^2J(^1H-^{119}Sn)$= 56.0 Hz; IR (film) 3050, 2980, 2920, 1620, 1585, 1550, 1500, 1420, 1285, 1140, 1130, 940, 820, 770, 745. Anal. Calcd for $C_{12}H_{15}NSn$ (291.97): C, 49.36; H, 5.18; N, 4.80. Found: C, 49.40; H, 5.43; N, 4.99.

5-Tri-n-butylstannyl-2-furannecarbaldehyde (12). n-Butyllithium (12 mmol) was slowly added to a cold (-75°C) solution of furfural diethyl acetal (1.70 g; 10.0 mmol) in dry THF (40 mL). The resulting solution was reacted for 1h at -75°C. A solution of tributyltin chloride (2.71 mL; 10.0 mmol in 10 mL of THF) was slowly added and stirring was continued for 2h at -50°C before hydrolysis at 0°C by 1N hydrochloric acid solution (30 mL). Extraction by ether, drying over $MgSO_4$ and solvent removal afforded a crude oil which was purified by flash chromatography on silica (ethyl acetate/hexane: 2/8). The yield was 71% of 12. This product was obtained as an oil: ^1H NMR ($CDCl_3$) δ 0.60 to 1.65 (m, 27H, $SnBu_3$), 6.65 (d, 1H, H_3), 7.20 (d, 1H, H_4), 9.65 (s, 1H, CHO), J_{3-4}= 4.0 Hz; IR (film) 2960, 2920, 2870, 2850, 1685, 1560, 1460, 1375, 1075, 1050, 750. Anal. Calcd for $C_{17}H_{30}O_2Sn$ (385.12): C, 53.02; H, 7.85. Found: C, 52.84; H, 8.12.

2-Trimethylstannylthiophene (13). n-Butyllithium (0.050 mole) was slowly added to a cold (0°C) solution of thiophene (4.21 g; 0.050 mole) in dry THF (100 mL). The resulting solution was reacted for 2h at 0°C. A solution of trimethyltin chloride (10.0 g; 0.050 mole in 30 mL of THF) was slowly added and stirring was continued for 1h at 0°C before hydrolysis at 0°C by 50 mL of water. Extraction by ether, drying over $MgSO_4$ and solvent removal afforded a crude liquid which was purified by distillation at reduced pressure (180°C/ 40 mmHg). The yield was 85% of 13: ^1H NMR ($CDCl_3$) δ 0.42 (s, 9H, $SnMe_3$), 7.26 to 7.32 (m, 2H, H_3+ H_4), 7.69 (dd, 1H, H_5), J_{3-4}= 3.2 Hz, J_{4-5}= 4.5 Hz, J_{3-5}= 1.0 Hz, $^2J(^1H-^{119}Sn)$= 56.0 Hz; IR (film) 3060, 3040, 2980, 2910, 1495, 1390, 1215, 1190, 1080, 945, 845, 775, 700, 535. Anal. Calcd for $C_7H_{12}SSn$ (246.93): C, 34.05; H, 4.90. Found: C, 33.87; H, 4.80.

General procedure for cross-coupling of 2,2-dimethyl-N-(2-(2-chloro-3-fluoro-4-pyridyl)phenyl)propanamide (4) with hetarylstannanes (10-13). 2,2-dimethyl-N-(2-(2-chloro-3-fluoro-4-pyridyl)phenyl)propanamide (4) (1.0 mmol) was added in deoxygenated toluene (10 mL). The resulting mixture was stirred 0.5h under argon atmosphere. The corresponding stannane (1.0 mmol) and tetrakis(triphenylphosphine)palladium[0] (35 mg, 0.03 mmol) were added and this mixture was refluxed for 60h. Cooling, filtration, decantation, extraction by toluene, drying over $MgSO_4$ and solvent removal afforded a crude product, which was purified by preparative flash chromatography on silica (ethyl acetate/hexane: 2/8).

2,2-Dimethyl-N-(2-(3-fluoro-2-(2′-pyridyl)-4-pyridyl)phenyl) propanamide (9b). The foregoing procedure, applied to 4 and 10 gave 92% of 9b: mp 175-176°C; ^1H NMR ($CDCl_3$) δ 1.05 (s, 9H, tBu), 7.20 to 7.65 (m, 3H, $2H_{arom.}$+ NH), 7.75 to 8.10 (m, $6H_{arom.}$), 8.60 (d, 1H, H_6), 8.75 (d, 1H, $H_{6'}$), J_{5-6}= 5.0 Hz, $J_{5'-6'}$= 4.5 Hz; IR (KBr) 3300, 3060, 2960, 2930, 2870, 1660, 1585, 1515, 1490, 1410, 1100, 805, 755. Anal. Calcd for $C_{21}H_{20}FN_3O$ (349.41): C, 72.19; H, 5.77; N, 12.03. Found: C, 72.40; H, 5.51; N, 12.24.

2,2-Dimethyl-N-(2-(3-fluoro-2-(2'-quinolyl)-4-pyridyl)phenyl) propanamide (9c). The foregoing procedure, applied to **4** and **11** gave 78% of **9c**: mp 136 °C; ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 9H, tBu), 7.10 to 8.00 (m, 9H, $8H_{arom.}$+ NH), 8.05 to 8.25 (m, $3H_{arom.}$), 8.55 (d, 1H, H_6), J_{5-6}= 5.0 Hz; IR (KBr) 3280, 3060, 2950, 2920, 1650, 1520, 1500, 1415, 1220, 835, 755. Anal. Calcd for $C_{25}H_{22}FN_3O$ (399.47): C, 75.17; H, 5.55; N, 10.52. Found: C, 75.30; H, 5.50; N, 10.47.

2,2-Dimethyl-N-(2-(3-fluoro-2-(5'-formylfuran-2'-yl)-4-pyridyl) phenyl) propanamide (9d). The foregoing procedure, applied to **4** and **12** gave 51% of **9d**: mp 173-174 °C; ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9H, tBu), 7.15 to 7.60 (m, $7H_{arom.}$), 7.85 (d, 1H, $H_{3'}$), 8.60 (d, 1H, H_6), 9.85 (s, 1H, CHO), J_{3-4}= 7.0 Hz, J_{5-6}= 5.0 Hz; IR (KBr) 3370, 3170, 3100, 2980, 2860, 1665, 1515, 1440, 1420, 1040, 815, 765. Mass calcd for $C_{21}H_{19}FN_2O_3$ (366.40), found (M+1) 367 (chemical ionization). Anal. Calcd for $C_{21}H_{19}FN_2O_3$ (366.40): C, 68.84; H, 5.23; N, 7.65. Found: C, 68.98; H, 5.39; N, 7.44.

2,2-Dimethyl-N-(2-(3-fluoro-2-(2'-thienyl-4-pyridyl)phenyl) propanamide (9e). The foregoing procedure, applied to **4** and **13** gave 89% of **9e**: mp 126-127 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9H, tBu), 7.15 (m, 2H), 7.30 (m, 3H), 7.48 (m, 2H), 7.82 (comp, 1H, H_5 thienyl), 8.05 (d, 1H, $H_{3'}$), 8.46 (d, 1H, H_6), $J_{3'-4'}$= 8.1 Hz, J_{5-6}= 4.8 Hz; IR (KBr) 3300, 3260, 3060, 2970, 2930, 1650, 1610, 1500, 1445, 1400, 1210, 1170, 830, 750, 720, 710. Anal. Calcd for $C_{20}H_{19}FN_2OS$ (354.45): C, 67.77; H, 5.40; N, 7.90. Found: C, 67.99; H, 5.40; N, 7.61.

General procedure for metalation of 2,2-dimethyl-N-(2-(3-fluoro-4-pyridyl) phenyl)propanamide (8). n-Butyllithium (2.0 mmol) was slowly added to a cold (-75 °C) solution of 2,2-dimethyl-N-(2-(3-fluoro-4-pyridyl)phenyl) propanamide (8) (545 mg, 2.0 mmol) in dry THF (50 mL). The resulting solution was reacted for 1h30 at -75 °C. A solution of electrophile (2.0 mmol in 10 mL of THF) was slowly added. Stirring was continued for 1h at -75 °C, before hydrolysis at 0 °C. Extraction by ethyl acetate, drying over $MgSO_4$ and solvent removal afforded a crude product, which was purified by flash chromatography on silica (ethyl acetate/hexane: 5/5).

2,2-Dimethyl-N-(2-deutero-3-fluoro-4-pyridyl)phenyl)propanamide (14a). The foregoing procedure with deuterium oxide as electrophile gave 98% of **14a**. The physical characteristics of this product were found to be identical to those described for 2,2-dimethyl-N-(3-fluoro-4-pyridyl)phenyl)propanamide[4] except for the ^{1}H NMR spectrum where the H_2 signal has disappeared.

2,2-Dimethyl-N-(3-fluoro-2-iodo-4-pyridyl)phenyl)propanamide (14b). The foregoing procedure with iodine as electrophile gave 89% of **14b**: mp 159-160 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H, tBu), 7.20 (d, 1H, H_5), 7.24 to 7.33 (comp, 3H), 7.46 (m, 1H), 7.81 (d, 1H, H_3 phenyl), 8.27 (d, 1H, H_6), J_{5-6}= 5.0 Hz, J_{3-4}= 8.0 Hz; IR (KBr) 3280, 2960, 2860, 1655, 1490, 1395, 770, 755, 645. Anal. Calcd for $C_{16}H_{16}FIN_2O$ (398.22): C, 48.26; H, 4.05; N, 7.03. Found: C, 48.45; H, 4.03; N, 6.82.

2,2-Dimethyl-N-(3-fluoro-2-methyl-4-pyridyl)phenyl)propanamide (14c). The foregoing procedure with methyliodide as electrophile gave 70% of **14c**: mp 130-131 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9H, tBu), 2.50 (d, 1H, CH_3), 6.95 (d, 1H, H_5), 7.05 to 7.65 (m, 5H), 7.80 (comp, 1H), 8.25 (d, 1H, H_6), 8.35 (d, 1H), J_{CH3-F}= 4.0 Hz, J_{5-6}= 5.0 Hz; IR (KBr) 3260, 3060, 2970, 2960, 2860, 1665, 1620, 1510, 1495, 1205, 1175, 770, 650. Anal. Calcd for $C_{17}H_{19}FN_2O$ (286.35): C, 71.31; H, 6.69; N, 9.78. Found: C, 71.47; H, 6.66; N, 9.67.

2,2-Dimethyl-N-(2-ethyl-3-fluoropyrid-4-yl)phenyl)propanamide (14d). The foregoing procedure with ethyliodide as electrophile gave 48% of **14d**: mp 111-112 °C; ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 9H, tBu), 1.35 (t, 3H, CH_3), 2.95 (dq, 2H, CH_2), 7.13 (t, 1H, H_5), 7.22 to 7.30 (m, 3H, $2H_{arom.}$+ NH), 7.45 (comp, 1H), 8.07 (d, 1H, H_3 phenyl), 8.43 (d, 1H, H_6), J_{CH2-F}= 2.5 Hz, $J_{CH2-CH3}$= 7.6 Hz, J_{5-6}= 5.2 Hz, J_{3-4}= 8.1 Hz; IR (KBr) 3270, 3060, 3020, 2980, 2940, 2900, 2870, 1655, 1620, 1495, 1425, 1205, 1175, 845, 760, 650. Anal. Calcd for $C_{18}H_{21}FN_2O$ (300.38): C, 71.98; H, 7.05; N, 9.33. Found: C, 71.75; H, 7.22; N, 9.25.

2,2-Dimethyl-N-(2-formyl-3-fluoro-4-pyridyl)phenyl)propanamide (14e). The foregoing procedure with ethylformiate as electrophile gave 81% of **14e**: mp 157-158 °C; ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 9H, tBu), 7.27 to 7.38 (m, 4H, $3H_{arom.}$+ NH), 7.50 (comp, 1H), 7.72 (d, 1H, H_3 phenyl), 8.66 (d, 1H, H_6), 10.25 (s, 1H, CHO), J_{5-6}= 4.7 Hz, J_{3-4}= 7.8 Hz; IR (KBr) 3260, 3060, 3020, 2960, 2860, 2800, 1720, 1650, 1510, 1490, 1225, 1170, 770, 755, 650. Anal. Calcd for $C_{17}H_{17}FN_2O_2$ (300.34): C, 67.99; H, 5.71; N, 9.33. Found: C, 68.05; H, 5.99; N, 9.38.

2-2-Dimethyl-N-(2-(1'-hydroxyethyl)-3-fluoro-4-pyridyl)phenyl) propanamide (14f). The foregoing procedure with acetaldehyde as electrophile gave 76% of **14f**, this compound was obtained as an oil. ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9H, tBu), 1.51 (d, 3H, CH_3), 4.48 (d, 1H, OH), 5.14 (comp, 1H, CH), 7.20 to 7.30 (m, 4H, $3H_{arom.}$+ NH), 7.44 (comp, 1H), 7.93 (d, 1H, H_3 phenyl), 8.43 (d, 1H, H_6), J_{CH-OH}= 6.0 Hz, J_{CH3-CH}= 6.5 Hz, J_{5-6}= 4.8 Hz, J_{3-4}= 8.1 Hz; IR (film) 3400, 3300, 3060, 3030, 2960, 2920, 2900, 2860, 1645, 1610, 1500, 1480, 1420, 1210, 1110, 1065, 1020, 840, 755. Anal. Calcd for $C_{18}H_{21}FN_2O_2$ (316.38): C, 68.34; H, 6.69; N, 8.85. Found: C, 68.52; H, 6.35; N, 8.56. Mass calcd for $C_{18}H_{21}FN_2O_2$ (316.38), found ($MS^{+\cdot}$) 316.

2,2-Dimethyl-N-(2-(1-hydroxybenzyl)-3-fluoro-4-pyridyl)phenyl) propanamide (14g). The foregoing procedure with benzaldehyde as electrophile gave 83% of **14g**: mp 58-60°C; ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 9H, tBu), 5.41 (d, 1H, CH), 5.99 (d, 1H, OH), 7.14 (s, 1H, NH), 7.20 to 7.34 (m, $7H_{arom.}$), 7.35 to 7.47 (m, $2H_{arom.}$), 7.89 (d, 1H, H_3 phenyl), 8.48 (d, 1H, H_6), J_{5-6}= 4.8 Hz, J_{3-4}= 8.4 Hz; IR (KBr) 3430, 3320, 3060, 3020, 2960, 2920, 2860, 1660, 1610, 1510, 1490, 1205, 1160, 1050, 760, 700. Anal. Calcd for $C_{23}H_{23}FN_2O_2$ (378.45): C, 73.00; H, 6.13; N, 7.40. Found: C, 72.97; H, 6.26; N, 7.30.

2,2-Dimethyl-N-(3-fluoro-2-trimethylsilyl-4-pyridyl)phenyl) propanamide (14h). The foregoing procedure with trimethylsilyl chloride as electrophile gave 83% of **14h**: mp 99-100°C; ^{1}H NMR ($CDCl_3$) δ 0.41 (d, 9H, $SiMe_3$), 1.13 (s, 9H, tBu), 7.20 (d, 1H, H_5), 7.23 to 7.30 (m, 3H, 2H $_{arom.}$+ NH), 7.47 (comp, 1H), 8.09 (d, 1H, H_3 phenyl), 8.70 (dd, 1H, H_6), $J_{SiMe3-F}$= 1.2 Hz, J_{5-6}= 4.8 Hz, J_{H6-F}= 2.2 Hz, J_{3-4}= 8.1 Hz; IR (KBr) 3280, 3060, 3040, 2960, 2900, 2870, 1670, 1650, 1610, 1515, 1490, 1380, 1245, 1200, 1170, 855, 840, 745. Anal. Calcd for $C_{19}H_{25}FN_2OSi$ (344.51): C, 66.24; H, 7.31; N, 8.13. Found: C, 66.42; H, 7.14; N, 8.26.

2,2-Dimethyl-N-(3-fluoro-2-trimethylstannyl-4-pyridyl)phenyl) propanamide (14i). The foregoing procedure with trimethyltin chloride as electrophile gave 91% (NMR) of **14i**, this product was obtained as a crude oil and was instable. So, only NMR spectrum is given. ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 9H, $SiMe_3$), 1.50 (s, 9H, tBu), 7.40 to 8.00 (m, 5H, $4H_{arom.}$+ NH), 8.40 (comp, 1H), 9.05 (dd, 1H, H_6), J_{5-6}= 4.8 Hz, J_{H6-F}= 5.0 Hz, $^2J(^1H-^{119}Sn)$= 56.0 Hz.

2,2-Dimethyl-N-(3-fluoro-2-tri-n-butylstannyl-4-pyridyl)phenyl) propanamide (14j). The foregoing procedure with tributyltin chloride as electrophile gave 78% of **14j**, this product was obtained as an oil. ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 9H, $3CH_3$), 1.13 (s, 9H, tBu), 1.17 to 1.43 (comp, 12H, 3 CH_2-CH_2), 1.48 to 1.66 (comp, 6H, 3 CH_2-Sn), 7.14 (dd, 1H, H_5), 7.23 to 7.29 (comp, 1H), 7.30 (s, 1H, NH), 7.45 (comp, 2H), 8.13 (d, 1H, H_3'), 8.69 (dd, 1H, H_6), J_{H6-F}= 2.3 Hz, J_{5-6}= 4.7 Hz, J_{3-4}= 8.1 Hz; IR (film) 3440, 3330, 3060, 2980, 2930, 2870, 2850, 1695, 1585, 1515, 1450, 1370, 1290, 1195, 1160, 770, 750. Anal. Calcd for $C_{28}H_{43}FN_2OSn$ (561.36): C, 59.91; H, 7.72; N, 4.99. Found: C, 60.29; H, 8.08; N, 4.69.

2,2-Dimethyl-N-(2-(9-bora-bicyclo[3.3.1]nonan-9-yl)-3-fluoro-4-pyridyl) phenyl) propanamide (14k). The foregoing procedure with 9-methoxy-9-bora-bicyclo[3.3.1]nonane as electrophile gave 73% of **14k**: mp 182-184°C; ^{1}H NMR (DMSO) δ 0.96 (s, 9H, tBu), 1.10 to 1.90 (comp, 14H, BBN), 7.30 to 7.55 (comp, 4H), 7.72 (t, 1H), 8.65 (t, 1H), 9.68 (s, 1H), J= 6.0 Hz; IR (KBr) 3370, 3220, 2080, 2960, 2920, 2880, 2840, 1640, 1620, 1510, 1490, 1445, 1220, 835, 750. Anal. Calcd for $C_{24}H_{30}BFN_2O$ (392.33): C, 73.48; H, 7.71; N, 7.14. Found: C, 73.63; H, 7.91; N, 6.83.

2,2-Dimethyl-N-(2-cyano-3-fluoro-4-pyridyl)propanamide (14l). The foregoing procedure with tosyl cyanide as electrophile gave 42% of 14l; According to the Vowinkel and Bartel's procedure, see reference 8. mp 142-143°C; ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9H, tBu), 7.32 (m, 2H); 7.41 à 7.58 (m, 4H); 8.55 (d, 1H, H_6); J_{5-6}= 4.6 Hz; IR (KBr): 3290, 3060, 3030, 2970, 2930, 2240, 1645, 1500, 1495, 1420, 1225, 880, 760. Anal. Calcd for $C_{17}H_{16}FN_3O$ (297.33): C, 68.67; H, 5.42; N, 14.13. Found: C, 68.34; H, 5.75; N, 13.82.

General procedure for synthesis of 1-substituted-9H-pyrido[3,4-b]indole. Anhydrous pyridinium chloride (10g) at the boiling point (210°C) was added to the corresponding 2,2-dimethyl-N-(2-(3-fluoro-2-substituted-4-pyridyl)phenyl) propanamide (1.0 mmol) and the mixture was refluxed for 15 min. The resulting hot solution was pourred on a mixture (20 mL) of ice and concentrated ammonia. Filtration of the precipitate, washing with water and drying gave a first crop of the corresponding carbolines. Extraction of the aqueous layer by ethyl acetate, drying over $MgSO_4$, solvent removal and cristallization from toluene gave an additional product.

1-Phenyl-9H-pyrido[3,4-b]indole (15a). The foregoing procedure, applied to 9a gave 86% of 15a: mp 244-245°C; ^{1}H NMR (DMSO) δ 7.26 (td, 1H, H_6), 7.49 to 7.68 (m, 5$H_{arom.}$), 8.02 (m, 2$H_{arom.}$), 8.13 (d, 1H, H_4), 8.26 (d, 1H, H_5), 8.45 (d, 1H, H_3), 11.40 (s, 1H ,NH), J_{5-6}= 7.9 Hz, J_{3-4}= 5.2 Hz, J_{6-8}= 1.0 Hz; ^{13}C NMR (DMSO) δ 141.50, 140.97, 137.43, 132.61, 129.14, 128.42, 128.36, 128.12, 128.04, 121.35, 120.40, 119.29, 113.69, 112.13; IR (KBr) 3400, 3100, 3050, 2960, 2860, 1625, 1560, 1495, 1465, 1415, 1320, 1235, 735. Anal. Calcd for $C_{17}H_{12}N_2$ (244.30): C, 83.58; H, 4.95; N, 11.47. Found: C, 83.39; H, 4.79; N, 11.52.

1-(2'-Pyridyl)-9H-pyrido[3,4-b]indole (15b). The foregoing procedure, applied to 9b gave 75% of 15b: mp 179-180°C; ^{1}H NMR (DMSO) δ 7.25 (t, 1H, H_6), 7.49 (t, 1H, H_7), 7.57 (t, 1H, H_8), 7.88 (d, 1H, $H_{5'}$), 8.01 (t, 1H, $H_{4'}$), 8.21 (t, 1H, H_4), 8.25 (d, 1H, H_5), 8.48 (d, 1H, H_3), 8.63 (d, 1H, $H_{3'}$), 8.87 (d, 1H, $H_{6'}$), 10.95 (s, 1H, NH), J_{3-4}= 5.0 Hz, J_{5-6}= 7.9 Hz, J_{6-7}= 7.4 Hz, J_{7-8}= 7.5 Hz; $J_{3'-4'}$= 8.4 Hz, $J_{5'-6'}$= 5.0 Hz; ^{13}C NMR (DMSO) δ 157.42, 149.03, 141.34, 138.41, 138.01, 137.51, 133.90, 130.24, 128.67, 123.66, 121.92, 121.17, 120.67, 119.87, 115.96, 113.22; IR (KBr) 3380, 3040, 2980, 2920, 1620, 1595, 1450, 1415, 1320, 1235, 1150, 745. Anal. Calcd for $C_{16}H_{11}N_3$ (245.29): C, 78.35; H, 4.52; N, 17.13. Found: C, 78.52; H, 4.40; N, 16.80.

1-(2'-Quinolyl)-9H-pyrido[3,4-b]indole or Nitramarine (15c). The foregoing procedure, applied to 9c gave 83% of 15c: mp 177-178°C; ^{1}H NMR (DMSO) δ 7.31 (t, 1H, H_6), 7.63 (td, 1H), 7.67 (td, 1H), 7.89 (td, 1H), 8.01 (d, 1H), 8.05 (d, 1H), 8.30 (d, 1H, H_4), 8.32 (d, 1H, $H_{8'}$), 8.54 (d, 1H, $H_{3'}$), 8.57 (d, 1H, H_3), 8.74 (d, 1H, $H_{5'}$), 8.83 (d, 1H, $H_{4'}$), J_{3-4}= 5.0 Hz, J_{5-6}= 7.9 Hz, J_{6-7}= 7.4 Hz, J_{7-8}= 7.5 Hz; ^{13}C NMR (DMSO) δ

163.04, 152.91, 146.81, 143.61, 143.48, 142.63, 139.74, 135.84, 135.48, 135.41, 134.21, 133.55, 133.11, 132.75, 127.42, 126.20, 125.54, 124.52, 121.92, 118.88; IR (KBr) 3360, 3040, 1630, 1590, 1500, 1240, 1220, 1150, 760, 740. Anal. Calcd for $C_{20}H_{13}N_3$ (295.35): C, 81.33; H, 4.44; N, 14.23. Found: C, 81.05; H, 4.69; N, 14.13.

1-(2'-Thienyl)-9H-pyrido[3,4-b]indole (15d). The foregoing procedure, applied to **9e** gave 68% of **15d**: mp 148-149°C; ^{1}H NMR ($CDCl_3$) δ 7.03 (dd, 1H, $H_{4'}$), 7.27 (td, 1H, H_6), 7.36 (dd, 1H, $H_{5'}$), 7.47 (m, 2H, H_7+ H_8), 7.76 (dd, 1H, $H_{3'}$), 7.82 (d, 1H, H_4), 8.07 (d, 1H, H_5), 8.45 (d, 1H, H_3), 9.59 (s, 1H, NH), J_{3-4}= 5.25 Hz, J_{5-6}= 8.0 Hz, J_{6-7}= 6.9 Hz, J_{6-8}= 2.2 Hz, $J_{3'-4'}$= 3.7 Hz, $J_{4'-5'}$= 5.1 Hz, $J_{3'-5'}$= 0.95 Hz; ^{13}C NMR ($CDCl_3$) δ 111.81, 113.69, 120.22, 121.46, 121.54, 125.22, 127.02, 127.86, 128.44, 130.29, 132.18, 137.01, 138.74, 140.74, 142.64; IR (KBr) 3420, 3200, 3060, 1630, 1570, 1500, 1475, 1460, 1440, 1430, 1325, 1240, 915, 750, 710. Anal. Calcd for $C_{15}H_{10}N_2S$ (250.32): C, 71.97; H, 4.03; N, 11.19. Found: C, 72.09; H, 4.27; N, 10.93.

1-Methyl-9H-pyrido[3,4-b]indole or Harmane (15e). The foregoing procedure, applied to **14c** gave 84% of **15e**: mp 235-236°C (lit[15] mp: 235-238°C); ^{1}H NMR (DMSO) δ 2.81 (s, 3H, CH_3), 7.20 (t, 1H, H_6), 7.52 (t, 1H, H_7), 7.63 (d, 1H, H_8), 7.88 (d, 1H, H_4), 8.15 (d, 1H, H_5), 8.23 (d, 1H, H_3), 11.35 (s, 1H, NH), J_{3-4}= 5.3 Hz, J_{5-6}= 7.8 Hz, J_{6-7}= 7.4 Hz, J_{7-8}= 8.0 Hz; ^{13}C NMR (DMSO) δ 142.02, 140.37, 137.39, 134.42, 127.61, 126.86, 121.50, 121.00, 119.01, 112.43, 111.79, 20.32; IR (KBr) 3420, 3120, 3060, 2960, 2880, 2780, 1625, 1565, 1510, 1450, 1330, 1255, 1240, 820, 745. Anal. Calcd for $C_{12}H_{10}N_2$ (182.23): C, 79.09; H, 4.95; N, 15.37. Found: C, 78.86; H, 5.54; N, 15.21.

1-Ethyl-9H-pyrido[3,4-b]indole (15f). The foregoing procedure, applied to **14d** gave 79% of **15f**: mp 202-203°C (lit[16] mp: 194-195°C); ^{1}H NMR (DMSO) δ 1.34 (t, 3H, CH_3), 3.10 (q, 2H, CH_2), 7.22 (td, 1H, H_6), 7.51 (td, 1H, H_7), 7.56 (t, 1H, H_8), 7.90 (d, 1H, H_4), 8.17 (d, 1H, H_5), 8.22 (d, 1H, H_3), 11.35 (s, 1H, NH),J_{3-4}= 5.3 Hz, J_{5-6}= 7.5 Hz, J_{6-7}= 8.1 Hz, J_{7-8}= 7.9 Hz; ^{13}C NMR (DMSO) δ 146.30, 139.76, 137.19, 133.26, 127.20, 126.59, 121.16, 120.54, 118.57, 112.15, 111.34, 26.16, 12.10; IR (KBr) 3400, 3120, 3060, 2960, 2920, 2860, 2780, 1620, 1600, 1560, 1500, 1430, 1320, 1240, 1225, 1020, 740. Anal. Calcd for $C_{13}H_{12}N_2$ (196.25): C, 79.56; H, 6.16; N, 14.27. Found: C, 79.35; H, 6.02; N, 14.42.

1-Vinyl-9H-pyrido[3,4-b]indole or Pavettine (15g). The foregoing procedure, applied to **14f** gave 76% of **15g**: mp 158-159°C; ^{1}H NMR (DMSO) δ 5.59 (dd, 1H, H_{vinyl}), 6.47 (dd, 1H, H_{vinyl}), 7.23 (t, 1H, H_6), 7.35 to 7.64 (m, $3H_{arom.}$), 8.01 (d, 1H, H_4), 8.20 (d, 1H, H_5), 8.32 (d, 1H, H_3), 10.15 (s, 1H, NH), J_{vinyl}= 2.1, 10.8 and 17.2 Hz, J_{3-4}= 5.1 Hz, J_{5-6}= 8.1 Hz; ^{13}C NMR (DMSO) δ 140.42, 139.66, 138.77, 133.61, 132.67, 132.31, 129.78, 128.32, 121.53, 120.02, 118.90, 113.93, 111.52; IR (KBr) 3200, 3160, 3080, 3060, 2950, 2920, 2860, 1620, 1570, 1500, 1450, 1425, 1320, 1235, 1200, 820, 745. Anal. Mass calcd for $C_{13}H_{10}N_2$ (194.24), found ($MS^{+\cdot}$) 194. Anal. Calcd for $C_{13}H_{10}N_2$ (194.24): C, 80.39; H, 5.19; N, 14.42. Found: C, 80.25; H, 5.11; N, 14.49.

1-Cyano-9H-pyrido[3,4-b]indole (15h). The foregoing procedure, applied to 14l gave 78% of 15h: mp 230-231°C (lit[12] mp: 230-232°C); ^{1}H NMR ($CDCl_3$) δ 7.40 (dt, 1H, J= 6.3 and 1.7 Hz); 7.61 to 7.69 (m, 2H); 8.15 to 8.20 (m, 2H); 8.58 (d, 1H, H_3); 9.10 (s, 1H, NH); J_{3-4}= 5.1 Hz; IR (KBr): 3440, 3130, 2925, 2225, 1625, 1455, 1435, 1325, 1285, 1250, 1230, 1065, 740, 640, 570. Anal. Calcd for $C_{12}H_7N_3$ (193.21): C, 74.60; H, 3.65; N, 21.75. Found: C, 74.45; H, 3.78; N, 21.62.

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