A New Synthesis of α-Substituted δ-Carbolines

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Received February 21, 1997

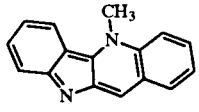
The paper describes a new general synthesis of α-substituted δ-carbolines based on key steps such as metalation, cross-coupling and cyclization.

J. Heterocyclic Chem., **34**, 1205 (1997).

Introduction.

Numerous alkaloids belong to the carboline series and display interesting biological properties, β-carbolines mainly [1]. δ-Carbolines are very rare in nature, and the best representative of this series is Cryptolepine, 5-methyl-5*H*-indolo[3,2-*b*]quinoline, a benzo-δ-carboline isolated in 1929 from *cryptolepis triangularis* [2] (Scheme 1). Until 1985, few syntheses of δ-carbolines have been developed, mainly by Suvorov *et al.* [3]. During the last decade, a number of syntheses of δ-carbolines have been published or patented mainly in the benzo series because of their antimalarial properties [4].

Scheme I



Cryptolepine

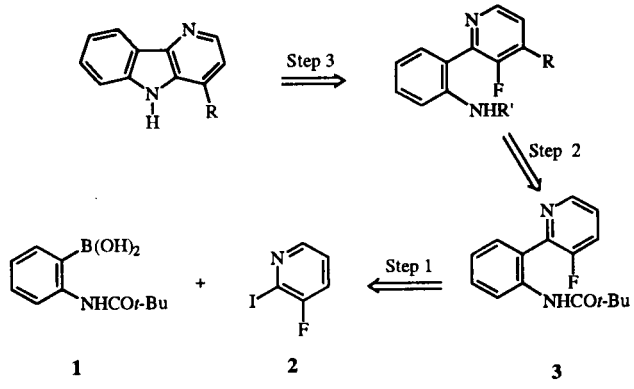
Most previously described syntheses of δ-carbolines have used indole or an indole derivative as starting material [5]. This limits the scope of these methods to specific series, or compounds, and subsequent functionalizations.

In previous papers, we have described a new general and convergent route to α, β, γ and δ-carbolines [6], as well as α-substituted β-carbolines [7]. This synthesis is based on metalation [8] and cross-coupling [9] reactions. We wish to report on an extension of this method to the total synthesis of α-substituted δ-carbolines starting from simple benzene and pyridine derivatives.

Retrosynthesis.

From a retrosynthetic analysis (Scheme II), α-substituted δ-carbolines could be prepared by cyclization of conveniently functionalized phenylpyridines (step 3). These phenylpyridines could be obtained by a directed metallation of the heterobiaryl **3** (step 2), taking advantage of the *ortho*-directing effect of the fluorine atom. The heterobiaryl **3** could be prepared *via* a coupling reaction (step 1) between the required benzene and pyridine building blocks.

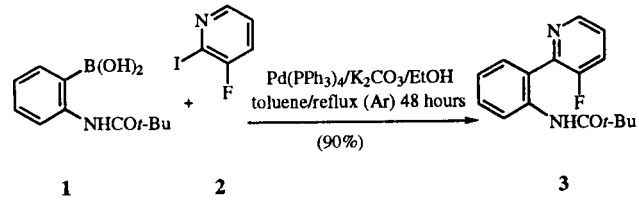
Scheme II



Results and Discussion.

Palladium catalyzed cross-coupling between boronic acid **1** [6] and iodopyridine **2** [10] using the Suzuki procedure [9] gave the heterobiaryl **3** in a very good yields (Scheme III). Biaryl **3** has previously been described but the yield had not been optimized [10].

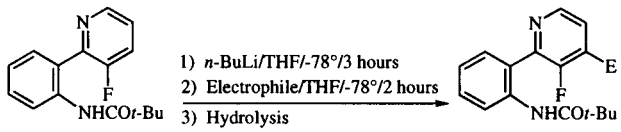
Scheme III



The 2-phenyl-3-fluoropyridine **3** was subjected to lithiation with *n*-butyllithium at low temperature. Metallation occurred almost quantitatively and regioselectively at the C-4 position of the pyridine ring as shown by deuterium incorporation (deuterium oxide) and reaction with various electrophiles (Scheme IV and Table I).

Metallation of **3** is regioselectively directed by the fluorine atom at the most acidic C-4 position of the pyridine ring. No reaction can be observed at the C-6 position or on the benzene ring which could be due to the *ortho*-directing effect of the pivaloylamino moiety.

Scheme IV



3 4a-k

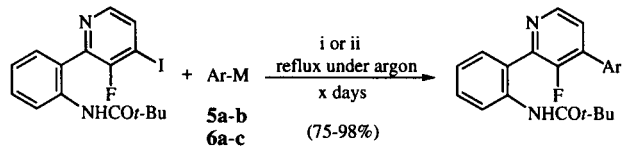
Table I

Electrophile	E	Product	Yield (%)
D_2O	D	**4a**	> 95 [a]
I_2	I	**4b**	98
C_2Cl_6	Cl	**4c**	70
CH_3I	CH_3	**4d**	81
C_2H_5I	C_2H_5	**4e**	65
CH_3CHO	$CH_3CH(OH)$	**4f**	83
PhCHO	PhCH(OH)	**4g**	65
Ph_2CO	$Ph_2C(OH)$	**4h**	35
$Si(CH_3)_3Cl$	$Si(CH_3)_3$	**4i**	62
CO_2	CO_2H	**4j**	41
HCO_2Et	CHO	**4k**	46

[a] ^1H nmr integration.

The palladium catalyzed cross-coupling reaction between iodo compound **4b** and various arylboronic acids **5a-b** or stannanes **6a-c** led to the corresponding triaryl compounds **7a-e** in very good yields (Scheme V and Table II).

Scheme V



4b 7a-e

i (boronic acids): $Pd(PPh_3)_4/K_2CO_3$ 2*M*/EtOH/toluene (x = 2)
ii (stannanes): $Pd(PPh_3)_4$/toluene (x = 3)

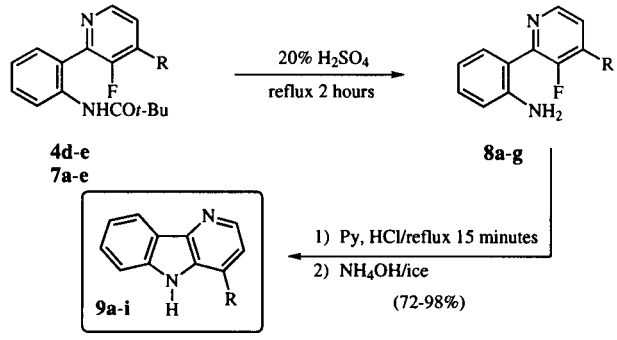
Table II

Ar-M	Ar-	Product	Yield (%)
$PhB(OH)_2$ (**5a**)	Ph-	**7a**	98
2-NHPiv-$C_6H_4B(OH)_2$ (**5b**)	2-NHPiv-C_6H_4-	**7b**	88
2-pyridyl-$SnMe_3$ (**6a**)	2-pyridyl-	**7c**	75
2-thienyl-$SnMe_3$ (**6b**)	2-thienyl-	**7d**	83
2-quinolyl-$SnMe_3$ (**6c**)	2-quinolyl-	**7e**	90

Boronic acids and stannanes were prepared by transmetalation of the corresponding lithio-derivatives.

It should be noted that cyclization of phenylpyridines **4** and **7** required the previous hydrolysis [11] of the pivaloylamino group to the amine for better yields. Then, the amines **8a-g** were cyclized by treatment in boiling pyridinium chloride at 215°. Hydrolysis and basic workup yielded the corresponding α-substituted δ-carbolines **9a-i** in good yields (Scheme VI and Table III).

Scheme VI



4d-e 7a-e 8a-g 9a-i

Table III

Reagent	R	Product	Yield (%)
3	H	**9a**	80 [a]
8a	Me	**9b**	91
8b	Et	**9c**	72
8c	Ph	**9d**	72
8d	2-NH_2-C_6H_4	**9e** and **9f**	78 [b]
8e	2-pyridyl	**9g**	98
8f	2-thienyl	**9h**	90
8g	2-quinolyl	**9i**	80

[a] Cyclization carried out on the undeprotected material; [b] β- and δ-Carbolines in a 1/1 ratio, see [12].

Conclusion.

This is the first synthesis of α-substituted δ-carbolines starting from benzene and pyridine blocks. It relies on key steps such as metalation, cross-coupling and cyclization. The strategy is fully convergent, regioselective, and allows 47-80% overall yields in 2 or 3 steps. Some molecules prepared are analogues of biologically active α-substituted β-carbolines. The present work is currently being extended to the preparation of polysubstituted δ-carbolines starting from more highly substituted pyridine reagents.

EXPERIMENTAL

General Data.

The ^1H nmr spectra were obtained on a 200 MHz Bruker spectrometer. The 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}. Elemental analyses were performed on a Carlo-Erba CHN apparatus.

Tetrahydrofuran was distilled from benzophenone/sodium. The water content of the solvent was estimated lower than 45 ppm by the modified Karl-Fischer method [13]. Commercial diisopropylamine was distilled from calcium hydride under a dry argon atmosphere and used directly. Commercial 2.5 *M* solution of *n*-butyllithium in hexane was stored and transferred under a dehydrated and deoxygenated argon atmosphere. (2-Pivaloylaminophenyl)boronic acid **1** was prepared by metalation and boronation of the protected aniline [6] in a 50-58% yield. 3-Fluoro-2-iodopyridine **2** was prepared [10] in 96% yield by metalation-iodination of the corresponding fluoropyridine followed by an halogen-dance reaction. Hetarylstannanes **6a-c** were prepared [7] in good yields by halogen-metal exchange followed by action of trimethylstannyl chloride.

General Procedure A. Cross-coupling Reaction Between Haloiodopyridines and Benzeneboronic Acids.

The required arylboronic acid (x mmoles) and 3-fluoroiodopyridine (x mmoles) were added to an aqueous solution of potassium carbonate (2*M*, x ml) and ethanol (x/2 ml) in deoxygenated toluene (10x ml). The resulting mixture was stirred for one hour under an argon atmosphere. Tetrakis(triphenylphosphine)palladium(0) (3 mol%) was added, and the reaction mixture was refluxed for 48 hours. Cooling, filtration, extraction with toluene, drying over magnesium sulfate, and solvent removal afforded a crude oil which was purified by flash chromatography on silica (eluent).

2,2-Dimethyl-*N*-(2-(3-fluoro-2-pyridyl)phenyl)propanamide (**3**).

General procedure A (x = 50), applied to **1** and **2**, gave 12.28 g (90%) of **3** (cyclohexane/ethyl acetate: 8/2) as a yellow solid, mp 92°; ^1H nmr (deuteriochloroform): δ 1.30 (s, 9H, *t*-Bu), 7.17 (td, 1H, 4-H, J = 1.5 Hz, J = 7.7 Hz), 7.35 (m, 1H, 5'-H), 7.44 (td, 1H, 5-H, J = 1.5 Hz, J = 8.0 Hz), 7.62 (ddd, 1H, 4'-H, J = 1.4 Hz, J = 8.3 Hz, J = 10.3 Hz), 7.71 (ddd, 1H, 3-H, J = 1.5 Hz, J = 4.3 Hz, J = 7.7 Hz), 8.44-8.52 (m, 2H, 6-H and 6'-H), 11.05 (s, 1H, NH); ir (potassium bromide): ν (3310, 3070, 2970, 2870, 1680, 1590, 1525, 1460, 1440, 1315, 1255, 1185, 1165, 1105, 755 cm^{-1}.

Anal. Calcd. for $C_{16}H_{17}FN_2O$: C, 70.57; H, 6.29; N, 10.29. Found: C, 70.31; H, 6.32; N, 10.51.

2,2-Dimethyl-*N*-(2-(3-fluoro-4-phenyl-2-pyridyl)phenyl)propanamide (**7a**).

General procedure A (x = 1), applied to **4b** and **5a**, gave 0.342 g (98%) of **7a** (cyclohexane/ethyl acetate: 9/1), mp 119°; ^1H nmr (deuteriochloroform): δ 1.27 (s, 9H, *t*-Bu), 7.17-7.63 (m, $9H_{arom}$), 8.44-8.54 (m, 2H, 6-H and 6'-H), 10.92 (s, 1H, NH); ir (potassium bromide): ν 3260, 2961, 1664, 1435, 758, 696 cm^{-1}.

Anal. Calcd. for $C_{22}H_{21}FN_2O$: C, 75.84; H, 6.08; N, 8.04. Found: C, 75.78; H, 6.02; N, 8.15.

2,2-Dimethyl-*N*-(2-(3-fluoro-4-(2-pivaloylaminophenyl)-2-pyridyl)phenyl)propanamide (**7b**).

General procedure A (x = 1), applied to **4b** and **5b**, gave 0.394 g (88%) of **7b** (cyclohexane/ethyl acetate: 9/1), mp 158°; ^1H nmr (deuteriochloroform): δ 1.07 (s, 9H, *t*-Bu), 1.26 (s, 9H, *t*-Bu), 7.13-7.55 (m, $6H_{arom}$ and NH), 7.65 (com, $1H_{arom}$), 7.89 (comp, $1H_{arom}$), 8.45 (dd, 1H, 6-H, J = 1.0 Hz, J = 8.0 Hz), 8.58 (d, 1H, 6'-H, J = 4.9 Hz), 10.90 (s, 1H, NH); ir (potassium bromide): ν 3302, 2963, 2868, 1675, 752, 730 cm^{-1}.

Anal. Calcd. for $C_{27}H_{30}FN_3O_2$: C, 72.46; H, 6.75; N, 9.39. Found : C, 72.10; H, 6.51; N, 9.19.

General Procedure B. Metalation of 2,2-Dimethyl-*N*-(2-(3-fluoro-2-pyridyl)phenyl)propanamide (**3**).

n-Butyllithium 2.5 *M* (1.75 ml, 4.4 mmoles) was slowly added to a cold (-78°) solution of 2,2-dimethyl-*N*-(2-(3-fluoro-2-pyridyl)phenyl)propanamide **3** (545.0 mg, 2.0 mmoles) in anhydous tetrahydrofuran (50.0 ml). The resulting solution was stirred 3 hours at -78°, and the electrophile (4.5 mmoles) in 10.0 ml of tetrahydrofuran was slowly added. Stirring was continued for 2 hours at -78° before hydrolysis at 0° by a 5% aqueous ammonium chloride solution (30 ml). Extraction with ethyl acetate, drying over magnesium sulfate and solvent removal afforded a crude product which was purified by flash chromatography on silica (cyclohexane/ethyl acetate: 9/1).

2,2-Dimethyl-*N*-(2-(4-deuterio-3-fluoro-2-pyridyl)phenyl)-propanamide (**4a**).

General procedure B, using deuterium oxide as the electrophile, gave 95% (^1H nmr integration) of **4a**. The physical characteristics of this product were found to be identical to those described for 2,2-dimethyl-*N*-(2-(3-fluoro-2-pyridyl)phenyl)propanamide **3** except for the ^1H nmr spectrum where the 4-H signal has disappeared.

2,2-Dimethyl-*N*-(2-(3-fluoro-4-iodo-2-pyridyl)phenyl)propanamide (**4b**).

General procedure B, using iodine as the electrophile, gave 0.781 g (98%) of **4b**, mp 124°; ^1H nmr (deuteriochloroform): δ 1.20 (s, 9H, *t*-Bu), 7.17 (td, 1H, 4-H, J = 1.2 Hz, J = 7.6 Hz), 7.45 (td, 1H, 5-H, J = 1.5 Hz, J = 7.83 H), 7.63 (ddd, 1H, 3-H, J = 1.5 Hz, J = 4.7 Hz, J = 7.6 Hz), 7.77 (dd, 1H, 5'-H, J = 5.1 Hz, J = 4.3 Hz), 8.12 (d, 1H, 6'-H, J = 5.1 Hz), 8.43 (dd, 1H, 6-H, J = 1.2 Hz, J = 7.8 Hz), 10.71 (s, 1H, NH); ir (potassium bromide): ν 3283, 2964, 1670, 760, 681 cm^{-1}.

Anal. Calcd. for $C_{16}H_{16}FIN_2O$: C, 48.26; H, 4.05; N, 7.09. Found: C, 48.45; H, 4.03; N, 6.82.

2,2-Dimethyl-*N*-(2-(4-chloro-3-fluoro-2-pyridyl)phenyl)propanamide (**4c**).

General procedure B, using hexachloroethane as the electrophile, gave 0.430 g (70%) of **4c**, mp 68-70°; ^1H nmr (deuteriochloroform): δ 1.17 (s, 9H, *t*-Bu), 7.20 (td, 1H, 4-H, J = 1.1 Hz, J = 7.7 Hz), 7.43 (dd, 1H, 5'-H, J = 5.1 Hz), 7.45 (td, 1H, 5-H, J = 1.5 Hz, J = 8.0 Hz), 7.65 (ddd, 1H, 3-H, J = 1.5 Hz, J = 4.7 Hz, J = 7.7 Hz), 8.40 (d, 1H, 6'-H, J = 5.1 Hz), 8.45 (dd, 1H, 6-H, J = 1.1 Hz, J = 8.0 Hz), 11.05 (s, 1H, NH); ir (potassium bromide): ν 3185, 3057, 2963, 1683, 1588, 1163, 75 cm^{-1}.

Anal. Calcd. for $C_{16}H_{16}ClFN_2O$: C, 62.65; H, 5.26; N, 9.13. Found: C, 62.78; H, 5.11; N, 8.98.

2,2-Dimethyl-*N*-(2-(3-fluoro-4-methyl-2-pyridyl)phenyl)propanamide (**4d**).

General procedure B, using methyl iodide as the electrophile, gave 0.464 g (81%) of **4d**, mp 80°; ^1H nmr (deuteriochloroform): δ 1.20 (s, 9H, *t*-Bu), 2.40 (d, 3H, CH_3, J = 1.9 Hz), 7.17 (td, 1H, 4-H, J = 1.0 Hz, J = 7.7 Hz), 7.19 (t, 1H, 5'-H, J = 4.8 Hz), 7.42 (td, 1H, 5-H, J = 1.5 Hz, J = 8.1 Hz), 7.65 (ddd, 1H, 3-H, J =

1.5 Hz, J = 4.5 Hz, J = 7.7 Hz), 8.34 (d, 1H, 6'-H, J = 4.8 Hz), 8.48 (dd, 1H, 6-H, J = 1.0 Hz, J = 8.1 Hz), 10.95 (s, 1H, NH); ir (potassium bromide): ν 3276, 3028, 2958, 2866, 1671, 1522, 1440, 1167, 1094, 755, 691 cm^{-1}.

Anal. Calcd. for $C_{17}H_{19}FN_2O$: C, 71.39; H, 6.69, N, 9.78. Found: C, 71.06; H, 6.72; N, 9.61.

2,2-Dimethyl-*N*-(2-(4-ethyl-3-fluoro-2-pyridyl)phenyl)propanamide (**4e**).

General procedure B, using ethyl iodide as the electrophile, gave 0.391 g (65%) of **4e**, mp 74°; ^1H (deuteriochloroform): δ 1.24 (s, 9H, *t*-Bu), 1.32 (t, 3H, CH_3, J = 7.5 Hz), 2.80 (q, 2H, CH_2, J = 7.5 Hz), 7.16 (td, 1H, 4-H, J = 1.1 Hz, J = 7.6 Hz), 7.21 (t, 1H, 5'-H, J = 4.9 Hz), 7.42 (td, 1H, 5-H, J = 1.5 Hz, J = 8.0 Hz), 7.66 (ddd, 1H, 3-H, J = 1.5 Hz, J = 4.6 Hz, J = 7.6 Hz), 8.38 (d, 1H, 6'-H, J = 4.9 Hz), 8.47 (dd, 1H, 6-H, J = 1.1 Hz, J = 8.0 Hz), 10.95 (s, 1H, NH); ir (potassium bromide): ν 3276, 3028, 2958, 2866, 1671, 1522, 1440, 1167, 1094, 755, 691 cm^{-1}.

Anal. Calcd. for $C_{18}H_{21}FN_2O$: C, 71.98; H, 7.05; N, 9.33. Found: C, 72.23; H, 7.28; N, 9.06.

2,2-Dimethyl-*N*-(2-(3-fluoro-4-(1-hydroxyethyl)-2-pyridyl)-phenyl)propanamide (**4f**).

General procedure B, using acetaldehyde as the electrophile, gave 0.526 g (83%) of **4f**, mp 109°; ^1H nmr (deuteriochloroform): δ 1.23 (s, 9H, *t*-Bu), 1.56 (d, 3H, CH_3, J = 6.5 Hz), 2.54 (d, 1H, OH, J = 4.2 Hz), 5.27 (m, 1H, CH), 7.16 (td, 1H, 4-H, J = 1.1 Hz, J = 7.6 Hz), 7.42 Hz (td, 1H, 5-H, J = 1.5 Hz, J = 8.0 Hz), 7.56 (t, 1H, 5'-H, J = 4.9 Hz), 7.64 (ddd, 1H, 3-H, J = 1.5 Hz, J = 4.5 Hz, J = 7.6 Hz), 8.42 (dd, 1H, 6-H, J = 1.1 Hz, J = 8.0 Hz), 8.48 (d, 1H, 6'-H, J = 4.9 Hz), 10.95 (s, 1H, NH); ir (potassium bromide): ν 3396, 2965, 2869, 1682, 1654, 1585, 1405, 1192, 926, 910, 842, 826, 768 cm^{-1}.

Anal. Calcd. for $C_{18}H_{21}FN_2O_2$: C, 68.34; H, 6.69; N, 8.85. Found: C, 68.24; H, 6.62; N, 8.56.

2,2-Dimethyl-*N*-(2-(3-fluoro-4-(1-hydroxybenzyl)-2-pyridyl)-phenyl)propanamide (**4g**).

General procedure B, using benzaldehyde as the electrophile, gave 0.492 g (65%) of **4g**, mp 150°; ^1H nmr (deuteriochloroform): δ 1.21 (s, 9H, *t*-Bu), 6.21 (s, 1H, CH), 7.12 (td, 1H, 4-H, J = 1.0 Hz, J = 7.7 Hz), 7.30-7.50 (comp, 6H arom and OH), 7.58 (ddd, 1H, 3-H, J = 1.5 Hz, J = 4.5 Hz, J = 7.7 Hz), 7.68 (t, 1H, 5'-H, J = 4.9 Hz), 8.42 (dd, 1H, 6-H, J = 1.0 Hz, J = 8.0 Hz), 8.51 (d, 1H, 6'-H, J = 4.9 Hz), 10.95 (s, 1H, NH); ir (potassium bromide): ν 3262, 2952, 1654, 765, 697 cm^{-1}.

Anal. Calcd. for $C_{23}H_{23}FN_2O_2$: C, 73.00; H, 6.13; N, 7.40. Found: C, 72.96; H, 6.27; N, 7.15.

2,2-Dimethyl-*N*-(2-(3-fluoro-4-(1-hydroxydiphenylmethyl)-2-pyridyl)phenyl)propanamide (**4h**).

General procedure B, using benzophenone as the electrophile, gave 0.319 g (35%) of **4h**, mp 125°; ^1H nmr (deuteriochloroform): δ 1.22 (s, 9H, *t*-Bu), 3.38 (d, 1H, OH, J = 6.9 Hz), 7.01 (t, 1H, 5'-H, J = 5.2 Hz), 7.09 (td, 1H, 4-H, J = 1.2 Hz, J = 7.7 Hz), 7.29-7.41 (comp, $11H_{arom}$), 7.44 (comp, 1H, 3-H), 8.40 (dd, 1H, 6-H, J = 1.2 Hz, J = 8.0 Hz), 8.41 (d, 1H, 6'-H, J = 5.2 Hz), 10.82 (s, 1H, NH); ir (potassium bromide): ν 3305, 2966, 2840, 1647, 1513, 1233, 1171, 1035, 827, 752, 707 cm^{-1}.

Anal. Calcd. for $C_{29}H_{27}FN_2O_2$: C, 76.63; H, 5.99; N, 6.16. Found: C, 76.52; H, 5.83; N, 6.32.

2,2-Dimethyl-*N*-(2-(3-fluoro-4-trimethylsilyl-2-pyridyl)phenyl)-propanamide (**4i**).

General procedure B, using trimethylsilyl chloride as the electrophile, gave 0.428 g (62%) of **4i**, mp 114-115°; ^1H nmr (deuteriochloroform): δ 0.40 (s, 9H, $Si(CH_3)_3$), 1.25 (s, 9H, *t*-Bu), 7.17 (m, 1H, 4-H), 7.34 (t, 1H, 5'-H, J = 4.9 Hz), 7.43 (comp, 1H, 5-H), 7.66 (ddd, 1H, 3-H, J = 1.5 Hz, J = 4.6 Hz, J = 7.7 Hz), 8.43-8.47 (m, 2H, 6-H and 6'-H), 10.95 (s, 1H, NH); ir (potassium bromide): ν 3215, 2964, 1673, 1484, 838, 749 cm^{-1}.

Anal. Calcd. for $C_{19}H_{25}FN_2OSi$: C, 66.24; H, 7.31; N, 8.13. Found: C, 66.34; H, 7.55; N, 7.81.

3-Fluoro-2-(2-pivaloylaminophenyl)-4-pyridinecarboxylic Acid (**4j**).

General procedure B, using solid carbon dioxide as the electrophile, gave 0.260 g (41%) of **4j**, mp 178°; ^1H nmr (deuteriochloroform): δ 1.24 (s, 9H, *t*-Bu), 7.22 (td, 1H, 4-H, J = 1.0 Hz), 7.49 (td, 1H, 5-H, J = 1.3 Hz, J = 8.0 Hz), 7.70 (ddd, 1H, 3-H, J = 1.3 Hz, J = 4.6 Hz, J = 7.6 Hz), 7.85 (t, 1H, 5'-H, J = 4.9 Hz), 8.39 (dd, 1H, 6-H, J = 1.0 Hz, J = 8.0 Hz), 8.64 (d, 1H, 6'-H, J = 4.9 Hz), 9.10 (s, 1H, COOH), 10.40 (s, 1H, NH); ir (potassium bromide): ν 3400, 2964, 1734, 1634, 750, 706, 638 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}FN_2O_3$: C, 64.55; H, 5.42; N, 8.86. Found: C, 64.18; H, 5.37; N, 8.68.

2,2-Dimethyl-*N*-(2-(3-fluoro-4-formyl-2-pyridyl)phenyl)propanamide (**4k**).

General procedure B, using ethyl fomiate as the electrophile, gave 0.277 g (46%) of **4k**, mp 100°; ^1H nmr (deuteriochloroform): δ 1.24 (s, 9H, *t*-Bu), 7.21 (td, 1H, 4-H, J = 1.0 Hz, J = 7.7 Hz), 7.48 (comp, 1H, 5-H), 7.67-7.75 (m, 2H, 5'-H and 3-H), 8.44 (m, 1H, 6-H), 8.68 (d, 1H, 6'-H, J = 4.9 Hz), 10.53 (s, 1H CHO), 10.71 (s, 1H, NH); ir (potassium bromide): ν 3205, 2973, 2870, 1706, 1664, 1526, 750 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}FN_2O_2$: C, 67.99; H, 5.71; N, 9.33. Found: C, 67.93; H, 5.90; N, 9.27.

General Procedure C. Cross-coupling Between 2,2-Dimethyl-*N*-(2-(3-fluoro-4-iodo-2-pyridyl)phenyl)propanamide (**4b**) with Hetarylstannanes.

2,2-Dimethyl-*N*-(2-(3-fluoro-4-iodo-2-pyridyl)phenyl)propanamide **4b** (398.3 mg, 1.0 mmole) was added in deoxygenated toluene (10 ml). The resulting mixture was stirred 30 minutes under an argon atmosphere. The corresponding stannane (1.0 mmole) and tetrakis(triphenylphosphine)palladium(0) (30.0 mg, 0.03 mmole) were added and the mixture was refluxed for 60 hours. Cooling, filtration, decantation, extraction by toluene, drying over magnesium sulfate and solvent removal afforded a crude product which was purified by flash chromatography (cyclohexane/ethyl acetate: 9/1).

2,2-Dimethyl-*N*-(2-(3-fluoro-4-(2-pyridyl)-2-pyridyl)phenyl)-propanamide (**7c**).

General procedure C, using 2-trimethylstannylpyridine, gave 0.263 g (75%) of **7c**, mp 165-167°; ^1H nmr (deuteriochloroform): δ 1.23 (s, 9H, *t*-Bu), 7.14 (td, 1H, 4'-H, J = 1.0 Hz, J = 7.5 Hz), 7.26-7.42 (m, $2H_{arom}$), 7.72-7.82 (m, 2, H_{pyr} and H_{arom}), 7.97 (dd, $1H_{pyr}$, J = 0.9 Hz, J = 7.9 Hz), 8.28-8.38 (comp, 2H, H_{pyr} and H_{arom}), 8.53 (dd, 1H, H_{pyr}, J = 0.9 Hz, J = 4.9 Hz), 8.75 (comp, $1H_{pyr}$), 10.74 (s, 1H, NH); ir (potassium bromide): ν 3057, 2962, 2870, 1673, 1437 1120, 765, 722 cm^{-1}.

Anal. Calcd. for $C_{21}H_{20}FN_3O$: C, 72.19; H, 5.77; N, 12.03. Found: C, 72.51; H, 5.62; N, 12.24.

2,2-Dimethyl-*N*-(2-(3-fluoro-4-(2-thienyl)-2-pyridyl)phenyl)-propanamide (**7d**).

General procedure C, using 2-trimethylstannylthiophene, gave 0.295 g (83%) of **7d**, mp 120°; ^{1}H nmr (deuteriochloroform): δ 1.25 (s, 9H, *t*-Bu), 7.10-7.80 (m, $7H_{arom}$), 8.40-8.58 (m, $2H_{arom}$), 10.75 (s, 1H, NH); ir (potassium bromide): ν 3278, 3066, 2961, 1675, 1596, 1518, 1442, 1206, 1162, 832, 758 cm^{-1}.

Anal. Calcd. for $C_{20}H_{19}FN_2OS$: C, 67.77; H, 5.40; N, 7.90. Found: C, 67.75; H, 5.19; N, 7.70.

2,2-Dimethyl-*N*-(2-(3-fluoro-4-(2-quinolyl)-2-pyridyl)phenyl)-propanamide (**7e**).

General procedure C, using 2-trimethylstannylquinoline, gave 0.360 g (90%) of **7e**, mp 140°; ^{1}H nmr (deuteriochloroform): δ 1.25 (s, 9H, *t*-Bu), 7.19 (td, $1H_{arom}$, J = 1.0 Hz, J = 7.5 Hz), 7.46 (td, $1H_{arom}$, J = 1.5 Hz, J = 8.2 Hz), 7.64 (td, $1H_{arom}$, J = 1.1 Hz, J = 7.5 Hz), 7.74 (comp, $1H_{arom}$), 7.81 (td, $1H_{arom}$), 7.91 (d, $1H_{arom}$, J = 8.1 Hz), 7.98 (dd, $1H_{quino}$, J = 2.9 Hz, J = 8.6 Hz), 8.09 (t, 1H, 5'-H, J = 5.2 Hz), 8.27 (d, $1H_{arom}$, J = 8.4 Hz), 8.31 (d, $1H_{quino}$, J = 8.6 Hz), 8.49 (d, $1H_{arom}$, J = 8.4 Hz), 8.66 (d, 1H, 6'-H, J = 5.2 Hz), 10.85 (s, 1H, NH); ir (potassium bromide): ν 3288, 2954, 1670, 1585, 1037, 828, 768 cm^{-1}.

Anal. Calcd. for $C_{25}H_{22}FN_3O$: C, 75.17; H, 5.55; N, 10.52. Found: C, 75.17; H, 5.75; N, 10.37.

General Procedure D. Synthesis of 4-Substituted-5*H*-pyrido[3,2-*b*]-indole or α-Substituted δ-Carbolines.

Anhydrous pyridinium chloride (10 g) at the boiling point (215°) was added to the corresponding phenylpyridines **4** and **7** (deprotected amine) (1.0 mmole) and the mixture was refluxed for 15 minutes. The resulting hot solution was poured on a mixture (20 ml) of ice and concentrated ammonia. Extraction of the aqueous layer by ethyl acetate, drying over magnesium sulfate, solvent removal and flash chromatography on silica (cyclohexane/ethyl acetate: 5/5) afforded a pure product.

5*H*-pyrido[3,2-*b*]indole or δ-Carboline (**9a**).

General procedure D, using **3** (undeprotected amine) gave 0.135 g (80%) of **9a**, mp 206°; ^{1}H nmr (DMSO-d_6): δ 7.23 (td, 1H, 8-H, J = 1.2 Hz, J = 7.3 Hz), 7.37 (dd, 1H, 3-H, J = 4.6 Hz, J = 8.2 Hz), 7.48 (td, 1H, 7-H), 7.52 (d, 1H, 6-H, 7.86 (dd, 1H, 4-H, J = 1.3 Hz, J = 8.2 Hz), 8.18 (d, 1H, 9-H, J = 7.3 Hz), 8.42 (dd, 1H, 2-H, J = 1.3 Hz, J = 4.6 Hz), 11.40 (s, 1H, NH); ir (potassium bromide): ν 3400, 3120, 3060, 2760, 2690, 1630, 1560, 1505, 1460, 1400, 1320, 125, 890, 780, 740, 715 cm^{-1}.

Anal. Calcd. for $C_{11}H_8N_2$: C, 78.55; H, 4.79; N, 16.65. Found: C, 78.42; H, 4.90; N, 16.59.

4-Methyl-5*H*-pyrido[3,2-*b*]indole or 4-methyl-δ-carboline (**9b**).

General procedure D, using **8a**, gave 0.166 g (91%) of **9b**, mp >250°; ^{1}H nmr (DMSO-d_6): δ 2.58 (s, 3H, CH_3), 7.20-7.24 (m, $2H_{arom}$), 7.43-7.57 (m, $2H_{arom}$), 8.14 (d, 1H, 9-H, J = 7.8 Hz), 8.31 (d, 1H, 2-H, J = 4.7 Hz), 11.43 (s, 1H, H); ir (potassium bromide): ν 3120, 3050, 2960, 2900, 2820, 2760, 2680, 1620, 1610, 1460, 1380, 1320, 1230, 750 cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.09; H, 5.53; N, 15.37. Found: C, 78.88; H, 5.52; N, 15.06.

4-Ethyl-5*H*-pyrido[3,2-*b*]indole or 4-Ethyl-δ-carboline (**9c**).

General procedure D, using **8b**, gave 0.142 g (72%) of **9c**, mp 240°; ^{1}H nmr (DMSO-d_6): δ 1.32 (t, 3H, CH_3, J = 7.5 Hz), 2.96 (q, 2H, CH_2, J = 7.5 Hz), 7.17-7.24 (m, 2H, 3-H and H_{arom}), 7.43-7.57 (m, $2H_{arom}$), 8.13 (d, 1H, 9-H, J = 7.8 z), 8.35 (d, 1H, 2-H, J = 4.7 Hz), 11.45 (s, 1H, NH); ir (potassium bromide): ν 3131, 3061, 2968, 2898, 2815, 2672, 1624, 1608, 1377, 1228, 881, 745 cm^{-1}.

Anal. Calcd. for: $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.34; H, 6.19; N, 14.49.

4-Phenyl-5*H*-pyrido[3,2-*b*]indole or 4-Phenyl-δ-carboline (**9d**).

General procedure D, using **8c**, gave 0.176 g (72%) of **9d**, mp 235°; ^{1}H nmr (DMSO-d_6): δ 7.38 (comp, 1H, H_{arom}), 7.60-7.71 (m, 5H), 7.76 (d, 1H, 3-H, J = 5.5 Hz), 7.86-7.90 (m, $2H_{arom}$), 8.36 (d, $1H_{arom}$, J = 7.8 Hz), 8.71 (d, 1H, 2-H, J = 5.5 Hz), 11.35 (s, 1H, NH); ir (potassium bromide): ν 3261, 3064, 1665, 1436, 757, 697, 578 cm^{-1}.

Anal. Calcd. for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.50; H, 4.77; N, 11.58.

4-(2-Aminophenyl)-5*H*-pyrido[3,2-*b*]indole or 4-(2-Amino-phenyl)-δ-carboline (**9e**).

General procedure D, using **8d**, gave 0.203 g (78%) of two carbolines (δ-/β-carboline: 1/1), mp 230°; δ-carboline **9e**: ^{1}H nmr (DMSO-d_6): δ 4.40 (s, 2H, NH_2), 6.67-6.92 (m, $2H_{arom}$), 7.17-7.23 (m, $3H_{arom}$ and 6-H), 7.32 (d, 1H, 3-H, J = 4.8 Hz), 7.41-7.61 (m, 2H, 7-H and 8-H), 8.19 (d, 1H, 9-H, J = 7.8 Hz), 8.47 (d, 1H, 2-H, J = 4.8 Hz), 11.50 (s, 1H, NH); ir (potassium bromide): ν 3348, 3229, 3048, 1625, 1497, 133, 785, 732 cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.20. Found: C, 78.57; H, 5.06; N, 15.92.

β-Carboline **9f** had mp 245°; ^{1}H nmr (DMSO-d_6): δ 4.52 (s, 2H, NH_2), 6.78 (td, $1H_{arom}$, J = 7.4 Hz), 6.87 (d, $1H_{arom}$, J = 7.1 Hz), 7.17 (comp, $1H_{arom}$), 7.24 (comp, $1H_{arom}$), 7.46-7.63 (m, $3H_{arom}$), 8.07 (d, 1H, 4-H, J = 5.3 Hz), 8.22 (d, 1H, 5-H, J = 8.24 Hz), 8.39 (d, 1H, 3-H, J = 5.3 Hz), 11.30 (s, 1H, NH); ir (potassium bromide): ν 3347, 3226, 3048, 1626, 1417, 1234, 732 cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.20. Found: C, 78.46; H, 4.88. N, 16.28.

4-(2-Pyridyl)-5*H*-pyrido[3,2-*b*]indole (**9g**).

The foregoing procedure with **8e** gave 0.241 g (98%) of **9g**, mp 204°; ^{1}H nmr (DMSO-d_6): δ 7.23 (td, 1H, 8-H), 7.49-7.55 (m, $2H_{arom}$), 7.80 (d, 1H, J = 8.2 Hz), 8.02 (d, 1H, 3-H, J = 5.2 Hz), 8.04 (comp, $1H_{arom}$), 8.22 (d, 1H, 9-H, J = 7.8 Hz), 8.57 (d, 1H, 2-H, J = 5.2 Hz), 8.91 (dd, $1H_{pyr}$, J = 4.8 Hz, J = 0.9 Hz), 10.90 (s, 1H, NH); ir (potassium bromide): ν 3357, 1454, 1317, 1147, 792, 746 cm^{-1}.

Anal. Calcd. for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13. Found: C, 78.17; H, 4.72; N, 16.85.

4-(2-Thienyl)-5*H*-pyrido[3,2-*b*]indole (**9h**).

General procedure D, using **8f** gave 0.226 g (90%) of **9h**, mp 210°; ^{1}H nmr (DMSO-d_6): δ 7.27 (td, 1H, 8-H, J = 7.8 Hz, J = 0.9 Hz), 7.37 (dd, 1H, 4'-H, J = 3.7 Hz, J = 5.1 Hz), 7.52 (d, 1H, 3-H, J = 4.9 Hz), 7.53 (td, 1H, 7-H, J = 7.5 Hz, J = 1.5 Hz), 7.67 (d, 1H, 6-H, J = 8.0 Hz), 7.84 (dd, 1H, 5'-H, J = 5.1 Hz, J = 1.1 Hz), 7.89 (d, 1H, 3'-H, J = 3.7 Hz, J = 1.1 Hz), 8.19 (d, 1H, 5-H, J = 7.8 Hz), 8.47 (d, 1H, 2-H, J = 4.9 Hz), 11.40 (s, 1H, NH); ir (potassium bromide): ν 3067, 1378, 1226, 739 cm^{-1}.

Anal. Calcd. for $C_{15}H_{10}N_2S$: C, 71.97; H, 4.03; N, 11.19. Found: C, 71.68; H, 3.85; N, 10.95.

4-(2-Quinolyl)-5*H*-pyrido[3,2-*b*]indole (**9i**).

General procedure D, using **8g**, gave 0.237 g (80%) of **9i**, mp 205-206°; ^1H nmr (DMSO-d_6): δ 7.31 (td, 1H, 8-H), 7.58 (td, $1H_{quino}$, J = 7.10 Hz, J = 1.18 Hz), 7.70 (td, $1H_{quino}$, J = 7.46 Hz, J = 1.18 Hz), 7.67-7.95 (m, $2H_{arom}$), 8.08 d, 1H, J = 8.2 Hz), 8.22 (d, 1H, 3-H, J = 5.20 Hz), 8.24 (m, $1H_{arom}$), 8.51 (d, $1H_{arom}$, J = 8.8 Hz), 8.61 (d, 1H, J = 8.3 Hz), 8.64 (d, 1H, 2-H), 8.68 (comp, $1H_{quino}$), 10.98 (s, 1H, NH); ir (potassium bromide): ν 3372, 1377, 1212, 1143, 819, 764 cm^{-1}.

Anal. Calcd. for $C_{20}H_{13}N_3$: C, 81.34; H, 4.43; N, 14.23. Found: C, 80.98; H, 4.41; N, 14.33.

Acknowledgment.

The authors are grateful to Véronique Chassagne and Nicole Vaqué for their skillful technical supports.

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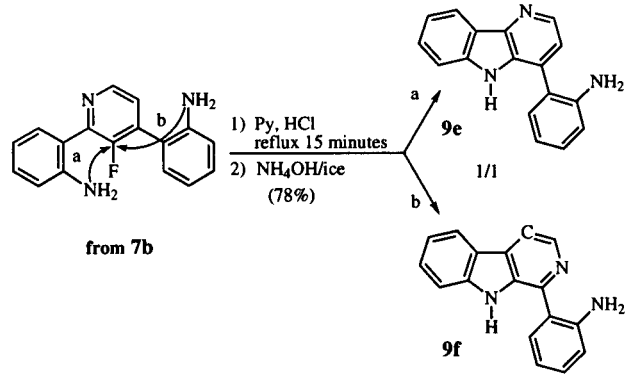
[11] This hydrolysis was carried out in a 20% sulfuric acid and yields were almost quantitatives. The crude amines were thus used for cyclization to δ-carbolines.

[12] About compound **8d**, a competition took place between the two amino groups and both carbolines, β- and δ-carbolines with the same substituted group, were obtained in a 1/1 ratio as shown on the following scheme:



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