Carbolines. Part VII. Anisidines, Convenient Tools to Synthesize Hydroxy-β-Carbolines

Patrick Rocca, Francis Marsais, Alain Godard and Guy Quéguiner*

Institut de Recherche en Chimie Organique Fine Hétérocyclique de l'IRCOF associé au CNRS - INSA de Rouen, BP 08, F-76131 Mont-Saint-Aignan cédex, France

Luqman Adams and Babajide Alo

Chemistry Department, University of Lagos, Nigeria

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The paper describes a convenient synthesis of hydroxy-β-carbolines from commercial anisidines based on key steps such as metalation, cross-coupling and cyclization. The first total synthesis of a major cytotoxic constituent of a marine bryozoan is also reported, the 8-hydroxy-1-vinyl-β-carboline.

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Introduction.

Numerous alkaloids of the β-carboline series bearing various substituents on the benzene ring display interesting biological properties [1]. Among these substituents, hydroxyl is one of the most important and widely found in nature [2]. Most syntheses of such hydroxylated molecules are based on condensation reactions between the appropriate tryptophan or tryptamine derivatives and aldehydes [3]. Some related compounds are prepared from available β-carboline reagents through specific reactions [4]. 5-Hydroxy-β-carbolines are found in nature in *canthinone* structures [10]. 6- and 7-Hydroxy-β-carbolines are widely present in nature like *eudistomins* [11a] as well as in 9-hydroxycanthin-6-one [11b]. 8-Hydroxy-β-carbolines are found in *picrasidines* [12] and some bis-carbolines [13].

We have previously described [5] a general and convergent route to carbolines based on metalation [6] and cross-coupling [7] reactions, as well as a convenient synthesis of 6-hydroxyharmane [8]. We wish to report here an extension of this fruitful method to the total synthesis of the 4 parent hydroxy-β-carbolines **1-4** and to the first total synthesis of 8-hydroxy-1-vinyl-β-carboline **5**. This alkaloid has been isolated in 1991 by Munro *et al.* [9] from *cribricellina criberia* and characterized as the major cytotoxic constituent of this New Zealand marine bryozoan (Scheme I).

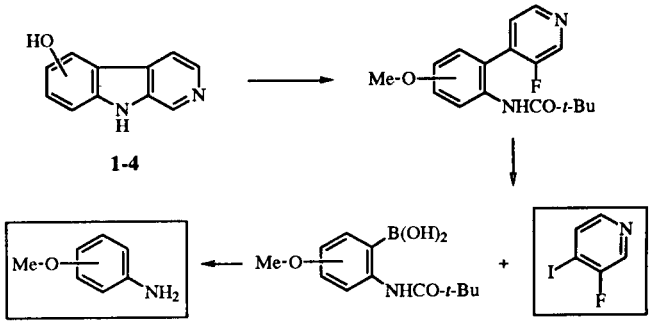
Scheme I

1-4 **5**

Retrosynthesis.

From a retrosynthetic analysis (Scheme II), hydroxy-β-carbolines **1-4** could be prepared by cyclization of conveniently functionalized methoxyphenylpyridines. These phenylpyridines could be obtained by a cross-coupling reaction between the required anisidine building blocks and 3-fluoro-4-iodopyridine.

Scheme II



Results and Discussion.

Arylboronic acids **11-13** were prepared by metalation-boronation [5a] of the corresponding anisidines protected as a pivaloyl in 50-52% yields (Scheme III and Table I). Compound **10** was prepared in a similar way from the carboxylated compound **7**. The carboxylic group was used as a protective group of the 2-position of compound **6** and

Scheme III

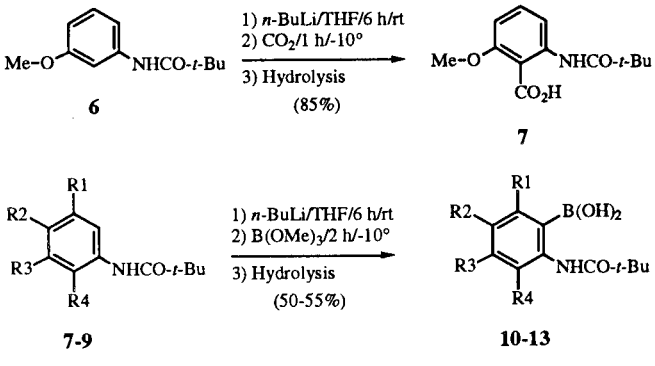


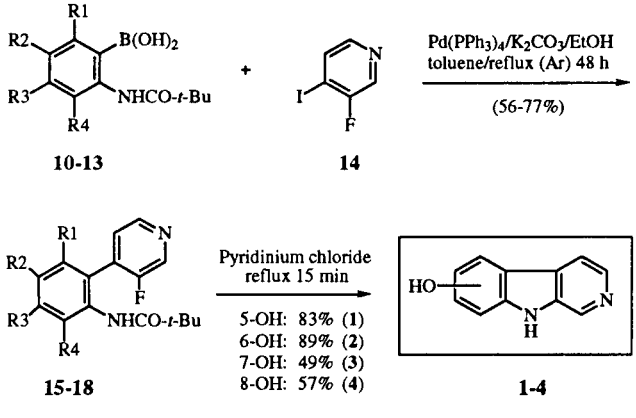
Table I

Product	R1	R2	R3	R4	Yield (%)
11	OMe	H	H	H	52
12	H	OMe	H	H	51
10	H	H	OMe	COOH	55
13	H	H	H	OMe	50

will be removed in the final cyclization step.

The palladium catalyzed cross-coupling reaction between phenylboronic acids **10-13** and 3-fluoro-4-iodopyridine **14** using the Suzuki conditions gave the corresponding heterobiaryls **15-18** in good yields (Scheme IV and Table II). The phenylpyridines **15-18** were cyclized by treatment with boiling pyridinium chloride (215°). Hydrolysis and basic workup yielded the corresponding hydroxy-β-carbolines **1-4** in good yields. Under these conditions, the expected hydrolysis of methoxy groups (compounds **15-18**) as well as a decarboxylation (compound **17**) were observed (Scheme IV).

Scheme IV

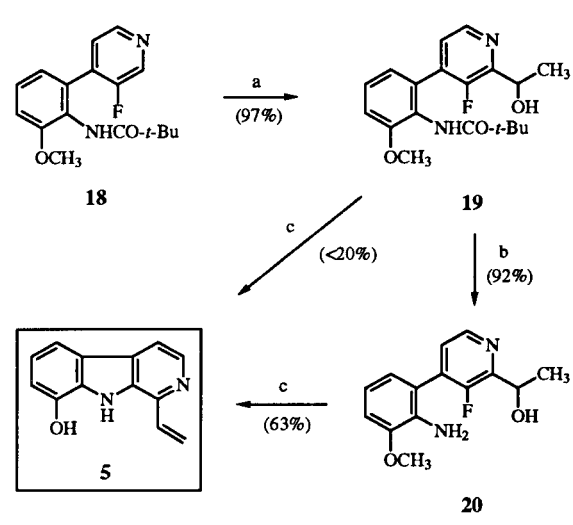


Based on our previously reported synthesis of pavettine [5b], **5** was obtained in two steps from the biaryl **18**. Regioselective metalation of **18** with *n*-butyllithium in tetrahydrofuran at low temperature and reaction of the resulting lithioderivative with acetaldehyde afforded the corresponding phenylpyridine **19** in 97% yield. Hydrolysis of **19** to amine **20** was carried out in 20% sulfuric acid (92% yield). Cyclization of **20** to 8-hydroxy-1-vinyl-β-carboline **5** was best achieved by treatment with pyridinium chloride at 180° followed by basic workup. In these conditions, cyclization of **20** occurs simultaneously with dehydration of the hydroxyethyl group and hydrolysis of the methoxy group to give the expected β-carboline **5** (Scheme V). It can be noted that the one-step cyclization of **19** to **5** is also possible but in low yield (<20%).

Table II

Product	R1	R2	R3	R4	Yield (%)
15	OMe	H	H	H	77
16	H	OMe	H	H	70
17	H	H	OMe	COOH	56
18	H	H	H	OMe	63

Scheme V



a: 1) BuLi/THF/-75°/1.5 h 2) CH_3CHO/-75°/1 h 3) H_2O
b: 20% H_2SO_4/100°/1.5 h
c: Pyridinium chloride/180°/15 min

Conclusion.

The reported syntheses of the 4-parent hydroxy-β-carbolines **1-4** relies on key steps such as metalation, cross-coupling and cyclization. The strategy is fully convergent, regioselective and allows interesting 15-33% overall yield in 3 or 4 steps. The methodology was successfully applied for the first total synthesis of the natural alkaloid **5** in a 18% overall yield (5 steps). The present work is currently being extended to the preparation of more complex related carbolines.

EXPERIMENTAL

General Data.

The ^1H nmr spectra were obtained on a Varian T60 spectrometer (60 MHz) spectrometer (and were recorded in ppm downfield from internal standard, TMS in deuteriochloroform, or HMDS in DMSO-d_6) or on a 200 MHz Brüker 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}. Mass spectra were obtained on a JEOL D700 instrument, and 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 [15]. Commercial diisopropylamine was distilled from calcium hydride and stored over calcium hydride under a dry argon atmosphere. 3-Fluoro-4-iodopyridine (**15**) was prepared [5a] by metalation-iodination of the corresponding fluoropyridine. Methoxypivaloylaminobenzenes **6**, **8** and **9** were prepared from commercial anisidines according to a procedure described in a previous paper [5a] in very good yields (92-97%). Commercial 2.5*M* solution of *n*-butyllithium in hexane was stored and transferred under a dehydrated and deoxygenated argon atmosphere.

6-Methoxy-2-(pivaloylamino)phenylcarboxylic Acid (**7**).

n-Butyllithium (60 ml, 0.15 mole) was slowly added to a cold (-25°) solution of 2,2-dimethyl-*N*-(3-methoxyphenyl)propanamide (**6**) (10.36 g, 0.05 mole) in anhydrous tetrahydrofuran (100 ml). The resulting solution was stirred 6 hours at room temperature and a creamy precipitate appeared. The mixture was cooled to -20°, and a large excess of solid carbon dioxide (~20 g) was added. Stirring was continued for 1 hour at -10° before hydrolysis at -15°. After decantation and extraction with methylene chloride, the aqueous layer was acidified with 1/5 hydrochloric acid (*p*H = 1) to isolate the orange precipitate which was purified by flash chromatography on silica (ethyl acetate) to yield 10.68 g (85%) of **7**, mp 114-116°; ^{1}H nmr (deuteriochloroform): δ 1.26 (s, 9H, *t*-Bu), 3.72 (s, 3H, OCH_3), 6.62 (d, 1H, 5-H, J = 8.5 Hz), 7.38 (t, 1H, 4-H, J = 8.5 Hz), 8.47 (d, 1H, 3-H, J = 8.5 Hz), 9.50 (s, 1H, NH), 12.80 (s, 1H, COOH); ir (potassium bromide): ν 3450, 3252, 2969, 1698, 1583, 1472 cm^{-1}.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.93; H, 6.98; N, 5.39.

General Procedure A: Synthesis of Arylboronic Acids.

n-Butyllithium (60 ml, 0.15 mole) was slowly added to a cold (-25°) solution of the corresponding protected anisidine (0.05 mole) in anhydrous tetrahydrofuran (100 ml). The resulting solution was stirred 6 hours at room temperature and a creamy precipitate appeared. The mixture was cooled to -20°, and trimethylborate (17 ml, 0.15 mole) was slowly added. Stirring was continued for 2 hours at -15° before hydrolysis at 0°. After filtration and extraction by methylene chloride, the aqueous layer was acidified with hydrochloric acid 1/5. The medium was immediately extracted with methylene chloride (3 x 50 ml). Drying over magnesium sulfate and solvent removal afforded the corresponding boronic acid.

3-Carboxy-4-methoxy-2-(pivaloylamino)phenylboronic Acid (**10**).

The general procedure A applied to **7** using 0.20 mole of *n*-butyllithium, gave 8.12 g (55%) of **10** (unstable and moisture sensitive); ^{1}H nmr (DMSO-d_6): δ 1.20 (s, 9H, *t*-Bu), 3.60 (m, 2H, $B(OH)_2$), 3.77 (s, 3H, OCH_3), 6.80 (d, 1H, 5-H, J = 8.0 Hz), 7.55 (d, 1H, 6-H, J = Hz), 9.59 (s, 1H, NH), 13.50 (s, 1H, COOH); ir (potassium bromide): ν 3450, 3208, 2967, 1706, 1608, 1585, 1467 cm^{-1}.

6-Methoxy-2-(pivaloylamino)phenylboronic Acid (**11**).

The general procedure A applied to **6** gave 6.53 g (52%) of **11**, mp 168-170°; ^{1}H nmr (DMSO-d_6): δ 1.10 (s, 9H, *t*-Bu), 3.16 (m, 2H, $B(OH)_2$), 3.61 (s, 3H, OCH_3), 6.62 (d, 1H, 5-H, J = 8.1 Hz), 7.09 (t, 1H, 4-H, J = 8.1 Hz), 7.36 (d, 1H, 3-H, J = 8.1 Hz), 10.80 (s, 1H, NH); ir (potassium bromide): ν 3284, 2966, 1612, 1579, 1553, 1463 cm^{-1}.

Anal. Calcd. for $C_{12}H_{18}BNO_4$: C, 57.40; H, 7.23; N, 5.58. Found: C, 57.13; H, 7.30; N, 5.25.

5-Methoxy-2-(pivaloylamino)phenylboronic Acid (**12**).

The general procedure A, applied to **8**, gave 6.40 g (51%) of **12**, mp >260°; ^{1}H nmr (DMSO-d_6): δ 1.10 (s, 9H, *t*-Bu), 3.18 (m, 2H, $B(OH)_2$), 3.62 (s, 3H, OCH_3), 6.83 (comp, 1H, 4-H), 7.56-7.75 (m, 3H, $2H_{arom}$ + NH); ir (potassium bromide): ν 3323, 2967, 1654, 1602, 1534, 1490 cm^{-1}.

Anal. Calcd. for $C_{12}H_{18}BNO_4$: C, 57.40; H, 7.23; N, 5.58. Found: C, 57.05; H, 7.18; N, 5.33.

3-Methoxy-2-(pivaloylamino)phenylboronic Acid (**13**).

The general procedure A, applied to **9**, gave 6.28 g (50%) of **13**, mp 137-139°; ^{1}H nmr (DMSO-d_6): δ 1.10 (s, 9H, *t*-Bu), 3.10 (m, 2H, $B(OH)_2$), 3.75 (s, 3H, OCH_3), 6.80-7.05 (m, 3H, 4-H + 5-H + 6-H), 9.40 (s, 1H, NH); ir (potassium bromide): ν 3427, 2966, 1684, 1626, 1545, 1466 cm^{-1}.

Anal. Calcd. for $C_{12}H_{18}BNO_4$: C, 57.40; H, 7.23; N, 5.58. Found: C, 57.19; H, 6.85; N, 5.38.

General Procedure B: Cross-coupling Reaction Between 3-Fluoro-4-iodopyridine and Benzeneboronic Acids.

The required arylboronic acid (2.0 mmoles) and 3-fluoro-4-iodopyridine (**14**) (2.0 mrnoles) were added to an aqueous solution of potassium carbonate (2*M*, 2.0 ml) and ethanol (1.0 ml) in deoxygenated toluene (20 ml). The resulting mixture was stirred for 30 minutes under an argon atmosphere. Tetrakis(triphenylphosphine)-palladium(0) (70 mg, 0.060 mmole) 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*-(3-methoxy-2-(3-fluoro-4-pyridyl)phenyl)propanamide (**15**).

The general procedure B, applied to **11**, gave 0.466 g (77%) of **15** (hexane/ethyl acetate: 1/1), mp 141-143°; ^{1}H nmr (deuteriochloroform): δ 1.10 (s, 9H, *t*-Bu), 3.79 (s, 3H, OCH_3), 6.83 (d, 1H, 4-H, J = 8.8 Hz), 7.03 (s, 1H, NH), 7.29 (d, 1H, 5'-H, J = 4.9 Hz), 7.43 (t, 1H, 5-H, J = 8.2 Hz), 7.80 (d, 1H, 6-H, J = 8.2 Hz), 8.53 (d, 1H, 6'-H, J = 4.9 Hz), 8.63 (s, 1H, 2'-H); ir (potassium bromide): ν 3348, 2957, 1685, 1609, 1587, 1469 cm^{-1}.

Anal. Calcd. for $C_{17}H_{19}FN_2O_2$: C, 67.53; H, 6.33; N, 9.27. Found: C, 67.38; H, 6.12; N, 9.03.

2,2-Dimethyl-*N*-(4-methoxy-2-(3-fluoro-4-pyridyl)phenyl)propanamide (**16**).

The general procedure B, applied to **12**, gave 0.423 g (70%) of **16** (hexane/ethyl acetate: 1/1), mp 184-186°; ^{1}H nmr (deuteriochloroform): δ 1.33 (s, 9H, *t*-Bu), 3.82 (s, 3H, OCH_3), 6.98 (d, 1H, J = 8.9 Hz), 7.31 (comp, 1H, 6-H), 7.45-7.58 (m, 3H, $2H_{arom}$ + NH), 8.43 (d, 1H, 6'-H, J = 4.9 Hz), 8.50 (s, 1H, 2'-H); ir (potassium bromide): ν 3280, 1670, 1601 cm^{-1}.

Anal. Calcd. for $C_{17}H_{19}FN_2O_2$: C, 67.53; H, 6.33; N, 9.27. Found: C, 67.86; H, 6.50; N, 9.25.

6-Methoxy-2-pivaloylamino-3-(3-fluoro-4-pyridyl)phenylcarboxylic Acid (**17**).

The general procedure B, applied to **10** (after extraction with

toluene, the clear aqueous layer was acidified (2*M* hydrochloric acid) to *p*H = 1 and extracted again with methylene chloride), gave 0.388 g (56%) of **17** (hexane/ethyl acetate: 1/1), mp 90-92°; ^{1}H nmr (deuteriochloroform): δ 1.10 (s, 9H, *t*-Bu), 6.50 (d, 1H, 5-H, J = 8.0 Hz), 7.05-7.32 (m, 2H), 8.30 (m, 1H), 8.90 (s, 1H, NH), 13.20 (s, 1H, COOH); ir (potassium bromide): ν 3192, 2960, 1702, 1585, 1472 cm^{-1}.

Anal. Calcd. for $C_{18}H_{19}FN_2O_4$: C, 62.42; H, 5.53; N, 8.09. Found: C, 62.64; H, 5.85; N, 8.36.

2,2-Dimethyl-*N*-(6-methoxy-2-(3-fluoro-4-pyridyl)phenyl)propanamide (**18**).

The general procedure B, applied to **13**, gave 0.381 g (63%) of **18** (hexane/ethyl acetate: 1/1), mp 176-178°; ^{1}H nmr (deuteriochloroform): δ 0.95 (s, 9H, *t*-Bu), 3.79 (s, 3H, OCH_3), 6.95 (dd, 1H, J = 6.4, 1.3 Hz), 7.16 (dd, 1H, J = 8.4, 1.3 Hz), 7.27 (m, 3H, 2H + NH), 8.38 (dd, 1H, J = 4.9, 1.1 Hz), 8.56 (d, 1H, J = 1.9 Hz), 8.65 (s, 1H, 2'-H); ir (potassium bromide): ν 3281, 2971, 1666, 1585, 1506, 1466 cm^{-1}.

Anal. Calcd. for $C_{17}H_{19}FN_2O_2$: C, 67.53; H, 6.33; N, 9.27. Found: C, 67.84; H, 6.57; N, 9.21.

2,2-Dimethyl-*N*-(6-methoxy-2-(3-fluoro-1-hydroxyethyl-4-pyridyl)phenyl)propanamide (**19**).

n-Butyllithium (3.0 mmoles) was slowly added to a cold (-75°) solution of **17** (0.302 g, 1.0 mmole) in anhydrous tetrahydrofuran (25 ml). The resulting solution was reacted for 1 hour and 30 minutes at -75°. Three equivalents of acetaldehyde (0.132 g in 5 ml of tetrahydrofuran) was added. Stirring was continued for 1 hour at -75°, before hydrolysis at 0°. Extraction with ethyl acetate, drying over magnesium sulfate and solvent removal afforded a crude product, which was purified by flash chromatography on silica (ethyl acetate/hexane: 1/1) to yield 0.336 g (97%) of **19** (oil); ^{1}H nmr (deuteriochloroform): δ 0.96 (s, 9H, *t*-Bu), 1.06 (m, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.70 (m, 1H, CH), 5.20 (comp, OH), 6.95 (d, 1H, J = 7.6 Hz), 7.15 (d, 1H, J = 8.4 Hz), 7.25-7.40 (m, 2H$_{arom}$), 8.30 (d, 1H, 6'-H, J = 4.8 Hz), 8.70 (s, 1H, NH); ir (potassium bromide): ν 3322, 2978, 1675, 1586, 1503, 1424 cm^{-1}.

Anal. Calcd. for $C_{19}H_{23}FN_2O_3$: C, 65.88; H, 6.69; N, 8.09. Found: C, 66.15; H, 6.87; N, 7.87.

1-(3-Fluoro-4-(2-amino-3-methoxy-1-phenyl)pyrid-1-yl)ethanol (**20**).

Compound **19** (1.0 mmole) was added to a 20% solution of sulfuric acid (10 ml) and refluxed 2 hours. The resulting cold solution was diluted with water (20 ml). Extraction with ethyl acetate removed pivalic acid. Basification at 0° with ammonia to *p*H = 6-7 followed by several extraction with ethyl acetate (5 x 10 ml), and drying over magnesium sulfate afforded the crude amine **20** which was purified by flash chromatography on silica (ethyl acetate) to yield 0.224 g (92%) of **20** (oil); ^{1}H nmr (deuteriochloroform): δ 1.51 (t, 3H, CH_3), 3.90 (s, 2H, NH_2), 3.95 (s, 3H, OCH_3), 4.50 (dd, 1H, CH, J = Hz), 5.20 (comp, OH), 6.80-7.10 (m, 2H$_{arom}$), 7.30-7.40 (m, 2H, 1H$_{arom}$ + NH), 8.42 (dd, 1H, 6'-H, J = Hz); ir (potassium bromide): ν 3343, 1675 cm^{-1}.

Anal. Calcd. for $C_{14}H_{15}FN_2O_2$: C, 64.11; H, 5.76; N, 10.68. Found: C, 64.32; H, 5.92; N, 10.55.

General Procedure C: Synthesis of Hydroxy-β-carbolines.

Anhydrous boiling (215°) pyridinium chloride (10 g) was added to the required phenylpyridines (1.0 mmole), and the resulting mixture was refluxed for 15 minutes. The resulting hot solution was poured onto a mixture of ice and concentrated ammonia. Filtration of the precipitate, washing with water, and drying gave a first crop of the corresponding carboline. Extraction of the aqueous layer by ethyl acetate, drying over magnesium sulfate, solvent removal, and crystallization from toluene (or acetone) gave an additional crop.

5-Hydroxy-9*H*-pyrido[3,4-*b*]indole or 5-Hydroxy-β-carboline (**1**).

The general procedure C, applied to **15**, gave 0.153 g (83%) of **1**, mp 164-165°; ^{1}H nmr (DMSO-d_6): δ 6.60 (d, 1H, 6-H, J = 7.5 Hz), 6.98 (d, 1H, 8-H, J = 8.0 Hz), 7.30 (dd, 1H, 7-H, J = 7.5, 8.0 Hz), 8.01 (dd, 1H, 4-H, J = 0.7, 5.1 Hz), 8.27 (d, 1H, 3-H, J = 5.1 Hz), 8.79 (d, 1H, 1-H, J = 0.7 Hz), 10.35 (s, 1H, OH), 11.45 (s, 1H, NH); ir (potassium bromide): ν 3100, 2962, 1591, 1449 cm^{-1}.

Anal. Calcd. for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.97; H, 4.49; N, 15.06.

6-Hydroxy-9*H*-pyrido[3,4-*b*]indole or 6-hydroxy-β-carboline (**2**).

The general procedure C, applied to **16**, gave 0.164 g (89%) of **2**, mp 189-190°; ^{1}H nmr (DMSO-d_6): δ 7.03 (d, 1H, 8-H, J = 7.6 Hz), 7.40 (dd, 1H, 7-H, J = 7.6, 2.2 Hz), 7.50 (d, 1H, 5-H, J = 2.2 Hz), 7.98 (d, 1H, 4-H, J = 5.1 Hz), 8.25 (d, 1H, 3-H, J = 5.1 Hz), 8.80 (s, 1H, 1-H), 9.12 (s, 1H, OH), 11.25 (s, 1H, NH); ir (potassium bromide): ν 3275, 3049, 2966, 2567, 1580, 1458 cm^{-1}.

Anal. Calcd. for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.61; H, 4.47; N, 15.33.

7-Hydroxy-9*H*-pyrido[3,4-*b*]indole or 7-Hydroxy-β-carboline (**3**).

The general procedure C, applied to **17**, gave 0.090 g (49%) of **3**, mp >260°; ^{1}H nmr (DMSO-d_6): δ 6.69 (dd, 1H, 6-H, J = 2.0, 8.5 Hz), 6.86 (d, 1H, 8-H, J = 2.0 Hz), 7.89 (d, 1H, 4-H, J = 5.1 Hz), 7.97 (d, 1H, 5-H, J = 8.5 Hz), 8.22 (d, 1H, 3-H, J = 5.1 Hz), 8.72 (s, 1H, 1-H), 9.75 (s, 1H, OH), 11.27 (s, 1H, NH); ir (potassium bromide): ν 3278, 1560, 1458 cm^{-1}.

Anal. Calcd. for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.91; H, 4.60; N, 15.05.

8-Hydroxy-9*H*-pyrido[3,4-*b*]indole or 8-Hydroxy-β-carboline (**4**).

The general procedure C, applied to **18**, gave 0.105 g (57%) of **4**, mp 250° dec; ^{1}H nmr (DMSO-d_6): δ 6.92-7.09 (m, 2H, 5-H + 6-H), 7.65 (d, 1H, 7-H, J = 7.5 Hz), 8.02 (d, 1H, 4-H, J = 5.2 Hz), 8.28 (d, 1H, 3-H, J = 5.2 Hz), 8.82 (s, 1H, 1-H), 10.10 (s, 1H, OH), 11.40 (s, 1H, NH); ir (potassium bromide): ν 3060, 1508, 1450 cm^{-1}.

Anal. Calcd. for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.90; H, 4.24; N, 15.43.

8-Hydroxy-1-vinyl-9*H*-pyrido[3,4-*b*]indole or 8-Hydroxy-1-vinyl-β-carboline (**5**).

The general procedure C, applied to **20**, gave 0.132 g (63%) of **5**, mp 158-160° (lit [9], oil); ^{1}H nmr (DMSO-d_6): δ 5.52 (dd, 1H, 2'-Hb (vinyl), J = 10.6, 2.5 Hz), 6.49 (dd, 1H, 2'-Ha (vinyl), J = 16.9, 2.5 Hz), 6.96-7.15 (m, 3H, 5-H + 6-H + 1'-H (vinyl)), 7.64 (d, 1H, 7-H, J = 7.7 Hz), 7.94 (d, 1H, 4-H, J = 5.1 Hz), 8.28 (d, 1H, 3-H, J = 5.1 Hz), 10.09 (s, 1H, OH), 11.37 (s, 1H, NH);

ir (potassium bromide): ν 3205, 2966, 1586, 1430 cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32. Found: C, 74.53; H, 4.53; N, 13.21.

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REFERENCES AND NOTES

[1] K. Hirai and T. Ishiba, *Heterocycles,* **3**, 217 (1975); M. S. Allen, Y. C. Tan, M. L. Trundell, K. Narayanan, L. R. Schindler, M. J. Matrin, C. Schultz, T. J. Hagen, K. F. Koehler, P. W. Codding, P. Skolnick and J. M. Cook, *J. Med. Chem.,* **33**, 2343 (1990).

[2] D. J. Faulkner, *Nat. Prod. Rep.,* **8**, 97 (1991).

[3] T. Hino, Z. Lai, H. Seki, R. Hara, T. Kuramochi and M. Nakagawa, *Chem. Pharm. Bull.,* **37**, 2596 (1989).

[4] Y. Murakami, H. Takahashi, Y. Nakagawa, M. Koshimizu, T. Watanabe and Y. Y. Yokoyama, *Tetrahedron Letters,* **30**, 2099 (1989).

[5a] P. Rocca, F. Marsais, A. Godard and G. Quéguiner, *Tetrahedron,* **49**, 49 (1993); [b] P. Rocca, F. Marsais, A. Godard and G. Quéguiner, *Tetrahedron,* **49**, 3325 (1993); [c] P. Rocca, F. Marsais, A. Godard and G. Quéguiner, *Tetrahedron Letters,* **34**, 2937 (1993).

[6] For a comprehensive review on directed *ortho* metalation, see: H. W. Gschend and H. R. Rodriguez, *Org React.,* **26**, 1 (1976); V. Snieckus, *Chem. Rev.,* **90**, 879 (1990); For a recent review on π-deficient heterocycle metalation, see: G. Quéguiner, F. Marsais, V. Snieckus and J. Epsztajn, *J. Adv. Heterocylic Chem.,* **52**, 187 (1991).

[7] N. Miyaura, T. Yanagi and A. Suzuki, *Synth Commun.,* **11**, 513 (1981); N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh and A. Suzuki, *J. Am. Chem. Soc.,* **111**, 314 (1989); For a recent review on cross-coupling of heterocycles: V. N. Kalinin, *Russ. Chem. Rev. (Eng),* **60**, 173 (1991).

[8] P. Rocca, F. Marsais, A. Godard and G. Quéguiner, *Tetrahedron Letters,* **35**, 2003 (1994).

[9] F. E. Wu, K. Koike, T. Nikaido, Y. Sakamato, T. Ohmoto and K. Ikeda, *Chem. Pharm. Bull.,* **37**, 1808 (1989); M. R. Prinsep, J. W. Blunt and M. H. G. Munro, *J. Nat. Prod.,* **54**, 1068 (1991).

[10] G. R. Pettit, S. B. Singh, A. Goswami and R. A. Nieman, *Tetrahedron,* **44**, 3349 (1988); R. Vanhaelen-Fastré, M. Vanhaelen, B. Diallo and H. Breyne, *Planta Med.,* **56**, 241 (1990).

[11a] J. Kobayashi, M. Ishibashi, U. Nagai and Y. Ohizumi, *Experentia,* **45**, 782 (1989); [b] L. B. S. Kardono, C. K. Angerhofer, S. Tsauri, K. Padmawinata, J. M. Pezzuto and A. D. Kinghorn, *J. Nat. Prod.,* **54**, 1360 (1991).

[12] D. Arbain, L. T. Byrne, M. V. Sargent, B. W. Skelton and A. H. White, *Aust. J. Chem.,* **43**, 433 (1990).

[13] K. Koike, T. Ohmoto and T. Higuchi, *Phytochemistry,* **26**, 3375 (1987).

[14] W. Barz, H. Herzbeck, W. Hüsemann, G. Schneiders and H. K. Mangold, *Planta Med.,* **40**, 137 (1980).

[15] J. Bizot, *Bull. Soc. Chim. France,* **1**, 151 (1967).