Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 16 Feb 2007.

To cite this article: Patrick Rocca , Francis Marsais , Alain Godard & Guy Quéguiner (1995): Carbolines, Part VI. First Total Synthesis of Bauerine B and Its Demethyl Analogue, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:19, 2901-2908

To link to this article: http://dx.doi.org/10.1080/00397919508011420

SYNTHETIC COMMUNICATIONS, 25(19), 2901-2908 (1995)

CARBOLINES, PART VI. FIRST TOTAL SYNTHESIS OF BAUERINE B AND ITS DEMETHYL ANALOGUE.

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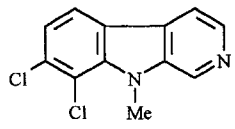
Abstract. *Short and convergent syntheses of Bauerine B and its demethyl analogue are reported. The approach is based on a convergent methodology which involves such reactions as metalation, heteroring cross-coupling and cyclization.*

Introduction.

Bauerine B: 7,8-dichloro-9-methyl-β-carboline (**1**) (scheme 1) was isolated in 1994 by R.E. Moore et al. from the terrestrial blue-green alga *Dichothrix baueriana GO-25-2*.[1] This cytotoxic alkaloid shows activity against herpes simplex virus type 2. Up to now, any synthesis of this new alkaloid has been described. Recently, we published a new general synthesis of the 4-parent carbolines[2] and α-substituted-β-carbolines.[3] We wish to report here on the extension of this fruitful strategy to the total synthesis of Bauerine B (**1**) and its demethyl analogue (**2**) starting from benzene and pyridine derivatives.

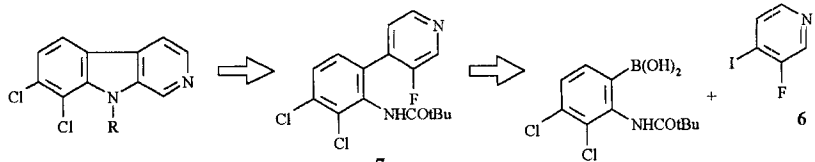


1 (Bauerine B) 2

Scheme 1

Retrosynthetic analysis.

A retrosynthetic analysis (scheme 2) suggests that these structures could be prepared by cyclization of the biaryl 7. This latter compound could be obtained from benzene and pyridine building blocks via metalation[4] and cross-coupling[5] reactions.

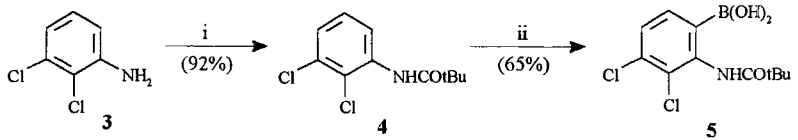


R= Me (1), H (2). 7 5 6

Scheme 2

Results and Discussion.

Boronic acid **5** was prepared by metalation-boronation[2] of 2,3-dichloro-*N*-pivaloylaminobenzene **4** in 65% yield (scheme 3).



3 4 5

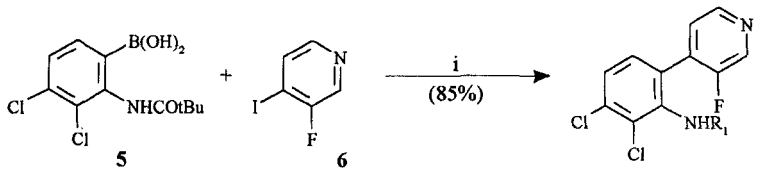
i: ClCOtBu/10% Na_2CO_3/ CH_2Cl_2/1h30/ r.t.

ii: 1) BuLi/ THF/ -15°C/ 6h; 2) $B(OMe)_3$/ -15°C/ 2h; 3) Hydrolysis.

Scheme 3

It can be noted that this metalation reaction gave better results at -15°C instead of room temperature as it is usually described for aminobenzenes.[2,6] Moreover, metalation took only place in the alpha position of the pivaloylamino group.

Palladium catalyzed cross-coupling between boronic acid **5** and iodopyridine **6**[2] using the Suzuki procedure[5] gave the partly hydrolyzed biaryl in good yield (scheme 4). The observed hydrolysis can be explained by the electron withdrawing effect of the two chlorine atoms on the benzene ring which decreases the stability of the amide bond.

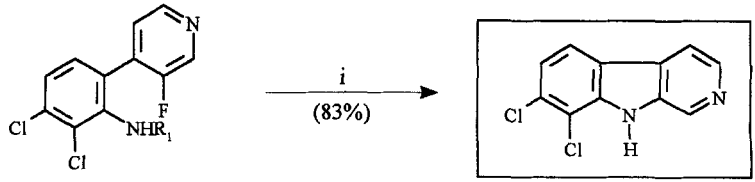


i: $Pd(PPh_3)_4$/ 2M K_2CO_3/ toluene/ reflux (Ar) 30h.

R_1= COtBu (**7**); H (**8**).
ratio**7**/**8**: 33/67

Scheme 4

Cyclization[2] of the mixture of **7** and **8** to the corresponding β-carboline **2** was best achieved by treatment with boiling pyridinium chloride at 215°C (scheme 5).



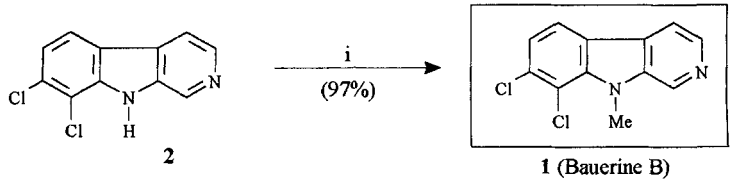
R_1= COtBu (**7**); H (**8**).

2

i: 1) Pyridinium chloride/ reflux 15 min.; 2) NH_4OH/ ice.

Scheme 5

Ultimately, N-methylation[7] of the β-carboline **2** by phase transfer catalysis with methyl iodide afforded Bauerine B (**1**) in a very good yield (scheme 6).



i: CH_3I/ 50% NaOH/ $HSO_4N(Bu)_4$/ toluene/ 2 days at r.t.

Scheme 6

Conclusion.

The first reported total synthesis of Bauerine B (**1**) and its demethyl analogue (**2**) relies on key steps such as metalation, cross-coupling and cyclization. It is fully convergent and regioselective and allows an interesting 45% overall yield (4 steps) and 41% (5 steps) respectively. This strategy is currently being extended to the preparation of natural products in related series.

EXPERIMENTAL

General data. The ^1H NMR spectra were obtained on a 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}. Elementary analyses were performed on a Carlo Erba CHN apparatus.

Tetrahydrofuran (THF) was distilled from benzophenone/sodium. The water content of the solvent was estimated lower than 45 ppm by the modified Karl-Fischer method.[8]

3-Fluoro-4-iodopyridine (**6**) was prepared by metalation and iodination of 3-fluoropyridine as previously described.[2] Commercial 2.5 M solutions of n-butyllithium in hexane was stored and transferred under a dehydrated and deoxygenated argon atmosphere.

2,2- Dimethyl-*N*-(2,3-dichlorophenyl)propanamide (4).

2,2-Dimethyl-*N*-(2,3-dichlorophenyl)propanamide (**4**) was prepared from commercial 2,3-dichloroaniline (**3**) according to Gschwend's procedure.[6] The yield was 92% (white solid): mp: 66°C; bp: 106-108°C/ 0.2 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9H, tBu), 7.12 (m, 2H, $H_4 + H_5$), 8.00 (s broad, 1H, NH), 8.28 (t, 1H, H_6, J= 5.0 Hz); IR (KBr) 3316, 2960, 2872, 1654, 1504. Anal. Calcd for $C_{11}H_{13}Cl_2NO$ (214.16): C, 53.68; H, 5.32; N, 5.69. Found: C, 53.69; H, 5.55; N, 5.43.

3,4-Dichloro-2-(pivaloylamino)benzeneboronic acid (5).

N-Butyllithium (44 mL, 0.11 mol) was slowly added to a cold (-75°C) of amide **4** (12.3 g, 0.05 mol) in dry THF (150 mL). The resulting solution was stirred 6h at -15°C (NaCl/ice bath) and a creamy precipitate appeared. The mixture was cooled to -75°C, and trimethylborate (12.5 mL, 0.11 mol) was slowly added. Stirring was continued for 2h at -15°C before hydrolysis at 0°C. After decantation and extraction by ether (to remove by-products), the aqueous layer was acidified by HCl 1/5. Extraction of the aqueous layer by ether, drying over $MgSO_4$ and solvent removal afforded boronic acid **5** as a creamy product in a 65% yield; mp: 150°C

(dec.); ^{1}H NMR (DMSO-d_6) δ 1.00-1.43 (m, 9H, tBu), 1.65 (m, 1H, B-OH), 3.50 (m, 1H, B-OH), 7.35 (m, 2H, H_5 + H_6), 9.55 (s broad, 1H, NH); IR (KBr) 3413, 2970, 1686, 1602, 1532. Anal. Calcd for $C_{11}H_{14}BCl_2NO_3$ (289,96): C, 45.57; H, 4.87; N, 4.83. Found: C, 45.60; H, 4.59; N, 4.71.

Compounds 7 and 8.

3-Fluoro-4-iodopyridine **6** (10.0 mmol) and boronic acid **5** (10.0 mmol) were added to a solution of potassium carbonate (2M, 10 mL) and ethanol (5 mL) in deoxygenated toluene (100 mL). The resulting mixture was stirred at room temperature for 0.5h under an argon atmosphere. Tetrakis(triphenylphosphine) palladium (0) (350 mg, 0,30 mmol) was added, and the reaction mixture was refluxed for 30h. Cooling, filtration through celite, extraction with toluene (2x50 mL), drying over $MgSO_4$, and solvent removal afforded a crude solid which was purified by flash chromatography on silica (eluent: cyclohexane/ ethyl acetate: 6/4). A mixture of compound **7** and **8** (molar ratio: 33/67) was obtained as a white solid and it was not possible to seperate both compounds. The yield was 85%. Compound **7**: ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 9H, tBu), 7.20-7.45 (m, 4H, $H_{arom.}$ + NH), 8.48 (d, 1H, H_6, J= 4.9 Hz), 8.62 (s, 1H, H_2). Compound **8**: ^{1}H NMR ($CDCl_3$) δ 4.32 (s broad, 2H, NH_2), 6.99 (s, 2H, $H_{arom.}$), 7.20-7.45 (m, 2H, $H_{arom.}$), 7.52-7.61 (m, 1H, $H_{arom.}$), 8.53 (d, 1H, H_6, J= 4.9 Hz), 8.62 (s, 1H, H_2). IR (KBr) of the mixture: 3464, 3327, 3166, 2965, 1654, 1622, 1493, 1459.

7,8-Dichloro-9H-pyrido[3,4-b]indole or 7,8-dichloro-β-carboline (2).

Anhydrous boiling (215°C) pyridinium chloride (20g) was added to the mixture of biaryls **7** and **8** (1,20 g, 4.28 mmoles), and the resulting mixture was refuxed for 15 min. The resulting hot solution was poured into a mixture of ice and

concentrated ammonia. Filtration of the white precipitate, washing with cold water, and drying gave 83% of the expected β-carboline **2** as a white product: mp > 260°C (subl.); ^{1}H NMR (DMSO-d_6) δ 7.44 (d, 1H, H_6), 8.15 (d, 1H, H_4), 8.24 (d, 1H, H_5), 8.40 (d, 1H, H_3), 8.95 (s, 1H, H_1), 10.74 (s, 1H, NH), J_{3-4}= 5.3 Hz, J_{5-6}= 8.4 Hz; ^{13}C NMR (DMSO-d_6) δ 114.89, 115.50, 121.37, 121.50, 122.02, 127.81, 130.48, 135.11, 136.85, 138.85, 139.57; IR (KBr) 3117, 3026, 2922, 2839, 2741, 1629, 1445. Anal. Calcd for $C_{11}H_6Cl_2N_2$ (237.09): C, 55.73; H, 2.55; N, 11.82. Found: C, 55.68; H, 2.29; N, 11.59.

7,8-Dichloro-9-methyl-β-carboline or Bauerine B (1).

β-Carboline **2** (237 mg, 1.0 mmol) was added to a mixture of toluene (10 mL) containing methyl iodide (124 μL, 2.0 mmol), 50% aqueous sodium hydroxide solution (5 mL), and tetra-n-butylammonium hydrogen sulfate (170 mg). The mixture was stirred at room temperature for 2 days and then diluted with water (10 mL). The organic layer was separated, washed with water and dried over anhydrous magnesium sulfate. The solvent and excess of methyl iodide were removed under reduced pressure to give a crude product. Purification by flash chromatography on silica (ethyl acetate) gave 97% of **1** as a creamy solid: mp: 147-148°C; ^{1}H NMR ($CDCl_3$) δ 4.21 (s, 3H, N-Me), 7.27 (d, 1H, H_6, J= 8.4 Hz), 7.80 (m, 2H, H_4 + H_5), 8.49 (d, 1H, H_3, J= 5.2 Hz), 8.85 (s, 1H, H_1). ^{13}C NMR ($CDCl_3$) δ 32.43, 113.77, 115.44, 119.99, 121.56, 121.98, 127.04, 132.38, 133.19, 137.58, 137.68, 139.73; IR (KBr) 3044, 2931, 1619, 1561, 1450, 1436 1407. Anal. Calcd for $C_{12}H_8Cl_2N_2$ (252.12): C, 57.40; H, 3.21; N, 11.16. Found: C, 57.26; H, 3.12; N, 10.95.

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(Received in the UK 08 February 1995)