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1,9-Dimetalated ß-Carbolines. Versatile Building Blocks for the Total Synthesis of Alkaloids[1]

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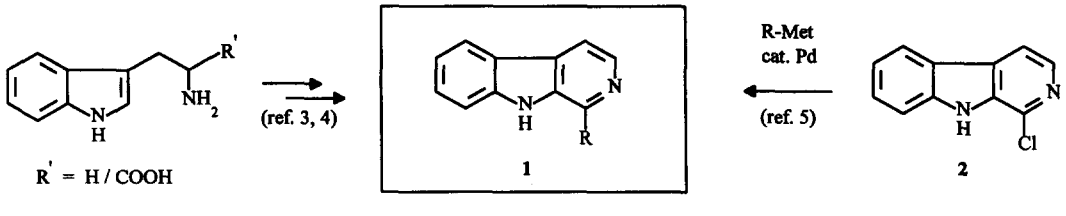
Abstract: Reactions of the dimetalated ß-carboline **6**, prepared from 1-bromo-ß-carboline (**4**), with electrophiles are key steps in the syntheses of various ß-carboline alkaloids. Transmetalation of **6** with $ZnCl_2$ followed by palladium-catalyzed cross coupling reaction with 2-chloroquinoline gave the alkaloid nitramarine (**14**).

1-Substituted ß-carbolines **1** represent a large class of biologically active alkaloids[2]. The classical approaches to ß-carbolines (Bischler/Napieralski[3], Pictet/Spengler[4]) suffer from the lack of convergence, since the group "R" is introduced into the molecule already in the first step of the reaction sequence. Very recently, we worked out a convergent strategy for the synthesis of ß-carboline alkaloids *via* palladium-catalyzed cross coupling reactions of 1-chloro-ß-carboline (**2**) with various organometallic compounds[5,6] (scheme 1). Thus, compounds of type **1** can be prepared conveniently by reaction of a preformed ß-carboline unit **2** with *nucleophiles*.



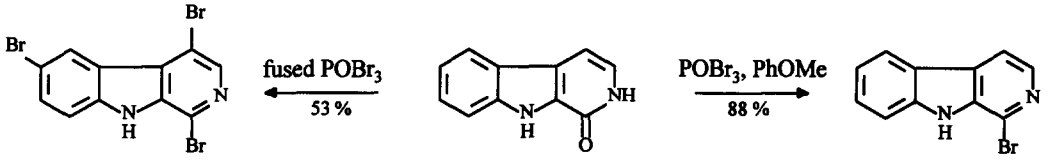
Scheme 1

In this paper we report the preparation of a novel 1,9-dimetalated ß-carboline building block which allows substitution at C-1 with *electrophiles*. By this way total syntheses of alkaloids that are only poorly accessible or even unaccessible by other strategies could be realized.

RESULTS AND DISCUSSION

Since aryllithium compounds are most conveniently prepared by halogen-metal exchange of appropriate haloarenes with alkyllithium reagents, the hitherto unknown 1-bromo-ß-carboline (**4**) was chosen as starting material. Initial attempts to prepare **4** by bromination of the oxo-ß-carboline **3**[5a] with fused $POBr_3$ at 120°C gave an unexpected result. The product was not the desired **4**, but 1,4,6-tribromo-ß-carboline **5**. This compound was unambiguously identified as a tribromo derivative on the basis of the typical pattern of molecular ions in the mass spectrum (*m/z* 402/404/406/408; relative intensities 35:100:100:32). The positions of the bromine substituents could be elucidated by NMR spectroscopy. This represents one of the very few[7] examples of additional ring bromination by $POBr_3$. This side reaction may be due to liberation of bromine during thermal decomposition of $POBr_3$.

Finally, the monobromo derivative **4** could be obtained in high yield by reaction of **3** with $POBr_3$ dissolved in anisole. Anisole should prevent undesired ring brominations by trapping any bromine formed by decomposition of $POBr_3$. In other solvents (chloroform, toluene, xylenes) only marginal conversion of **3** could be obtained.

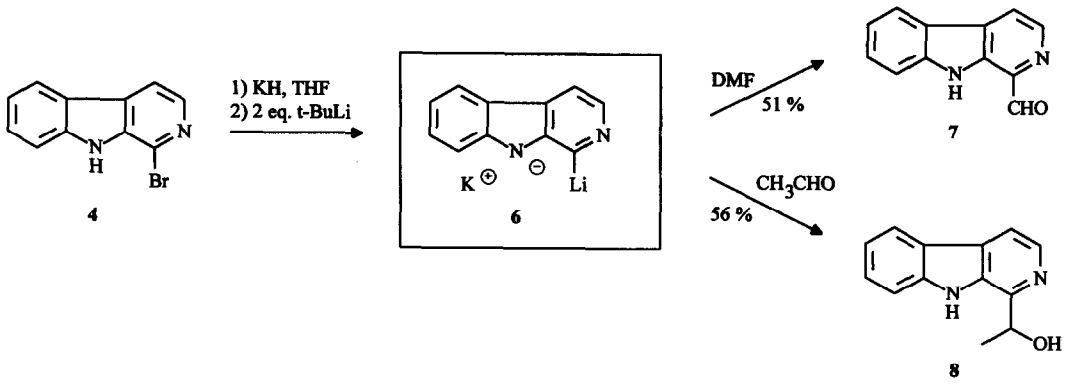


5 **3** **4**

Scheme 2

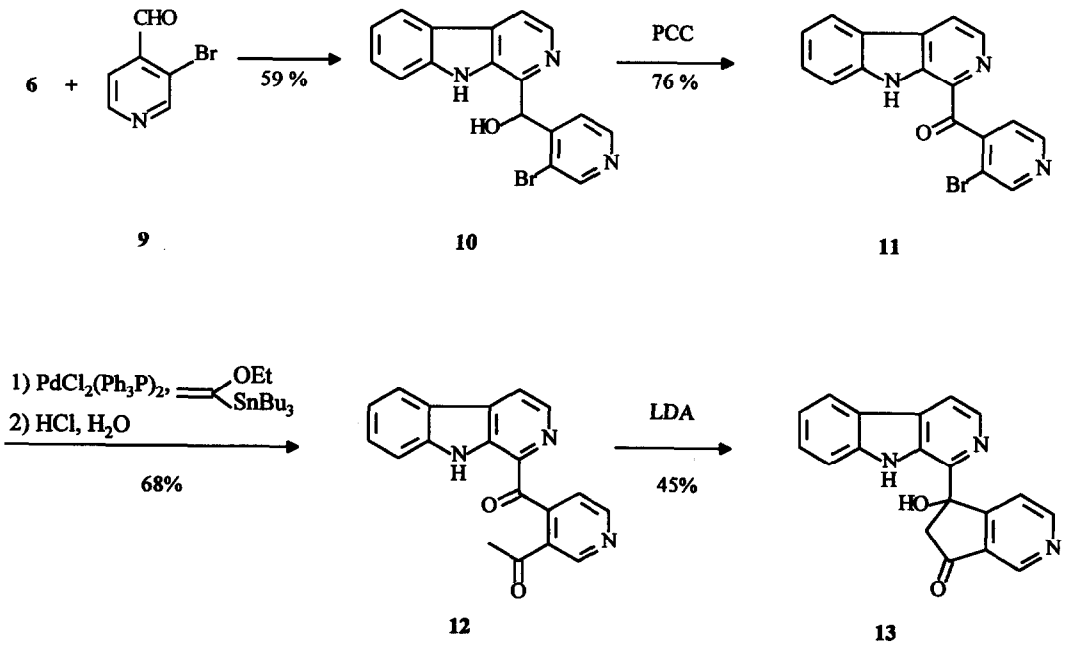
In order to get a straightforward synthesis of the alkaloids, no attempts were made to protect the indole nitrogen. Therefore, **4** was directly converted to the dimetalated species **6** by successive deprotonation with KH in THF and halogen-lithium exchange with *tert.*-butyllithium. **6** is a versatile building block for the synthesis of ß-carboline alkaloids (scheme 3).

Formylation of **6** with DMF gave the alkaloid 1-formyl-ß-carboline (**7**)[8]. Trapping of **6** with acetaldehyde offered an easy access to the marine alkaloid (±)-1-(1-hydroxyethyl-)ß-carboline (**8**)[5b,9].



Scheme 3

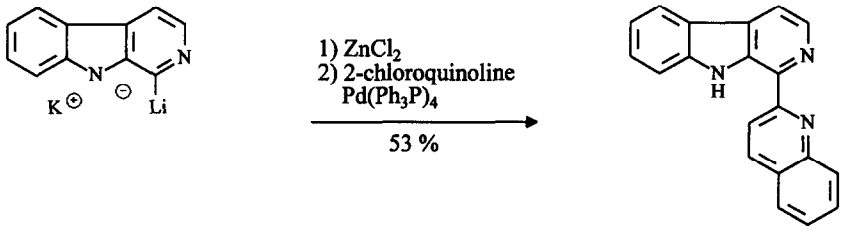
The first total syntheses of the alkaloids pauridianthine (**12**) and pauridianthinine (**13**)[10] could be realized starting from **6**. Thus, reaction with 3-bromopyridine-4-carboxaldehyde (**9**)[11] gave the alcohol **10** which in turn was oxidized to the ketone **11** with pyridinium chlorochromate. Reaction of **6** with an excess (>2 eq.) of the aldehyde **9** gave a mixture of the secondary alcohol **10** and the ketone **11**. Obviously, the intermediate alkoxide was transformed into **11** by the excess aldehyde in an *Oppenauer* oxidation. This hypothesis was supported by the isolation of 3-bromo-4-hydroxymethylpyridine as a by-product.



Scheme 4

The acetyl group was introduced into **11** by Pd(II)-catalyzed cross coupling with 1-ethoxyvinyl tributylstannane and subsequent hydrolysis of the resulting enol ether with dilute hydrochloric acid[5b,12] to give pauridianthine (**12**). The related (±)-pauridianthinine (**13**)[10] was prepared from **12** by intramolecular aldolization with LDA.

Finally the dimetalated compound **6** could also be used as a starting material for a transition metal catalyzed biaryl synthesis. Transmetalation of **6** with excess $ZnCl_2$ gave an organozinc intermediate which was converted to nitramarine (**14**)[5b,13] by Pd(0)-catalyzed cross coupling with 2-chloroquinoline (scheme 5).



6 **14**

Scheme 5

In conclusion, reaction of the readily available 1,9-dimetalated ß-carboline **6** with various electrophiles provides a new convenient entry to 1-substituted ß-carbolines.

EXPERIMENTAL PART

Melting points: Leitz Heiztischmikroskop HM-lux. IR spectra: Perkin Elmer PE 398. NMR spectra: Jeol JNM-GX-400, TMS as internal standard. Mass spectra (EI): Vacuum Generators 7070 H. Flash column chromatography: Kieselgel 60 (230 - 400 mesh), Merck. THF and toluene were freshly distilled from sodium, all other solvents were purified by distillation.

1-Bromo-9H-pyrido[3,4-b]indole (**4**). 736 mg (4.0 mmol) **3**[5a] and 8.0 g (27.9 mmol) $POBr_3$ in anisole (8 mL) were heated at 120°C with stirring for 4 h. Then conc. sodium carbonate solution (100 mL) was added, followed by extraction with ethyl acetate (2 x 150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 2:1) to give 865 mg (88%) of **4** as a pale yellow solid: m.p. 152°C; ^{1}H NMR (D_6-DMSO) δ 11.8 (s, 1H, NH), 8.25 (d, J = 7.9 Hz, 1H, 3-H), 8.17 (m, 2H, 4-H, 5-H), 7.69 (br. d, J = 8.2 Hz, 1H, 8-H), 7.62 (m, 1H, 7-H), 7.31 (m, 1H, 6-H); ^{13}C NMR (D_6-DMSO) δ 140.6, 138.0, 134.7, 129.3, 128.7, 123.9, 122.0, 121.0, 120.0, 114.9, 112.5; MS *m/z* 248 (100, M^+), 246 (98, M^+), 167 (85), 166 (54), 140 (48), 139 (29), 84 (20); IR (KBr) $\tilde{\nu}$ 3160, 1542, 1452, 1320, 1236, 1182, 729 cm^{-1}. Anal. Calcd. for $C_{11}H_7BrN_2$ (247.10): C, 53.46; H, 2.83; N, 11.34. Found: C, 53.09; H, 2.96; N, 11.34.

1,4,6,-Tribromo-9H-pyrido[3,4-b]indole (**5**). A mixture of 368 mg (2.0 mmol) **3** and 4.0 g (14.0 mmol) $POBr_3$ was stirred at 120°C for 4 h. After cooling 25 g of crushed ice were added followed by neutralization with saturated sodium carbonate solution. Extraction with ethyl acetate (2 x 80 mL), drying over Na_2SO_4 and solvent removal afforded a crude product which was purified by flash column chromatography (hexane/ethyl acetate, 2:1) to give 433 mg (53%) **5** as pale yellow needles: m.p. 288°C (methanol/ethyl acetate); ^{1}H NMR (D_6-DMSO) δ 12.3 (s, 1H, NH), 8.59 (d, J = 1.9 Hz, 1H, 5-H), 8.27 (s, 1H, 3-H), 7.79 (dd, J = 1.9/ 8.9 Hz, 1H, 7-H), 7.65 (d, J = 8.9 Hz, 1H, 8-H); ^{13}C NMR (D_6-DMSO) δ 139.3, 139.2, 135.6, 131.8, 125.9, 124.3, 123.2, 122.1, 114.8, 112.9, 112.2; MS *m/z* 408 (32, M^+), 406 (100, M^+), 404 (100, M^+), 402 (35, M^+), 326 (27), 246 (34), 245 (31), 244 (33), 165 (30); IR (KBr) $\tilde{\nu}$ 1473, 1443, 1230, 1179, 1056 cm^{-1}. Anal. Calcd. for $C_{11}H_5Br_3N_2$ (404.90): C, 32.62; H, 1.23; N, 6.92. Found: C, 32.82; H, 1.47; N, 6.85.

Preparation of the 1,9-dimetalated β-carboline **6**. Potassium hydride suspension (35% in mineral oil; 115 mg, 1.0 mmol) was diluted with anhydrous THF (1 mL) under nitrogen atmosphere and cooled to 0°C. Then a solution of 247 mg (1.0 mmol) **4** in anhydrous THF (4 mL) was added with stirring. The mixture was stirred at 0°C for 40 min and then cooled to −78°C. Then a solution of *tert.*-BuLi (1.6 M in pentane; 1.25 mL, 2.0 mmol) was added dropwise. The deep red solution was stirred for additional 20 min at −78°C and then treated with electrophiles as described below.

1-Formyl-9H-pyrido[3,4-b]indole (**7**). To a stirred solution of **6** (1.0 mmol), prepared as described above, a solution of anhydrous DMF (321 mg, 4.4 mmol) in anhydrous THF (6.0 mL) was added dropwise at −78°C. Then the dry ice bath was removed and stirring was continued for 4 h. After addition of saturated ammonium chloride solution (60 mL), extraction with ethyl acetate (2 x 60 mL), drying over Na_2SO_4, and evaporation the crude product was purified by flash column chromatography (hexane/ethyl acetate, 1:1) to give 100 mg (51%) **7** as pale yellow crystals: m.p. 202°C (ref.[8]: m.p. 202°C); ^{1}H NMR (D_6-DMSO) δ 12.08 (s, 1H, NH), 10.28 (s, 1H, CHO), 8.61 (d, J = 5.0 Hz, 1H, 3-H), 8.47 (d, J = 5.0 Hz, 1H, 4-H), 8.32 (br. d, J = 7.26 Hz, 1H, 5-H), 7.82 (br. d, J = 7.58 Hz, 1H, 8-H), 7.63 (m, 1H, 7-H), 7.34 (m, 1H, 6-H); ^{13}C NMR (D_6-DMSO) δ 194.6, 141.9, 138.5, 135.9, 132.7, 130.9, 129.0, 121.8, 120.4, 119.7, 119.6, 113.0; MS *m/z* 196 (77, M^+), 168 (100), 167 (20), 141 (16), 140 (37), 113 (11); IR (KBr) $\tilde{\nu}$ 3280, 1680, 1450, 1125, 745 cm^{-1}. Anal. Calcd. for $C_{12}H_8N_2O$ (196.21): C, 73.47; H, 4.08; N, 14.29. Found: C, 73.57; H, 3.71; N, 14.31.

1-(1-Hydroxyethyl-)9H-pyrido[3,4-b]indole (**8**). To a stirred solution of **6** (1.0 mmol), prepared as described above, a solution of acetaldehyde (88 mg, 2.0 mmol) in anhydrous THF (6.0 mL) was added dropwise at −78°C. Then the dry ice bath was removed and the mixture was stirred for additional 2 h. Workup and purification as described in the foregoing procedure gave 119 mg (56%) **8** as a white solid: m.p. 197°C (ref.[9]: m.p. 163-169°C); ^{1}H NMR (D_6-DMSO) δ 11.22 (s, 1H, NH), 8.24 (d, J = 5.10 Hz, 1H, 3-H), 8.20 (br. d, J = 7.90 Hz, 1H, 5-H), 7.98 (d, J = 5.10 Hz, 1H, 4-H), 7.71 (br. d, J = 8.20 Hz, 1H, 8-H), 7.52 (m, 1H, 7-H), 7.21 (m, 1H, 6-H), 5.68 (d, J = 4.70 Hz, 1H, OH), 5.23 (m, 1H, CH-O), 1.58 (d, J = 6.30 Hz, 3H, CH_3); ^{13}C NMR (D_6-DMSO) δ 148.6, 140.5, 136.5, 132.2, 128.2, 127.7, 121.2, 120.4, 118.9, 113.4, 112.3, 69.2, 22.8; MS *m/z* 212 (72, M^+), 197 (52), 195 (25), 194 (65), 193 (100), 169 (27), 168 (39); IR (KBr) $\tilde{\nu}$ 3268, 1626, 1569,

1497, 1239 cm^{-1}. Anal. Calcd. for $C_{13}H_{12}N_2O$ (212.25): C, 73.58; H, 5.66; N, 13.20. Found: C, 73.84; H, 5.70; N, 12.85.

(9H-Pyrido[3,4-b]indol-1-yl)(3-bromopyrid-4-yl)carbinol (**10**). To a stirred solution of **6** (1.0 mmol), prepared as described above, a solution of 3-bromopyridine-4-carboxaldehyde (**9**)[11] (279 mg, 1.5 mmol) in anhydrous THF (3 mL) was added dropwise at −78°C. Then the dry ice bath was removed and the mixture was stirred for additional 2 h. Standard workup, as described for **7**, followed by flash column chromatography (ethyl acetate) gave 208 mg (59%) **10** as a yellow solid: m.p. 199°C; ^1H NMR (D_6-DMSO) δ 12.30 (s, 1H, NH), 8.89 (s, 1H, 2'-H), 8.74 (d, J = 5.10 Hz, 1H, 3-H), 8.48 (d, J = 4.74 Hz, 1H, 6'-H), 8.47 (d, J = 4.74 Hz, 1H, 5'-H), 8.34 (br. d, J = 7.90 Hz, 1H, 5-H), 7.87 (br. d, J = 8.21 Hz, 1H, 8-H), 7.68 (d, J = 5.10 Hz, 1H, 4-H), 7.64 (m, 1H, 7-H), 7.36 (m, 1H, 6-H), 4.55 (d, J = 4.74 Hz, 1H, CH-O); ^{13}C NMR (D_6-DMSO) δ 151.2, 148.7, 148.1, 142.0, 138.0, 135.3, 134.1, 131.5, 129.2, 123.3, 121.9, 120.6, 120.1, 119.9, 117.0, 113.1, 61.7; MS *m/z* 353 (4, M^+-2), 351 (4, M^+-2), 273 (20), 272 (100), 244 (10); IR (KBr) $\tilde{\nu}$ 3382, 1664, 1629, 1560, 1496, 1397, 1314, 1286, 1221, 726 cm^{-1}. Anal. Calcd. for $C_{17}H_{12}BrN_3O$ (354.21): C, 57.64; H, 3.39; N, 11.87. Found: C, 57.78; H, 3.11; N, 11.72.

(9H-Pyrido[3,4-b]indol-1-yl)(3-bromopyrid-4-yl)ketone (**11**). To a suspension of 380 mg (1.76 mmol) pyridinium chlorochromate and 300 mg silica in CH_2Cl_2 (15 mL), cooled to 0°C, a solution of 415 mg (1.17 mmol) **10** in CH_2Cl_2 (30 mL) was added slowly. The mixture was stirred at 0°C for 30 min and at room temperature for 1 h. Then the solid was filtered off and extracted with ethyl acetate several times. The combined organic solutions were washed with water (100 mL), dried over Na_2SO_4 and evaporated. Purification by flash column chromatography (ethyl acetate) gave 315 mg (76%) **11** as a yellow solid: m.p. 203°C; ^1H NMR (D_6-DMSO) δ 12.28 (s, 1H, NH), 8.88 (s, 1H, 2'-H), 8.73 (d, J = 4.74 Hz, 1H, 6'-H), 8.49 (d, J = 5.05 Hz, 1H, 3-H), 8.46 (d, J = 4.74 Hz, 1H, 5'-H), 8.34 (br. d, J = 8.20 Hz, 1H, 5-H), 7.87 (br. d, J = 8.20 Hz, 1H, 8-H), 7.66 (d, J = 5.05 Hz, 1H, 4-H), 7.64 (m, 1H, 7-H), 7.35 (m, 1H, 6-H); ^{13}C NMR (D_6-DMSO) δ 194.6, 151.2, 148.7, 148.1, 142.0, 138.1, 135.3, 134.1, 131.5, 129.3, 123.2, 121.9, 120.6, 120.1, 119.8, 116.9, 113.0; MS *m/z* 353 (5, M^+), 351 (5, M^+), 273 (19), 272 (100), 244 (9), 137 (11); IR (KBr) $\tilde{\nu}$ 3370, 1662, 1428, 1314, 1218, 723, 639 cm^{-1}. Anal. Calcd. for $C_{17}H_{10}BrN_3O$ (352.20): C, 57.97; H, 2.84; N, 11.94. Found: C, 57.78; H, 3.29; N, 12.30.

Pauridianthine (**12**). A solution of 242 mg (0.69 mmol) **11**, 324 mg (0.90 mmol) 1-ethoxyvinyl tributylstannane and 24 mg (0.034 mmol) $PdCl_2(Ph_3P)_2$ in anhydrous toluene (20 mL) under nitrogen atmosphere was refluxed for 4 h. After cooling water (3 mL) and conc. HCl (3 mL) were added and the mixture was stirred vigorously for 2 h at room temperature. The mixture was neutralized with sodium carbonate solution and extracted with ethyl acetate (3 x 80 mL). The combined organic layers were dried over Na_2SO_4, evaporated and purified by flash column chromatography (ethyl acetate) to give 148 mg (68%) **11** as yellow crystals: m.p. 271°C (MeOH) (ref.[10]: m.p. 271°C); ^1H NMR (D_6-DMSO) δ 12.13 (s, 1H, NH), 9.32 (s, 1H, 2'-H), 8.96 (d, J = 5.10 Hz, 1H, 3-H), 8.38 (d, J = 4.73 Hz, 1H, 6'-H), 8.31 (br. d, J = 8.21 Hz, 1H, 5-H), 8.31 (d, J = 4.73 Hz, 1H, 5'-H), 7.87 (br. d, J = 8.21 Hz, 1H, 8-H), 7.65 (d, J = 5.10 Hz, 1H, 4-H), 7.64 (m, 1H, 7-H), 7.33 (m, 1H, 6-H), 2.61 (s, 3H, CH_3); ^{13}C NMR (D_6-DMSO) δ 197.9, 196.6, 153.2, 149.7, 147.5,

141.9, 137.4, 135.4, 134.4, 132.2, 131.0, 129.0, 122.3, 121.8, 120.3, 119.8, 119.1, 113.0, 27.2; MS *m/z* 315 (14, M^+), 300 (22), 272 (100), 153 (8), 137 (11); IR (KBr) $\tilde{\nu}$ 2920, 1683, 1656, 1437, 1185, 540 cm^{-1}. Anal. Calcd. for $C_{19}H_{13}N_3O_2$ (315.33): C, 72.38; H, 4.13; N, 13.33. Found: C, 72.57; H, 4.30; N, 13.60.

Pauridianthinine (**13**). To a solution of 101 mg (1.0 mmol) diisopropylamine in anhydrous THF (4 mL), cooled to –78°C under nitrogen atmosphere, was added *n*-BuLi (1.6 M in hexane; 0.63 mL, 1.0 mmol). The solution was stirred at –78°C for 30 min followed by the addition of a solution of **12** (38 mg, 0.12 mmol) in anhydrous THF (5 mL). After 15 min the dry ice bath was removed and stirring was continued at room temperature for 5 h. Then water (20 mL) was added and the mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (ethyl acetate) to give 17 mg (45%) **13** as a pale yellow solid: m.p. 237°C (ref.[10]: no m.p. given); ^{1}H NMR (D_6-DMSO) δ 11.46 (s, 1H, NH), 8.94 (s, 1H, 2'-H), 8.73 (d, J = 5.12 Hz, 1H, 6'-H), 8.22 (br. d, J = 7.81 Hz, 1H, 5-H), 8.13 (d, J = 5.13 Hz, 1H, 3-H), 8.00 (d, J = 5.12 Hz, 1H, 5'-H), 7.85 (br. d, J = 8.30 Hz, 1H, 8-H), 7.74 (d, J = 5.13 Hz, 1H, 4-H), 7.57 (m, 1H, 7-H), 7.24 (m, 1H, 6-H), 3.70 (d, J = 18.06 Hz, 1H, 2"-H), 3.18 (d, J = 18.06 Hz, 1H, 2"-H); ^{13}C NMR (D_6-DMSO) δ 201.9, 165.5, 154.4, 146.0, 144.7, 140.7, 136.7, 132.3, 130.3, 129.4, 128.1, 121.2, 120.1, 120.0, 119.1, 113.8, 112.7, 80.3, 53.3; MS *m/z* 315 (58, M^+), 297 (31), 287 (31), 177 (43), 272 (100), 270 (37), 269 (41), 149 (23), 140 (23); IR (KBr) $\tilde{\nu}$ 3429, 1726, 1627, 1595, 1426, 1321, 1121, 746 cm^{-1}. Anal. Calcd. for $C_{19}H_{13}N_3O_2$ x 0.5 H_2O (324.34): C, 70.37; H, 4.32; N, 12.96. Found: C, 70.90; H, 4.25; N, 12.74.

Nitramarine (**14**). To a stirred solution of **6** (1.0 mmol), prepared as described above, $ZnCl_2$ solution (0.5 M in THF; 4.4 mL, 2.2 mmol) was added at –78°C. The mixture was stirred at –20°C for 1 h and then transformed into a solution of 180 mg (1.1 mmol) 2-chloroquinoline and 46 mg (0.04 mmol) $Pd(Ph_3P)_4$ in anhydrous THF (4 mL) under nitrogen atmosphere. The resulting mixture was refluxed for 22 h, then treated with water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (hexane/ethyl acetate, 10:1) to give 156 mg (53%) **14** as yellow needles: m.p. 178°C (ref.[13]: 172-173°C; ref.[14]: 180.5-182°C); ^{1}H NMR ($CDCl_3$) δ 11.61 (s, 1H, NH), 8.82 (d, J = 8.50 Hz, 1H, 4'-H), 8.53 (d, J = 5.20 Hz, 1H, 3-H), 8.25 (br. d, J = 8.50 Hz, 1H, ArH), 8.22 (br. d, J = 8.50 Hz, 1H, ArH), 8.11 (br. d, J = 7.60 Hz, 1H, 5-H), 7.98 (d, J = 5.20 Hz, 1H, 4-H), 7.81 (br. d, J = 7.90 Hz, 1H, ArH), 7.72 (m, 1H, ArH), 7.62 (br. d, J = 8.20 Hz, 1H, 8-H), 7.53 (m, 2H, 2 ArH), 7.25 (m, 1H, 6-H); ^{13}C NMR ($CDCl_3$) δ 157.8, 147.7, 140.7, 138.0, 138.0, 136.8, 135.2, 130.8, 129.8, 129.2, 128.7, 127.9, 127.8, 126.9, 121.8, 121.1, 120.1, 119.1, 115.8, 112.1; MS *m/z* 295 (100, M^+), 294 (39), 167 (32), 149 (56); IR (KBr) $\tilde{\nu}$ 3358, 1590, 1236, 1149, 828, 750 cm^{-1}. Anal. Calcd. for $C_{20}H_{13}N_3$ x 0.5 H_2O (304.35): C, 78.93; H, 4.64; N, 13.81. Found: C, 78.91; H, 4.58; N, 13.48.

ACKNOWLEDGEMENTS

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