β-Carboline Alkaloids 9 [1]. Total Synthesis of the β-Carboline Alkaloids Arenarine A and (±)Arenarine B

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The first total synthesis of the β-carboline alkaloids arenarine A (**1**) and arenarine B (**2**) is described. Methanolysis of the α-bromoketone **9** gives **1** in good yield. Alternatively **1** can be obtained from the diazoketone **11** with boron trifluoride/methanol in poor yield. Reduction of **1** with sodium borohydride gives racemic arenarine B (**2**). Regioselective homolytic methylation of norharmane (**4**) with *tert*-butyl hydroperoxide/ferrous sulfate gives the alkaloid harmane (**6**).

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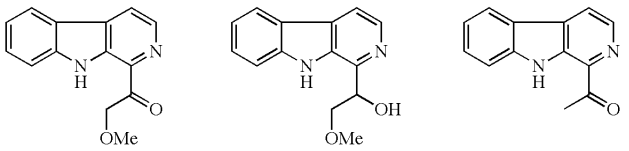
1-Substituted β-carbolines represent a large group of biologically active natural products. Consequently, the total synthesis of these alkaloids has found widespread interest in the past. Numerous approaches have been published for the synthesis of 1-alkyl-, 1-aryl- and 1-heteroaryl-β-carbolines, either by building up the heterocyclic ring system starting from tryptamine derivatives or by substitution reactions of 1-substituted β-carbolines [2]. In contrast, 1-acyl-β-carbolines cannot be readily prepared by the classical methods. Some time ago we published new strategies for the synthesis of 1-acyl-β-carbolines starting from 1-bromo-β-carboline (**7**) [3] or from norharmane (**4**) [1] following the *Minisci* reaction [4].

Here we present the extension of these methods to the synthesis of the alkaloids arenarine A (**1**) and arenarine B (**2**). These alkaloids (Scheme 1) were isolated, together with 1-acetyl-β-carboline (**3**) and 1-methoxycarbonyl-β-carboline, from the Chinese medical plant *Arenaria kansuensis* (Caryophyllaceae). This plant (Chinese name: Xue ling zhi) is used in Chinese folk medicine for the treatment of influenza, lung inflammation, jaundice, and rheumatism [5].

The absolute configuration of arenarine B, a formal reduction product of arenarine A, has not yet been determined, nor has the optical rotation of the natural product been published.

Scheme 1

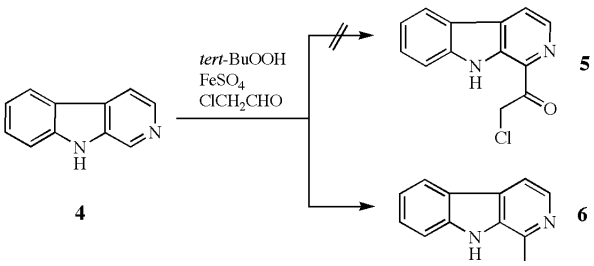


1 **2** **3**

Since arenarine A (**1**) is simply a α-methoxy derivative of the readily available 1-acetyl-β-carboline (**3**) [1,3], we envisaged to prepare this alkaloid by regioselective homolytic acylation of norharmane (**4**) with an appropriate aldehyde in close analogy to the synthesis of **3** [1]. This radical reaction worked well with various aromatic and aliphatic aldehydes [6], so we planned to use chloroacetaldehyde as a source of the acyl radical. The resulting chloroketone **5** should then be converted to the methyl ether **1** under standard *Williamson* conditions.

In fact, **4** reacted with chloroacetaldehyde under *Minisci* conditions (ferrous sulfate heptahydrate, *tert*-butyl hydroperoxide in dilute sulfuric acid) to give a new product. But surprisingly the spectral data clearly indicated that the product was harmane (**6**). Careful investigation of the reaction conditions showed that **6** was also formed in the absence of chloroacetaldehyde. The methyl group introduced into the β-carboline ring obviously originates from *tert*-butyl hydroperoxide. A few similar ring methylations of heteroaromatic compounds with the ferrous sulfate/*tert*-butyl hydroperoxide system have been reported in the literature [7,8]. This unexpected reaction represents a new total synthesis of the alkaloid harmane (**6**) (Scheme 2).

Scheme 2



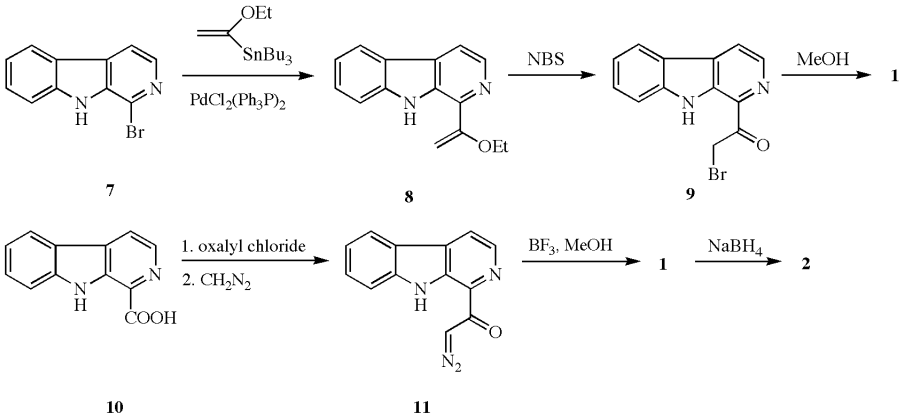
The failure of the direct acylation of **4** prompted us to work out an alternative approach to a α-haloacetyl-β-carboline. Enol ether **8** is an intermediate in the synthesis of 1-acetyl-β-carboline (**3**). In our previous work we prepared **8** by palladium-catalyzed cross-coupling of 1-chloro-β-carboline with tributyl(1-ethoxyvinyl)stannane and we directly hydrolyzed the enol ether to the methyl ketone **3** [3]. For our present purpose **8** was prepared from the even more reactive 2-bromo-β-carboline (**7**) [9] and further treated with *N*-bromosuccinimide in tetrahydrofuran/water [10] to give the bromoketone **9** in 77% yield. Surprisingly,

any attempts to convert **9** to arenarine A (**1**) with sodium methoxide [11] resulted in extremely poor yields, as the alkaloid could only be detected in traces in the reaction mixture. Finally, we found that alcoholysis of the bromoketone **9** with methanol at 54 °C over several days gives **1** in 64% yield while in refluxing methanol we obtained significantly lower yields of **1**. The spectroscopic data of the synthetic product are in accordance with those published for the natural product [5].

Since the conversion of **9** to **1** gave disappointing results for quite a long time, we worked out another, completely different approach to alkaloid **1**. Carboxylic acid **10** is readily available from harmane (**6**) by condensation with benzaldehyde and subsequent oxidative cleavage of the resulting benzylidene derivative with potassium permanganate [12]. Carboxylic acid **10** was converted to the corresponding acid chloride with oxalyl chloride in toluene, and further to the diazoketone **11** with diazomethane [13]. Finally, **11** could be converted to arenarine A (**1**) with boron trifluoride/methanol [14] in 15% yield.

Conversion of arenarine A (**1**) to racemic arenarine B (**2**) was accomplished in high yield by reduction with sodium borohydride in methanol [3].

Scheme 3



In conclusion, we have worked out efficient total syntheses of the alkaloids **1** and **2**. Moreover, the reactive intermediates **9** and **11** should offer the possibility to prepare numerous further substituted β-carbolines. Work is in progress to evaluate the synthetic potential of these building blocks for alkaloid total synthesis.

EXPERIMENTAL

Melting points were determined with a Büchi Melting Point B-540 apparatus. Elemental analyses were performed on a CHN Elemental Analyser (Heraeus). FTIR spectra were recorded on a Perkin Elmer FT-IR Spectrometer PARAGON. NMR spectra were recorded in deuteriochloroform or dimethylsulfoxide-d_6 with tetramethylsilane as internal standard on Joel JNM-GX 400, JNM-ECP 400 (400 MHz) and Joel JNM-ECP 500 (500 MHz) spectrometers. Chemical shifts are given as δ values (ppm) downfield from internal tetramethylsilane. Mass spectra were recorded on a Hewlett Packard 59827A spectrometer. Flash column chromatography was carried out on Merck Kieselgel 60 (230-400 mesh). Norharmane (**4**) was supplied from Aldrich Co.

Harmane (1-Methyl-9*H*-pyrido[3,4-*b*]indole; **6**).

Norharmane (**4**) (200 mg, 1.19 mmoles) was suspended in an ice-cooled mixture of water (3 ml), glacial acetic acid (3 ml) and conc. sulfuric acid (0.6 ml) by means of ultrasound irradiation. Then a solution of ferrous sulfate heptahydrate (1.0 g, 3.6 mmoles) in water (3.6 ml) and *tert*-butyl hydroperoxide (70% solution in water) (0.5 ml, 3.6 mmoles) was added simultaneously with stirring. After stirring at 0° for 1 hour the same amounts of ferrous sulfate heptahydrate and *tert*-butyl hydroperoxide were added again in the way described above and stirring was continued for one more hour at 0°. The mixture was poured into water (100 ml), neutralized with solid potassium carbonate and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were dried (sodium sulfate) and evaporated. The residue was purified by flash column chromatography (ethanol/dichloromethane = 1/14) to give 162 mg (75%) **6** as white needles. The product was identified by comparison with an authentic sample [15] (tlc, nmr, ir).

1-(1-Ethoxyvinyl)-9*H*-pyrido[3,4-*b*]indole (**8**).

1-Bromo-ß-carboline (**7**) [3] (368 mg, 1.49 mmoles), dichlorobis(triphenylphosphine)-palladium(II) (52 mg, 0.074 mmoles) and tributyl(1-ethoxyvinyl)stannane (704 mg, 1.95 mmoles) in anhydrous toluene (4 ml) were refluxed under a nitrogen atmosphere for 17 hours. After cooling to room temperature the mixture was poured into water (30 ml) and extracted with ethyl acetate (2 x 120 ml). Evaporation of the organic solvents *in vacuo* gave a residue, which was separated by flash column chromatography (ethyl acetate/hexane = 1/4) to give 298 mg (84%) **8** as an unstable, partially crystallizing viscous oil; ir (potassium bromide): 3469, 2973, 1623, 1606, 1560, 1490, 1421, 1366, 1316, 1246, 1190, 1065, 968; ^{1}H nmr (dimethylsulfoxide-d_6): δ 8.33 (dd, 1H, 3-H, J = 4.9, 0.6 Hz), 8.22 (d, 1H, 5-H, J = 7.9 Hz), 8.10 (d, 1H, 4-H, J = 4.9 Hz), 7.73 (d, 1H, 8-H, 8.2 Hz), 7.55

(ddd, 1H, 7-H, J = 8.2, 7.1, 1.2 Hz), 7.24 (ddd, 1H, 6-H, J = 7.9, 7.1, 0.7 Hz), 5.34 (d, 1H, 2'-H, J = 1.7 Hz), 4.55 (d, 1H, 2'-H, J = 1.7 Hz), 4.18 (q, 2H, OCH_2, J = 6.9 Hz), 1.50 (t, 3H, CH_3, J = 6.9 Hz); ^{13}C nmr (dimethylsulfoxide-d_6): δ 159.60 (C1'), 141.14 (C8a), 138.06 (C3), 138.03 (C9a), 132.65 (C1), 130.20 (C4a), 128.79 (C7), 121.99 (C5), 120.75 (C4b), 119.89 (C6), 115.28 (C4), 113.00 (C8), 86.06 (C2'), 63.96 (OCH_2), 14.61 (CH_3); ms (EI): m/z 238 (M^+, 52), 223 (58), 209 (16), 193 (100), 168 (40), 140 (30). HRMS Calcd. for $C_{15}H_{14}N_2O$ *m/z*: 238.1106. Found *m/z*: 238.1111.

2-Bromo-1-(9*H*-pyrido[3,4-*b*]indol-1-yl)ethanone (**9**).

A solution of **8** (100 mg, 0.42 mmoles) in tetrahydrofuran (7.5 ml) and water (3 ml) was cooled to 0°. Then *N*-bromosuccinimide (75 mg, 0.42 mmoles) was added in one portion under stirring. The solution was allowed to warm up to room temperature over a period of 30 minutes. Water (50 ml) was added and the mixture was extracted with dichloromethane (2 x 50 ml). The combined organic layers were dried (sodium sulfate) and evaporated. The yellow residue was purified by flash column chromatography (ethyl acetate/hexane = 1/4) to give 93 mg (77%) **9** as yellow needles, mp 175-176°; ir (potassium bromide): 3394, 3309, 1654, 1622, 1492, 1462, 1432, 1316, 1253, 1215, 1120, 1055 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.52 (d, 1H, 3-H, J = 4.9 Hz), 8.18 (dd, 1H, 4-H, J = 4.9, 0.6 Hz), 8.16 (d, 1H, 5-H, J = 7.9 Hz), 7.60 (m, 2H, 8-H, 7-H), 7.35 (ddd, 1H, 6-H, J = 7.9, 7.0, 1.3 Hz), 5.04 (s, 2H, 2'-H); ^{13}C nmr (deuteriochloroform): δ 194.91 (C=O), 141.13 (C1), 138.30 (C3), 135.89 (C8a), 133.01 (C9a), 131.94 (C4a), 129.65 (C7), 121.93 (C5), 121.12 (C6), 120.49 (C4b), 119.81 (C4), 112.08 (C8), 32.08 (C2'); ms (EI): m/z 290 (M^+, 13), 288 (M^+, 13), 210 (100), 182 (43), 168 (68), 140 (39).

Anal. Calcd. for $C_{13}H_9BrN_2O$: C, 54.00; H, 3.14; N, 9.69. Found: C, 54.11; H, 3.22; N, 9.67.

2-Diazo-1-(9*H*-2-Diazo-1-(9*H*-pyrido[3,4-*b*]indol-1-yl)ethanone (**11**).

A solution of carboxylic acid **10** [12] (500 mg, 2.35 mmoles) in anhydrous toluene (7 ml) was cooled to 0° under a nitrogen atmosphere. Then oxalyl chloride (0.81 ml, 9.4 mmoles) in anhydrous toluene (5 ml) was added slowly and the solution was stirred at 55° for 4 hours. Evaporation of the volatile components *in vacuo* gave a white crystalline residue. This was suspended in anhydrous diethyl ether (50 ml) and cooled to 0°. To the stirred suspension a solution of diazomethane in diethyl ether was added dropwise until no further nitrogen evolved. Then the mixture was stirred at 0° for additional 3 hours. The solvent was evaporated and the residue was separated by flash column chromatography (ethanol/dichloromethane = 1/14) to give 340 mg (60%) of **11** as pale yellow needles, mp 167°; ir (potassium bromide): 3354, 3135, 2095, 1601, 1389, 1351, 1317, 1288 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.40 (d, 1H, 3-H, J = 4.9 Hz), 8.16 (d, 1H, 5-H, J = 8.1 Hz), 8.12 (d, 1H, 4-H, J = 4.9 Hz), 7.60 (ddd, 1H, 7-H, J = 8.0, 7.0, 1.2 Hz), 7.56 (dd, 1H, 8-H, J = 8.1, 0.7 Hz), 7.32 (ddd, 1H, 6-H, J = 8.1, 7.0, 1.2 Hz), 6.92 (s, 1H, 2'-H); ^{13}C nmr (deuteriochloroform): δ 188.28 (C=O), 141.15 (C8a), 137.72 (C3), 134.79 (C9a), 134.64 (C1), 131.56 (C4a), 129.31 (C7), 121.80 (C5), 120.62 (C6), 120.43 (C4b), 118.78 (C4), 111.98 (C8), 53.58 (C2'); ms (EI): m/z 236 (M^+, 56), 208 (63), 179 (100), 168 (40), 153 (29), 140 (26), 126 (20).

Anal. Calcd. for $C_{13}H_8N_4O$: C, 66.10; H, 3.41; N, 23.72. Found: C, 65.76; H, 2.97; N, 23.59.

Arenarine A (1-Methoxymethylcarbonyl-9*H*-pyrido[3,4-*b*]-indole; **1**).

Method A.

Bromoketone **9** (200 mg, 0.69 mmoles) was dissolved in anhydrous methanol (40 ml) under a nitrogen atmosphere and the solution was stirred at 54° for 9 days. Then the solvent was evaporated and the residue was purified by flash column chromatography (ethanol/dichloromethane = 1/14) to give 107 mg (64%) **1** as pale yellow crystals, mp 181° (lit. [5] mp 182-183°); ir (potassium bromide): 3309, 1691, 1452, 1323, 1205, 1121, 1066, 1025 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.48 (d, 1H, 3-H, J = 4.9 Hz), 8.15 (d, 1H, 4-H, J = 4.9 Hz), 8.14 (dd, 1H, 5-H, J = 7.8, 0.8 Hz), 7.61 (m, 2H, 7-H, 8-H), 7.34 (ddd, 1H, 6-H, J = 7.9, 5.3, 2.8 Hz), 5.24 (s, 2H, 2'-H), 3.61 (s, 3H, OCH_3); ^{13}C nmr (deuteriochloroform): δ 199.45 (C=O), 141.21 (C8a), 138.00 (C3), 135.13 (C9a), 134.17 (C1), 131.71 (C4a), 129.46 (C7), 121.81 (C5), 120.89 (C6), 120.45 (C4b), 119.38 (C4), 112.09 (C8), 74.96 (C2'), 59.53 (OCH_3) [16]; ms (EI): m/z 240 (M^+, 29), 225 (100), 197 (10), 167 (55), 140 (27).

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.77; H, 4.96; N, 11.54.

Method B.

Diazoketone **11** (340 mg, 1.44 mmoles) was suspended in anhydrous methanol (40 ml) under a nitrogen atmosphere. Then boron trifluoride diethyl etherate (0.50 ml, 4.0 mmoles) was added dropwise and the mixture was stirred at room temperature for 10 minutes. After evaporation the residue was separated by flash column chromatography (hexane/ethyl acetate = 4/1) to give 52 mg (15%) **1** as pale yellow crystals, mp 181°.

(±)-Arenarine B (1-(2-Methoxy-1-hydroxyethyl-9*H*-pyrido[3,4-*b*]indole; **2**).

Arenarine A (**1**) (50 mg, 0.21 mmoles) was suspended in anhydrous methanol (6 ml) under a nitrogen atmosphere. After addition of sodium borohydride (8 mg, 0.2 mmoles) the mixture was stirred at room temperature for two hours. The solution was poured into water (50 ml) and the mixture was extracted with ethyl acetate (3 x 20 ml). The combined organic layers were dried (sodium sulfate) and evaporated. The residue was purified by flash column chromatography (ethanol/dichloromethane = 1/14) to give 44 mg (87%) **2** as white crystals, mp 168° (lit. [5] mp 157-158°); ir (potassium bromide): 3266, 3090, 2891, 1626, 1498, 1433, 1322, 1237, 1128, 1075 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.34 (d, 1H, 3-H, J = 5.3 Hz), 8.11 (d, 1H, 5-H, J = 7.9 Hz), 7.89 (d, 1H, 4-H, J = 5.3 Hz), 7.53 (m, 2H, 8-H, 7-H), 7.28 (ddd, 1H, 6-H, J = 7.9 Hz, 6.8, 1.6 Hz), 5.38 (t, 1H, 1'-H, J = 6.2 Hz), 3.88 (dd, 1H, 2'-H, J = 9.5, 6.2 Hz), 3.84 (dd, 1H, 2'-H, J = 9.5, 6.2 Hz), 3.48 (s, 3H, OCH_3); ^{13}C nmr (deuteriochloroform): δ 143.23 (C1) [17], 140.74 (C8a), 137.19 (C3), 133.88 (C9a), 130.11 (C4a), 128.83 (C7), 121.94 (C5), 121.49 (C4b), 120.20 (C6), 114.35 (C4), 112.04 (C8), 77.00 (C2'), 72.43 (C1'), 59.46 (OCH_3); ms (EI): m/z 242 (M^+, 16), 225 (10), 197 (100), 168 (14).

HRMS Calcd. for $C_{14}H_{14}N_2O_2$ *m/z*: 242.1055. Found *m/z*: 242.1055.

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[16] An additional peak at 29.4 ppm is reported in lit. [5]. This peak does not make sense.

[17] This peak is missing in lit. [5], instead a peak at 128.7 ppm is reported.