Synthesis of Hyrtiosin B, a Bis-indole Alkaloid from the Okinawan Marine Sponge *Hyrtios erecta*

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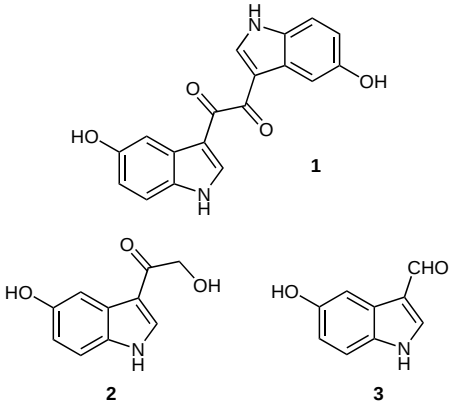
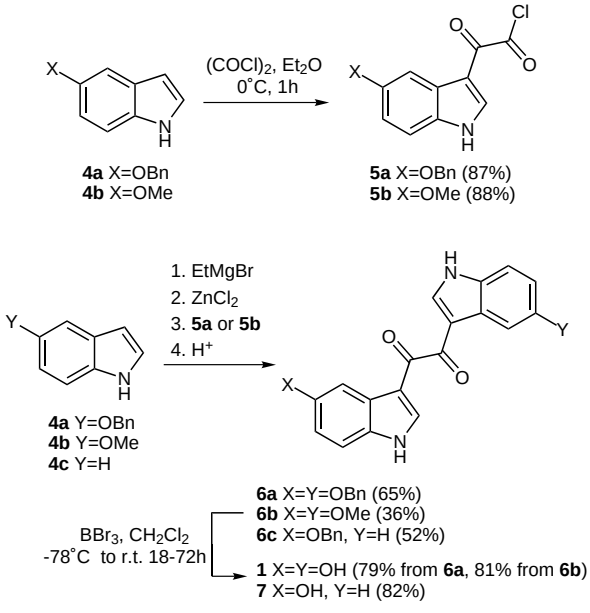
Abstract: The bis-indole alkaloid hyrtiosin B **(1)** has been prepared in good yield from 5-benzyloxyindole **(4a)** or 5-methoxyindole **(4b)**, involving a coupling reaction of the zinc metallated indoles with the corresponding glyoxylyl chlorides **5a–b**, and finally debenzylation or demethylation using boron tribromide to yield the title compound **1**.

Key words: hyrtiosin B, bis-indole alkaloids, transmetallation, *O*-dealkylation

Several classes of compounds have been isolated from marine organisms belonging to the genus *Hyrtios*, such as terpenoids[1] and sterols.[2] In 1990, the first isolation of alkaloids from this genus was reported;[3] hyrtiosin B **(1)**, a bis-indole alkaloid, was found in the Okinawan marine sponge *Hyrtios erecta* together with the related compounds hyrtiosin A **(2)** and the previously reported 5-hydroxyindole-3-carboxaldehyde **(3)**,[4] and was demonstrated to possess cytotoxic activity against human epidermoid carcinoma KB cells in vitro.



We now describe a short and efficient synthesis of **1** in three steps from 5-benzyloxyindole **(4a)** or 5-methoxyindole **(4b)**. The indoles **4a** or **4b** were transformed in excellent yields into the corresponding indole-3-glyoxylyl chlorides **5a–b** according to the procedure of Speeter and Anthony.[5] The key step in our approach is a coupling reaction involving transmetallation of the indole magnesium halides based on the indoles **4a** or **4b** with anhydrous zinc chloride,[6] and subsequent treatment of the resulting zincated indoles with acid chlorides **5a–b**, which afforded the symmetrical coupled products **6a–b** in moderate yields (36–65%) (Scheme). Acylation of zincated indoles has previously been shown to give yields superior to those resulting from acylation of indole magnesium halides.[6] The final *O*-dealkylation was accomplished by treatment of **6a–b** with boron tribromide in dichloromethane to give hyrtiosin B **(1)** in good yields (79–81%) after purification by column chromatography. The benzyl derivative **6a** was debenzylated easily with BBr_3 (4 equiv), whereas demethylation of **6b** required a larger excess of BBr_3 (12 equiv) and longer reaction times. Attempted catalytic debenzylations of **6a** in ethanol or methanol failed, as did attempted dealkylations using Prey's method[7] (reflux in pyridine hydrochloride). The spectral data of synthetic hyrtiosin B were identical in all respects with those of the natural product. The possibility to prepare a wide diversity of unsymmetrical derivatives was demonstrated by preparation of compound **6c** by treatment of 1-indolylmagnesium bromide with **5a** as outlined in the Scheme.



Scheme

The monobenzyloxy substituted compound **6c** was similarly debenzylated using boron tribromide to yield the hydroxy derivative **7**, a compound closely related to hyrtiosin B **(1)**. A compound structurally related to **7** (Cl instead of OH) has previously been prepared by Van

Vranken et al.[8] using the technique previously developed by Bergman and Venemalm.[6]

5-Benzyloxyindole and 5-methoxyindole were purchased from Lancaster and Aldrich respectively. $ZnCl_2$ (1.0 M solution in Et_2O) was purchased from Aldrich. BBr_3 (1.0 M solution in CH_2Cl_2) was purchased from Lancaster. All solvents were purified by distillation, Et_2O was stored over sodium wire. The equipment for the anhydrous reactions was dried in an oven and was assembled hot. NMR spectra were recorded on a Bruker DPX 300 spectrometer (300 MHz, TMS) and the IR spectra were recorded using a Perkin Elmer 1600 FT-IR instrument. Mass spectra were obtained using a Micromass Platform II spectrometer. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Melting points were taken on a Büchi Melting Point B-545 apparatus and are uncorrected. Chromatography was performed on Merck silica gel 60, TLC analyses were run on Merck silica gel F_{254} plates.

(5-Benzyloxyindol-3-yl)glyoxylyl Chloride (5a)
A solution of 5-benzyloxyindole (**4a**; 1.12 g, 5.04 mmol) in anhyd Et_2O (20 mL) was cooled to 0°C. Oxalyl chloride (0.45 mL, 5.15 mmol) was added dropwise, producing an orange precipitate. The mixture was stirred at 0°C for 1 h, thereafter **5a** was collected as an orange solid, washed with anhyd Et_2O and dried; yield: 1.38 g (87%). The product was used immediately in the next step, or was stored in a dessicator; mp 149–151°C (dec) [Lit.[5] mp 146–150°C (dec)].

IR(KBr): ν = 3189, 1784, 1630, 1474, 1430, 1266, 988, 775, 716 cm^{-1}.

(5-Methoxyindol-3-yl)glyoxylyl Chloride (5b)
The same procedure as above was used, with 5-methoxyindole (**4b**; 735 mg, 5.00 mmol) and oxalyl chloride (0.45 mL, 5.15 mmol); yield: 1.05 g (88%); orange solid; mp 137–138°C (dec) (Lit.[9] mp 134°C).

IR(KBr): ν = 3195, 1781, 1624, 1476, 1427, 1267, 991, 774, 706 cm^{-1}.

1,2-Di(5-benzyloxyindol-3-yl)ethane-1,2-dione (6a)
To a solution of EtMgBr prepared from Mg (78 mg, 3.21 mmol) and bromoethane (0.24 mL, 3.22 mmol) in Et_2O (10 mL) was added a solution of **4a** (670 mg, 3.01 mmol) in Et_2O (15 mL) at r.t. The mixture was allowed to stir for 15 min, then a 1.0 M Et_2O solution of $ZnCl_2$ (3.1 mL, 3.1 mmol) was added, and the stirring was continued for 30 min, followed by addition of **5a** (941 mg, 3.00 mmol) in one portion. After stirring at r.t. for 3.5 h, the mixture was quenched with sat. aq NH_4Cl solution (50 mL), and extracted with EtOAc (100 mL). The organic phase was washed with brine (30 mL), dried ($MgSO_4$) and evaporated to dryness. Trituration of the residue with EtOH (15 mL) afforded **6a** as a yellow solid (710 mg). A second crop (260 mg) was collected after concentration of the mother liquor; total yield: 970 mg (65%); mp 233°C.

IR(KBr): ν = 3386, 3319, 1596, 1506, 1425, 1252, 1188, 1113, 784 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 5.20 (s, 4 H), 7.00 (dd, *J* = 2.5, 8.8 Hz, 2 H), 7.33–7.52 (m, 12 H), 7.89 (d, *J* = 2.2 Hz, 2 H), 8.16 (d, *J* = 2.9 Hz, 2 H), 12.15 (d, *J* = 2.2 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 69.7 (t), 104.6 (d), 112.4 (s), 113.4 (d), 113.7 (d), 126.5 (s), 127.6 (d), 127.7 (d), 128.4 (d), 131.7 (s), 137.4 (d), 154.9 (s), 188.7 (s).

Anal. Calcd for $C_{32}H_{24}N_2O_4$: C, 76.79; H, 4.83; N, 5.60. Found: C, 76.88, H, 4.81; N, 5.62.

1,2-Di(5-methoxyindol-3-yl)ethane-1,2-dione (6b)
To a solution of EtMgBr prepared from Mg (102 mg, 4.20 mmol) and bromoethane (0.315 mL, 4.22 mmol) in Et_2O (10 mL) was added a solution of **4b** (588 mg, 4.00 mmol) in Et_2O (15 mL) at r.t. After 15 min a 1.0 M Et_2O solution of $ZnCl_2$ (4.1 mL, 4.1 mmol) was added and the mixture was stirred for 30 min. Compound **5b** (954 mg, 4.01 mmol) was then added in one portion, and the stirring was continued for 3.5 h. Workup with sat. aq NH_4Cl solution (50 mL) and extraction with EtOAc (100 mL) [in this case addition of MeOH (2 mL) was necessary in order to obtain a clear two-phase mixture], washing of the organic extracts with brine, drying ($MgSO_4$) and subsequent evaporation of the solvent gave a residue that afforded **6b** (455 mg) as a pink solid after trituration with EtOH (15 mL). A second crop (50 mg) was collected after concentration of the mother liquor; yield: 505 mg (36%); mp 309–310°C.

IR (KBr): ν = 3190, 1606, 1477, 1426, 1265, 1211, 783, 710 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.83 (s, 6 H), 6.92 (dd, *J* = 2.5, 8.8 Hz, 2 H), 7.44 (d, *J* = 8.8 Hz, 2 H), 7.79 (d, *J* = 2.4 Hz, 2 H), 8.17 (s, 2 H), 12.13 (br s, 2H).

^{13}C NMR (DMSO-d_6): δ = 55.3 (q), 103.1 (d), 112.4 (s), 113.2 (d), 113.4 (d), 126.6 (s), 131.5 (s), 137.4 (d), 155.9 (s), 188.7 (s).

MS (EI, 70 eV): *m/z* = 348 (M^+, 5), 175 (11), 174 (100), 159 (18), 146 (17), 131 (23), 119 (11), 103 (17), 76 (14).

HRMS (EI): *m/z* Calcd for $C_{20}H_{16}N_2O_4$: 348.1110. Found: 348.1094.

Hyrtiosin B (1) by Debenzylation of 6a
A 1.0 M solution of BBr_3 in CH_2Cl_2 (4.0 mL, 4.0 mmol) was added dropwise to a stirred suspension of **6a** (500 mg, 1.00 mmol) in CH_2Cl_2 (20 mL) at –78°C under N_2 atmosphere. The mixture was allowed to reach r.t. over 18 h and H_2O (30 mL) was added. Extraction of the mixture with three portions of EtOAc (total 120 mL), washing of the combined extracts with brine, drying ($MgSO_4$) and finally evaporation of the solvent gave a brown residue, which was subjected to column chromatography using EtOAc as eluent to yield pure hyrtiosin B **(1)** (254 mg, 79%) as a pale green solid; mp >400°C (Lit.[3] mp >310°C).

IR(KBr): ν = 3259 (br), 1595, 1514, 1466, 1421, 1202, 786, 723 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 6.76 (dd, *J* = 2.3, 8.7 Hz, 2 H), 7.32 (d, *J* = 8.7 Hz, 2 H), 7.66 (d, *J* = 2.0 Hz, 2 H), 8.03 (d, *J* = 3.3 Hz, 2 H), 9.13 (br s, 2 H), 11.97 (d, *J* = 2.7 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 105.8 (d), 112.1 (s), 113.0 (d), 113.1 (d), 126.8 (s), 130.8 (s), 136.9 (d), 153.6 (s), 188.8 (s).

Anal. Calcd for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.38; H, 3.84; N, 8.62.

Hyrtiosin B (1) by Demethylation of 6b
A 1.0 M solution of BBr_3 in CH_2Cl_2 (6.0 mL, 6.0 mmol) was added to a suspension of **6b** (174 mg, 0.50 mmol) in CH_2Cl_2 (15 mL) at –78°C under a N_2 atmosphere. The mixture was allowed to reach r.t. over 72 h. The same workup procedure as above yielded hyrtiosin B **(1)** (130 mg, 81%) as a pale green solid, in all respects identical with the sample prepared by debenzylation of **6a**.

1-(5-Benzyloxyindol-3-yl)-2-(indol-3-yl)-ethane-1,2-dione (6c)
1-Indolylmagnesium bromide in Et_2O (15 mL), prepared from Mg (102 mg, 4.20 mmol), bromoethane (0.315 mL, 4.22 mmol) and indole (468 mg, 4.00 mmol), was transmetallated by treating with a 1.0 M solution of $ZnCl_2$ in Et_2O (4.1 mL, 4.1 mmol) at r.t. The resulting mixture was stirred for 30 min. Compound **5a** (1.25 g, 3.92 mmol) was added in one portion, and stirring was continued for 16 h. The mixture was quenched with sat. aq NH_4Cl solution (50 mL)

and extracted with EtOAc (100 mL). The organic extract was washed with brine (50 mL) and dried ($MgSO_4$). Evaporation of the solvent gave an orange residue, which was triturated with Et_2O (20 mL) containing EtOH (1 mL) to give **6c** (810 mg, 52%) as a cream coloured solid; mp 210.5–211.5°C.

IR(KBr): ν = 3232 (br), 1598, 1511, 1436, 1241, 1122, 782, 742 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 5.17 (s, 2 H), 7.01 (dd, *J* = 2.5, 8.8 Hz, 1 H), 7.28–7.57 (m, 9 H), 7.90 (d, *J* = 2.4 Hz, 1 H), 8.17 (d, *J* = 3.2 Hz, 1 H), 8.23 (d, *J* = 3.1 Hz, 1 H), 8.27–8.30 (m, 1 H), 12.16 (d, *J* = 2.5 Hz, 1 H), 12.25 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 69.7 (t), 104.7 (d), 112.4 (s), 112.5 (s), 112.6 (d), 113.4 (d), 113.7 (d), 121.3 (d), 122.4 (d), 123.4 (d), 125.6 (s), 126.5 (s), 127.6 (d), 127.7 (d), 128.4 (d), 131.7 (s), 136.7 (s), 137.3 (d), 137.4 (d), 137.4 (s), 154.9 (s), 188.6 (s), 188.8 (s).

MS (EI, 40 eV): *m/z* = 394 (M^+, 2), 251 (11), 250 (67), 160 (14), 159 (30), 144 (76), 131 (29), 116 (21), 103 (11), 91 (100), 89 (14).

HRMS (EI): *m/z* Calcd for $C_{25}H_{18}N_2O_3$: 394.1317. Found: 394.1320.

1-(5-Hydroxyindol-3-yl)-2-(indol-3-yl)-ethane-1,2-dione (7)

To a suspension of **6c** (197 mg, 0.50 mmol) in CH_2Cl_2 (15 mL) at –78°C under N_2 atmosphere was added a 1.0 M solution of BBr_3 in CH_2Cl_2 (3.0 mL, 3.0 mmol). The mixture was allowed to reach r.t. over 24 h, H_2O (30 mL) was added, followed by extraction with EtOAc (75 mL). The aqueous phase was extracted once more with EtOAc (25 mL). Washing of the combined organic extracts with brine, drying ($MgSO_4$), evaporation of the solvent and finally column chromatography (elution with EtOAc) gave **7** as a pale green solid (125 mg, 82%); mp 271–272°C.

IR(KBr): ν = 3408, 3291, 3244, 1597, 1508, 1423, 1240, 1112, 780, 729 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 6.77 (dd, *J* = 2.3, 8.7 Hz, 1 H), 7.25–7.29 (m, 2 H), 7.33 (d, *J* = 8.7 Hz, 1 H), 7.52-7.55 (m, 1 H), 7.68 (d, *J* = 2.2 Hz, 1 H), 8.06 (s, 1 H), 8.19 (s, 1 H), 8.24-8.27 (m, 1 H), 9.16 (br s, 1 H), 12.08 (br s, 2 H).

^{13}C NMR (DMSO-δ_6): δ = 105.6 (d), 112.1 (s), 112.5 (d), 112.6 (s), 113.0 (d), 113.2 (d), 121.3 (d), 122.4 (d), 123.4 (d), 125.6 (s), 126.8 (s), 130.8 (s), 136.7 (s), 137.0 (d), 137.2 (d), 153.6 (s), 188.5 (s), 189.1 (s).

MS (EI, 70 eV): *m/z* = 304 (M^+, 11), 160 (90), 144 (100), 132 (42), 116 (53), 105 (33), 89 (73), 77 (27).

HRMS (EI): *m/z* Calcd for $C_{18}H_{12}N_2O_3$: 304.0848. Found: 304.0844.

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