A Practical Synthesis of (*Z*)-Debromohymenialdisine

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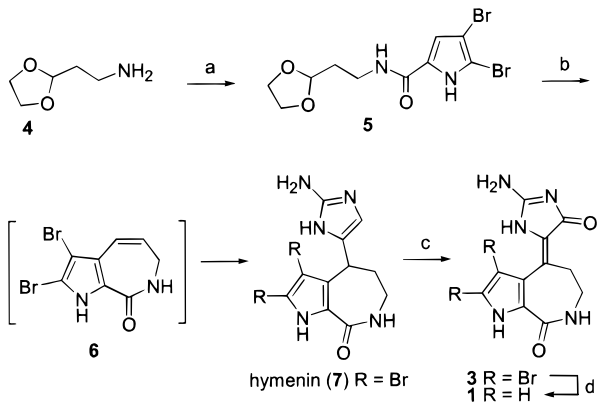
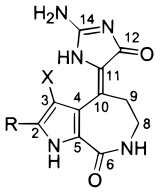
(*Z*)-Debromohymenialdisine [(*Z*)-DBH (**1**)], first isolated[1a] in 1980 from the caribbean sponge *Phakellia flabellata*, is a biologically significant member of the "oroidin" family of sponge metabolites.[2] Its corresponding (*E*) isomer is also known, having been isolated in 1996 from the common shallow-water sponge *Stylotella aurantium*.[3] Recently, a number of reports centering on (*Z*)-DBH and related analogue hymenialdisine (**2**)[1b] have appeared describing the modulation of protein kinase C and the proinflammatory transcription factor, nuclear factor κB (NFκB).[4] NFκB is believed to be involved in the regulated gene expression of the inflammatory enzyme, cyclooxygenase (COX-II).[4b] Together, these proteins play important roles as mediators of inflammation associated with arthritis. In addition, DBH has been shown to slow joint deterioration and cartilage degradation associated with osteoarthritis in animal models and is currently under development as a promising new drug candidate.[5] At present, there is no known pharmaceutical agent for the treatment of osteoarthritis, which is the most common manifestation of arthritic disease. Ongoing investigations have reached the point where a practical synthesis of DBH is needed for preclinical/clinical trials. Only limited supplies are available from natural sources. To address this problem, we report[6] a practical synthetic approach to (*Z*)-DBH (**1**) as well as the first synthesis of (*Z*)-3-bromohymenialdisine (**3**), a sponge metabolite from *Stylissa carteri*.[7]

Scheme 1[a]



[a] Key: (a) ref 9, 90%; (b) CH_3SO_3H, 45 °C, 4 d then 2-AI, 45 °C, 4 d, 60%; (c) 2 equiv Br_2, 23 °C, HOAc/NaOAc, 85%; (d) H_2, 10% Pd/C, NaOAc, 75%.



debromohymenialdisine (**1**) R = X =H
hymenialdisine (**2**) R = Br, X = H
3-bromohymenialdisine (**3**) R = X = Br

(*Z*)-DBH (**1**) has been the subject of two prior syntheses.[8,9] The synthesis reported by our group[9] in 1997 relies on the preparation of hymenin (**7**) which serves as the basis for the present investigation. Initial modifications to the original hymenin synthesis focused on developing a one-pot conversion of acetal **5**[9] to hymenin (**7**) from readily available materials, namely, amine **4**[10] and 4,5-dibromopyrrol-2-yl trichloromethyl ketone[11] (Scheme 1). This one-pot, two-step procedure commences with an intramolecular ring closure to afford intermediate **6** followed by an acid-facilitated coupling of 2-aminoimidazole (2-AI). This modification circumvents the deprotection and isolation of the corresponding aldehyde as well as the isolation of pyrroloazepinone **6**, which was done in the original synthesis. The overall transformation can be readily accomplished on a multigram scale in which racemic hymenin is produced in 60% overall yield.

Next, a method for installing the α,β unsaturated aminoimidazolidinone functionality of (*Z*)-DBH was pursued which required a two-fold oxidation of hymenin (**7**).

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While a number of reagents can be envisaged to accomplish this transformation, treatment of hymenin (**7**) with 2 equiv of bromine in an acetic acid/sodium acetate system cleanly provided the desired natural product, (*Z*)-3-bromohymenialdisine (**3**), in good yield. Spectral data of synthetic **3** were in satisfactory agreement with those reported for the natural material.[7] No evidence of formation of the less thermodynamically stable *E* isomer was observed.[12] Comparison of ^{13}C chemical shift values of **3** for the free base (C12 = 176.7, C14 = 166.7 ppm) and HCl salt (C12 = 163.2, C14 = 154.1 ppm) revealed a significant upfield shift upon protonation of the guanidino and imidazolidinone (C=O) carbons. This is consistent with earlier studies reported for neutral and protonated glycocyamidines.[13] Although tautomerism of (*Z*)-DBH has been reported,[3] we were unable to detect tautomerism of the dibromo analogue (*Z*)-**3** by ^1H and ^{13}C NMR spectroscopy upon dilution of the free base. Finally, reduction of the brominated pyrrole moiety of **3** was achieved with high chemoselectivity over the C10−C11 double bond using hydrogen and Pd/C to afford good yields of (*Z*)-DBH (**1**). The conjugative nature and steric hindrance of this double bond is believed to contribute to the selectivity of this reduction.

Efforts were also pursued in the oxidation of 2,3-didebromohymenin (**7**, R = H)[9] to (*Z*)-DBH (**1**). This approach met with limited success. Reagents such as $Cu(OAc)_2$ and base-catalyzed air oxidations produced (*Z*)-DBH but in a less efficient manner.

In summary, a practical synthesis of (*Z*)-DBH (**1**) has been accomplished in four steps from readily available starting materials (34% overall yield from amine **4**). Compared to the original (*Z*)-DBH synthesis, which produced low yielding mixtures of (*Z*)-DBH (**1**) and hymenialdisine (**2**), the present route represents a significant improvement in both efficiency and practicality. Noteworthy is the fact that the synthesis does not require the use of protecting groups on any of the five nitrogen functionalities or rely on chromatographic techniques for purification. The route should be directly amenable to scale-up processes.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. ^1H NMR and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers.

(±)-Hymenin (7). A solution of acetal **5** (75.5 g, 0.2 mol) was heated in methanesulfonic acid (400 mL) at 45 °C for 4 d. Next, 2-aminoimidazole·$1/2H_2SO_4$ (31.2 g, 0.24 mol) was added and the reaction was stirred an additional 4 d at 45 °C. The reaction was diluted with at least 10 volumes of ether and decanted (2×) to afford a sticky residue. Trituration from ethanol afforded hymenin (**7**) as the methanesulfonic salt[9] (60 g, 60% yield) which was used directly in the next reaction.

(*Z*)-3-Bromohymenialdisine (3). To a stirred solution of hymenin (**7**)·CH_3SO_3H (7.5 g, 15 mmol) and sodium acetate (6.3 g, 75 mmol) in acetic acid (240 mL) was added bromine (1.6 mL, 30 mmol) at 23 °C. The reaction was stirred for 1 h, concentrated, and azeotroped with hot ethanol several times to afford a solid. The solid was extracted with hot ethanol, decolorized with activated charcoal, and filtered. Concentration of the filtrate afforded a solid which was rinsed with a minimum amount of water to remove any remaining inorganic salts. The resulting material was dried under vacuum to afford **3** (5.13 g, 85% yield) as a colorless solid. ^1H NMR (DMSO-d_6) δ 3.15 (bs, 4H), 6.58 (bs, 1H, exch. D_2O), 7.88 (bs, 2H, exch. D_2O), 8.80 (bs, 1H, exch. D_2O), 13.09 (bs, 1H, exch. D_2O); ^{13}C NMR (DMSO-d_6) δ 33.7 (t), 38.6 (t), 98.1 (s), 106.4 (s), 114.1 (s), 123.3 (s), 126.2 (s), 130.2 (s), 163.8 (s), 166.9 (s), 176.7 (s). IR (KBr) 3343 (br), 1697, 1657, 1626, 1280 cm^{-1}. HRFABMS calcd for $C_{11}H_{10}O_2N_5{}^{79}Br_2$ (MH^+) 401.9202, found 401.9201. **3**·HCl: ^1H NMR (DMSO-d_6) δ 3.25 (bs, 4H), 8.07 (bs, 1H), 8.50 (bs, 1H), 9.30 (bs, 2H), 10.92 (bs, 1H), 13.4 (bs, 1H). ^{13}C NMR (DMSO-d_6) δ 35.2 (t), 38.6 (t), 98.5 (s), 107.4 (s), 120.7 (s), 123.7 (s), 125.9 (s), 127.3 (s), 154.1 (s), 162.5 (s), 163.3 (s). IR (film) 3273 (br), 1749, 1706, 1641, 1282 cm^{-1}.

(*Z*)-Debromohymenialdisine (1). A mixture of (*Z*)-3-bromohymenialdisine (**3**)·HCl (3.2 g, 8.0 mmol) in methanol (200 mL) containing 10% Pd/C (1.0 g) and sodium acetate (3.2 g, 40 mmol) was placed under a balloon of hydrogen. After 10 h, the reaction mixture was filtered through Celite and the resulting filtrate was concentrated and azeotroped with ethanol several times to afford a yellow solid. The solid was washed with a minimal amount of water to remove inorganic salts. The solid was dissolved in hot methanol, decolorized with activated charcoal, and filtered. Upon concentration of the filtrate, (*Z*)-DBH·CH_3OH crystallized from solution as light-yellow crystals (1.6 g, 75% yield).

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra of the free base of the synthetic (*Z*)-3-bromohymenialdisine (**3**). This material is available free of charge via the Internet at http://pubs.acs.org.

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