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Total Syntheses of Hymenialdisine and Debromohymenialdisine: Stereospecific Construction of the 2-Amino-4-Oxo-2-Imidazolin-5(Z)-Disubstituted Ylidene Ring System†

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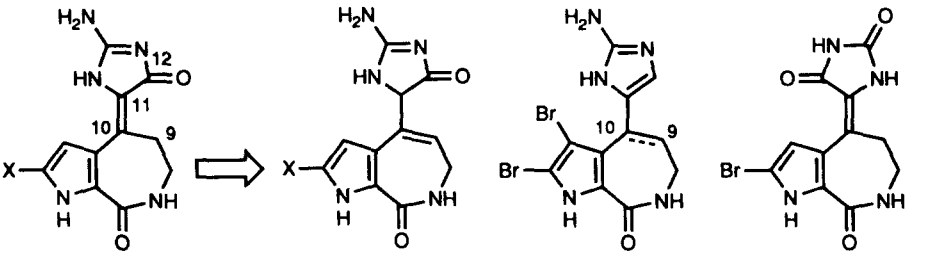
Abstract: The first total synthesis of hymenialdisine (**1a**) and debromohymenialdisine (**1b**) was achieved via a novel stereospecific construction of the 2-amino-4-oxo-2-imidazoline-5(Z)-disubstituted ylidene ring system.

Hymenialdisine (**1a**) was isolated from marine sponges[1] of the genera *Hymeniacidon* , *Acanthella*, *Axinella* and *Pseudaxinyssa*. The structure of **1a** was established on the basis of X-ray crystallography. Debromohymenialdisine (**1b**) was also isolated from sponges[1c-f, 2ab] of the same genera in addition to *Phakellia* and an unidentified Korolevu sponge.[2c] The hymenialdisines (**1ab**) represent a novel class of natural products,[3] including hymenin[4] (**3a**), stevensine[5] (or oriline)[1e] (**3b**), and axinohydantoin[1f] (**4**), that have in common a unique pyrrolo[2,3-c]azepine skeleton connected to a cyclic guanidine or hydantoin ring system. While hymenialdisine (**1a**) and debromohymenialdisine (**1b**) exhibit potent activity against murine P388 lymphocytic leukemia,[1f] hymenin (**3a**) has shown to possess α-blocking effect.[6] Recently, much attention has been paid to the synthesis of the members of this family because of their structural and biological interest.[7] In this communication, we report the first total synthesis of hymenialdisine (**1a**) and debromohymenialdisine (**1b**).



1a : X=Br
1b : X=H

2

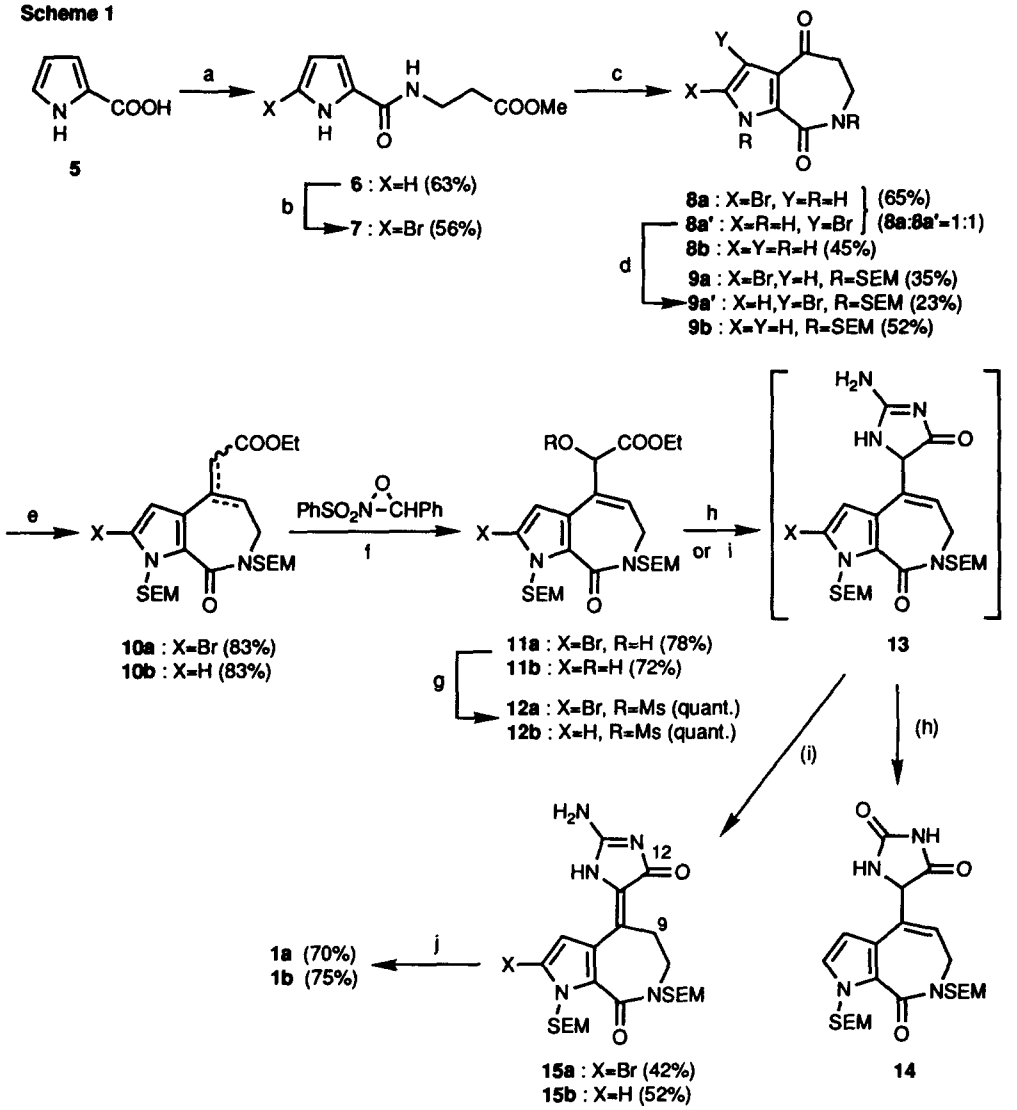
3a: C9-C10 single bond
3b: C9-C10 double bond

4

A successful total synthesis would require an efficient protocol of constructing the 2-amino-4-oxo-2-imidazolin-5(Z)-disubstituted ylidene ring system[8] with complete control of the exocyclic olefin geometry. The strategy we have adopted for this object depends upon the expectation that a possible structural isomer (**2**),

in which the C10-C11 double bond shifts within the azepine ring system, would be a conceptually synthetic equivalent of **1ab**. Consequently, we found that the β,γ-unsaturated-α-methanesulfonyloxy ester (**12ab**), upon treatment with guanidine, underwent the cyclization accompanied by isomerization of the double bond into the conjugated system (C10-C11) to produce the fully functionalized core structure **15ab** in a single step (**Scheme 1**).

Scheme 1



Reagents and conditions : (a) $SOCl_2$, cat. DMF, toluene, 60℃, 1h, then $H_2NCH_2CH_2COOMe$, Et_3N, CH_2Cl_2, r. t., 3h; (b) NBS, THF, r. t., 2h; (c)10% aq. NaOH-MeOH (2:1), r. t., 5h, then PPA-P_2O_5, 100℃, 1h; (d) NaH (2 eq.), SEMCl (2eq.), DMF, r. t., 2h; (e) $(EtO)_2POCH_2COOEt$, NaH, DME, 50℃, 24h; (f) KHMDS, THF, -78℃, 2h; (g) MsCl, Et_3N, CH_2Cl_2, 0℃; (h) guanidine, $AlMe_3$, toluene, 80℃, 4h, then $CHCl_3$-MeOH-H_2O; (i) guanidine, DMF, 50℃, 5h; (j) 5% aq. HCl-MeOH (1:1), 80℃, 2h.

Treatment of commercially available pyrrole-2-carboxylic acid (**5**) with $SOCl_2$/cat. DMF in toluene at 60°C, followed by condensation with β-alanine methylester gave **6** in 63% yield. Bromination of **6** using NBS gave the 2-bromopyrrole derivative (**7**) in 56% yield after recrystallization from n-hexane/ether. PPA cyclization, after hydrolysis of **7**, interestingly provided a 65% yield of a 1:1 mixture of 2-bromoaldisin[9] (**8a**) and 3-bromoaldisin (**8a'**), presumably due to 1,2-migration of the bromine atom induced by the strong acidic media.[10] Unfortunately, these isomers could not be separated by usual chromatography but were found to be easily separated after converting into the SEM [2-(trimethylsilyl)ethoxymethyl] protected derivatives. Thus, treatment of the mixture, **8a** and **8a'**, with NaH (2 eq.)/SEMCl (2 eq.) in DMF at 0°C, followed by separation of the isomers by chromatography over silica gel (hexane:ether=1:3) gave **9a** (35%) and **9a'**(23%). By the same procedure, aldisin[9,11] (**8b**) was obtained from **6** in 45% yield and protected by SEM group to give **9b** in 52% yield. The Horner-Emmons reactions of **9ab** with ethyl diethylphosphonoacetate/NaH in DME at 50°C gave **10a** (83%) and **10b** (83%), respectively, as a mixture of α,β-and β,γ-unsaturated esters.[12] Deprotonation of **10ab** with KHMDS in THF at -78°C generated the ester anions, which were quenched with 2-benzenesulfonyl-3-phenyloxaziridine[13] to give the α-hydroxy-β,γ-unsaturated esters, **11a** (78%) and **11b** (72%), as single regioisomers. Reaction of **11b** with guanidine (1.5 eq.) in the presence of $AlMe_3$[14] (5 eq.) in toluene at 80°C caused cyclization to afford the hydantoin derivative **14**[15] in 22% yield, which was presumably derived from hydrolysis of the initial guanidine adduct (**13**) during work-up procedure. Despite extensive experimentation, we have not been able to isolate the intermediate **13**. Even attempts by the work-up under non-aqueous and/or basic conditions ($MeOH/NH_3$, THF/NH_3, THF /tetramethylethylendiamine or 10%-aq. NaOH/MeOH) gave only **14**.

Considering the structural difference between **13** and the natural products (**1ab**) which should be stable to handle, these results would suggest that isomerization of the C9-C10 double bond into the conjugated system (C10-C11) is essential to give rise to a reasonable stability of the cyclic guanidine moiety in terms of resonance effect. Thus, we examined the reaction under basic conditions after converting **11ab** into the mesylates (**12ab**). When **12ab** were treated with guanidine (5 eq.) in DMF[16] at 50°C, the cyclization proceeded with isomerization of the double bond into the conjugated system in a stereospecific manner to yield the desired products, **15a**[17] (42%) and **15b**[17] (52%), respectively. The stereochemistries of the C10-C11 double bond of **15ab** were determined to be Z-configration by comparison of their NMR data with those of the natural products. In the ^{1}H-NMR (400MHz, CD_3OD), the signals attributable to the C9-methylene protons appeared at δ 3.37 (triplet, J=5.3Hz) in **15a** and δ 3.38 (triplet, J=5.5Hz) in **15b**, both of which are shifted to lower field than that of the geometric isomer, axinohydantoin (**4**) (δ 2.67),[1f] by anisotropic effect of the C12-amide carbonyl group, but correspond very closely to those of hymenialdisine (**1a**) (δ 3.3)[1a] and debromohymenialdisine (**1b**) (δ 3.3).[2a] It should be noted that complete control of regio- and stereochemistry of these conversions promises to be of potential synthetic value. Finally, deprotections of both the SEM groups in **15ab** by exposure to MeOH/5%-aq. HCl furnished hymenialdisine (**1a**) (70%) and debromohymenialdisine (**1b**) (75%), respectively, after chromatographic purification over silica gel [$CHCl_3$:MeOH:H_2O (2%AcOH) = 65:35:10]. The synthetic samples were identical with authentic samples generously provided by Dr. Randall K. Johnson in TLC behavior and spectroscopic properties (^{1}H- and ^{13}C-NMR, IR, HRFABMS).

Applications of the strategy described here to the synthesis of the other members of the pyrroloazepine alkaloids are in progress and will be reported in due course.

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9. The aldisins (**8ab**) were obtained from the sponges *Acanthella carteri*,[1d] *Pseudoxinyssa cantharella*,[1e] and *Hymeniacidon aldis* [2c] as well as $KMnO_4$ oxidation of **1ab**.[1e, 2a] However, it is proposed [2c, 7a] that **8ab** may be artefacts produced during isolation of **1ab**.
10. The crude product of **7** contained a small amount of the 3-bromopyrrole isomer, which was separated by chromatography over silica gel (hexane:ether=1:2) and subjected to hydrolysis followed by PPA cyclization to afford a mixture of **8a** and **8a'** in the same ratio (1:1).
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15. **14**; ^{1}H-NMR (400MHz, $CDCl_3$) δ: -0.04 (9H, s), -0.005 (9H, s), 0.88 (2H, t, J=8.2Hz), 0.92 (2H, m), 3.49 (2H, t, J=8.2Hz), 3.52 (2H, m), 3.76 (1H, dd, J=14 and 6.9Hz), 3.79 (1H, dd, J=14 and 6.9 Hz), 4.87 (1H, d, J=10.3Hz), 5.00 (1H, d, 10.3Hz), 5.39 (1H, s), 5.60 (1H, d, J=9.6Hz), 5.65 (1H, brs, NH, exchangeable with D_2O), 5.78 (1H, d, J=9.6Hz), 6.23 (1H, t, J=6.9Hz), 6.28 (1H, d, 2.9Hz), 7.04 (1H, d, J=2.9Hz), 8.45 (1H, brs, NH, exchangeable with D_2O).
16. The reaction using the other solvents such as toluene and tetrahydrofuran gave **15ab** in low yield.
17. **15a**; ^{13}C-NMR (500MHz, CD_3OD) δ: 176.3, 165.1, 163.6, 129.8, 125.9, 125.4, 119.7, 111.4, 110.5, 75.0, 74.2, 65.7, 65.1, 45.1, 34.2, 17.5, 17.3, -2.7, -2.8; **15b** (CD_3OD) δ: 178.3, 166.8, 165.9, 130.2, 129.1, 126.6, 125.5, 122.6, 109.4, 78.0, 76.3, 67.1, 66.4, 46.6, 35.7, 18.9, 18.7, -1.3, -1.4.

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