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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†

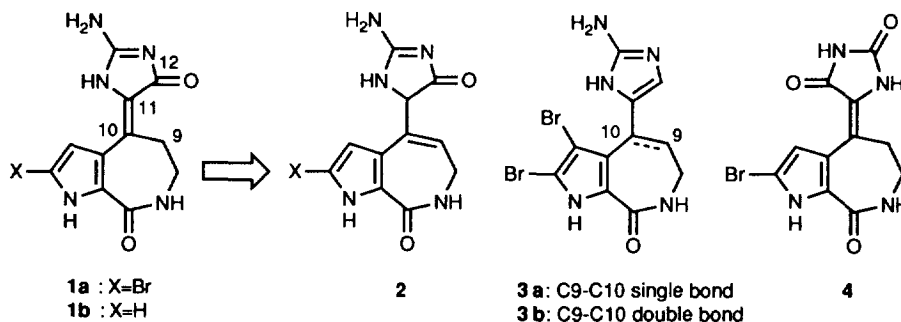
Hirokazu Annoura\* and Toshio Tatsuoka

Suntory Institute for Biomedical Research,

1-1-1, Wakayama-dai, Shimamoto-cho, Mishima-gun, Osaka 618, Japan

**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-imidazolin-5(Z)-disubstituted ylidene ring system.

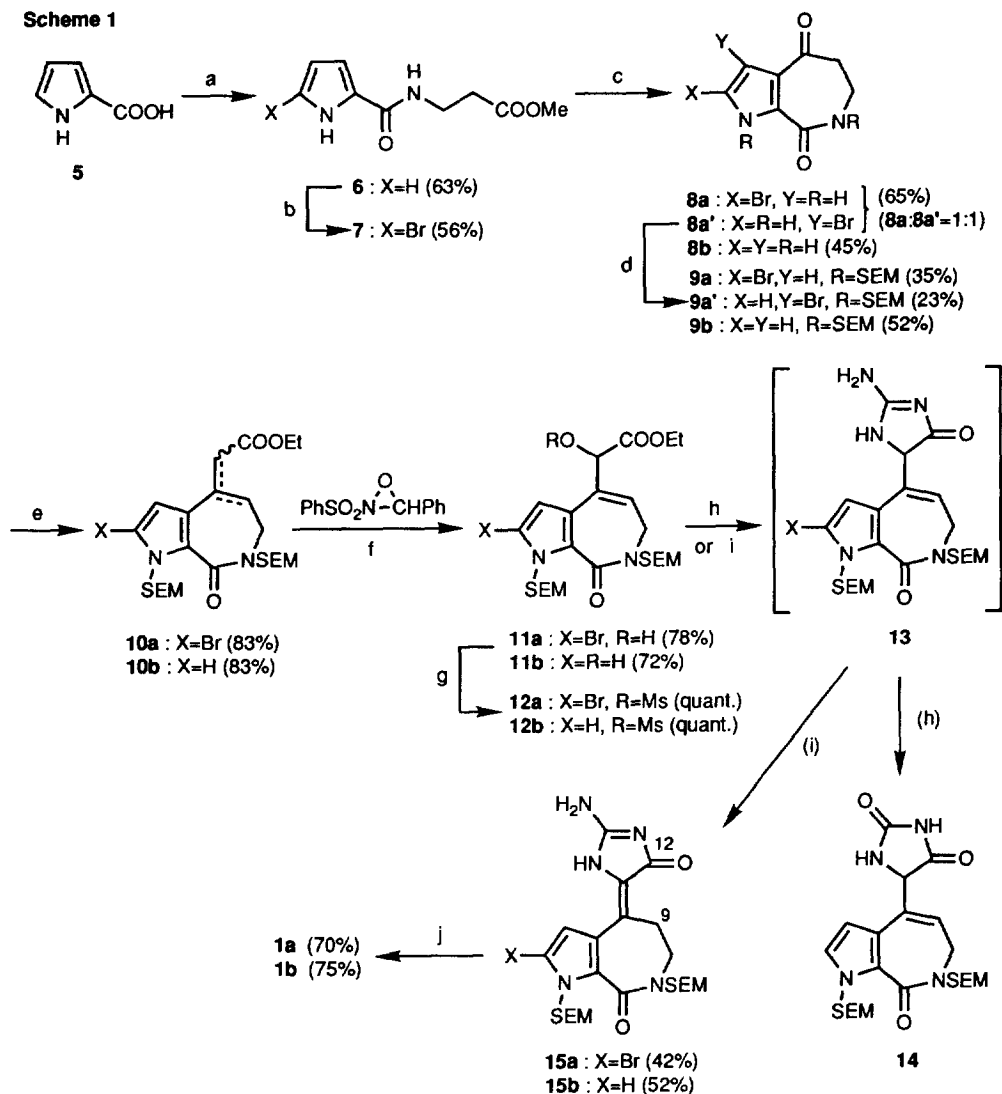
Hymenialdisine (**1a**) was isolated from marine sponges<sup>1</sup> of the genera *Hymeniacidon*, *Acanthella*, *Axinella* and *Pseudaxinyssa*. The structure of **1a** was established on the basis of X-ray crystallography. Debromohymenialdisine (**1b**) was also isolated from sponges<sup>1c-f, 2ab</sup> of the same genera in addition to *Phakellia* and an unidentified Korolevu sponge.<sup>2c</sup> The hymenialdisines (**1ab**) represent a novel class of natural products,<sup>3</sup> including hymenin<sup>4</sup> (**3a**), stevensine<sup>5</sup> (or oriline)<sup>1e</sup> (**3b**), and axinohydantoin<sup>1f</sup> (**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,<sup>1f</sup> hymenin (**3a**) has shown to possess  $\alpha$ -blocking effect.<sup>6</sup> Recently, much attention has been paid to the synthesis of the members of this family because of their structural and biological interest.<sup>7</sup> In this communication, we report the first total synthesis of hymenialdisine (**1a**) and debromohymenialdisine (**1b**).



A successful total synthesis would require an efficient protocol of constructing the 2-amino-4-oxo-2-imidazolin-5(Z)-disubstituted ylidene ring system<sup>8</sup> 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  $\beta,\gamma$ -unsaturated- $\alpha$ -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)  $\text{SOCl}_2$ , cat. DMF, toluene,  $60^\circ\text{C}$ , 1h, then  $\text{H}_2\text{NCH}_2\text{CH}_2\text{COOMe}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , r. t., 3h; (b) NBS, THF, r. t., 2h; (c) 10% aq.  $\text{NaOH-MeOH}$  (2:1), r. t., 5h, then  $\text{PPA-P}_2\text{O}_5$ ,  $100^\circ\text{C}$ , 1h; (d)  $\text{NaH}$  (2 eq.),  $\text{SEMCl}$  (2eq.), DMF, r. t., 2h; (e)  $(\text{EtO})_2\text{POCH}_2\text{COOEt}$ ,  $\text{NaH}$ , DME,  $50^\circ\text{C}$ , 24h; (f)  $\text{KHMDS}$ , THF,  $-78^\circ\text{C}$ , 2h; (g)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ; (h) guanidine,  $\text{AlMe}_3$ , toluene,  $80^\circ\text{C}$ , 4h, then  $\text{CHCl}_3\text{-MeOH-H}_2\text{O}$ ; (i) guanidine, DMF,  $50^\circ\text{C}$ , 5h; (j) 5% aq.  $\text{HCl-MeOH}$  (1:1),  $80^\circ\text{C}$ , 2h.

Treatment of commercially available pyrrole-2-carboxylic acid (**5**) with  $\text{SOCl}_2/\text{cat. DMF}$  in toluene at  $60^\circ\text{C}$ , followed by condensation with  $\beta$ -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<sup>9</sup> (**8a**) and 3-bromoaldisin (**8a'**), presumably due to 1,2-migration of the bromine atom induced by the strong acidic media.<sup>10</sup> 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  $0^\circ\text{C}$ , 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<sup>9,11</sup> (**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  $50^\circ\text{C}$  gave **10a** (83%) and **10b** (83%), respectively, as a mixture of  $\alpha,\beta$ - and  $\beta,\gamma$ -unsaturated esters.<sup>12</sup> Deprotonation of **10ab** with KHMDS in THF at  $-78^\circ\text{C}$  generated the ester anions, which were quenched with 2-benzenesulfonyl-3-phenyloxaziridine<sup>13</sup> to give the  $\alpha$ -hydroxy- $\beta,\gamma$ -unsaturated esters, **11a** (78%) and **11b** (72%), as single regioisomers. Reaction of **11b** with guanidine (1.5 eq.) in the presence of  $\text{AlMe}_3$ <sup>14</sup> (5 eq.) in toluene at  $80^\circ\text{C}$  caused cyclization to afford the hydantoin derivative **14**<sup>15</sup> 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 ( $\text{MeOH}/\text{NH}_3$ ,  $\text{THF}/\text{NH}_3$ ,  $\text{THF}/\text{tetramethylethylenediamine}$  or 10%-aq.  $\text{NaOH}/\text{MeOH}$ ) 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  $\text{DMF}$ <sup>16</sup> at  $50^\circ\text{C}$ , the cyclization proceeded with isomerization of the double bond into the conjugated system in a stereospecific manner to yield the desired products, **15a**<sup>17</sup> (42%) and **15b**<sup>17</sup> (52%), respectively. The stereochemistries of the C10-C11 double bond of **15ab** were determined to be *Z*-configuration by comparison of their NMR data with those of the natural products. In the  $^1\text{H-NMR}$  (400MHz,  $\text{CD}_3\text{OD}$ ), the signals attributable to the C9-methylene protons appeared at  $\delta$  3.37 (triplet,  $J=5.3\text{Hz}$ ) in **15a** and  $\delta$  3.38 (triplet,  $J=5.5\text{Hz}$ ) in **15b**, both of which are shifted to lower field than that of the geometric isomer, axinohydantoin (**4**) ( $\delta$  2.67),<sup>1f</sup> by anisotropic effect of the C12-amide carbonyl group, but correspond very closely to those of hymenialdisine (**1a**) ( $\delta$  3.3)<sup>1a</sup> and debromohymenialdisine (**1b**) ( $\delta$  3.3).<sup>2a</sup> 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  $\text{MeOH}/5\text{-aq. HCl}$  furnished hymenialdisine (**1a**) (70%) and debromohymenialdisine (**1b**) (75%), respectively, after chromatographic purification over silica gel [ $\text{CHCl}_3:\text{MeOH}:\text{H}_2\text{O}$  (2%  $\text{AcOH}$ ) = 65:35:10]. The synthetic samples were identical with authentic samples generously provided by Dr. Randall K. Johnson in TLC behavior and spectroscopic properties ( $^1\text{H}$ - and  $^{13}\text{C}$ -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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## REFERENCES AND NOTES

- † This paper is dedicated to professor Yasumitsu Tamura on the occasion of his 70th birthday.
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9. The aldisins (**8ab**) were obtained from the sponges *Acanthella carteri*,<sup>1d</sup> *Pseudoxinyssa cantharella*,<sup>1e</sup> and *Hymeniacidon aldis*<sup>2c</sup> as well as KMnO<sub>4</sub> oxidation of **1ab**.<sup>1e, 2a</sup> However, it is proposed<sup>2c, 7a</sup> 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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12. When the derivatives protected by acetyl or tosyl group were employed instead of **9ab**, the reaction gave unsatisfactory results: See also ref. 7a.
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15. **14**; <sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 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<sub>2</sub>O), 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<sub>2</sub>O).
16. The reaction using the other solvents such as toluene and tetrahydrofuran gave **15ab** in low yield.
17. **15a**; <sup>13</sup>C-NMR (500MHz, CD<sub>3</sub>OD) 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<sub>3</sub>OD) 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.