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A New Glycociamidine Ring Precursor: Syntheses of (*Z*)-Hymenialdisine, (*Z*)-2-Debromohymenialdisine, and (±)-*endo*-2-Debromohymenialdisine†

Gianluca Papeo,* Helena Posteri, Daniela Borghi, and Mario Varasi

Department of Chemistry, BU-Oncology, Nerviano Medical Sciences, Viale Pasteur 10, 20014 Nerviano (MI), Italy

gianluca.papeo@nervianoms.com

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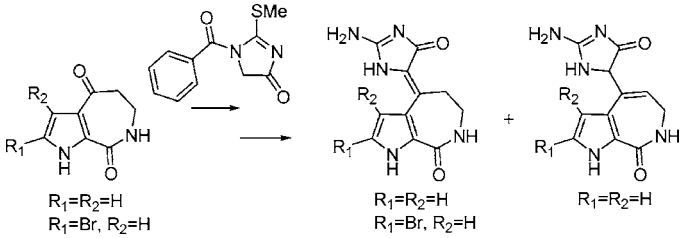
ABSTRACT



The synthesis of the $C_{11}H_5$ marine sponge alkaloids, (*Z*)-hymenialdisine and (*Z*)-2-debromohymenialdisine, is described. A key step was the condensation between aldisine or its monobromo derivative and a new, efficient imidazolinone-based glycociamidine precursor. In the first case, the main product turned out to be the unprecedented (±)-*endo*-2-debromohymenialdisine.

(*Z*)-Hymenialdisine[1] **1**, (*Z*)-2-debromohymenialdisine[2] **2**, and (*Z*)-3-bromohymenialdisine[3] **3** are naturally occurring pyrrole−imidazole alkaloids[4] extracted from marine sponges belonging to the genera *Hymeniacidon*, *Acanthella*, *Axinella* (*syn. Stylissa*), and *Pseudoaxinyssa* (Figure 1). The corresponding (*E*)-isomers are also present in nature;[5] however, (*Z*)-isomers possess superior thermodynamic stability.[3b]

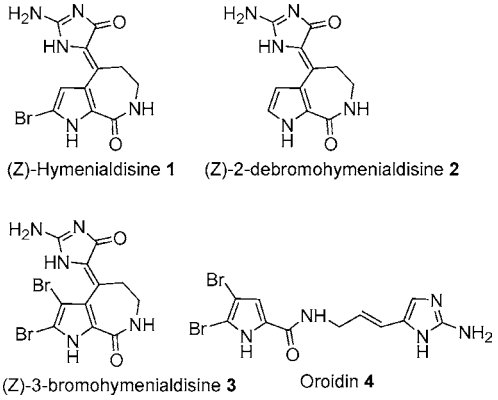


Figure 1.

These secondary metabolites formally represent cyclized derivatives of oroidin **4**, a potent chemical defense substance

* To whom correspondence should be addressed. Tel: +39-0331581537. Fax: +39-0331581757.

† Dedicated to Professor Stephen Hanessian for his seminal contributions to natural product chemistry.

(1) (a) Cimino, G.; De Rosa, S.; De Stefano, S.; Mazzarella, L.; Puliti, L.; Sodano, G. *Tetrahedron Lett.* **1982**, *23*, 767. (b) Kitagawa, I.; Kobayashi, M.; Kitanaka, K.; Kido, M.; Kyogoku, Y. *Chem. Pharm. Bull.* **1983**, *31*, 2321.

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of the aforementioned families of sponges against predatory reef fish[6,7b] (Figure 1).

Biogenesis elucidation of these marine alkaloids still remains a partially unresolved task. However, recent publications[7] help to cast some light on this subject, especially in identifying amino acids proline **5**, ornithine **6**, and histidine **7** as their potential precursors (Figure 2).

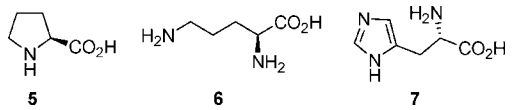


Figure 2.

(*Z*)-Hymenialdisine **1** was found to be a nanomolar inhibitor of mitogen-activated protein kinase 1 (MEK-1),[8] glycogen synthase kinase-3β (GSK-3β),[9] casein kinase 1 (CK1),[9] and different cyclin-dependent kinases (crystals of the complex with CDK2 have been obtained).[9a] Furthermore, (*Z*)-2-debromohymenialdisine **2** was found to possess nanomolar inhibitory activity of the G_2 DNA damage checkpoint and protein kinases Chk1 and Chk2.[10] A number of patents claiming pharmacological activities of these compounds for the prevention and treatment of neurodegenerative disorders,[8] diabetes,[11] inflammatory pathologies,[11] cancer,[8,12] osteoarthritis,[13] and ocular disorders[14] have recently appeared. These data prompted us to devise a common short synthetic pathway to the most biologically relevant alkaloids, namely, **1** and **2**. Large-scale preparation of (*Z*)-2-debromohymenialdisine **2**[15,16] and (*Z*)-3-bromohymenialdisine **3**[15] has been recently described. On the other hand, total synthesis of (*Z*)-hymenialdisine **1**, the most pharmaceutically intriguing compound in the triad, was accomplished by Annoura's[17a] and Horne's[17b] groups in the 1990s. Well-precedented disconnection showed aldisine **8a**[17,18a,19] and 2-bromoaldisine **8b**[17a] as promising intermediates for achieving our goals (Figure 3).

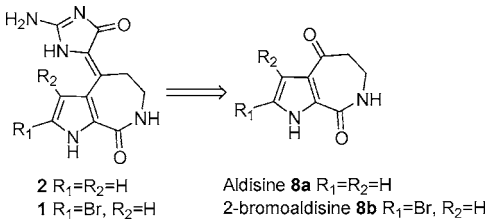
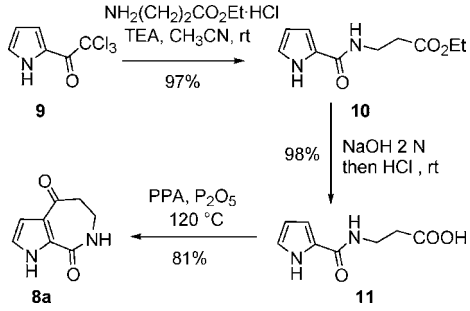


Figure 3.

Thus, reacting the commercially available 2-trichloroacetylpyrrole **9** with ethyl 3-aminopropionic acid hydrochloride led to amide **10**, which underwent alkaline hydrolysis to give acid **11**. After intramolecular cyclization, we obtained the required aldisine **8a** in an improved 78% overall yield without resorting to a time-consuming continuous extraction[18b] (Scheme 1).

Scheme 1



We then proceeded to the more synthetically challenging 2-bromoaldisine **8b**. The previously reported preparation[17a] suffered from the observed bromine atom scrambling during the PPA/P_2O_5-mediated cyclization step. Furthermore, regioselective bromination of the pyrrole amide **10** proved to be much more difficult than expected.

Contrary to the previously reported results[17a] on the corresponding methyl ester, bromination in THF using NBS

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(9) (a) Meijer, L.; Thunnissen, A. M.; White, A. W.; Garnier, M.; Nikolic, M.; Tsai, L. H.; Walter, J.; Cleverley, K. E.; Salinas, P. C.; Wu, Y. Z.; Biernat, J.; Mandelkow, E. M.; Kim, S. H.; Pettit, G. R. *Chem. biol.* **2000**, *7*, 51. (b) Meijer, L. Eur. Patent Appl. EP 1106180, 2001, 38 pp.

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(13) (a) Inoue, H.; Takamori, M.; Nagata, N.; Nishikawa, T.; Oda, H.; Yamamoto, S.; Koshihara, Y. *Inflamm. Res.* **2001**, *50*, 65. (b) Chipman, S.; Faulkner, D. J. U.S. Patent 5591740, 1997, 11 pp. (c) DiMartino, M.; Wolff, C.; Patil, A.; Nambi, P. *Inflamm. Res.* **1995**, *44*, 123.

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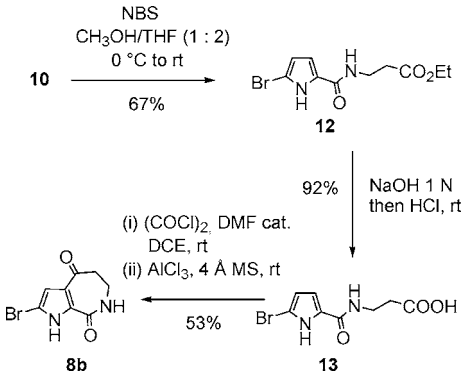
delivered 2-bromopyrrole amide **12** in only 28% yield. Eventually, using a set of reaction conditions reported by Feldman and Saunders[19a] and later by Hale et al.,[19b] a regioselective bromination was achieved affording **12** in 67% yield (Scheme 2). Subsequent hydrolysis secured acid **13**, the desired precursor for intramolecular cyclization.

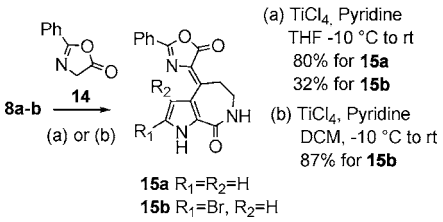
Scheme 2



We then applied milder Friedel−Crafts-type cyclization conditions to the unstable acyl chloride derived from **13** in a one-pot process that added $AlCl_3$ and 4 Å molecular sieves as an acid scavenger. By this method, 2-bromoaldisine **8b** was obtained without any bromine scrambling in an improved 53% yield (Scheme 2).

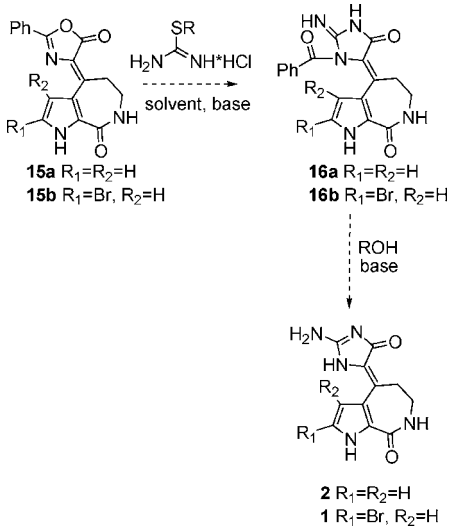
At this point, the main issue remained the incorporation of the glycociamidine ring. We first capitalized on the observation made by Tepe et al.,[20] who recently succeeded in condensing the commercially available phenyloxazolone **14** on indoloazepinedione derivatives, using the previously reported[21] Ti(IV)/pyridine combination of reagents. Using these reaction conditions, aldisine **8a** cleanly afforded **15a** in excellent yield (Scheme 3).

Scheme 3



However, 2-bromoaldisine **8b** delivered the expected tricyclic derivative in only 32% yield. We attributed the observed poor reactivity to the low solubility of **8b** in THF. Indeed, changing the reaction solvent from THF to DCM afforded **15b** in 87% yield. Despite a clear prevalence of one isomer in both **15a** (4:1) and **15b** (>9:1), the lack of nOe effects did not allow us to establish the double bond geometry of the major isomers. The final step of this approach required our conversion of the phenyloxazolone moiety into the corresponding glycociamidine[22] via a ring-opening/ring-closing one-pot sequence, based on the counter-attack principle[23] (Scheme 4).

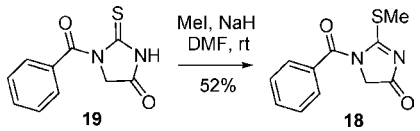
Scheme 4



Commonly used nucleophilic solvents for this type of transformation, such as ethanol or 2-propanol, acted competitively in the ring-opening step.[24] Use of a poorly nucleophilic solvent (*t*-BuOH) for the first stage of the process (Scheme 4) followed by introduction of the nucleophilic environment (MeOH), required for the removal of the benzoyl protecting group, was also unproductive. Failure of this strategy has been attributed to the (base-enhanced) presence of poorly electrophilic enolate/azafulvene-type tautomers.

These previous unsuccessful attempts prompted us to design a new imidazolinone-based glycociamidine ring precursor. Thus, unprecedented compound **18** would behave like **14** in the condensation step. 1-Benzoyl-2-methylsulfanyl-1,5-dihydroimidazol-4-one **18**, easily obtained on a multigram scale by *S*-methylation of *N*-benzoylthiohydantoin **19**[25] (Scheme 5), turned out to be the reagent of choice in this respect.

Scheme 5



The condensation reactions were performed in a fashion similar to the one applied when the phenyloxazolone was

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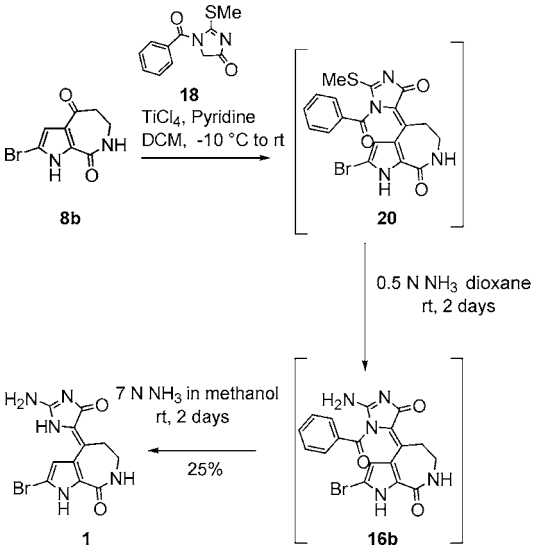
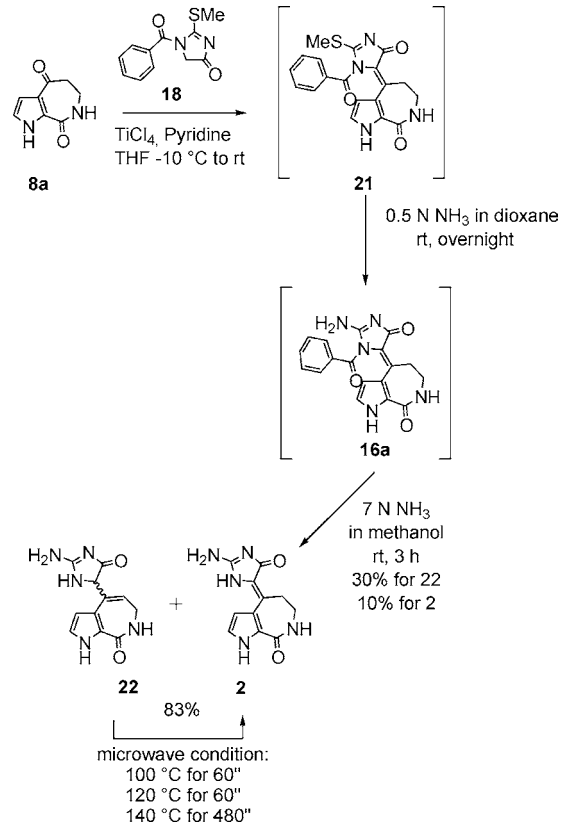
Scheme 6



used as the reagent (Scheme 6 and Scheme 7). DCM proved to be mandatory in order to successfully achieve the condensation with 2-bromoaldisine **8b** (Scheme 6).

The condensation products **20** and **21** appeared to be sensitive to both adventitious nucleophiles and chromatography. They, therefore, had to be immediately processed without isolation. Fine-tuning of the nitrogen source was then required in order to complete the synthesis. This was performed by first adding diluted (0.5 N) ammonia solution in dioxane to secure the displacement of the methylthio group, while leaving the benzoyl-protective group untouched. Subsequent evaporation of the solvent and exposure of the crude mixture of **16a** and **16b** to concentrated (7 N) ammonia solution in methanol resulted in the clean removal of the aforementioned protective group.

Scheme 7



Surprisingly, while (*Z*)-hymenialdisine **1** (Scheme 6) was synthesized by this one-pot three-step methodology in moderate overall yield (25%), the main product (30%), arising from application of the same protocol (Scheme 7) onto the unsubstituted aldisine **8a**, turned out to be the (±)-*endo*-2-debromohymenialdisine **22**, along with the expected (*Z*)-2-debromohymenialdisine **2** (10%). This could retrospectively be explained by comparison of the pK_as of the unsubstituted pyrrole versus the corresponding 2-bromopyrrole. The enhanced acidity of the latter,[19b] along with longer reaction times, ensured the positioning of the double bond into the more thermodynamically stable *exo*-(*Z*)-orientation.[3b] The isolation of the unprecedented *endo*-isomer **22** does help shed light on the biosynthetic path of the oxidative cascade from aminoimidazole- (i.e., hymenin,[7b] stevensine[7b,c]) to glycociamidine-containing alkaloids.

Finally, the high yield (83%) conversion of **22** into the more thermodynamically stable **2** could be readily accomplished by exposing the *endo*-isomer to diluted aqueous ammonia under irradiation conditions.

In conclusion, intermediate ketones **8a** and **8b** have been efficiently prepared (78 and 35% overall, respectively), overcoming problems with low overall yields, regioselective bromination, and bromine atom scrambling during the cyclization step. Tuning the previously reported glycociamidine precursors allowed us to synthesize the unprecedented imidazolinone **18**. Condensation of this reagent with the corresponding ketones, followed by treatment with ammonia in different solvents, afforded **1**, **2**, and the hitherto unreported (±)-*endo*-2-debromohymenialdisine **22** in moderate overall yield. The latter was easily isomerized to the target (Z)-2-debromohymenialdisine **2** by use of aqueous ammonia under microwave irradiation. Ongoing biological evaluation of **22** as well as the application of **18** to the synthesis of parent axinohydantoin alkaloids will be the subject of further communications.

Supporting Information Available: Experimental details and analytical data for most relevant synthetic intermediates and final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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