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Concise synthesis of Didebromohamacanthin A and Demethylaplysinopsine: Addition of Ethylenediamine and Guanidine Derivatives to the Pyrrole-Amino Acid Diketopiperazines in Oxidative Conditions

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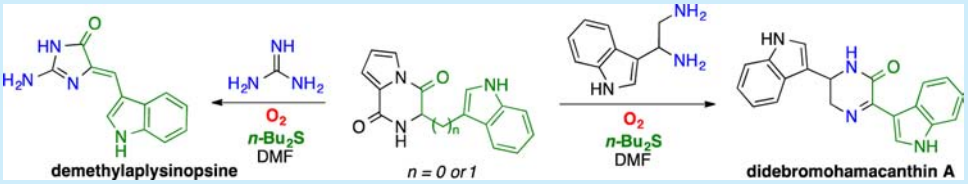
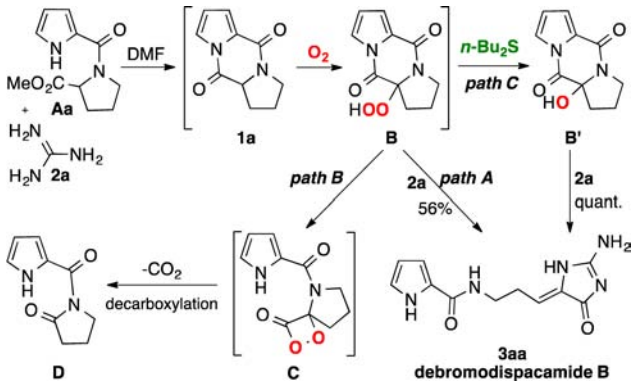
Supporting Information



ABSTRACT: Oxidative nucleophilic addition of ethylenediamine and guanidine derivatives to pyrrole-amino acid diketopiperazines was shown to provide substituted 5,6-dihydro-2(1*H*)-piperazinones, quinoxalinones, and 2-aminoimidazolones. On the basis of this methodology, a concise approach to natural products didebromohamacanthin A and demethylaplysinopsine has been demonstrated.

In the course of our studies on biomimetic syntheses of the pyrrole-2-aminoimidazole alkaloids, we reported the unexpected oxidative conversion of the pseudopeptide derived from pyrrole-2-carboxylic acid and methyl ester of proline **Aa** into debromodispacamide B **3aa**, a natural product belonging to this family.[1] This cascade transformation proceeds in the presence of guanidine **2a** as a base and air oxygen and includes the nucleophilic addition of guanidine to oxidized pyrrole-proline diketopiperazine **1a** formed in situ (path A, Scheme 1). Along with the addition product, we also observed the formation of the side product **D** resulting from decarboxylation of the probable intermediate 1,2-dioxetanone **C** (path B). Recently our detailed studies of this reaction revealed that the main product of the pyrrole-assisted diketopiperazine autoxidation was diketopiperazine hydroperoxide **B**.[2] It was also found that this oxidation in the presence of a mild reducing agent such as di-*n*-butyl sulfide or triphenylphosphine afforded the corresponding hydroxy derivative in excellent yield by in situ reduction of the primary hydroperoxyde **B**. As a result, the side decarboxylation could be completely suppressed.

Scheme 1. Oxidative Rearrangement of Pyrrole-Proline Pseudopeptide into Debromodispacamide



We next investigated the synthetic applications of the reaction, and we report here the extension of this methodology to (i) other bis-nucleophilic entities as urea, thio-urea, and substituted ethylendiamines and (ii) other α-amino acid partners, which allows an easy access to a number of natural alkaloids and their analogues.[3] As an example of synthetic application of this approach, we also described a rapid access to didebromohamacanthin A[4] and the aplysinopsine skeleton.[5]

As previously reported, debromodispacamide B **3aa** was obtained from pyrrole-proline diketopiperazine **1aa** and guanidine **2a** in moderate yield (56%) (Scheme 1, path A).[1c] To our delight, the presence of *n*-Bu_2S at 60 °C improved the reaction significantly, i.e., **3aa** was obtained in nearly quantitative yield (Table 1, entry 3) for 2 h (path C). Seemingly, the reducing *n*-Bu_2S blocks the path B leading to the formation of the decarboxylated product **D**. Indeed, in the presence of the *n*-Bu_2S, hydroperoxide **B** (Scheme 1) was reduced cleanly into hydroxy **B′**, which could be transformed smoothly into **3aa** as a consequence of nucleophilic attack of guanidine **2a**.

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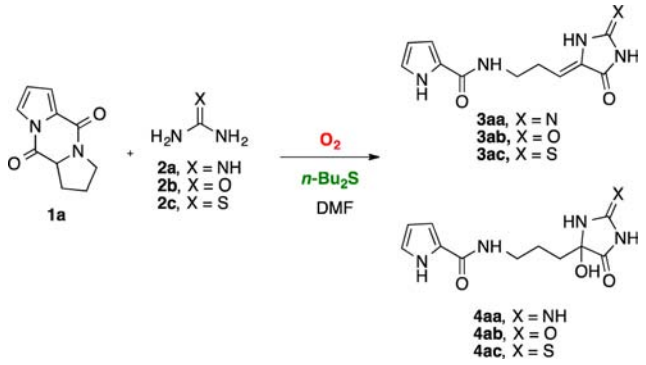
Table 1. Reaction of Diketopiperazine 1a with Guanidine Analogues 2a−c in the Presence of O_2/n-Bu_2S

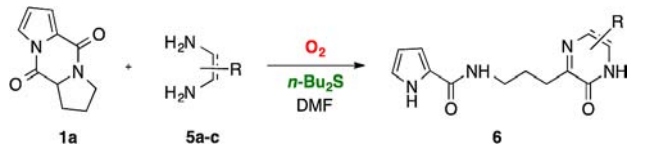


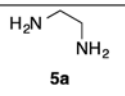
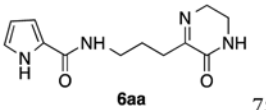
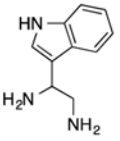
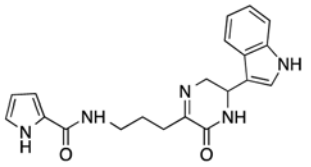
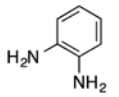
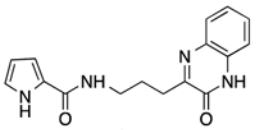
entry	2	conditions	3, yield (%)	4, yield (%)
1	2a	60 °C, 1 h	3aa, 90	4aa, 0
2	2a	rt, 1.5 h	3aa, 15	4aa, 80
3	2a	rt, 1 h then 60 °C, 1 h	3aa, 95	4aa, 0
4	2b	rt, 2 h, DBU (2 equiv)	3ab, 40	4ab, 0
5	2c	rt, 2.5 h, DBU (1.5 equiv)	3ac, 0	4ac, 55

Running the same reaction at room temperature led to 5-hydroxy-2-aminoimidazolidinone **4aa** in 80% yield together with the debromodispacamide B **3aa** in 15% yield (Table 1, entry 1). Subsequent heating (rt, then 60 °C) of the reaction mixture completed the dehydratation step and afforded **3aa** in 95% yield. The configuration of the double bond was assigned to be (*Z*) ($^3J_{C-H}$ = 5.2 Hz) as in the case of debromodispacamide B (**3aa**).[1c] It is noteworthy that **3aa** has previously been prepared by Lindel as a mixture of *Z*/*E* stereoisomers by condensation of hydantoin phosphonate or thiohydantoins with the requisite y-amino aldehyde.[6] As far as we are concerned, we wanted to test our reaction with other bis-nucleophiles than the guanidine. Under the same conditions, urea and thiourea were found to be less reactive than guanidine and afforded the dispacamide derivatives only in the presence of a strong base such as DBU. Addition of urea **2b** to the diketopiperazine **1a** was followed by a spontaneous dehydratation step even at room temperature and led to a debromo analogue **3ab** of the natural product mukanadine B[7] in 40% yield. Interestingly, in the case of thiourea **2c**, the reaction of **1a** furnished exclusively 5-hydroxy substituted thiohydantoin **4ac** in 55% (Table 1, entry 5). Attempts to dehydrate this compound by simple heating of the reaction mixture led only to unidentified degradation products.

With success in the synthesis of hydantoins imino- and thio-imidazolidinones **3** and **4**, we set about to extend this methodology to the ethylenediamine series to provide 5,6-dihydro-2(1*H*)-piperazinone and quinoxalin-2-one cores (Table 2). Addition of ethylenediamine **5a** to the diketopiperazine **1a** led to desired 5,6-dihydro-2(1*H*)-piperazinone **6aa** at room temperature in 75% yield (Table 2, entry 1). However, when (indol-3-yl)-1,2-diaminoethane **5b**[8] was used as nucleophile under the same conditions, the piperazinone **6ab** was obtained in only 33% yield with longer reaction time, along with unidentified polar side products possibly issued from the oxidation of the unprotected indole moiety (Table 2, entry 2). *o*-Phenylenediamine **5c** was also tested and was found to be less reactive than its aliphatic analogue **5a** in this reaction. The formation of the quinoxalinone ring was achieved only by heating at 80 °C, affording **6ac** in 55% yield (Table 2, entry 3).

Table 2. Reaction of Diketopiperazine 1a with 1,2-Diamines: Synthesis 5,6-Dihydro-2(1*H*)-piperazinone and Quinoxalinone



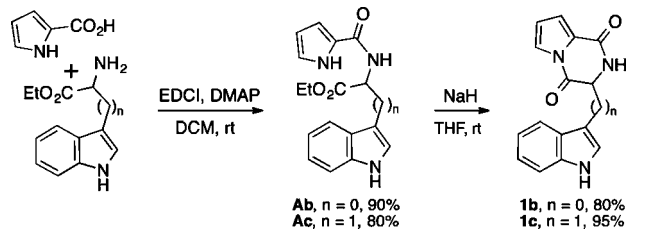
entry	5a-c	conditions	6, yield (%)
1	 5a	4 equiv	rt, 5 h	 6aa	75
2	 5b	1.3 equiv	rt, 15 h	 6ab	33
3	 5c	2 equiv	80 °C, 2 h	 6ac	55

In contrast to the five-membered ring in **3aa−3ac** and as expected for the six-membered ring in **6aa−6ac**, the subsequent dehydratation led to the formation of a more stable favorable endocyclic double bond in all these cases.[9] The regioselectivity of the reaction was determined by HMBC correlations (see Supporting Information).

To further extend the synthetic scope of this reaction, next we investigated the reactivity of diketopiperazines derived from such α-amino acids as tryptophan and (indol-3-yl)glycine. These amino acids were chosen on the basis of their possible application to the synthesis of indole alkaloids.

The diketopiperazine **1b** was prepared by the coupling of pyrrole-2-carboxylic acid and ethyl (indol-3-yl)glycinate[10] followed by base-induced cyclization (Scheme 2). The tryptophan-derived diketopiperazine **1c** was prepared by the same procedure as described earlier.[3]

Scheme 2. Synthesis of Diketopiperazine 1b,c



Reaction of diketopiperazine **1c** with guanidine **2a** under standard condition afforded the demethyl analogue of a natural product aplysinopsine **7ca** also as the (*Z*)-isomer ($^3J_{C-H}$ = 5.2 Hz) in one step, albeit in low yield of 20% (Scheme 3). Again, the oxidation of the unprotected indole moiety was probably responsible for the low yield due to numerous unidentified

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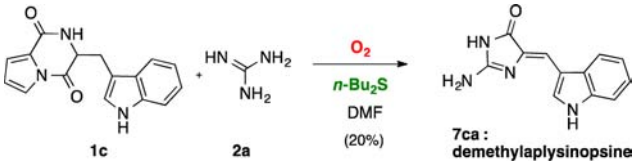
Scheme 3. Demethylaplysinopsine Synthesis



byproducts. Despite the low yield, this method has some advantage, particularly for the combinatorial synthesis of analogues, as previously reported approaches to aplysinopsine include lengthy multistep protection−deprotection sequences.[11]

Reactions of diketopiperazine derived from (indol-3-yl)-glycine **1b** with ethylenediamine derivatives **5a,b,d** were selected for testing in connection with the synthesis of alkaloids of the hamacanthine family (Table 3). Thus, reaction with

Table 3. Reaction of Diketopiperazine 1b and Indolic 1,2-Diamines: Synthesis of the Hamacanthine Skeleton

entry	5	8	yield (%)
1	4 equiv	8ba	22
2	1.3 equiv	8bb dedibromohamacanthin	15
3	1.3 equiv	8bd	21

unsubstituted ethylenediamine **5a** at room temperature led to the model 5,6-dihydro-2(1*H*)-piperazinone **8ba** in 22% yield (Table 3, entry 1), as compared to 75% yield for proline-derived diketopiperazine **1a** under the same conditions (Table 2, entry 1).

The addition of (indol-3-yl)-1,2-diaminoethane **5b** to diketopiperazine **1b** afforded the desired natural alkaloid didebromohamacanthin A **8bb**[12] in 15% yield (Table 3, entry 2). In an attempt to reduce the undesirable oxidation of the sensitive indole moiety, (*N*-Boc-indol-3-yl)ethylenediamine **5d**[13] was used as bis-nucleophile (Table 3, entry 3). As expected, *N*-Boc-protected didebromohamacanthin A **8bd** was obtained in a comparable yield as in the model reaction with ethylenediamine **5a** (Table 3, entry 1).

In conclusion, we demonstrated that the spontaneous oxidation of pyrrole-amino acid diketopiperazines **1** followed by the in situ reaction with bis-nucleophiles **2** and **5** provided a concise access to imidazolidinone and piperazinone cores, including natural indole alkaloids didebromohamacanthin A and demethylaplysinopsine and their analogues.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, product characterization, and copies of the ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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