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# A Likely Biogenetic Gateway Linking 2-Aminoimidazolinone Metabolites of Sponges to Proline: Spontaneous Oxidative Conversion of the Pyrrole-Proline-Guanidine Pseudo-peptide to Dispacamide A

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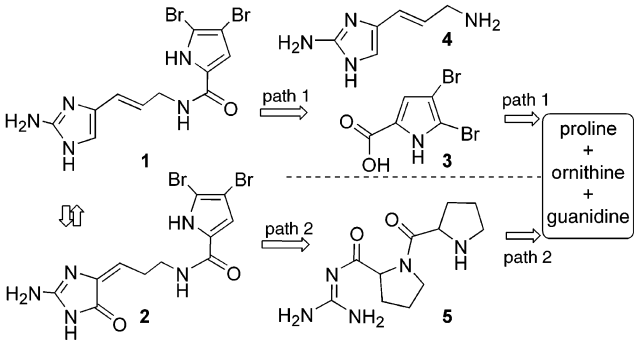
A number of structurally related biologically active pyrrole 2-aminoimidazole metabolites have been isolated worldwide from marine sponges belonging to the Agelasidae, Axinellidae, and Halichondriidae families.[1] Among these is oroidin (**1**),[2] which is the formal biogenetic building block and is considered to be the key precursor in the elaboration of polycyclic $C_{11}N_5$ "oroidin" derivatives.[3] The isolation of dispacamide A (**2**)[4] from phylogenetically related sponges raises the question as to which of **1** or **2** is the forerunner. These two compounds are frequently found in sponges together with their closely related polycyclic derivatives. Thus, the common metabolic intermediates **1** and **2** are good candidates for linking amino acid precursors to the pyrrole 2-aminoimidazole family.

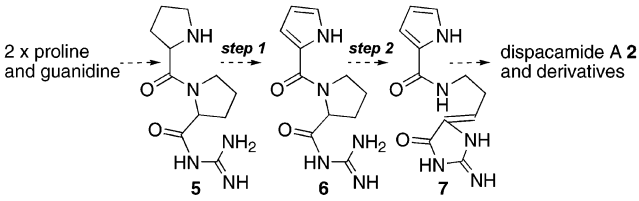
Although these compounds are important for their pharmacological activities[5] and for chemotaxonomic considerations,[1] their biosynthesis remains in question. From an ecological point of view, the antipredatory role of oroidin-based alkaloids could be their most important biological function.[6] Kitagawa[7] and later Braeckman and Van Soest[1] proposed that proline, ornithine, and guanidine are probable precursors of both the bromopyrrole and 2-aminoimidazolinone moieties (Scheme 1, paths 1 and 2). Ornithine and proline have been respectively used in the synthesis of "oroidin-based" dibromophakellin by Büchi[8] and dibromophakellstatin by Romo.[9] Kerr[10] has conducted what is so far the only biosynthetic experiment in cell cultures of the sponge which produces stevensine (odiline).[11] The study showed that [$^{14}$C]-labeled proline, ornithine, and histidine were incorporated into stevensine. Natural compounds **3** and **4** were proposed as intermediates. We have considered that the pseudo-dipeptide pyrrole-proline-guanidine **6** (Scheme 2) could be the precursor leading to the amide-connected $C_{11}N_5$ pyrrole and 2-aminoimidazolinone sections. Our choice was also influenced by the intriguing fact that the metabolism of proline in some plants and microorganisms is known to be stress dependent.[12] Although the ecological role of proline in sponges is not known, one can suppose that its role under stress conditions is also crucial. Thus, if proline is involved in $C_{11}N_5$ formation under oxidative conditions, this would be in accordance with the ecological role of "oroidin-based" alkaloids used by sponges as a chemical arsenal for their defense. The first specific step in pyrrole 2-aminoimidazole biosynthesis would involve proline-based peptide synthesis of **5** (Scheme 2), followed by oxidation of the proline to pyrrole section and then by the oxidation rearrangement of proline-guanidine moiety to the 2-aminoimidazolinone (**7**). We have tested step 2, considering that the self-catalyzed intramolecular transamination reaction transforming **6** into **7** would be the critical step of the biomimetic process.

The required pseudo-peptide **10** (Scheme 3) was prepared from pyrrole-2-carboxylic acid (**8**) and L-proline methyl ester (**9**) using standard reactions.[13,14] Activation of **10** via N1−C cyclization to **11** was cleanly performed in THF in the presence of NaH at 0 °C.

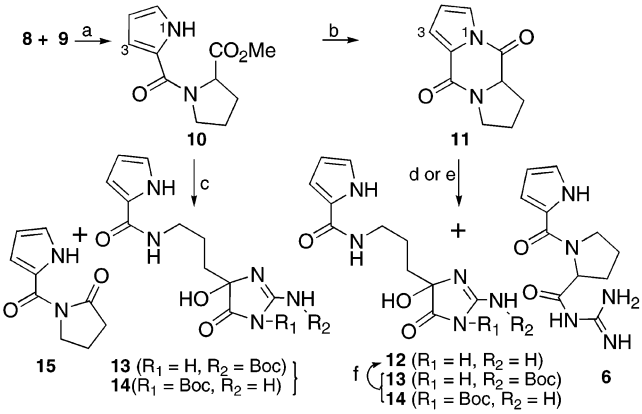
***Scheme 1.*** Possible Biogenetic Sequences Relating Proline/Ornithine to Oroidin (**1**) and Dispacamide (**2**)




***Scheme 2.*** Sequential Pyrrole and 2-Aminoimidazolinone Sections Formation




***Scheme 3*** [a]



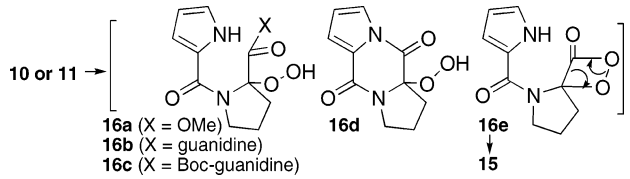

[a] Reagents and conditions: (a) $CH_2Cl_2$, EDCI, DMAP, 0 °C, 90%; (b) NaH, THF, 0 °C, 74%; (c) THF, Boc-guanidine, 3 h reflux, **13** + **14** (46%) and **15** (7%); (d) THF, guanidine (HCl), NaOH (1.2 equiv), 1 h, **6** (44%) and **12** (42%); (e) $CH_2Cl_2$, Boc-guanidine, rt, 1 night, **13** + **14** (42%); (f) $CH_2Cl_2$, TFA, rt, quantitative.

The unsymmetrical compound **11** showed high sensitivity to nucleophilic agents. To our delight, in the presence of guanidine, **11** gave intermediate **6** in 44% yield, together with the oxidized 2-aminoimidazolinone **12** in 42% yield. Running the same reaction with Boc-guanidine led to the 2-aminoimidazolinone regioisomers

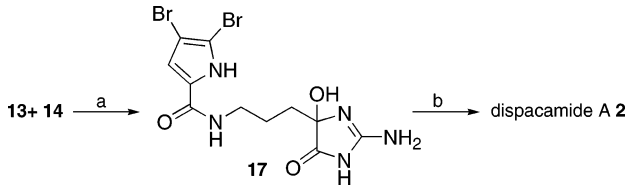


**10.1021/ja047574e CCC: $27.50** 

***Scheme 4.*** Possible Peroxide Intermediates




***Scheme 5*** [a]




[a] Reagents and conditions: (a) (i) AcOH, $Br_2$, rt, (ii) $CH_2Cl_2$, TFA, rt, 74%; (b) $CH_3SO_3H$, 80 °C, 65%.

**13** + **14** in 42% yield. Direct reaction of methyl ester **10** with Boc-guanidine also gave **13** + **14** in 46% yield and the decarboxylated compound **15** in 7% yield. To the best of our knowledge, this is the first example of an oxidative rearrangement of a proline-guanidine skeleton into a substituted 2-aminoimidazolinone. Importantly, the transamination reaction occurs under mild conditions and requires air oxygen. When the reaction with guanidine was run under argon in degassed solvent, no rearrangement of proline to 2-aminoimidazolinone was observed.

The mechanism of the reaction seems to be close to that described for bioluminescent reaction involving the formation of dioxetanones in marine organisms.[15]

Formation of the byproduct **15** from **10** (Scheme 4) in the presence of guanidine and air oxygen confirms the suggested mechanism occurring through the species **16a**−**e**. The presence of guanidine is important for the catalyzed enolization/oxidation of **10** and **11** to **16a**−**e**. Subsequent dismutation and intramolecular transamination of **16b** and **16c** lead to **12** and the regioisomers **13** + **14** respectively. Loss of $CO_2$ from the dioxetanone **16e** gives **15**.

This is an efficient aerobic oxidation under atmospheric pressure and without any catalyst or addition of oxidant. The intramolecular nucleophilic substitution by guanidine and the dismutation of peroxide lead to the cleavage of the crucial N−C bond of proline and the formation of the 2-aminoimidazolinone **12**, whose structure is very close to those of natural dispacamide A (**2**) and mauritamide A.[16] The dispacamide A (**2**) synthesis (Scheme 5) was accomplished by dibromination of the mixture **13** + **14** using 2 equiv of bromine, followed by TFA-promoted Boc deprotection to **17** in 74% yield for both steps. Subsequent dehydration by treatment with methanesulfonic acid gave dispacamide A (**2**) in 65% yield.[17]

In summary, a new biomimetic spontaneous conversion of proline to 2-aminoimidazolinone derivatives using a self-catalyzed intramolecular transamination reaction together with peroxide dismutation as a key step is described. The reaction requires the *N*-acylation of proline by pyrrole-2-carboxylic acid and the presence of air oxygen. This result also points to dispacamide A (**2**) as the forerunner of oroidin (**1**). Natural compounds **3** and **4** are probably hydrolysis products of oroidin (**1**) and not the precursors. We are continuing our investigations in order to deepen our understanding of the mechanism of the reaction and to discover additional transformations linking the triad pyrrole-proline-guanidine with other polycyclic "oroidin-based" alkaloids. The study of the pH-dependent behavior of the key intermediate **17** is underway and will be reported in due course.

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**Supporting Information Available:** Detailed experimental procedures and characterization for **2**, **10**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Note that heating of **12** or the protected derivatives (**13** and **14**) in TFA did not lead to the dehydrated compound but to polycyclic derivatives. The latest results will be published as a full paper in due course.

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