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# SYNTHESIS OF CERATINAMINE AND MOLOKA'IAMINE: ANTIFOULING AGENTS FROM THE MARINE SPONGE *Pseudoceratina purpurea*

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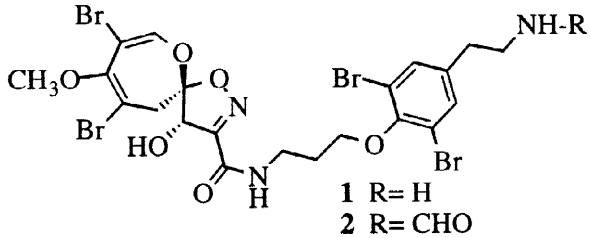
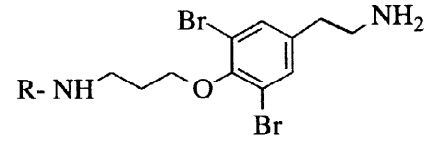
***Abstract:*** Syntheses of the title compounds (**4** and **5**, respectively) are described together with a biogenetic hypothesis that rationalizes the origin of ceratinamine's unique cyanoformamide functionality.


Tin-containing antifouling paints, which prevent the growth of marine organisms on ships' hulls that increases hydrodynamic drag, are associated with several significant environmental problems, including acute toxicity in marine mammals, long-term reproductive effects, and increased shell thickness in crustaceans.[1,2] Since 1987, a ban on tin-containing paints has been enforced in Europe, North America, and Australasia, prompting the quest for safe and effective alternatives.

Several laboratories have searched for natural antifouling agents in marine organisms, where potent chemical defense systems keep the larvae of predators from settling and attaching to their prey. Many of the active antifouling compounds identified to date are bromotyrosine derivatives, including psammaplysin A **1** from the verongid sponge *Psammaplysilla purpurea*.[3] Together with **1**, ceratinamide A **2**, ceratinamide B **3**, ceratinamine **4** and moloka'iamine **5** have been isolated from the sponge *Pseudoceratina purpurea* collected near Japan.[4,5] Here we report practical and efficient total syntheses of ceratinamine, the first example of a cyanoformamide-containing natural product, as well as moloka'iamine. The cyanoformamide in **4** is seen to arise as part of a unified scheme for the biogenesis of **1-5** from a common bromotyrosine-derived precursor.




**1** R= H
**2** R= CHO
**3** R= $CO(CH_2)_{11}CH(CH_3)_2$




**4** R= COCN
**5** R= H

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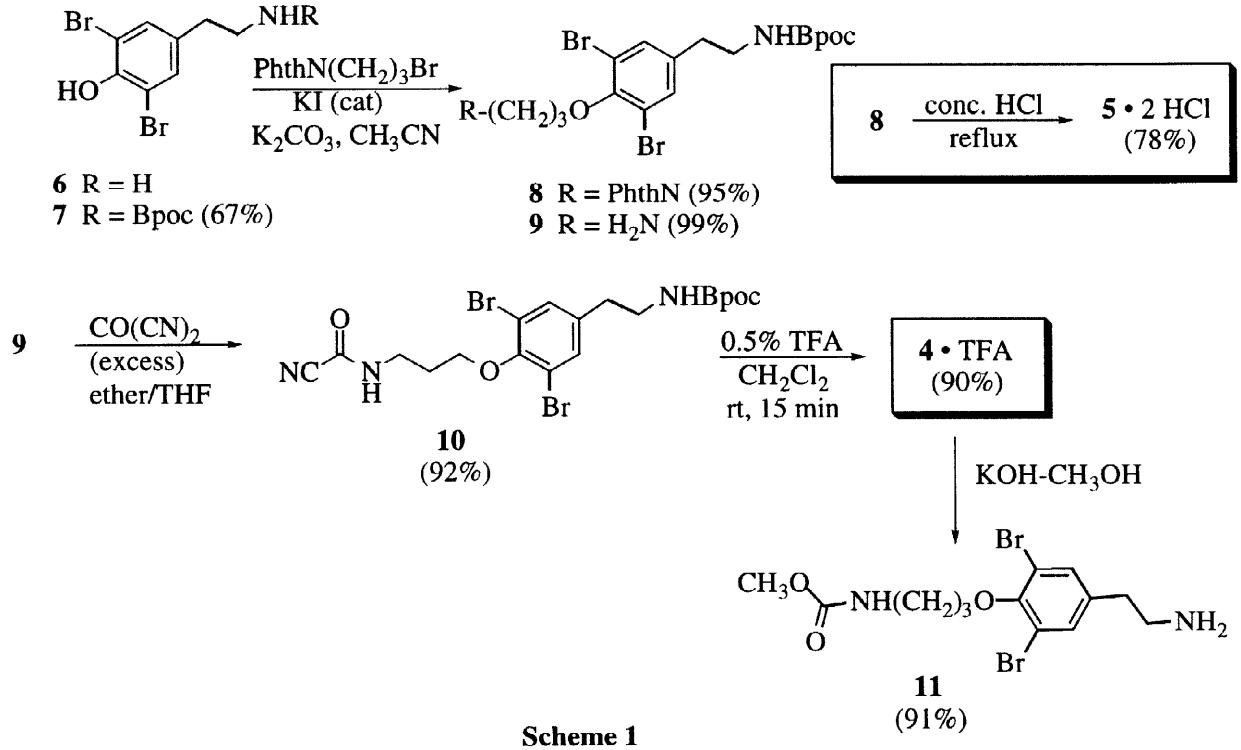
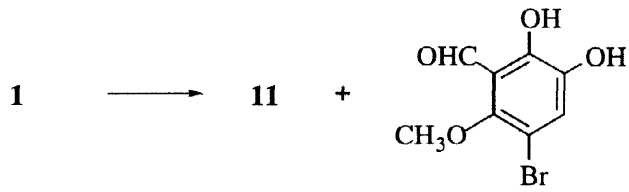
Retrosynthetic analysis suggested that both **4** and **5** might be accessible from a congener of **5** having an appropriately protected aminoethyl group. Planning a deprotection strategy, however, was limited by the scant literature on ceratinamine, and on cyanoamides in general.[6,7] Fortunately, the isolation of **4** involved a successful HPLC purification using $CH_3CN$-$H_2O$ containing 0.01% trifluoroacetic acid (TFA), conditions under which rapid cleavage of the acid-labile 2-(4-biphenylyl)-prop-2-yloxycarbonyl (Bpoc) protecting group[8] was expected to occur. Condensation of dibromotyramine **6** (Scheme 1)[9] with Bpoc-$OC_6H_4$(p-$CO_2CH_3$) (Fluka) using Triton B catalyst[10] afforded **7**, which was subsequently aminopropylated to give aminoether **9** in high yield after deprotection. Direct deprotection of **8** afforded moloka'iamine **5**• 2 HCl (mp >300 °C) whose $^1$H-NMR spectrum was identical with that of a naturally derived sample. Acylation of **9** with carbonyl cyanide, prepared using a slight modification[7] of the *Organic Syntheses* procedure,[11] furnished **10** (92%). Removal of the Bpoc group with dilute acid gave ceratinamine **4**•TFA (90%, mp 133-4 °C), which was spectroscopically identical with an authentic sample. Overall, the synthesis produced **4** in 5 steps and 52% yield from dibromotyramine.




**Scheme 1**

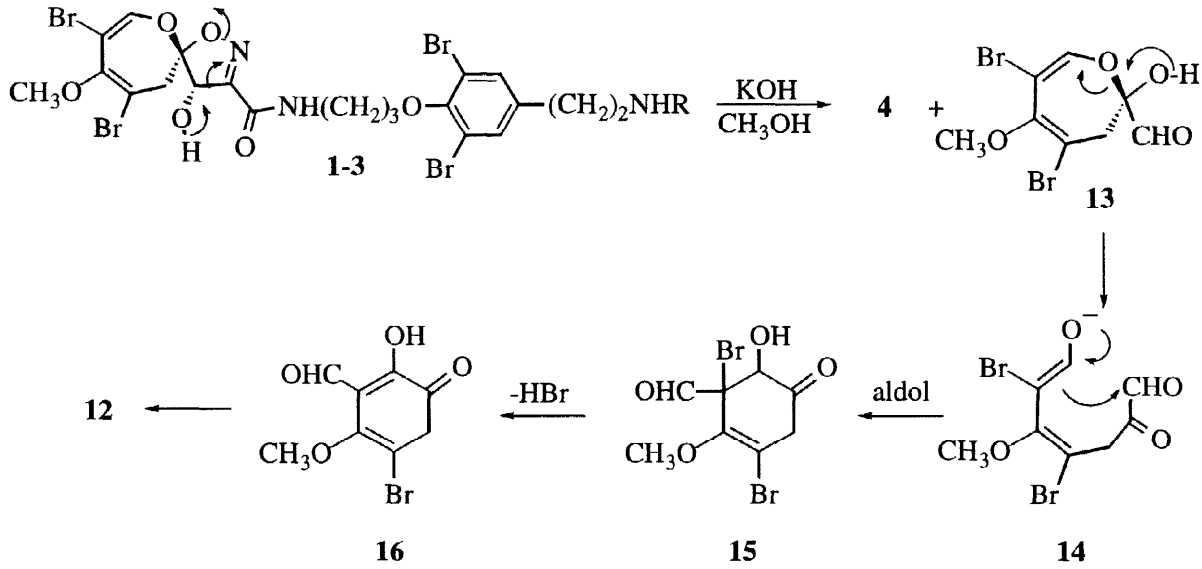
The TFA salt of **4** was stable in $CD_3OD$ at rt, but underwent slow hydrolysis in $D_2O$ ($t_{1/2}$ = 31 days at 24 °C, pD 5.5). In 1% KOH-$CH_3OH$, **4** was rapidly converted to the known[12] carbamate **11** with release of cyanide (positive benzidine test).

The biogenesis of **1-5**, as well as other bromotyrosine metabolites, has elicited widespread interest.[3,13] No reports have addressed the origin of ceratinamine's unique cyanoformamide group, although in retrospect, an important clue surfaced during the isolation of psammaplysin A. In that work, Rotem *et al.* noted[12] that treatment of **1** with methanolic base gave carbamate **11** along with an aryl aldehyde that was subsequently identified[5] as **12**.




**12**

In Scheme 2, we propose a mechanism for the base-catalyzed rupture of the spiro[4,6]-dioxazaundecane framework to form ceratinamine **4**, which we have now shown is converted to **11** under the reaction conditions. The other primary fragmentation product, hydroxyaldehyde **13**, would subsequently be transformed into **12** as shown. Similar isoxazole-to-nitrile fragmentations have been observed under physiological conditions with 3-unsubstituted isoxazoles, 3-acylisoxazoles, and isoxazole-3-carboxylic acids.[14,15]




**Scheme 2**

Interestingly, cyanide can be detected when sponges of the genus *Psammaplysilla* and *Pseudoceratina* are broken into pieces.[3] The mechanism proposed in Scheme 2 along with experimental data on the stability of ceratinamine rationalize this observation, since further hydrolysis of the cyanoformamide in **4** to moloka'iamine **5** would result in the release of HCN.

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