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Total Synthesis of the Natural Product (±)-Dibromophakellin and Analogues

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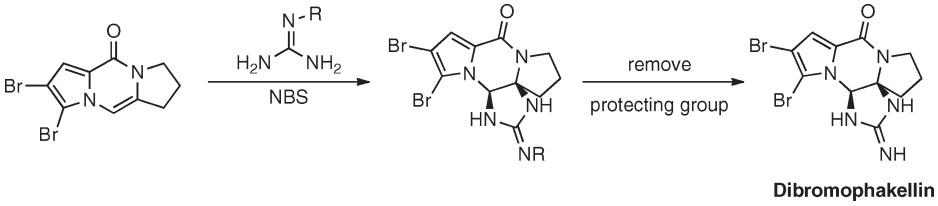
ABSTRACT



Dibromophakellin

(±)-Dibromophakellin has been synthesized in two steps from a known alkene intermediate. The key step in the synthesis is the NBS olefin activation to facilitate the addition of a guanidine molecule across the double bond.

The oroidin family of alkaloids is a highly diverse and complex class of biologically active secondary marine sponge metabolites containing characteristic pyrrole-2-carboxamide and 2-aminoimidazoline (or derivatives thereof) moieties. Arguably the most well-known member of the pyrrole-imidazole family is palau'amine (Figure 1), which exhibits exciting cytotoxic and immunosuppressive activity.[1] The architecturally daunting natural product finally succumbed to total synthesis by Baran and co-workers in 2010.[2]

Recently, much attention has been given to other members of this family of pyrrole-imidazole marine alkaloids, including dibromophakellin and dibromophakellstatin (Figure 1), which share a similar tetracyclic framework with palau'amine. The structural similarities between palau'amine and the phakellins and phakellstatins sparked our interest in the synthesis of these agents and their analogues, in order to further explore their biological properties.[3,4]

The phakellins and phakellstatins have been the focus of a number of synthetic efforts. The total synthesis of dibromophakellstatin has been completed, both racemically and asymmetrically.[5−15] Additionally, the syntheses of the analogues bromophakellstatin[8,9] and phakellstatin have been accomplished,[6,13−15] the latter often as an intermediate in the total synthesis of dibromophakellstatin.

The closely related natural product (−)-dibromophakellin was first isolated in 1969 by Sharma,[16,17] and its enantiomer, (+)-dibromophakellin, was later isolated in 1985 by Ahond and Poupat.[18] Since that time, the total synthesis of dibromophakellin has been completed racemically,[11,12,19] as

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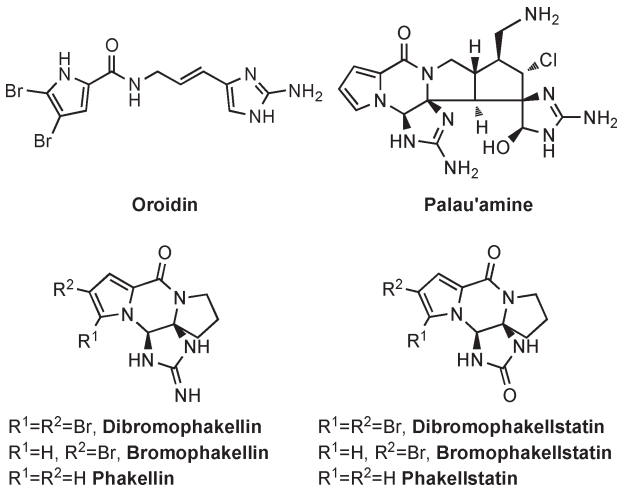


Figure 1. Structures of oroidin, palau'amine, phakellins, and phakellstatins.

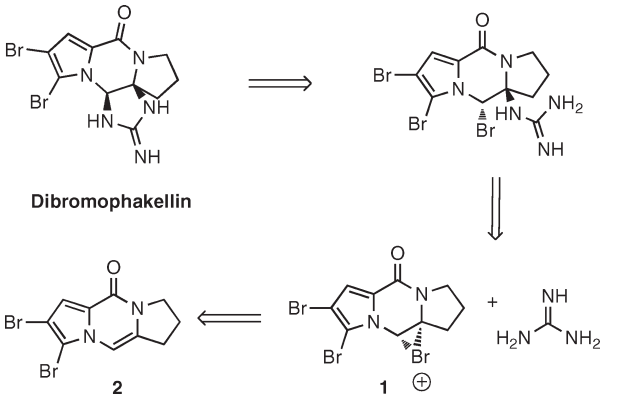
well as asymmetrically.[15,20] In addition, the enantioselective synthesis of related (+)-bromophakellin[21] and (+)-phakellin[15,20,21] has also been accomplished.

In order to prepare the natural product dibromophakellin as well as its un-natural analogues, we pursued a general divergent route into this class of compounds. Herein, we report the total synthesis of dibromophakellin via a one-pot addition of protected guanidine across a double bond, mediated by *N*-bromosuccinimide (NBS). This methodology has also been applied as a general approach to access several of its analogues.

In our retrosynthetic analysis of dibromophakellin, we envisioned that guanidine could serve as a nucleophile to open a bromonium ion (**1**), followed by a subsequent intramolecular displacement of the bromide, to complete the tetracyclic natural product (Scheme 1). Alternatively, the electrons on the amide nitrogen may open the bromonium ion, forming an *N*-acyliminium ion, which could be attacked by the guanidine nucleophile. We planned on forming the intermediate bromonium ion **1**, by treatment of alkene intermediate **2** with a source of electrophilic bromine, such as NBS.

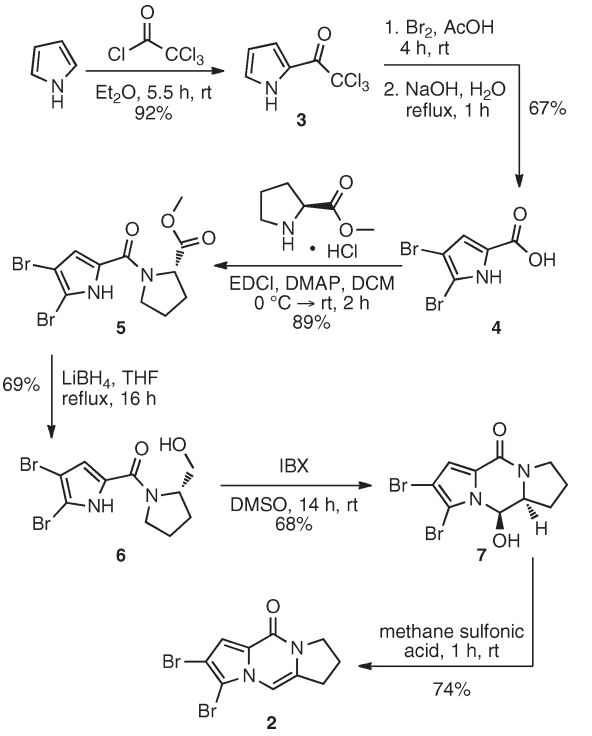
The synthesis of pivotal alkene intermediate **2** was accomplished via a modified route as previously reported,[22,23] starting from inexpensive pyrrole (Scheme 2). The synthesis began with the acetylation of pyrrole with trichloroacetyl chloride in good yield.[24] This was followed by bromination of 2-(trichloroacetyl)pyrrole (**3**) with bromine in acetic acid and subequent hydrolysis of the

Scheme 1. Retrosynthetic Analysis of the Synthesis of Dibromophakellin



trichloroketone to the carboxylic acid[25] **4** in 67% overall yield.

Scheme 2. Synthesis of Alkene Intermediate **2** from Pyrrole



Next, coupling of **4** with L-proline methyl ester hydrochloride with EDCI gave amide **5** in 89% yield. Reduction of the ester was achieved with lithium borohydride in refluxing THF to afford the primary alcohol **6** in 69% yield. Oxidation with IBX in DMSO[22] afforded hemiaminal **7** as a single diastereomer in 68% yield, which is in agreement with the spectroscopic data reported by Lindel's

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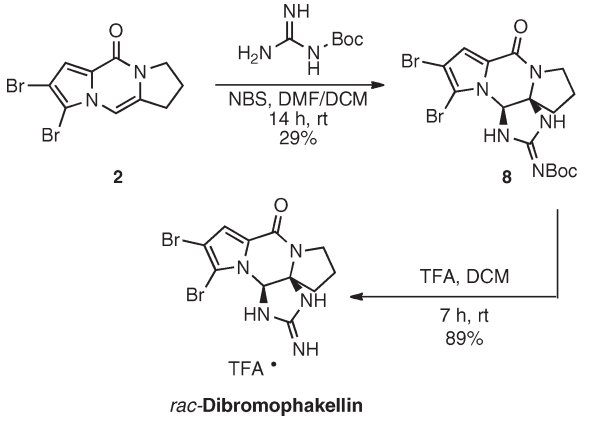
group.[22] Treatment of **7** with methane sulfonic acid led to the desired elimination product **2** in 74% yield.[23]

With alkene intermediate **2** in hand, we set out to form the final cyclic guanidine ring, in what is the key step of this synthesis. In early attempts to make dibromophakellin, guanidine hydrochloride was employed as the nucleophilic counterpart. The desired product was observed by mass spectrometry; however isolation of the very polar compound proved difficult. Inspired by work done in the Al-Mourabit group,[26,27] we decided to protect the guanidine as its Boc or Cbz derivative in order to ease the isolation and purification. Both guanidine derivatives were employed successfully; however, the Boc-guanidine gave slightly better yields and is reported here (Scheme 3).

Scheme 3. Two-Step Synthesis of Dibromophakellin from Alkene Intermediate **2**



Treatment of alkene **2** with NBS in the presence of Boc-protected guanidine gave the Boc-proctected natural product **8** in 29% yield. Deprotection of the Boc group with trifluoroacetic acid in dichloromethane afforded dibromophakellin in 89% yield, as the TFA salt. This methodology represents a convenient method to access the natural product in only two steps from a readily available alkene intermediate (**2**) and eight steps from commercially available pyrrole.

We next used this methodology to synthesize the indole analogue of dibromophakellin (**14**). The synthesis of the indole derivative of the natural product followed a similar overall strategy. The synthesis began with the EDCI coupling of commercially available indole-2-carboxylic acid with L-proline methyl ester hydrochloride to give amide **9** in good yield (Scheme 4).

Interestingly, reduction of **9** occurs with concomitant attack of the indole nitrogen on the newly generated aldehyde to give the isolated hemiaminal **10** in 76% yield. This obviated the need for the reduction–oxidation sequence used in the synthesis of the natural product

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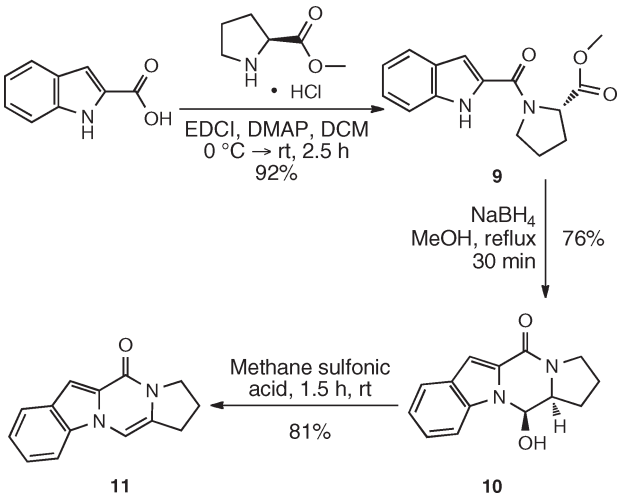
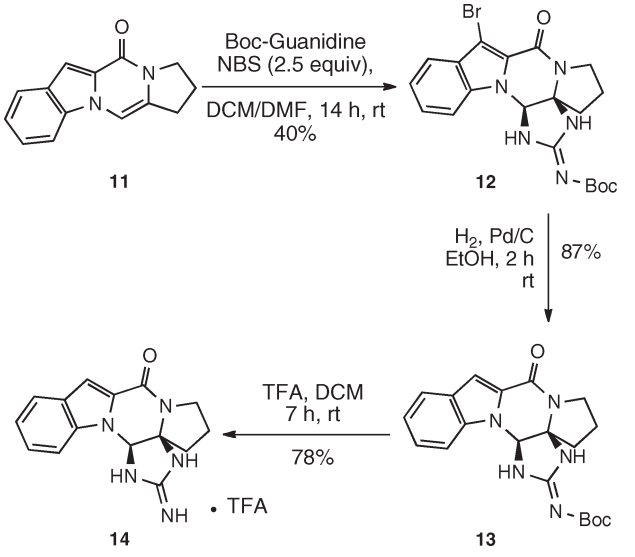
Scheme 4. Synthesis of Alkene Intermediate **11**



(Scheme 2). Subsequent dehydration with methane sulfonic acid gave the alkene **11** in 81% yield.

Treatment of **11** with NBS in the presence of Boc-protected guanidine gave intermediate **12** in 40% yield (Scheme 5). It should be noted that it was necessary to use at least 2 equiv of NBS, because the 3-position of the indole was brominated prior to bromination of the alkene. Next, removal of the bromine from the indole ring by Pd-catalyzed hydrogenation afforded **13** in 87% yield. Finally, removal of the Boc protecting group was completed by treatment of **13** with 5% TFA in DCM to furnish the indole analogue of dibromophakellin (**14**) in only six steps and 15.4% overall yield from indole-2-carboxylic acid.

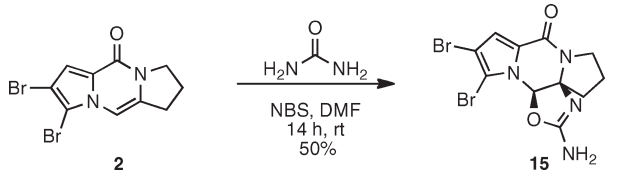
Scheme 5. Synthesis of Indole Analogue of Dibromophakellin (**14**)



Upon replacement of the guanidine nucleophile with urea, we obtained a second analogue of dibromophakellin

(Scheme 6). Treatment of alkene intermediate **2** with NBS in the presence of urea gave oxazoline **15** in 50% yield, which was confirmed by an X-ray crystal structure (see Supporting Information). Extension of this methodology to access the phakellstatins (Figure 1) and their analogues is currently ongoing in our laboratory.

Scheme 6. Synthesis of **15** When Guanidine Is Replaced with Urea



In conclusion, the total synthesis of dibromophakellin has been achieved in eight linear steps from pyrrole, in 4.9% overall yield. The key step involves activation of an alkene intermediate by NBS in the presence of a protected guanidine nucleophile. This methodology allows rapid entry into the pyrrole-imidazole family of molecules and has also been extended to the indole and oxazoline analogues of dibromophakellin. The biological activities of the natural product as well as its analogues will be reported by our group in the near future.

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Supporting Information Available. Experimental procedures and characterization data for compounds **1**, **2**, **5**–**15**. X-ray crystal data are available for compound **15**. This material is available free of charge via the Internet at http://pubs.acs.org.