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Hypervalent Iodine-Mediated Vicinal Syn Diazidation: Application to the Total Synthesis of (±)-Dibromophakellstatin

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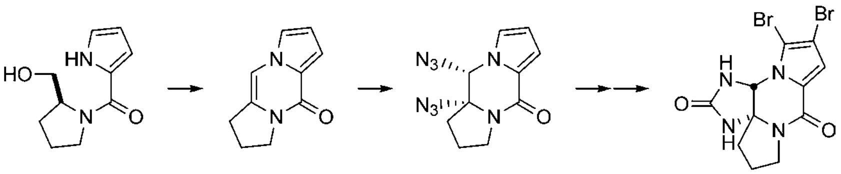
ABSTRACT



The total synthesis of (±)-dibromophakellstatin is described. The molecule is constructed from a key *syn*-diazide, formed by a hypervalent iodine-mediated diazidation of a dihydrodipyrrolopyrazinone ring structure.

The guanidine moiety remains a ubiquitous structural motif found in many marine natural products isolated within the last 20 years,[1] as exemplified by the structurally related molecules dibromophakellstatin **1**,[2] dibromophakellin **2**,[3] dibromoisophakellin **3**,[4] palau'amine **4**,[5] and styloguanidine **5**.[6] Despite their widespread appearance in nature and their general biological activity, specific cellular targets for many of these molecules, particularly palau'amine **4** and styloguanidine **5**, remain unknown. This fact, combined with their exquisite structure, has made them the center of much recent attention.[7] Due to the structural similarity between palau'amine **4** and the phakellins and phakellstatins (**1**−**3**), we endeavored to develop a synthetic approach to phakellstatin that augmented our previous efforts toward the synthesis of the carbocyclic ring of palau'amine.[8] Herein we report the synthesis of (±)-dibromophakellstatin **1**, which utilizes a hypervalent-iodine mediated syn diazidation to construct a diamine appropriate for the installation of the urea moiety on the dipyrrolopyrazinone core of the natural product.

Of all the naturally occurring guanidine-containing molecules, palau'amine **4** remains the most challenging. Isolated from the marine sponge *Stylotella aurantium*, it exhibits antibiotic, antifungal, and immunosuppressive activity.[5,9] Palau'amine's structural complexity (six contiguous rings, eight stereocenters, and a concave, syn-fused 5,5-ring system), combined with its impressive biological activity, make it an attractive and formidable target for total synthesis.[8,10] It is therefore not surprising that dibromophakellstatin **1** and dibromophakellin **2** have also received much recent attention given their own biological activity[2,3] and similarity

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to the top half of palau'amine **4**. Buchi et al. were the first to report a synthesis of (±)-dibromophakellin **2** using a biomimetic approach.[11] Horne and co-workers reported the synthesis of both (±)-dibromophakellstatin **1** and (±)-dibromoisophakellin **3** using an approach based on a putative biomimetic strategy.[12] Romo et al. described an enantioselective strategy to this ring structure,[13] which ultimately led to the synthesis of the unnatural enantiomer (+)-dibromophakellstatin.[14] Our approach to dibromophakellstatin **1** proceeds through a late-stage dibromination of phakellstatin **6** with *N*-bromosuccinimide (NBS),[15] a strategy that had previously been successfully employed.[14] Formation of the cyclic urea moiety of phakellstatin was envisioned as coming from *syn*-diamine **7**. Our approach to dibromophakellstatin, through diamine **7**, was inspired by the formation of dihydrodipyrrolopyrazinone **9** during the attempted preparation of related diketopiperidine molecules. Others have also reported the formation of this molecule.[3,16] Compound **10** is obtained by the coupling of pyrrole and prolyl-containing precursors, providing convenient access to a variety of potential derivative molecules. Despite the ready formation of pyrazinone **9**, conversion of this molecule to vicinal *syn*-diamine **7**, which could ultimately lead to either a guanidine or related moiety, represented the major synthetic challenge of our approach.

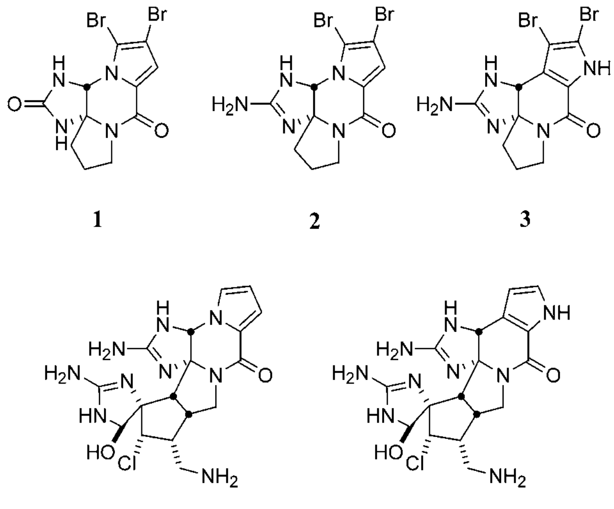
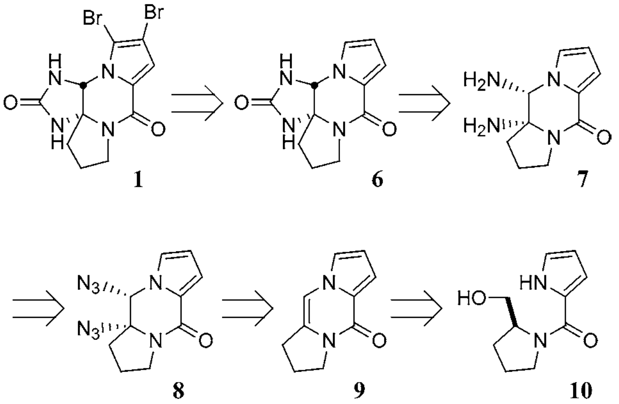


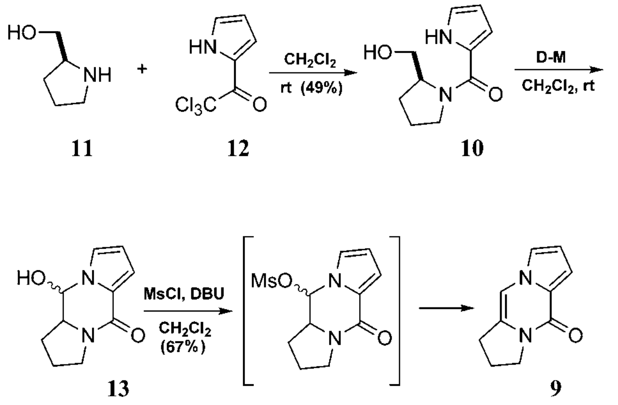
Figure 1. Various urea-, guanidine-, and bisguanidine-containing natural products.

Scheme 1. Retrosynthetic Analysis for the Synthetic Approach to (±)-Dibromophakellstatin (**1**)



Synthesis of 2,3-dihydrodipyrrolopyrazinone **9** was achieved by coupling of (*S*)-(+)-2-pyrrolidinemethanol **11** with 2-(trichloroacetyl) pyrrole **12** in dichloromethane to form alcohol **10** in 49% yield (Scheme 2). Alcohol **10** could be directly oxidized by treatment with Dess–Martin periodinane to furnish the hydroxydipyrrolopyrazinone intermediate **13**. Small amounts of the elimination product **9** could be detected in the crude material; however, complete conversion to the alkene required treatment with methanesulfonyl chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). After purification, this provided dihydrodipyrrolopyrazinone **9** in 67% yield. Lindel et al. observed formation of a related alkene after chlorination and subsequent elimination.[16]

Scheme 2. Formation of Dihydrodipyrrolopyrazinone **9**



A number of methods for the direct formation of vicinal diazides from alkenes have been reported.[17] For our purpose,

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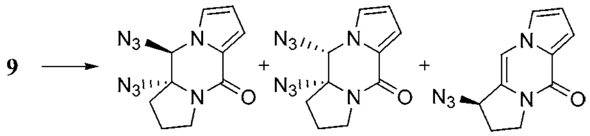
Scheme 3. Product and Yields for the Various Diazidation Reaction Conditions[a]

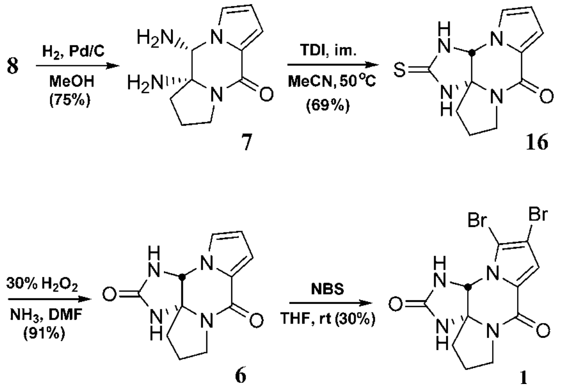


Conditions	Reagent	**14**	**8**	**15**
I	IN_3	62%	0%	0%
II	resin-$^{-}I(N_3)_2$	19%	24%	0%
III	$PhI(N_3)_2$	0%	0%	26%
IV	$^{-}I(N_3)_2$	7%	41%	0%

[a] Conditions: [I] (a) ICl, NaN_3, MeCN, −10 °C; [II] resin−$^{+}NH_3[^{-}I(N_3)_2]$, rt; [III] (a) $PhI(OAc)_2$, $TMSN_3$, −30 °C, warm to room temperature; [IV] (a) $PhI(OAc)_2$, $TMSN_3$, −30 °C. (b) Et_4NI (2 equiv), −30 °C, warm to room temperature.

iodine azide (IN_3) represented a convenient and mild reagent for this transformation.[18] We envisioned the formation of a diazide addition product as proceeding through an intermediate iodonium ion, allowing potential attack of both azides from the same face. Treatment of pyrazinone **9** with iodine azide (IN_3) formed in situ by treatment with iodine monochloride in the presence of sodium azide (conditions I) formed the *anti*-diazide **14** (Scheme 3) as the sole product. Since this direct diazidation provided only *anti*-diazide, we attempted a haloazidation reaction, using resin-bound hypervalent iodoazide species reported by Kirschning and coworkers,[19] in the hope that a two-step synthetic approach, involving subsequent nucleophilic displacement of the azide, would furnish a *syn*-diazide product. Surprisingly, treatment of dihydrodipyrrolopyrazinone **9** with resin-bound $^{-}I(N_3)_2$ (conditions II) provided two products, *anti*-diazide **14** in 19% yield and *syn*-diazide **8** in 24% yield. The structures of both *anti*-azide **14** and *syn*-azide **8** were confirmed by X-ray diffraction analysis.[20] No haloazide product was detected in the crude reaction mixture.

Scheme 4. Formation of (±)-Dibromophakellstatin **1**, from the Vicinal *syn*-Diazide **8**



7 **16** **6** **1**

Encouraged by the formation of both *syn*- and *anti*-diazides using solid-phase $^{-}I(N_3)_2$, we decided to explore the use of hypervalent iodine in solution. Moriarty et al. reported the formation of both *syn*- and *anti*-diazides upon in situ formation of a hypervalent iodine species using C_6H_5IO−HOAc−NaN_3.[21] Other hypervalent iodine azides such as $PhI(N_3)_2$ (conditions III) led to exclusive formation of *allyl*-azide **15**[20] (Scheme 3), consistent with observations reported by Magnus and Lacour.[22] Treatment of pyrazinone **9** with solution-phase hypervalent iodine, by in situ formation of $^{-}I(N_3)_2$ (conditions IV), provided *syn*-diazide **8** as the major diastereomer (41%) and the *anti*-diazide **14** as a minor diastereomer (7%).

It is interesting that no iodoazide product was observed when pyrazinone **9** was treated with $^{-}I(N_3)_2$ under either solid-phase or solution-phase conditions (Scheme 3).[21] It is possible that an iodoazide is initially formed but is unstable due to the two adjacent heteroatoms attached to the alkene. Either nitrogen could facilitate iodine expulsion, stabilizing an intermediate carbocation and allowing attack by a second azide. It is also possible that the iodoazide is never formed and the diazide product proceeds directly through either a highly reactive iodonium[18] or carbocation species,[22] both of which are potential intermediates in iodine-mediated azide addition reactions. Indeed, a combination of these reaction mechanisms may be operative, which would explain the observed preference for *syn*-diazide formation over *anti*-diazide under solution-phase $^{-}I(N_3)_2$ conditions. Direct azide displacement of either an iodoazide intermediate or iodonium species would lead to formation of syn product, while azide attack onto a carbocation intermediate would likely result in anti product due to a more favorable approach from the least hindered face.

It is therefore plausible that syn product formation proceeds though an initial nucleophilic displacement to give an iodonium ion species or an *anti*-haloazide intermediate, which is subjected to bimolecular nucleophilic substitution by excess azide, under the solution-phase conditions, to form *syn*-diazide **8**. Neighboring group participation by either of the adjacent nitrogens, which are well suited to stabilize a positive charge, may serve to displace the iodide, or iodonium ion, by stabilizing the intermediate carbocation.[3] In this case the second azide displacement reaction would then be expected to proceed through addition from the less sterically hindered face, under solid-phase conditions, to produce the *anti*-diazide product.

Synthesis of dibromophakellstatin **1** from *syn*-diazide **8** was completed by hydrogenation in the presence of 10% Pd/C in methanol to afford *syn*-diamine **7**[20] in 63% yield as

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[20] Crystallographic data on compounds **7**, **8**, **14**, and **15** deposited with Cambridge Cryatallographic Database.

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a white powder. Treatment with 1,1-thiocarbonyldiimidazole gave thiourea **16** in good yield. Peroxide treatment provided phakellstatin **6**. Bromination with *N*-bromosuccinimide (NBS) gave the natural product (±)-dibromophakellstatin **1** in 30% isolated yield. The low yield of this transformation, relative to that previously reported,[14] is predominantly due to the extensive chromatography required to vigorously remove unwanted NBS-related side-products. Studies of alternate methods for facilitating this transformation, including the use of *N*-bromophthalimide, a more conveniently removed reagent, are currently underway.

In conclusion, we have described reaction conditions that allow for the preferential syn azidation of pyrazinone **9**. The vicinal *syn*-diamine in **7** serves as a starting point for the formation of the cyclic urea, leading ultimately to the total synthesis of the natural product (±)-dibromophakellstatin **1**. Given the similarity between the natural products dibromophakellstatin **1** and dibromophakellin **2** with palau'amine **4**, the present synthesis may also serve as our top-half approach to this molecule. Future efforts will include the application of this methodology to the syn azidation of additional alkene substrates and their use in the synthesis of guanidine-containing natural products.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1**, **6**−**10**, **14**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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