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Extending Pummerer Reaction Chemistry. Synthesis of (±)-Dibromophakellstatin by Oxidative Cyclization of an Imidazole Derivative

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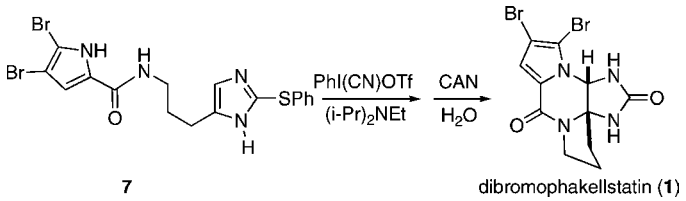
ABSTRACT



7 dibromophakellstatin (**1**)

The diastereoselective oxidative cyclization of a dihydrooroidin derivative is reported. The thioimidate product formed by application of a new variant of the Pummerer reaction serves as a precursor to dibromophakellstatin.

Oxidation of 2-aminoimidazole systems with concomitant cyclization of a tethered nucleophile has been postulated to underlie the biosynthesis of many polycyclic marine alkaloids,[1] and the mimicry of this process has fueled several concise synthesis strategies for these species,[2] inter alia. However, not all heterocycle-based oxidative cyclization biosynthesis blueprints translate readily to the laboratory, as complications due to overoxidation and/or lack of regiocontrol upon nucleophile attack can compromise these approaches.[3] Recently, a new approach for avoiding these issues in indole oxidative cyclizations at C(3), which relies on a variant of the Pummerer reaction,[4] was reported.[5] Extension of this process to the imidazole nucleus would enable facile access to spirocyclic 4,4-disubstituted imidazolines, a molecular framework that defines many biologically active sponge metabolites.[1a,6] Seminal work in this area by Büchi (Br_2 as oxidant),[2a] with recent improvements by Horne (NBS as oxidant),[2f] illustrate the value of this strategy for rapid access to the relatively simple targets dibromophakellstatin (**1**)[6a] and dibromophakellin (**2**).[6b] However, the use of the Pummerer process described below, with its well-defined and unambiguous site of oxidative initiation, may hold some value in oxidative cyclization attempts directed toward the more structurally complex and functionally rich members

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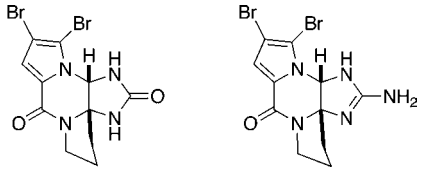
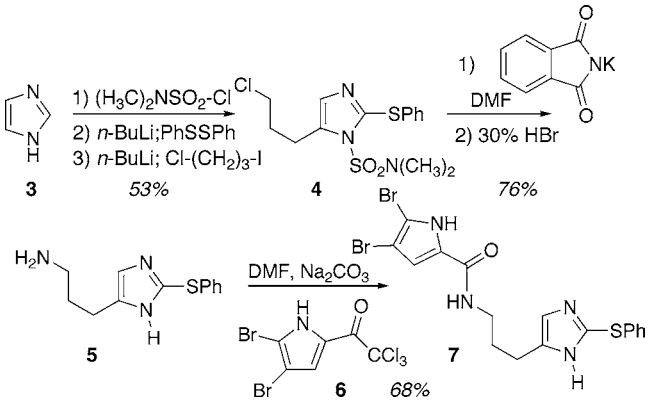


Figure 1. Two dihydrooroidin-derived sponge metabolites.

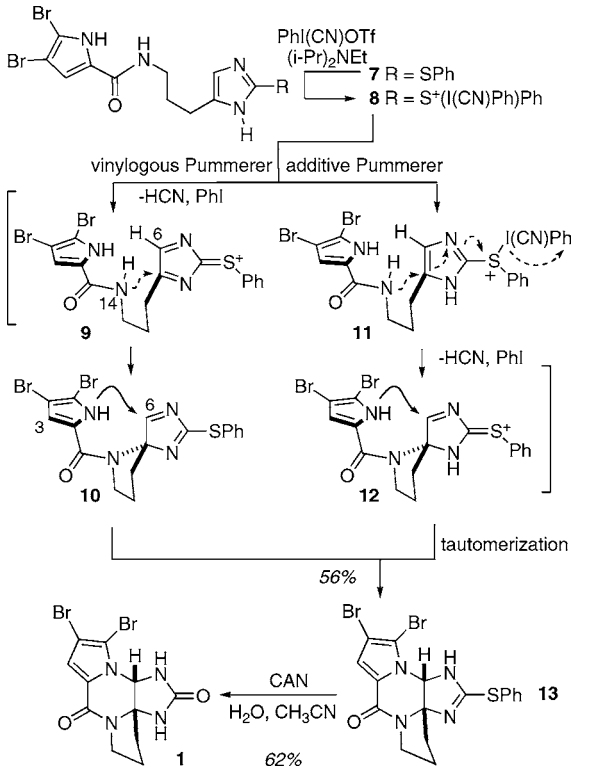
of this family, such as palau'amine[6c] or styloguanine.[6d] As a stepping stone toward those goals, the synthesis of **1** was pursued in order to establish the feasibility of the Pummerer-based strategy in imidazole oxidative cyclization chemistry. The key cyclization substrate **7** was prepared to test this premise (Scheme 1). The imidazole C(2)/C(5) functionalization procedure described by Vollinga[7] was employed to generate the chloride **4** from imidazole (**3**). This species was then converted to the amine **5** through straightforward chemistry. Dibromoacylpyrrole attachment to the primary amine of **5** afforded the polyfunctional dihydrooroidin derivative **7**, ready for the oxidative cyclization sequence.

Scheme 1. Synthesis of Pummerer Oxidative Cyclization Precursor



Treatment of sulfide **7** with Stang's reagent,[8] PhI(CN)-OTf, in the presence of diisopropylethylamine initiated the oxidative cyclization sequence that delivered the tetracyclic material **13** (Scheme 2). A putative mechanistic course might

Scheme 2. Oxidative Cyclization of Pummerer Precursor, with Mechanistic Speculation and Conversion of Cyclization Product to Dibromophakellstatin



encompass the structures **8**−**12**. Initial formation of the activated sulfur intermediate **8** sets up a mechanistic dichotomy involving either a *vinylogous* Pummerer pathway[9] or an alternative *additive* Pummerer sequence.[10] The vinylogous path bears some resemblance to S_N1 chemistry in that initial ionization of the nucleofuge precedes nucleophile

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addition, whereas the additive path is more closely aligned with S_N2'-type chemistry in that nucleophilic addition and iodine departure are concerted. At present, there is no evidence in hand that permits discrimination between these two hypotheses. The intermediacy of the tricyclic species **10**/**12** remains a matter of speculation as well, as only tetracyclic product is observed even under short reaction times. Regioselectivity upon cyclization appears to be complete. No product of C−N bond formation between N(14) and C(6) was detected (cf. **9**), nor was there any evidence for C(3)-to-C(6) cyclization (cf. **10**). Control experiments demonstrated that product **13** (1) is only very slightly degraded (<10%) upon exposure to Stang's reagent under long reaction times and (2) survives chromatographic purification without decomposition.

The thioimidate moiety within **13** serves as a convenient precursor to the sponge metabolite **1** through further functional group interchange. Oxidative hydrolysis[11] of the thioimidate **13** furnished the urea-containing species (±)-dibromophakellstatin (**1**). No disruption of either aminal function is seen during this transformation.

The successful acquisition of this marine alkaloid illustrates the role that Pummerer oxidative cyclization chemistry can play in the synthesis of dihydrooroidin-derived natural products. The transformation proceeds without interference byproduct overoxidation or regiochemical complexities upon nucleophile addition, and these attributes may find value upon application of this chemistry to more complex members of this class.

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Supporting Information Available: Spectral data including ^{1}H NMR, ^{13}C NMR, IR, and MS for **1**, **4**, **5**, **7**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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