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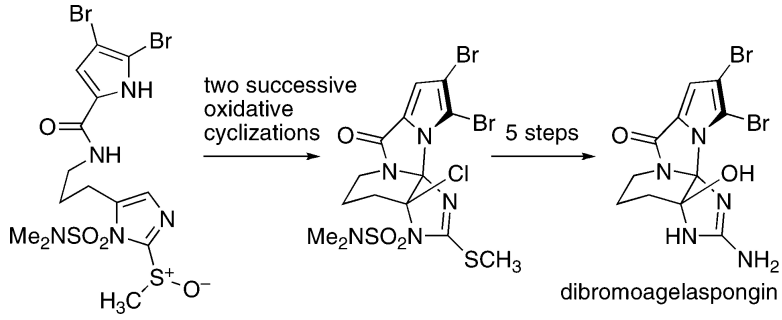
J. Am. Chem. Soc., **2008**, 130 (45), 14964-14965 • DOI: 10.1021/ja807020d • Publication Date (Web): 18 October 2008



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Extending Pummerer Reaction Chemistry. Application to the Total Synthesis of (±)-Dibromoagelaspongin

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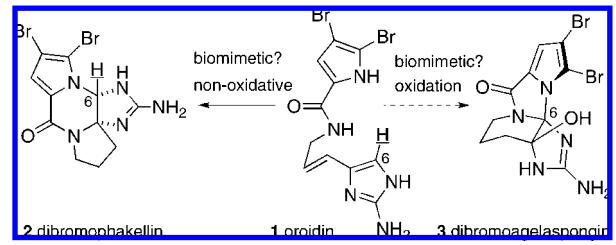
Received September 4, 2008; E-mail: ksf@chem.psu.edu

Sponge-derived secondary metabolites originating from cyclization events of the pivotal pyrrole-imidazole oroidin (**1**) comprise an expanding family of structurally complex guanidinium alkaloids that exhibit a broad range of biological activities.[1] Dibromophakellin (**2**) and its many structural analogues describe one well-populated branch of this oroidin-derived family. Dibromoagelaspongin (**3**), on the other hand, represents a structurally unique variant isolated from an *Agelas sp.* sponge.[2] The structure of this unusual triaminomethane[3] derivative was secured by single crystal X-ray analysis, and the natural product may, in fact, be racemic.[4] A nonoxidative cyclization (isomerization) of **1** is thought to define dibromophakellin's biosynthesis, and an oxidative variant of this process with *dihydro*oroidin derivatives has led to efficient biomimetic syntheses of **2** and related species.[5] In contrast, an oxidative cyclization is implicated in the biosynthesis of dibromoagelaspongin (**3**) from **1**, as the C(6)−H bond of **1** is formally replaced with a C−N bond to furnish the triaminomethane core of the tetracyclic product. Thus, any chemical synthesis of **3** from a suitably functionalized version of **1** must address the question of forming two successive C−N bonds to the same carbon (C(6)) of the imidazole core, a higher-order challenge quite distinct from that of dibromophakellin synthesis, where C−N bond formation occurs at two adjacent carbons.

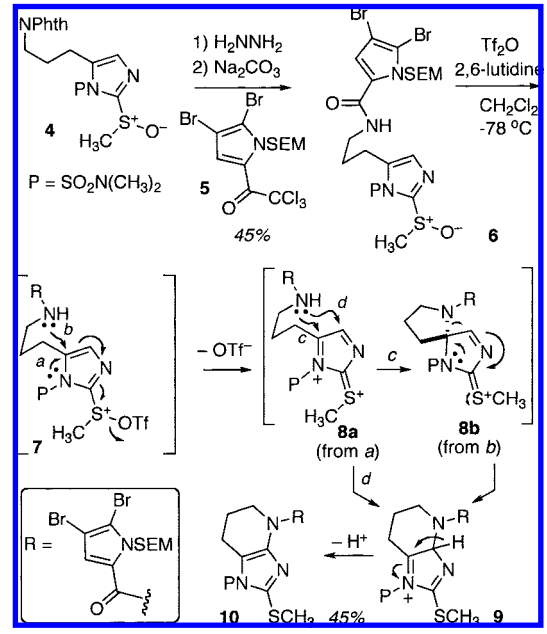
The use of imidazole-2-sulfoxides or -2-sulfides in Pummerer-based oxidative cyclization protocols has been developed as an effective method for the regioselective C−H → C−N functionalization of the imidazole core, and this chemistry underlies recent biomimetic syntheses of dibromophakellin and the related species dibromophakellstatin.[5c,d] The successful application of sequential Pummerer and then halonium (possibly Pummerer)-based oxidative cyclizations for converting a dihydrooroidin derivative into (±)-dibromoagelaspongin is described below.

The synthesis of dibromoagelaspongin commences with the imidazole sulfoxide **4**, a species prepared in five steps from imidazole paralleling that in the phenylthio series reported earlier (Scheme 2).[5d] Deprotection of the phthalimide moiety and acylation of the resulting primary amine with SEM-protected dibromopyrrole derivative **5** furnished the key Pummerer cyclization substrate **6**. Treatment of this sulfoxide with the standard Pummerer initiator triflic anhydride promoted a series of reactions that ultimately afforded the fused, annelated imidazole sulfide **10** in good yield. The mechanistic course of this transform is an open question at present, and some possible pathways connecting **6** with **10** are shown in Scheme 2. Thus, additive Pummerer chemistry evolving from **7** along pathway *b* would afford the spirocyclic thionium ion **8b** directly, a species that is related to the fused bicyclic product **9** via a lone-pair promoted 1,2-*N* shift. Alternatively, a vinylogous Pummerer sequence along pathway *a* would deliver a doubly cationic diazacyclopentadienylthionium ion **8a**, which itself could partition down two competing channels (labeled *c* and *d*) to furnish the fused bicyclic iminium ion **9** en route to the isolated product

Scheme 1. Oroidin Cyclization in Guanidine Alkaloid Biosynthesis



Scheme 2. Initial Pummerer-Mediated Oxidative Cyclization



10. The formation of a fused ring product **10** can be contrasted with the formation of an isolated spirocyclic isomer related to **8b** in the dibromophakellin work when $P = H$ (and the pyrrole nitrogen is unprotected). Thus, the regiochemical control of dihydrooroidin oxidative cyclization (dibromoagelaspongin fused system or dibromophakellin spiro system) is responsive to the nature of the imidazole *N* substituent.

The second oxidative cyclization as required to forge the triaminomethane core began with the free pyrrole **11**, Scheme 3. Numerous attempts to achieve further controlled oxidative cyclization with **11** under previously established Pummerer conditions (imidazole-2-sulfide + PhI(CN)OTf)[5c] failed to generate any characterizable material. This disappointing turn led to a broader exploration of oxidative cyclization protocols, and eventually conditions for chlorinative oxidative cyclization of **11** to yield tetracyclic material were identified. These conditions harken back to the original Büchi dibromophakellin work, with later modifica-

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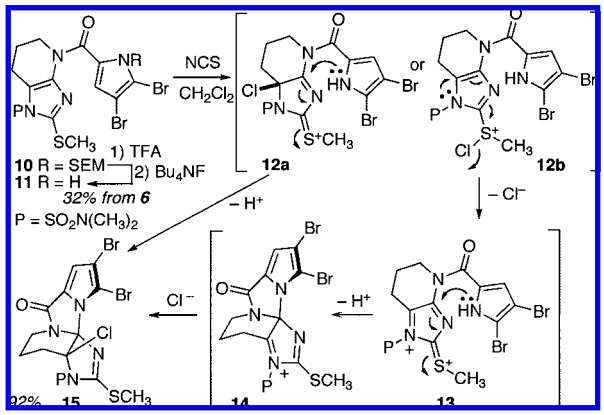
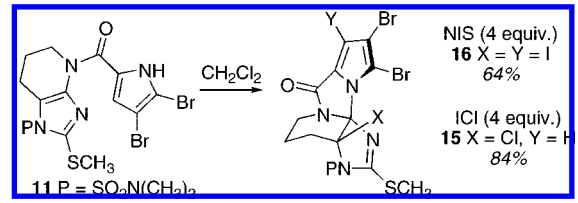
Scheme 3. Oxidative Cyclization of **11** to Furnish Tetracycle **15**



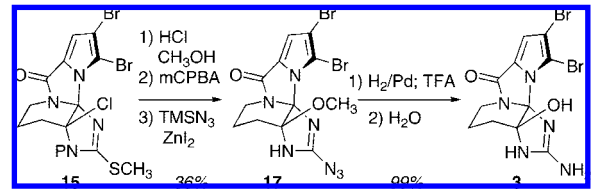
tions by Horne.[5b] Much like the initial oxidative cyclization, the presence of heteroatom lone pairs and much unsaturation raise the prospects of mechanistic complexity for this transformation also. Thus, it is possible that direct electrophilic chlorination of the electron-rich imidazole ring proceeds to generate a transient thionium ion **12a** that is rapidly quenched via nucleophilic addition of the proximal pyrrole to deliver tetracycle **15**. Alternatively, Pummerer chemistry may be in play for this oxidative cyclization as well, if sulfur chlorination leads to a sulfonium ion intermediate **12b** that is poised for subsequent cyclization of the nucleophilic pyrrole (**12b** → **13** → **14**). In this latter scenario, the chloride is then delivered to **14** as Cl^-. This mechanistic dichotomy was probed by the experiments described in Scheme 4. Thus, treatment of **11** with 4 equiv of NIS cleanly afforded the diodo tetracycle **16** in an analogous process to the formation of **15** from **11**/NCS. [Note: Use of 1 equiv of NIS just led to pyrrole iodination without any cyclization.] In contrast, exposure of **11** to ICl furnished only the chloride-containing product **15**. As a control, exposure of **16** to 4 equiv of *n*-Bu_4NCl under identical reaction conditions did not lead to any incorporation of the exogenous chloride. Thus, the formation of **15** from **11**/ICl cannot occur by addition of electrophilic iodine to the imidazole ring (cf. **12a** with I in place of Cl), since that process would have delivered **16** (with Y = H). However, the formation of **15** from **11**/ICl can be rationalized by a Pummerer pathway, which involves electrophilic activation of the sulfur function with I^+, followed by Cl^- addition to the derived iminium ion. By inference, the formation of **15** from **11** + NCS may follow the same Pummerer path (**12b** in Scheme 3).

The completion of the dibromoagelaspongin synthesis required five operations, Scheme 5. The first two transforms, substitution of Cl by OCH_3 and $(CH_3)_2NSO_2$ removal, could be accomplished conveniently by simply treating **15** with methanolic HCl. The next operation, SCH_3 → "N" replacement, entailed some experimentation, but eventually a procedure involving first oxidation of the sulfide of **15** into the corresponding sulfoxide and then treatment

Scheme 4. Mechanistic Probes of the Second Oxidative Cyclization



Scheme 5. Completion of the Dibromoagelaspongin Synthesis



of this crude material with azide furnished the protected guanidine moiety of **17** in good yield. Deprotection of the amine and alcohol functionalities by first hydrogenolysis and then acid-mediated hydrolysis delivered (±)-dibromoagelaspongin which could be isolated as its TFA salt. In summary, the unusual triaminomethane-containing sponge metabolite dibromoagelaspongin was prepared in 16 steps from imidazole in a route featuring successive Pummerer-like oxidative cyclizations to direct delivery of the two nitrogen nucleophiles to the imidazole core in a completely regioselective manner.

Acknowledgment. Financial support from the National Science Foundation (CHE-041877) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and full spectral data (IR, MS, ^1H NMR, ^{13}C NMR) for **6**, **10**, **11**, **15**, **16**, **17**, and **3**. This material is available free of charge via the Internet at http://pub.acs.org.

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JA807020D