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Note

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Biomimetic Synthesis of Thiaplidiaquinones A and B

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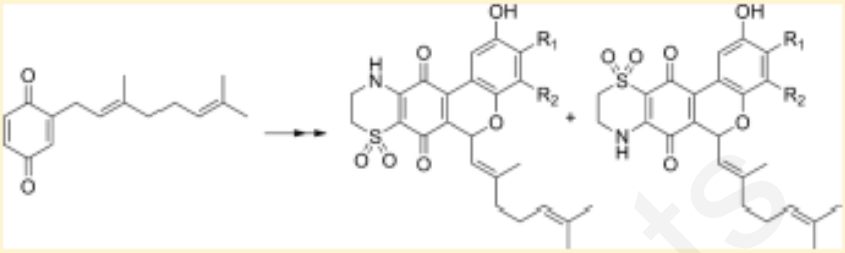
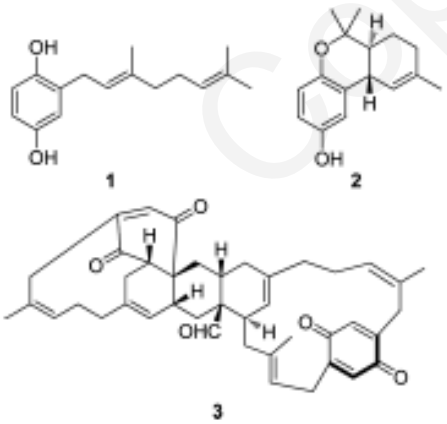
Supporting Information

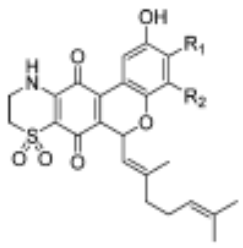


ABSTRACT: A biomimetic synthesis of the biologically active ascidian metabolites thiaplidiaquinones A and B is described. Reaction of geranylbenzoquinone with Et_3N in CH_2Cl_2 yielded two isomeric quinones, comprising the benzo[*c*]chromene-7,10-dione core of the natural products. Subsequent reaction with hypotaurine yielded the title compounds and their dioxothiazino regioisomers.

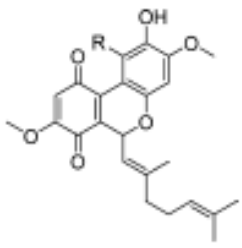
While the majority of metabolites biosynthesized by ascidians are alkaloids or peptide related,[1] ascidians of the genus *Aplidium* are known as a rich source of prenylated quinone and hydroquinone natural products.[2] Derived from geranylated or farnesylated hydro- or benzoquinone (e.g., **1**),[3] these typically bioactive metabolites can embody intramolecular (e.g., conicol, **2**[4]) or intermolecular ring closures (e.g., longithorone A, **3**[5]), yielding complex architectural scaffolds.



More recently, meroterpenoids bearing a benzo[*c*]chromene-7,10-dione skeleton have been reported from geographically remote species of *Aplidium* ascidians. In 2005, Fattorusso's group isolated thiaplidiaquinones A and B (**4**, **5**) from a Mediterranean ascidian, *Aplidium conicum*, determining that both natural products induced apoptosis in Jurkat cells by a mechanism involving the intracellular production of reactive oxygen species.[6] In contrast, the related metabolite scabellone B (**6**), isolated from a New Zealand collection of *Aplidium scabellum*, was found to be a relatively nontoxic antimalarial lead compound.[7] As part of our interest in exploring the structure–activity relationships of benzo[*c*]chromene-7,10-dione natural products,[8] herein we report a biomimetic synthesis of both thiaplidiaquinones A (**4**) and B (**5**) and their anticipated natural product dioxothiazine regioisomers. While this paper was in preparation, Carbone et al. reported a synthesis of thiaplidiaquinone A.[9]



4 R_1 = H, R_2 = geranyl
5 R_1 = geranyl, R_2 = H



6 R = geranyl

We speculated that the biosynthetic origin of the thiaplidiaquinones could stem from hypotaurine addition to one of two tricyclic pyranoquinones (**7**, **8**), in turn derived from oxa-6π electrocyclization[10] of *ortho*-quinone methide tautomers (**9**, **10**) of bis-benzoquinones (**11**, **12**) (Scheme 1).

However, while Carbone et al. constructed bis-benzoquinones **11** and **12** via a Suzuki–Miyaura reaction, we speculated that such coupling could be achieved simply by allowing geranylbenzoquinone (**13**) to tautomerize in the presence of triethylamine, undergo Michael reaction with another equivalent of quinone, and then follow a cascade of oxidation and

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