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Total Synthesis of Conulothiazole A

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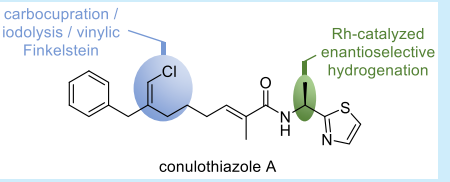
Supporting Information

ABSTRACT: An efficient total synthesis of the chlorinated thiazole-containing natural product conulothiazole A is reported. Key features of this synthesis include a novel rhodium-catalyzed enantioselective hydrogenation of a 2-enamido-thiazole and a vinylic Finkelstein reaction that could be implemented at all stages of the synthesis to install the chlorinated alkene.



Because of the variety of their structures, natural products have long been a source of inspiration for the development of new drugs and have been making a comeback in the pharmaceutical industry recently.[1] The intrinsic utility of natural products as drug leads can indeed not be questioned anymore, especially after the failure of combinatorial chemistry to provide small molecule drug candidates.[2] Advances in separation and structure elucidation technologies have moreover facilitated the discovery of an array of novel natural products that can be fully characterized at the microgram scale. The discovery of new natural products on such a scale however implies the design and development of short, efficient, and robust synthetic routes for their chemical synthesis in order to apprehend their biological activities and potentially prepare analogues in a diversity-oriented synthesis approach.

Amid all sources of natural products, marine organisms, and in particular sponges and their associated microorganisms, are among the most productive.[3] They have indeed provided over the years a range of bioactive substances that have often served as starting points for biomedical applications.

In the course of the study of Caribbean sponges, the Costantino group reported in 2016 the isolation and structure elucidation of various nonribosomal peptide/polyketides hybrid compounds from the holobiome of *Smenospongia conulosa* (i.e., the sponge and its associated microbiota) among which include conulothiazoles A (**1**) and B (**2**) (Figure 1).[4] These two novel natural products, isolated and characterized at the microgram scale, possess an interesting polyketide-peptide structure flanked with an aminoethylthiazole and a chlorinated alkene. Related natural products include smenothiazoles A (**3**) and B (**4**)[5] as well as smenamides A (**5**) and B (**6**).[6]

In view of the high potency of such natural products—the smenamides and smenothiazoles displaying antiproliferative activities against various cancer cell lines at nanomolar concentrations—and based on their especially limited supply and extremely low isolation yields (0.00000006% for conulothiazole A) combined with our interest in natural product synthesis,[7] we envisioned developing a short and modular total synthesis of conulothiazole A **1**. Results from these studies are reported in this manuscript.

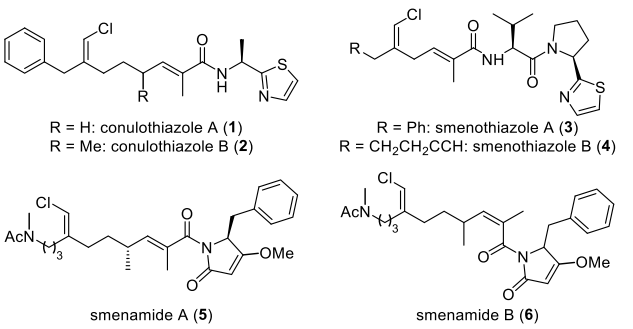


Figure 1. Structure of conulothiazole A and related natural products.

Despite its apparent simplicity, two main challenges are associated with the synthesis of conulothiazole A **1**. The first one actually lies in the enantioselective preparation of the aminoethylthiazole, the only route reported to date being based on a diastereoselective addition onto Ellman's chiral sulfinimines.[8] The second and main difficulty is due to the presence of the disubstituted chlorinated alkene, a structural element that is quite challenging to install with complete control of the stereochemistry. An analysis of total syntheses of natural products featuring such a chloroalkene, notably in the smenamide and smenothiazole series, indeed reveals the low levels of stereoselectivity obtained[9] or the need for multistep sequences.[10] In an attempt to address these limitations and to develop a straightforward and modular synthesis of conulothiazole A **1**, the disconnections shown in Figure 2 were selected. In this approach, the optically enriched aminoethylthiazole moiety could be obtained by an enantioselective hydrogenation of the corresponding enamido-thiazole in which the heterocycle could potentially serve for chelation with the catalyst and the disubstituted chloroalkene could be installed using a *syn*-carbocupration/iodolysis/vinylic Finkelstein reac-

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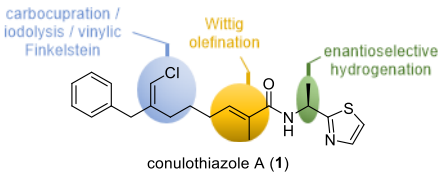

Figure 2. Disconnections envisioned for the total synthesis of conulothiazole A.

tion, while a simple Wittig olefination could be used to elaborate the central trisubstituted alkene.

With this retrosynthetic analysis of conulothiazole A in mind, we first focused our efforts on the asymmetric synthesis of the aminoethylthiazole subunit **8a** by an enantioselective hydrogenation of the corresponding enamide **7a**. A literature survey surprisingly revealed that while the related enantioselective hydrogenation in the pyridine series is well-documented,[11] the extension to other azoles still had to be developed, despite an important synthetic potential. A screening of catalytic systems and conditions was therefore performed: selected and representative results are shown in Figure 3. While a combination of $Rh(cod)_2BF_4$ and (*S*)-

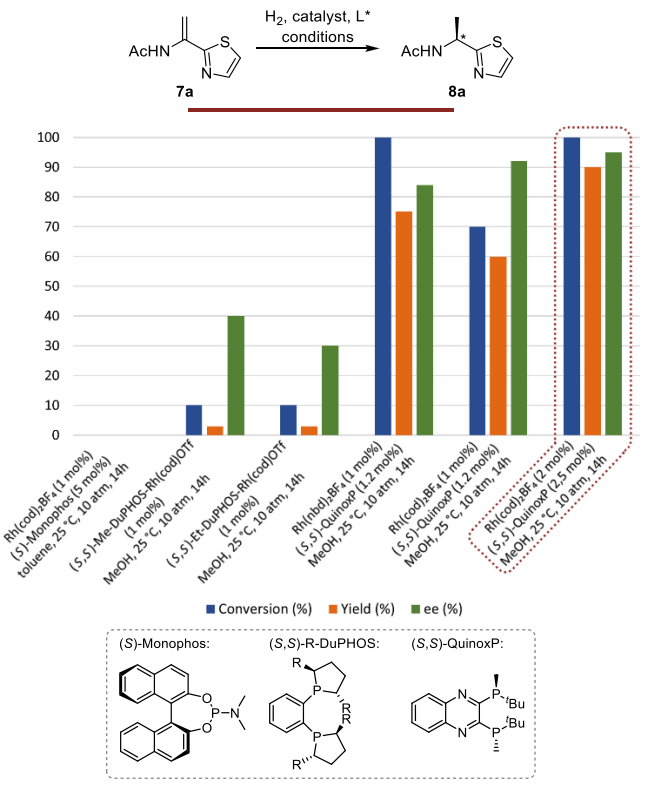

Figure 3. Optimization of the enantioselective hydrogenation of 2-enamido-thiazoles.

Monophos[12] was found to be totally inefficient, switching to rhodium−DuPHOS complexes[13] promoted an enantioselective hydrogenation of **7a** to **8a** with moderate levels of enantioselectivity but low conversions. A combination of $Rh(nbd)_2BF_4$ and (*S*,*S*)-QuinoxP[14] was gratifyingly found to be much more efficient in terms of conversion, yield, and enantioselectivity, the latter being however still not high enough (84%). Replacing the rhodium precatalyst by $Rh(cod)_2BF_4$ allowed 92% ee to be reached, although at the expense of the conversion which was limited to 70%. Finally, increasing the catalyst loading enabled a smooth enantioselective hydrogenation of **7a** to **8a** that could be isolated in 90% yield and 95% ee.[15]

Due to the efficiency of this enantioselective hydrogenation, we decided to initiate a brief survey of its scope by evaluating the reactivity of various enamido-heteroarenes: results from these studies are shown in Figure 4. The reaction was found to

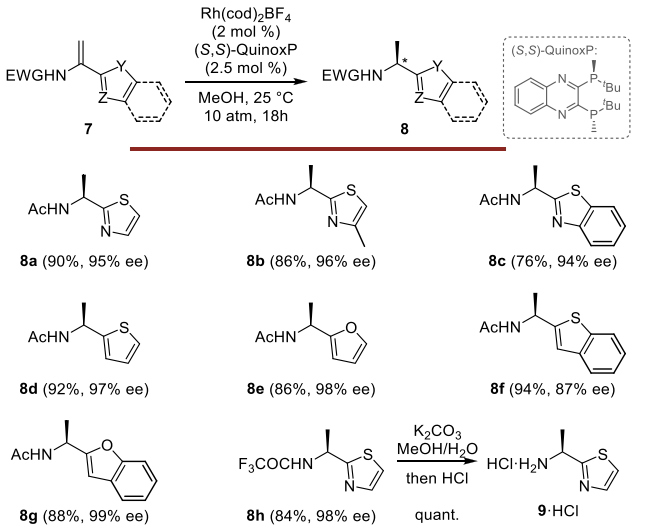

Figure 4. Scope of the enantioselective hydrogenation of 2-enamido-heteroarenes.

be rather general since it could be extended to benzothiazole (**8c**),[16] thiophene (**8d**),[16] furan (**8e**), benzothiophene (**8f**), and benzofuran (**8g**) derivatives, all of them giving excellent yields and enantioselectivities. The acetyl group in **8a** could moreover be replaced by a trifluoroacetyl without significant modifications of the yield and enantioselectivity, **8h**—whose methanolysis provided aminoethylthiazole **9** required for the synthesis of conulothiazole A—being obtained in 84% yield and 98% ee.

Having in hand an efficient route to the aminoethylthiazole subunit of conulothiazole A, we next initiated the synthesis of the polyketide subunit. The synthesis began with the carbocupration of 3-phenylprop-1-yne **10** followed by iodolysis of the resulting vinylcopper which resulted in a clean and fully stereoselective formation of iodoalkene $\mathbf{11}_I$ (Scheme 1). As a note, trapping the intermediate vinylcopper with electrophilic chlorination agents is not operative in such cases due to competing dimerization. Simple functional group transformation involving a selective oxidative cleavage of the terminal alkene in $\mathbf{11}_I$ followed by a Wittig reaction afforded intermediate $\mathbf{12}_I$ which was then subjected to the key vinylic retro-Finkelstein reaction.[17] Upon reaction under our previously reported conditions involving tetramethylammonium chloride and catalytic amounts of copper(I) iodide and *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine,[18a] a smooth, thermodynamically favored and irreversible iodine to chlorine exchange proceeded, enabling the isolation of $\mathbf{12}_{Cl}$ in 89% yield and full retention of the double bond geometry. Saponification of the ester in $\mathbf{12}_{Cl}$ followed by peptide coupling with aminoethylthiazole **9** finally led to conulothiazole A (**1**) whose spectral data were in complete agreement with those of the natural sample.[4]

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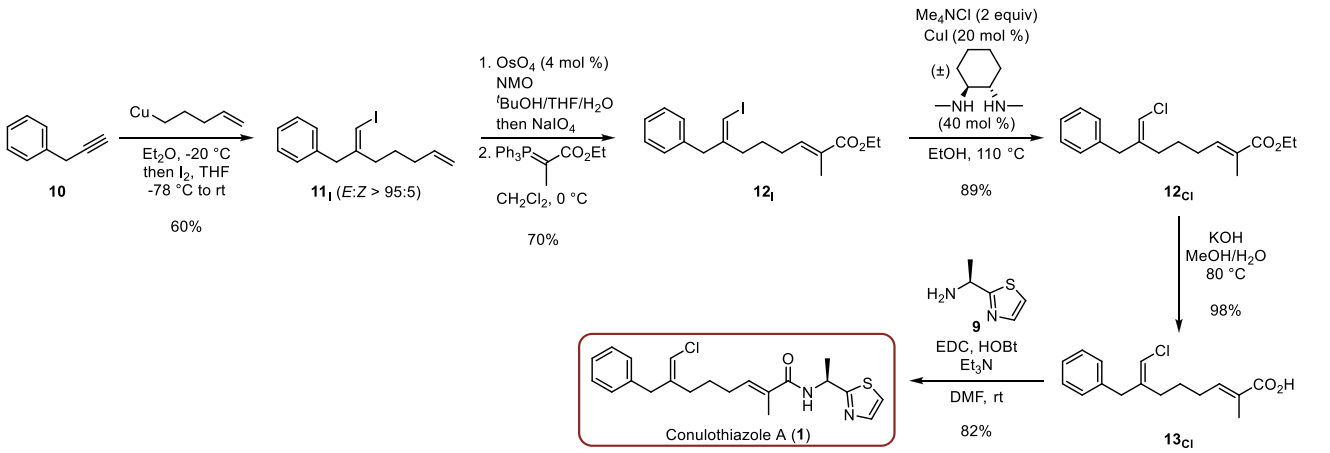
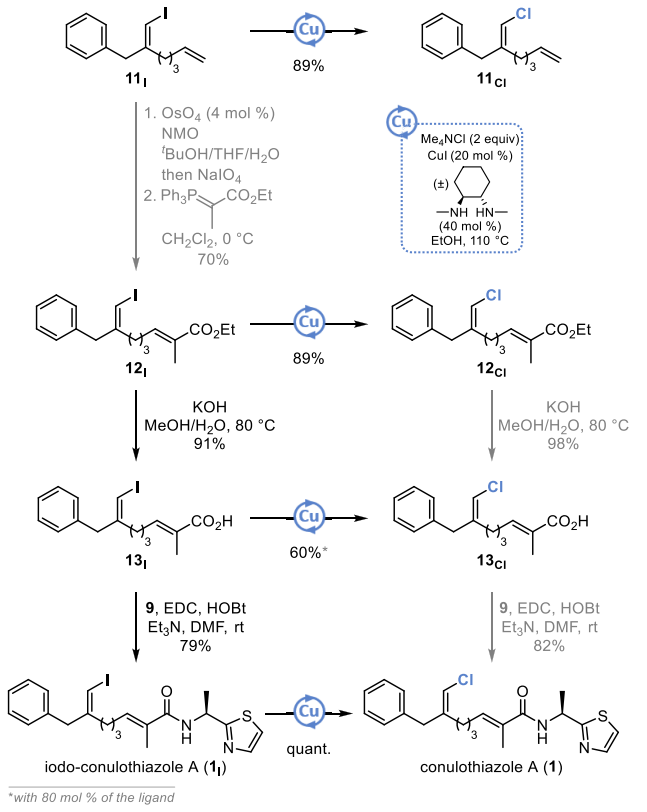
Scheme 1. Total Synthesis of Conulothiazole A



In a final effort to further demonstrate the synthetic usefulness of our copper-catalyzed vinylic halogen exchange reaction, we envisioned challenging its efficiency by performing the iodine to chlorine exchange on all synthetic intermediates. As demonstrated by results summarized in Scheme 2, the chlorination of all alkenyl iodides proceeded smoothly in all cases, a lower yield being however obtained in the presence of a carboxylic acid ($\mathbf{13_I} \rightarrow \mathbf{13_{Cl}}$, 60%). Remarkably, a late-stage halogen exchange performed on the iodinated analogue of conulothiazole A $\mathbf{1_I}$ allowed the formation of conulothiazole A **1** in quantitative yield.

Scheme 2. Early- and Late-Stage Copper-Catalyzed Vinylic Retro-Finkelstein Reactions en Route to Conulothiazole A



In conclusion, we have developed a short, modular, and efficient total synthesis of conulothiazole A in 7 steps (longest linear sequence) and 30% overall yield. This synthesis enables an easy preparation of hundreds of milligrams of this natural product, therefore providing an efficient supply for this nonribosomal peptide/polyketides hybrid compound that can hardly be obtained on a milligram scale from natural sources. Key features of our synthesis include a vinylic retro-Finkelstein reaction that can be performed at all stages of the synthesis as well as an efficient enantioselective rhodium-catalyzed hydrogenation of a 2-enamido-thiazole. Importantly, this asymmetric hydrogenation could be extended to other 2-enamido-heteroarenes, therefore providing an efficient entry to 2-aminoethyl-arenes, useful building blocks in synthesis and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01490.

Detailed experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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