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A scaleable formal total synthesis of dehydrogliotoxin

Travis C. McMahon [a], Sarah Stanley [b], Edward Kazyanskaya [b], Deborah Hung [b], John L. Wood [a,*]

[a] Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA
[b] The Broad Institute, Infectious Disease Initiative, 7 Cambridge Center, Cambridge, MA 02142, USA

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This manuscript is dedicated to Professor Harry Wasserman, a good friend and colleague, on the occasion of his 90th birthday

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ABSTRACT

A formal total synthesis of the epidithiodiketopiperazine natural product, dehydrogliotoxin (**2**), utilizing an intramolecular ring closure to form key intermediate **5** is described.

Tuberculosis, caused by *Mycobacterium tuberculosis* (MTB), affects approximately one third of the global population and is associated with nearly two million deaths annually.[1] The fact that most of the problems associated with TB reside in developing countries establishes a clear and continuing need for economically accessible treatments and the growing presence of TB strains resistant to current drug regiments serves to accentuate this need. As part of a collaborative effort we recently identified two related natural products, gliotoxin (**1**)[2,3] and dehydrogliotoxin (**2**),[4] as potential candidates for further exploration as anti-TB agents. Gliotoxin has previously been demonstrated to be a potent inhibitor of MTB, showing minimum inhibitory concentrations ranging from 6 to 45 nM.[5] Dehydrogliotoxin had not been tested against MTB; however, it has been shown to inhibit macrophage phagocytosis in concentrations similar to that of gliotoxin[6] and was thus also considered a compound of interest. Intrigued by the potential utility of these compounds we began developing a program directed toward the synthesis of gliotoxin, dehydrogliotoxin and a series of structurally related analogs. From a synthetic perspective the relative structural simplicity of **2** led us to consider this natural product as our initial target.

Due to their structural complexity, the epidithiodiketopiperazine family of natural products has received considerable attention from the synthetic community; however, despite this effort, relatively few syntheses of naturally occurring epidithiodiketopiperazines have been reported. In early efforts Kishi and Fukuyama

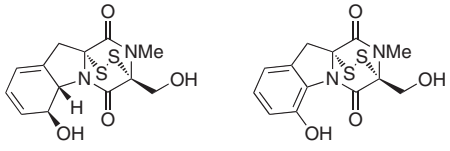

Figure 1. Gliotoxin (**1**) and dehydrogliotoxin (**2**).

reported the total syntheses of both **1** and **2** (Fig. 1).[7–9] Given that the primary objective of our efforts was analog generation, we initially decided to reproduce the elegant chemistry developed by Kishi with the intention of preparing analogs via appropriate modifications. As expected we found the Kishi synthesis to be absolutely sound; however, our efforts to increase the scale benefited from a few modifications. Herein we report the results of these studies and a scaleable formal total synthesis of dehydrogliotoxin (**2**).

A key intermediate in the Kishi synthesis of dehydrogliotoxin is diketopiperazine (DKP) **5**, the product of an Ullman-type coupling between aryl iodide **3** and DKP **4** (Scheme 1). Intermediate **3** was prepared by Kishi via a five-step sequence starting with *m*-cresol[10,11] and DKP **4** was obtained in four steps starting with sarcosine.[12] In the key coupling reaction, **3** and **4** were joined under forcing conditions, which afforded DKP **5**, after esterification.

Attempts on our part to utilize the Ullman-type coupling employed by Kishi proved effective but prohibitively low yielding

* Corresponding author. Tel.: +1 970 491 5703; fax: +1 970 491 1801.
E-mail address: john.l.wood@colostate.edu (J.L. Wood).

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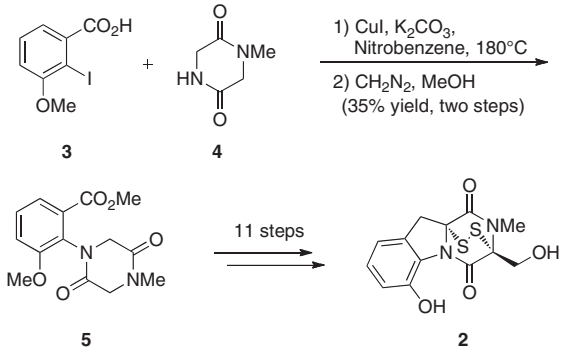
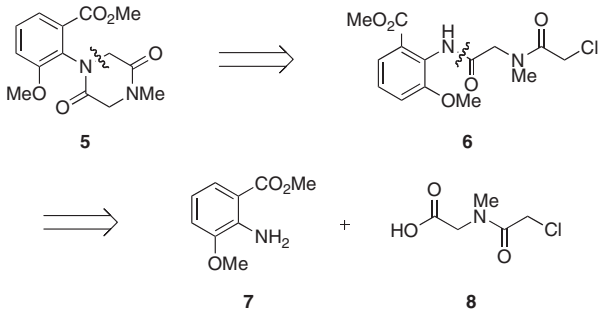


Scheme 1. Conditions employed by Kishi for the coupling of aryl iodide **3** and DKP **4** en route to dehydrogliotoxin (**2**).

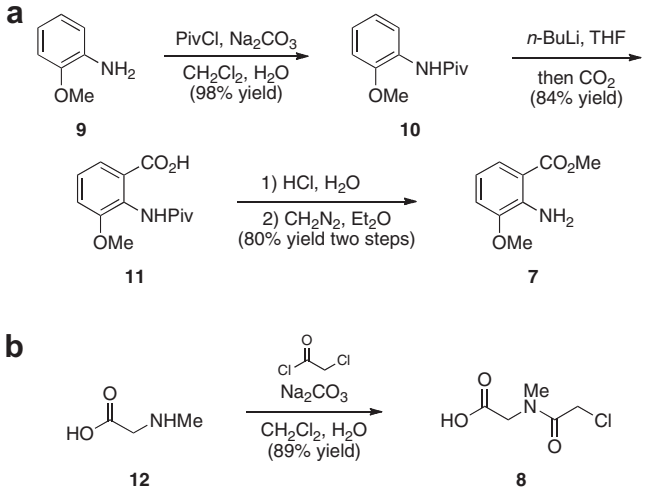


Scheme 2. Modified retrosynthetic analysis of DKP **5**.

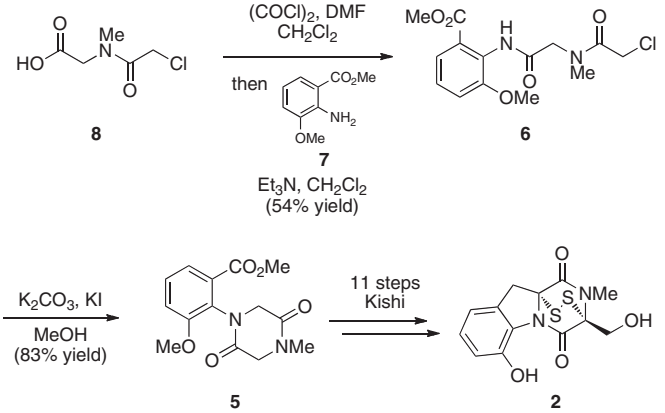
for eventual analog generation. Efforts to affect this coupling using more modern copper[13] or palladium[14] methodologies also failed to produce the desired aryl amide in synthetically useful yields. Attempts to couple the benzylic alcohol[15] or ester[16] variants of **3** under these types of conditions were also fruitless. These failures ultimately led us to explore alternative methods for accessing key intermediate **5**. To this end, we explored an approach to the DKP ring wherein the recalcitrant C–N bond was preassembled. Specifically, we envisioned that **5** would arise from ring closure[17,18] of alkyl chloride **6**, the bis-amide derived from coupling of aniline **7** with acid **8** (Scheme 2). In addition to convergency, a potential benefit of this approach was the absence of metal-mediated transformations that would prohibit the preparation of analogs bearing aryl halides.

Although simple esterification of the commercially available acid corresponding to aniline **7** would provide the first of the two coupling partners required for our approach, the extravagant cost of this acid prompted us to consider a more economical starting material. We were pleased to find that large quantities of aniline **7** could be accessed in high yield in four steps from inexpensive *o*-anisidine (**9**).[19] The second coupling partner, acid **8**, was prepared in accordance with a procedure reported by Ciufolini (Scheme 3).[20]

With the two components in hand, coupling commenced via initial conversion of **8** to the corresponding acid chloride followed by exposure to aniline **7**. Ring closure of the derived bis-amide **6** under basic conditions provided key intermediate **5** (Scheme 4). Although completion of **5** by this alternative route constituted a formal synthesis, our efforts continued through the remaining 11 steps reported by Kishi to deliver racemic **2**. This material was assayed for its ability to inhibit MTB and an IC_{50} of 0.13 μM was observed.[21]



Scheme 3. Synthesis of precursors (a) aniline **7** and (b) acid **8**.



Scheme 4. Synthesis of DKP **5**.

In summary, we have accessed DKP **5**, a key intermediate in the synthesis of dehydrogliotoxin, using an approach that is convergent, reproducible at scale and amenable to analog synthesis. Finally, we have advanced intermediate **5** to dehydrogliotoxin via the synthetic route reported by Kishi and found that the derived synthetic material exhibits an IC_{50} of 0.13 μM against MTB.

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21. Dehydrogliotoxin (**2**) was inoculated into a 96 well plate containing MTB at a final OD of 0.025. Cells were allowed to incubate for three days at which point bacterial growth was assessed by reading OD600.