

The First Synthesis of an Epidiselenodiketopiperazine

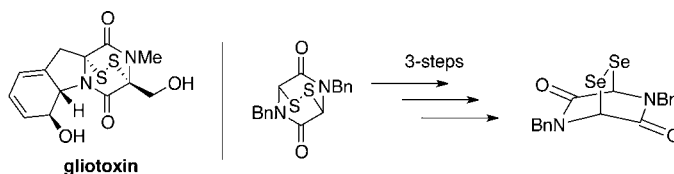
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ABSTRACT



Epidithiodiketopiperazines (ETPs) are natural products (e.g., gliotoxin) with varied and important biological activity, which often is attributed to the redox properties of the disulfide moiety. As such, analogs with altered redox properties and similar structural characteristics would be of value to biological investigations. The use of an ETP as the point of departure in the first synthesis of an epidiselenodiketopiperazine (ESeP) and its activity against *Mycobacterium tuberculosis* (MTB) is reported.

Approximately one-third of the global population is infected with tuberculosis, caused by *Mycobacterium tuberculosis* (MTB), leading to nearly two million deaths annually.¹ Although there are known cures for MTB, most of the problems associated with TB reside in developing countries that lack the infrastructure and resources to efficiently diagnose and then begin and complete treatment. This establishes a clear and continuing need for economically accessible treatments, and the growing presence of TB strains resistant to current drug regimes serves to accentuate this need. In 1950 Gliotoxin (**1**)² was shown to inhibit MTB with minimum inhibitory concentrations (MICs) ranging from 6 to 45 nM.³ As part of a collaborative effort we recently reported a formal total synthesis of dehydrogliotoxin⁴ (**2**) and demonstrated that this natural product is active against MTB with an MIC of 130 nM, thus establishing the broader gliotoxin family of natural products (Figure 1) as potential candidates for further

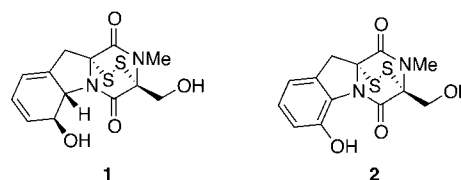


Figure 1. Gliotoxin (**1**) and dehydrogliotoxin (**2**).

exploration as anti-TB agents.⁵ Importantly, the gliotoxin family represents only a subset of a growing number of epidithiodiketopiperazine (ETP) natural products that have been isolated and shown to possess a broad range of interesting biological activities wherein the mode of action has yet to be fully delineated,⁶ however, it is believed that the bridging disulfide plays a major role. Unfortunately, the redox processes in which the disulfide moiety engages is also the likely culprit when it comes to the general toxicity

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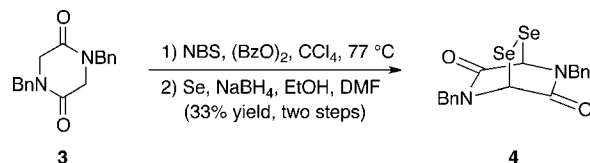
of ETPs.⁷ Given that the intracellular redox potential has been shown to vary at different stages of the cell cycle and in different diseases, we recognized that accessing and studying ETP-analogs with altered redox properties could provide insight into the possibility of developing compounds that would, on this basis, selectively engage diseased cells.⁸ In our initial studies to this end we were interested in replacing the disulfide with a diselenide.⁹ Herein we report the initial stages of this study which have culminated in the first synthesis of an epidiselenodiketopiperazine (ESeP).

Due to their structural complexity the ETP family of natural products have received considerable attention from the synthetic community,¹⁰ and several syntheses have appeared recently.¹¹ Although compounds in this class have clearly become more accessible there remains an absence of reports describing analogs wherein either one or both sulfur atoms have been replaced by selenium.¹² In fact, a literature search revealed only a limited number of bicyclic bridging diselenides,¹³ none of which were incorporated into a [2.2.2] framework. Unbiased by any reported approaches to ESePs we decide to develop a method that would allow for the conversion of an ETP to the corresponding ESeP, a strategy that would potentially enable one to employ gliotoxin, dehydrogliotoxin, or any other epidithiodiketopiperazine as a point of departure.

Prior to investigating an ETP to ESeP conversion we chose to familiarize ourselves with the potential reagents by exploring the conversion of a simple diketopiperazine (DKP) to the corresponding ESeP. To this end, known DKP **3** was converted to its corresponding dibromide¹⁴ which was then subjected to a diselenide dianion equivalent under conditions developed by Krief and Derock.¹⁵ Gratifyingly, under these conditions the desired bridging

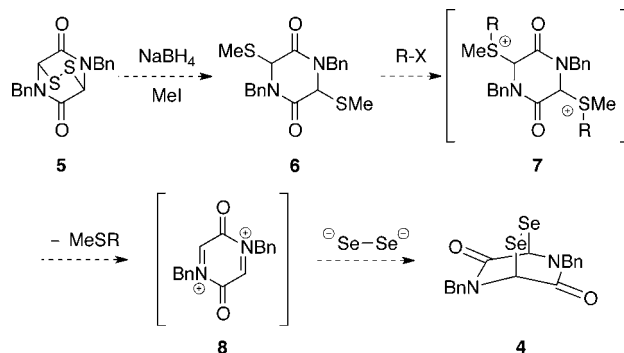
diselenide **4** was formed, presumably through the corresponding acyl-iminium intermediate (Scheme 1).

Scheme 1. Synthesis of Diselenide **4** from DKP **3**



Having established the viability of preparing a bridging diselenide from an intermediate bis-electrophile, we focused our efforts on the ETP to ESeP conversion. To this end it was envisioned that reduction of the disulfide and capture of the intermediate thiolates as their thiomethyl ethers would set the stage for an activation step wherein an intermediate bissulfonium (**7**) would give rise to the requisite acyl-iminium ion. Capture of this intermediate with a diselenide dianion equivalent in a manner analogous to our model study would then furnish the desired ESeP (**4**, Scheme 2).

Scheme 2. Planned Synthesis of Diselenide **4** from Disulfide **5**



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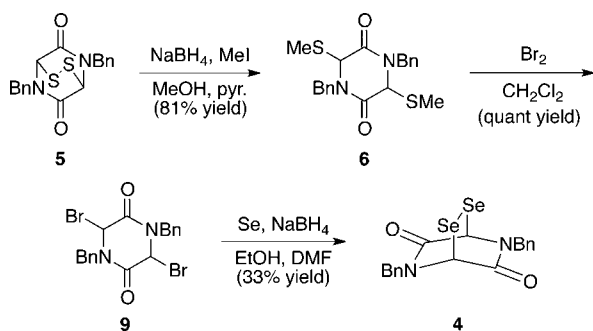
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To convert disulfide **5** to bithiomethyl ether **6** we first opened the disulfide with NaBH₄ and then treated the resultant dithiol with iodomethane.¹⁶ To activate the bithiomethyl ether we envisioned treating it with a variety of electrophiles including methylating reagents (to form dimethyl sulfide as a leaving group) or halogenating reagents. Ultimately bromine proved best, giving dibromide **9** when added to bithiomethyl ether **6**. As previously established the dibromide could be treated with the diselenide dianion equivalent to afford diselenide **4** (Scheme 3).

Having gained access for the first time to an ESeP (i.e., **4**) we decided to briefly look at its biological activity against MTB. For comparative purposes we also explored the activity of disulfide **5** and the corresponding bismethylthio- and bismethylseleno-analogs of **4** and **5** (i.e., **6** and **10**,

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Scheme 3. Synthesis of Diselenide **4** from Disulfide **5**



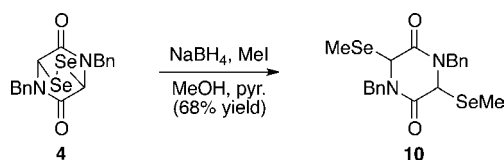
respectively). Our interest in the latter compounds was based on a study by Trown which demonstrated that conversion of the ETP acetylaranotin to its bistihiomethyl ether results in the loss of antiviral activity.¹⁷ In the event, the bisselenomethyl ether **10** was prepared in a similar fashion to **6** (Scheme 4), and the four compounds were assayed for their activity against MTB. Disulfide **5** which mimics the epidithiodiketopiperazine natural products exhibited an IC_{50} of $2.3 \mu\text{M}$. Gratifyingly, diselenide **4** showed comparable activity to that of the disulfide, with an IC_{50} of $2.7 \mu\text{M}$. Similar to what Trown observed, no activity was observed when the disulfide was replaced with a bistihiomethyl ether or when a methylene linker¹⁸ was added. Interestingly bisselenomethyl ether **10**, although

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(18) For the synthesis of the compound where a methylene linker is placed in the bridging disulfide, see the Supporting Information.

(19) For experimental details of the assay run, see the Supporting Information.

Scheme 4. Synthesis of Bisselenomethyl Ether **10**



not as potent, did show activity against MTB with an IC_{50} of $16.2 \mu\text{M}$.¹⁹

In summary, we have prepared the first epidiselenodiketopiperazine (ESeP) and established the viability of a route which employs ETPs as the point of departure. In addition, we have demonstrated that the derived ESeP shows activity against MTB that is comparable to the corresponding ETP. Investigations into the application of this method in more complex systems such as gliotoxin and dehydrogliotoxin as well as studies into the differential effects of ETPs and ESePs are ongoing and will be reported in due course.

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Supporting Information Available. Experimental details and copies of ^1H and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.