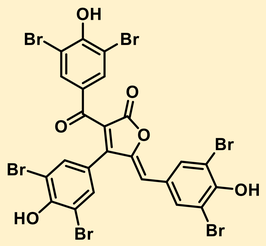

Laboratory Synthesis of Cadiolide Analogs

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Introduction

Cadiolide B is a marine natural product which has shown potential as a solution towards methicillin-resistant *Staphylococcus aureus* (MRSA). Cadiolides have been shown to possess minimum inhibitory concentrations (MIC) against MRSA growth that are similar to, or lower than, some leading antibiotics that currently exist on the market, such as Vancomycin[1,2,3]. A potential problem preventing Cadiolide B from being an orally-bioavailable drug is low solubility due to the presence of multiple lipophilic bromine atoms. Structure-Activity relationship studies by Franck's group[3] have shown that one bromine atom on each of the two Southern rings is sufficient to maintain activity. Moreover, when the Western ring is also replaced with a smaller and un-brominated furan ring, the resulting compound is four fold more potent against bacterial growth than Cadiolide B[3].

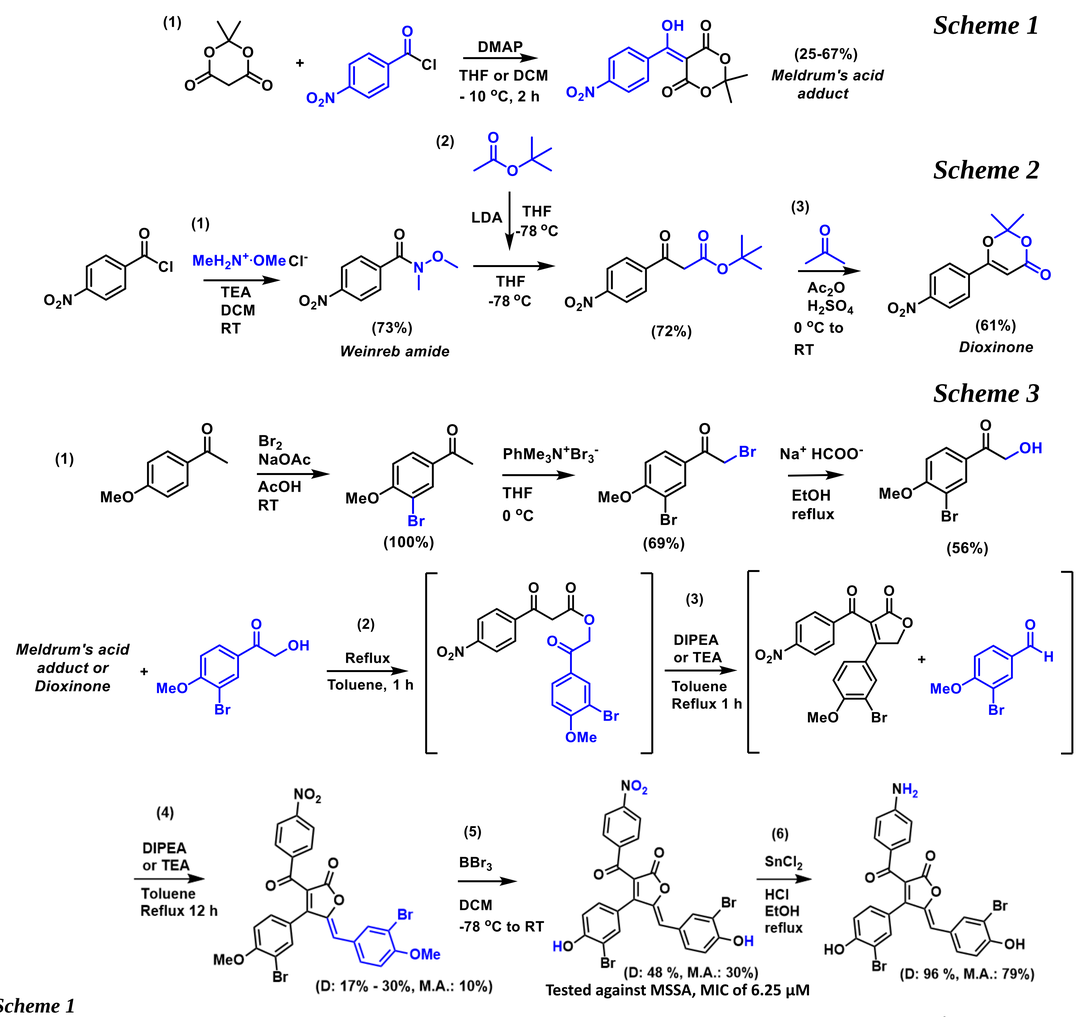
Objectives

The goal of this project was to investigate whether it is possible to enhance the antibiotic potential of the Cadiolides, especially against MRSA. To do so, I generated a number of sulfonamide containing Cadiolide analogs that results in a lowering of the clogP. Doing this is expected to improve the absorption of the molecule. Once these analogs were synthesized, they would be submitted for biological testing to determine the antibacterial potency against MRSA. This testing would be performed by collaborators at L^2 Diagnostics.

Our Approach

In this synthesis, the nitro substituent is introduced at the beginning by reacting a para-nitro-benzoyl chloride with Meldrum's acid. It is crucial that during this reaction and workup, the compound was kept cool to avoid decomposition of the adduct. As an alternative, a dioxinone was also produced then used in the same fashion as the Meldrum's acid adduct. After a series of reactions to reach the aniline functionality, the key intermediate was then converted into solubilizing polar functionalities, specifically sulfonamides. The results are outlined in *Schemes 1, 2,* and *3.*

Our Approach



Scheme 1
(1) Generation of Meldrum's acid adduct through the addition of the nitro-benzoyl chloride.

Scheme 2 [4]
(1) Generation of a Weinreb amide.
(2) Generation of a β-ketoester using LDA and the Weinreb amide.
(3) Conversion of the β-keto ester to the dioxinone using acetone.

Scheme 3
(1) Generation of the alcohol for the next step.[3]
(2) Formation of a β-ketoester through addition of the alcohol to the thermally decomposed Meldrum's acid adduct. The product was not isolated, but rather used in the next step in a one-pot fashion.[4]
(3) Formation of the acyl furanone through a Knoevenagel condensation.[4]
(4) Generation of the first key intermediate, the brominated methoxy acyl furanone.[4]
(5) Demethylation of the first key intermediate.[4] The resulting compound possessed a MIC of 6.25 µM, though it was found to be toxic to mammalian cells.
(6) The reduction of the amine to the aniline functionality.[5] The result is the second key intermediate. The reported yields are crude yields.
(7a,b) Conversion of the aniline to methyl and ethyl sulfonamides. The resulting compounds are still undergoing characterization.

Conclusions

Through this synthetic approach, four compounds were successfully synthesized: the nitro, the aniline, the methyl sulfonamide, and ethyl sulfonamide derivatives. The aniline is a handle to allow introduction of other solubilizing groups besides sulfonamides. As evidenced by the overall yield of approximately 1.09 % for the Meldrum's acid adduct scheme and 3.47 % for the dioxinone scheme towards the aniline, the reaction conditions must be optimized. The biological results, a MIC of 6.25 µM, for the nitro derivative are promising.

Future Work

The synthesis must be scaled up in order to produce more aniline and more analogs, such as ureas, carbamates, and amides. An interesting question that arose during the research is whether the use of a dioxinone or an acylated Meldrum's acid adduct is more efficient to reach the methylated nitro derivative. The Meldrum's acid approach has lower yields but is more time-efficient, whereas the dioxinone approach yields a higher quality intermediate, in greater amounts, but is more time consuming. The determination of which process is more efficient will be included in future research, as well as attempting to further optimize the Meldrum's acid approach. As more analogs are produced, we aim to continue testing their antibacterial potency against MRSA in collaboration with L^2 Diagnostics.

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