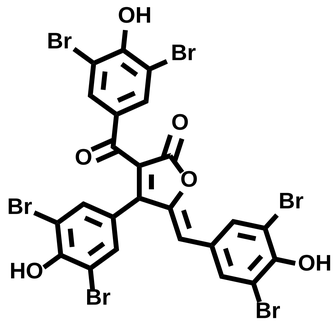
University of New Haven
Department of Chemistry and Chemical Engineering

# Total Laboratory Synthesis of Cadiolide B



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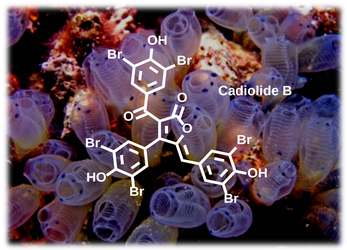
## Introduction

Infections due to strains of bacteria resistant to treatments, such as Methicillin-Resistant *Staphylococcus aureus* (MRSA), are rising in number. The search for new antibiotics is therefore vitally important. This search often begins from the discovery of natural products with antibacterial properties. Cadiolides were first isolated in 1998 as metabolites from *Botryllus* sp. in Indonesia (Figure 1)[1]. There are several varieties of Cadiolides, varying mostly on the level of bromination on the aromatic rings (Figure 2). These molecules have been found to be effective at inhibiting the growth of MRSA at concentrations similar to, or lower than the current leading antibiotics[2]. The mechanism of action for inhibition is not yet fully elucidated. Three separate syntheses of Cadiolides have been published to date[3,4,5], with one group reporting biological activity on closely related analogs[6]. For example, their Compound **9** (Figure 3) shows single digit micro molar inhibition of *S. aureus* (CECT 86). We wish to report on our own efforts toward the synthesis of Cadiolide B and analogs.

Figure 1.



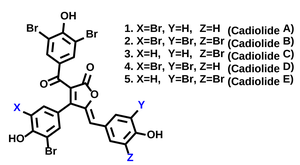




Figure 2.

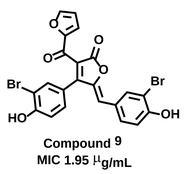



Figure 3.

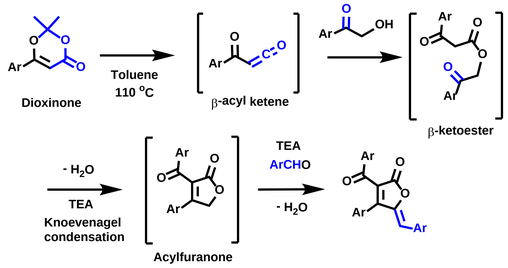
## Objectives

The goal of this project was to design an efficient laboratory synthesis for Cadiolides using reagents and methods that are available in an undergraduate setting. We hoped to achieve the synthesis of Cadiolide B, a natural product, as well as several analogs that are not naturally occurring to establish structure-activity relationships. Once the compounds are on hand, our goal is to submit them for testing to assess their potency at inhibiting the growth of several strains of MRSA. This would be done by collaborators at L² Diagnostics in New Haven, CT.

## Background

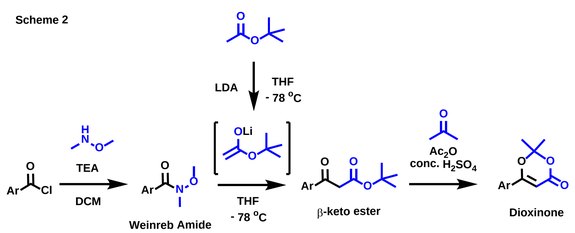
Peixoto *et al* published a synthesis of Cadiolides and analogs following a procedure outlined in Scheme 1. According to their procedure, the acylfuranone intermediate was synthesized via an intramolecular Knoevenagel condensation on a β-ketoester. The β-ketoester itself was made from a reactive β-acyl ketene obtained by thermal decomposition of a dioxinone.

Scheme 1




The synthesis of the dioxinone required the three steps outlined in Scheme 2, which included the use of LDA in anhydrous THF at -78 °C[4]. We therefore sought to simplify the approach by making use of an acylated Meldrum's acid adduct as the source of the β-acyl ketene, as it thermally decomposes similarly to the dioxinone (Scheme 3).

Scheme 2

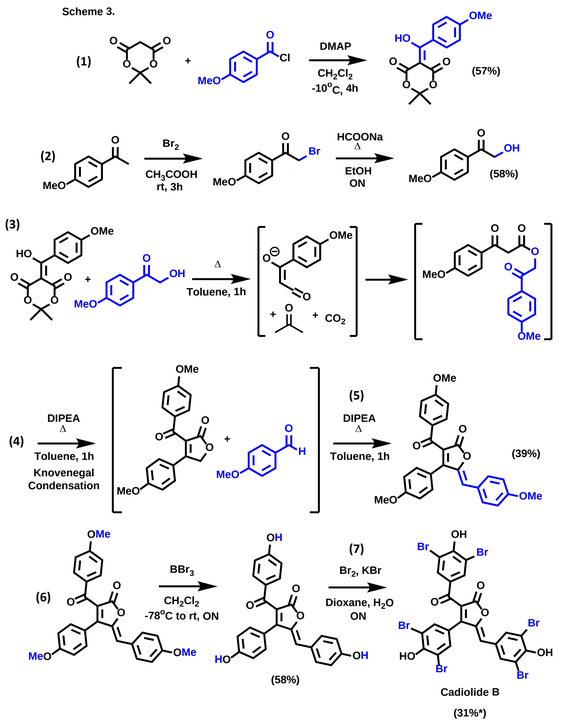



## Our Approach

After a number of setbacks, partly due to variability in the quality of commercial batches of Meldrum's acid, we were pleased to find that this approach worked well. Our results are outlined in Scheme 3. The key to our success is to acylate good quality Meldrum's acid at -10 °C (using a water, ice, and sodium chloride bath), to maintain the pH close to neutral during the extraction, and to keep the temperature of the Rotevap water cool during evaporation of the solvent. These precautions prevent the decomposition of the acylated material.

## Our Approach

Scheme 3.




**(1)** Generation of an acylated Meldrum's acid adduct through the slow addition of *p*-methoxybenzoyl chloride over 2 hours.
**(2)** Creation of an α-hydroxy-4-methoxyacetopenone to act as the nucleophile in the next step.
**(3)** Formation of a β-ketoester through addition to the β-acyl ketene generated from the thermal decomposition of the acyl Meldrum's adduct. The product was not isolated at this stage; the reaction proceeded through Step 5 in a one-pot fashion.
**(4)** Production of the acylfuranone through a Knovenegal condensation, similar to Piexoto *et al*.
**(5)** Generation of a key intermediate triaryl-furanone through addition of *p*-anisaldehyde.
**(6)** Demethylation of the triaryl-furanone to yield a trihydroxy-furanone using an acetone-dry ice bath.
**(7)** Synthesis of Cadiolide B through dibromination on each of the three aromatic rings.
*The final Cadiolide B product is still undergoing purification*

Through this seven-step sequence, the overall yield of the synthesis is **2.3%**.

## Conclusions

Our synthetic approach proved to be fairly successful as we were able to proceed through the reactions with reproducible results once the acylated Meldrum's acid adduct was on hand. This method shows promise to be a reliable way to synthesize Cadiolide B. However, with the overall yield of approximately 2.3% through the seven-step linear sequence, it is clear that the reaction conditions need to be optimized to maximize the amount of product produced at each stage.

## Future Research

Through modifications to the reaction procedures, analogous compounds can be made using the triaryl-furanone structure as a backbone. We hope to create several analogs of the Cadiolides, varying mainly in the presence of solubilizing groups on the aromatic rings, which will increase the drug-like characteristics of these compounds. After production of these compounds, we aim to test their antibacterial efficiency through analysis with collaborators at L² Diagnostics.

## References

[1] Smith *et al.* (1998) "Cadiolides A and B, New Metabolites from an Ascidian of the Genus Botryllus" *J. Org Chem. 63*: 4147-4150.
[2] Wang *et al.* (2012) "Antibacterial Butenolides From The Korean Tunicate *Pseudodistoma antinboja*" *J. Nat. Prods. 75:* 2049-2054.
[3] Boukouvalas and Pouliot (2005) "Short and Efficient Synthesis of Cadiolide B" *SYNLETT 2*: 343-345.
[4] Piexoto *et al.* (2013). "Versatile Synthesis of Acylfuranones by Reaction of Acylketenes with α-Hydroxyl Ketones: Application to the One-Step Multicomponent Synthesis of Cadiolide B and Its Analogues". *Eur. J. Org. Chem. 16:* 3316-3327.
[5] Boukouvalas, J. and Thibault, C. (2015). "Step-Economical Synthesis of the Marine Ascidian Antibiotics Cadiolide A, B, and D". *J. Org. Chem. 80:* 681-684.
[6] Boulange *et al.* (2015). "Synthesis and Antibacterial Activities of Cadiolides A, B, and C and Analogues". *Bioorg. & Med. Chem. 23 (13)*: 3618-3628.

## Acknowledgements

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