A Methodology for the Synthesis of Bioactive Butenolides

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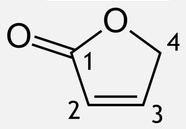
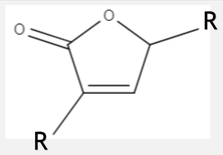
1 Background

Butenolides are a class of lactones with a four-carbon heterocyclic ring structure that can be synthesized and derivatized with different R groups. The compounds show important biological activities such as antibacterial and Antimicrobial[1]. Prior research led to the isolation of a group of these metabolites exhibited activity against *Candida* Albicans[2]. *Candida* infections, which are the most common types of yeast, show a potential response to the butenolides chemical[4]. This was found when using Bombardolides which are a group of butenolides that are unsaturated cyclic esters or lactones. The complications with using the butenolide chemicals is that many are not stable. A study was carried out which found butenolides to be thermically unstable and become decomposed through stomach digestion[7]. The objective of this research is to be able to find a way to use and synthesize a compound of butenolides that is a potentially useful yeast infections treatment. Past research carried out by other students at Winona State University on butenolides suggested that ring-closing metathesis (RCM) could be potentially be employed as an antimicrobial drug in the future. The RCM scheme, however, limits the potential for manipulating the R groups on the butenolide. Using a Suzuki coupling reaction will easily incorporate the desired R groups onto the substrate. A Suzuki coupling scheme would be able to proceed by purchasing an α-angelica lactone. Starting from this compound we would be able to synthesis it creating a substrate able to be carried out by an RCM.

Butenolide



Target Butenolide With R Group

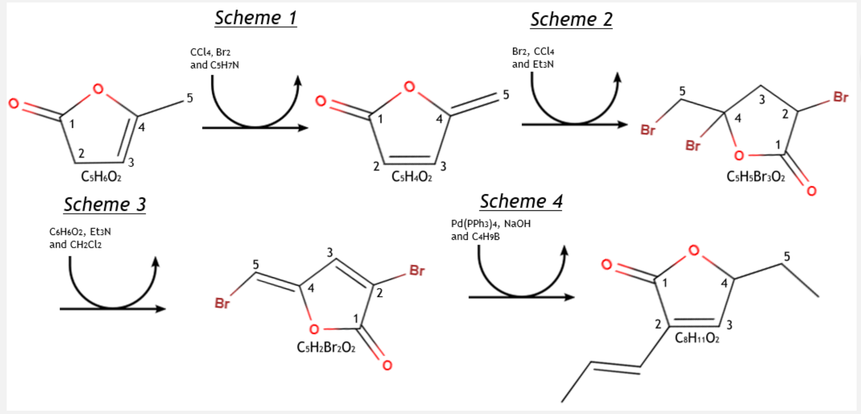


2 Process

A completion of a Suzuki coupling (Scheme 4) is the goal of this research. Before that is possible the starting butenolide compound must go through a four-scheme synthesis. The starting material chosen was a α-angelica lactone as a precursor for other butenolides because when converted to the substrate it would provide a suitable compound for Suzuki coupling. The first scheme would remove a hydrogen from carbon 2 resulting in a double bond being created between carbons two and three. The double bond that connects the third and fourth carbon would be changed to a single bond because a hydrogen is removed from carbon five via quinoline. This would then create a double bond connection between carbon 5 and carbon 4.

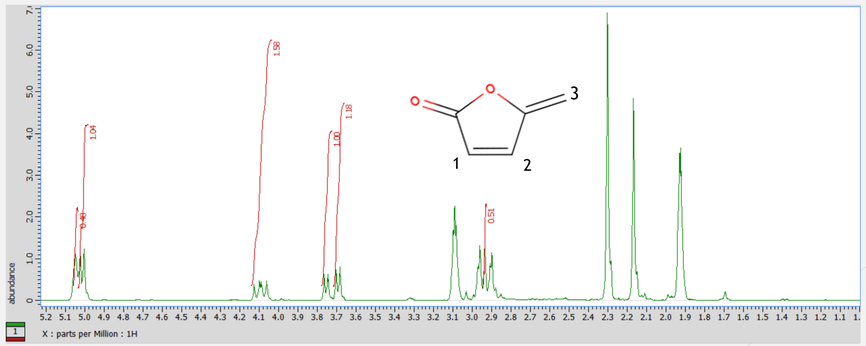
In the second scheme both the carbon/carbon double bonds would be broken due to the adding of bromines to carbon two, three and four. A hydrogen would be added to carbon three. The third scheme removes hydrogens from carbons 2, 3 and 5. It also removes the bromine group from carbon 4 creating a double bond between carbons 4 and 5. Scheme 4 goes through Suzuki coupling which removes the bromine off carbon two adding an allyl anion in place of it. A methyl group and one hydrogen are added to carbon 5 as well as a hydrogen to carbon 4 breaking the double bond between them. This creates the final $C_8H_{11}O_2$ product.

4 Scheme Process



3 Results

$C_5H_4O_2$ ^1H NMR Spectra



Assignment	Shift (ppm)
1	5.030
2	4.085
3	3.750 & 3.688

The ^1H NMR spectra above conforms the production of the wanted $C_5H_4O_2$ product. This spectra shows hydrogen 1 present at 5.030 ppm, hydrogen 2 present at 4.085 ppm and the last two hydrogen 3's are present at 3.750 and 3.688 ppm. The precent yield of scheme 1 was also calculated using the ^1H NMR. This was done by integrating the peaks from the product and remaining starting material and observing the relationship between them. Scheme 1's products integration was found to be: H1=01.04, H2=1.58 and H3=1.00 &1.08.The starting material remaining in the product of scheme 1 shows an integration number of 0.48 for H-1. Scheme 1's product $C_5H_4O_2$ then holds a yield of 69.421% from the original α-angelica lactone. Scheme 2, 3 and 4 were not able to be carried out due to time constraint and shipping delays.

4 Experimental

Scheme 1

CCl_4 (1 mol equiv.) & Br_2 (0.98 equiv.) were added to an RBF. α-angelica lactone (1 mol) was *Slowly* added and stirred on ice for 1 hour. After 1-hour Quinoline (2.1 mol) was added and stirred for 5 hours.

5 Conclusion & Future Work

From the results found, we conclude that this is a positive route towards the synthesis of the $C_8H_{11}O_2$ butanolide structure. By using the butenolide derivatives and utilizing the first outlined synthetic pathway the reaction came out to have an overall yield of 69.421%. The synthesized butanolide did not have a chance show activity against *Candida* albicans yeast. In future research edits to scheme two would need to be carried out. This may include a less time stirring and refluxing to try and keep the product a liquid instead of turning into a solid. Another possibility is work in smaller concentrations to ensure no miscalculations of reactants are added.

References

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