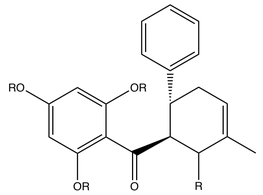
# Diels-Alder Reaction to Synthesize Biologically Active Molecules


## Emmaline Wittwer, Dr. Dana Horgen

Rhodes College, *2000 N. Parkway Memphis, TN 38112*

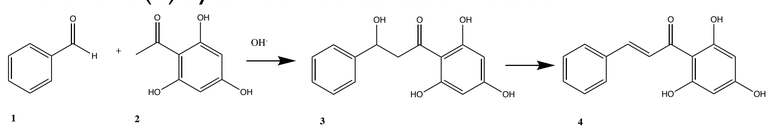

## Introduction

- An ethanol extract from the roots of *Boesenbergia pandurate* shows bioactivity which is harmful to the cells of PANC-1 human pancreatic cancer. Additionally, fifteen other molecules have been identified via purification of the extract[1].
- The target is this core structure that is present in nine of the fifteen identified molecules. If we create a reliable way to make the core structure then we could change the substituents on it to make the nine biologically active molecules.



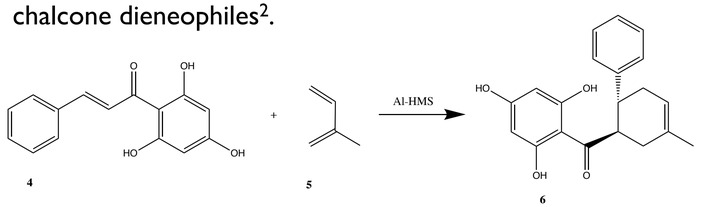

## Methods

- We will work to make the core structure by first synthesizing a chalcone (**4**) by an Aldol condensation reaction.




**Scheme 1.** The Aldol condensation reaction will produce the chalcone that will be used in the Diels-Alder reaction.

- We will use a Diels-Alder reaction with the synthesized Aldol condensation product (**4**) and isoprene (**5**) to make the core structure (**6**). This reaction requires the catalyst, aluminum hexagonal silica (Al-HMS), which has been shown to lead to high yields in the Diels-Alder reactions between similar diene and chalcone dieneophiles[2].




**Scheme 2.** This Diels-Alder reaction will synthesize the core structure that can be further reacted to synthesize biologically active molecules.

- hexadecylamine, tetraethyl orthosilicate, and aluminum isopropoxide were used to synthesize the catalyst (Al-HMS) for the Diels-Alder reaction[2].

## Results

Chalcone Attempt 1:

- The first attempt to make the chalcone did not form a solid after 15 M sodium hydroxide was added. We believe this to be due to the water present in the solution, as well as the water that was added in the form of ice.
- We added sulfuric acid to try to protonate any of the hydroxyl groups, hoping that the desired product would then crash out.
- A minimal amount of solid precipitated.
- We found that acetone caused a large amount of solid to crash out and we performed NMR analysis on the solid.

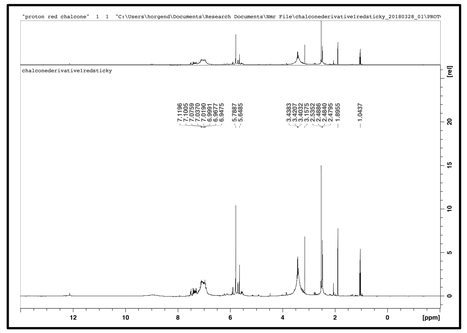



**Figure 1.** $^1$H NMR of crude product reaction mixture. Crude product was red and sticky. Aromatic peaks are present between 7-8 ppm as well as possible vinyl protons near 6 ppm.

Chalcone Attempt 2

- We tried the reaction again omitting the use of water. Upon the addition of sodium hydroxide pellets, a large amount of solid crashed out.

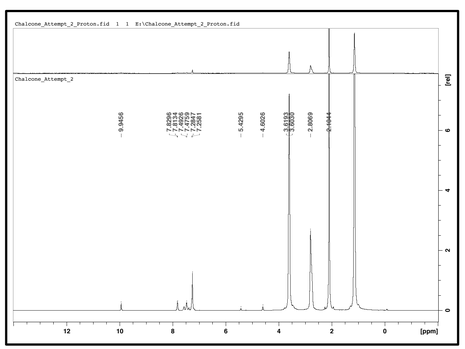
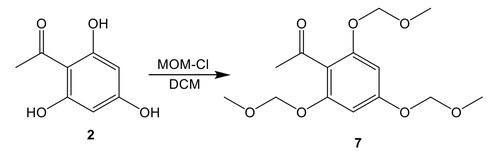



**Figure 2.** $^1$H NMR of crude product reaction mixture. The peak at 9.9 ppm may be due to either the desired hydroxyl groups, or it may be due to the hydrogen on benzaldehyde.

## Conclusions

- The $^1$H NMR for the crude product of attempt 2 suggests that it was more successful than the first attempt in which we added water to the reaction. Our future attempts with the aldol condensation reaction will not use water.
- The next steps for this project will be to remove the solvent ethanol from the chalcone attempt 2. The $^1$H NMR peaks at 3.6 ppm look like hydrogen on $CH_2$ in ethanol. The peak around 1.2 ppm looks like hydrogen on $CH_3$ in ethanol. Removing a large amount of ethanol and taking a new $^1$H NMR will help us determine if the peaks are due to solvent, or the product.
- Another method that we may utilize to make the chalcone is to protect the hydroxyl groups of the 2,4,6-trihydroxy acetophenone with methoxy methyl (MOM).




**Scheme 3.** Protection of the aryl hydroxy groups should help eliminate any issues with the presence of water, or other solvents that may prevent crystalization of the chalcone product..

- Once we are confident that we have synthesized the chalcone, we will be able to move on to the Diels-Alder reaction with isoprene to synthesize the core structure (**6**).

## References


1. Nguyen, N.T.; Nguyen M.T.T.; Nguyen H. X.; Dang P. H.; Dibwe D. F.; Esumi, H.; Awale, S. Constituents of the Rhizomes of *Boesenbergia pandurate* and Their Antiausterity Activities Against the PANC-1 Human Pancreatic Cancer Line. *J. Nat. Prod.*, **2017**, 80 (1), pp 141-148. DOI: 10.1021.
2. Corbett, J.L.; Weavers R. T. Aluminosilicate Catalysis of Chalcone Diels-Alder Reactions. *J. Synthetic Communications*. [Online]. **2007**, 4, 489-498 https://www.tandfonline.com/doi/full/10.1080/00397910701796527 (accessed February 20, 2018).
3. Stork, G; Takahashi, T. *JACS* **1997**, 991275.