The Conversion of Hemiacetals into Antiviral & Anticancer Compounds

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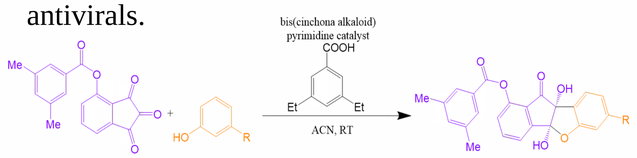
Research Purpose

The overarching goal is to create antiviral amine compounds by converting specific, isolated isomers of chiral cyclic hemiacetals.

Introduction

The *Picornaviridae* family of viruses cause diseases such as the flu, polio, and Hepatitis A. Dangerous newborn picornaviruses, including coronavirus, has led to a demand of drugs that can inhibit the function of these viruses.

Tetracyclic antivirals, a benzofuran, is an example of a potent picornavirus inhibitor for Ebola and Coronavirus. It has also been discovered that Tetracyclic antivirals contains anti-cancer properties[2]. This has prompted us to developed a modified catalytic asymmetric addition Interrupted Fiest-Bènary (IFB) reaction to create chiral cyclic hemiacetals, as depicted below. Using these hemiacetals, we can create amines with similar properties to Tetracyclic antivirals.



Acknowledgements

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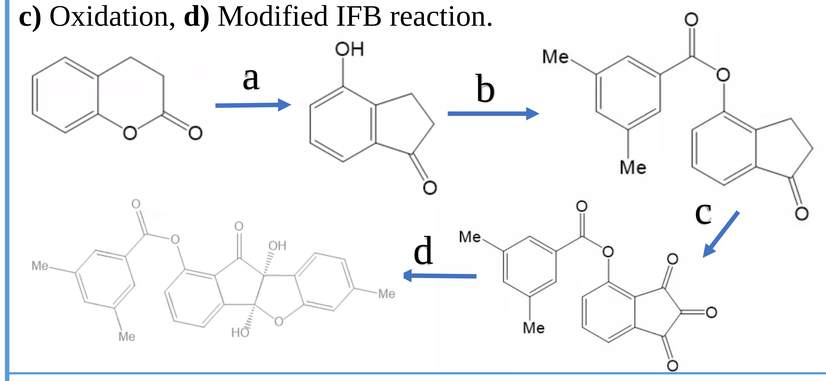
References

Throssell Yoana; Michael A. Calter. **2019** *Acid-Assisted Catalytic Assymmetric Interrupted Feist-Bènary-like Reactions of 1,2,3-Indantriones and Substituted Phenols, (b)Supporting Information Placeholder*

Methods

The synthesis of our chiral cyclic hemiacetal is a four-step reaction: **a)** Friedel-Craft Acylation, **b)** Esterification, **c)** Oxidation, **d)** Modified IFB reaction.



<u>The reaction conditions are as follows:</u>

a) Aluminum Chloride, Sodium Chloride @ 220 °C

b) Catalytic DMAP, DBU, Acetonitrile @ room temperature

c) Selenium Dioxide, Dioxane @ reflux

d) 10 mol% DABCO, Acetonitrile @ room temperature

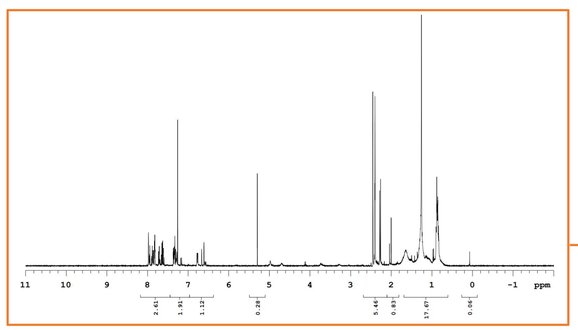
<u>Reaction 'a' troubleshooting</u>: First few reactions of step **'a'** produced a thick black gum instead of producing the desired powdered form of the indanone. Adding in the dihydrocoumarin dropwise solves the problem.

<u>Reaction 'b' troubleshooting:</u>

- Filter crude before work-up
- Run flash chromatography with 5%-70% EtOAc : Hexanes rather than 10%-15% EtOAc : Hexanes
- Dry load crude before flash chromatography column.

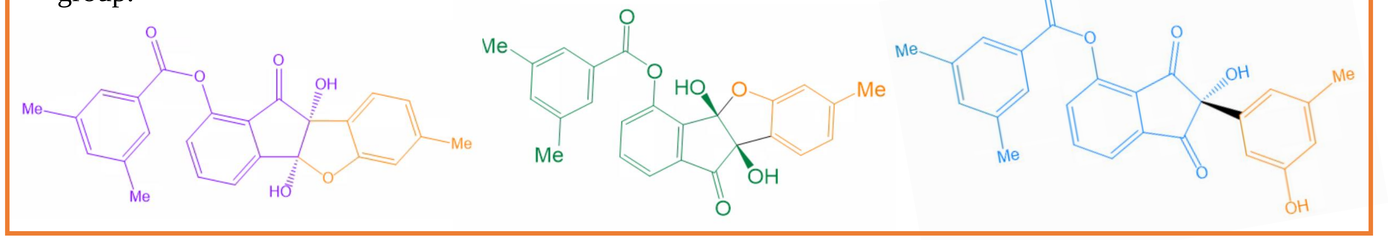
Methods: All reactions were performed under N_2 gas. The dry solvents were obtained from an activated alumina purification system and then purified via flash chromatography. ^{1}H-NMR were collected on Varian-400 (400 MHz) spectrometer. All NMR samples were collected in Chloroform-D.

Results



An ^{1}H-NMR confirms that the IFB reaction produced our desire chiral cyclic hemiacetals. The identity of this hemiacetal is (4bS,9bs)-4b,9b-dihydroxy-7-methyl-10-oxo-4b,9b-dihydro-10H-indeno[1,2-b]benzofuran-1-yI-3,5-dimethylbenzoate.

The three molecules below are possible configurations for our hemiacetal. These configurations are the result of exposure to acids strong enough to cause an acid-catalyzed hydrolysis. Though our desired product was made, we hope to be able to isolate each configuration to convert them into amine compound with antiviral & anticancer properties. This would be done by reducing the `hydrolyzing the ester and adding an amide group.



Conclusion

Although, we have yet to synthesize the desired amide, we have successfully synthesized the chiral cyclic hemiacetal through the reaction pathway outlined in the methods. However, from step b, product yields are low. In future experimentations, we will find solutions to increase yields.

Next Steps

Firstly, if the research period had been longer, an HPLC analysis would have been performed to investigate the composition of our final hemiacetal products. Furthermore, the next step in the synthesis, would be to remove the ester group on the hemiacetal. After this is done, two more reactions will have to performed to convert the hemiacetal into an amide. The retrosynthesis can be observed below: