Steps Towards the Synthesis of Amaryllidaceae Alkaloid Analogs

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Abstract

Amaryllidaceae isoquinoline alkaloids, as well as their analogs, have long been of interest in research for drug discovery due to their biologically active nature. Many of these compounds have been found to be anti-tumor agents. Moreover, there have also been studies that show the effectiveness of these molecules against diseases such as Yellow Fever and other RNA-containing flaviviruses. Though these compounds are pharmaceutical drug prospects, their low natural abundance lowers that potential. For this reason, many synthetic chemists have pursued novel routes to synthesize a wide variety of these compounds.

Techniques toward the synthesis of Pancratistatin-type natural products are presented herein. Manipulations were tested and optimized on a model system to save both time and funds while developing a synthetic pathway to be utilized in the formation of more complex compounds. Several challenges have been encountered such as the epoxide ring being opened when expanding the spiro ring to form the C ring. However, adjustments are being made to avoid such difficulties. Ideally, the proposed scheme will ultimately allow for the synthesis of multiple biologically active Phenanthridone analogs.

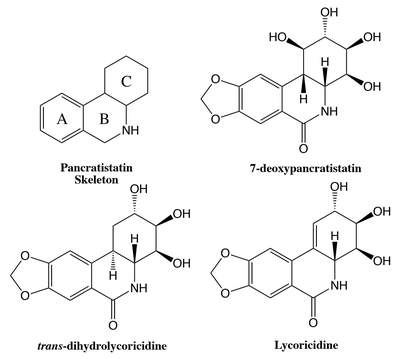

Figure 1. Structures of title compounds

Difficulties with Imide Ring Formation

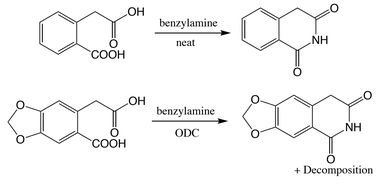

Figure 4. Previous Unsuccessful Model System for Imide Formation

The above model scheme reaction was successful for the model molecule, but proven ineffective for the synthetic approach. The new model scheme includes an anhydride ring formation, which has been shown to work on the synthetic scheme.

Synthetic Strategy

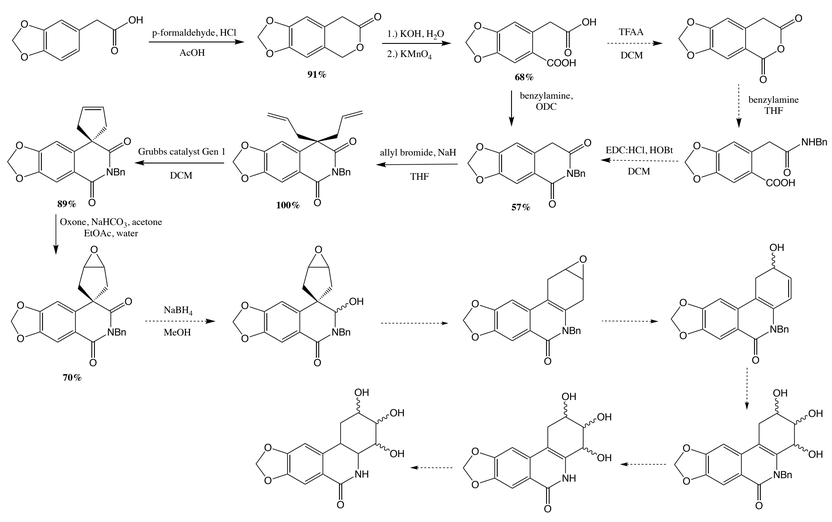

Figure 2. Synthetic Scheme for Pancratistatin-type Analogs

Our current strategy for synthesizing Pancratistatin-type analogs starts with methylenedioxyphenylacetic acid. This starting material includes the A ring as well as the characteristic methylenedioxy substituent. The B ring has been incorporated by reaction of the dicarboxylic acid with benzylamine to form an imide ring, with mixed results. A new scheme to form the B ring is by formation of an anhydride ring, which is then opened with benzylamine and was again closed to form an imide ring. The final ring is formed from a ring expanding reaction of a 5-membered spiro that is adjacent to a hemiaminal. Various other eliminations, oxidations deprotections, and reductions will also be used after transformations to reach the target molecules. Yields are provided for the transformations that have been completed successfully.

Ring Expansion without Affecting Epoxide

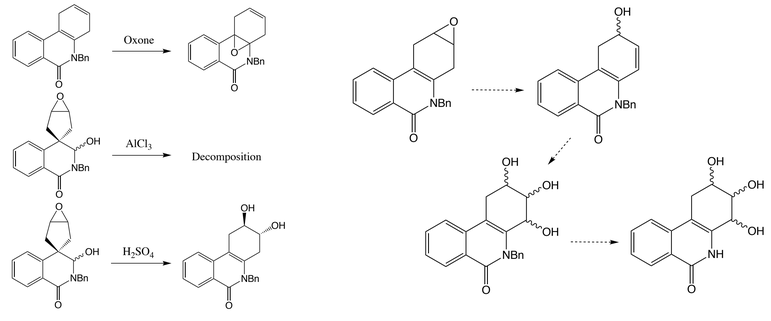

Figure 5. Functionality of and Attempts at Synthesizing Epoxide-Containing Six-Membered Ring

One of the main challenges facing this project is how to efficiently produce the necessary stereochemistry of the hydroxyl groups of the target molecules. One possible route to accomplish this is by keeping the epoxide intact when ring expanding from the five-membered ring to the six-membered ring. This will allow for elimination and oxidation reactions to effectively form the three necessary hydroxyl groups. The reactions would likely form enantiomers, which would need to be separated.

Model System Experimentation

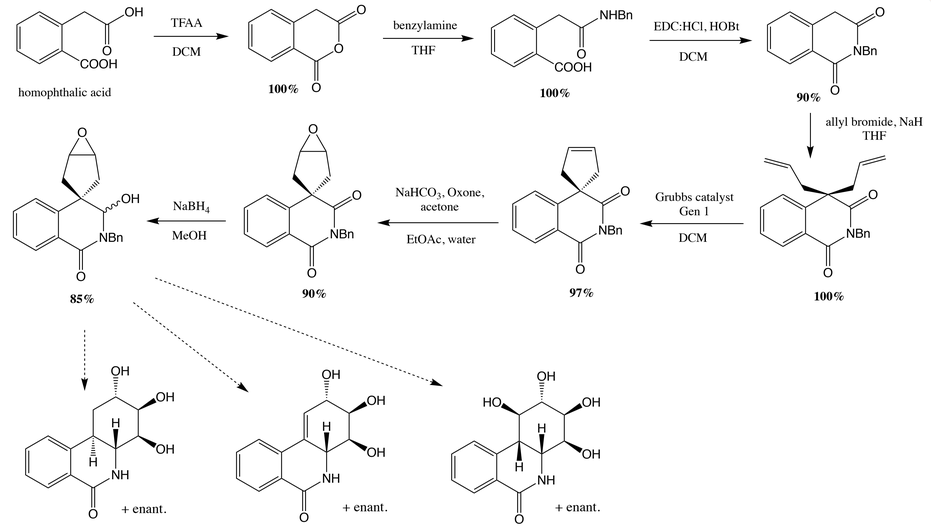

Figure 3. Model System Progress

All reactions were performed on a model system that was designed around homophthalic acid as the starting material. This reagent does not contain the methylenedioxy substituent found in the target molecules, but it is much more affordable than methylenedioxyacetic acid. Thus far, any reaction that has worked on the model system has also been successful on the system with the methylenedioxy group. Future plans for this project include determining a route that incorporates three or four hydroxyl groups on the C-ring with correct stereochemistry to form the model system equivalent of the target molecules. One potential route includes the ring expansion while keeping the attached epoxide intact as described in Fig. 4.

Conclusions

Our lab has already successfully installed two hydroxyl groups on the C-ring in both model and methylenedioxy systems. However, the target compounds contain either three or four hydroxyls on this ring. Having an epoxide on the C ring would likely make this challenge more attainable. The epoxide has proven to be difficult to maintain through ring expansion of the five-membered spiro ring to the six-membered ring. When ring expansion is attempted in the presence of a Lewis acid, it has so far been observed that the epoxide can react and open to form a diol. This creates the issue of increased difficulty in synthesizing the correct stereochemistry of the necessary hydroxyl substituents. Our lab is currently investigating methods of such transformations. Once we solve the issue of ring expansion without opening the epoxide ring, we are confident that our efforts will lead to the synthesis of one or more of the target compounds.

Acknowledgments

To Dr. Minter for his guidance on this project and for allowing me to join his research group as an undergraduate. To Adam Montoya for showing me how to conduct chemical research and how to enjoy it at the same time. To TCU chemistry professors for giving me the tools I need to be successful in a research environment. Lastly, to TCU for the facilities and funding that made this research possible.