Optimizing the Synthesis of a Pancratistatin Model System

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Abstract

Pancratistatin is a natural alkaloid that can be isolated from the bulbs of Hymenocallis littoralis, which is a tropical plant commonly referred to as the Spider Lily. Pancratistatin has been shown to have potent cytotoxic anti-tumor activity in biological testing, meaning that it could be a key component for designing natural anti-cancer drugs. The key structural component responsible for the cytotoxic activity of Pancratistatin is the phenanthridone ring system. Pancratistatin has also been proven to combat RNA-containing flaviviruses such as Yellow Fever, Zika, and West Nile Virus. Previously reported procedures for synthesizing Pancratistatin have been reasonably successful, but they all involve the use of lengthy sequences that produce low yields in order to reach the desired product. The purpose of this research project is to provide a more efficient synthesis by increasing the final yield and decreasing the number of steps required. Through successfully synthesizing Pancratistatin, several different analogs of the molecule that contain the phenanthridone ring will also be obtained.

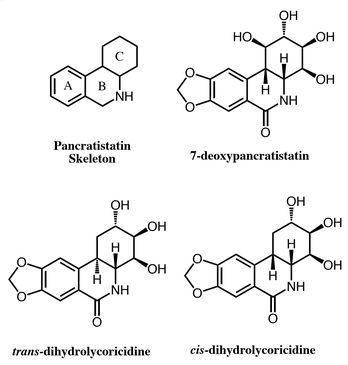

Figure 1. Structures of title compounds

Attempts to Bypass Ring-Closing Metathesis

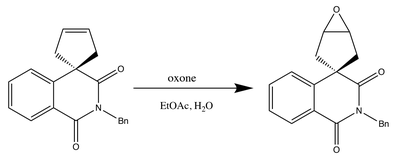

Figure 4. Strategies to Optimize the Yield of Oxone Epoxidation

Reproducibility of the Oxone reaction proved to be problematic. Purchasing new Oxone and reevaluating reaction conditions reestablished reproducibility.

Model System Synthetic Strategy

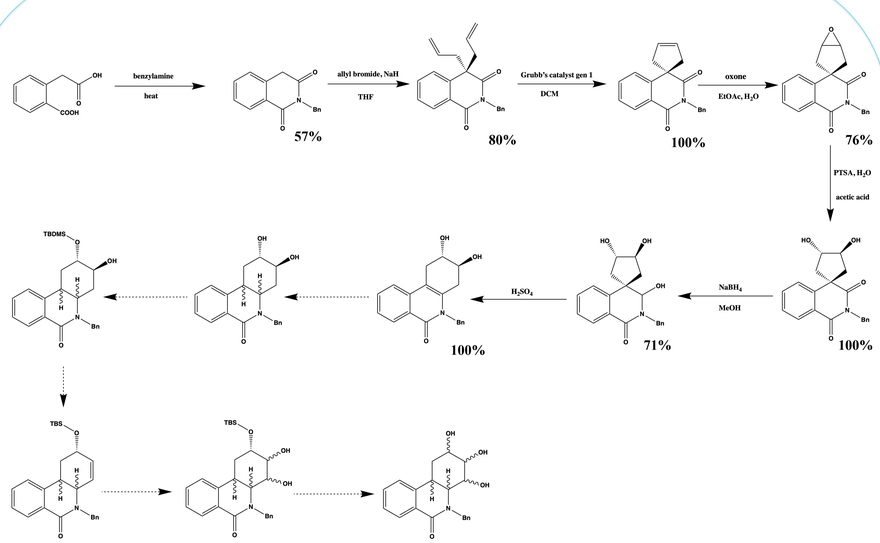

Figure 2. Synthetic Scheme for Pancratistatin-type Analogs

All reactions were performed on a model system that was designed around homophtalic 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. This model system was primarily used to optimize the reactions and increase yields before working with target molecules. The current synthetic scheme has been successful up until the elimination step after performing a ring expansion. Yields are provided for the transformations that have been completed successfully.

Attempts to Protect the Diol Prior to Reduction

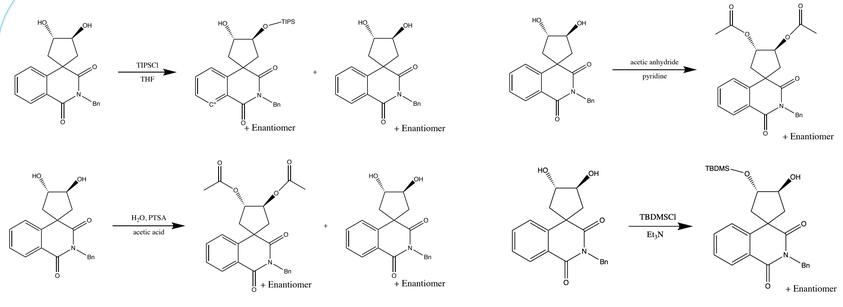

Figure 5. Attempted Reactions to Protect the Diol

Several reactions were attempted to protect the diol. The goal of these reactions was to find a protecting group that would selectively monoprotect the diol. There was difficulty finding a protecting group that would monoprotect successfully. TBDMSCl was the only group that consistently monoprotected the diol with a good yield. In future reactions TBDMSCl and Et_3N will be used to monoprotect the diol before eliminating in the following step.

Future Plans for Experimentation

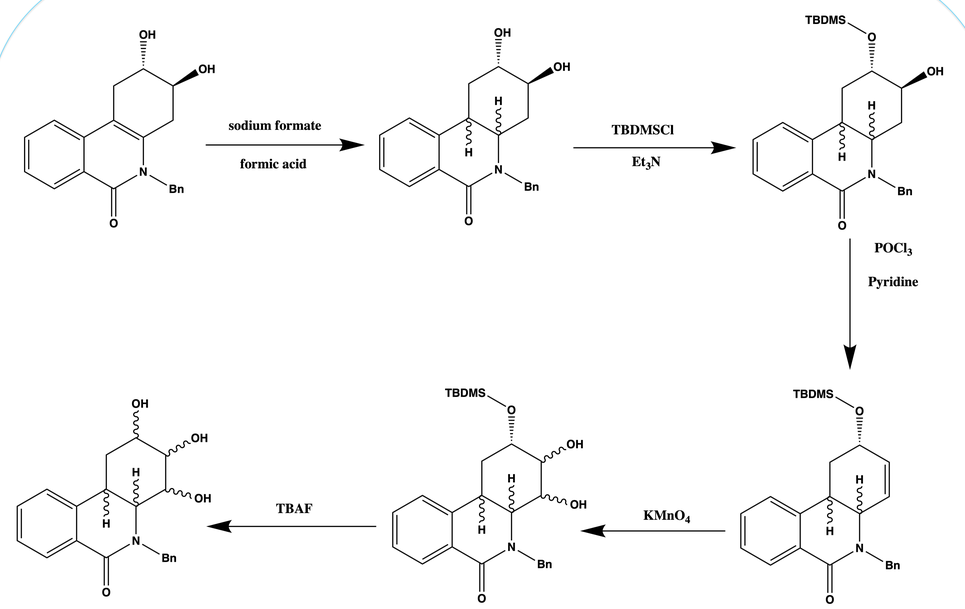

Figure 3. Future Reactions

Future plans for the reaction scheme are tentative, but the listed reagents will be used initially. It is expected that there will be some difficulty reducing the double bond in the first reaction due to previous issues in the project. Previous attempts have failed to react because tetra-substituted double bonds are difficult to reduce with platinum or palladium catalysts. Using formic acid and sodium formate should allow for a successful reduction to take place. The TBDMS protecting group step has been completed on a different starting material. This reaction should work on the model system but it is expected that a separatory technique will need to be used in order to isolate the desired monoprotected diol.

Conclusions

The model system has allowed for many unnecessary steps to be removed from the original synthetic scheme. The use of the epoxidation step caused the overall reaction scheme to be much more simpler and increased the overall yield. Modifying the reaction conditions of the reaction allowed for a more reproduceable procedure that consistently generated high yields. Solving the issue of monoprotecting the diol proved to be quite difficult. After attempting several different methods it was determined that the TBDMSCl reaction was the most efficient and selective. Selectivity of the protecting group is vital in order to successfully eliminate in the correct position during the following reaction. This creates the issue of now having to separate the mix of products. Our lab has successfully done this by using column chromatography. Future plans are to finish experimentation on the model system in order to later apply these methods to the target molecules. By optimizing the model system in theory these reactions will work on target molecules in order to successfully synthesize Pancratistatin.

Acknowledgments

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