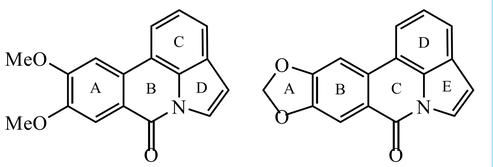
Total Synthesis of Hippadine and Pratosine: Intramolecular de Mayo Photocyclization

Charles I. Ochoa, David E. Minter*

Department of Chemistry and Biochemistry, Texas Christian University, Fort Worth, TX 76129

Abstract

Hippadine and pratosine are lycorine-type pharmacologically active *Amaryllidaceae* alkaloids. Although several total syntheses of these natural products have been developed, most of the routes require prohibitively expensive materials and/or give low overall yields. Our current research involves the development of new synthetic methods starting with 6,7-disubstituted isoquinolines that should be suitable for preparing these alkaloids on a large scale using inexpensive materials. The key step in the synthetic scheme centers around an intramolecular de Mayo photocyclization that uses the reaction of the alkene in an isocarbostyril with a 1,3-diketone contained within a six-carbon functionalized tether on nitrogen. The resulting tricyclic system should contain a 1,5-diketone grouping, but these functions are masked in the form of a cyclic hemiketal. Nevertheless, a base-catalyzed aldol addition reaction affords the ABCD-ring system present in hippadine and pratosine. Dehydration of this product affords a β,γ-enone that can be transformed to a diene in two steps. Oxidation of the diene with DDQ affords the target natural products after simple chromatographic purification. This synthetic pathway circumvents the use of catalysts that are either expensive or contain metals such as palladium or iridium. Moreover, our method allows for the syntheses of analogs in high yields by modifying the tether group on nitrogen.



Pratosine **Hippadine**

Figure 1. Structures of title compounds

Synthetic Strategy toward the Synthesis of Hippadine

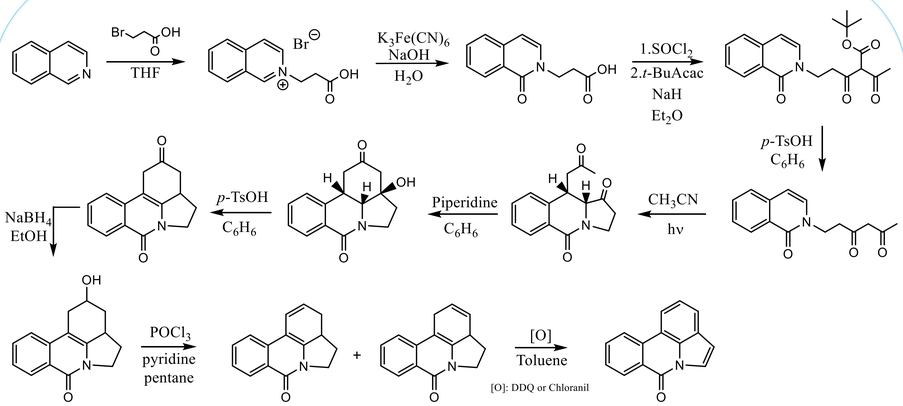


Figure 2. Synthesis of the Galanthan Skeleton

The Minter group has studied the formation of a galanthan-type system analogous to hippadine (without the methylenedioxy substituent) in order to find the optimal conditions to synthesize these natural products. The key step in the synthesis is a de Mayo photocyclization between a nitrogen tether (a 1,3-diketone) and the isolated double bond on the isocarbostyril unit of the molecule. Research has been done in order to achieve a fully aromatic system, deeming the synthetic route of the model system complete.

Solubility Problems During the Synthesis of the de Mayo Precursor

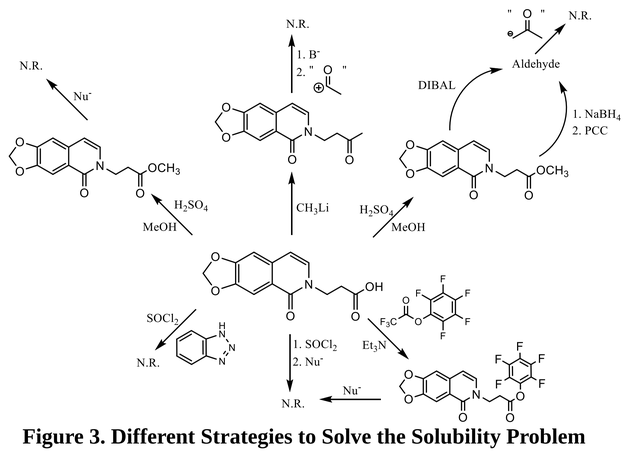


Figure 3. Different Strategies to Solve the Solubility Problem

When the same synthetic approach was applied to a system that would ultimately give hippadine as the product, a solubility problem arose: the 6,7-methylenedioxy carboxylic acid (and its acid chloride) was insoluble in every solvent necessary for the synthesis of the tricarbonyl compound. Several different avenues were investigated, including some which bypassed the synthesis of the tricarbonyl compound altogether.

Complete Synthesis of Hippadine and Pratosine

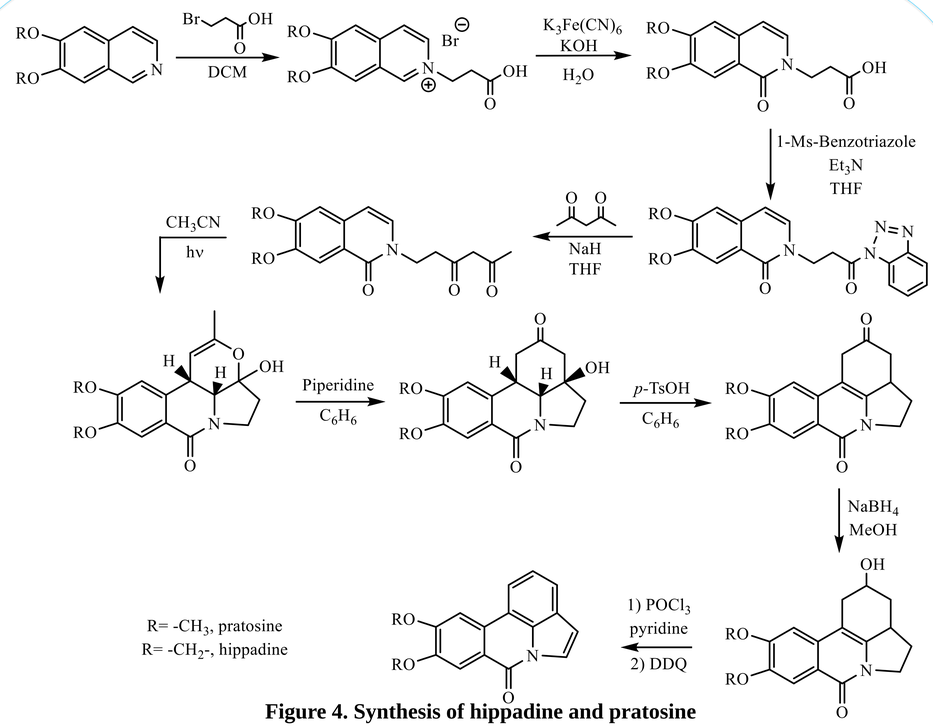


Figure 4. Synthesis of hippadine and pratosine

After various acyl substituents were tested, the *N*-acylbenzotriazole compound proved to be slightly soluble in THF. Although the tricarbonyl compound could be synthesized from here, we recently found that reacting the anion of 2,4-pentanedione in THF with the *N*-acylbenzotriazole provides the 1,3-diketone directly. The β-diketone was subjected to de Mayo photocyclization conditions, affording the 1,5-diketone masked as a hemiketal whose structure was elucidated by 1-D and 2-D NMR analysis. An aldol condensation reaction was done on the product, affording the β,γ-enone. Reduction of the ketone with $NaBH_4$, dehydration with $POCl_3$ and pyridine, and finally oxidation with DDQ afforded the desired alkaloids.

Conclusions

Two *Amaryllidaceae* alkaloids, hippadine and pratosine, have been synthesized starting from a 6,7-disubstituted isoquinoline starting material. Our synthetic route avoids the use of heavy metals or expensive catalysts and at the same time allows for the synthesis of several derivatives depending on the starting materials utilized. Furthermore, this is the first reported example of an intramolecular de Mayo photocyclization reaction for the synthesis of galanthan-type natural products.

Acknowledgments

To Dr. David Minter, for his direction on this project, help with preparing this poster, and his mentoring and support on my graduate career overall. To my committee members, for all their advice and discussions about chemistry and other aspects of graduate school. To the other members of the Minter group, for their constant support through the graduate school experience. Finally, to TCU, for providing the facilities and funding that are necessary for this research to take place.