Intramolecular deMayo Photocyclization: The Total Synthesis of Hippadine and Pratosine

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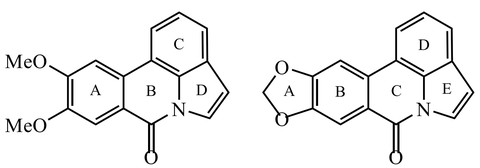
Abstract

Various total syntheses of the Lycorine-type pharmacologically active alkaloids hippadine and pratosine have been developed. However, most of these synthetic routes require prohibitively expensive materials and/or achieve yields that are subpar, making these schemes unlikely to be used in an industrial setting. Current research involves developing better synthetic methods for these two alkaloids starting with a 6,7-disubstituted isoquinoline. These syntheses are appealing since they utilize readily available starting materials and avoid expensive catalysts. The key step in the synthetic scheme centers around an intramolecular de Mayo photocyclization which involves a reaction between an alkene moiety in the isocarbostyril system and a 1,3-diketone (a functionalized tether on nitrogen), which forms a third ring in the structure of the molecule. Research on a model system (an isocarbostyril without the substituents at positions 6 and 7) for these natural products has been done in order to elucidate the optimal conditions for each step on the synthetic strategy. Initial attempts were made in order to synthesize the 6,7-disubstituted isocarbostyril with the 1,3-diketone tether so that the deMayo photocyclization could be performed. However, the established synthetic strategy led to compounds along the synthetic route that had very undesirable solubility properties. To resolve this issue, the substituents were replaced with bulkier, more non-polar moieties in order to increase the solubility of the compound in ethyl ether.



Pratosine **Hippadine**

Figure 1. Structures of title compounds

Synthetic Strategy toward the Synthesis of Hippadine

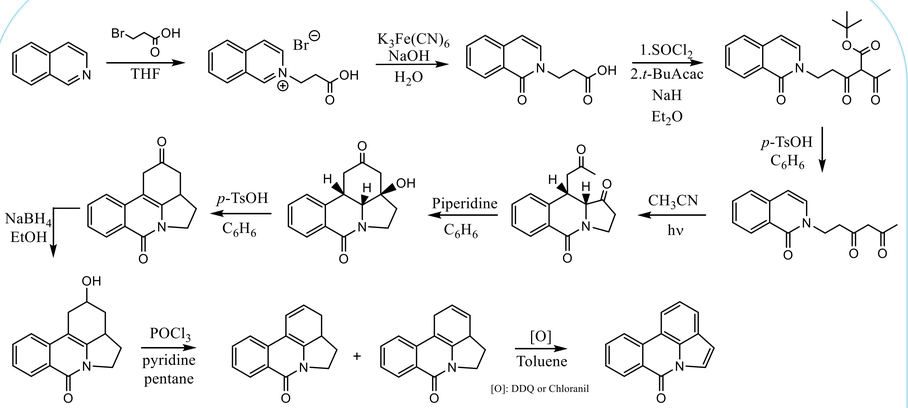


Figure 2. Synthesis of the Galanthan Skeleton

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 deMayo 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 deMayo Precursor

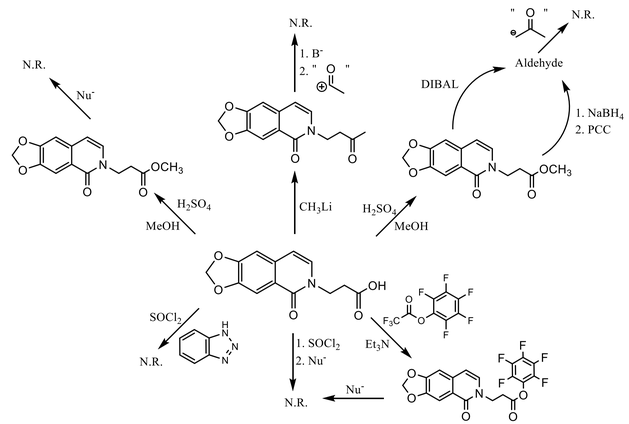


Figure 3. Different Strategies to Solve the Solubility Problem

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.

Current Progress toward the Synthesis of Hippadine and Pratosine

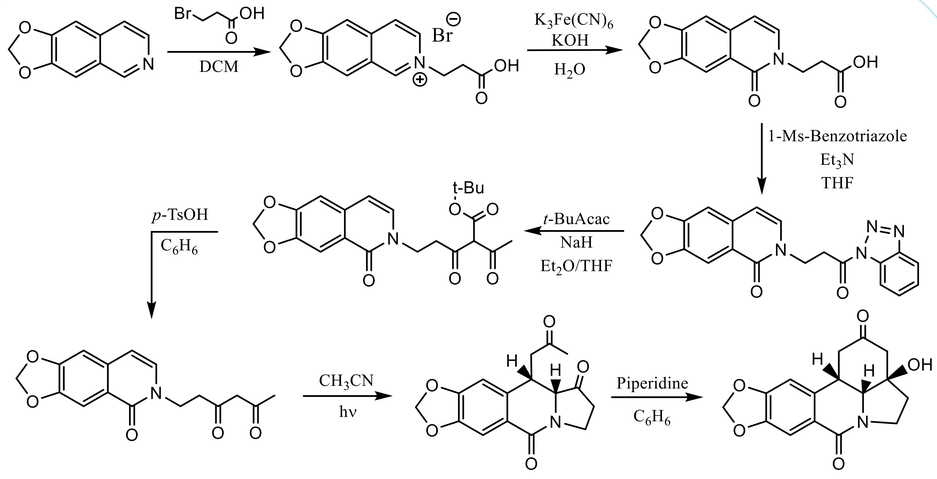


Figure 4. Synthesis of Aldol Product from 6,7-methylenedioxyisoquinoline

After various acyl substituents were tested, the N-acylbenzotriazole compound proved to be soluble in THF. The tricarbonyl compound was synthesized, followed by decarboxylation in order to yield the 1,3-diketone. The β-diketone was subjected to deMayo photocyclization conditions, affording the 1,5-diketone. An aldol condensation reaction was done on the product, affording the β-ketoalcohol. The project currently rests at this stage. Future research includes following this same pathway with the 6,7-dimethoxyisocarbostyril molecule, as well as the dehydration of the aldol product followed by the reduction of the ketone, which ultimately will afford hippadine after aromatization with either DDQ or Chloranil.

Conclusions

The 6,7-methylenedioxy-containing deMayo precursor was synthesized by utilizing a *N*-acylbenzotriazole substituent which resolved the solubility problem that was encountered when following the previously established synthesis. Although several synthetic routes were explored, the current method provides an easy pathway toward isocarbostyrils with a tether on nitrogen containing a β-dicarbonyl moiety which is necessary for carrying out an intramolecular deMayo photocyclization. Because the nitrogen tether is installed by using 3-bromopropionic acid, this synthetic scheme also provides the possibility of functionalization at various parts of the molecule: at the methylene positions on ring E, the methylene positions on ring D, or the carbonyl carbon on ring D after the aldol condensation is carried out. Dehydration of the aldol product, followed by reduction of the carbonyl affords an alcohol which can then be used to make other natural products. For example, we have been able to make an aromatized skeleton (from the model system) containing a methyl ether functionality.

Acknowledgments

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