# Toward Defining the Scope and Limitations of the Tandem Enamine-enal Cycloaddition/Pyridine Formation Approach to the Synthesis of the Cyclopenta[C]pyridine Substructure

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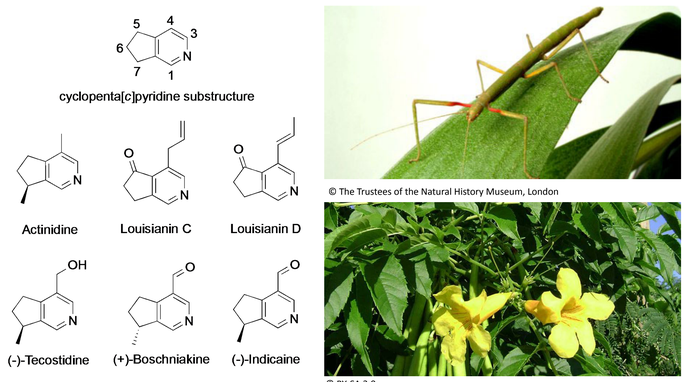
## Abstract

The cyclopenta[C]pyridine substructure has been identified in many natural products. However, such compounds are often isolated in infinitesimal quantities that do not facilitate their thorough biological characterization. Unfortunately, general procedures to assemble compounds containing the cyclopenta[C]pyridine substructure are not well established. The goal of my research is to develop and explore the scope and limitations of two general synthetic approaches that, when used, will be able to synthesize several derivatives containing the cyclopenta[C]pyridine substructure. Using these novel methods, we have synthesized substrates containing single methyl substitutions at the C3, C4, and C7 positions. However, previous tests examining the performance of the C7 1,8-enedial substrate were only successful using the tandem method. To confirm or disprove the inability of this substrate to undergo the sequential reaction sequence, my research goal is to resynthesize the C7 methyl-substituted substrate. We describe here our progress in this endeavor.

## Background and Target Molecules

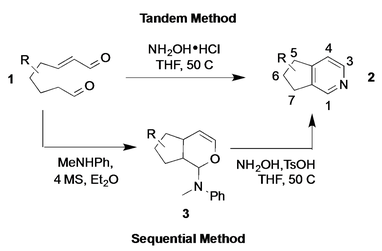






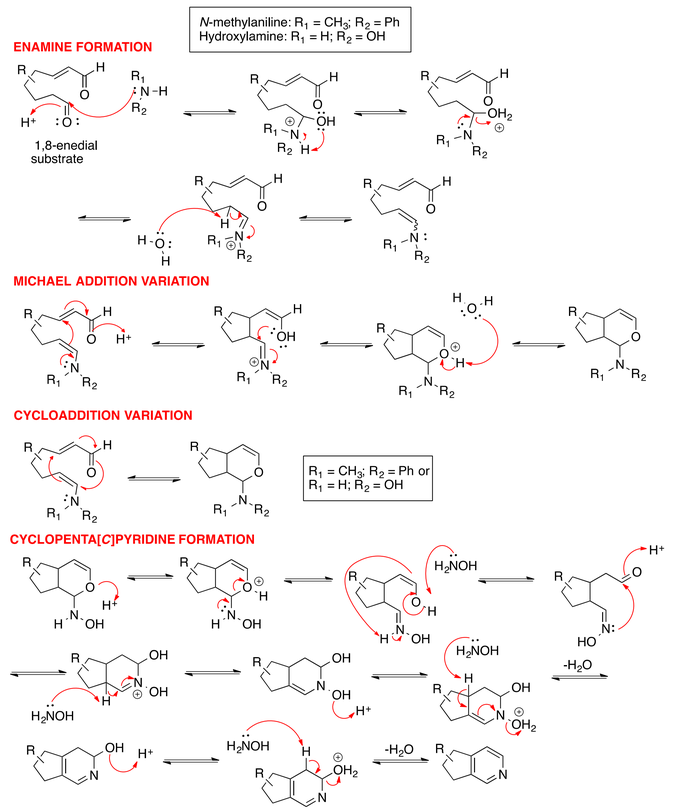
- The first example of a molecule containing the cyclopenta[*C*]pyridine substructure is actinidine. Found in the natural defense secretions of certain ants, actinidine protects these bugs from microbial infections and displays cat-exciting activity.[3,4]
- Another example are the bacterially-produced louisianines: Louisianines A-D are potent growth inhibitors of testosterone-responsive Shionogi carcinoma (mouse mammary carcinoma), while Louisianines C and D are also potent suppressors of vascular endothelial cells.[5]

## Access to the Cyclopenta[*C*]pyridine Substructure from Two General Methods

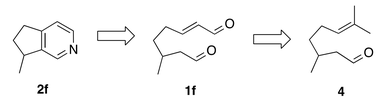



- Despite the potentially useful applications of natural products containing the cyclopenta[*C*]pyridine framework, current synthetic routes found in the literature are rather limited in scope.
- Our research efforts have amounted to the development of two methods to assemble molecules containing the cyclopenta[*C*]pyridine substructure with alkyl substitutions: a novel tandem enamine-enal cycloaddition pyridine formation reaction and a complimentary sequential two-step method that both transform 1,8-enedials into molecules with the cyclopenta[*C*]pyridine substructure.

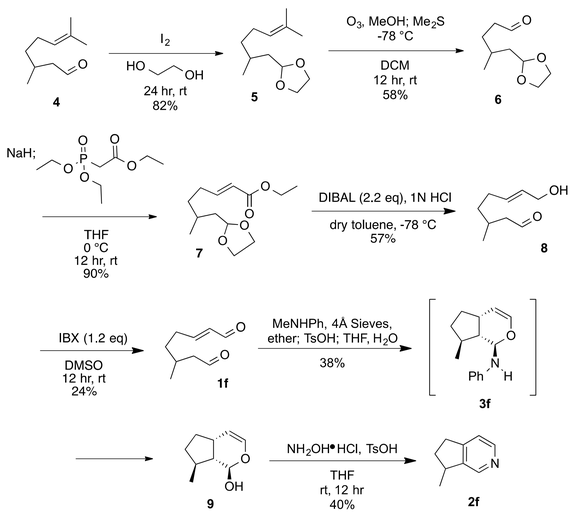
## Possible Mechanism of Key Step



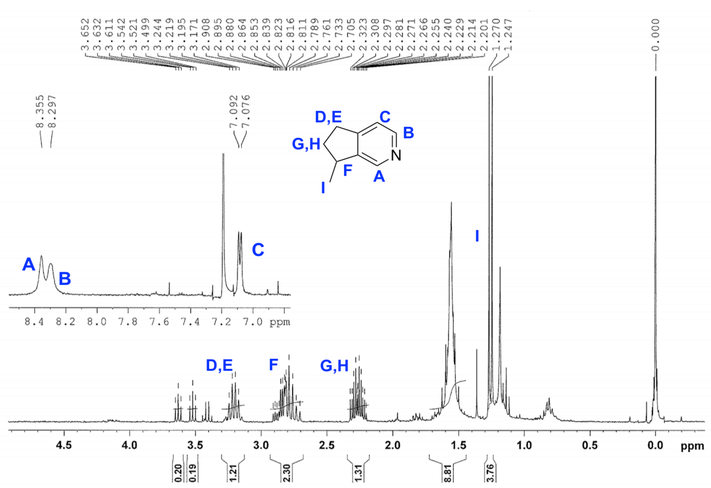

## Retrosynthetic Analysis of C7 Methyl Target




## Synthesis of C7 Methyl Target




## $^1$H NMR of 2f




## Methodology Results

**Isolated Yields Of Substituted Cyclopenta[C]Pyridine**

| Substrate Methyl Position | Tandem Method | Sequential Method[a] |
|---|---|---|
| Unadorned | 20% | 33% |
| C1 (**1a**) | NR | NR |
| C3 (**1c**) | 31% | 26%[b] |
| C4 (**1d**) | 56% | 40% |
| C5 (**1e**) | ??% | ??% |
| C6 (**1f**) | 35% | 12% |
| C7 (**1g**) | 43% | 15% |
| C7+C4 (**1h**) | 70% | 49% |

[a] Two-step isolated yield of **2**.

[b] **3c** and **3f** hydrolyzed prior to pyridine formation.

- Our tandem methodology has proven successful in synthesizing the cyclopenta[*C*]pyridine substructure from the corresponding 1,8-enedial with methyl substitutions at every available carbon except C1 and C5.
- Efforts to synthesize the C7 target compound from substrate **1g** by use of the two-step method were previously unsuccessful, as its corresponding aminal intermediate decomposed during silica gel chromatography. A method involving intentional hydrolysis of the crude aminal prior to pyridine formation is a more reliable method to successfully prepare **2**.
- Efforts to synthesize the C5 target compound from substrate **1e** are at an advanced stage and are a current focus of the research.

## Conclusions

- Using citronellal as starting material, the target compound **2f** has been prepared using the two-step sequential methodology we have developed.
- We have demonstrated the successful conversion of a broad variety of linear 1,8-enedial substrates (**1**) to corresponding cyclopenta[*C*]pyridine targets using our methodology.
- A variety of natural products containing the cyclopenta[*C*]pyridine skeleton have also been prepared.
- Synthesizing the C5 methylated target from **1e** is the focus of our current research. Completion of this objective will conclude our investigation of this methodology.

## Acknowledgements

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