Development of a Novel Synthesis of Natural Products Containing the Cyclopenta[c]pyridine Substructure

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Abstract

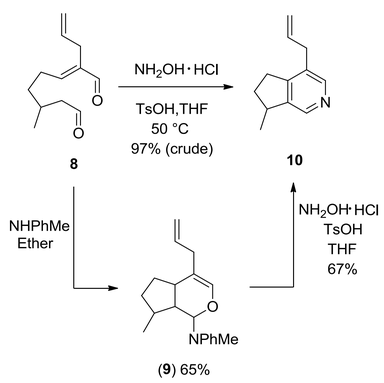
The cyclopenta[c]pyridine substructure appears in numerous natural products. Such compounds, however, are often isolated in minute quantities from their natural sources. Thus, laboratory syntheses of these compounds are necessary for their complete biological characterization. Currently, there is no general synthesis available for the preparation of molecules containing the cyclopenta[c]pyridine substructure and the goal of my Summer Science Research was to develop a direct, efficient, and general synthetic protocol for preparing this carbon scaffold. Specifically, the suitability of our synthetic approach to several natural products related to actinidine is being explored. The key step in our novel approach is the cyclization of appropriately substituted 1,8-enedial intermediates. We have now examined the synthetic potential of several such intermediates for the preparation of the target natural products. However, we have yet to find an ideal synthetic intermediate that is both readily prepared and forms the target molecules in sufficiently pure form to be unambiguously characterized. We present here the current status of this synthesis project.

Background and Target Molecules

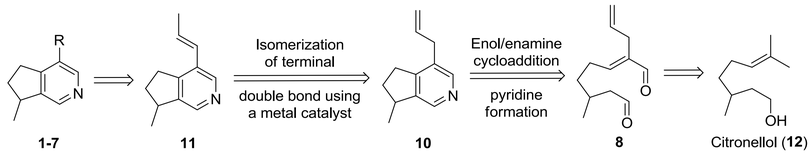
- Compounds containing the cyclopenta[c]pyridine substructure have been isolated from numerous plant, animal, and bacterial sources, but a general synthetic method for the preparation of such molecules is absent from the literature.[1, 2, 3]
- The Hofferberth research group has succeeded in preparing actinidine using a novel synthetic method.[4] Our current goal is to explore alternative methodologies for the synthesis of other structurally related natural products.
- The key step in our syntheses is the cyclization of a 1,8-endial intertermediate poised to afford the bicyclic, cyclopenta[c]pyridine framework.

	C7 Configuration	R	Can be Isolated From
(+)- or (-)-Actinidine (1)	R or S	CH_3	*Nepeta clarkei*
(+)-Deoxyrhexifoline (2)	R	CO_2Me	*Castilleja rhexifolia aff. Miniata*
(+)-Boschniakinic acid (3)	R	CO_2H	*Castilleja miniata* (Indian paint brush)
(+)-Boschniakine (4)	R	CHO	*Castilleja miniata* (Indian paint brush)
(-)-Plantagonine (5)	S	CO_2H	*Pedicularis olgae*
(-)-Indicaine (6)	S	CHO	*Plantago indica*
(-)-Tecostidine (7)	S	CH_2OH	*Tecoma stans Juss*

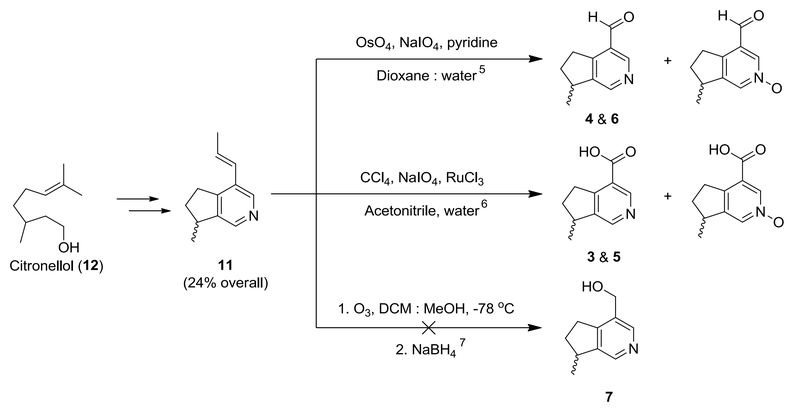
Cycloaddition/Pyridine Formation



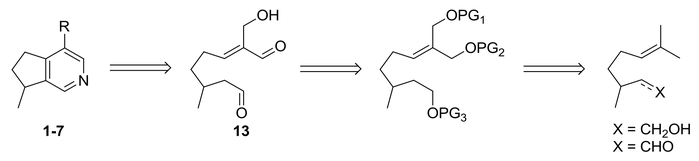
Initial Strategy



Attempts to synthesize the targets:



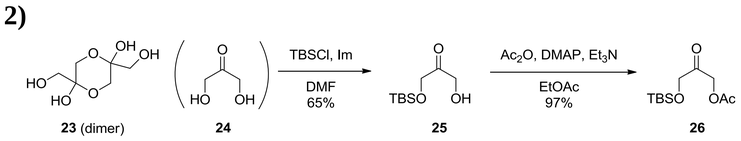
Current Strategy

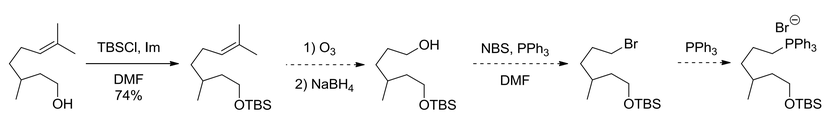


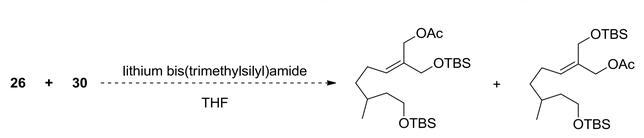
Approaches to the Desired 1,8-enedial

1)

2)

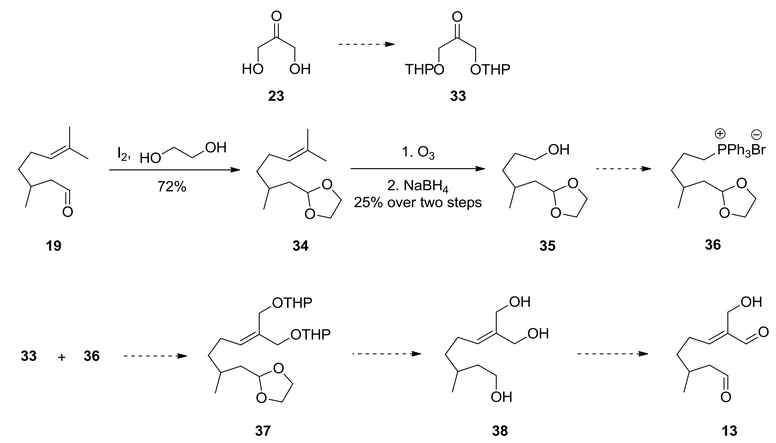






Approaches to the Desired 1,8-enedial

3)



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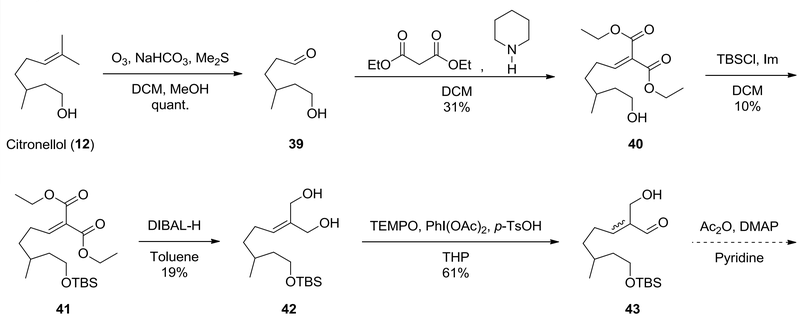

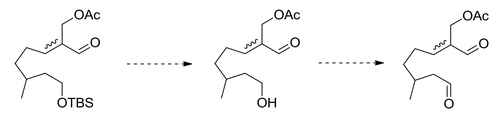

Conclusions

- Olefin cross metathesis is less suitable for developing our general method due to its need for highly specific coupling partners
- The most efficient entry into the cyclopenta[C]pyridine substructure likely involves the regioselective oxidation of allylic alcohols to generate the requisite 1,8-enedial intermediate
- Successful generation of **43** encourages us to further explore and optimize the fourth synthetic route
- Upon formation of **46**, the tandem cycloaddition step will be performed to yield the desired cyclopenta[C]pyridine substructure

Acknowledgements

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References

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