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

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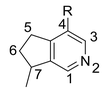
Abstract

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 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 specific carbon scaffold. Using our novel approach, the penultimate intermediate (**8**) in the synthesis of six natural products containing the cyclopenta[c]pyridine substructure from racemic citronellol was completed. The reaction conditions of this synthetic protocol have been optimized for the preparation of **8** in an overall yield of 24%. The key tandem cycloaddition/pyridine formation step proceeded in excellent yield (97%). In addition, reliable conditions for the rearrangement of the terminal olefin in **9** to give **8** have been established. Possibilities for the conversion of **8** to the six target molecules have been explored with promising results, and the optimization of the final synthetic steps is now underway.

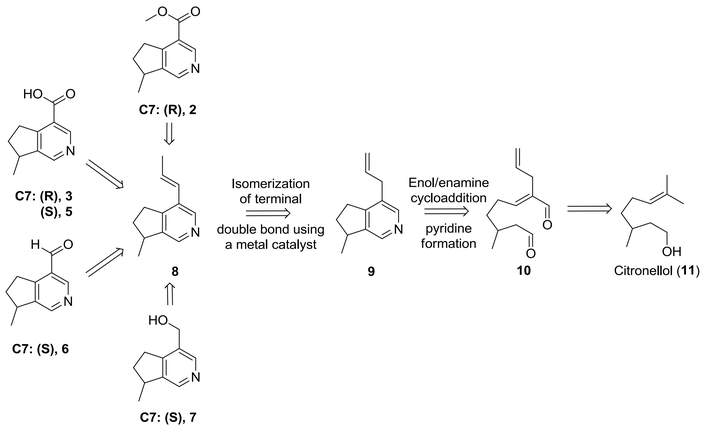
Background and Target Molecules

- 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 the synthesis of other natural products to determine the generality of the method.
- Commercially available citronellol will be converted into single isomers of six representative natural products.
- The key steps in this synthesis is the cyclization of a dialdehyde compound to afford the bicyclic, cyclopenta[c]pyridine framework and isomerization of a terminal olefin.



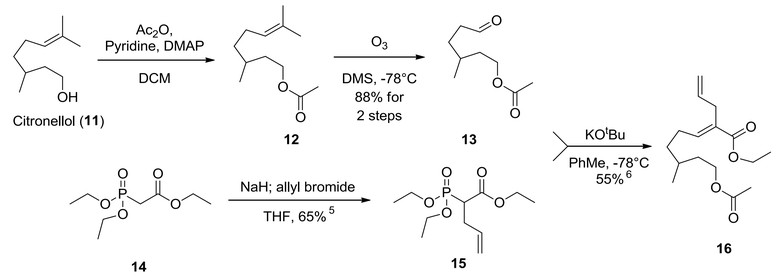
	C7 Configuration	R	Can be Isolated From
(+)- or (-)-Actinidine (1)	R or S	CH_3	*Nepeta clarkei*
(+)-Deoxyrhexifoline (2)	R	CO_2Me	*Castilleja rhexifolia aff. Miniata*
(+)-Boschniakinic acid (3)	R	CO_2H	*Castilleja miniata* (Indian paint brush)
(+)-Boschniakine (4)	R	CHO	*Castilleja miniata* (Indian paint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

Retrosynthetic Analysis

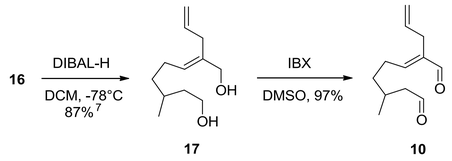


Synthesis of Substrate for Key Steps

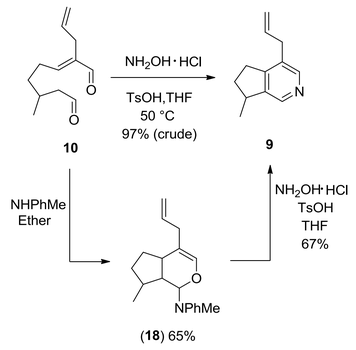
Synthesis of Diester **16**



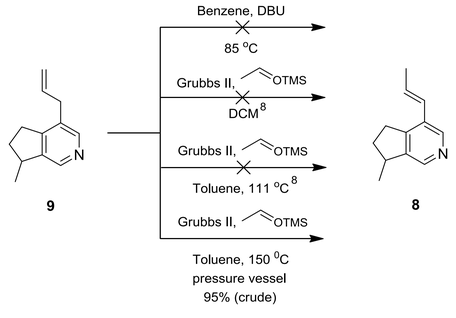
Synthesis of Enedial **10**



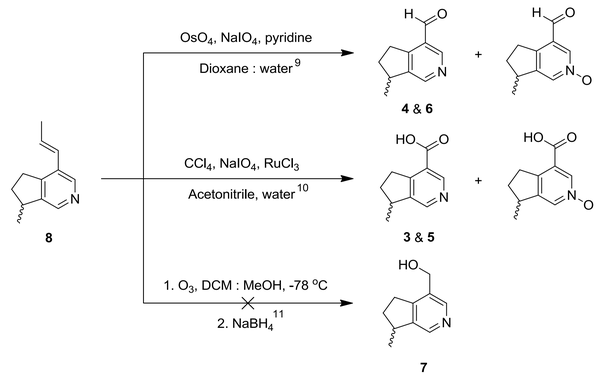
Cycloaddition/Pyridine Formation



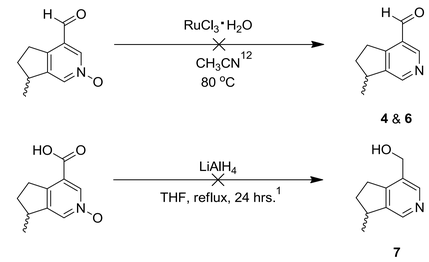
Isomerization of Terminal Olefin



Target Preparation



Attempts to Reduce the N-oxide



Conclusions

- The current synthetic route is capable of preparing a cyclopenta[c]pyridine framework (**8**) that is poised for the synthesis of the target compounds.
- Further optimization of this synthesis is underway to enable the production of samples of isomerically pure target compounds.

Acknowledgements

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