

Literature Report I

Total Synthesis of (-)-Ambiguine P

Reporter: Fei Cao

Checker: Yi-Xuan Ding

Date: 2019-12-2

Rawal, V. H. *et al. J. Am. Chem. Soc.* **2019**, *141*, 4820-4823

CV of Viresh H. Rawal

Education and Employment:

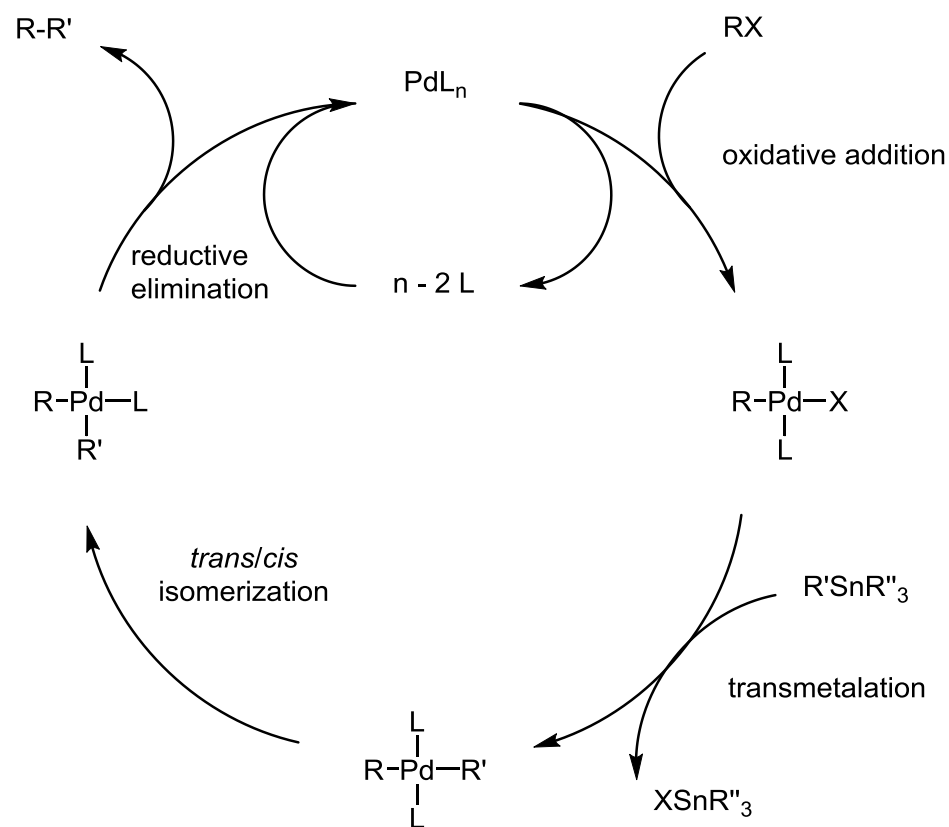
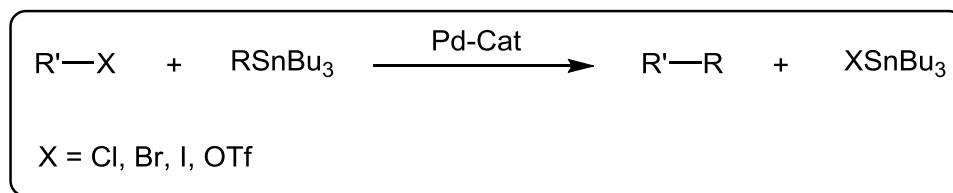
- **1976–1980** B.S., University of Connecticut
- **1980–1986** Ph.D., University of Pennsylvania
- **1986–1988** Postdoctor, Columbia University
- **1988–1994** Assistant Professor, Ohio State University
- **1994–1995** Associate Professor, Ohio State University
- **1995–Now** Professor, University of Chicago



Research Interests:

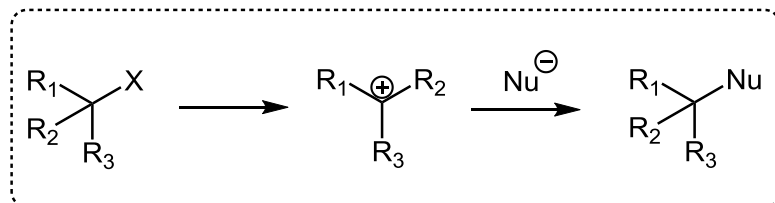
- Total synthesis of natural products (potent biological activities)
- The effective catalysts for enantioselective reactions

Stille coupling

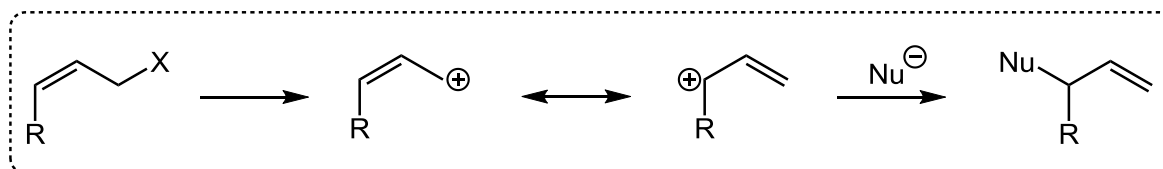


S_N1 and S_N1'

S_N1 route



S_N1' route



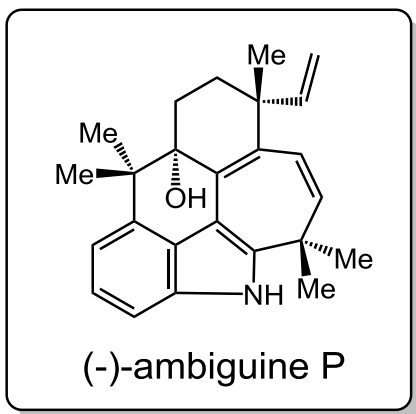
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2 The Synthesis of (-)-Ambiguine P

3 Summary

Introduction



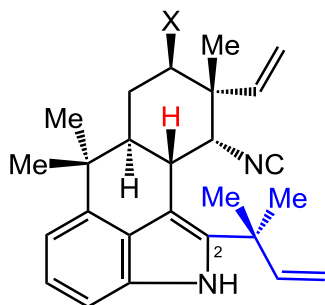
blue-green algae

- It was isolated from the roots of blue-green algae;
- It exhibits a broad range of bioactivities including antimycotic, antifungal and antibiotic properties;
- The first asymmetric synthesis of (-)-Ambiguine P was completed by Sarpong and co-workers. (*J. Am. Chem. Soc.* **2019**, *141*, 4820)

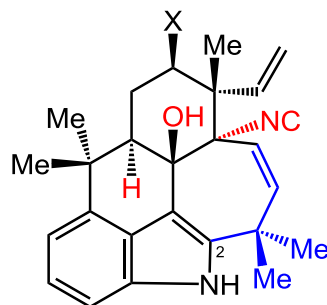
Smitka, T. A. *et al. J. Org. Chem.* **1992**, *57*, 857.

Introduction

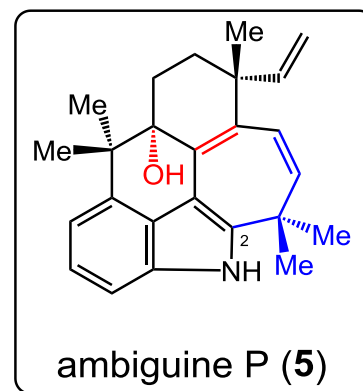
Representative members of the ambiguine group



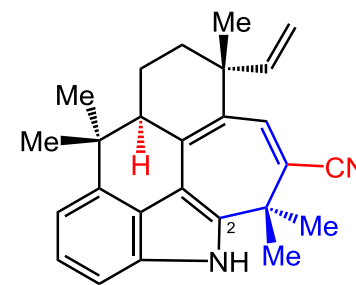
ambiguine A (1); X = Cl
ambiguine H (2); X = H



ambiguine K (3); X = Cl
ambiguine L (4); X = H

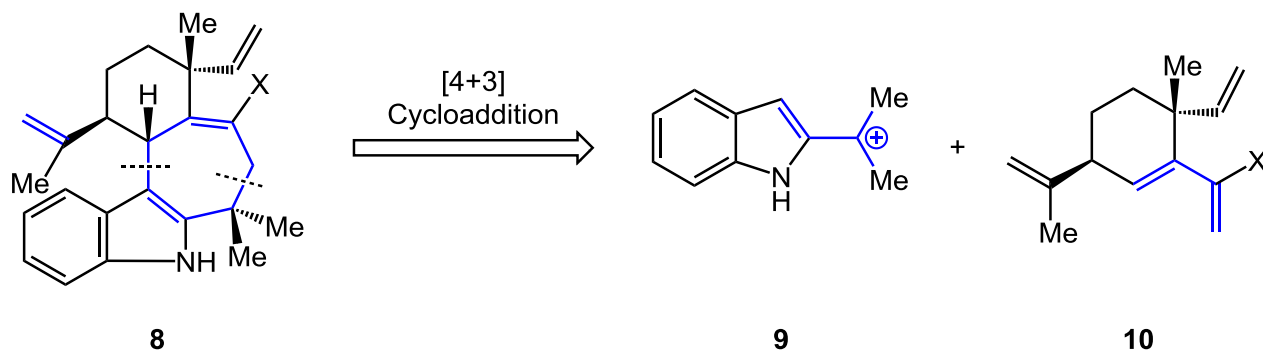
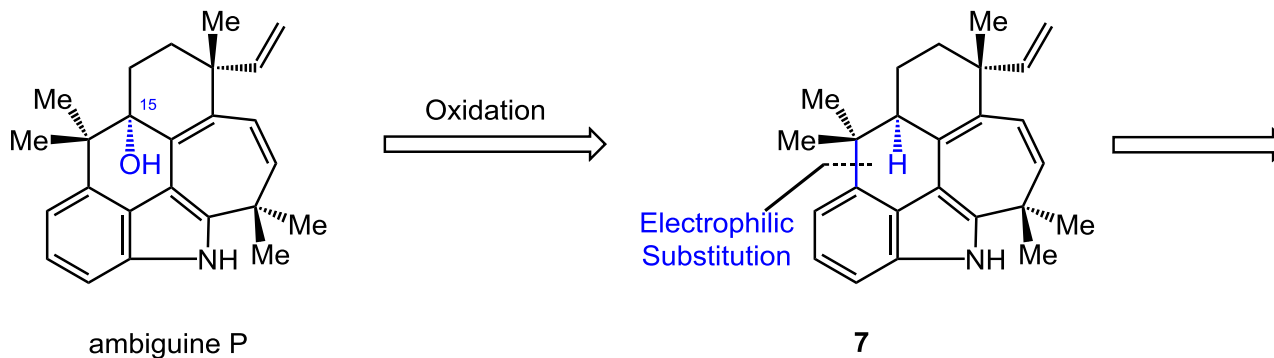


ambiguine P (5)

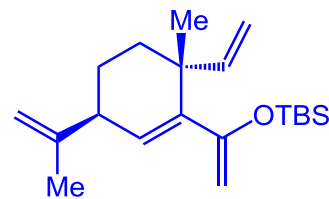
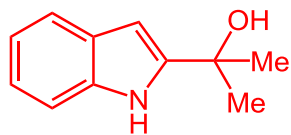
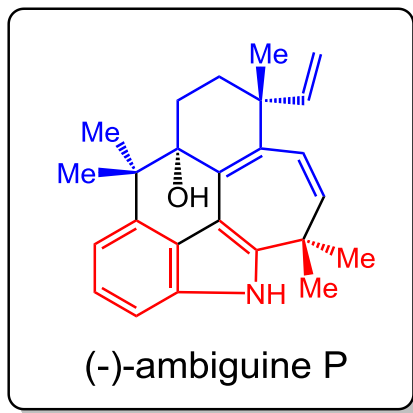


ambiguine Q (6)

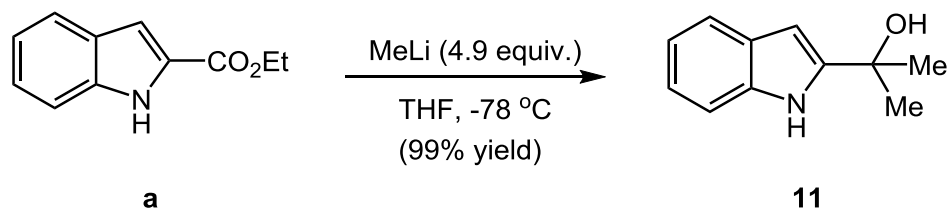
Synthetic strategy to access the Amibiguines



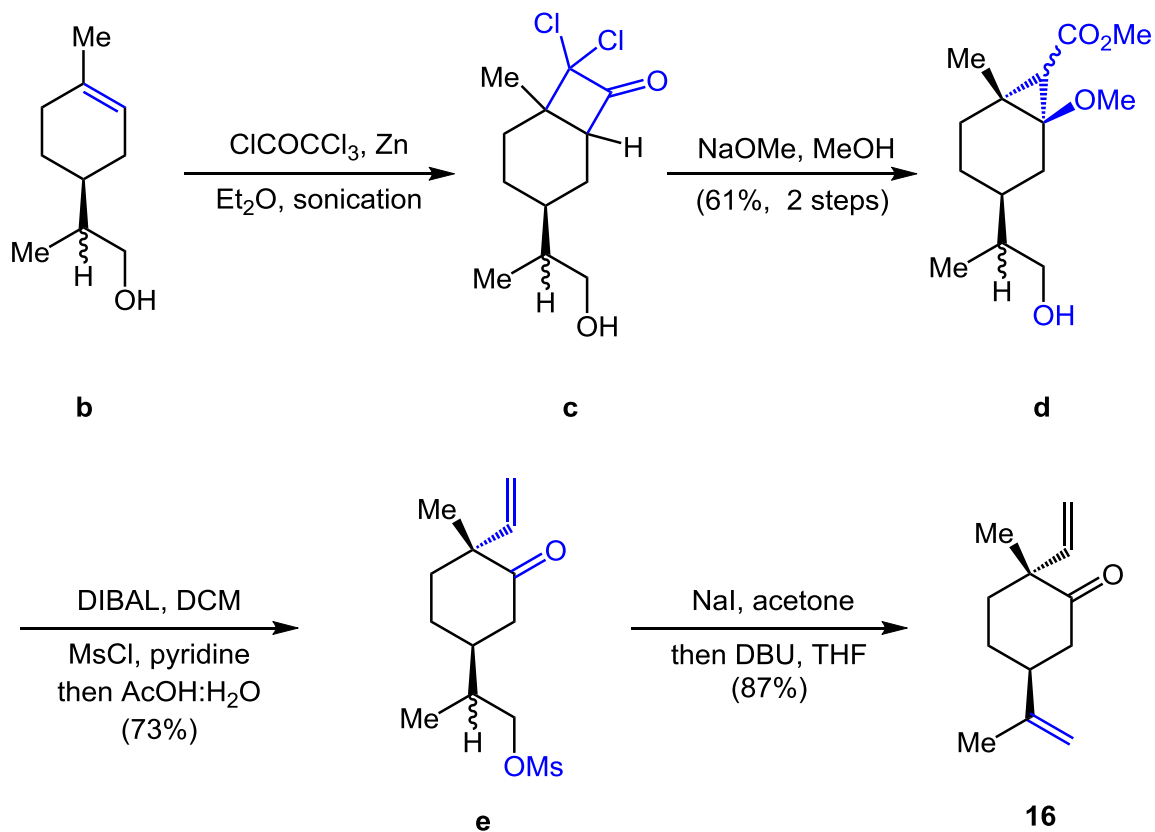
Synthesis of 11 and 19



Synthesis of 11

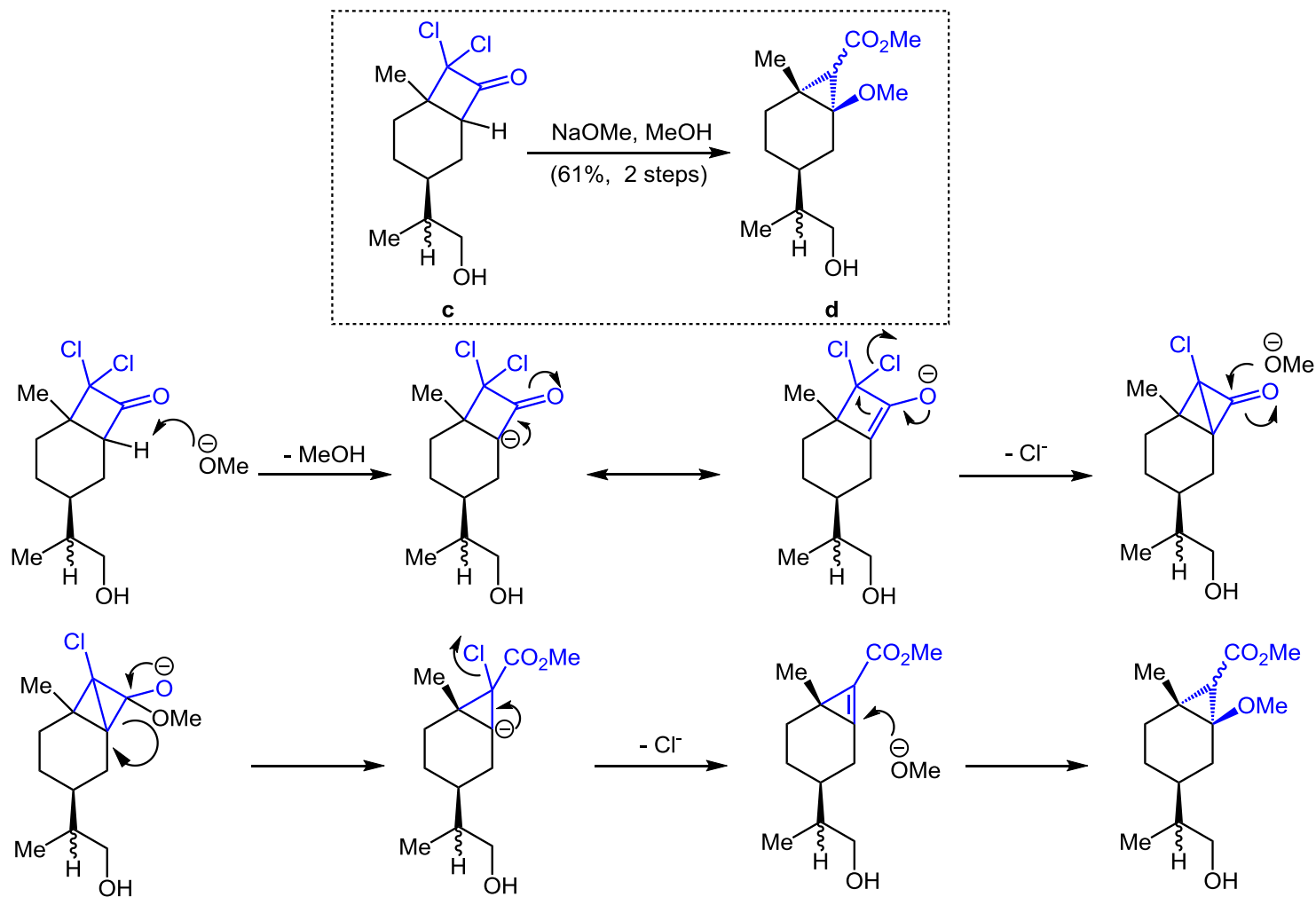


Synthesis of 16

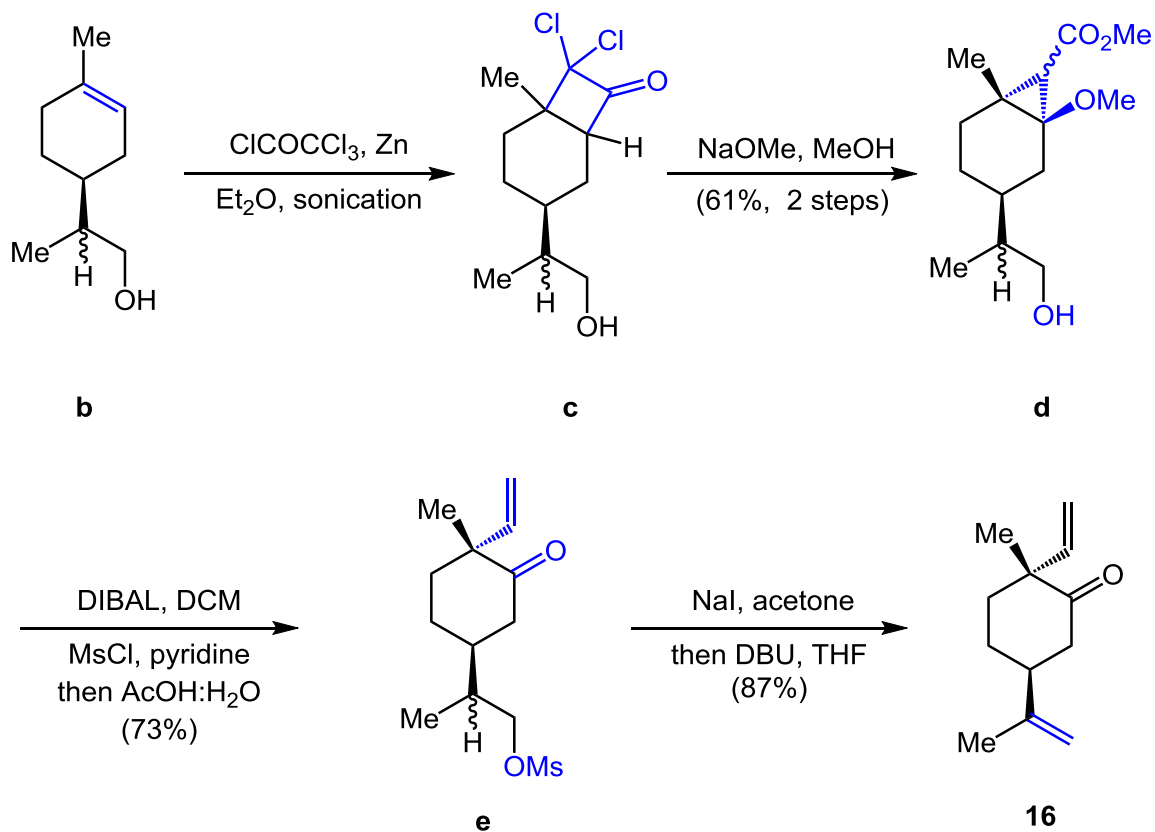


Richter, J. M. *et al. Nature* **2007**, *446*, 404-408

Probable mechanism of the c to d

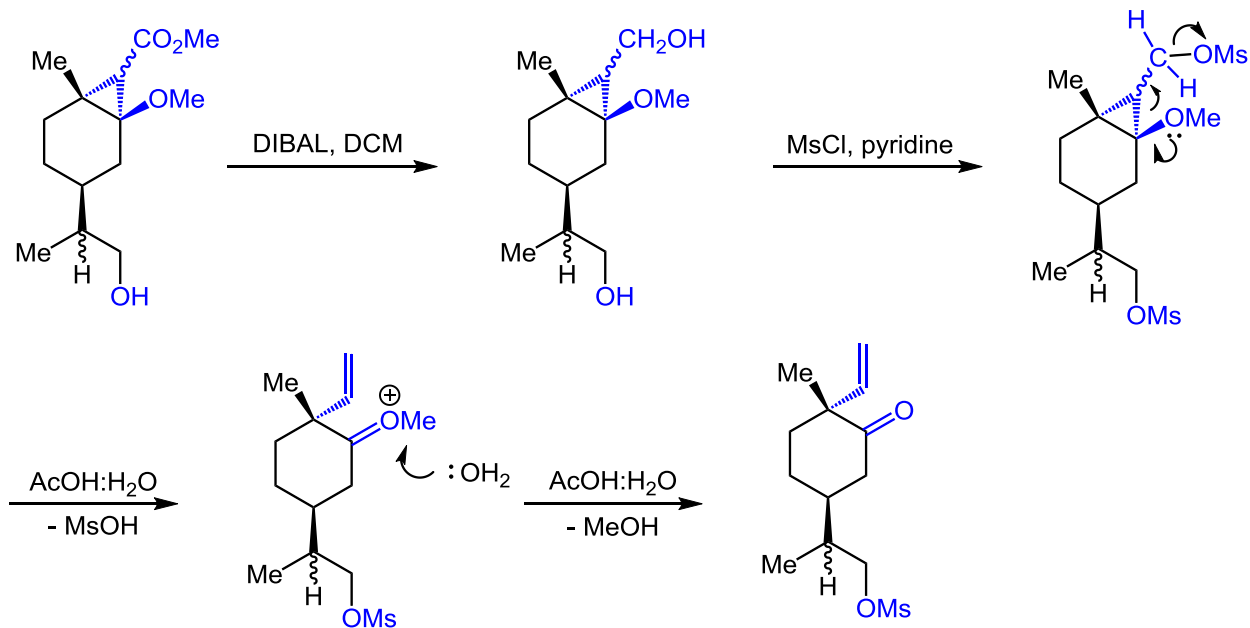
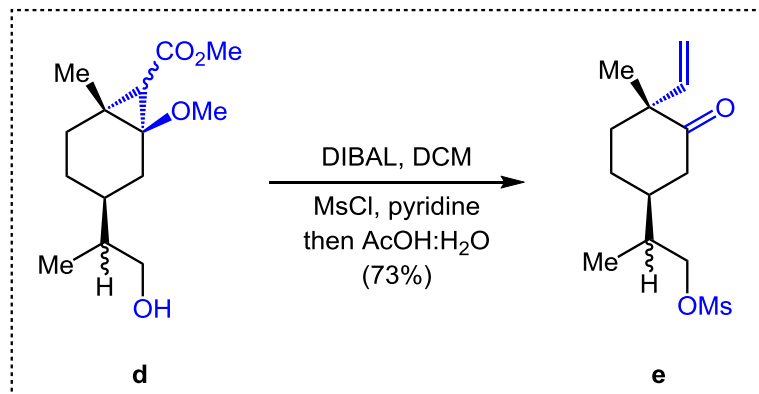


Synthesis of 16

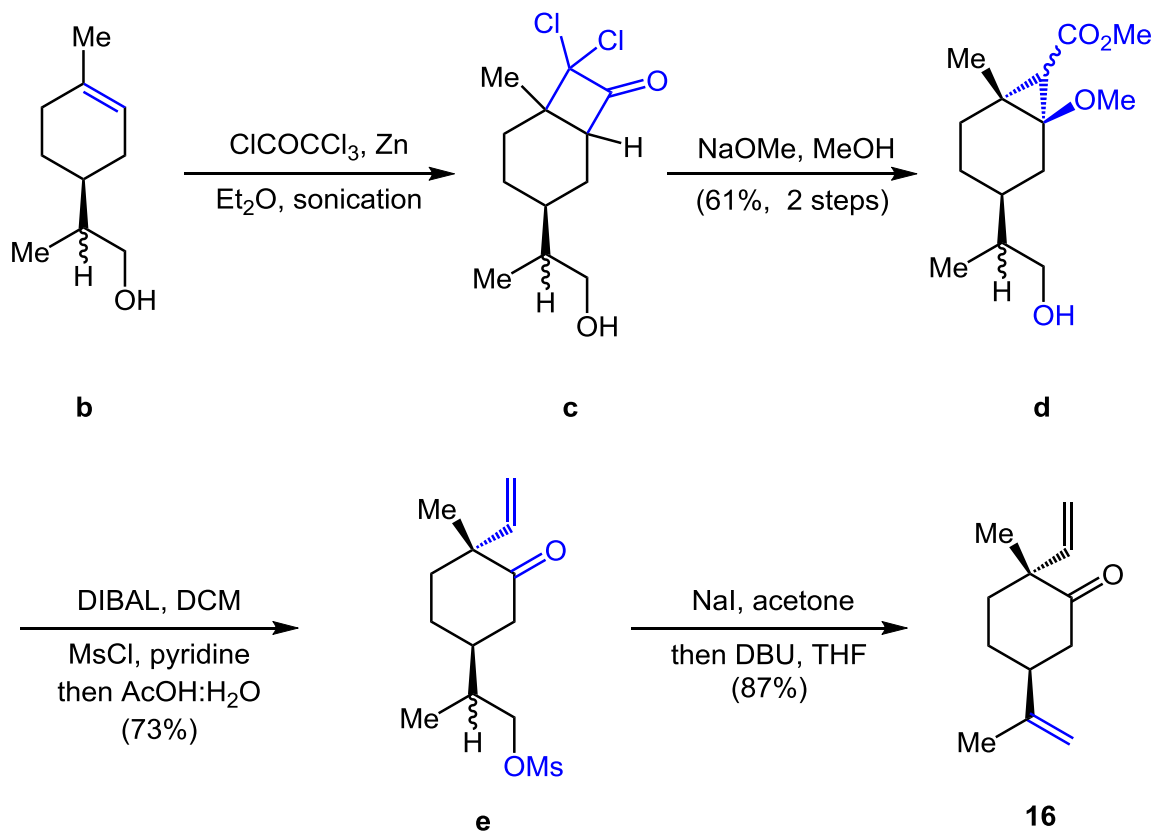


Richter, J. M. *et al. Nature* **2007**, *446*, 404-408

Probable mechanism of the d to e

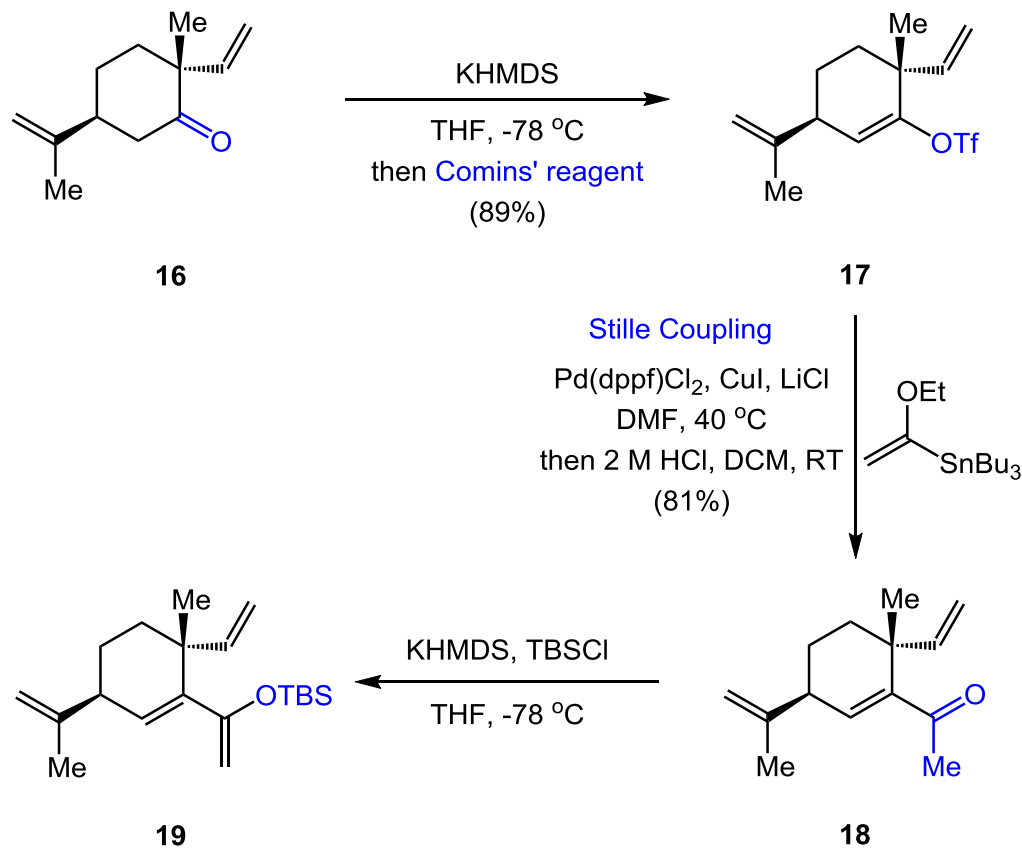


Synthesis of 16

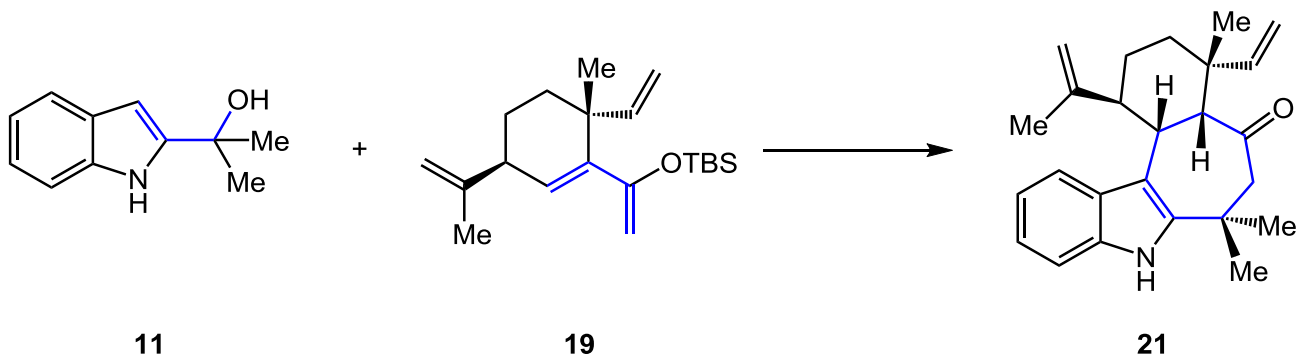
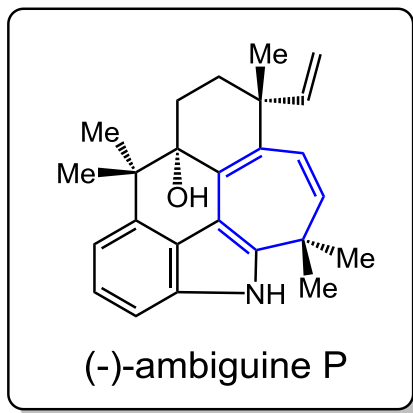


Richter, J. M. *et al. Nature* **2007**, *446*, 404-408

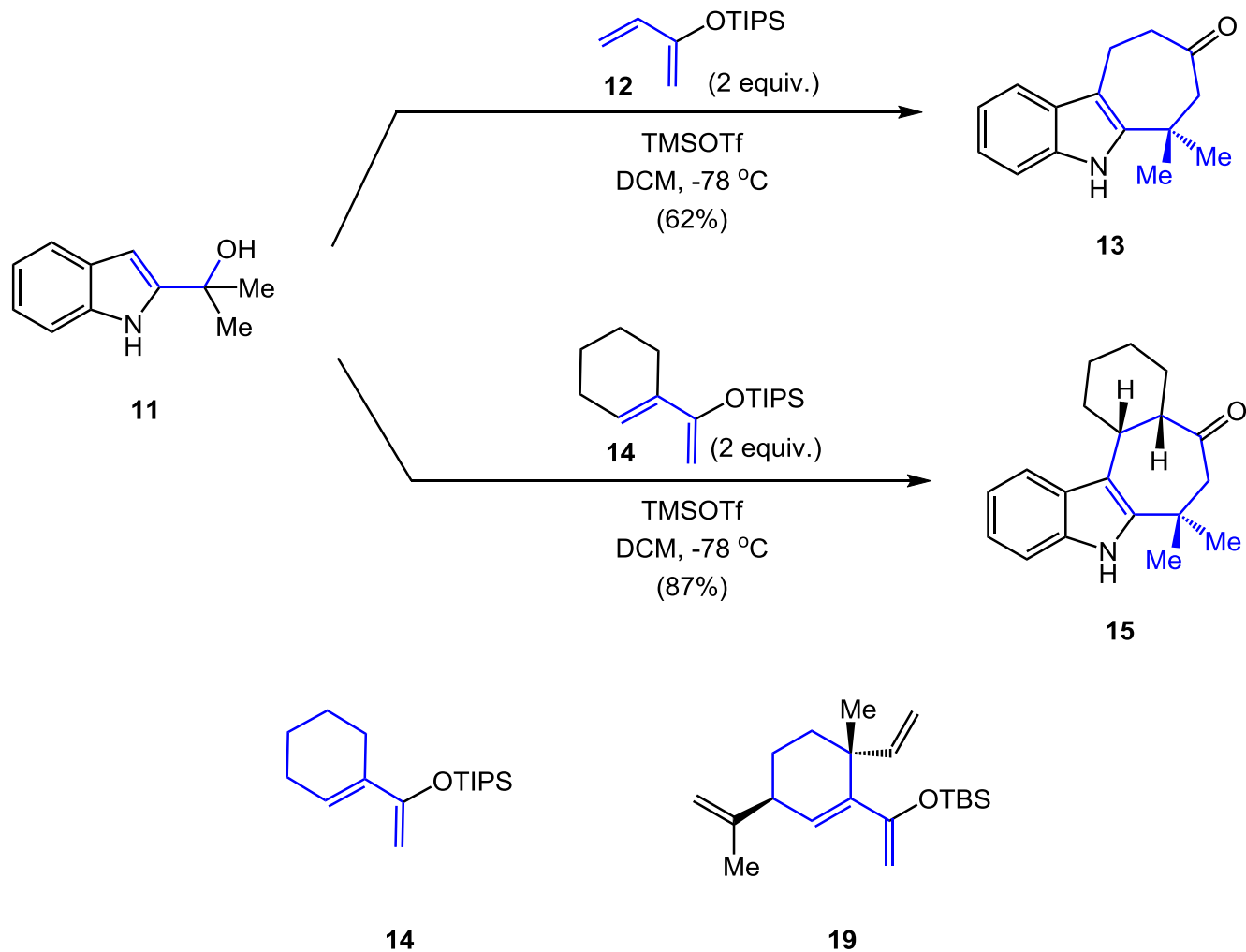
Synthesis of 19



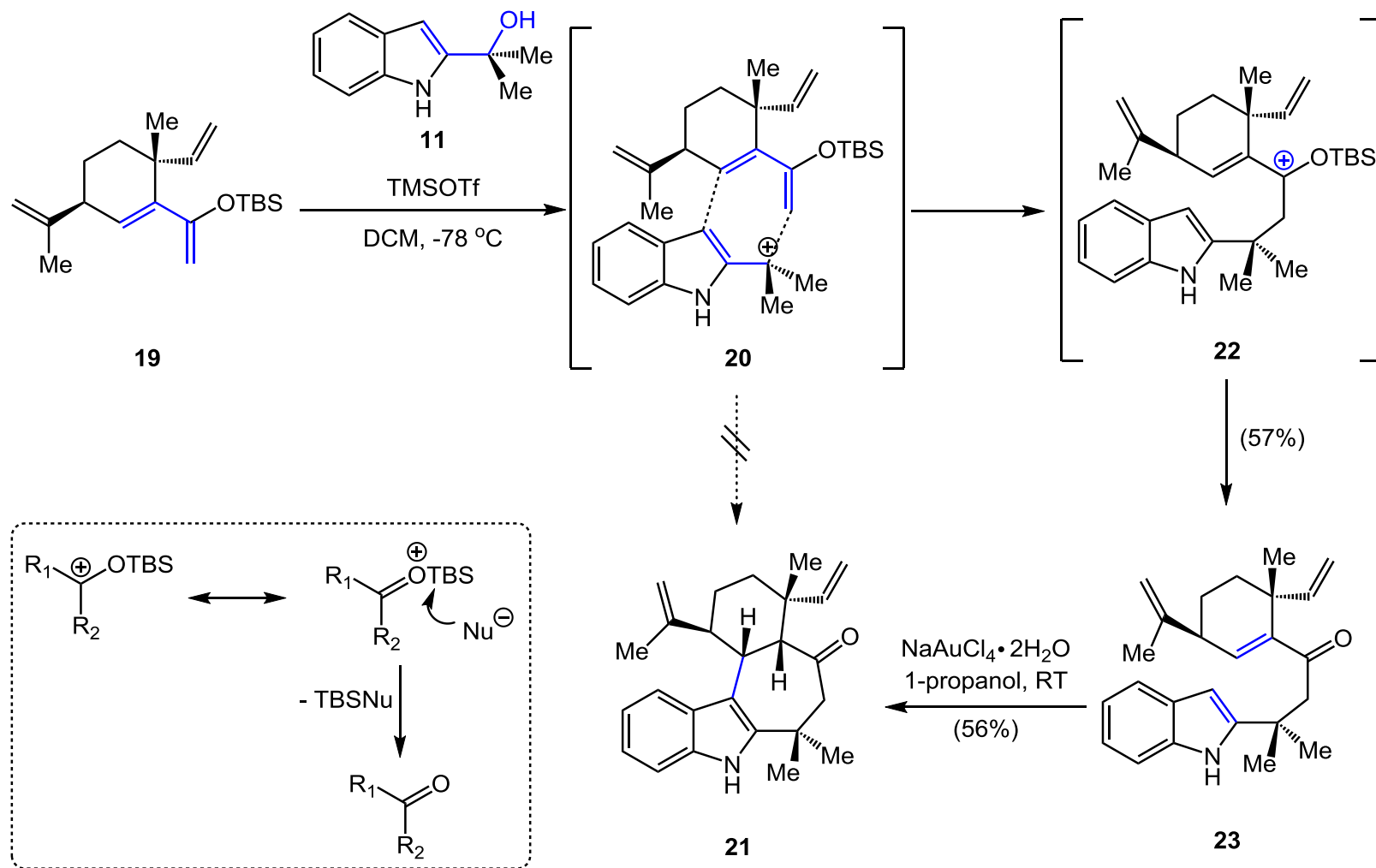
Exploration of the [4+3] cycloaddition



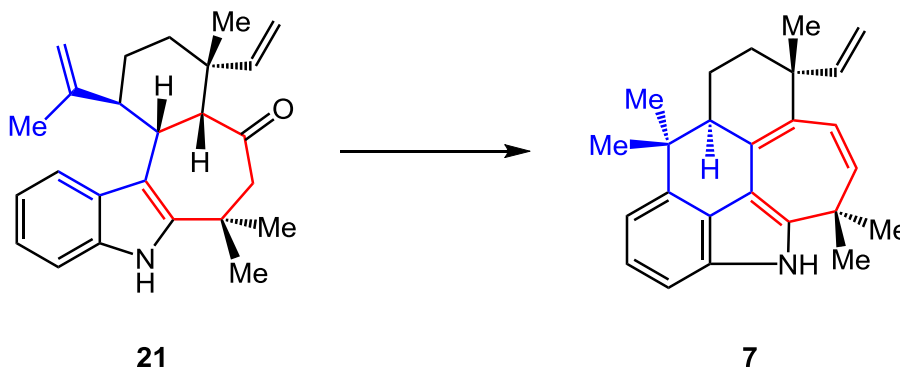
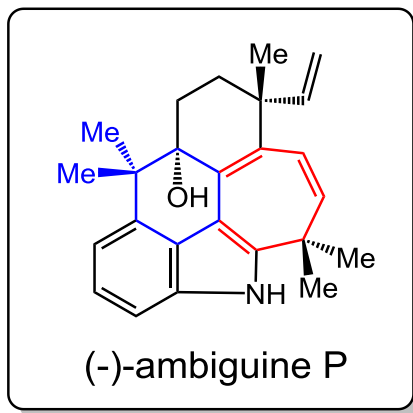
Exploration of the [4+3] cycloaddition



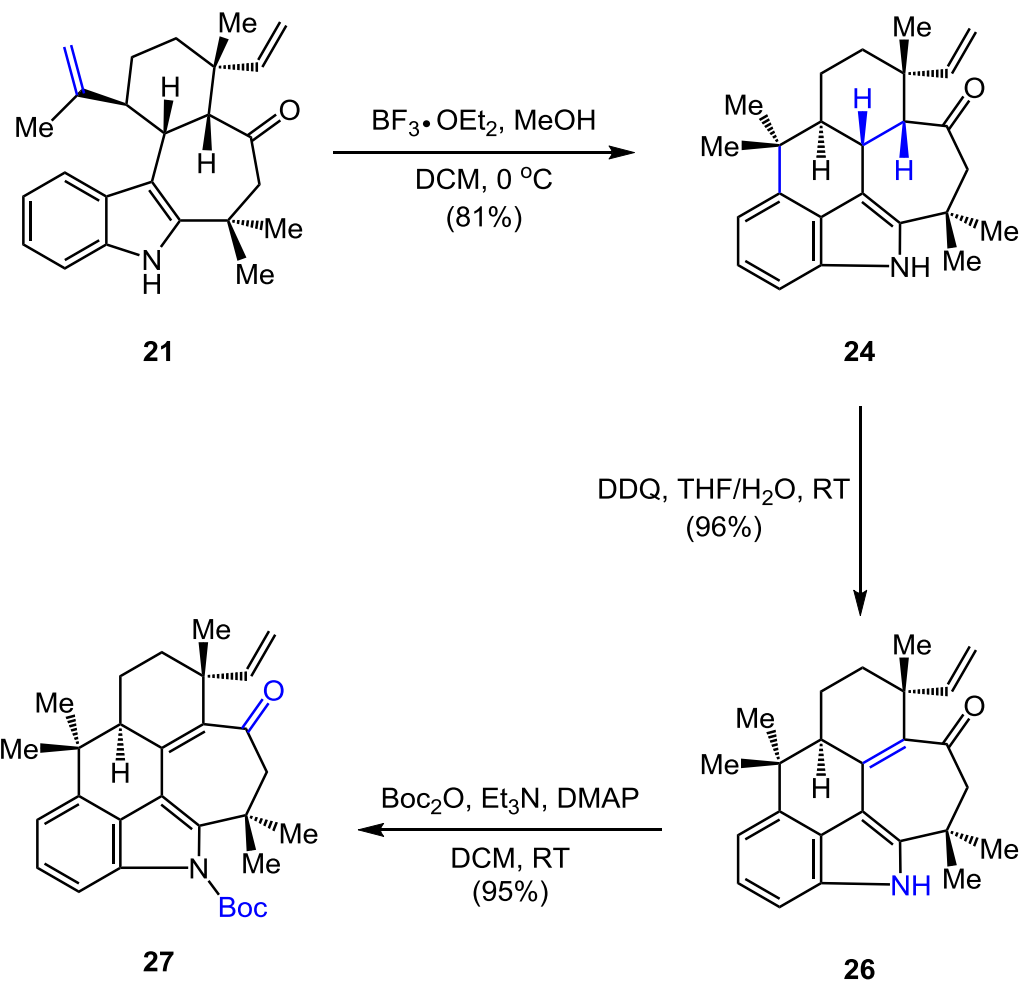
Synthesis of 21



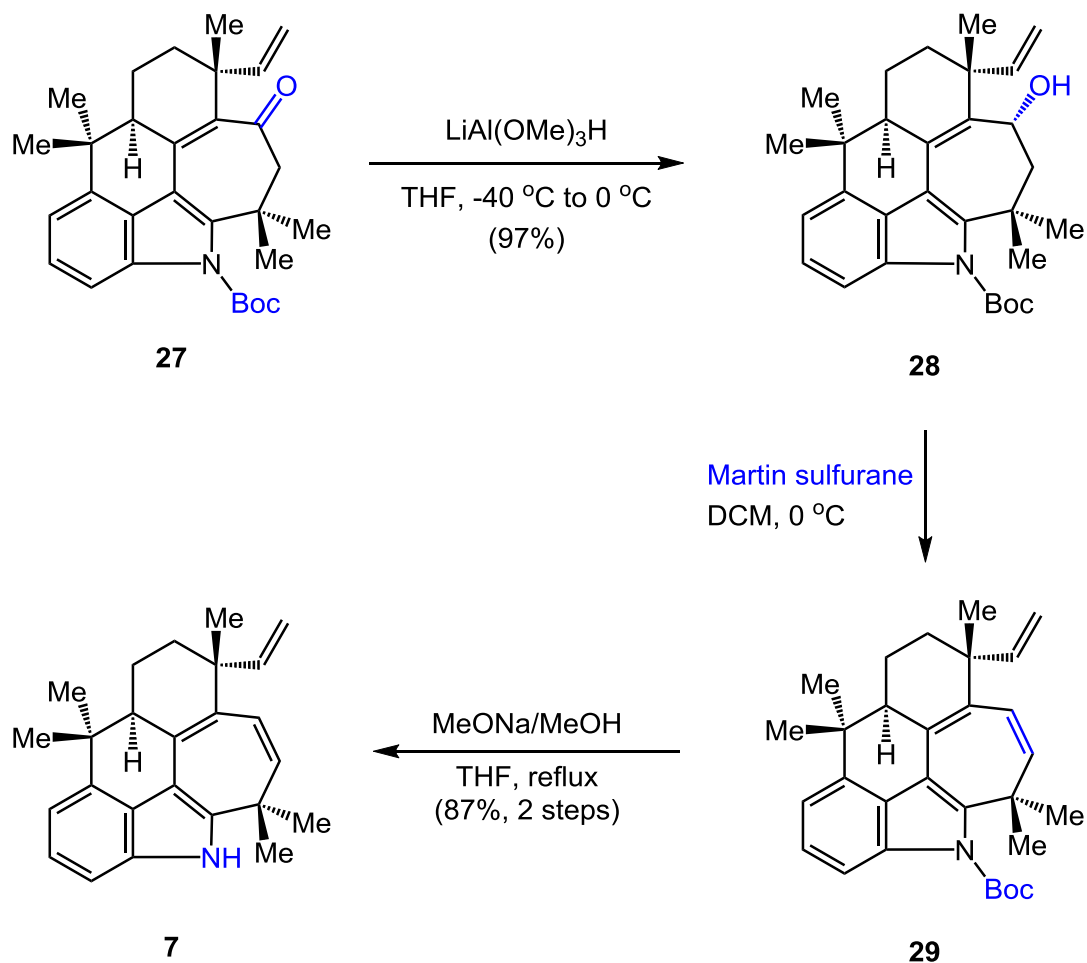
Synthesis of 7



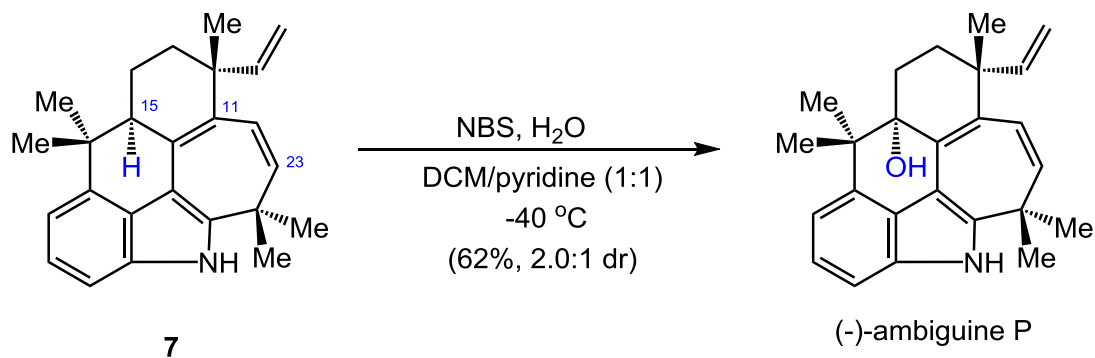
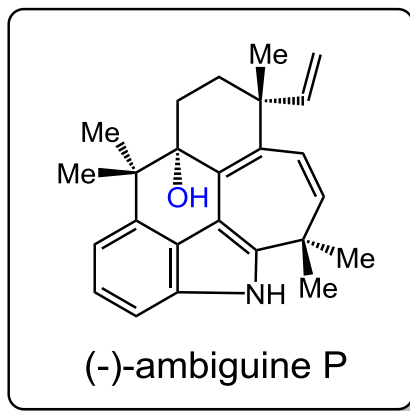
Synthesis of 7



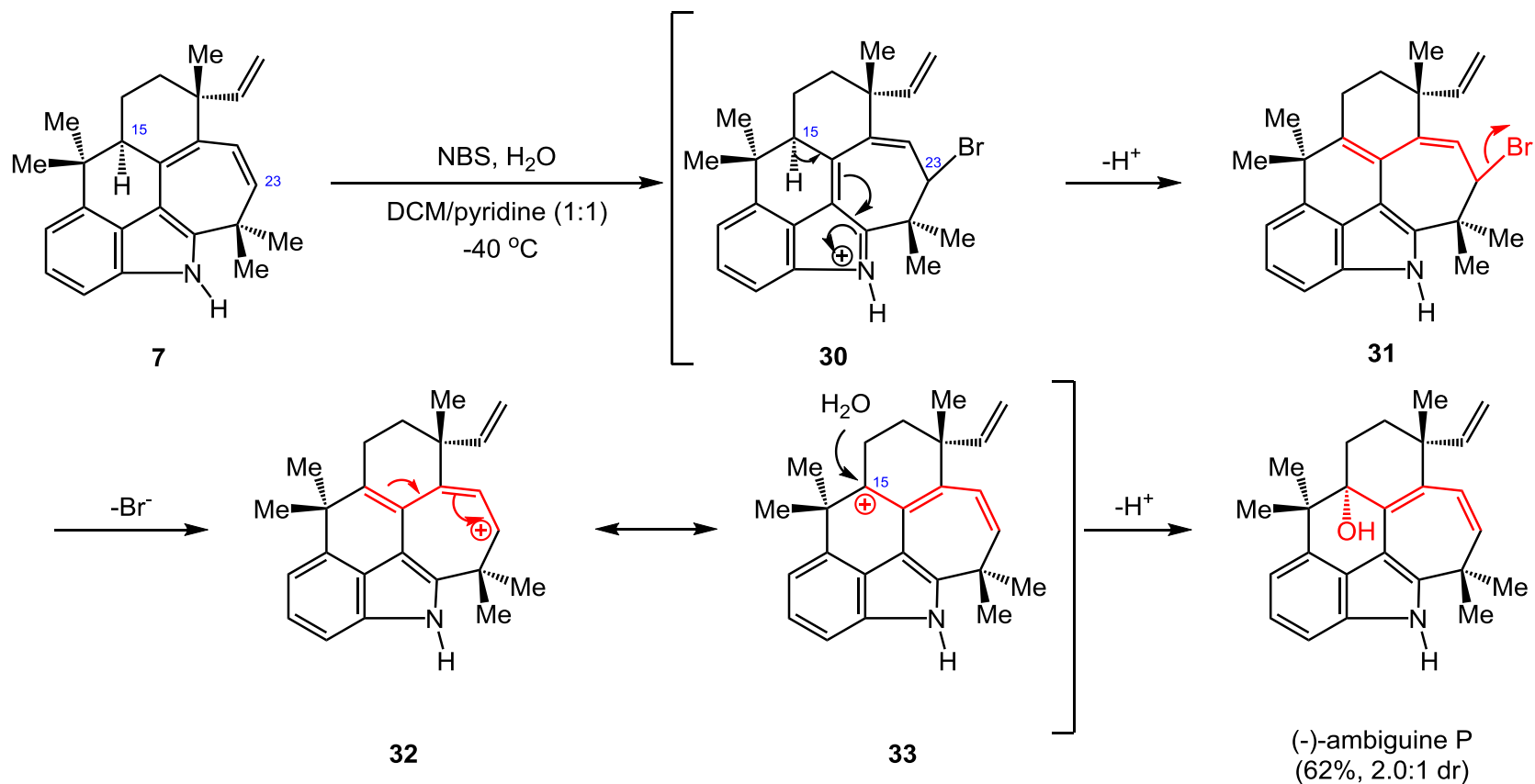
Synthesis of 7



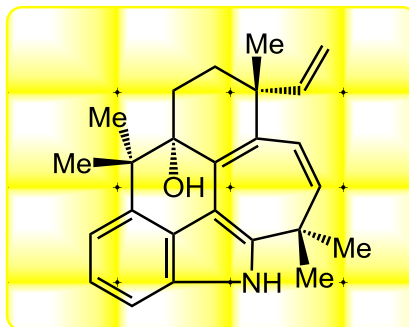
Synthesis of (-)-Ambiguine P



Probable mechanism for the (-)-Ambiguine P



Summary



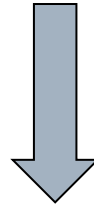
(-)-ambiguine P

- Total synthesis of (-)-Ambiguine P: 12 steps, 9% overall yield;
- Inspired by a [4+3] cycloaddition reaction/Friedel-Crafts reaction/NBS-mediated bromination/ S_N1' displacement.

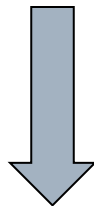
The first paragraph

Writing thought

Source of ambiguiene alkaloids



Importance of ambiguiene alkaloids



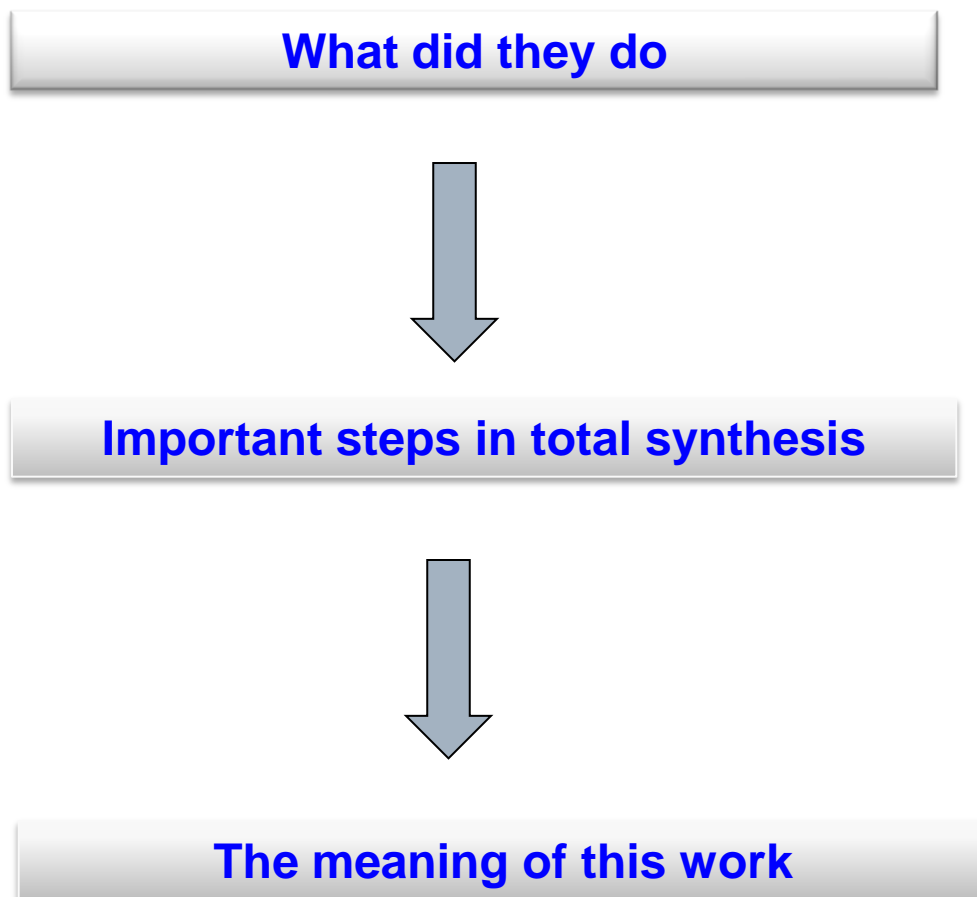
Structure feature of ambiguiene alkaloids

The first paragraph

Since the report of the first few ambigaine indole alkaloids from blue-green algae in 1992 by Smitka, Moore et al., a total of 18 members of this group of hapalindoles have been identified. These secondary metabolites exhibit a broad range of bioactivities including antimycotic, antifungal, and antibiotic properties, with two members showing activities comparable to clinical agents streptomycin, puromycin, and amphotericin. Ambiguines possess the core structure of hapalindoles, but with an additional reverse prenyl group at the C-2 position of the indole moiety. Frequently, as found in 13 members of the group, the prenyl group connects the indole C-2 position and the distal cyclohexane ring, to form a seven-membered ring.

The last paragraph

Writing thought



The last paragraph

In summary, we have completed the total synthesis of (-)-ambiguine P through a concise sequence starting from known ketone **16**. The synthesis, inspired by a [4+3] cycloaddition reaction, features a two-step sequence to construct the cyclohepta[*b*]indole motif and a Friedel-Crafts reaction to assemble the pentacyclic ambiguity framework. An NBS-mediated bromination in the presence of water achieved an electrophilic bromination/ S_N1' displacement to install the crucial C-15 hydroxy group of the natural product. The strategy is sufficiently general so as to lay the groundwork for accessing other pentacyclic members of the ambiguity alkaloid family.

Representative Examples

This objective was accomplished by treating **21** with $\text{BF}_3 \cdot \text{OEt}_2$ and MeOH, which formed the ambiguine framework in good yield.

Based on the encouraging results of the model studies, we embarked on the construction of the ambiguine pentacycle using a suitably decorated diene.

The unexpected formation of the C-15 hydroxylated product can be explained by plausible reactivity considerations.

The strategy is sufficiently general so as to lay the groundwork for accessing other pentacyclic members of the ambiguine alkaloid family.

***Thanks
for your attention***