Literature Report VII

Total Synthesis of the Diterpenoid Alkaloid Arcutinidine

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Checker: Chang-Bin Yu
Date: 2019-10-09

Sarpong, R. *et al. J. Am. Chem. Soc.* **2019**, *141*, 13713−13717.
Li, A. *et al. J. Am. Chem. Soc*. **2019**, *141*, 13718−13723.

CV of Professor Sarpong, R.

Sarpong, R.

Background:

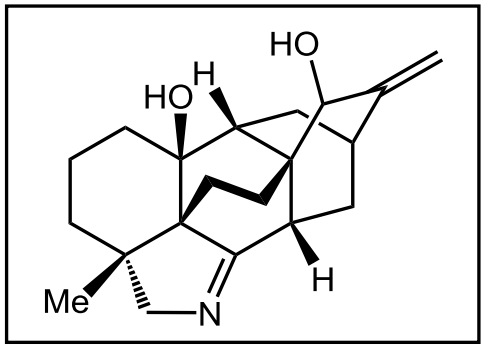
- **1991-1995** B.S. in Macalester College;
- **1995-2000** Ph.D. in Princeton University;
- **2000-2004** Postdoctoral Fellow, Caltech;
- **2004-Now** University of California, Berkeley.

Research:

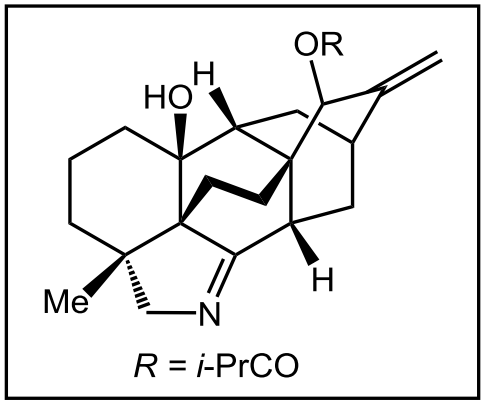
Organic and Organometallic Chemistry: Total synthesis of biologically active and architecturally complex natural products as a platform for the development of new synthetic methods and strategies.

Contents

Introduction



Arcutinidine



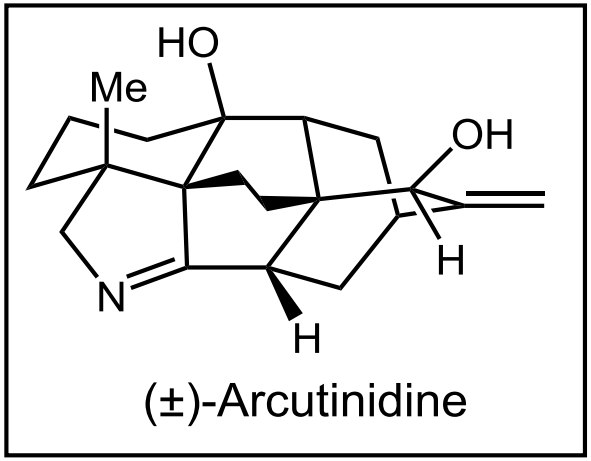
Arcutinine

Aconitum arcuatum

- Arcutinine was isolated from the aerial part of Aconitum arcuatum; Arcutinidine was obtained as a saponification product from Arcutinine;
- It possessed 8 stereocenters;
- The diterpenoid alkaloids possess wide-ranging activity as modulators of voltage-gated ion channels.

Saidkhodzhaeva, S. A. *et al. Chem. Nat. Compd.* **2001**, *37*, 466.

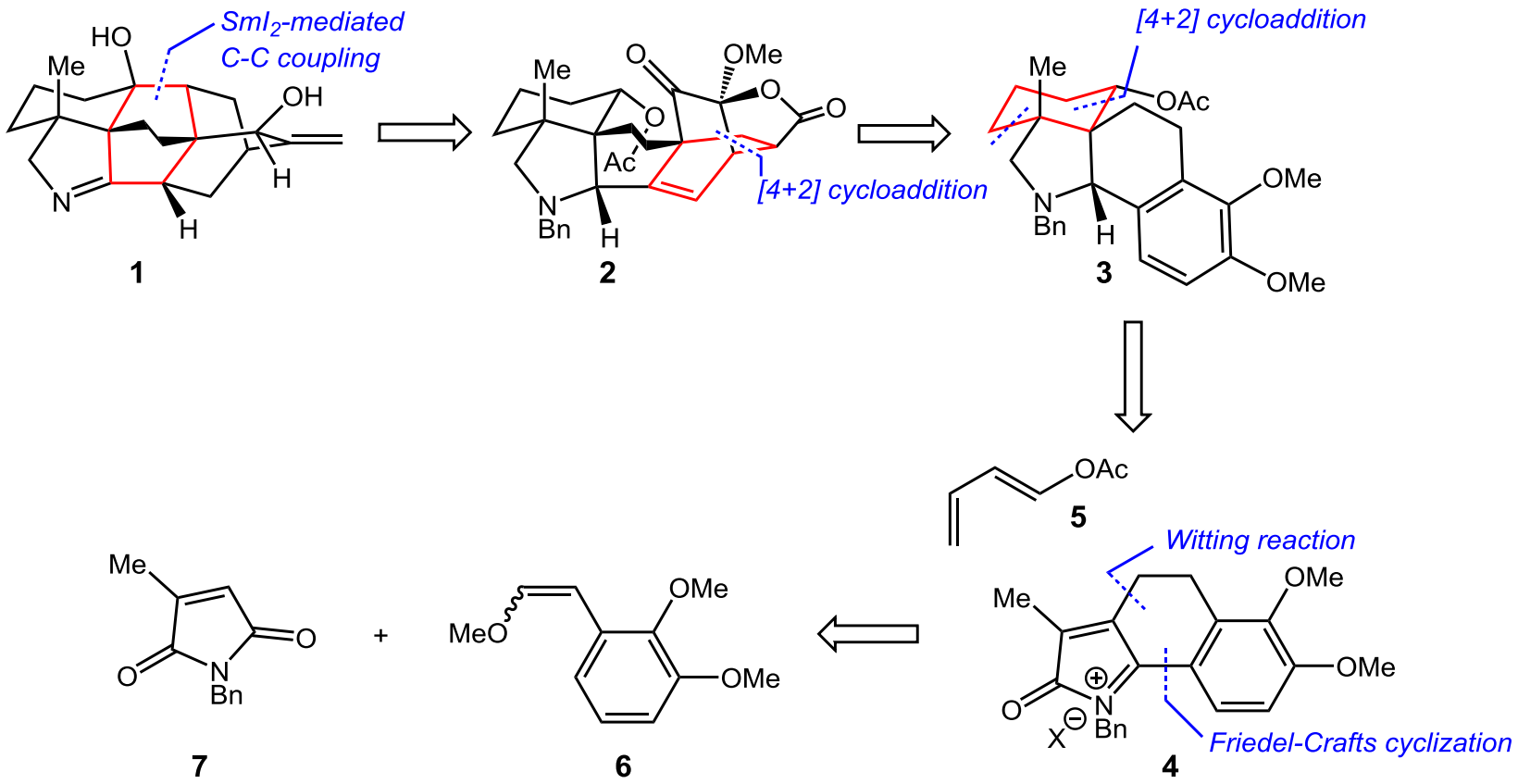
Total Synthesis of Arcutinidine



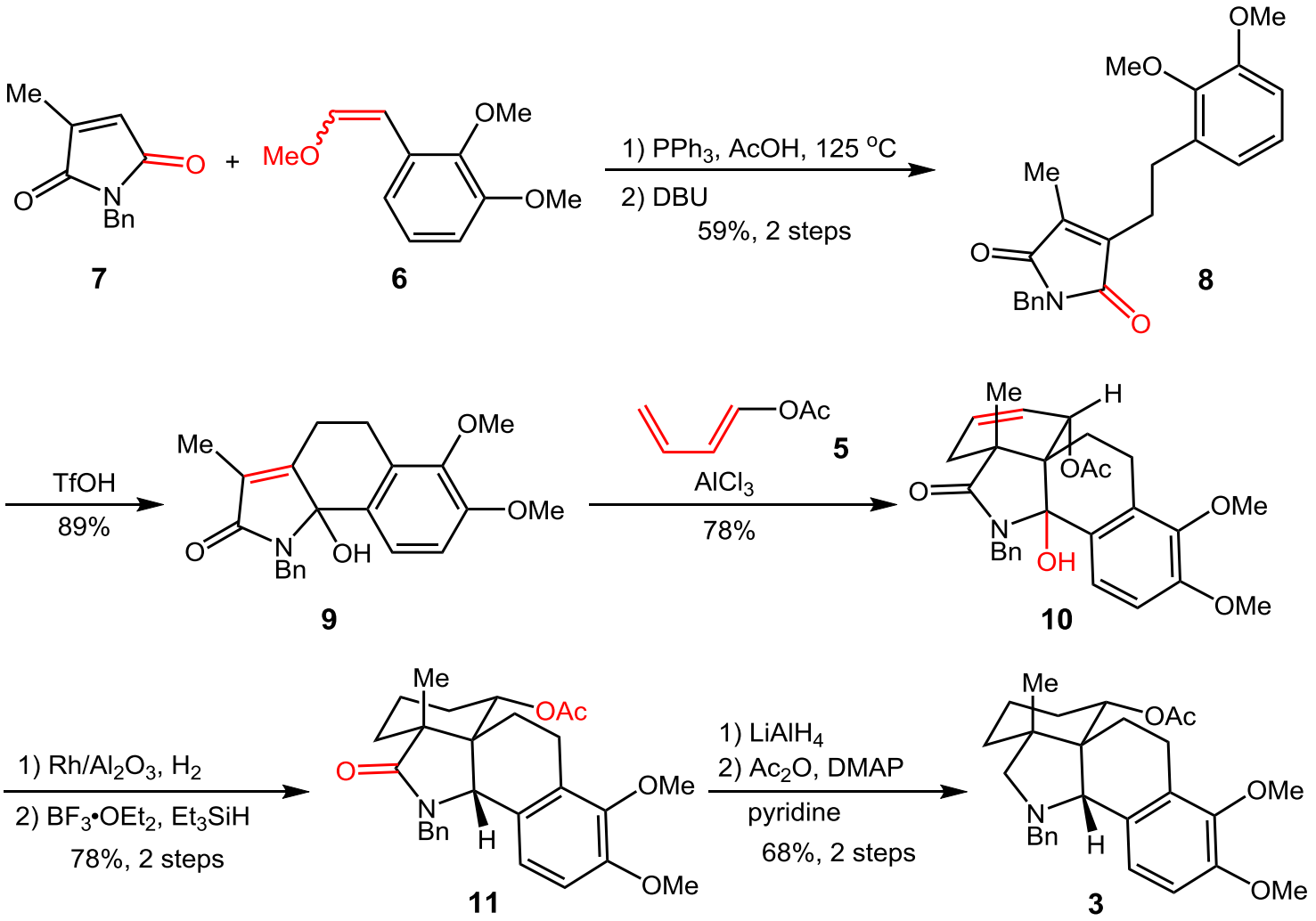
(±)-Arcutinidine

Sarpong, R. *et al. J. Am. Chem. Soc.* **2019**, *141*, 13713.

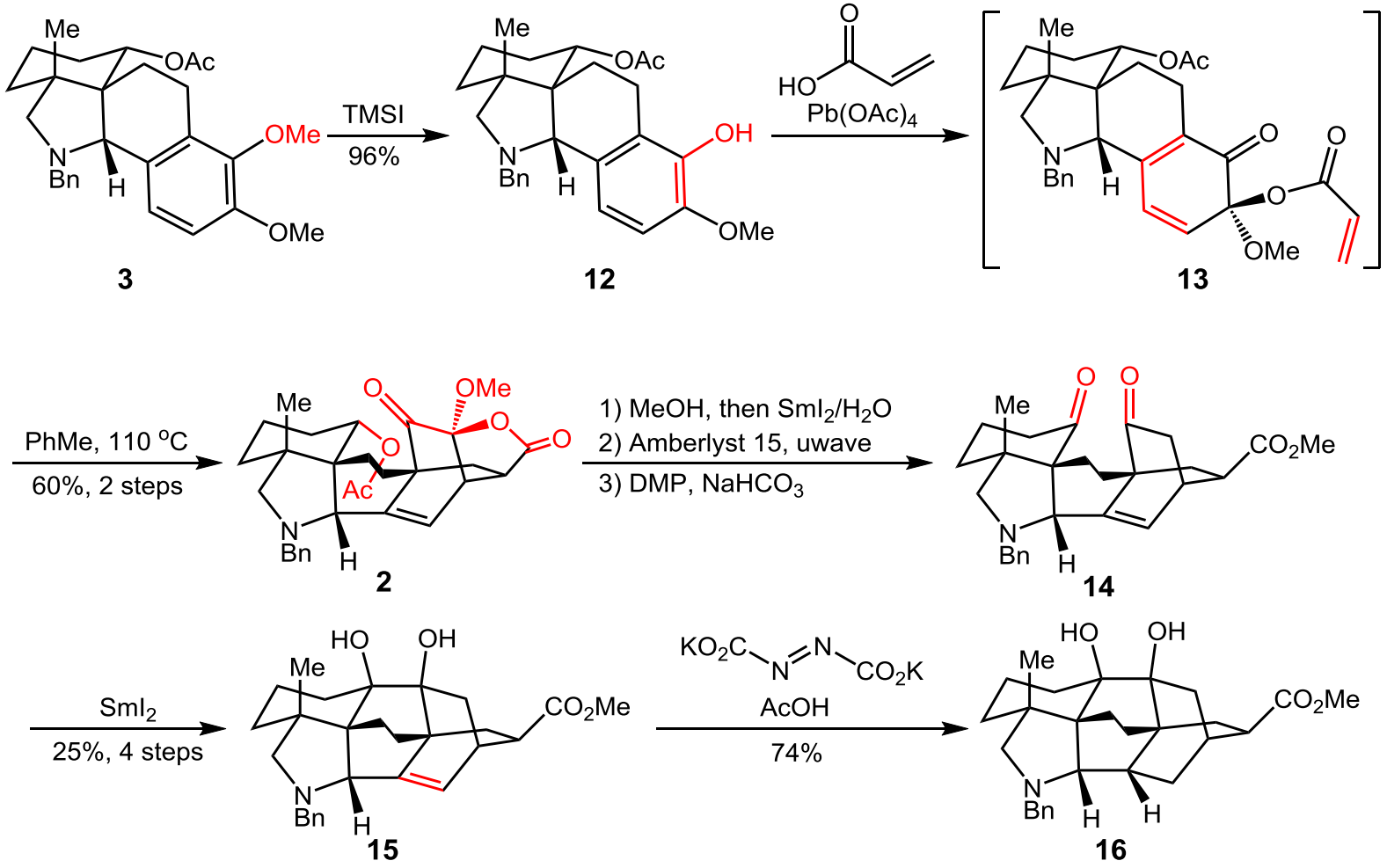
Retrosynthetic Analysis of Arcutinidine



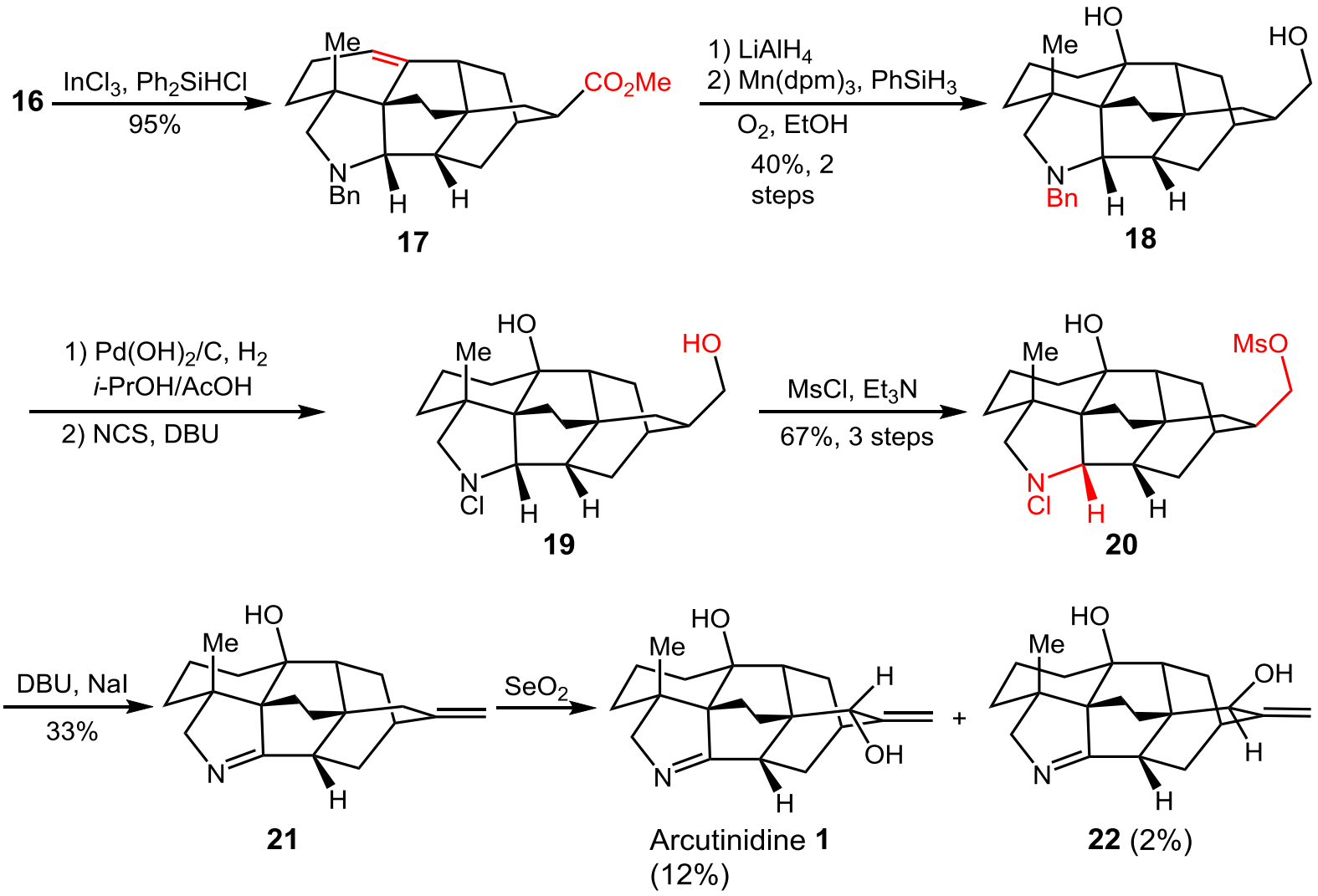
Synthesis of Key Tetracycle 3



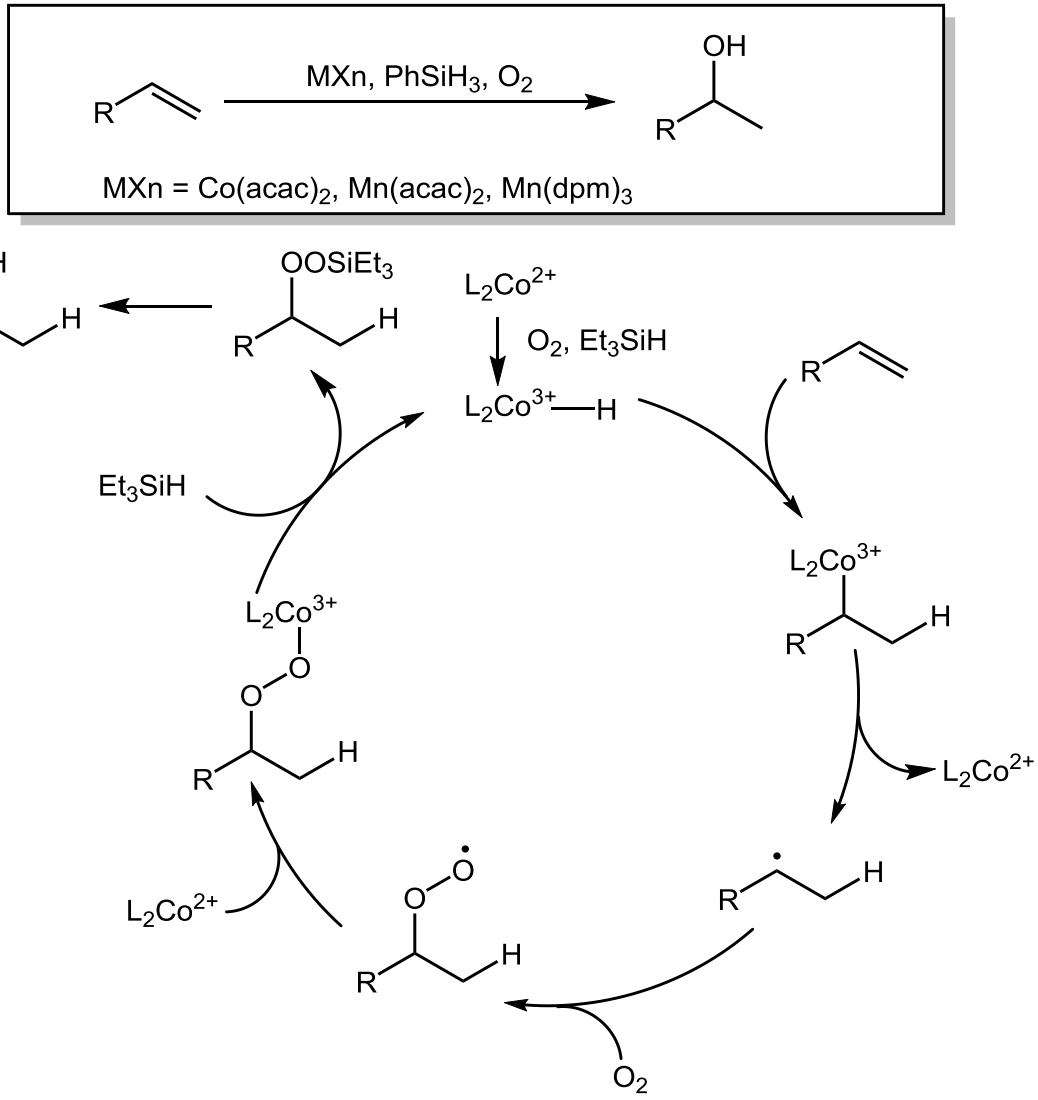
Synthesis of Compound 16



Completion of Arcutinidine 1

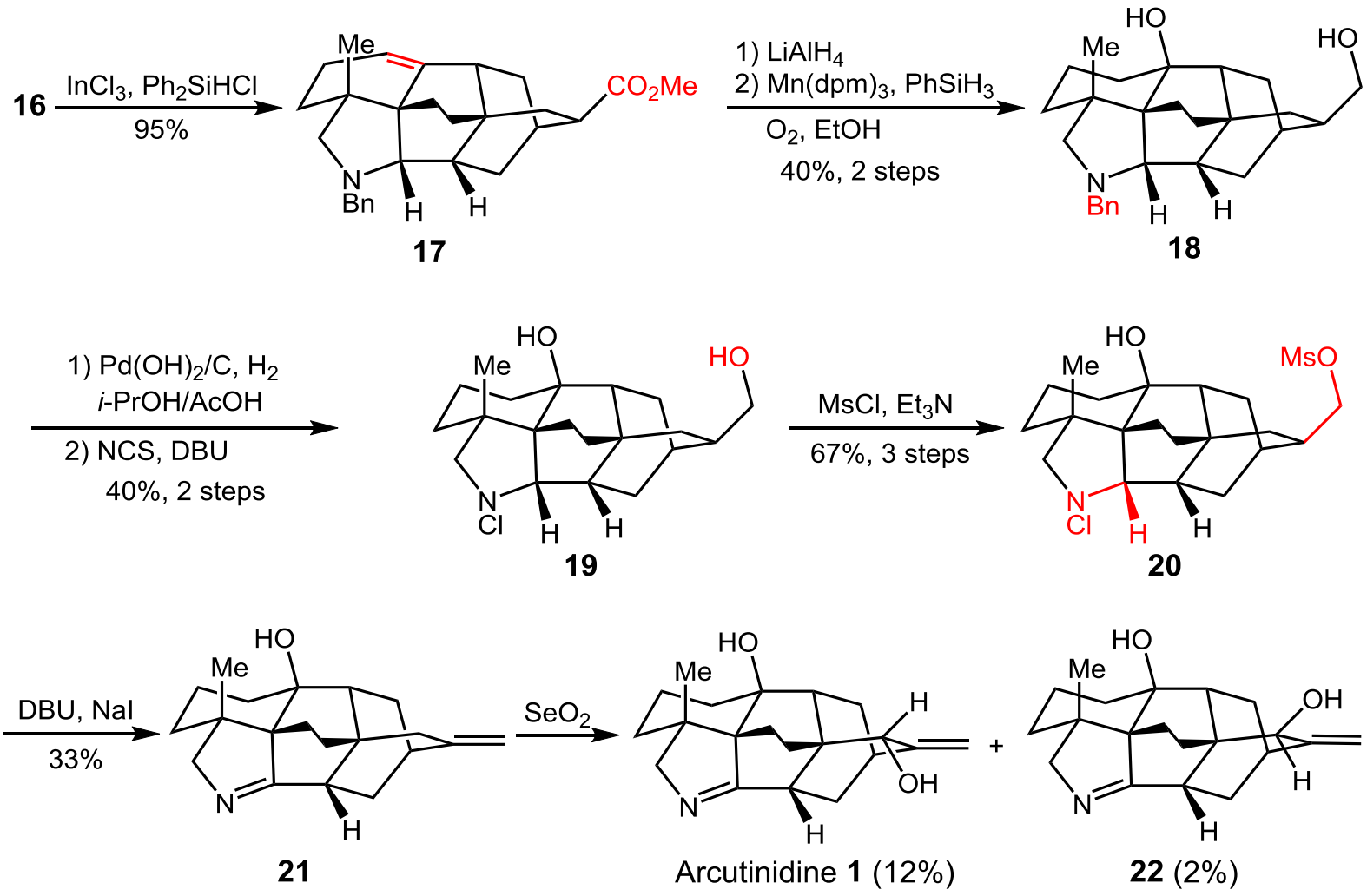


Mukaiyama Hydration

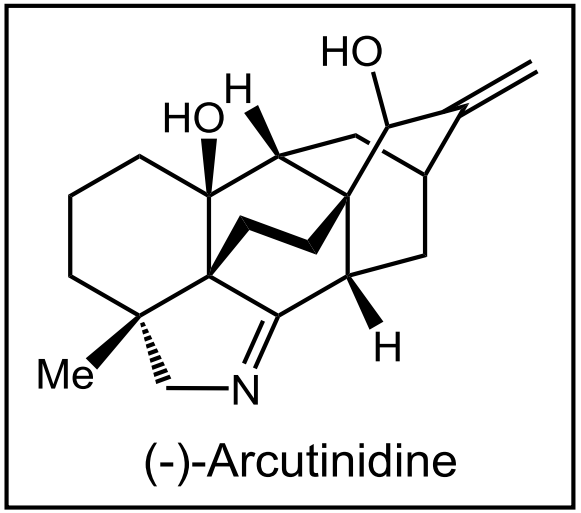


From Yang Zhao

Completion of Arcutinidine 1



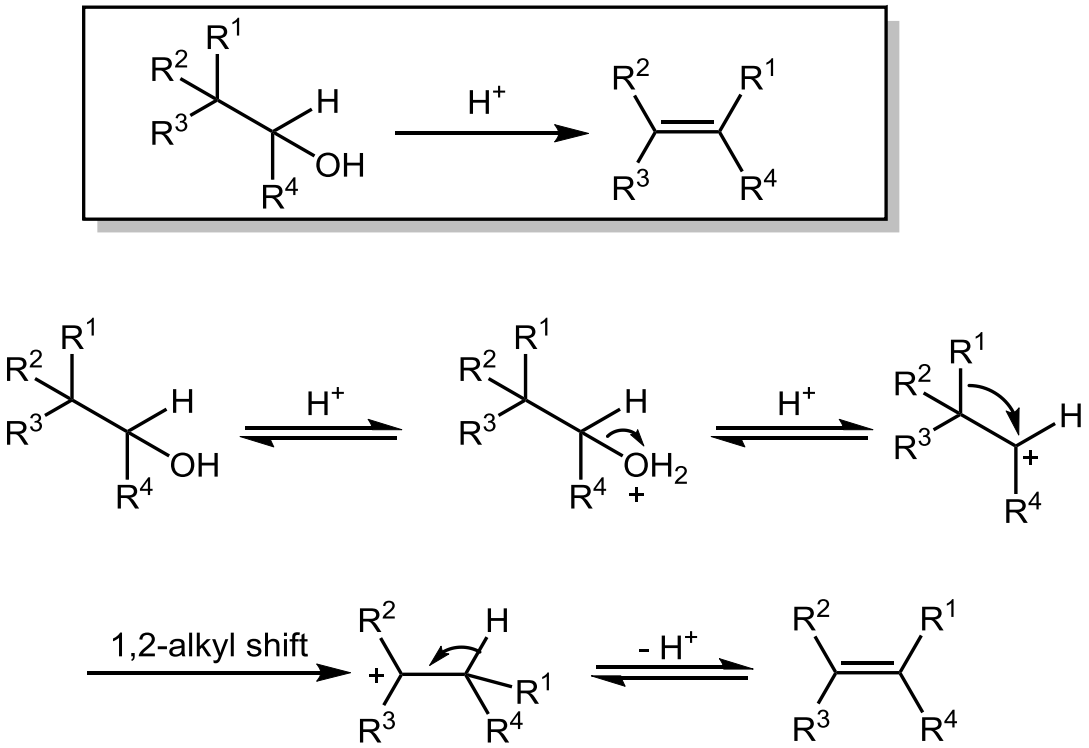
Asymmetric Total Synthesis of (-)-Arcutinidine



(-)-Arcutinidine

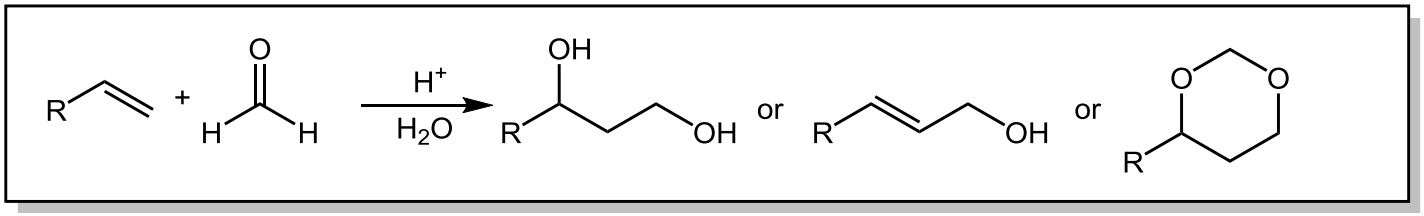
Li, A. *et al. J. Am. Chem. Soc*. **2019**, *141*, 13718.

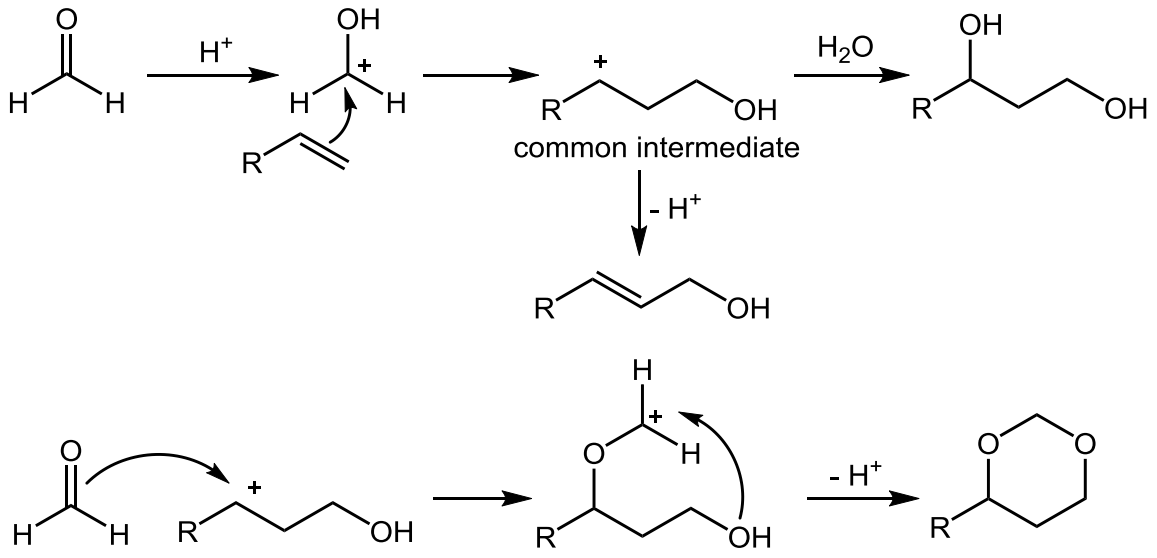
Wagner-Meerwein Rearrangement



From Name Reactions by Jie Jack Li

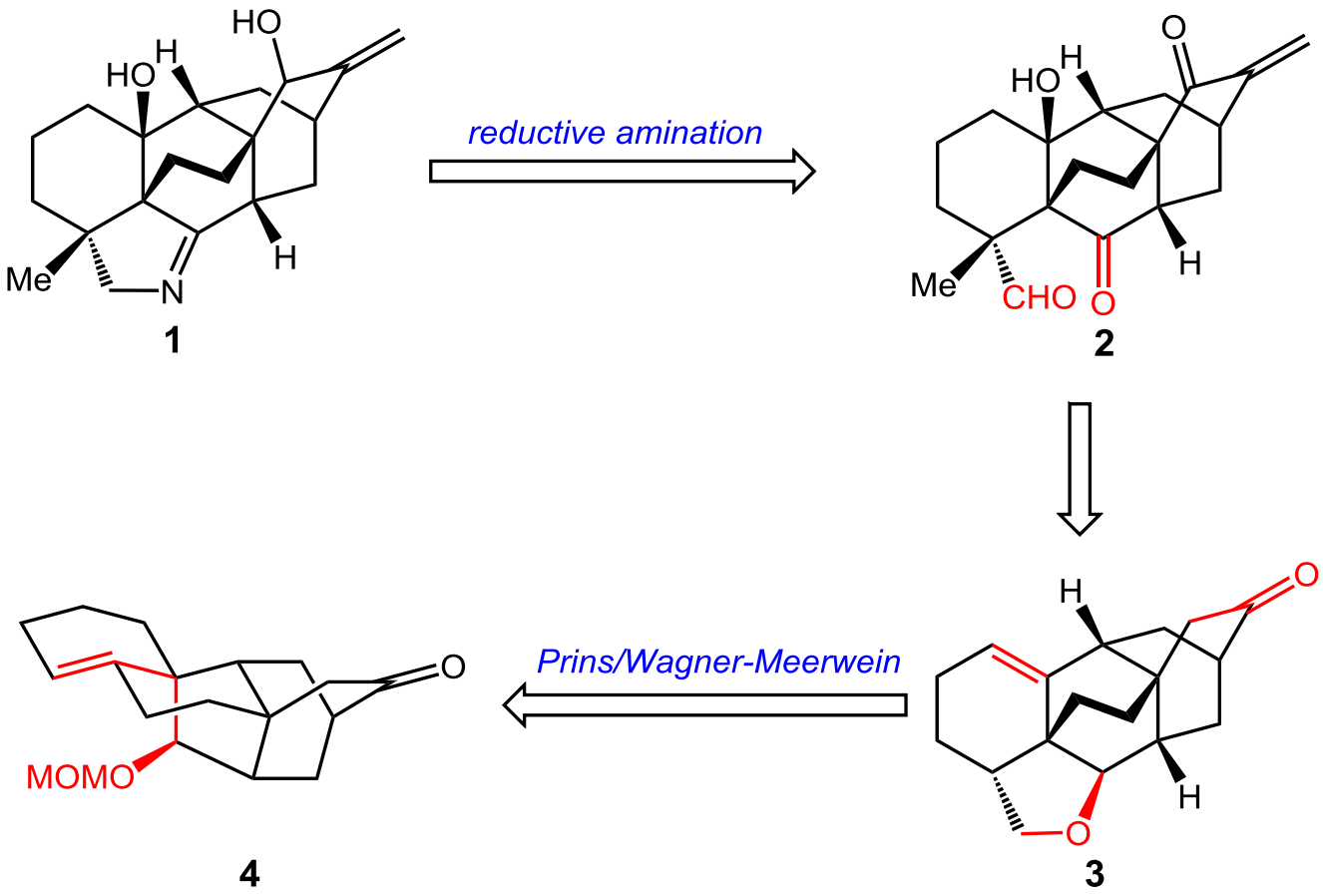
Prins Reaction



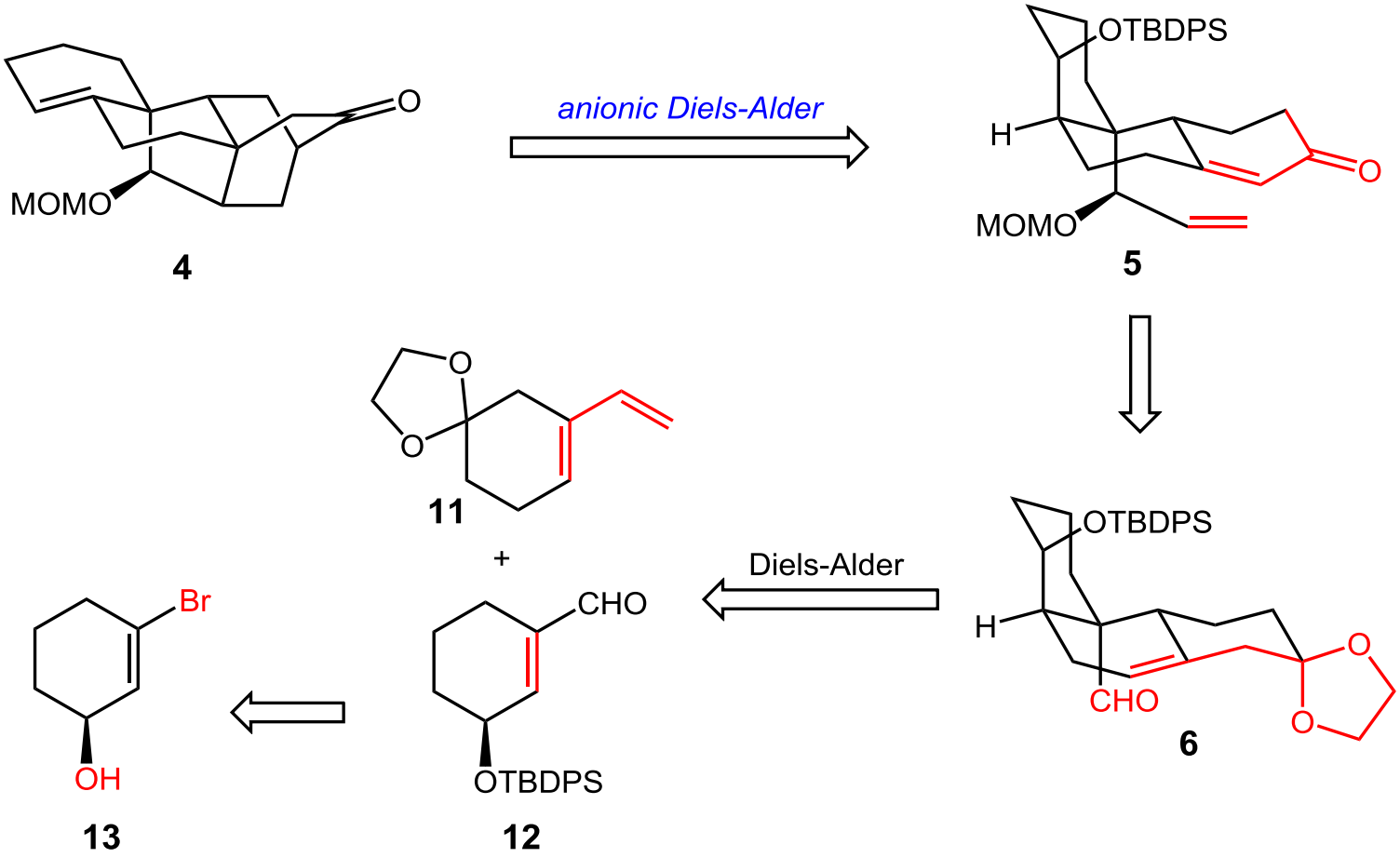


From Name Reactions by Jie Jack Li

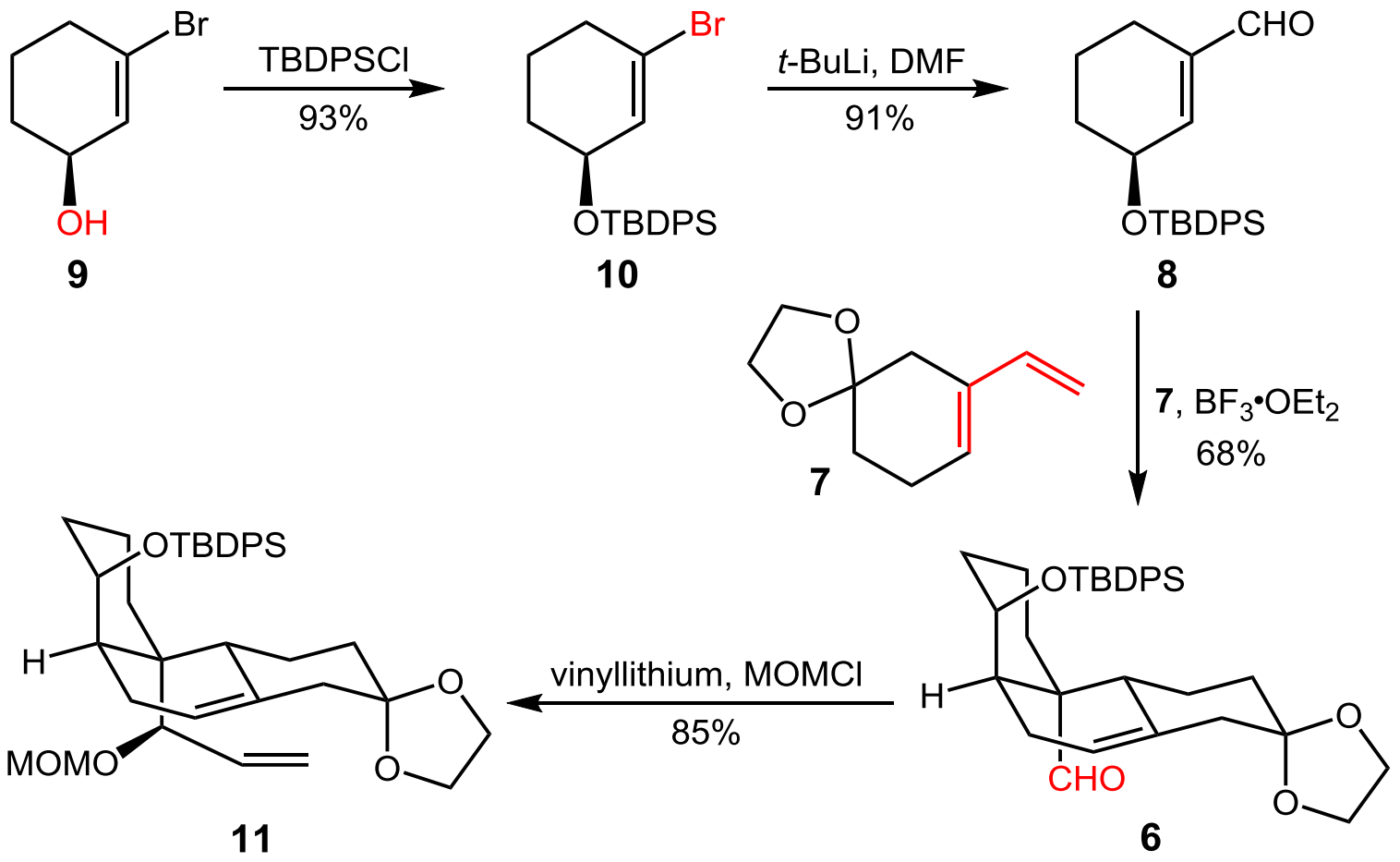
Retrosynthetic Analysis of (-)-Arcutinidine



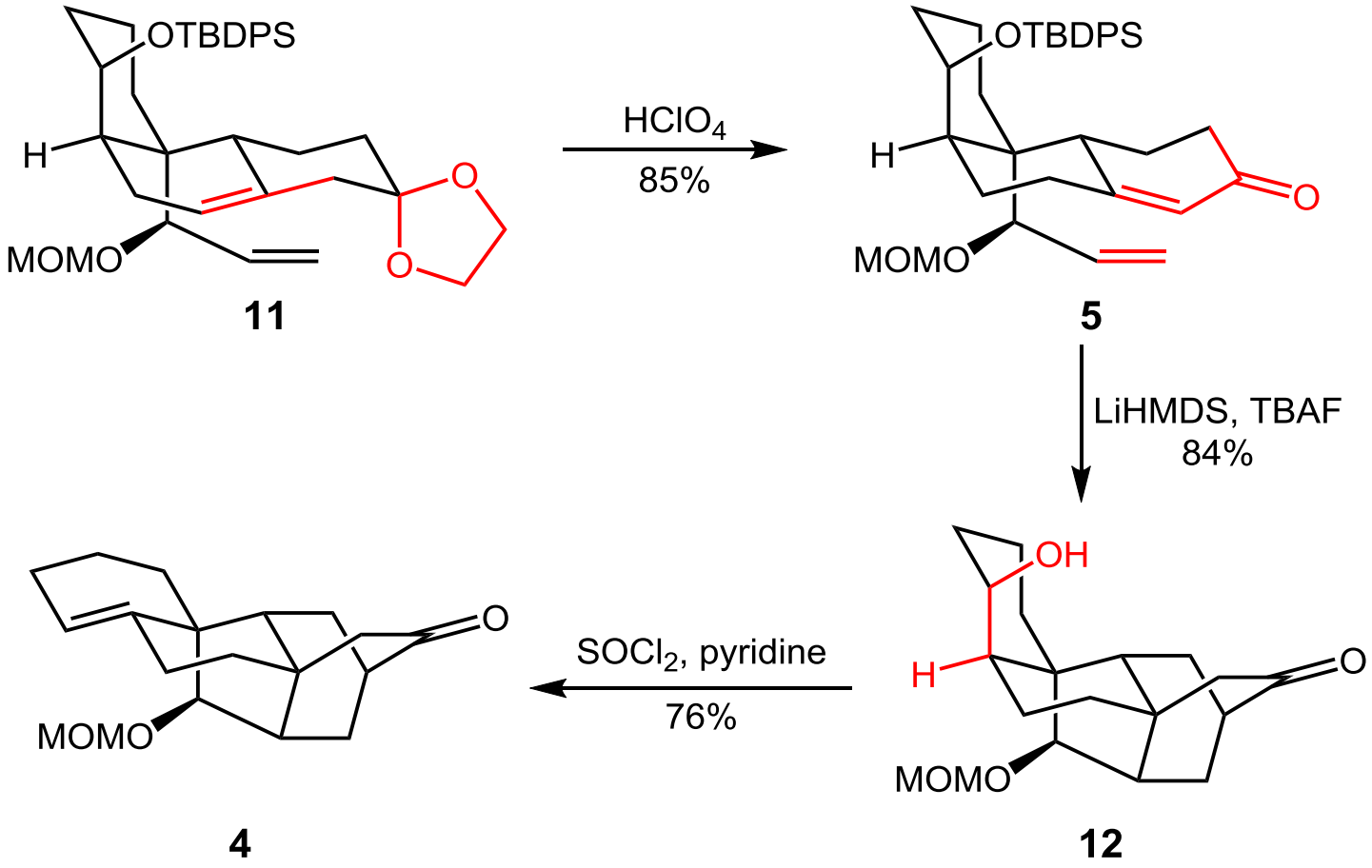
Retrosynthetic Analysis of 4



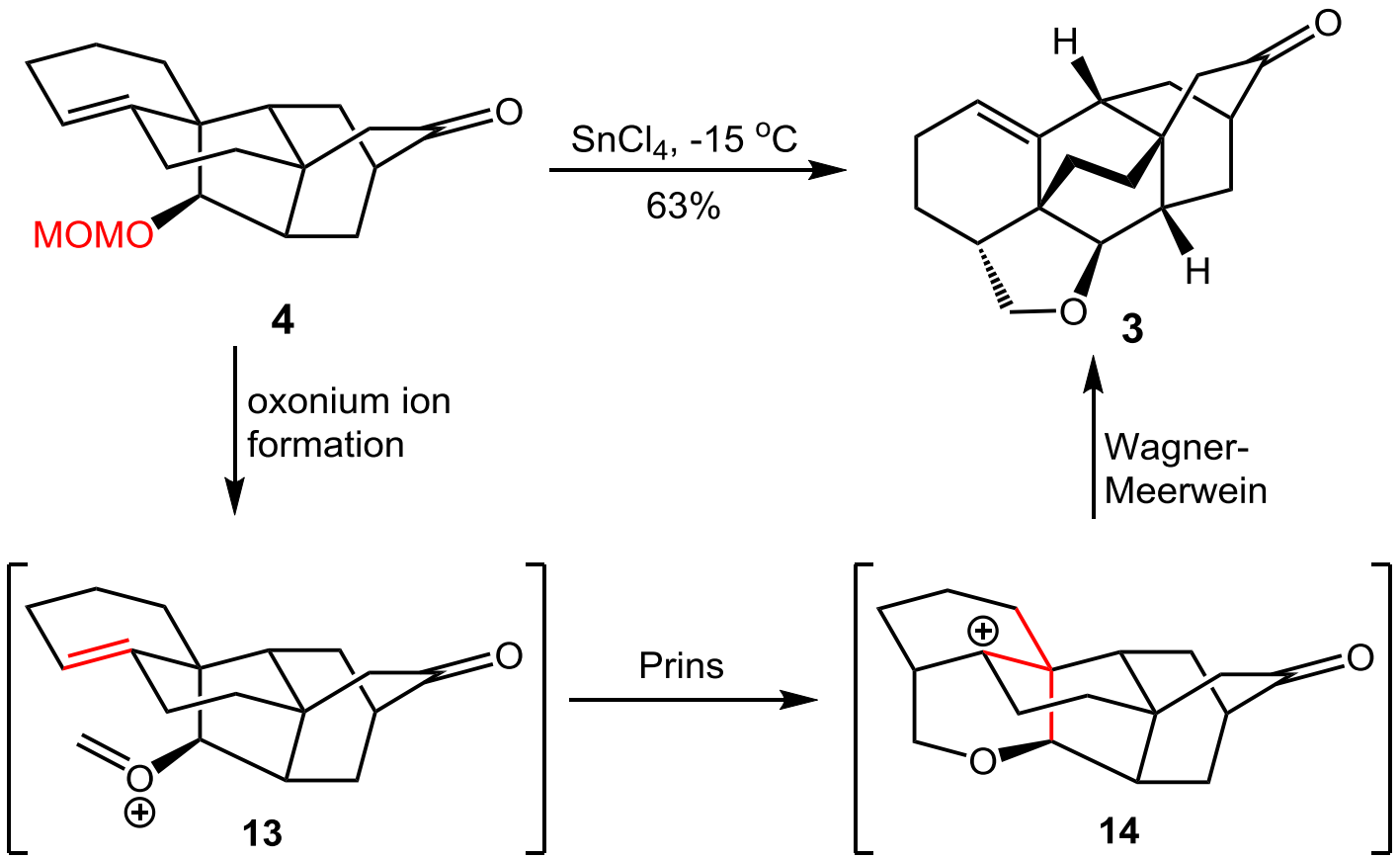
Synthesis of 11



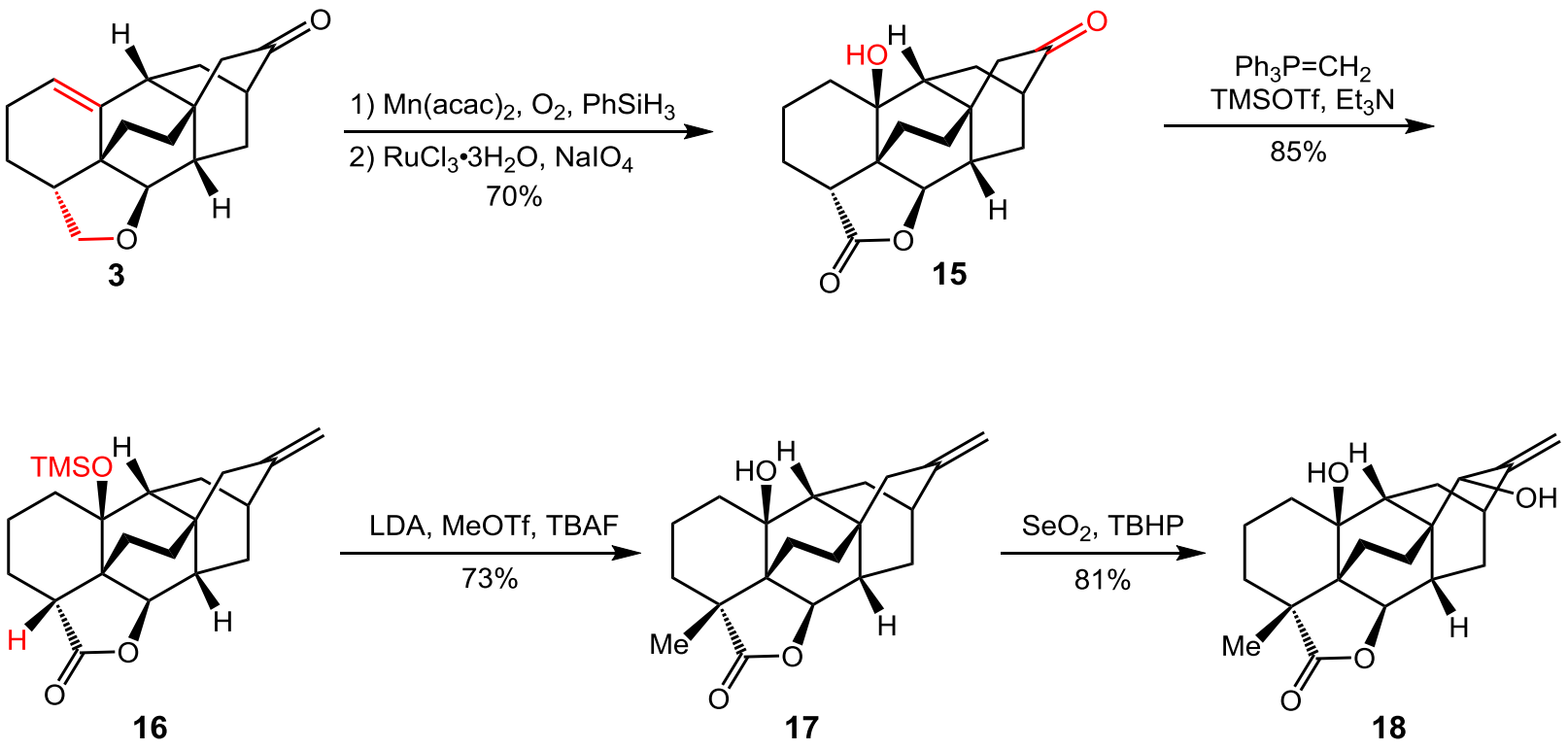
Construction of Pentacyclic Intermediate 4



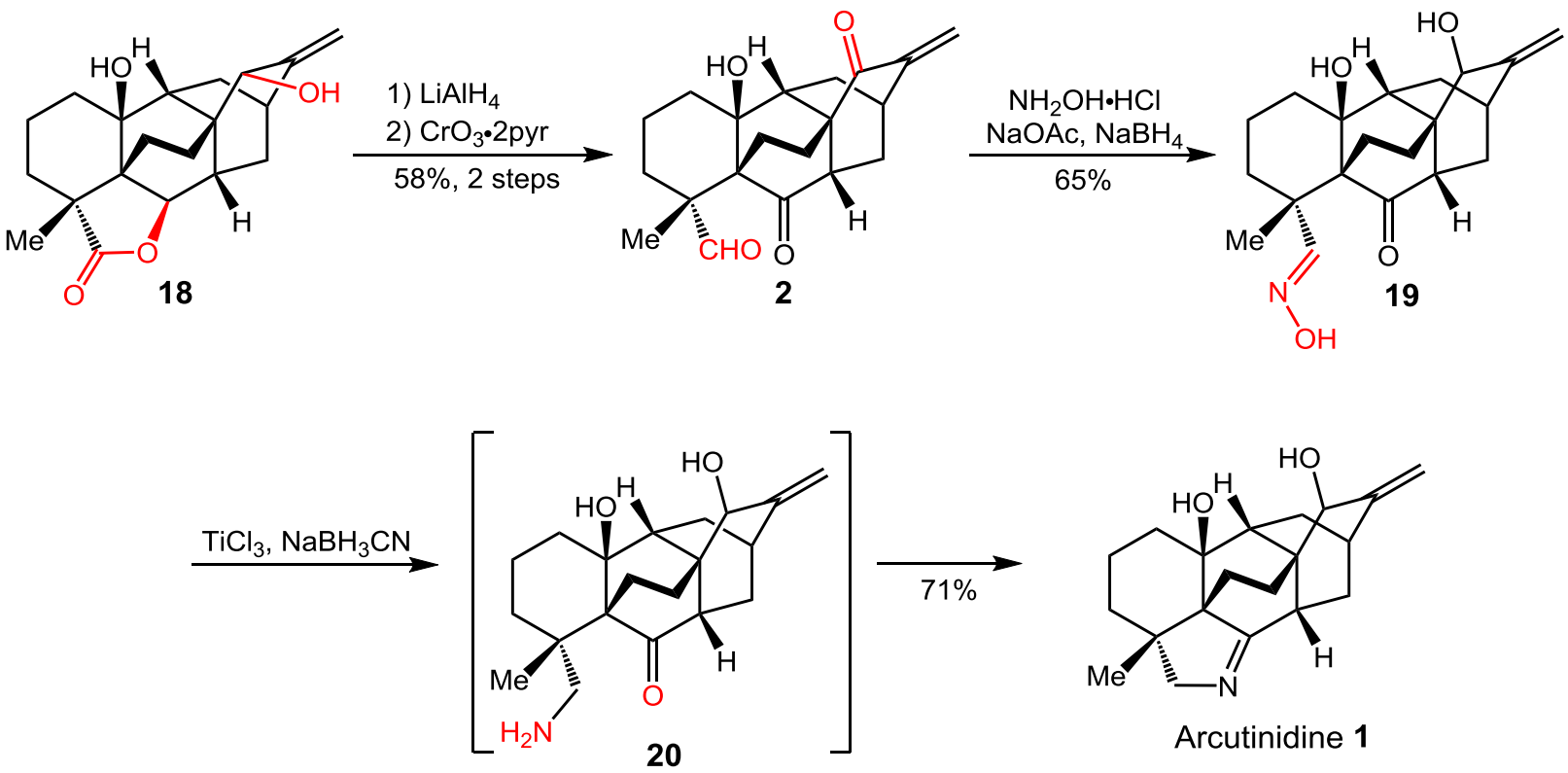
Cationic Cascade Reaction



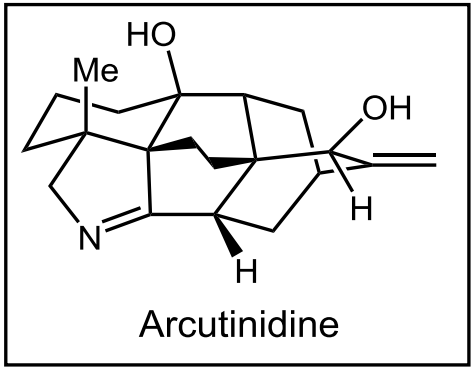
Preparation of 18



Completion of the Synthesis of 1



Summary



Arcutinidine

- 24 steps, 0.024 % overall yield;
- Unprecedented oxopyrrolium Diels−Alder cycloaddition;
- Diastereoselective oxidative dearomatization/cycloaddition sequence and a SmI_2-mediated C-C coupling.

Sarpong, R. *et al. J. Am. Chem. Soc.* **2019**, *141*, 13713.

- 17 steps, 1.1% overall yield;
- Bioinspired Prins/Wagner−Meerwein cascade;
- Chemoselective reductive amination followed by spontaneous imine formation.

Li, A. *et al. J. Am. Chem. Soc*. **2019**, *141*, 13718.

The First Paragraph

Natural products that possess a high degree of three-dimensional structural complexity pose significant challenges to identifying strategies for their chemical synthesis. By adopting a retrosynthetic plan that reduces the number of bridged rings in these architecturally intricate structures, the resulting fused ring systems can prompt retrons that guide subsequent disconnections. In 1975, Corey introduced a formalized “logic” for the retrosynthesis of bridged, polycyclic frameworks that expounded the virtues of identifying a “maximally bridged ring”, which upon disconnection provides maximal structural simplification. Furthermore, by applying two-bond disconnections, a rapid decrease in target complexity in the retrosynthetic direction can be realized. In this regard, cycloaddition transforms have proven indispensable.

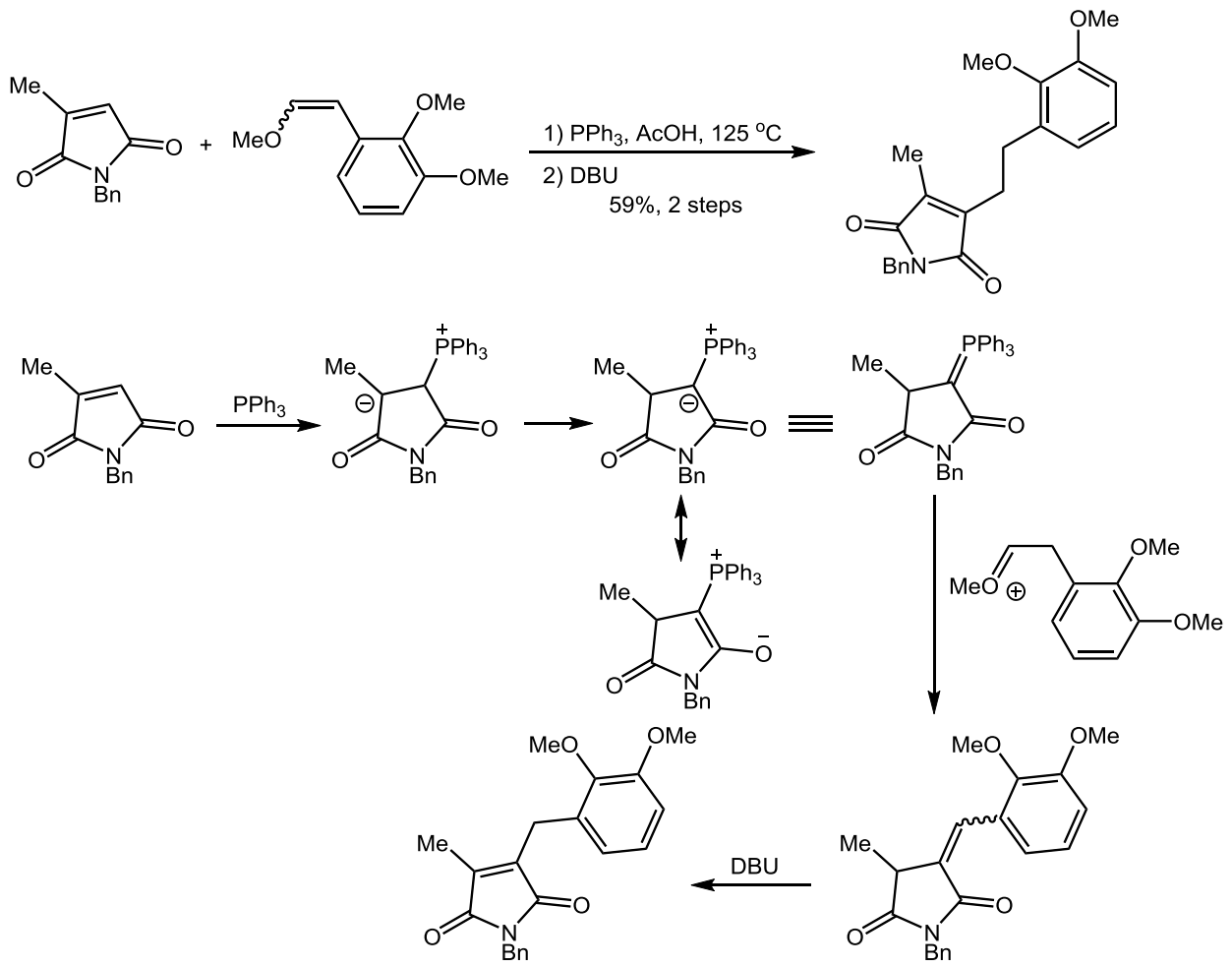
The Last Paragraph

In summary, we report the synthesis of the arcutane-type diterpenoid alkaloid arcutinidine. Our synthetic approach was inspired by chemical network analysis, which enabled rapid simplification of the three-dimensional architecture of the target compound through [4+2] cycloaddition transforms. Ultimately, these disconnections led us to identify an oxopyrrolium intermediate as a viable dienophile in an unprecedented [4+2] cycloaddition reaction. The synthesis reported herein sets the stage for the preparation of the related congeners. These studies, as well as the development of an enantioselective cycloaddition of the oxopyrrolium dienophile and the potential conversion of the arcutane skeleton to the hetidine skeleton, are the subject of ongoing investigations in our laboratory.

Acknowledgement

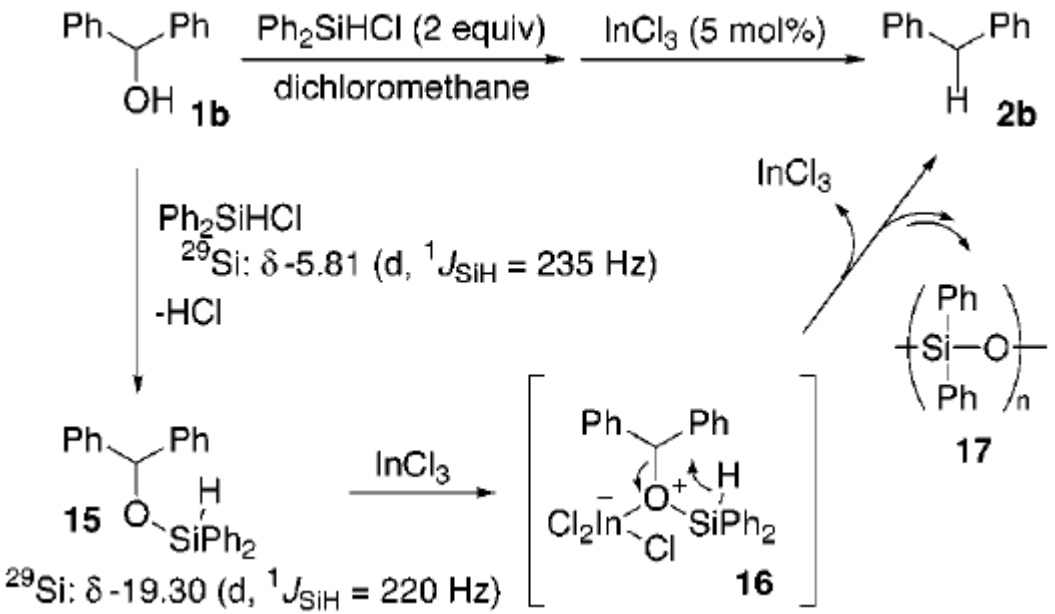
Thanks
for your attention

Modified Wittig reaction



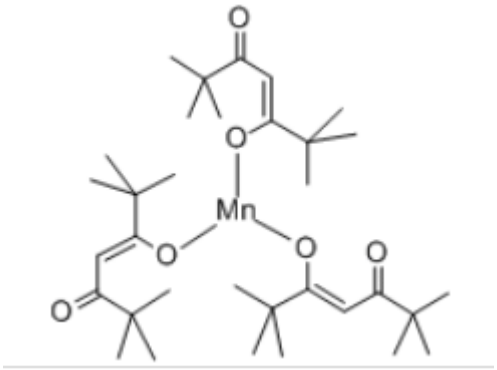
Hedaya, E. *et al. Tetrahedron* **1968**, *24*, 2241.

Reduction of Alcohols



Baba, A. *et al. J. Org. Chem.* **2001**, *66, 7741*.

Mukaiyama Hydration



$Mn(dpm)_3$