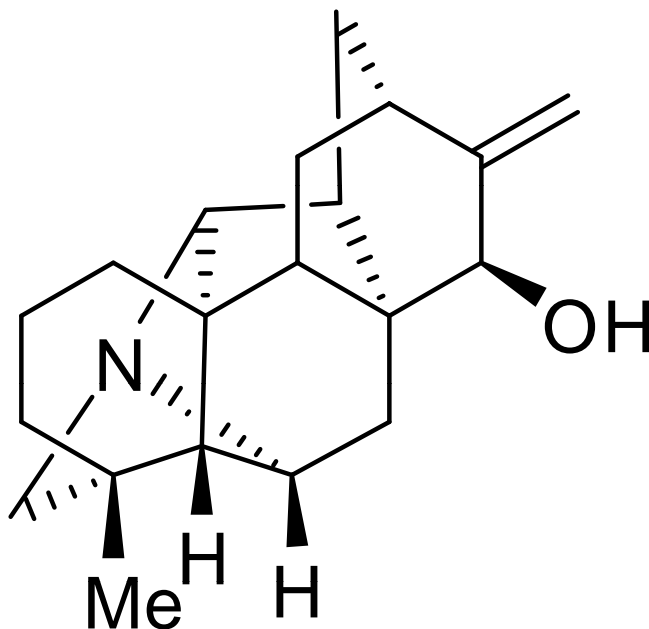


# Total Syntheses of Nominine

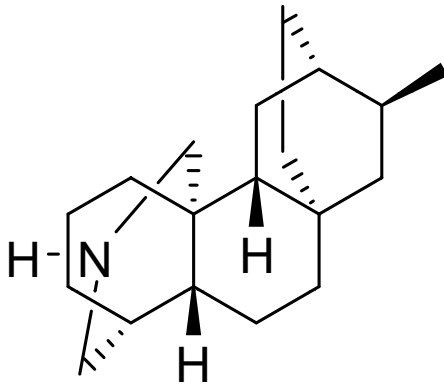


Literature Group Meeting

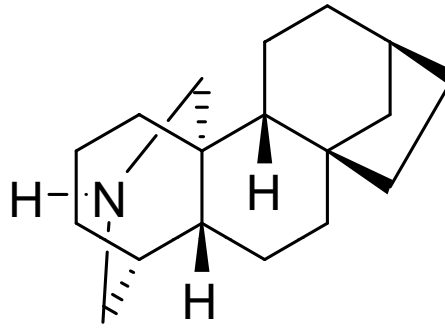
Lizzie O'Bryan

October 17, 2007

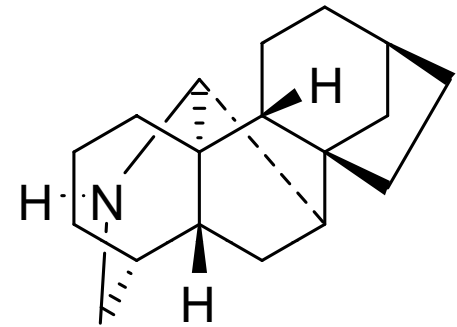
# Aconite Alkaloids



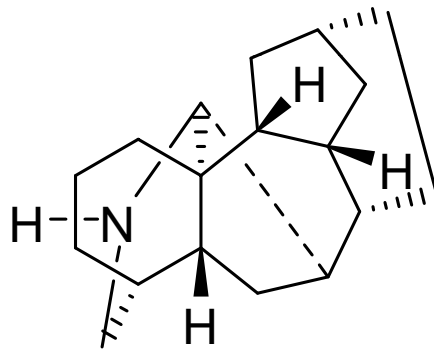
Atidane



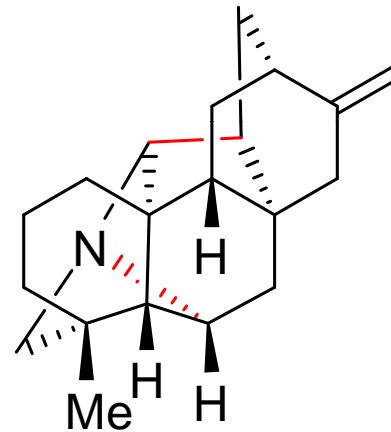
Veatchane



Cycloveatchane



Aconitane



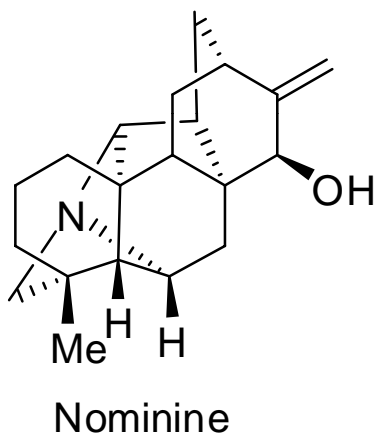
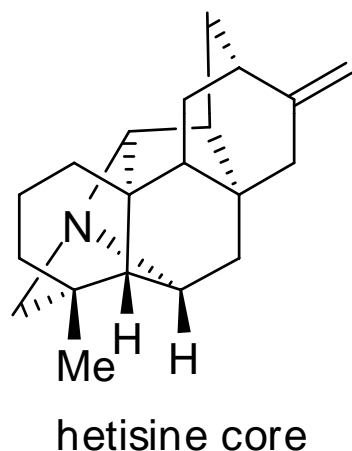
Hetisan

Muratake, H. M.; Natsume, M.; Nakai, H. *Tetrahedron*, **2006**, 62, 7093-7112.

Muratake, H. M.; Natsume, M. *Tetrahedron*, **2006**, 62, 7056-7070

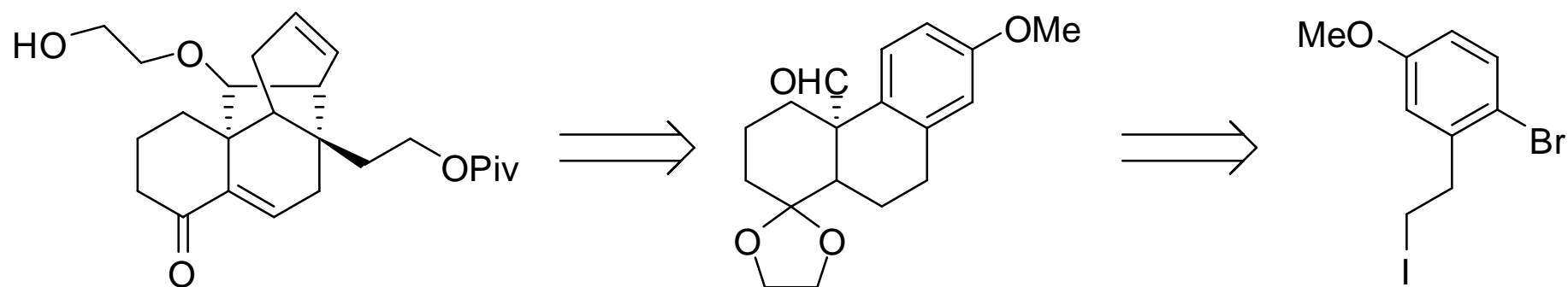
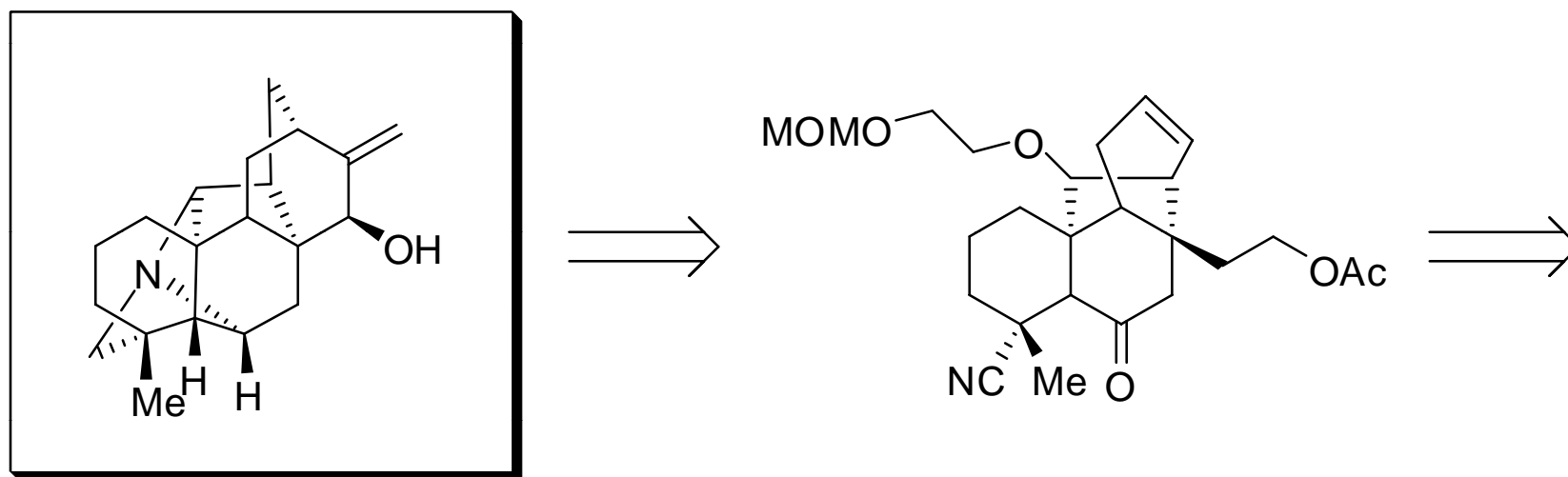
# Background

- Nominine is the simplest hetisine-type alkaloid.
- Aconite alkaloids are isolated from *Aconitum*, *Delphinium*, *Consolida*, *Thalictrum*, and *Spiraea*. Nominine was originally isolated from *Aconitum sanyoense* by Ochiai and coworkers in 1956.
- This family of natural products has been widely used in herbal medicine.
- Many of these alkaloids exhibit potent antiarrhythmic, immunomodulating, and analgesic activities in vivo.
- Muratake and Natsume's synthesis, completed in 2004, was the first total synthesis of a hetisine alkaloid.



Peese, K. M. and D. Y. Gin. *J. Am. Chem. Soc.* **2006**, *128*, 8734-8735.  
Muratake, H. M.; Natsume, M.; Nakai, H. *Tetrahedron*, **2006**, *62*, 7093-7112.  
Muratake, H. M.; Natsume, M. *Tetrahedron*, **2006**, *62*, 7056-7070.

# Muratake and Natsume's Synthetic Approach



Muratake, H. M.; Natsume, M.; Nakai, H. *Tetrahedron*, **2006**, 62, 7093-7112.

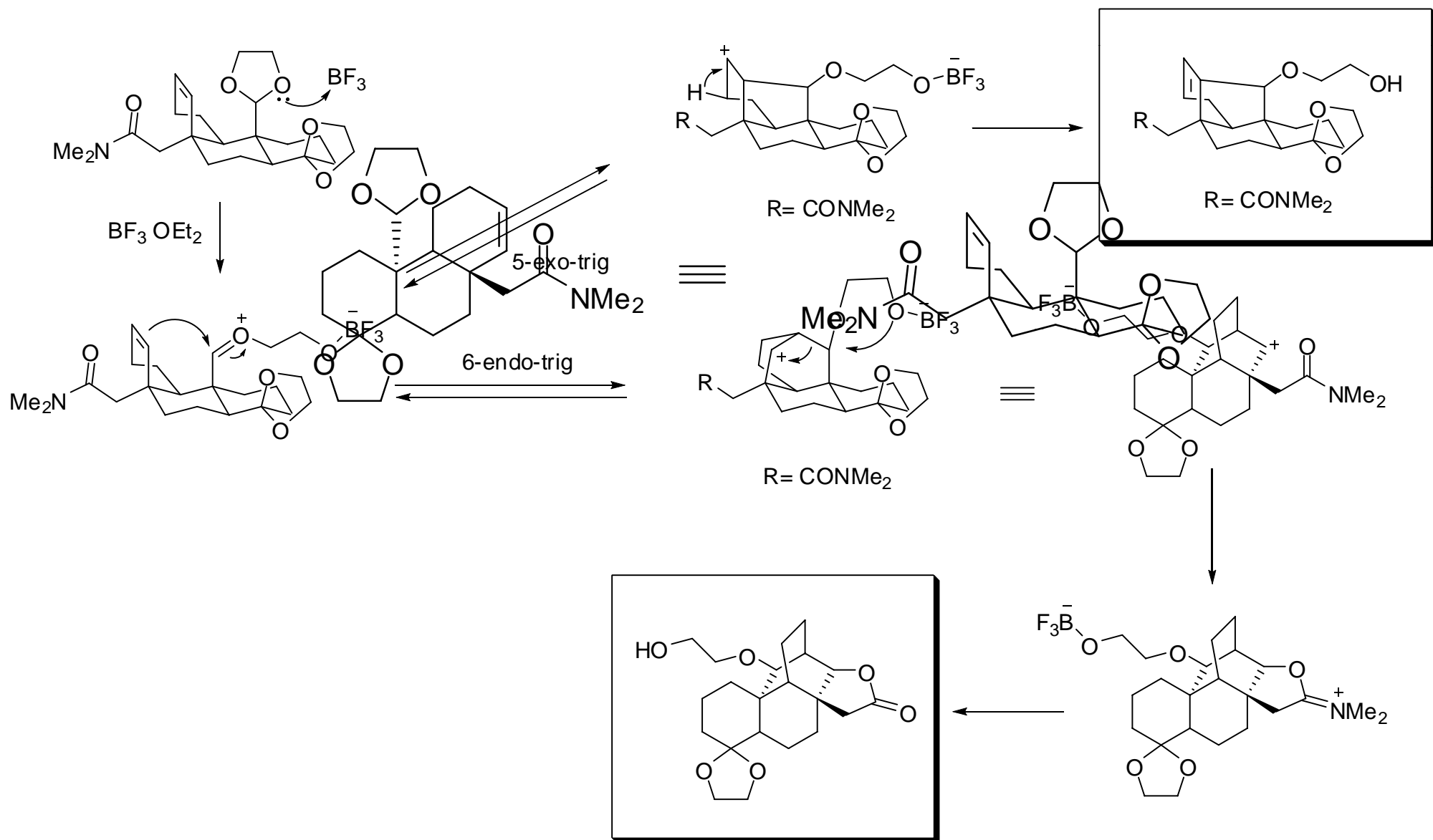
Muratake, H. M.; Natsume, M. *Tetrahedron*, **2006**, 62, 7056-7070.

Muratake, H. M.; Natsume, M. *Angew. Chem. Int. Ed.* **2004**, 43, 4646-4649.

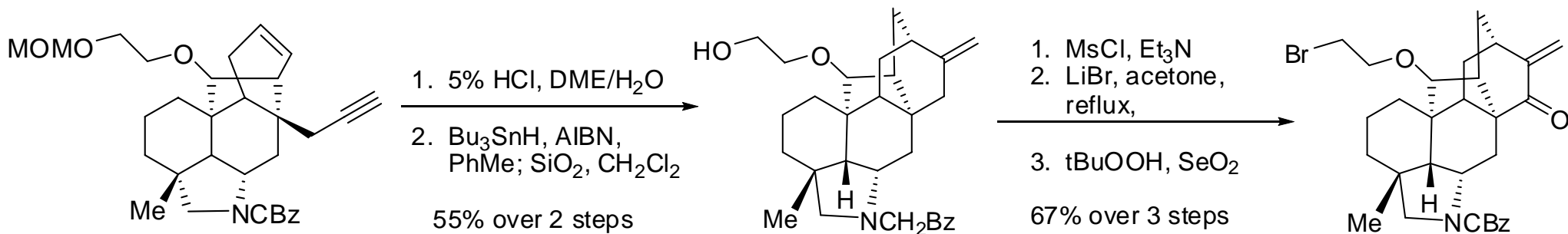
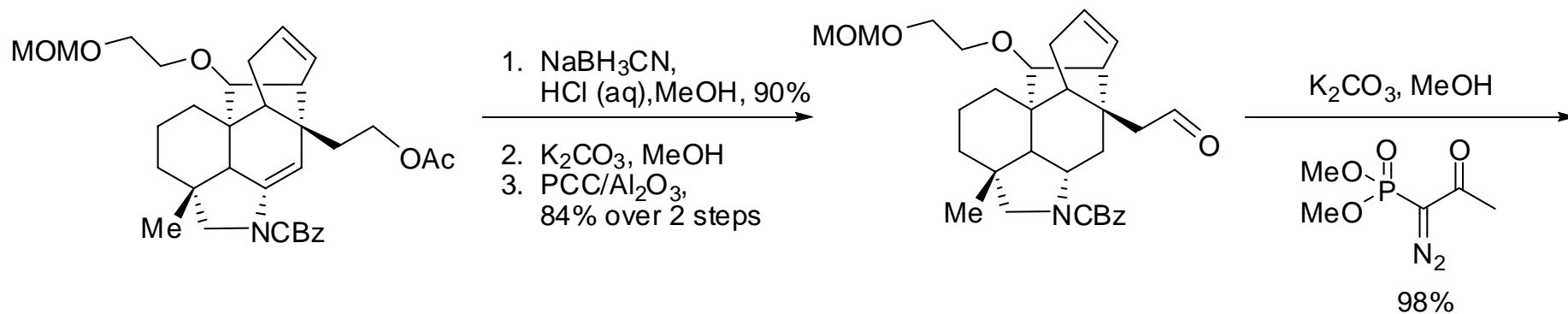
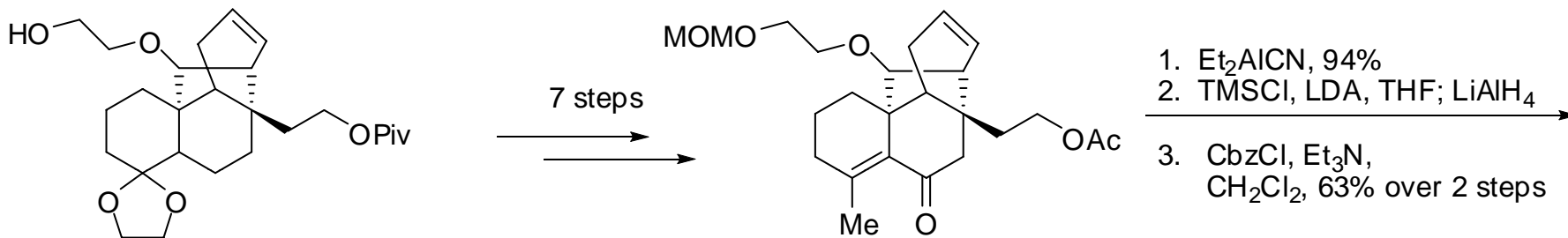
Muratake, H. M.; Natsume, M. *Tet. Lett.* **2002**, 43, 2913-2917.



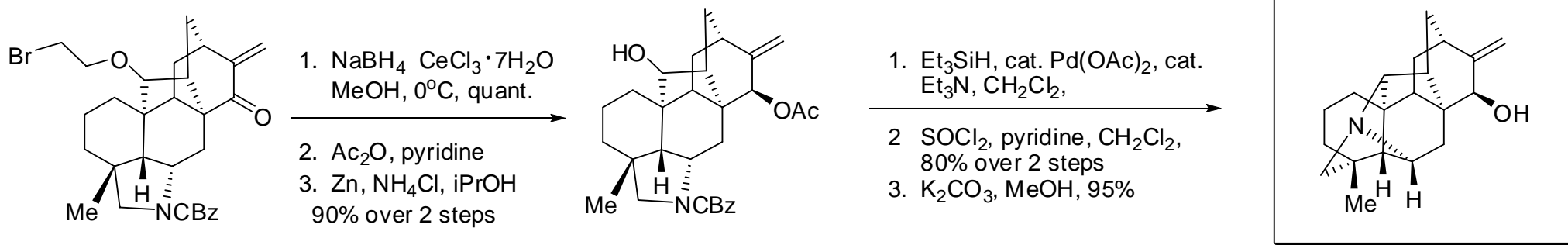
# Formation of the Tetracycle via an Acetal-Ene Reaction



# Elaboration of the tetracyclic intermediate

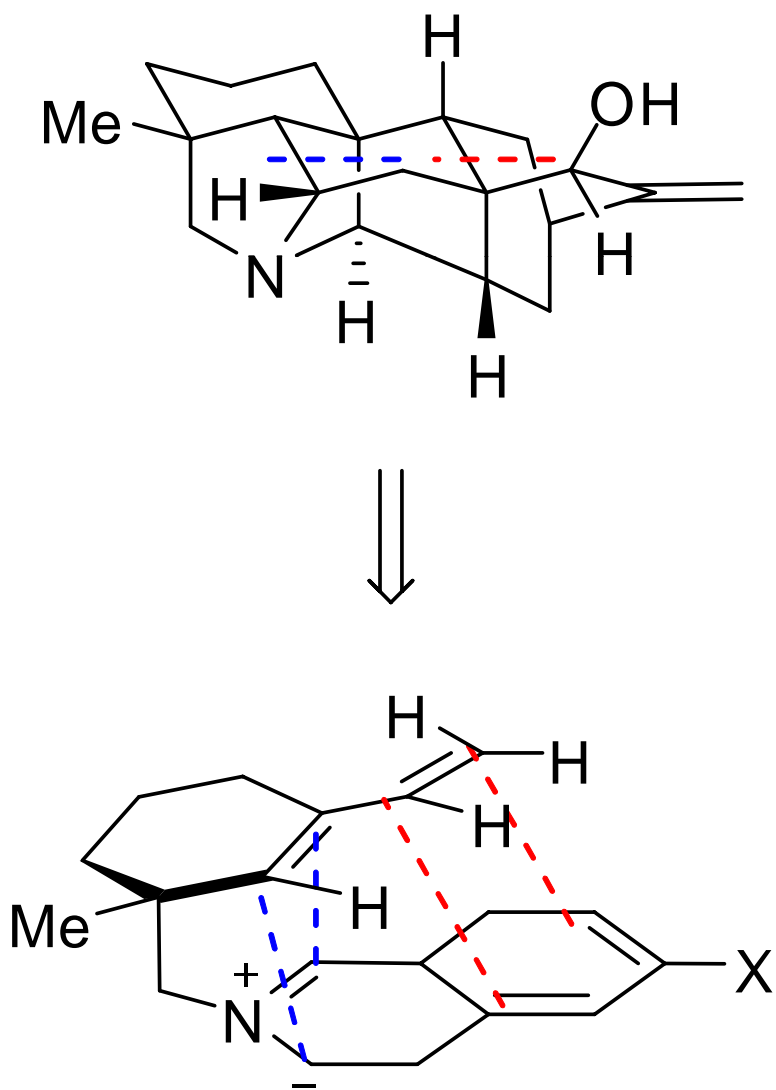


# Completion of the Synthesis



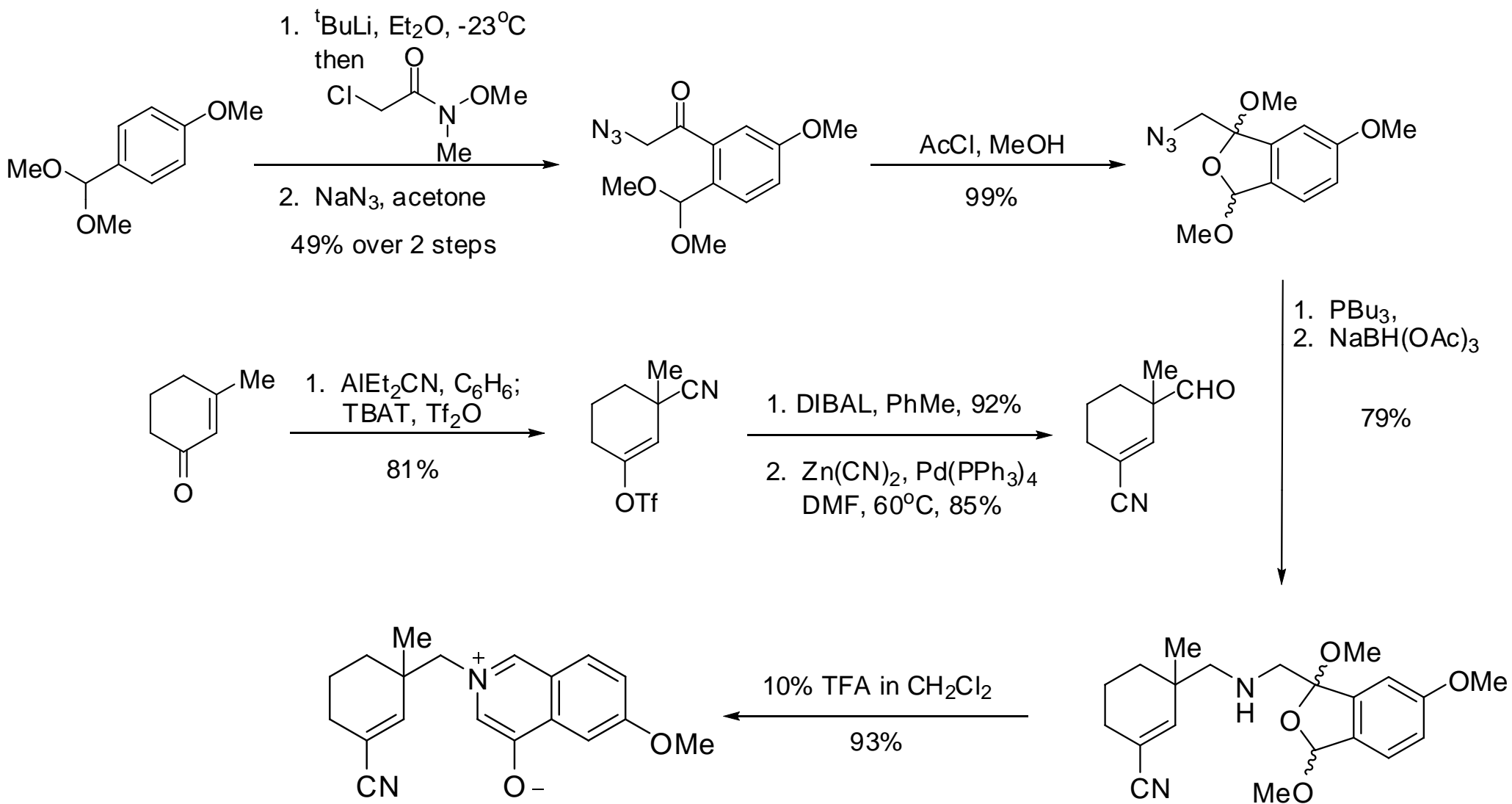
- Completed the first total synthesis a hetisine type alkaloid in 40 steps in 0.15% overall yield.
- Utilized Pd-catalyzed intramolecular  $\alpha$  arylation reaction developed in their laboratories.

# Gin's Approach

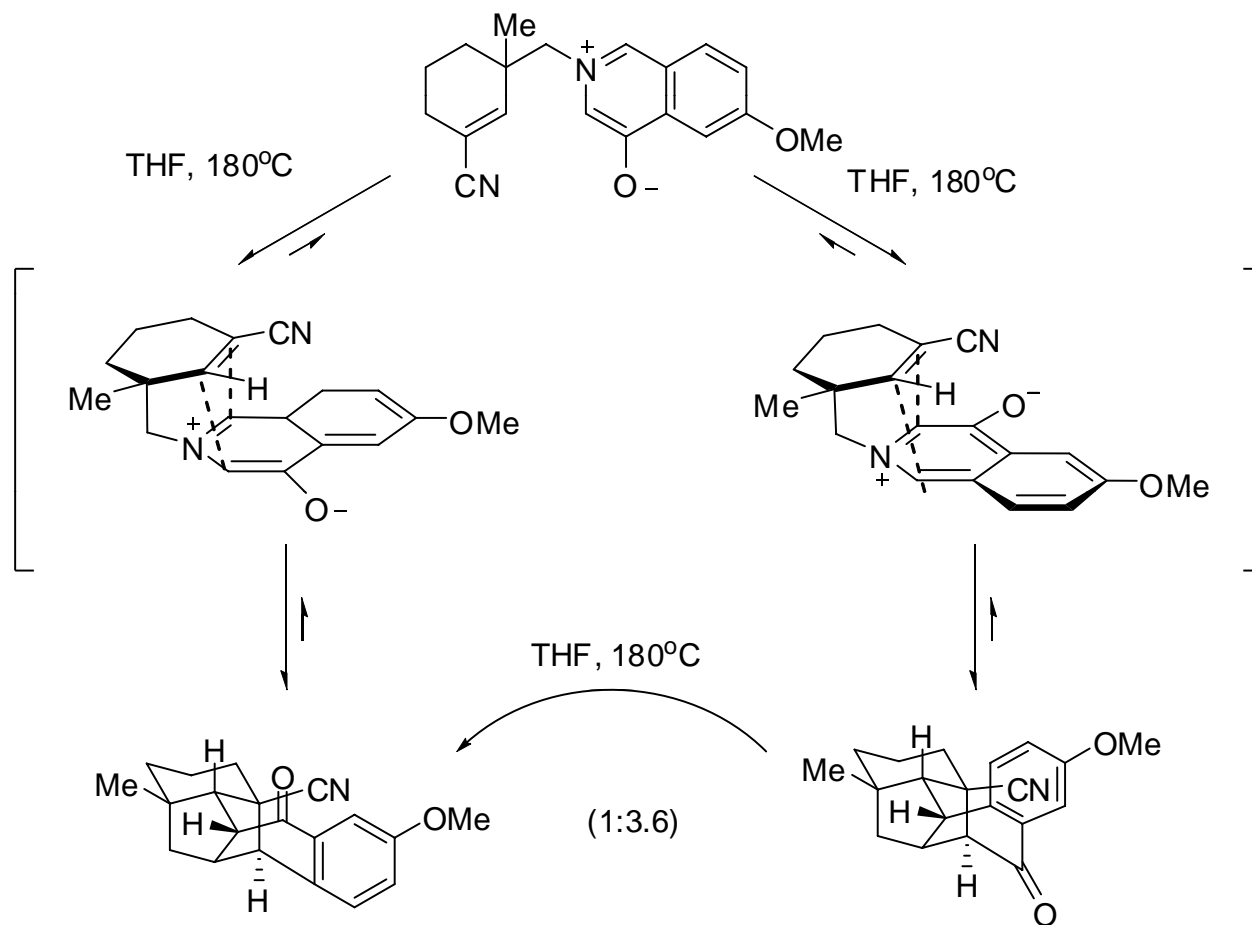


- Gin envisioned using two cycloadditions to gain access to the hetisine core in an efficient manner.
- An aza-1,3-dipolar cycloaddition would provide the bridged pyrrolidine ring.
- A Diels-Alder reaction would be used to assemble the [2.2.2]-bicyclic structure.

# Synthesis of the Aza-1,3-Dipole

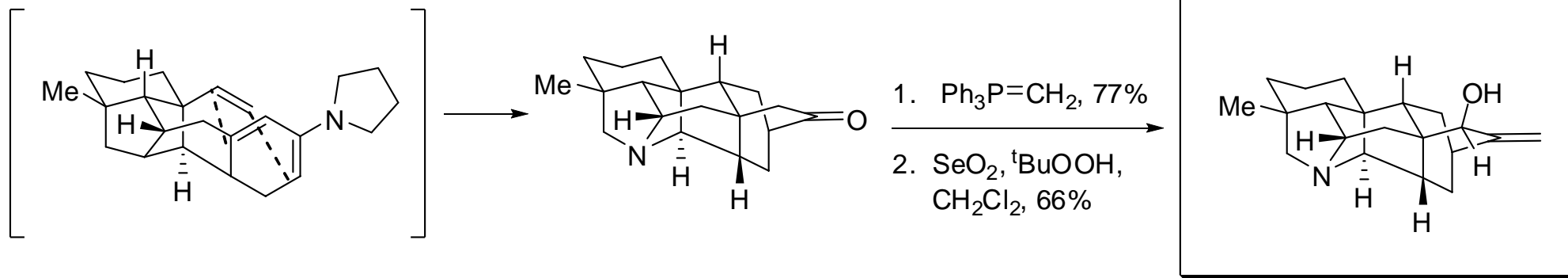
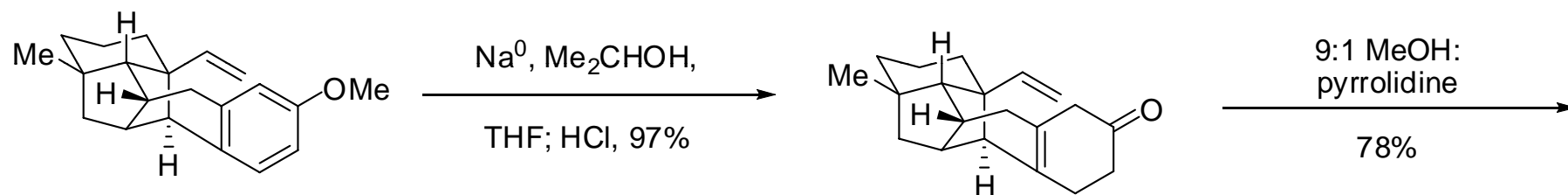
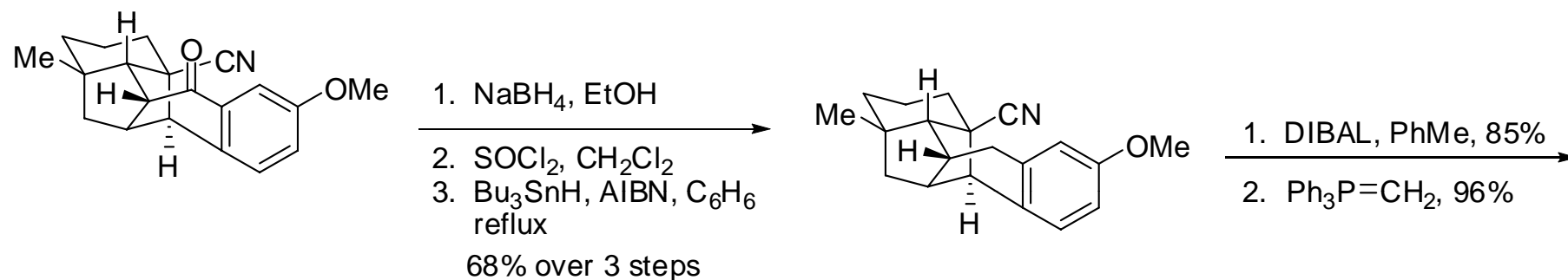


# 1, 3-Dipolar Cycloaddition



- 1: 3.6 ratio of desired: undesired
- Reaction is reversible, could recycle undesired product to desired by subjecting to initial cyclization conditions.

# End Game



# Summary of Gin's Synthesis

- Completed synthesis of norninine in 15 steps
- Only one protecting group manipulation in the synthesis
- Key steps include intramolecular 1,3-dipolar cycloaddition and Diels-Alder reactions.