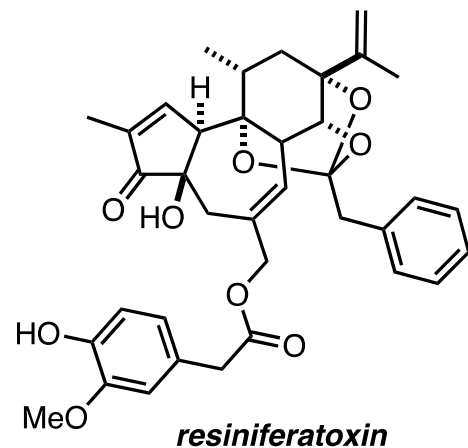


# Total Synthesis of Resiniferatoxin Enabled by Radical-Mediated Three-Component Coupling and 7-endo Cyclization



- Isolated from *Euphorbia resinifera*
- *Trans*-fused 5/7/6 tricyclic core
- 3-component radical coupling
- Radical cyclization
- 41 steps



*J. Am. Chem. Soc.* **2017**, 139, 16420

Presented by: Brendyn Smith

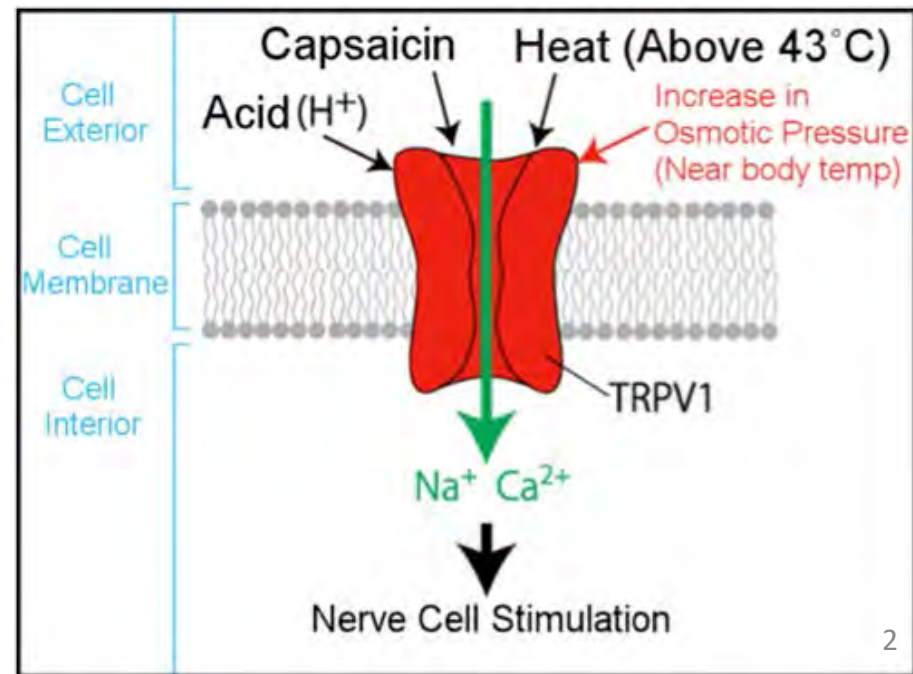
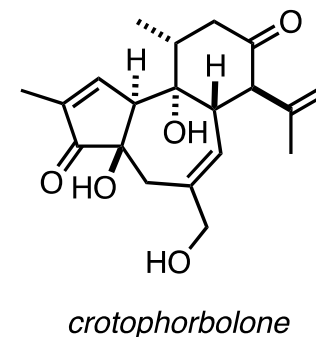
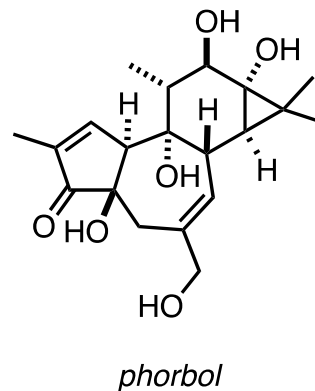
CEM 852 Presentation

January 26, 2019

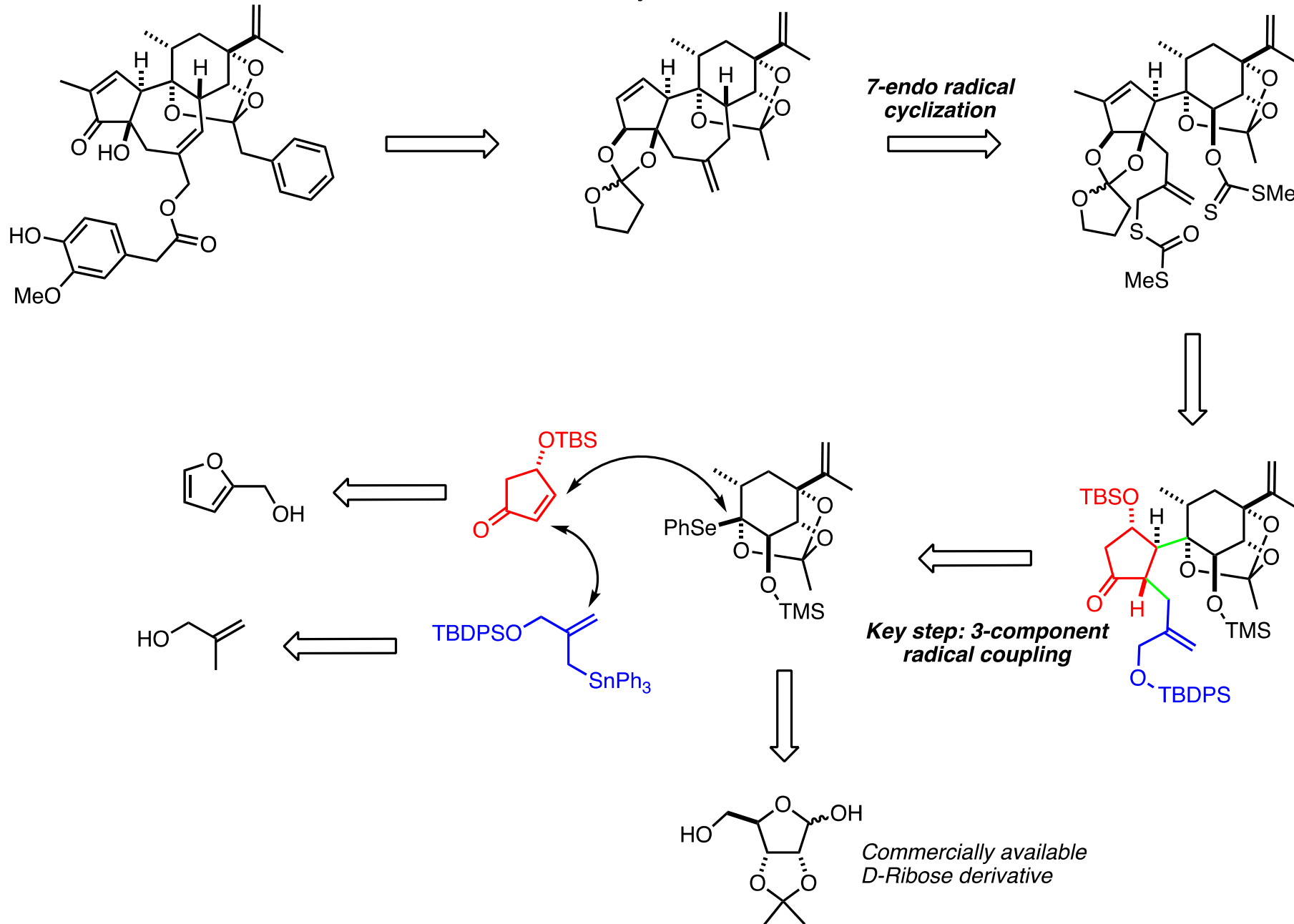
# Natural Product Background

- Isolated in 1975 from *Euphorbia resinifera*
- Belongs to daphnane diterpenoid class of natural products
- Potent activator of transient receptor potential vanilloid 1 (TRPV1)
- **16 billion** scoville units (~50,000X hotter than a habanero!)

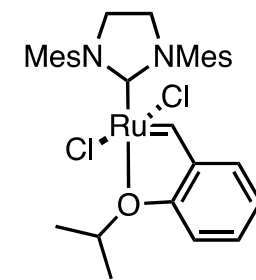
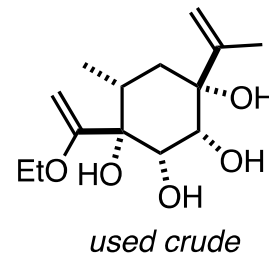
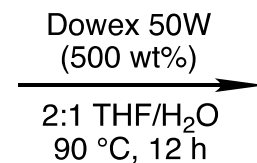
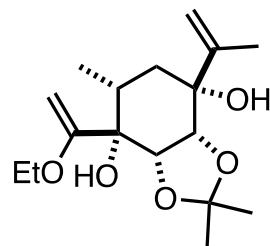
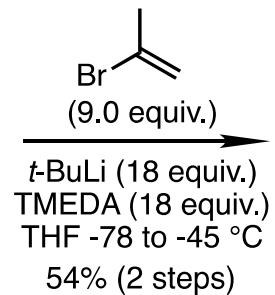
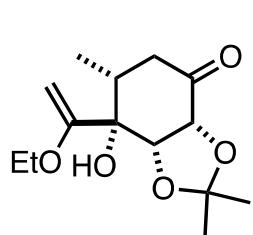
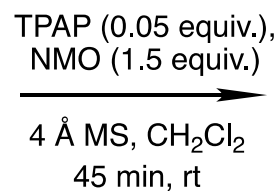
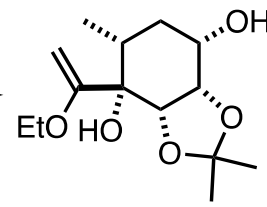
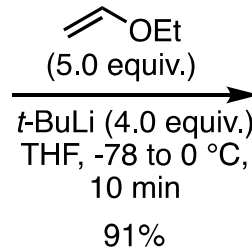
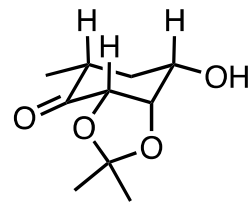
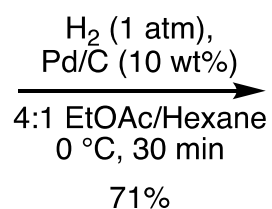
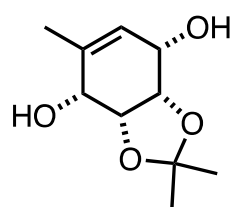
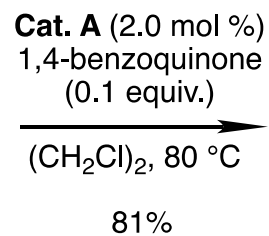
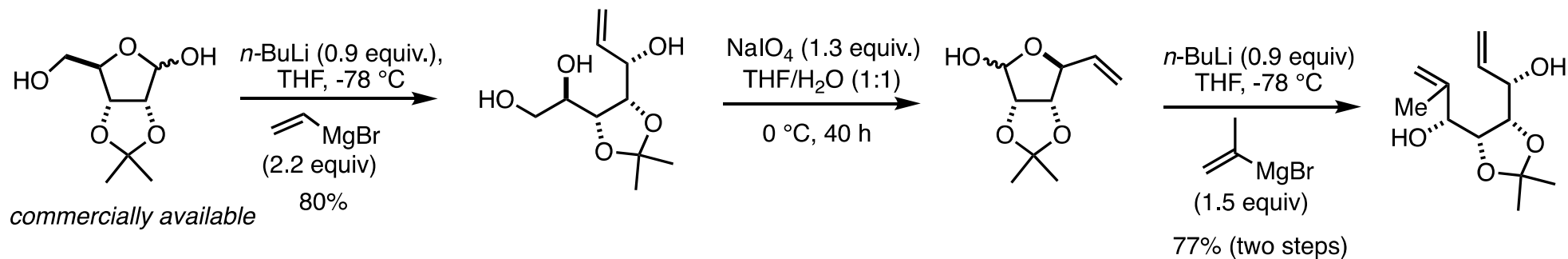
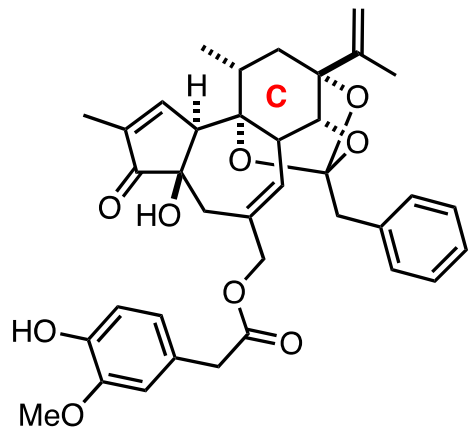
## Selected diterpenoids



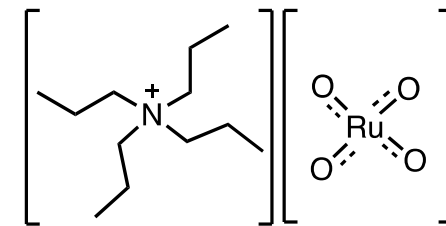
# Retrosynthesis



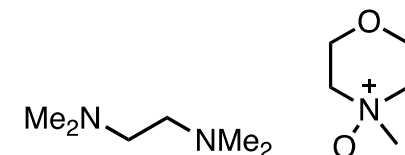
# Synthesis of C-ring



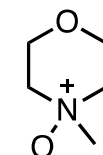
**Cat. A**



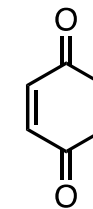
**TPAP**



**TMEDA**

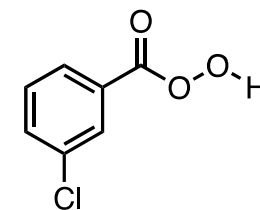
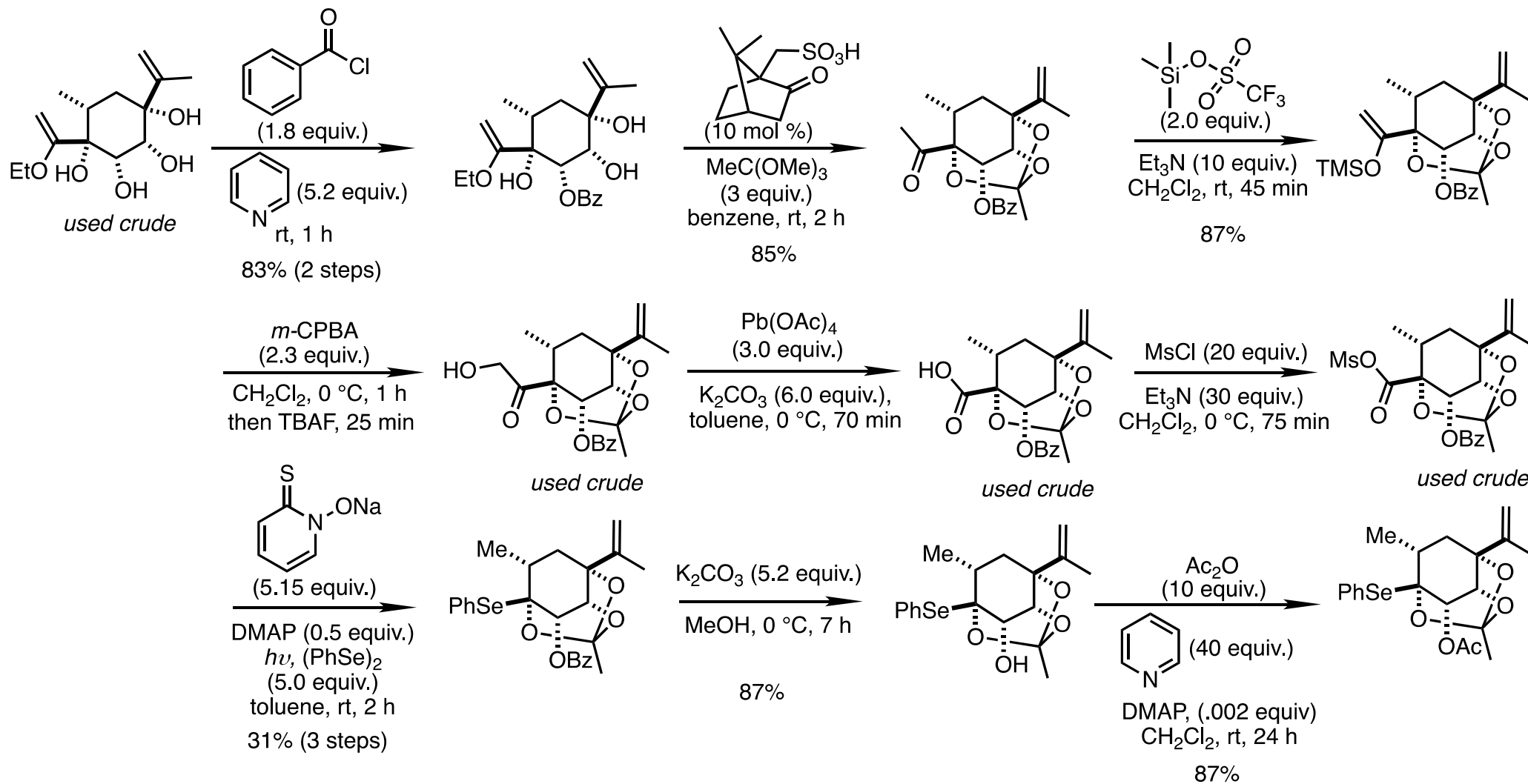


**NMO**

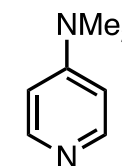


**1,4-benzoquinone**

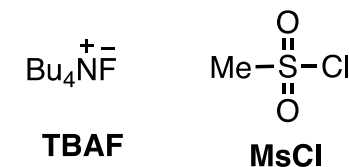
# Synthesis of C-ring



**m-CPBA**



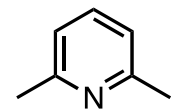
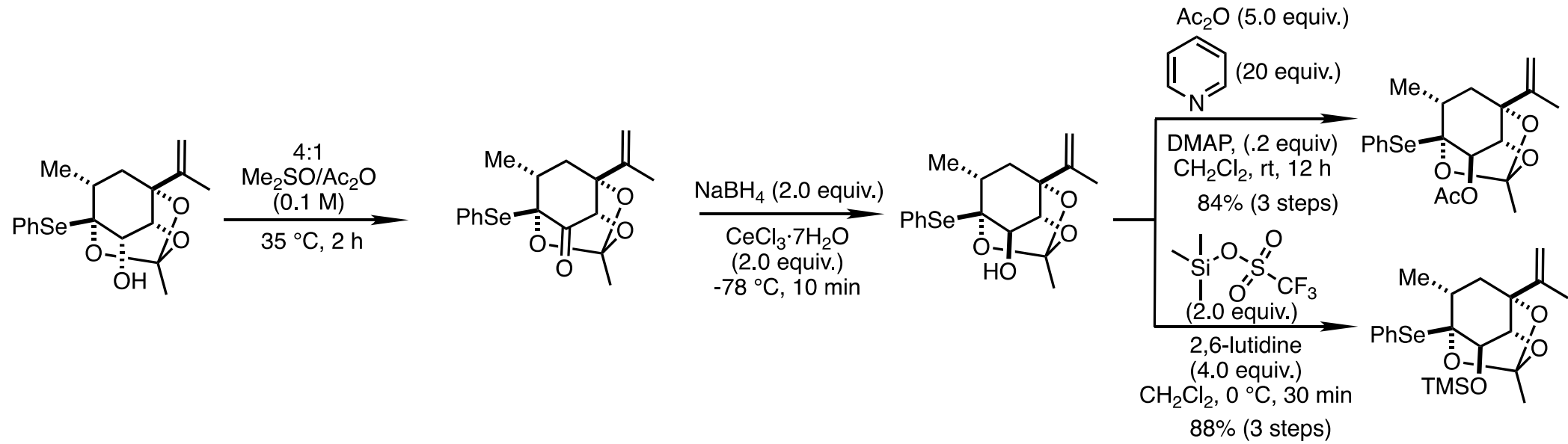
**DMAP**



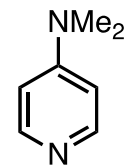
**TBAF**

**MsCl**

# Synthesis of C-ring

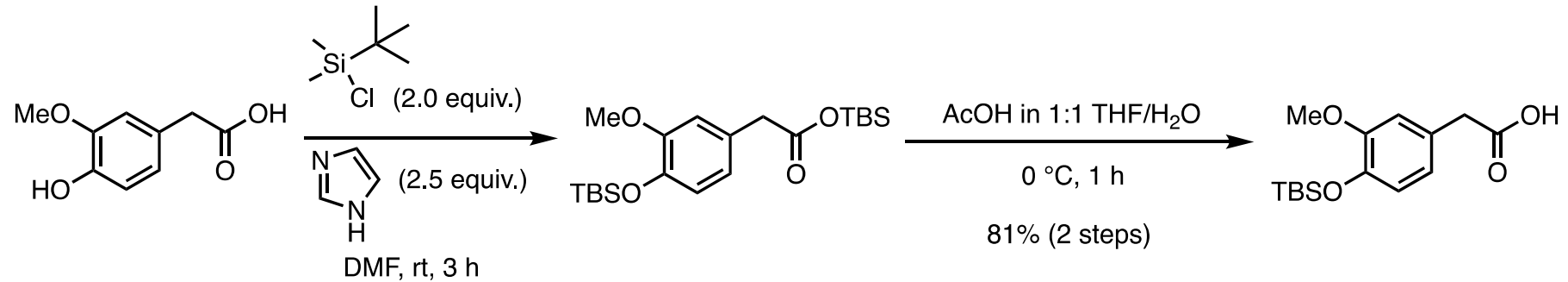


2,6-lutidine

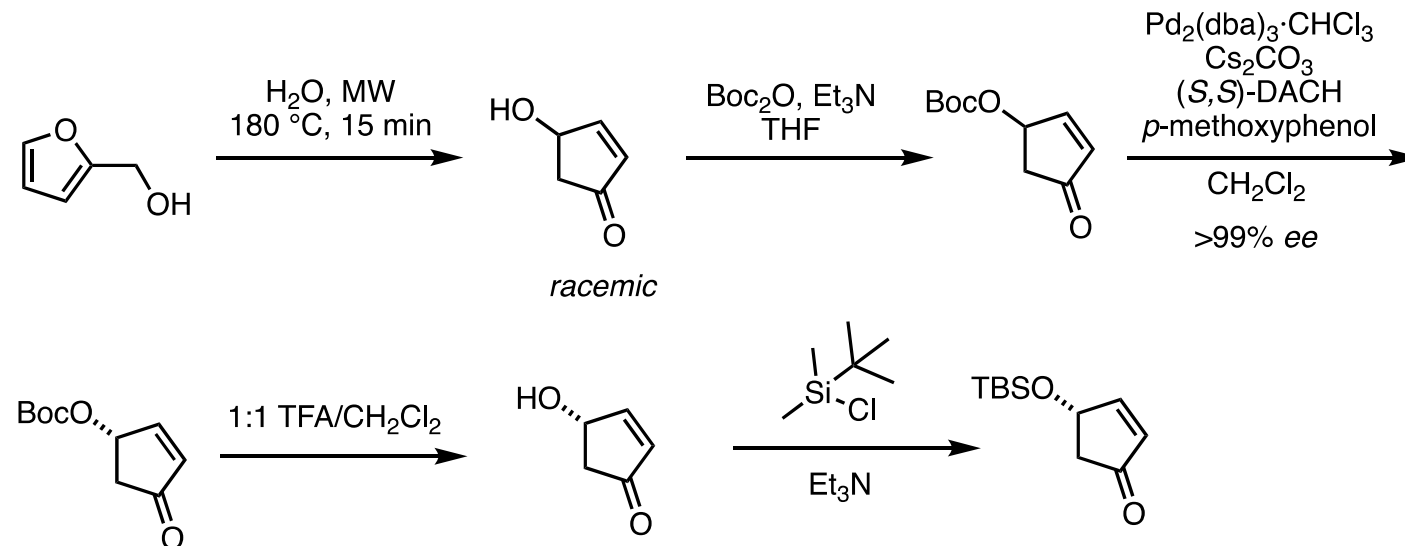
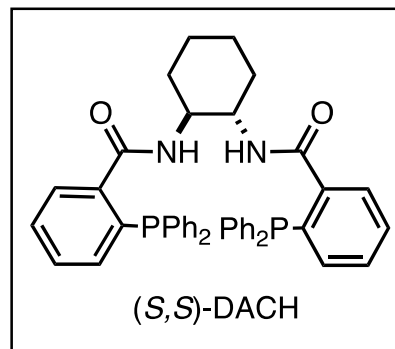


DMAP

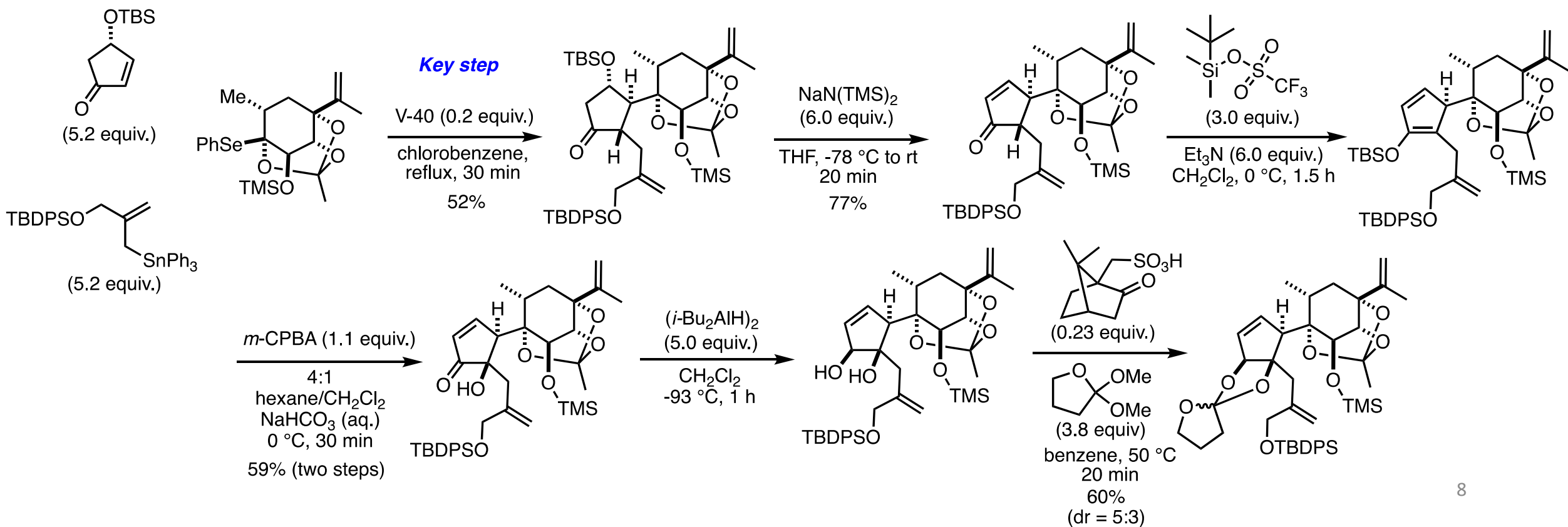
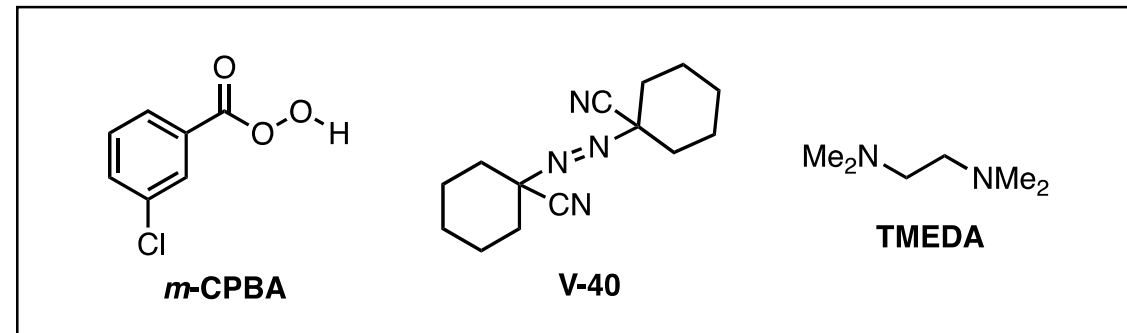
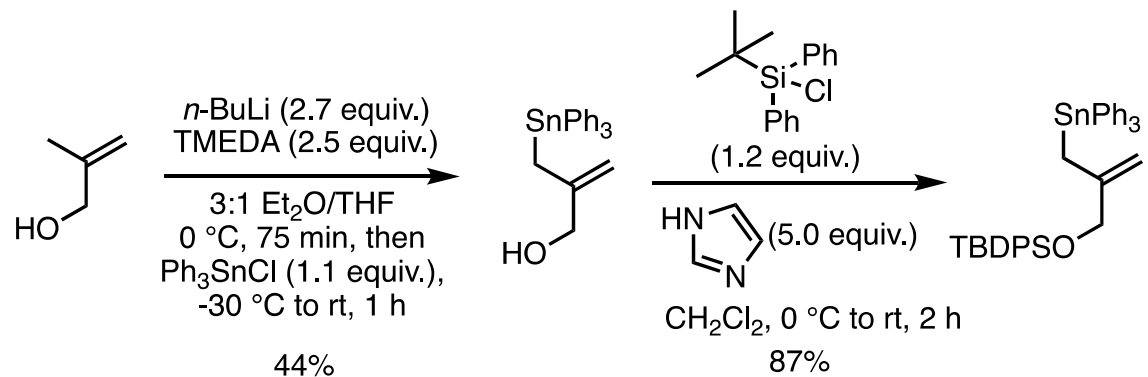
# Building block synthesis



**Proposed synthesis of chiral cyclopentenone synthon (not given in article)**  
adopted from: *JACS*. 2019, 141, 154-158

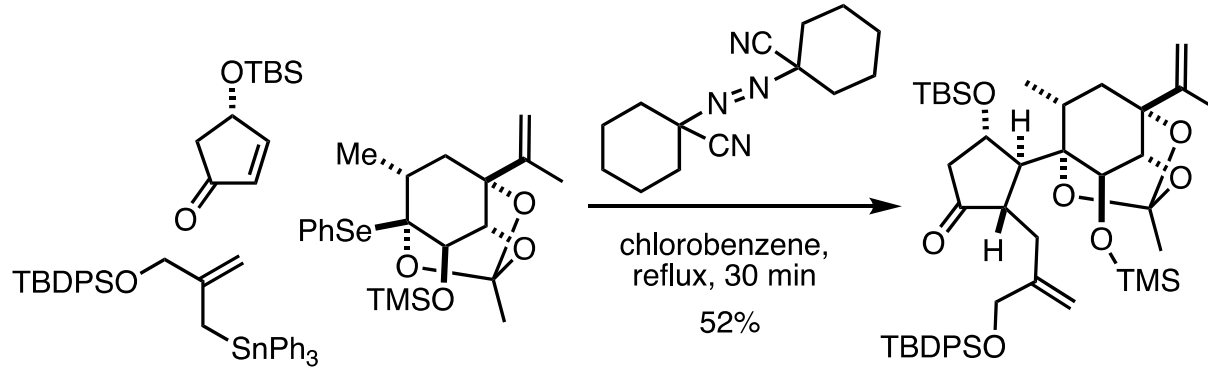


# Synthesis of allyl stannane + forging tricyclic framework

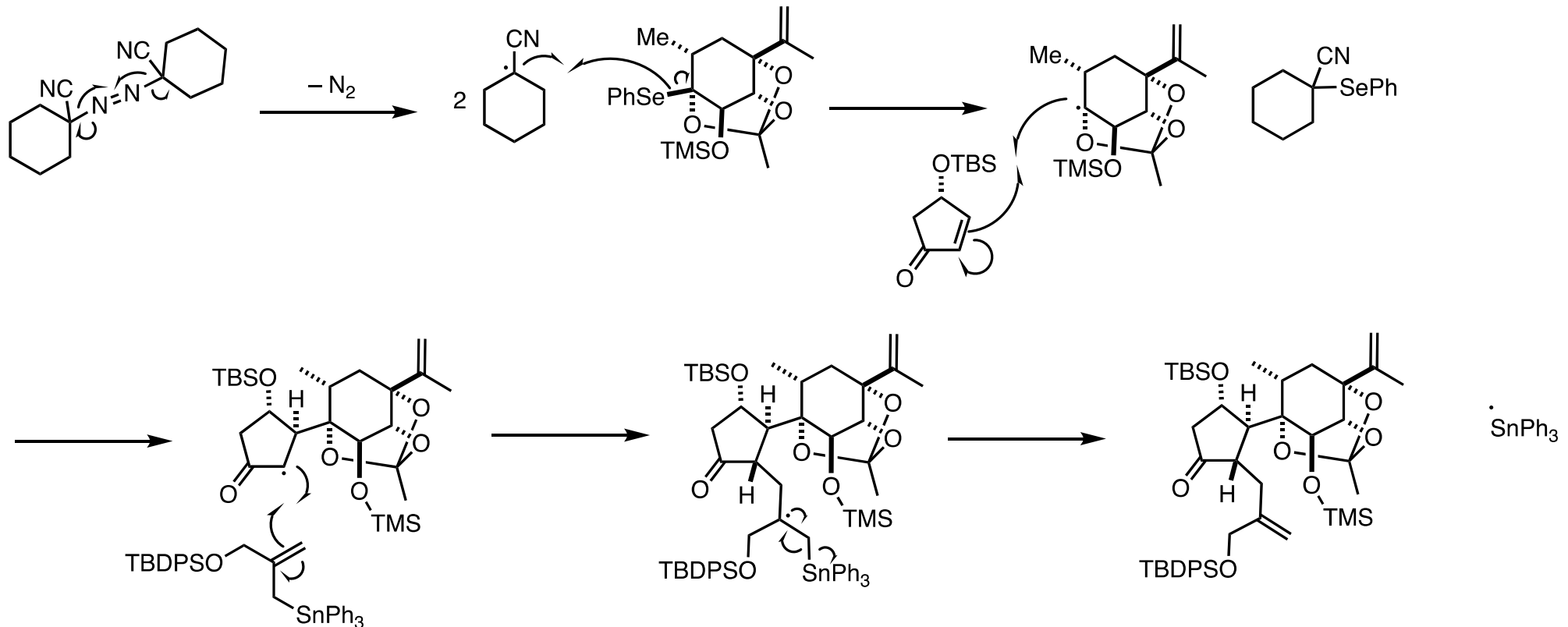




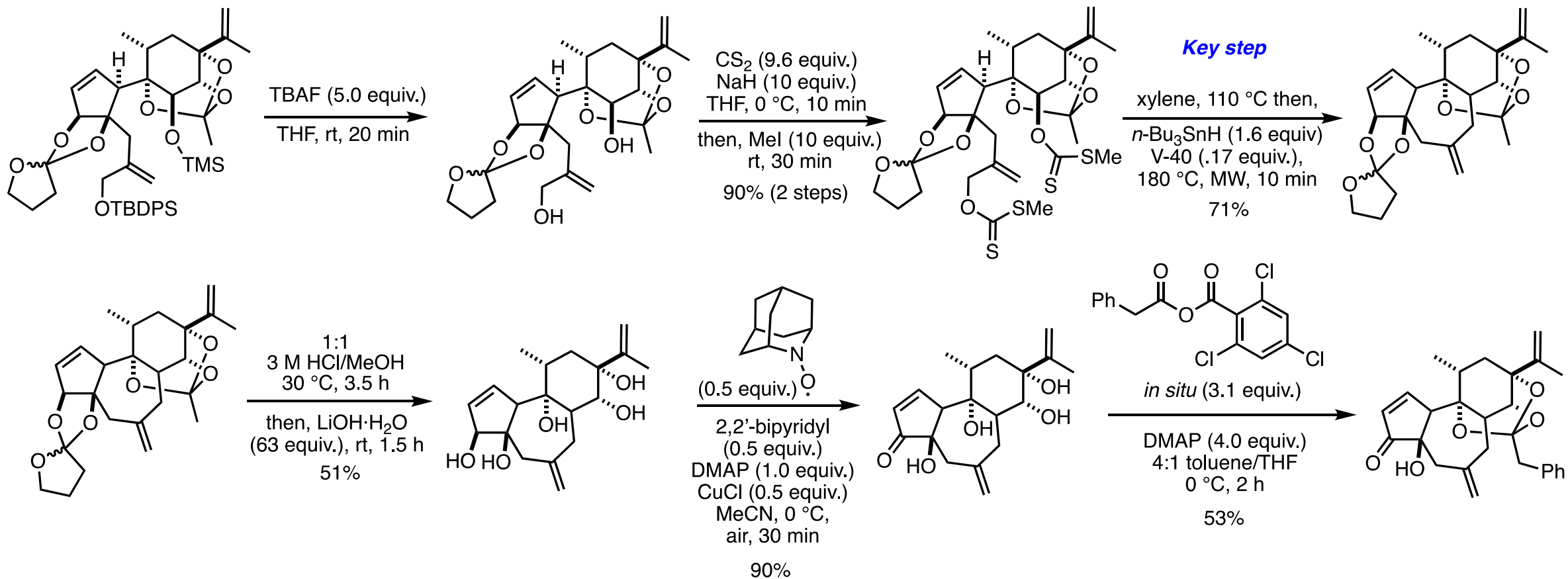
# Key step mechanism



## Mechanism

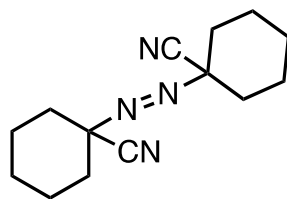


# Wrapping up tricycle + decorating scaffold

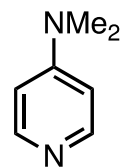


Bu<sub>4</sub>NF<sup>+</sup>

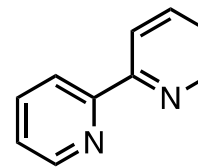
**TBAF**



**V-40**

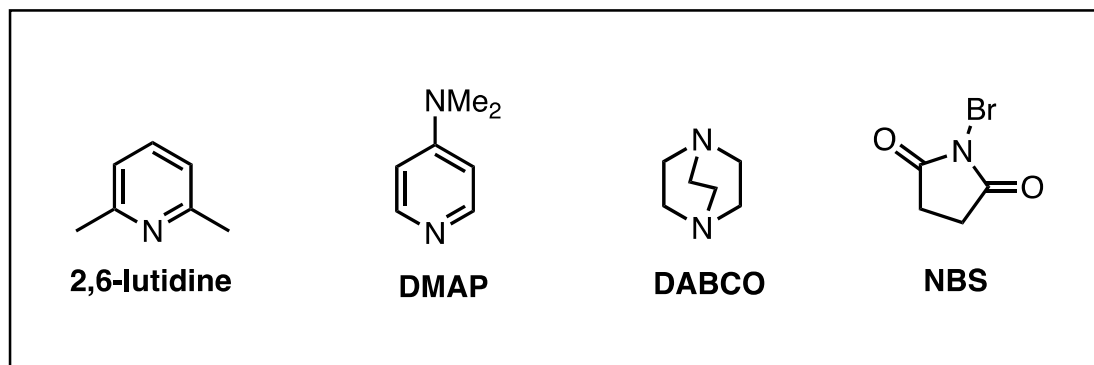
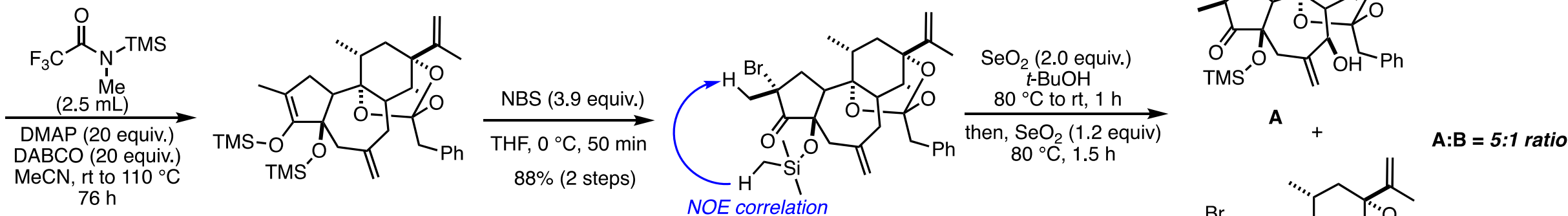
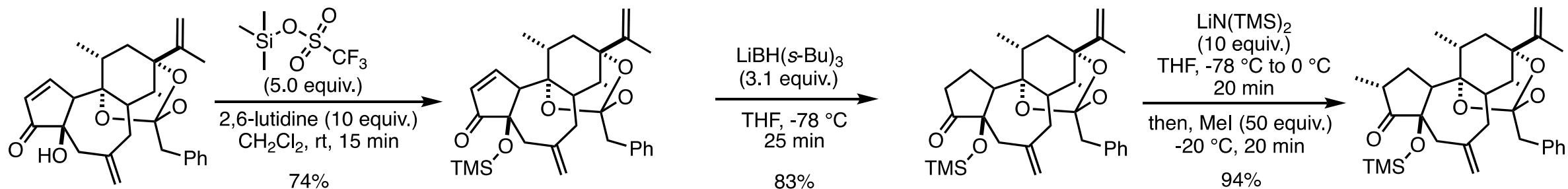


**DMAP**



**2,2'-bipyridyl**

# Finishing up...



# End game

