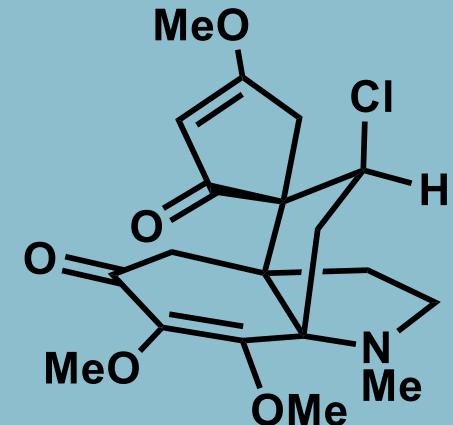
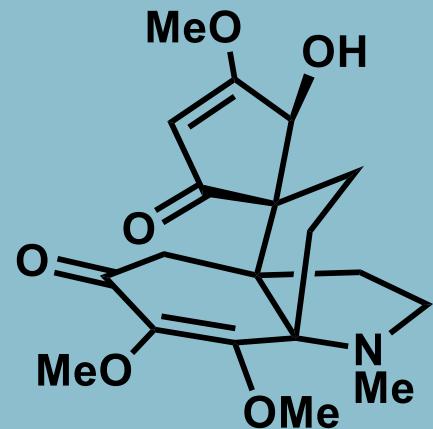
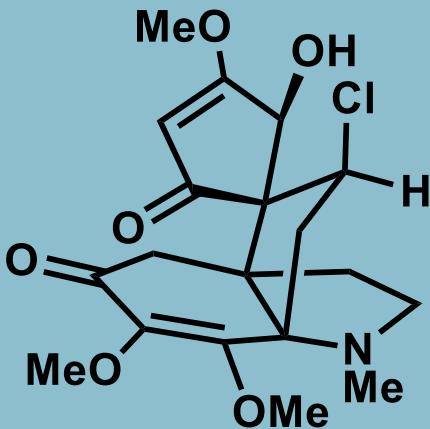


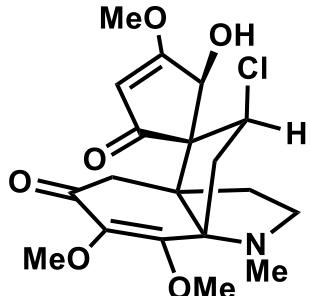
# *Synthetic Approaches to the Acutumine Alkaloids*



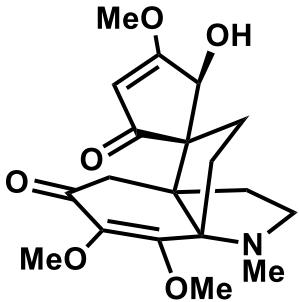
Sam He  
Literature Presentation  
6/24/22



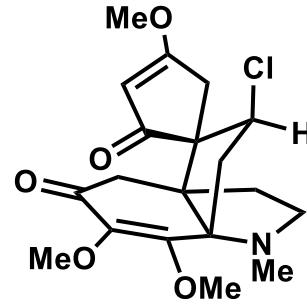
# *Isolation and Bioactivity*



(-)-acutumine



(-)-dechloroacutumine

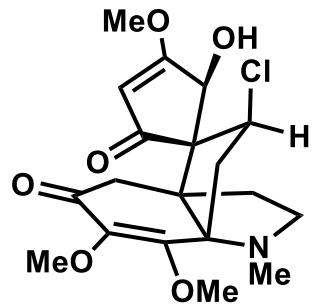


(-)-acutuminine

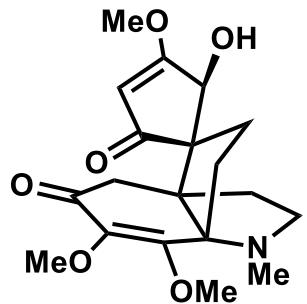


- (-)-acutumine isolated in 1929 from roots of *Sinomenium acutum*
- (-)-dechloroacutumine and (-)-acutuminine both isolated from *Menispermum dauricum*
- (-)-acutumine inhibits T-cell proliferation and exhibits anti-amnesic activity

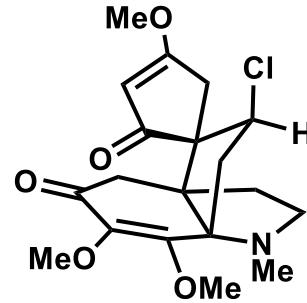
# *Structure(s)*



(-)-acutumine

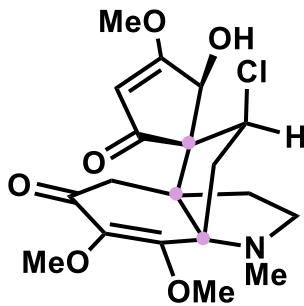


(-)-dechloroacutumine

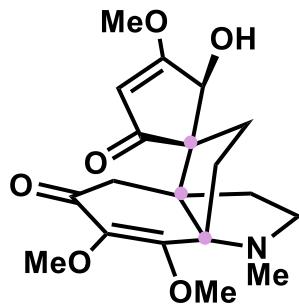


(-)-acutuminine

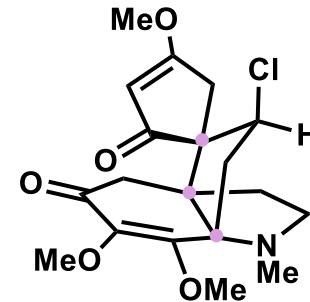
# **Structure(s)**



### (-)-acutumine



### (-)-dechloroacutumine



### (-)-acutuminine

- all 3 contain a propellane-type ring structure
  - acutumine and actuminine both contain a neopentylic chloride
  - 3 contiguous quaternary stereocenters

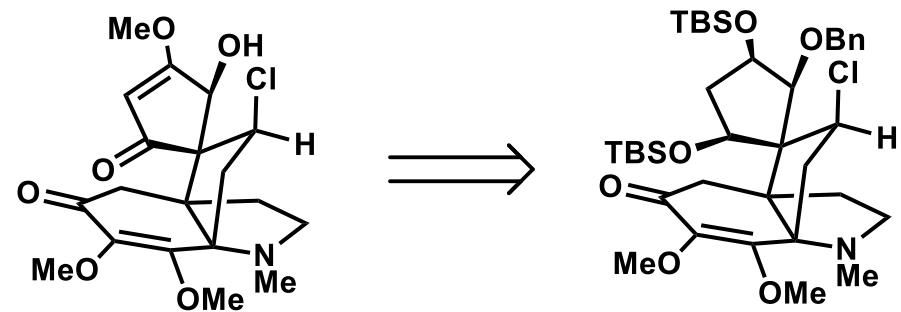
acutumine first synthesized by Castle *et al.* in 2009

Herzon et al. developed route to acutumine and dechloroacutumine in 2013

Reisman *et al.* developed route towards acutuminine in 2022

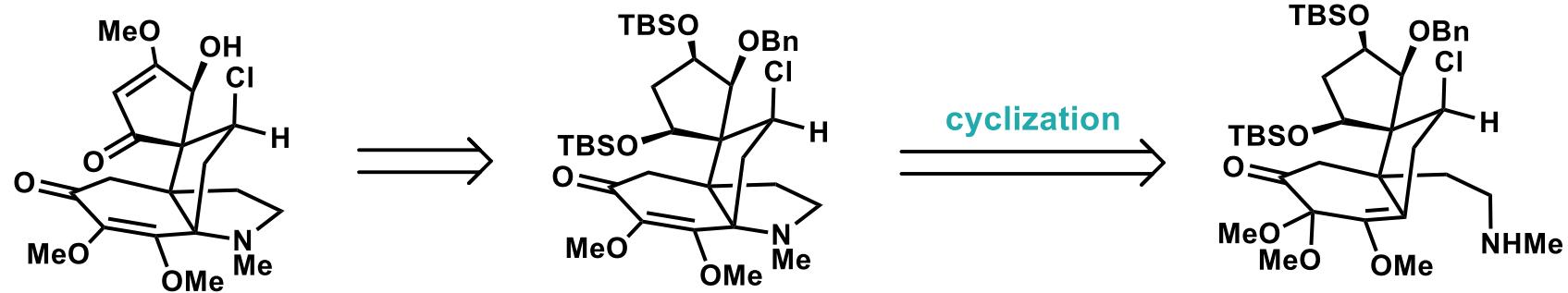
# Castle's Synthesis of Acutumine

Retrosynthesis



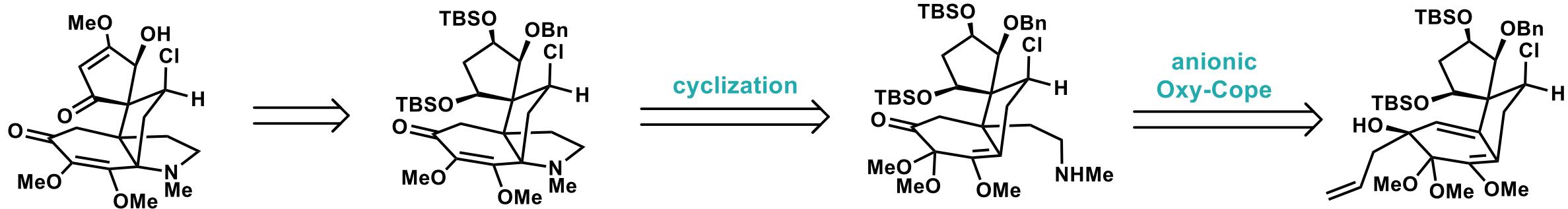
# Castle's Synthesis of Acutumine

Retrosynthesis



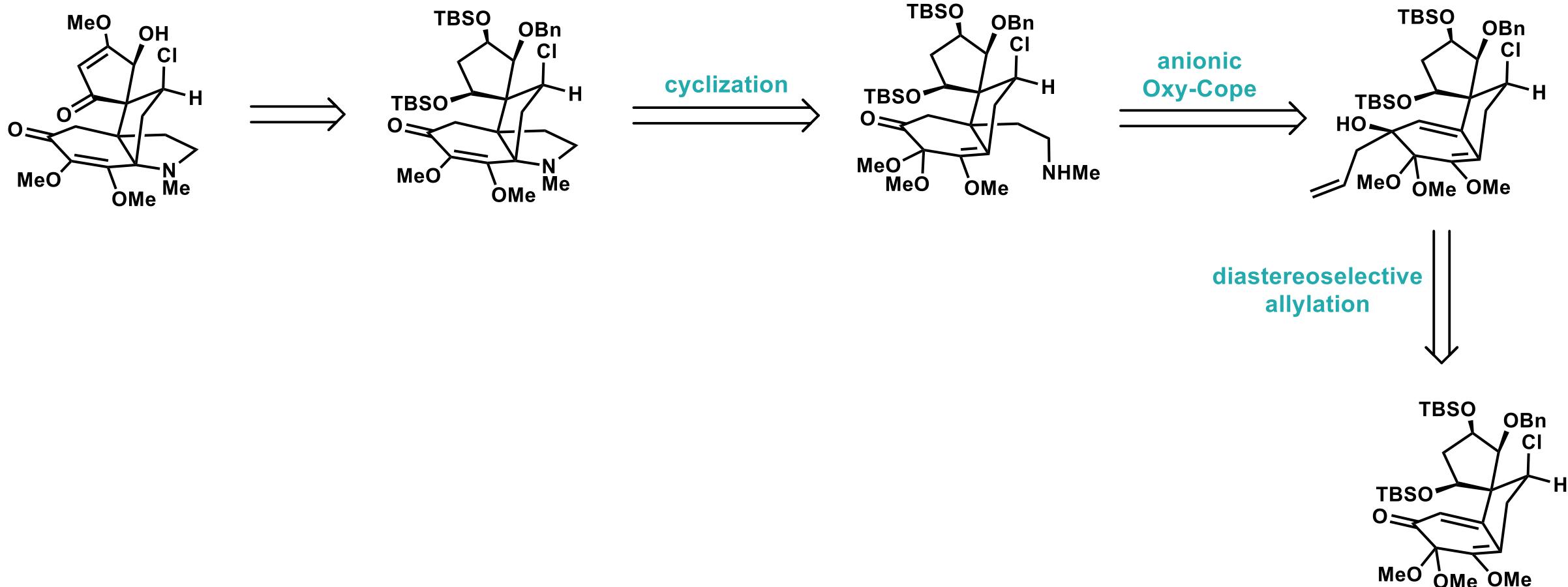
# Castle's Synthesis of Acutumine

Retrosynthesis



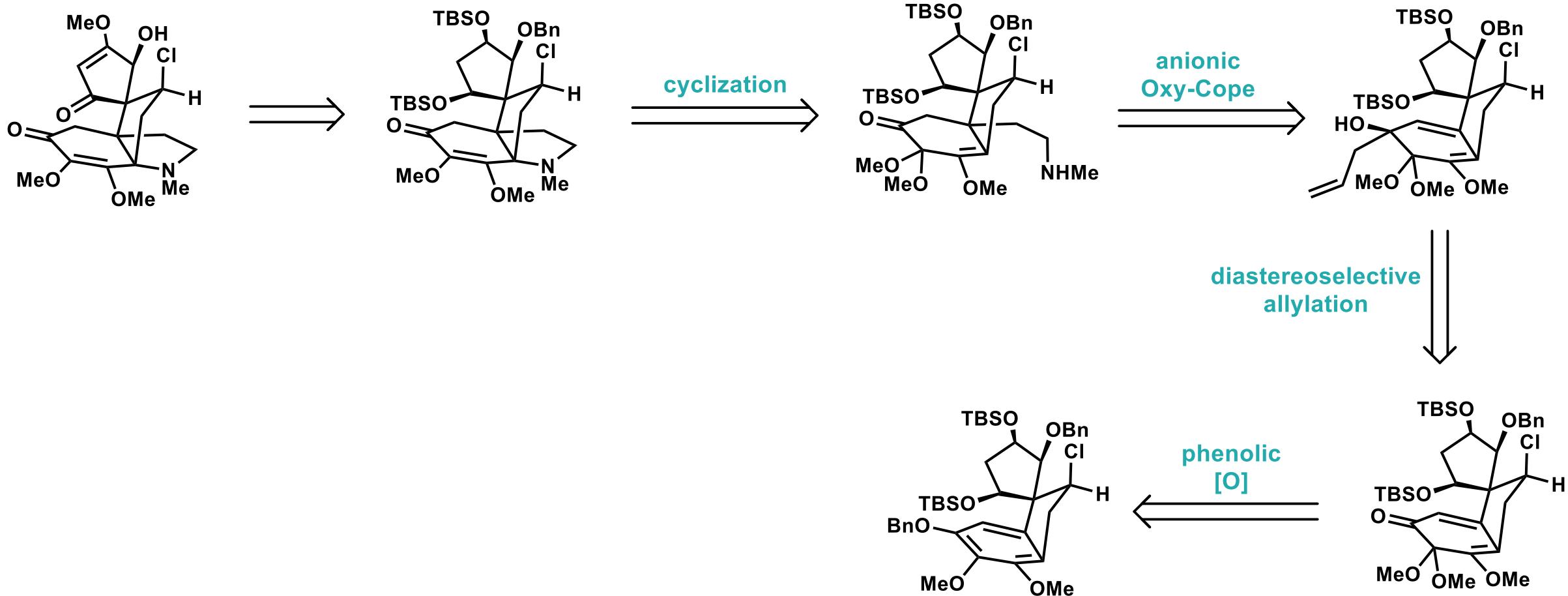
# Castle's Synthesis of Acutumine

Retrosynthesis



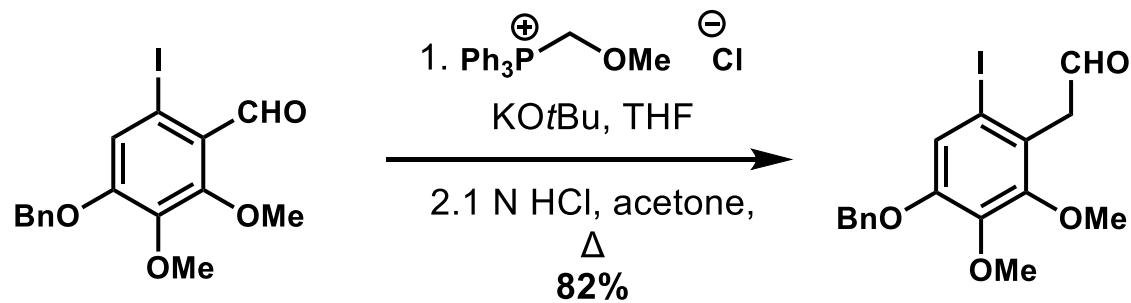
# Castle's Synthesis of Acutumine

## Retrosynthesis



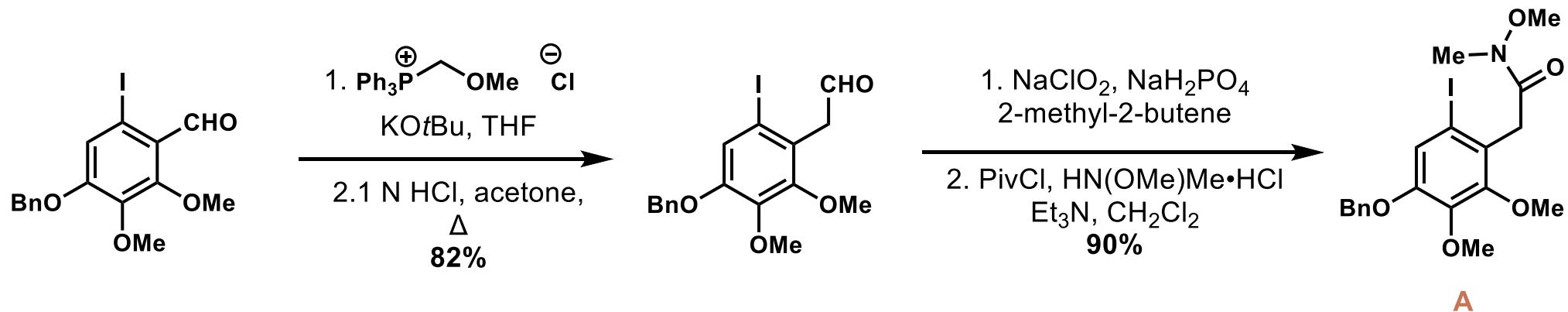
# Castle's Synthesis of Acutumine

*Building fragments towards radical-polar crossover*



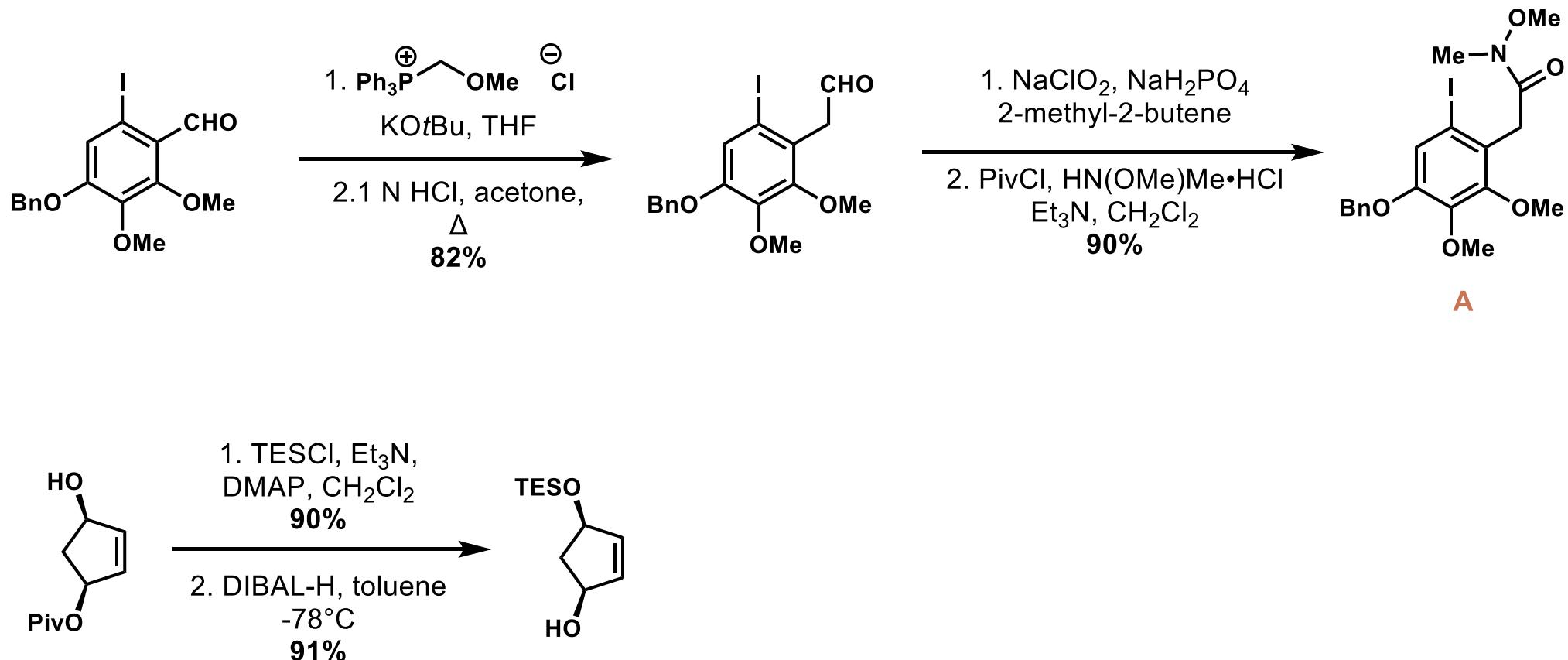
# Castle's Synthesis of Acutumine

*Building fragments towards radical-polar crossover*



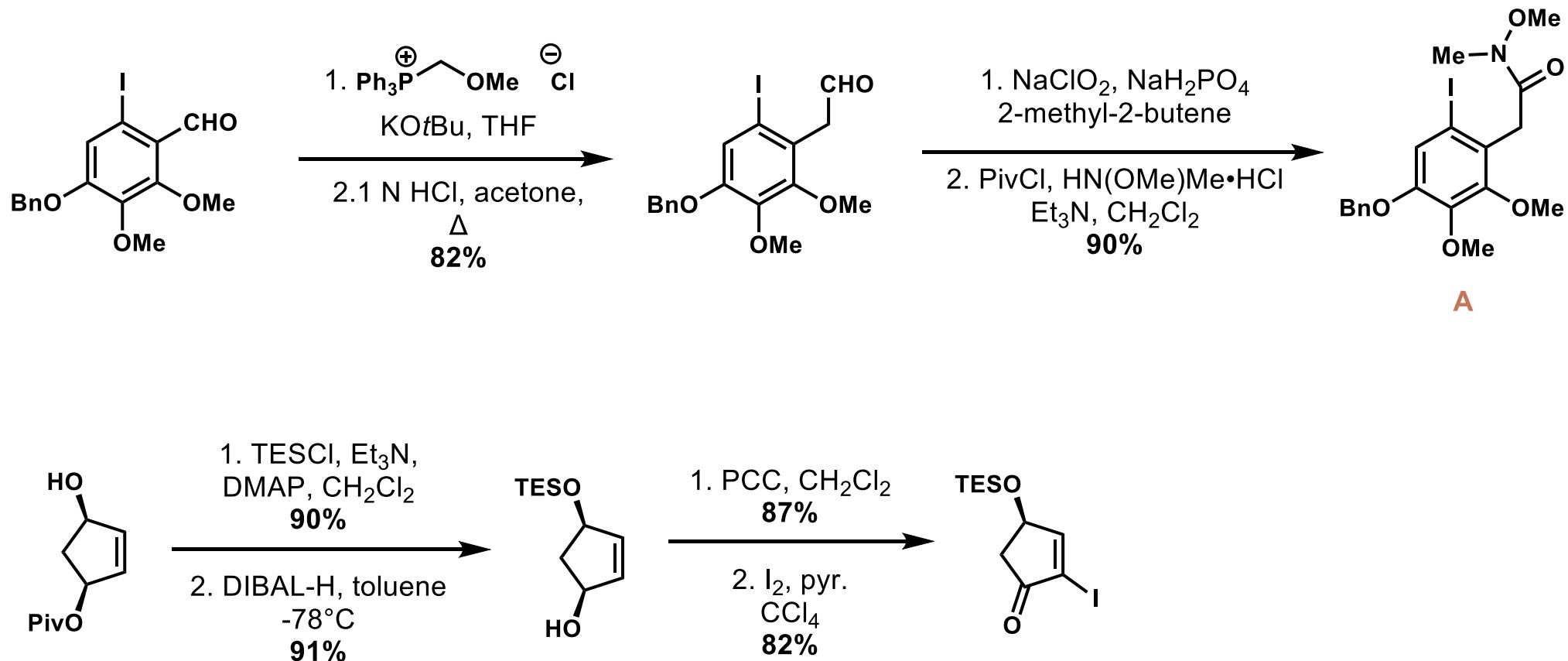
# Castle's Synthesis of Acutumine

*Building fragments towards radical-polar crossover*



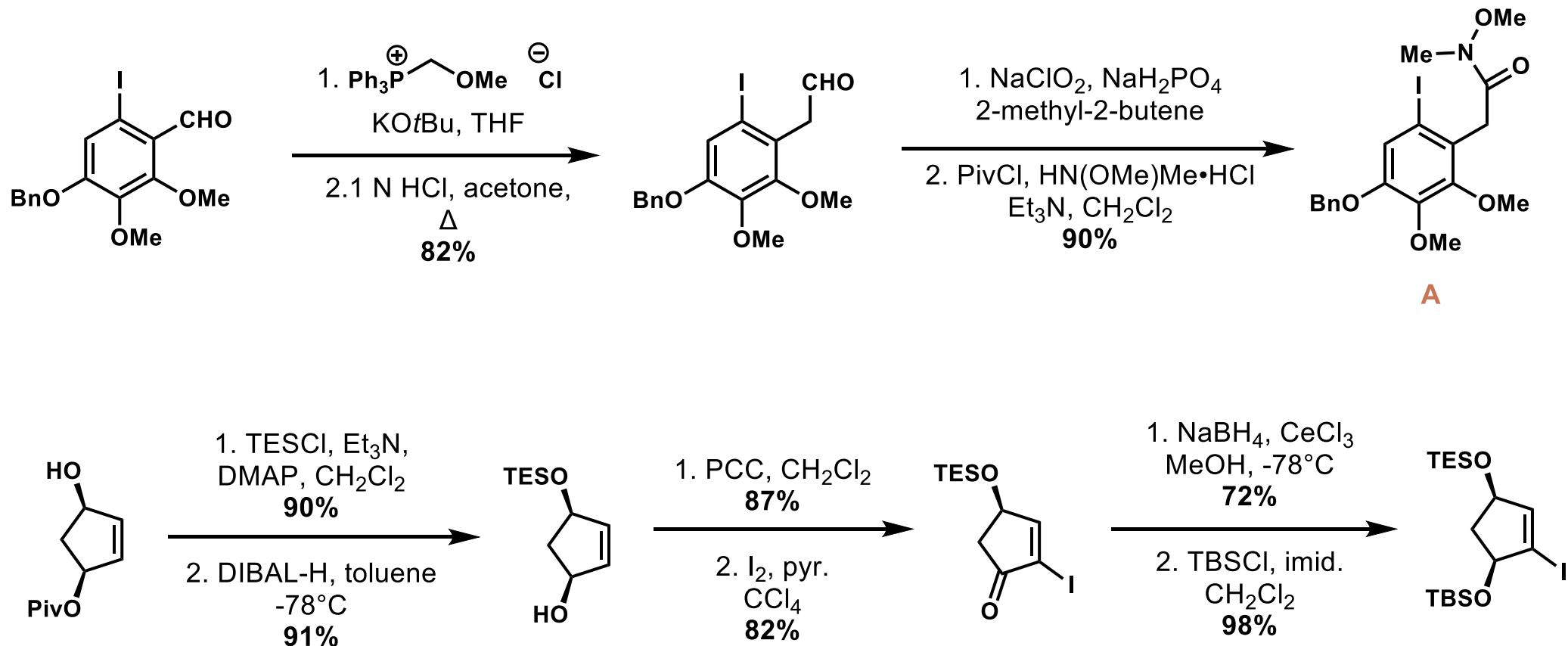
# Castle's Synthesis of Acutumine

*Building fragments towards radical-polar crossover*



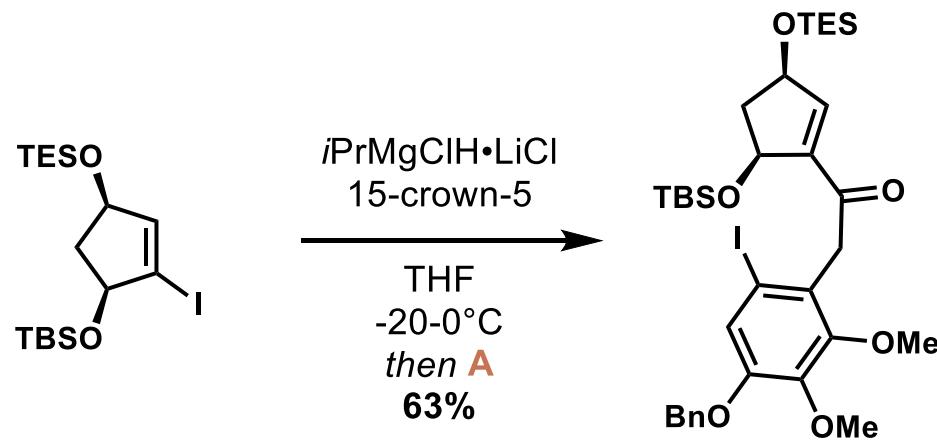
# Castle's Synthesis of Acutumine

*Building fragments towards radical-polar crossover*



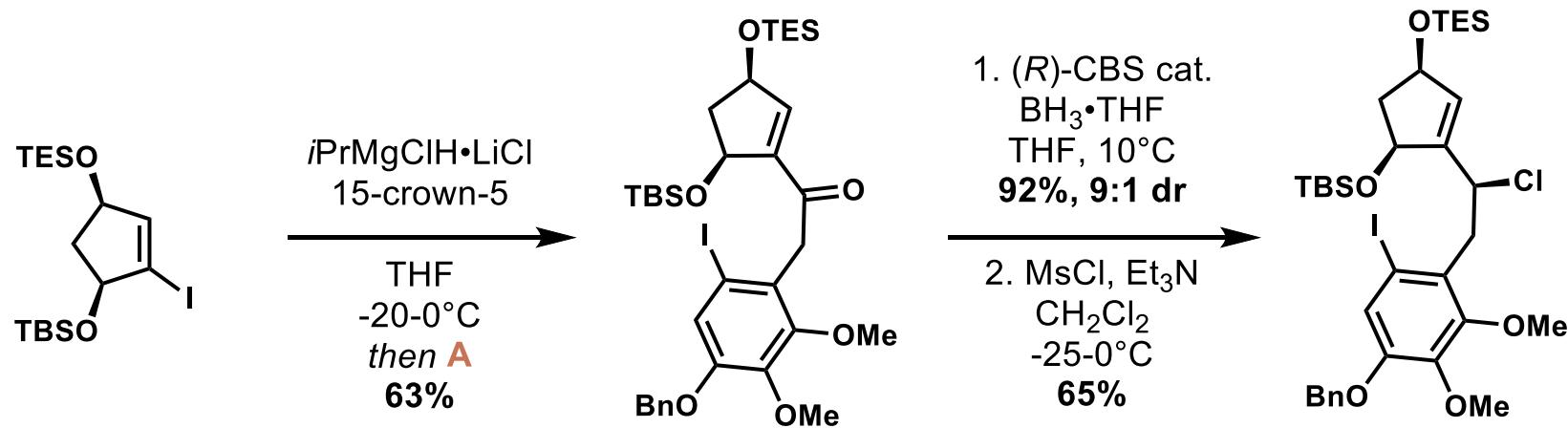
# Castle's Synthesis of Acutumine

*Building radical-polar crossover precursor*



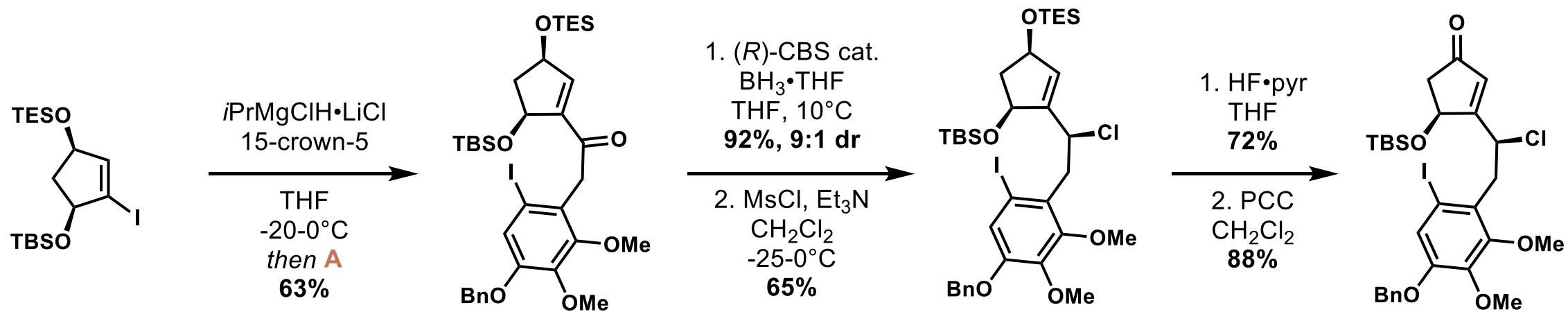
# Castle's Synthesis of Acutumine

Building radical-polar crossover precursor



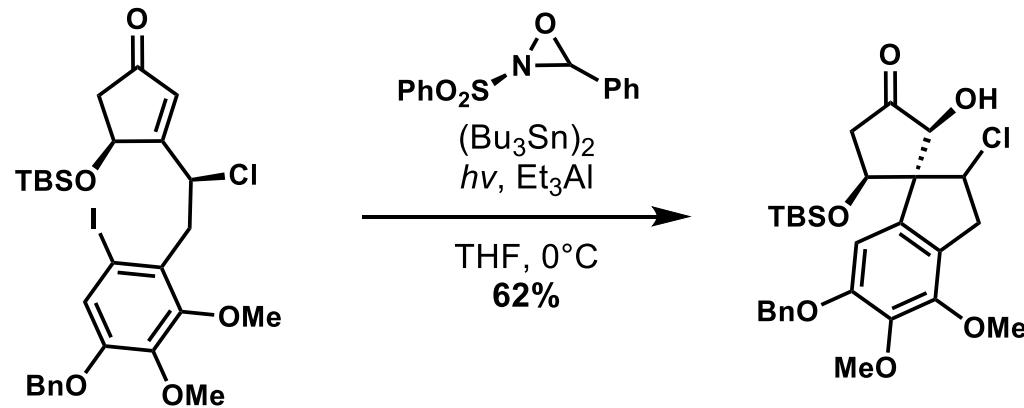
# Castle's Synthesis of Acutumine

Building radical-polar crossover precursor



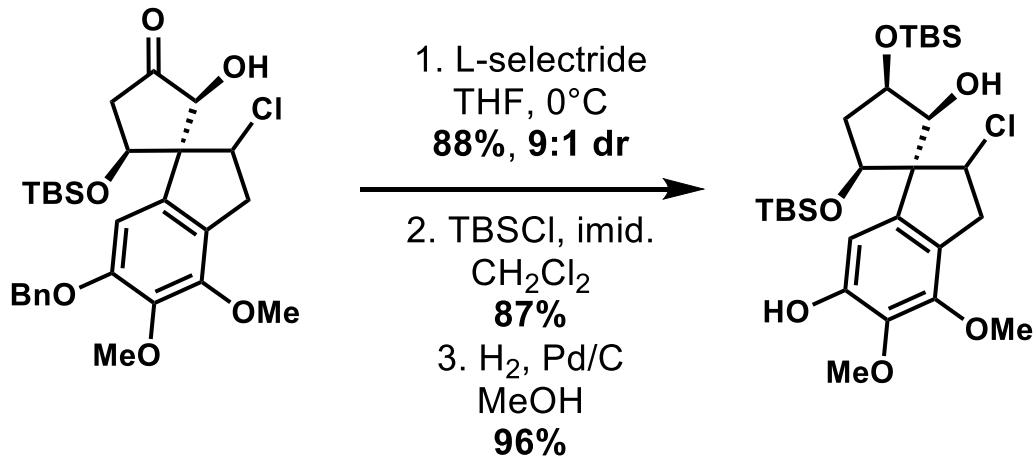
# Castle's Synthesis of Acutumine

*Key radical-polar crossover to build spirocycle*



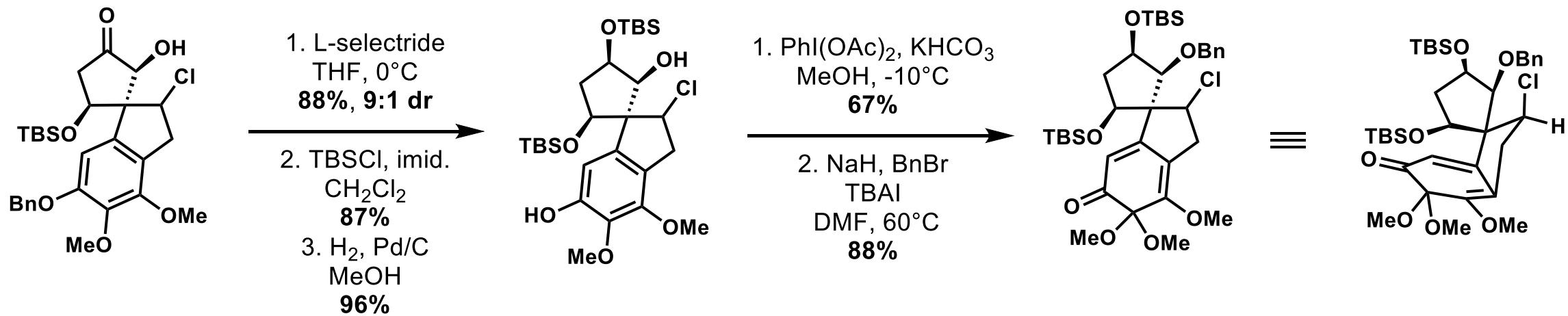
# Castle's Synthesis of Acutumine

Setting stage for ketone allylation



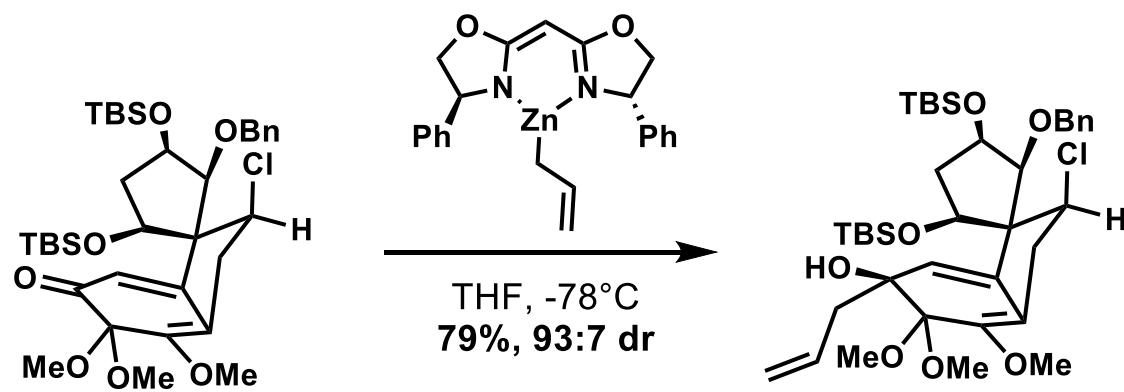
# Castle's Synthesis of Acutumine

Setting stage for ketone allylation



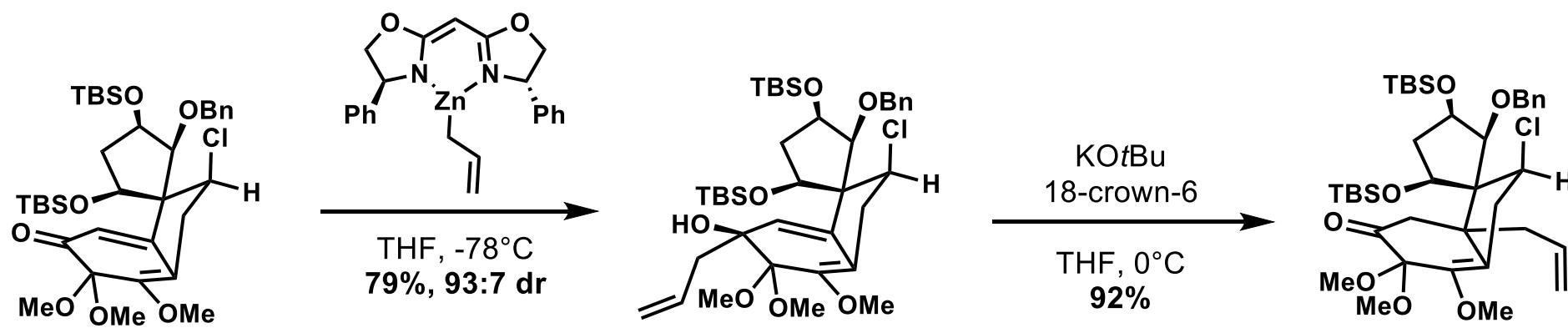
# Castle's Synthesis of Acutumine

*Constructing the propellane core*



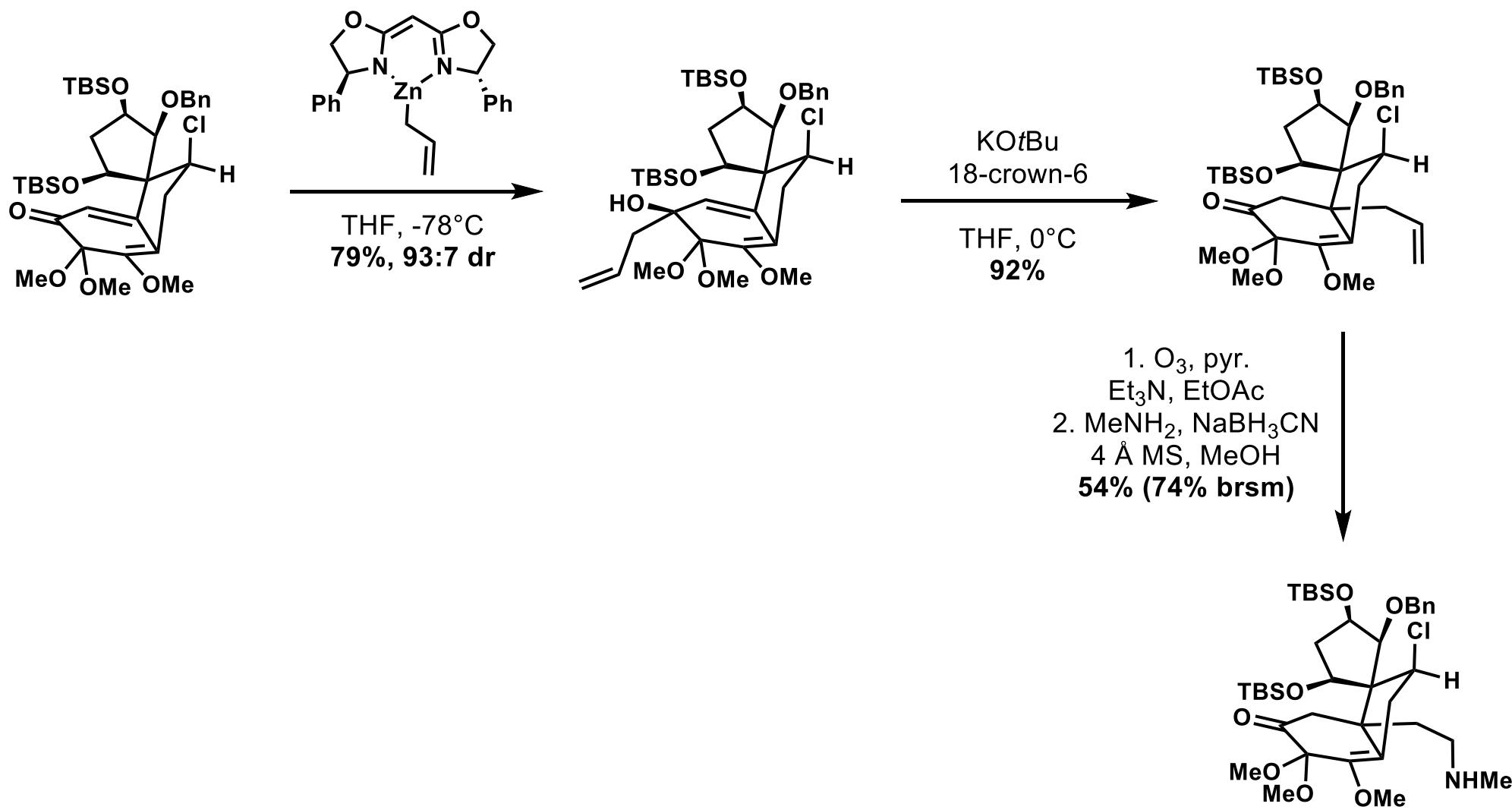
# Castle's Synthesis of Acutumine

Constructing the propellane core



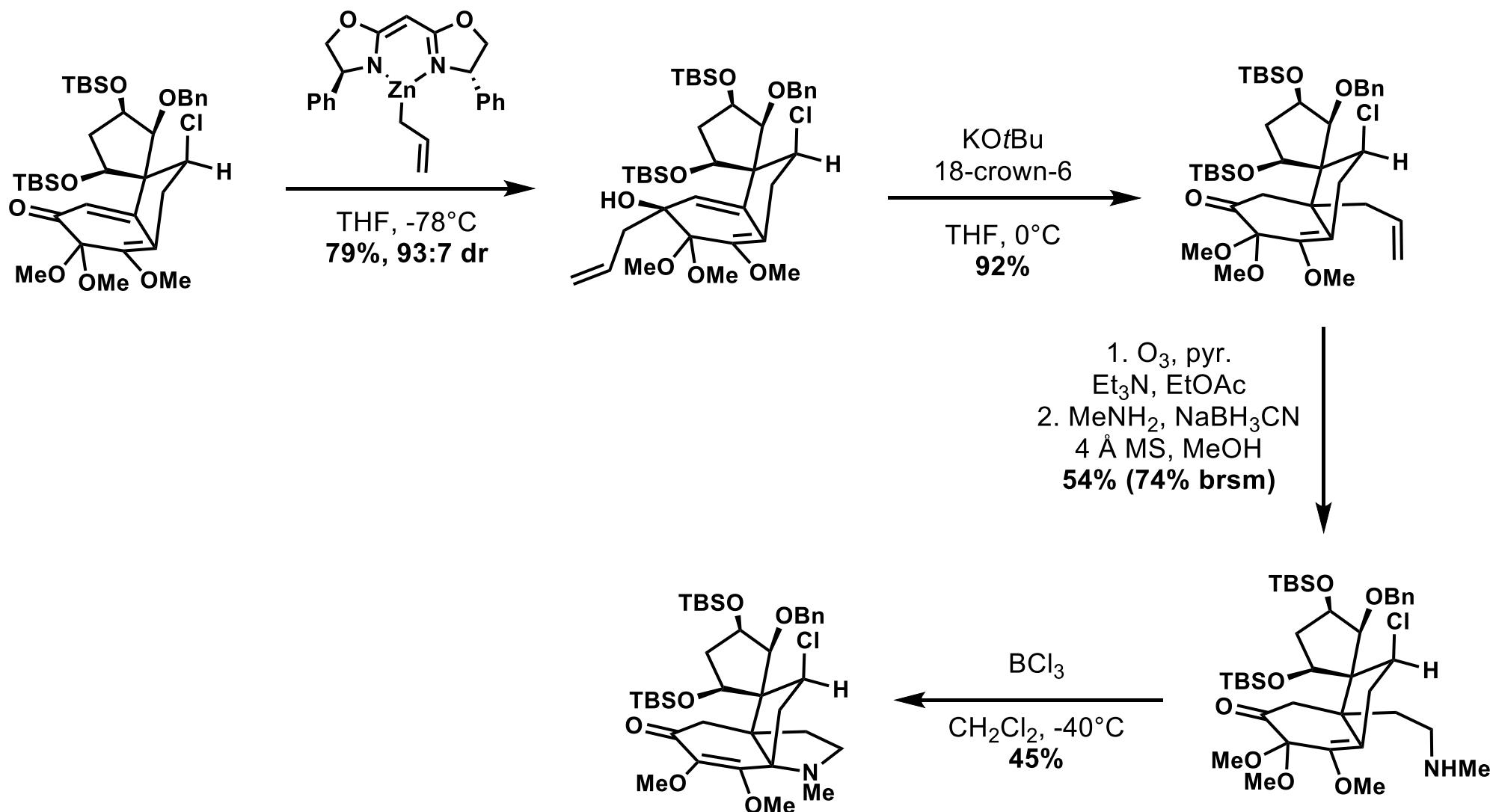
# Castle's Synthesis of Acutumine

Constructing the propellane core



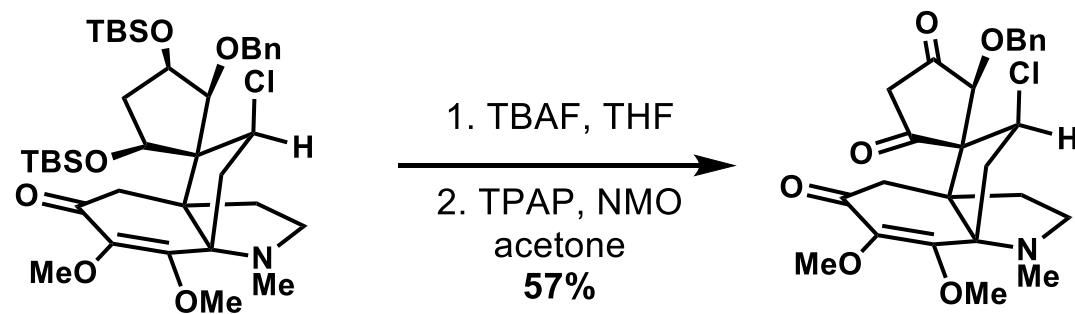
# Castle's Synthesis of Acutumine

Constructing the propellane core



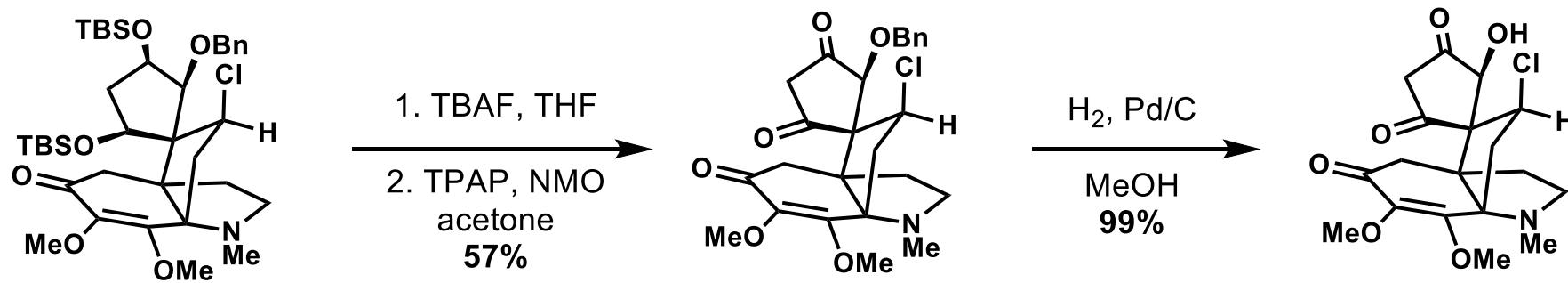
# Castle's Synthesis of Acutumine

Completing the natural product



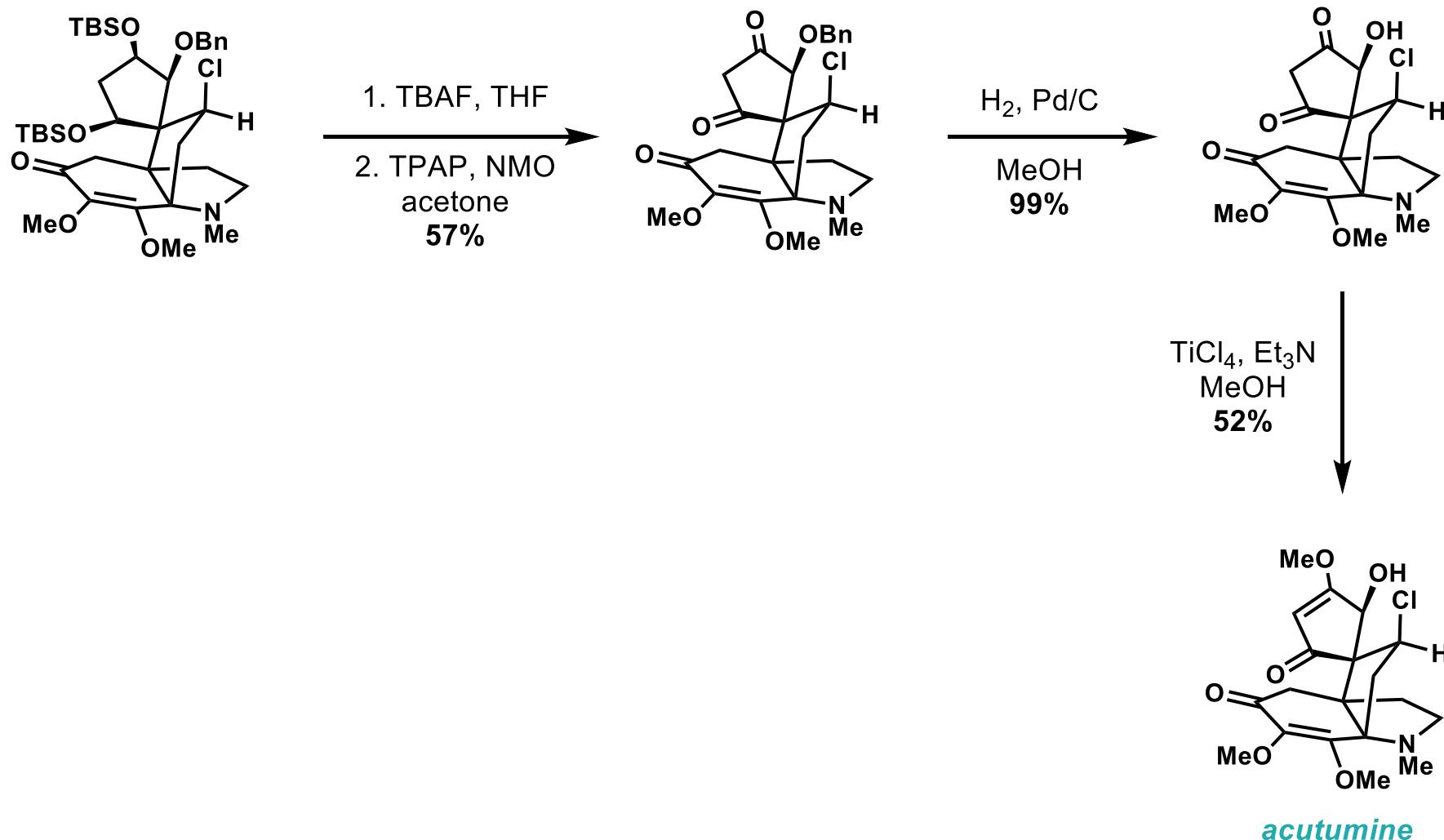
# Castle's Synthesis of Acutumine

Completing the natural product

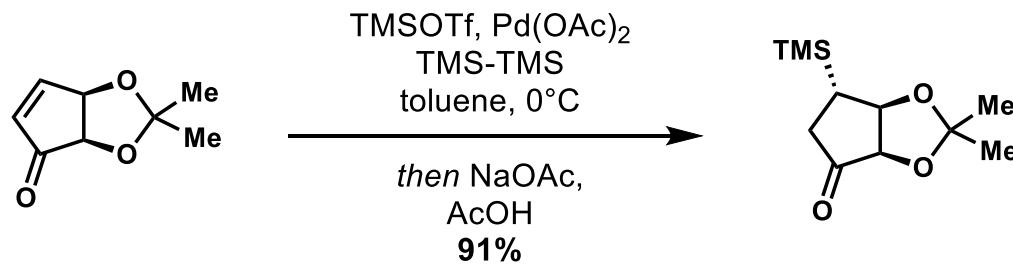


# Castle's Synthesis of Acutumine

Completing the natural product

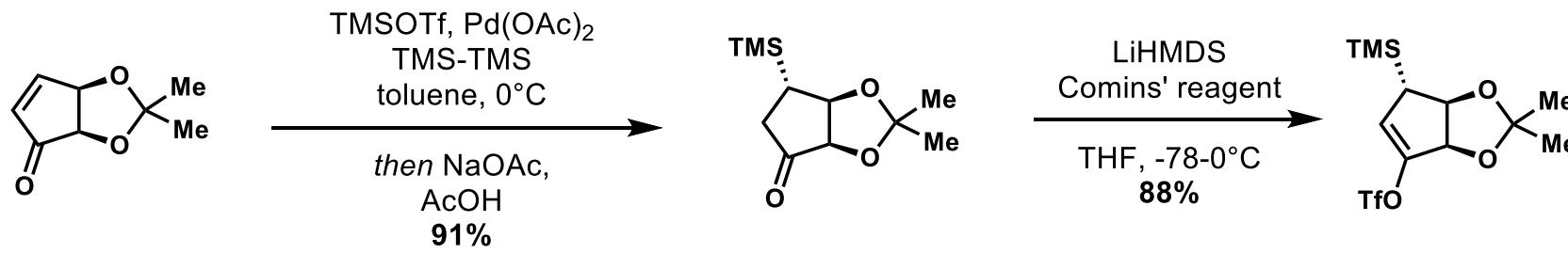


# *Herzon's Synthesis of Acutumine*



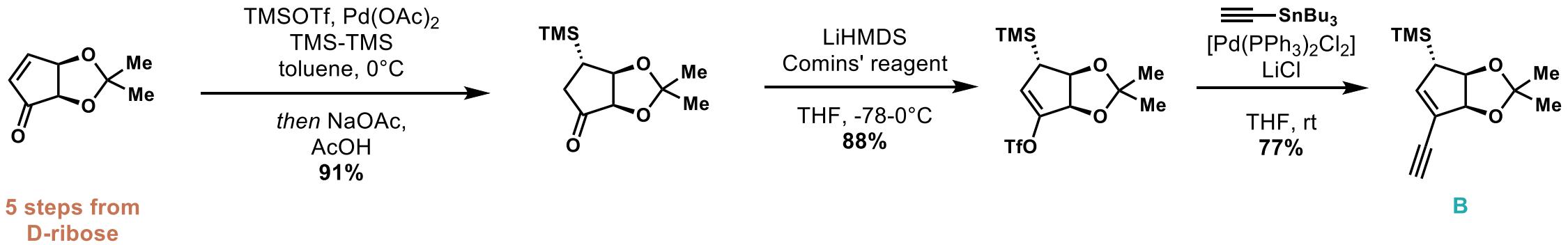
5 steps from  
D-ribose

# *Herzon's Synthesis of Acutumine*

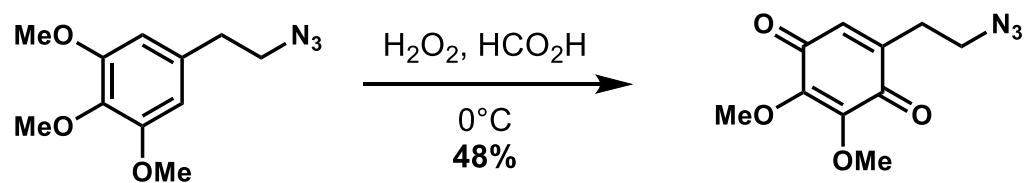
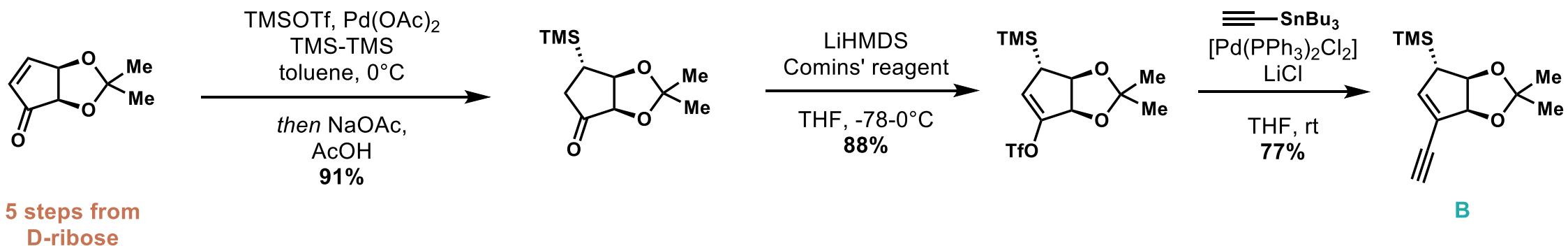


5 steps from  
D-ribose

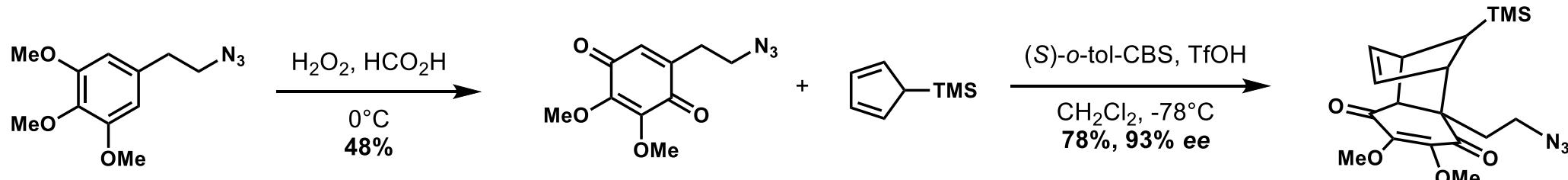
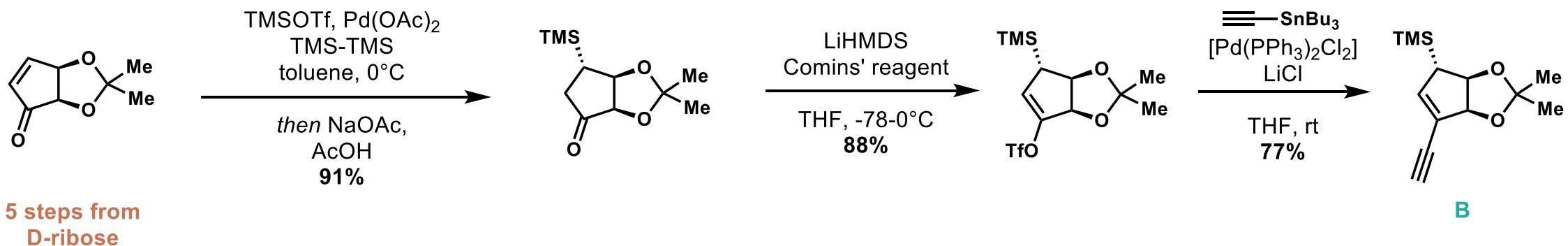
# *Herzon's Synthesis of Acutumine*



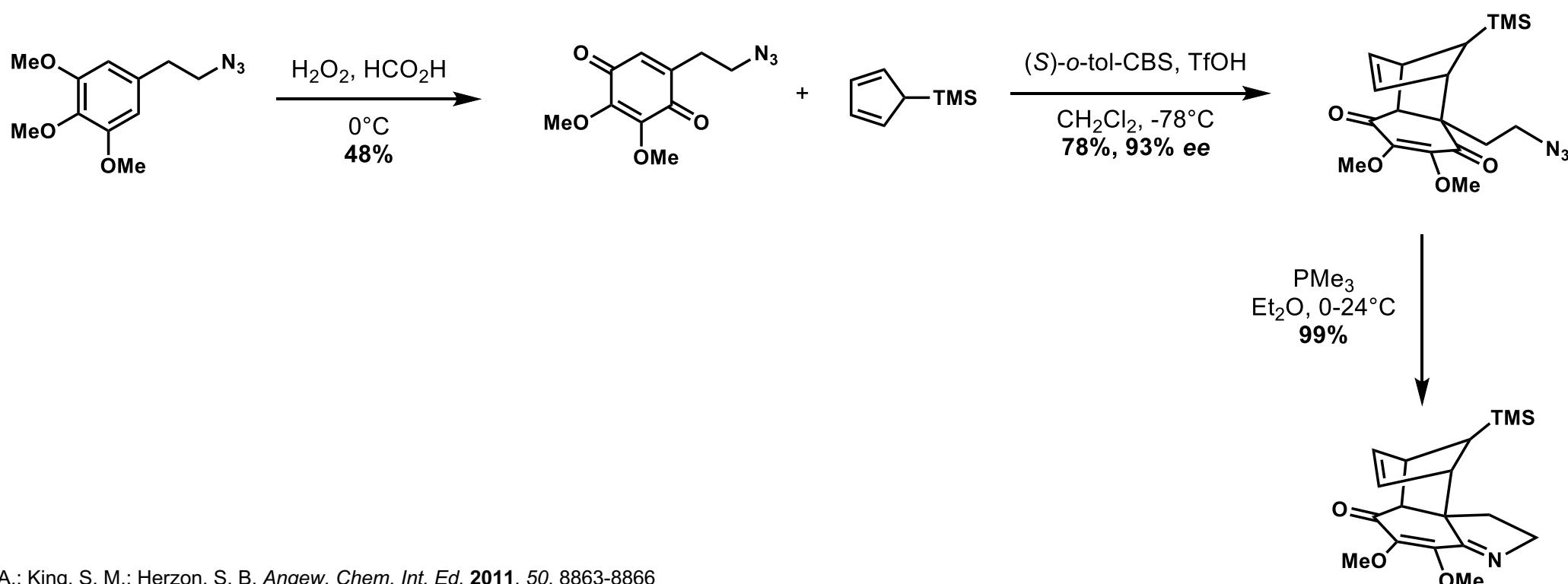
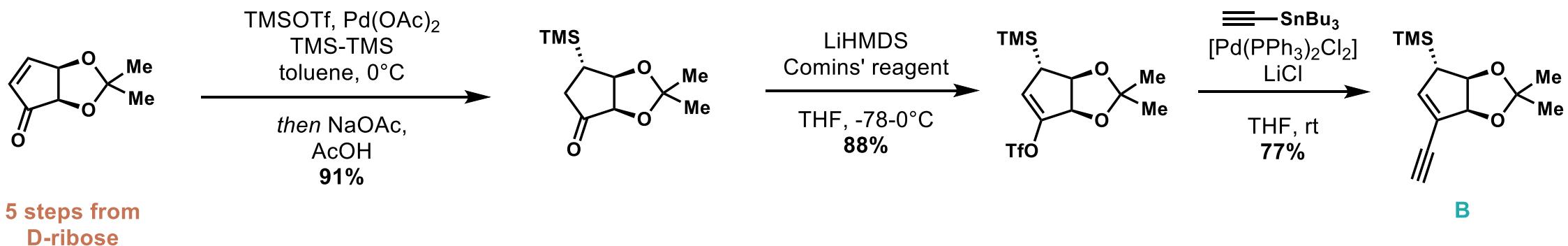
# Herzon's Synthesis of Acutumine



# Herzon's Synthesis of Acutumine

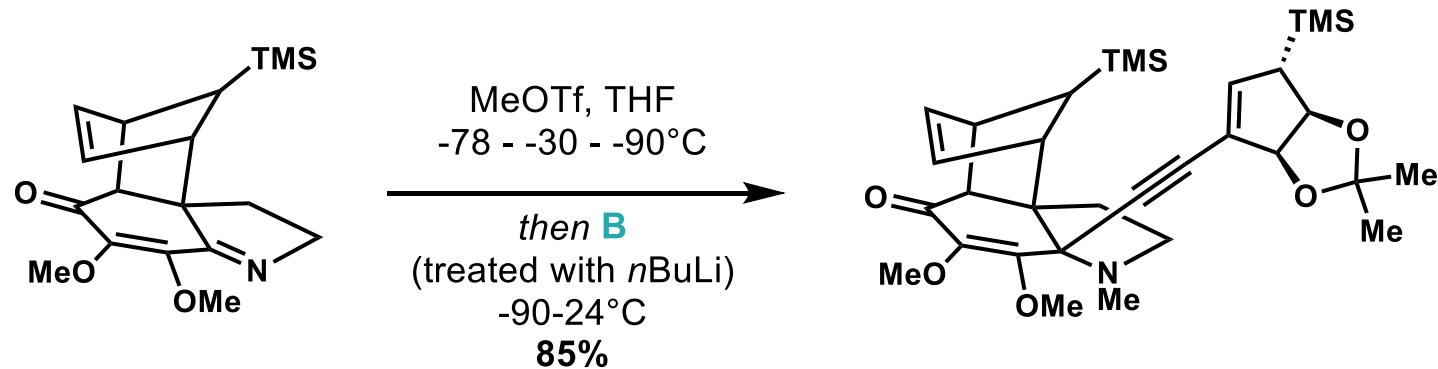


# Herzon's Synthesis of Acutumine



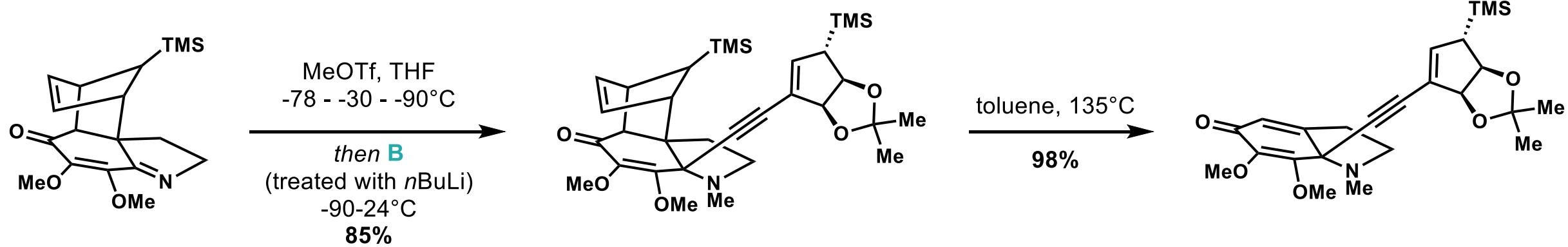
# Herzon's Synthesis of Acutumine

Constructing propellane and spirocycle



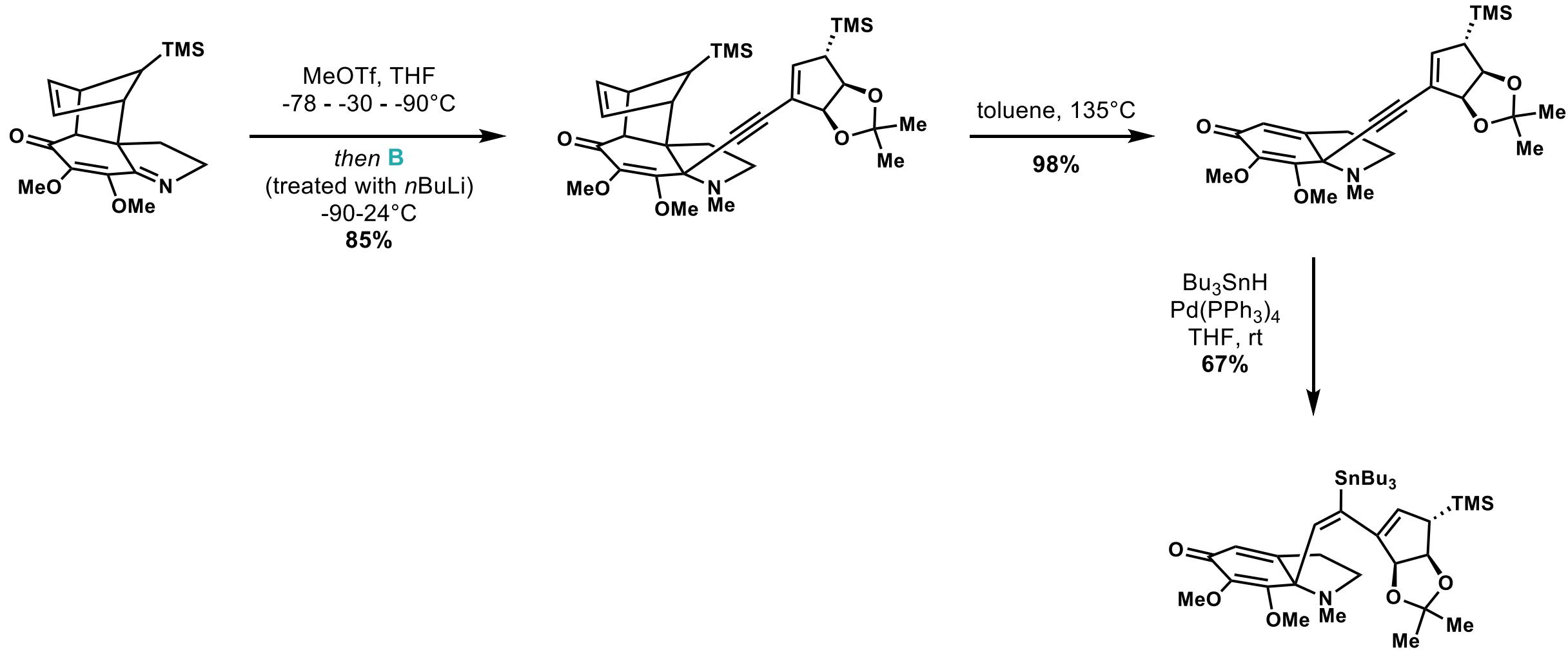
# Herzon's Synthesis of Acutumine

Constructing propellane and spirocycle



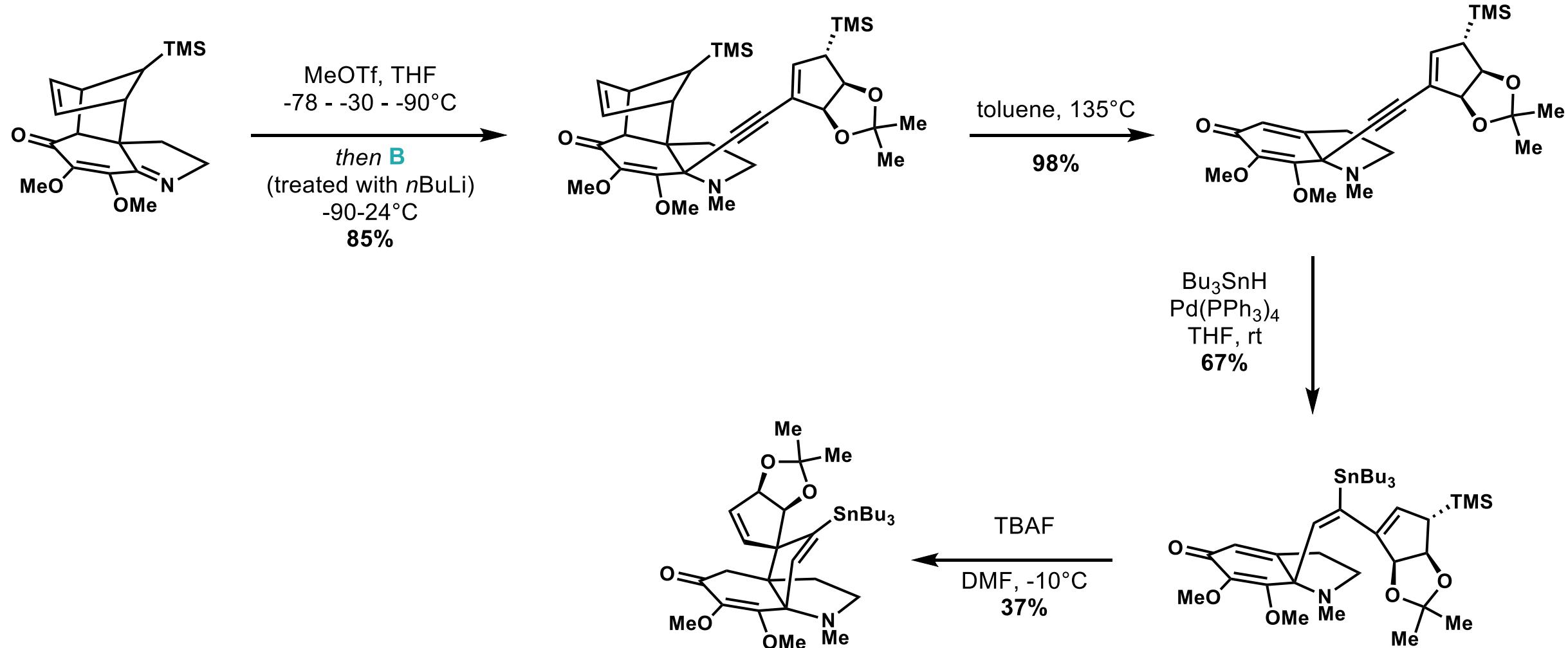
# Herzon's Synthesis of Acutumine

Constructing propellane and spirocycle



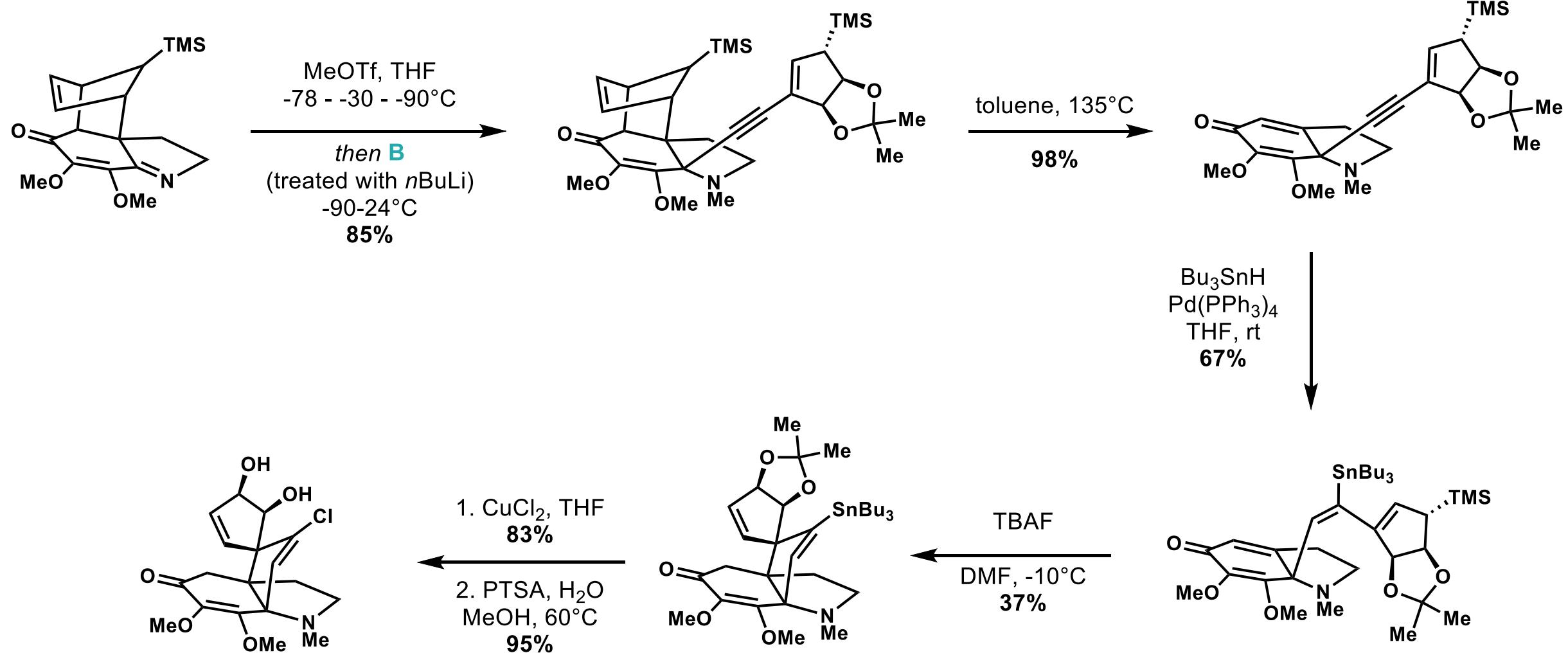
# Herzon's Synthesis of Acutumine

Constructing propellane and spirocycle

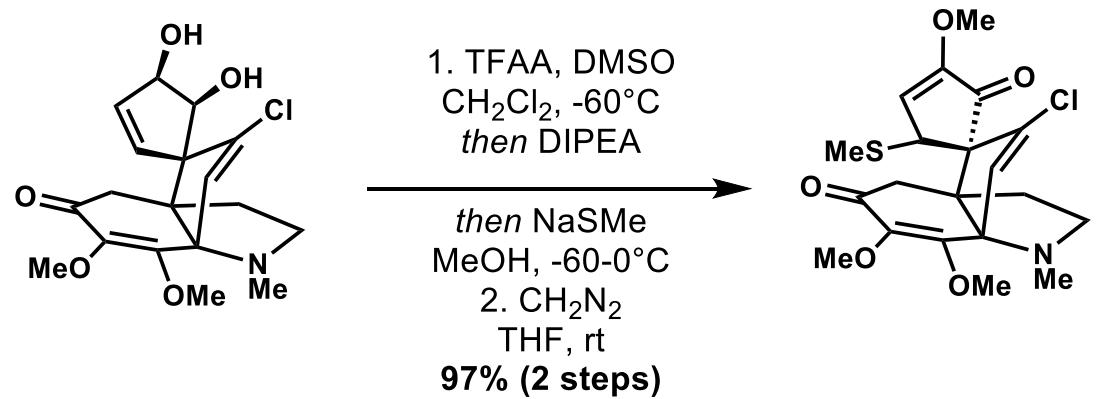


# Herzon's Synthesis of Acutumine

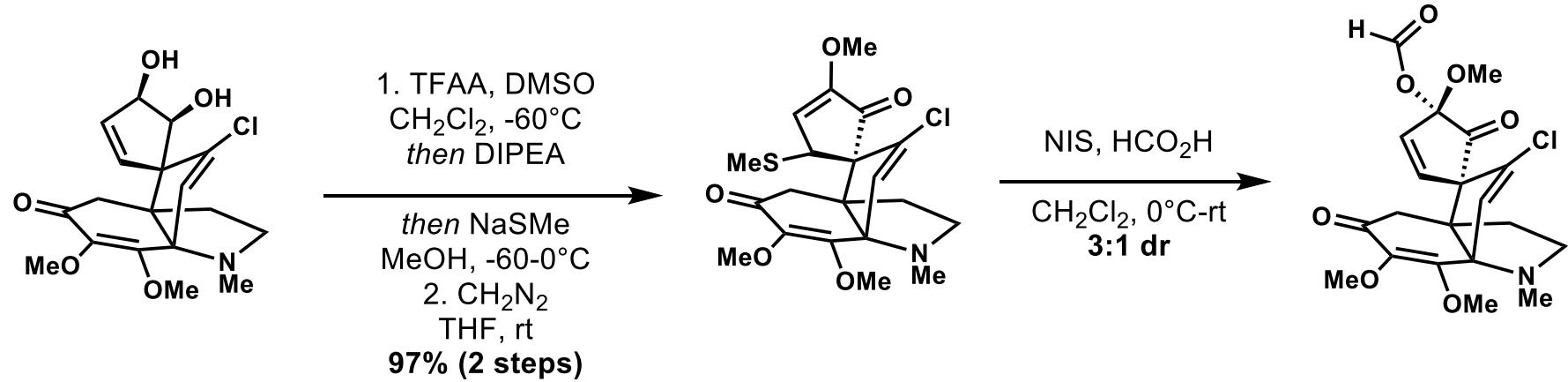
Constructing propellane and spirocycle



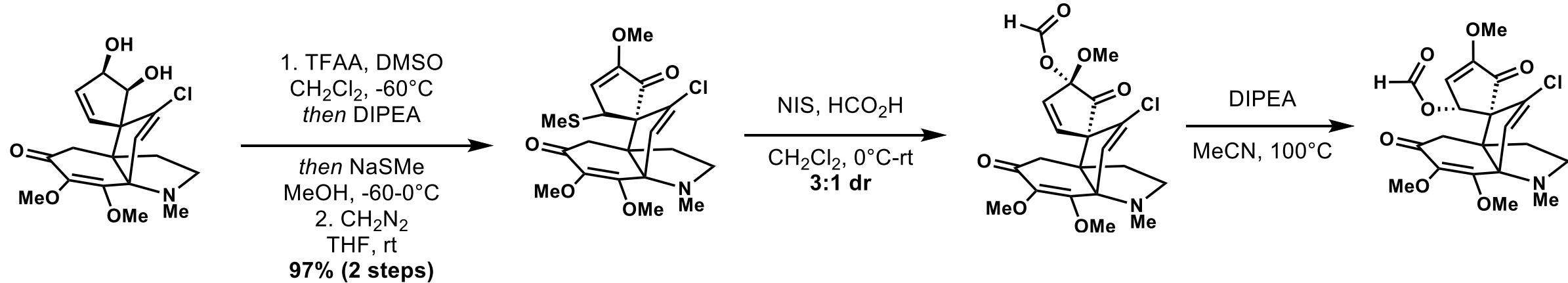
# *Herzon's Synthesis of Acutumine*



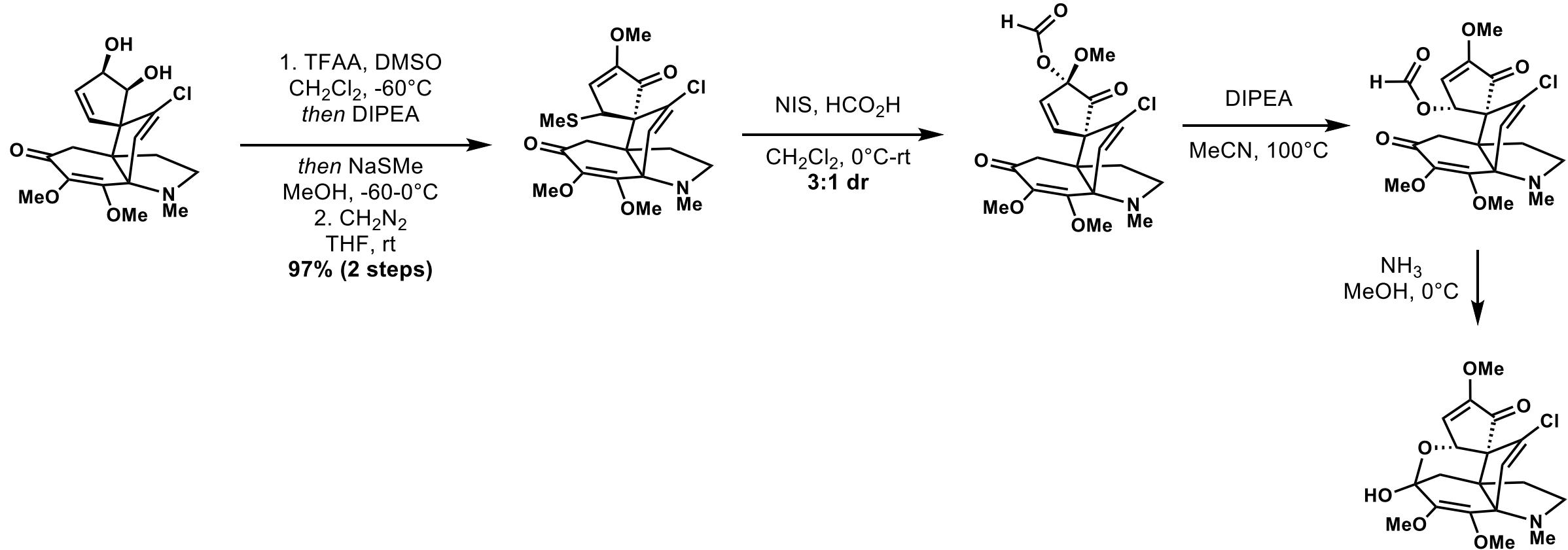
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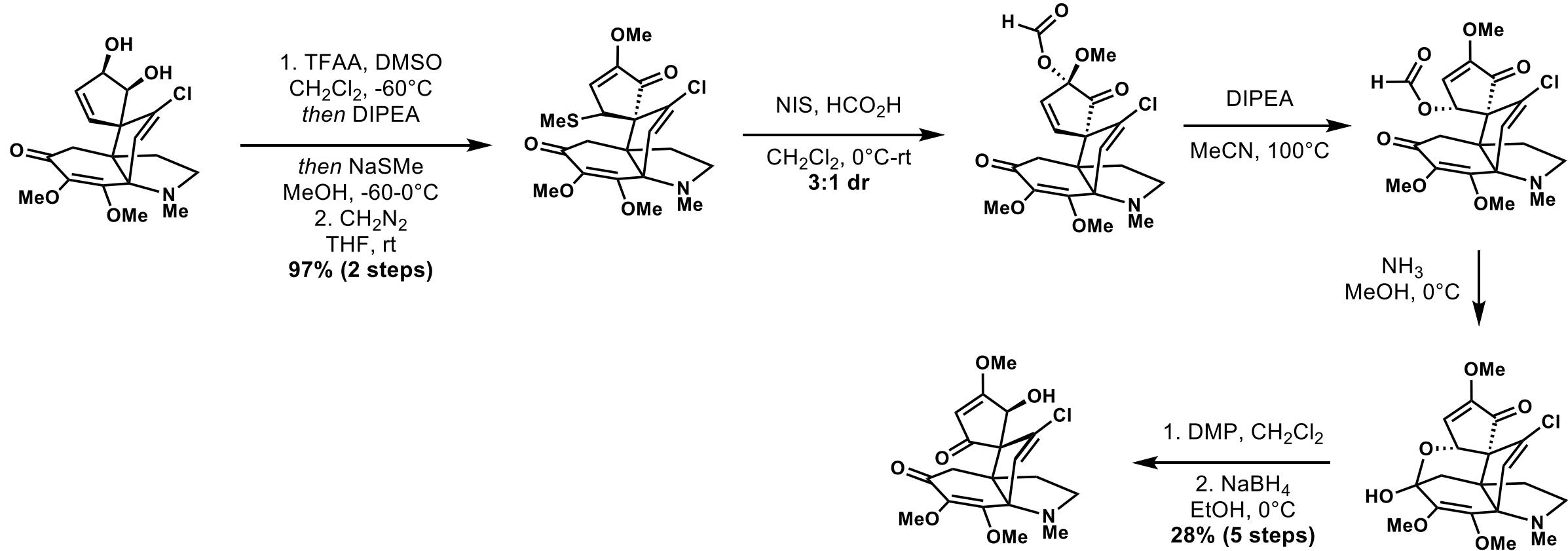
# *Herzon's Synthesis of Acutumine*



# *Herzon's Synthesis of Acutumine*

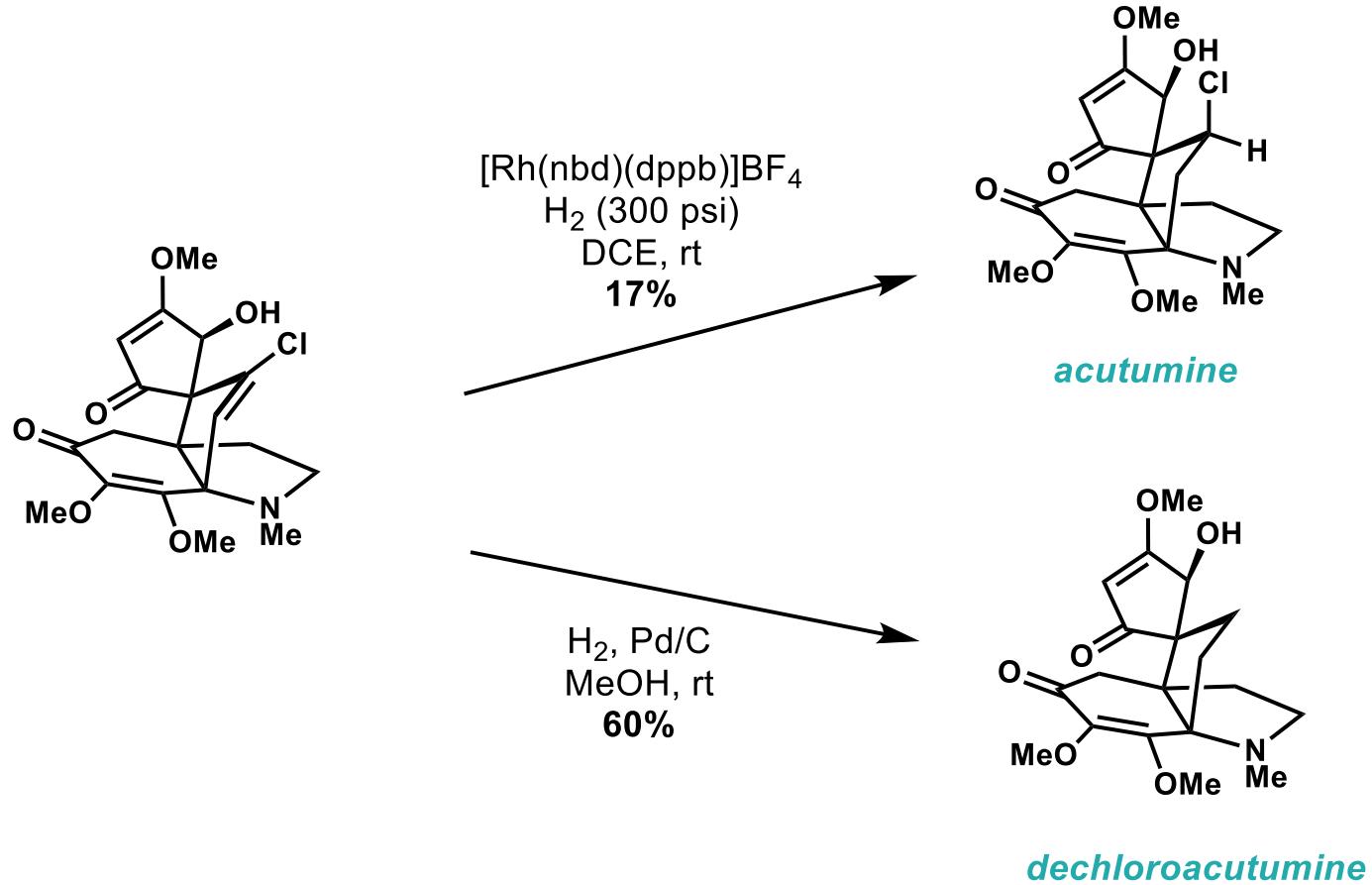


# *Herzon's Synthesis of Acutumine*



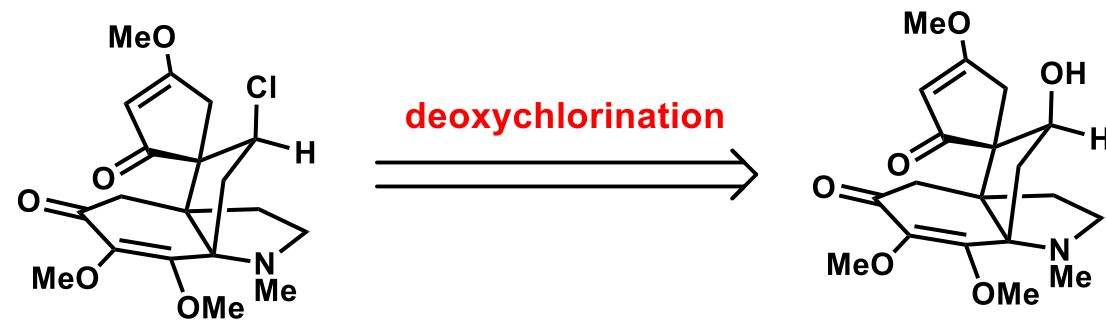
# **Herzon's Synthesis of Acutumine**

Divergent synthesis of two alkaloids



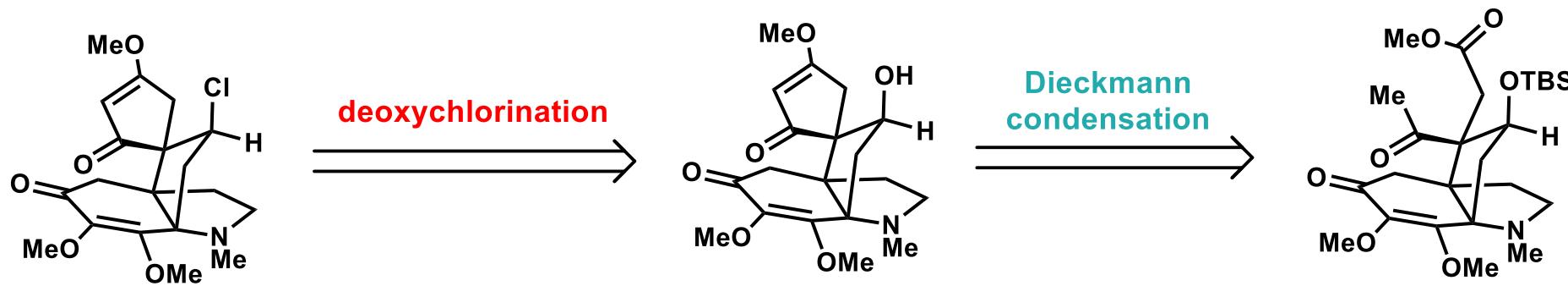
# *Reisman's Synthesis of Acutuminine*

## *Retrosynthesis*



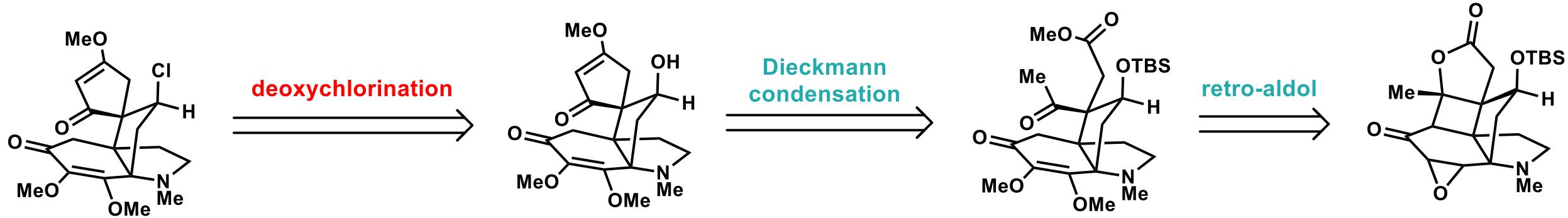
# *Reisman's Synthesis of Acutuminine*

## Retrosynthesis



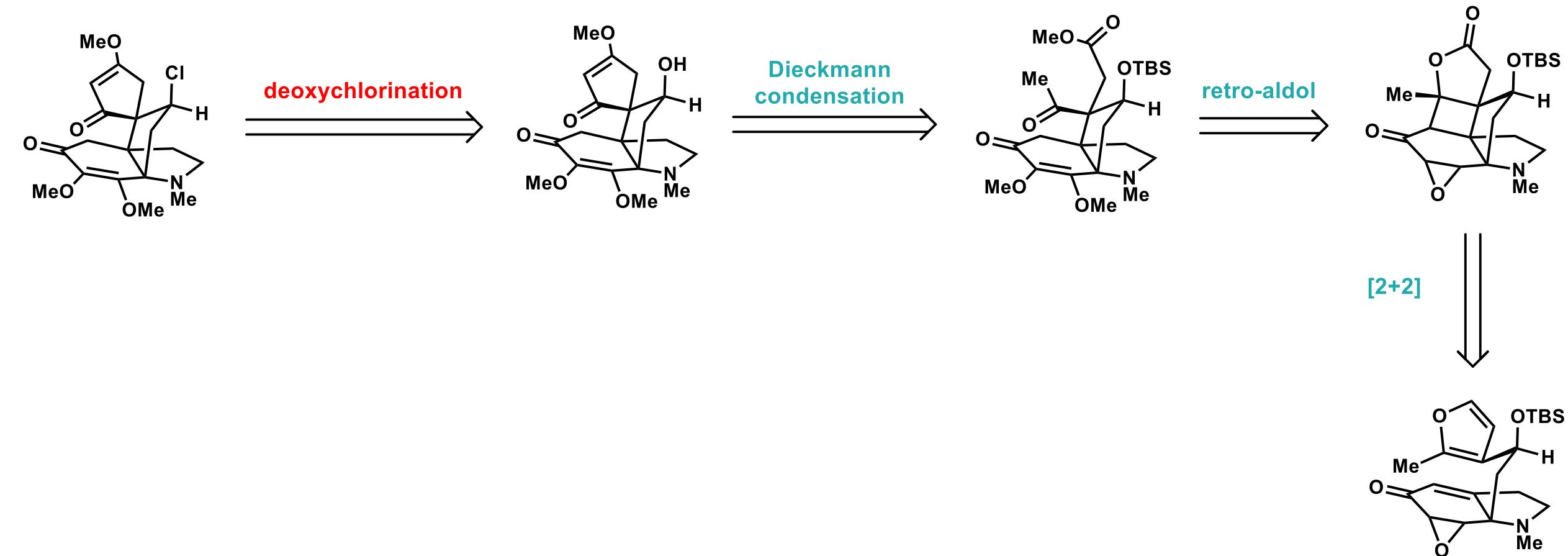
# *Reisman's Synthesis of Acutuminine*

## Retrosynthesis



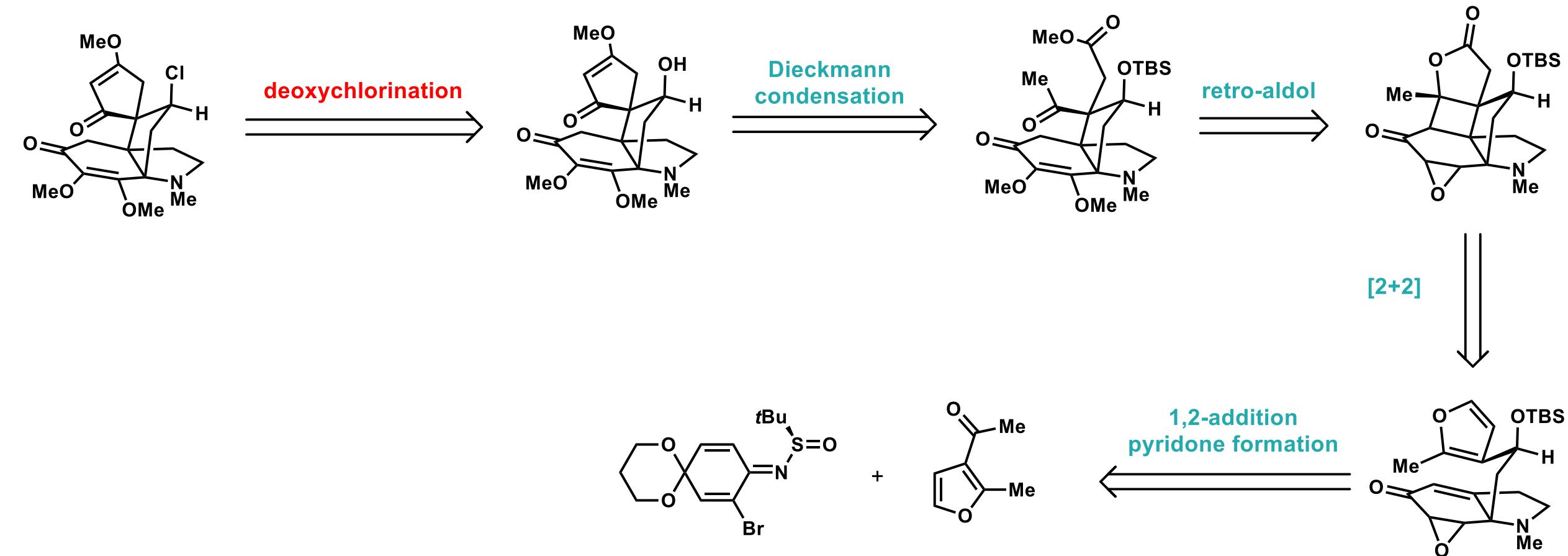
# *Reisman's Synthesis of Acutuminine*

## Retrosynthesis



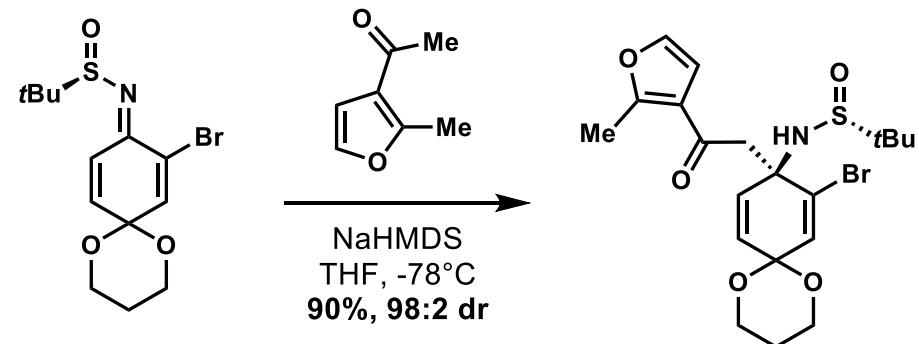
# *Reisman's Synthesis of Acutuminine*

## Retrosynthesis



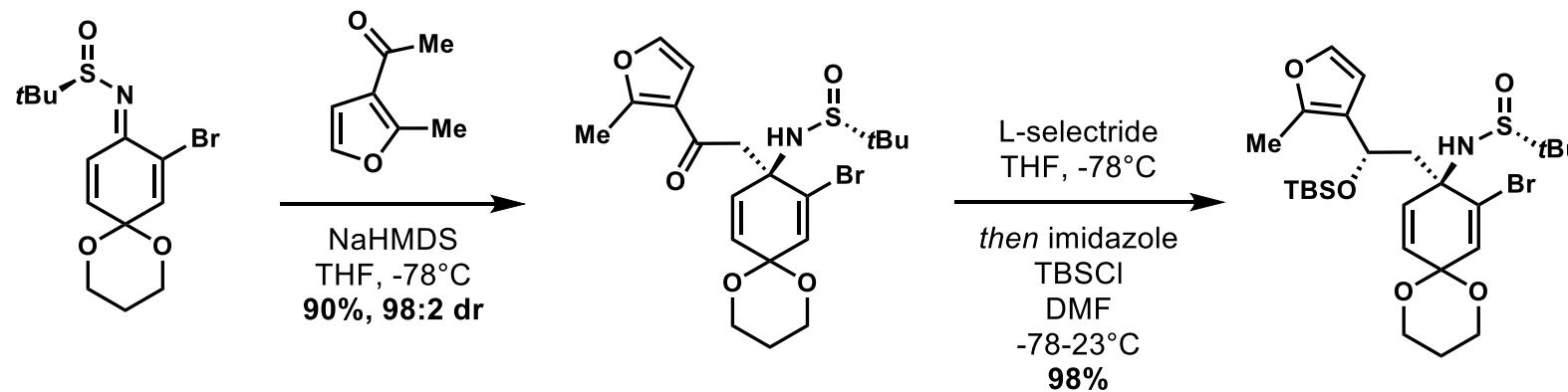
# *Reisman's Synthesis of Acutuminine*

*Formation of pyrrolidine*



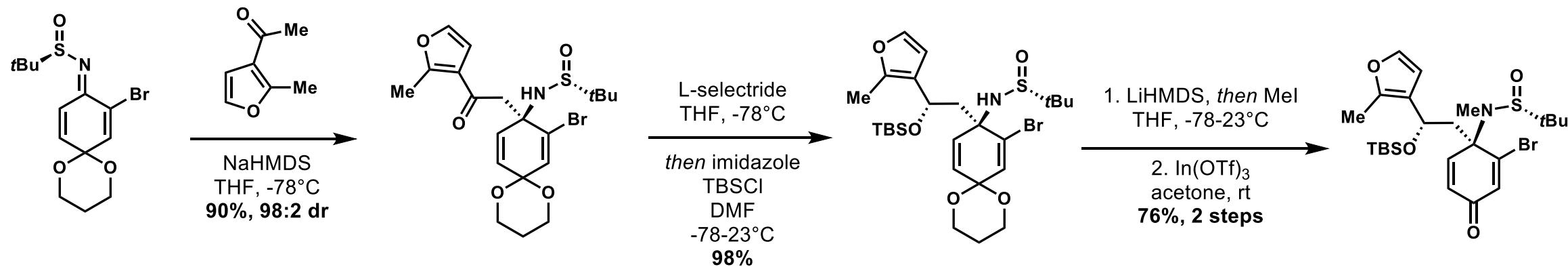
# *Reisman's Synthesis of Acutuminine*

*Formation of pyrrolidine*



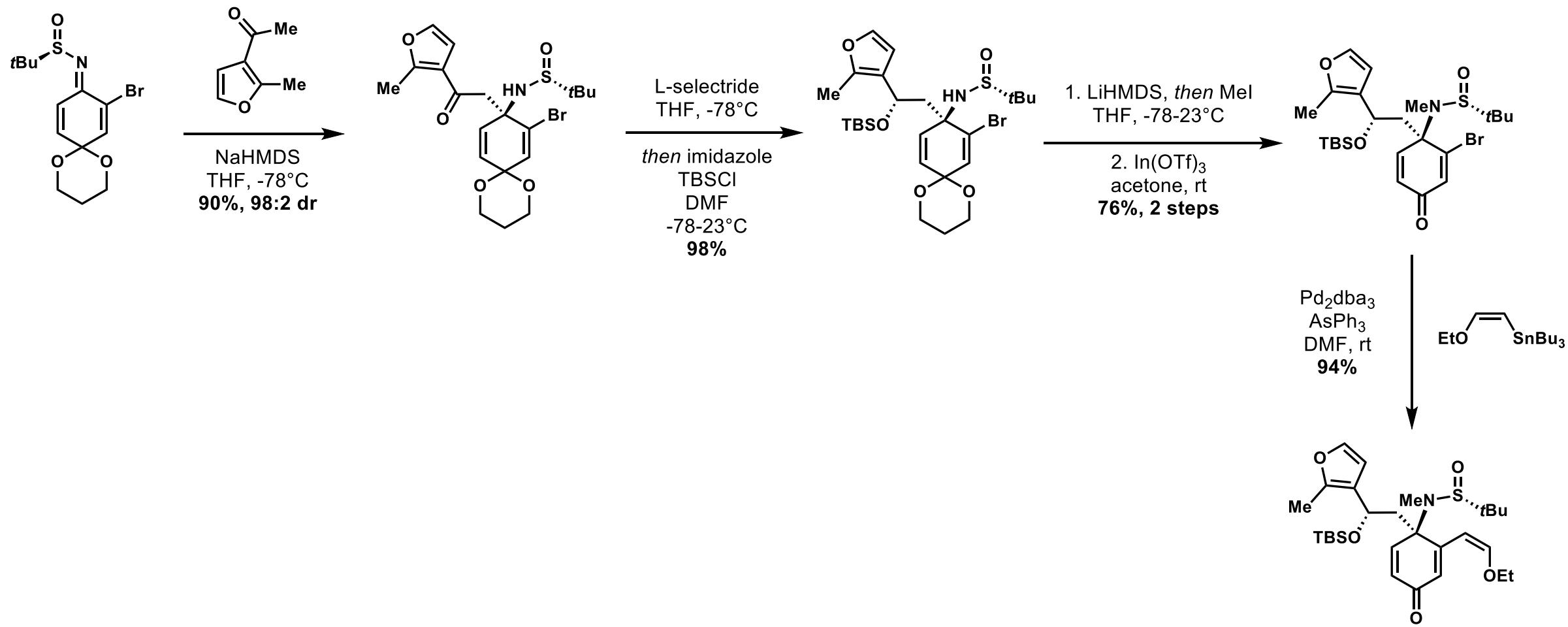
# *Reisman's Synthesis of Acutuminine*

*Formation of pyrrolidine*



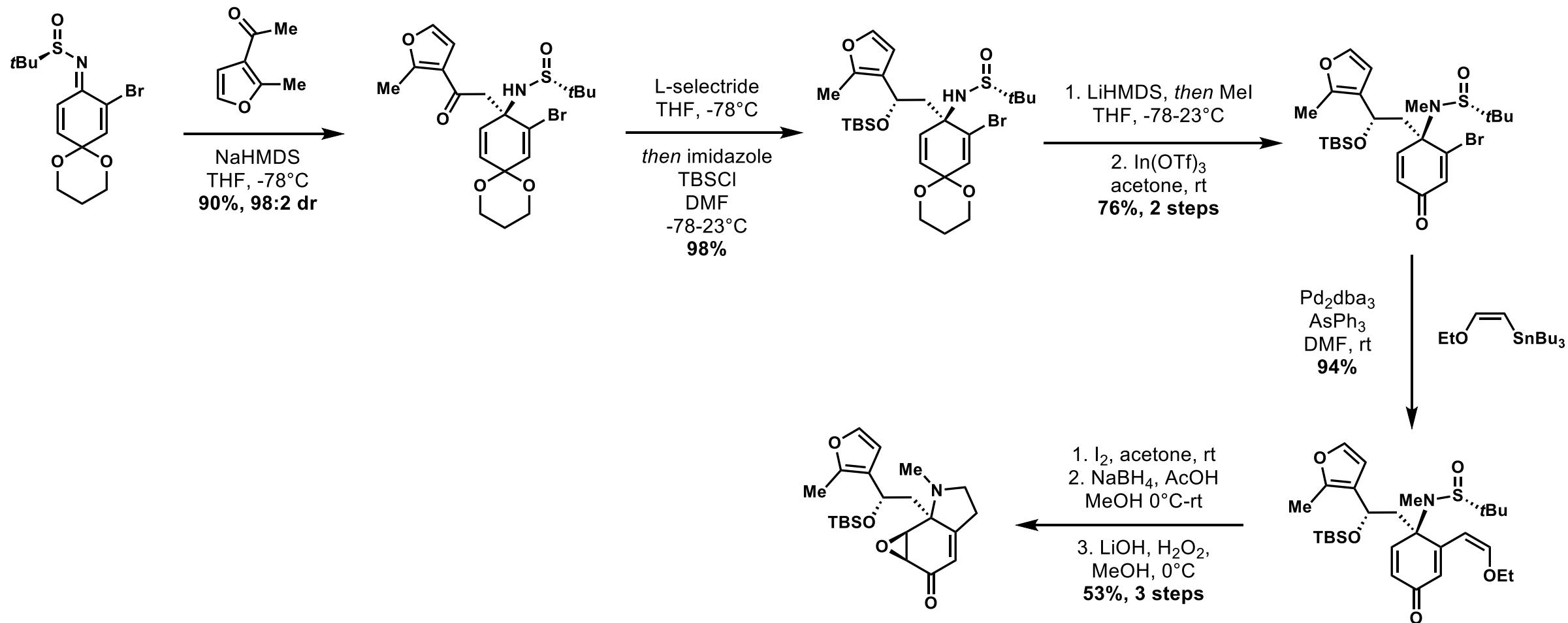
# *Reisman's Synthesis of Acutuminine*

*Formation of pyrrolidine*



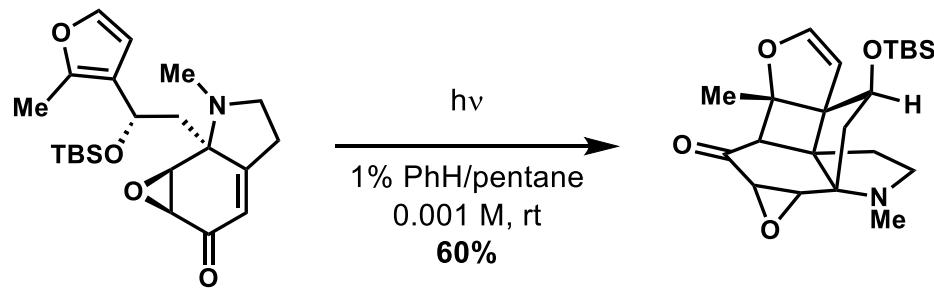
# Reisman's Synthesis of Acutuminine

*Formation of pyrrolidine*



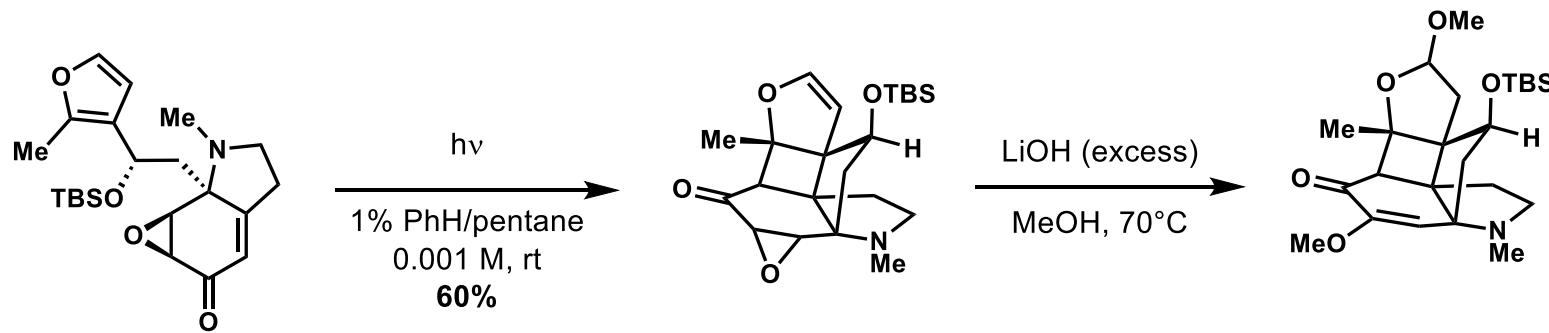
# *Reisman's Synthesis of Acutuminine*

Attempts towards Dieckmann



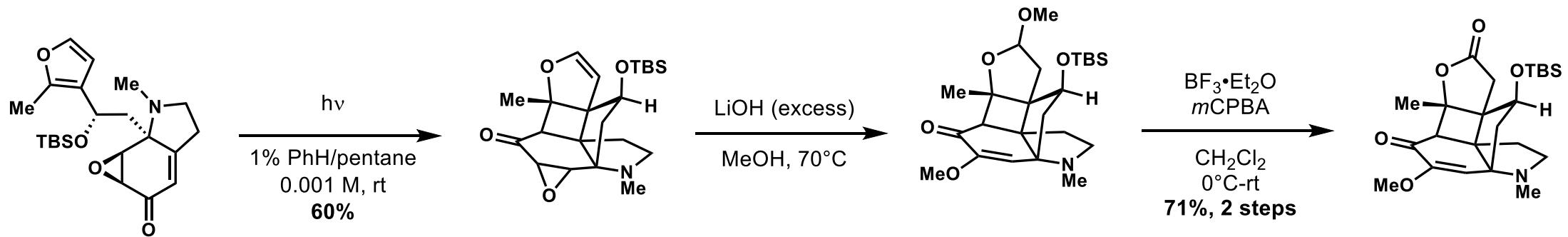
# *Reisman's Synthesis of Acutuminine*

Attempts towards Dieckmann



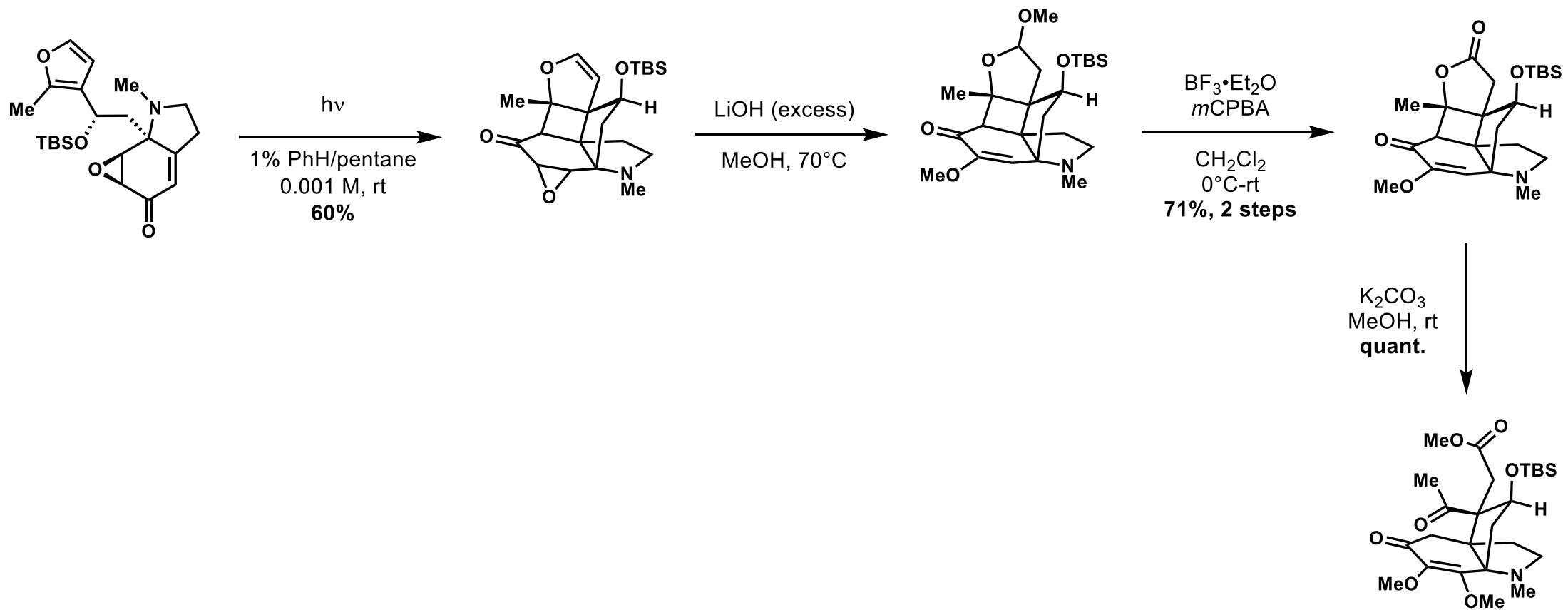
# *Reisman's Synthesis of Acutuminine*

## Attempts towards Dieckmann



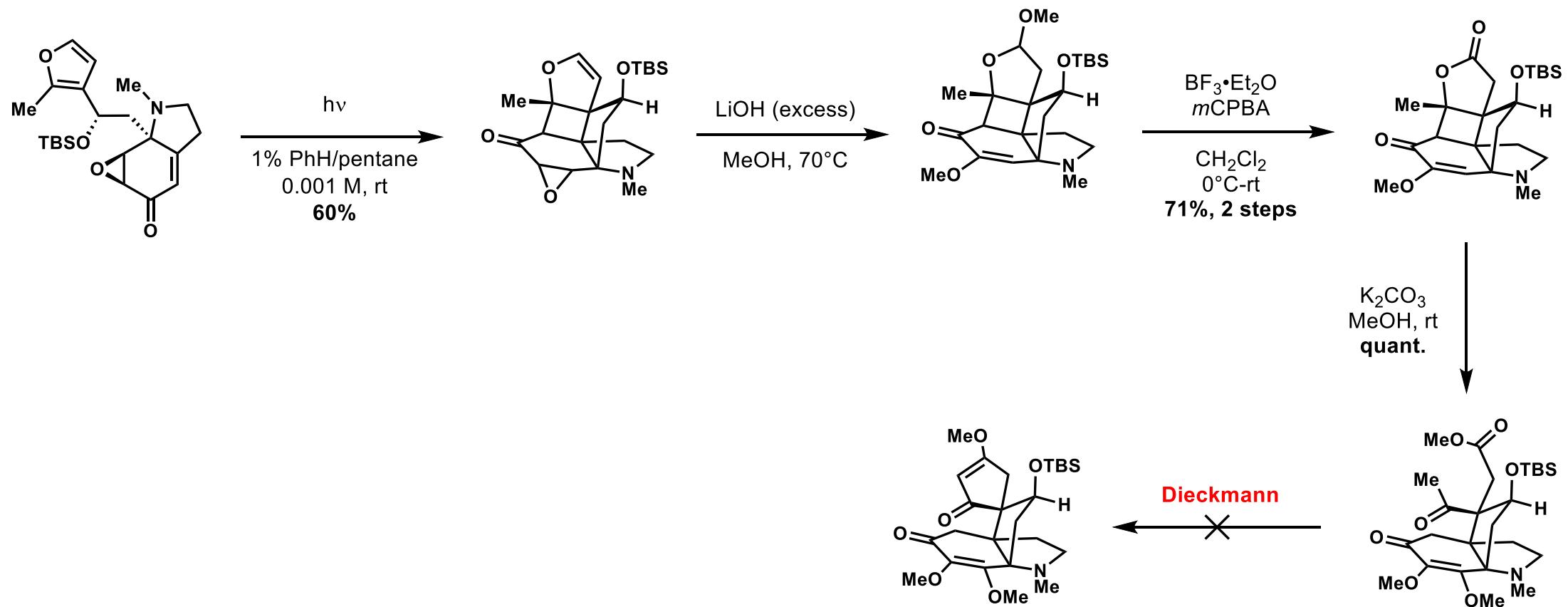
# *Reisman's Synthesis of Acutuminine*

## Attempts towards Dieckmann



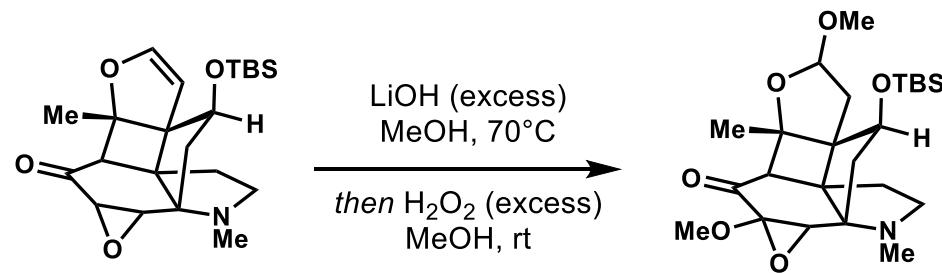
# *Reisman's Synthesis of Acutuminine*

## Attempts towards Dieckmann



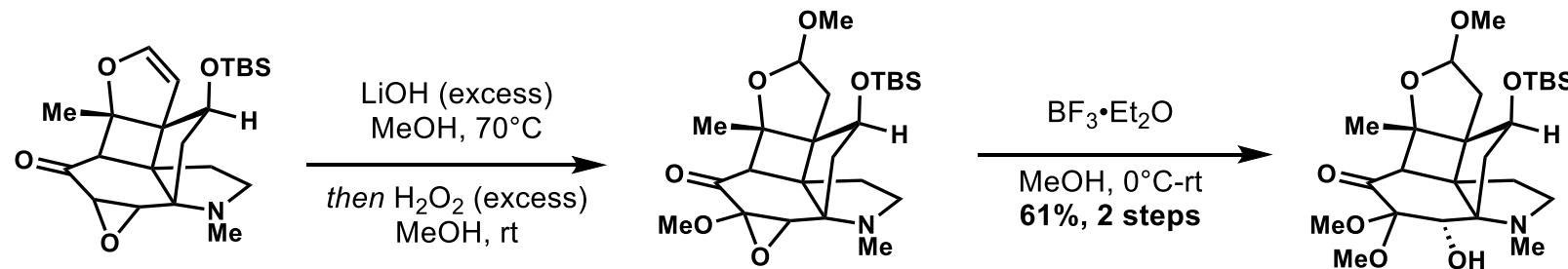
# *Reisman's Synthesis of Acutuminine*

Attempts towards Dieckmann



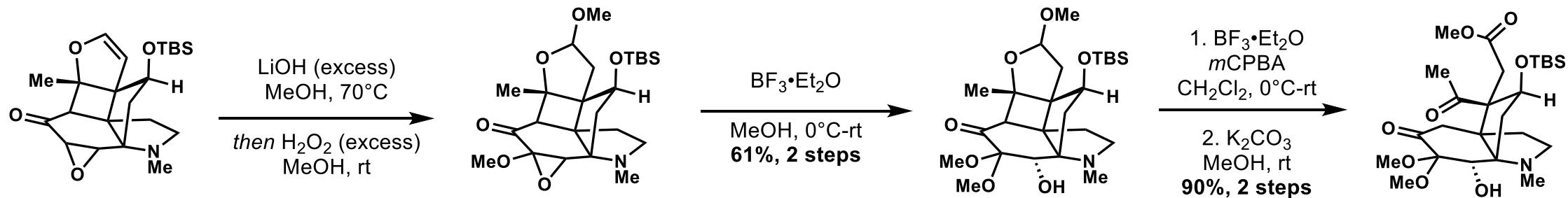
# *Reisman's Synthesis of Acutuminine*

## Attempts towards Dieckmann



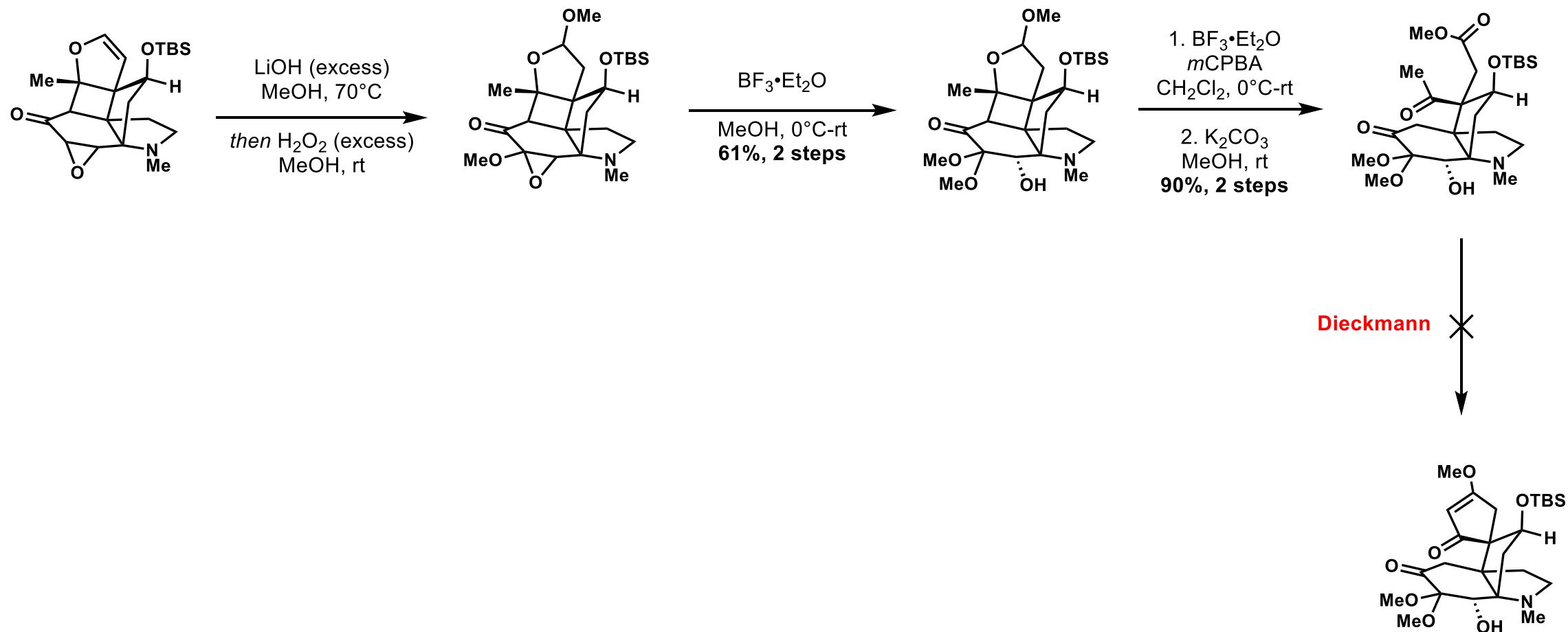
# *Reisman's Synthesis of Acutuminine*

## Attempts towards Dieckmann



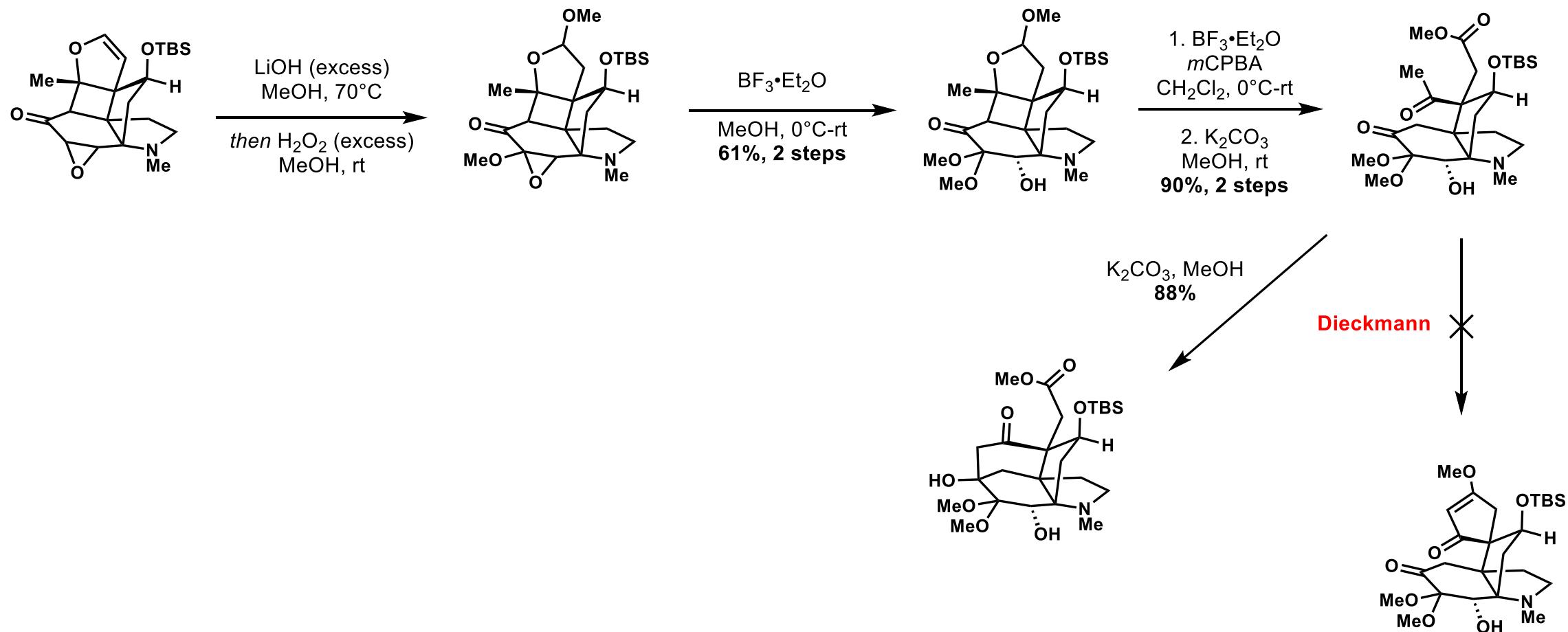
# *Reisman's Synthesis of Acutuminine*

## Attempts towards Dieckmann



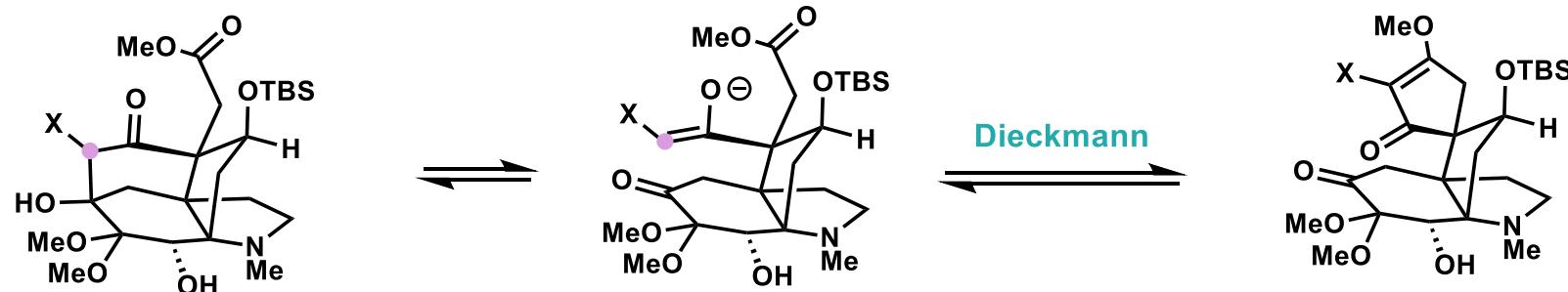
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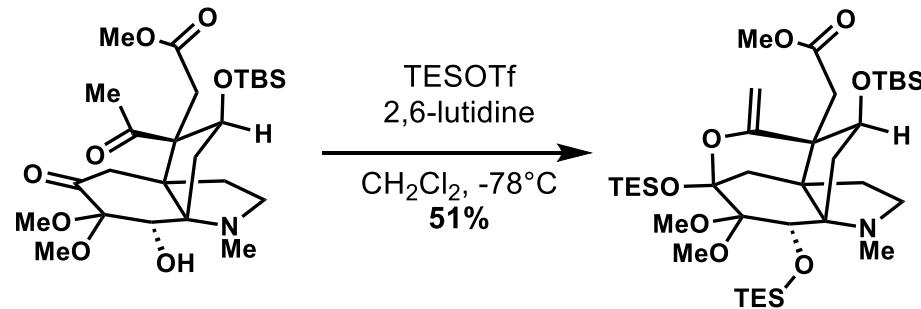
Attempts towards Dieckmann



lowering pKa of this C  
could lead to this equilibrium

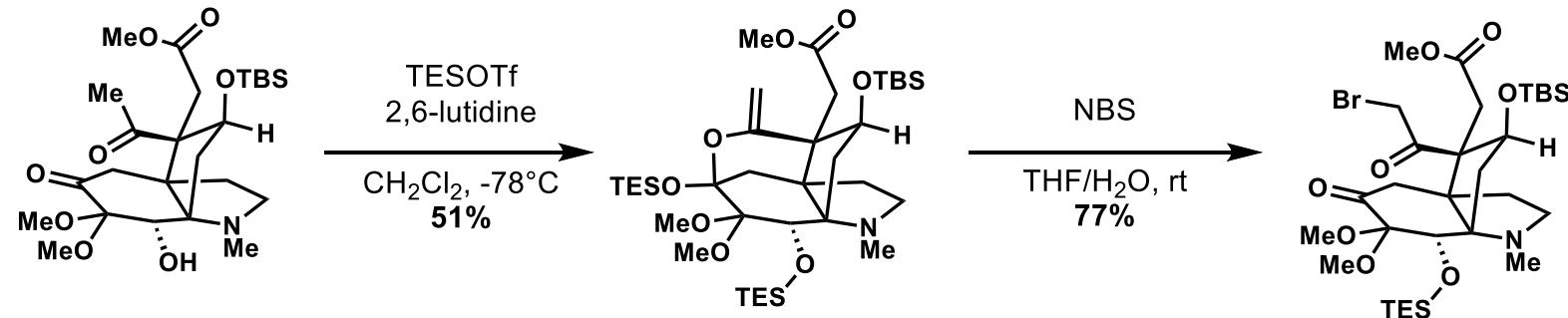
# **Reisman's Synthesis of Acutuminine**

*Successful Dieckmann – Advancing to natural product*



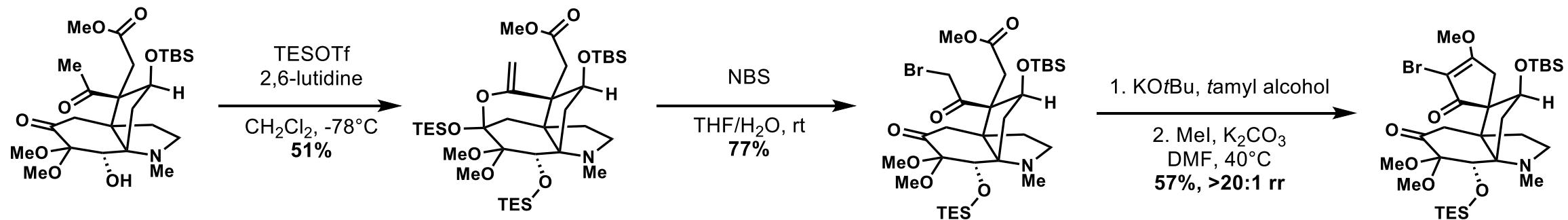
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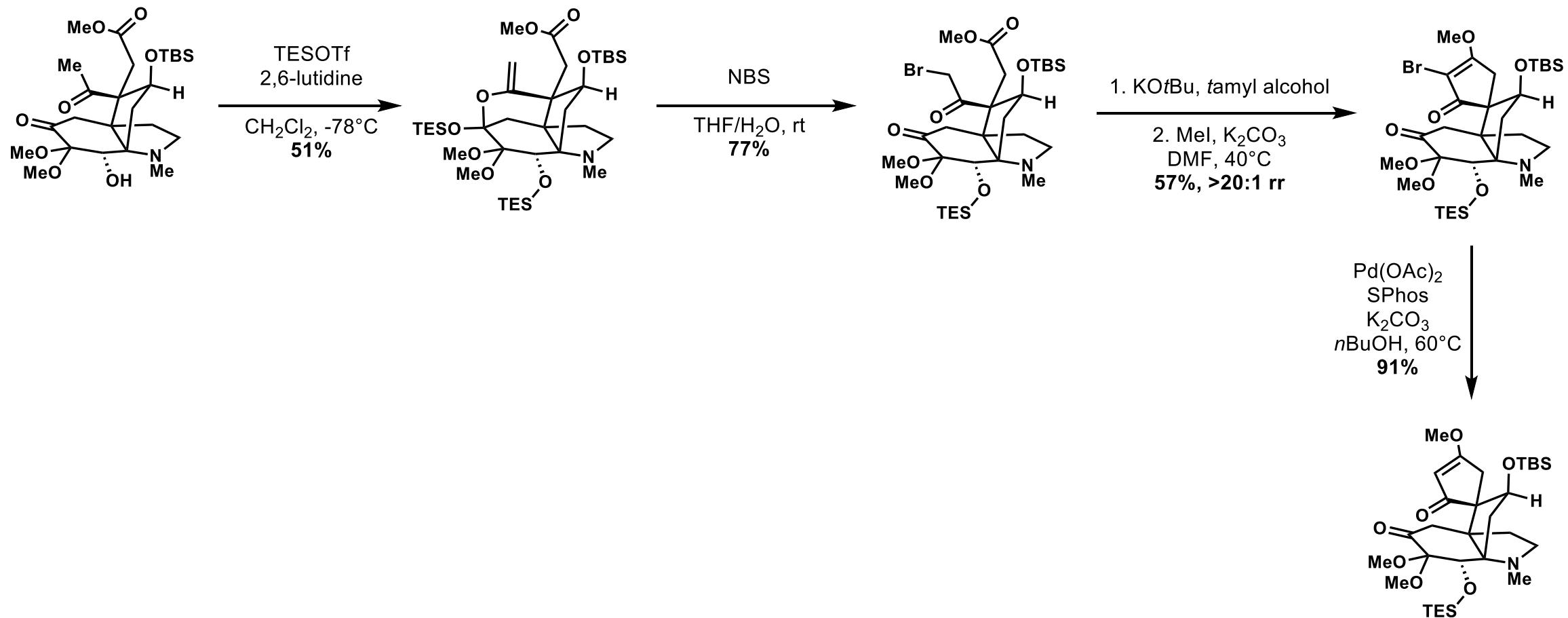
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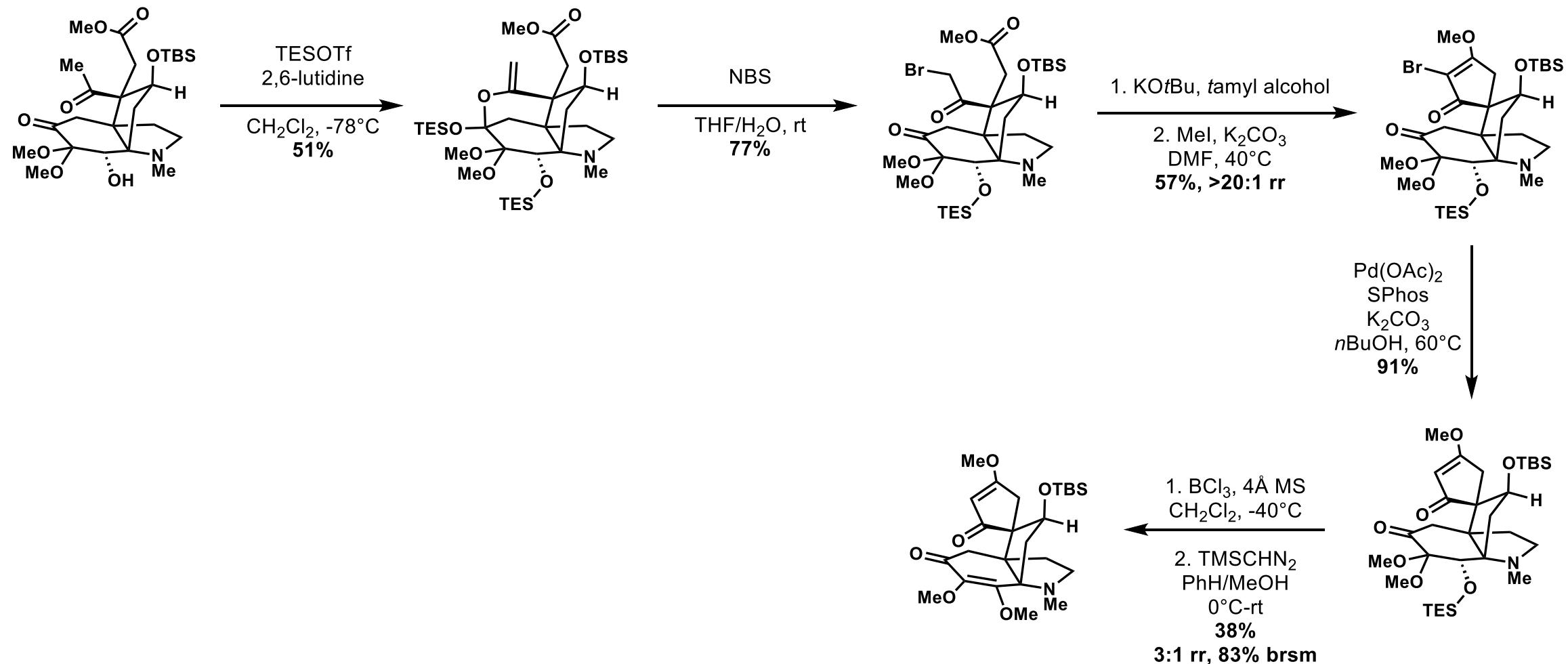
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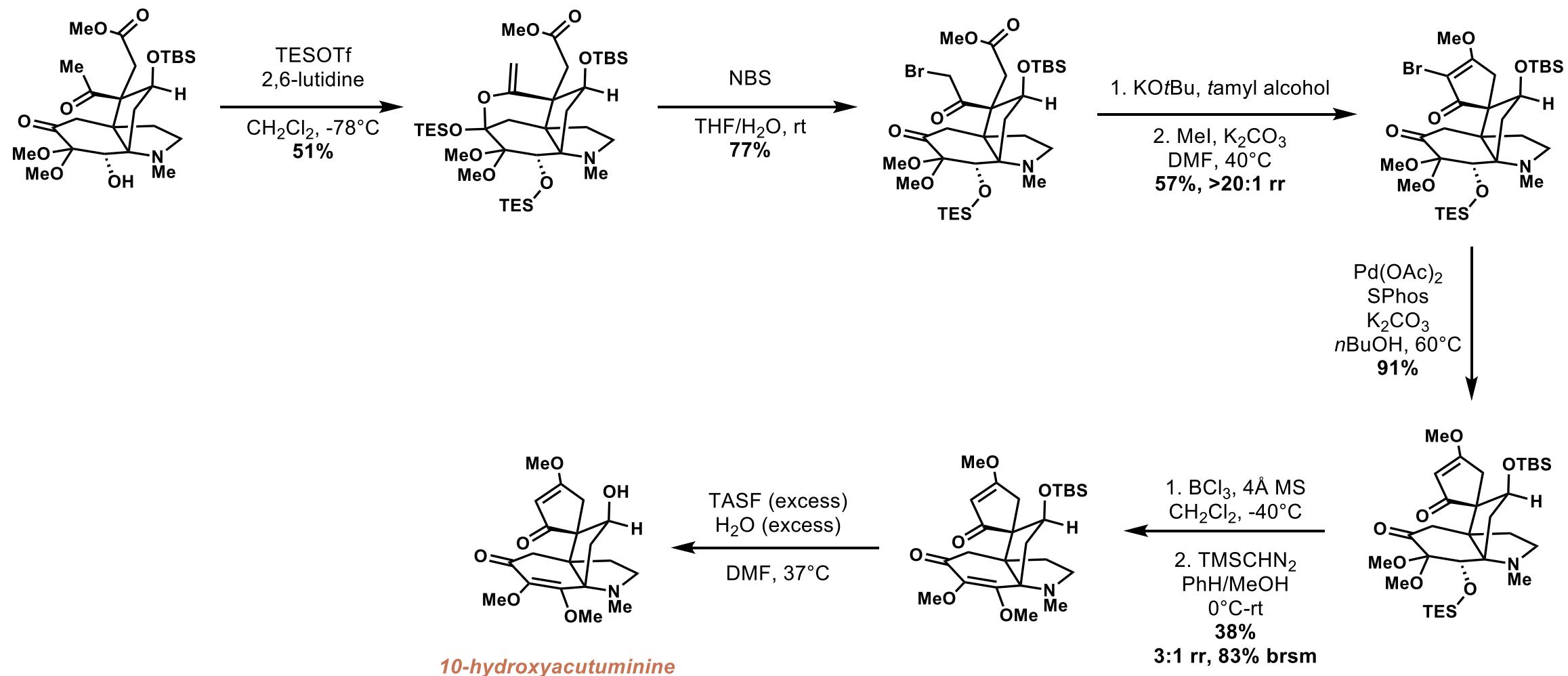
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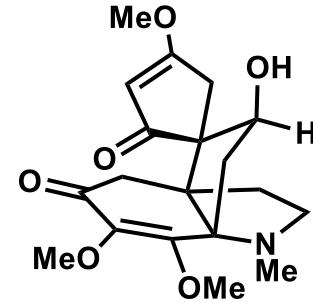
# Reisman's Synthesis of Acutuminine

Successful Dieckmann – Advancing to natural product



# *Reisman's Synthesis of Acutuminine*

*Deoxygenation*



# *Reisman's Synthesis of Acutuminine*

*Deoxygenation*

