

# Total Synthesis of Pseudolaric Acids A and B

Literature Group Meeting

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# Introduction

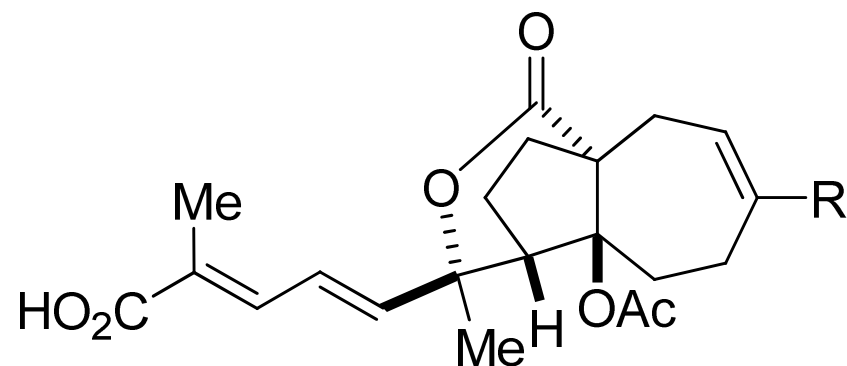
## Biological Activity:

- Pseudolaric acids A-C were isolated in 1965 from the bark of *Pseudolarix kaempferi* Gordon
- Extract from root bark of *P. kaempferi* is used as a Chinese herbal medicine called *tujinpi* for the treatment of fungal infections
- Pseudolaric acid B is a potent antifungal, antifertility, and cytotoxic agent; has shown significant activity against multi-drug resistant cancer cell lines



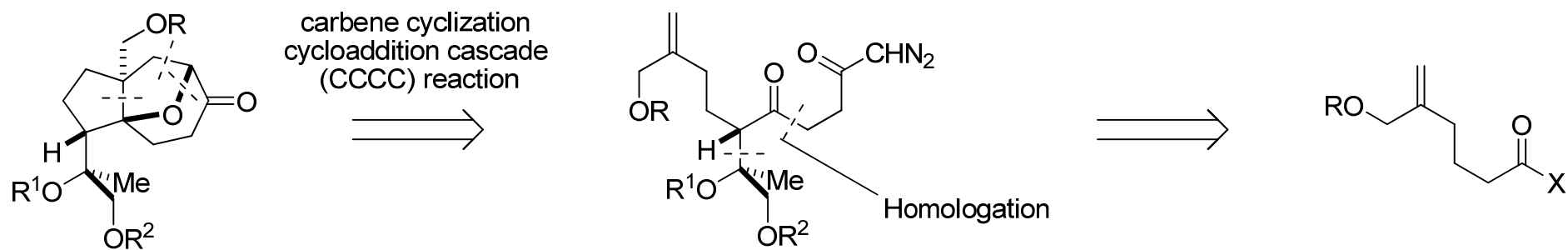
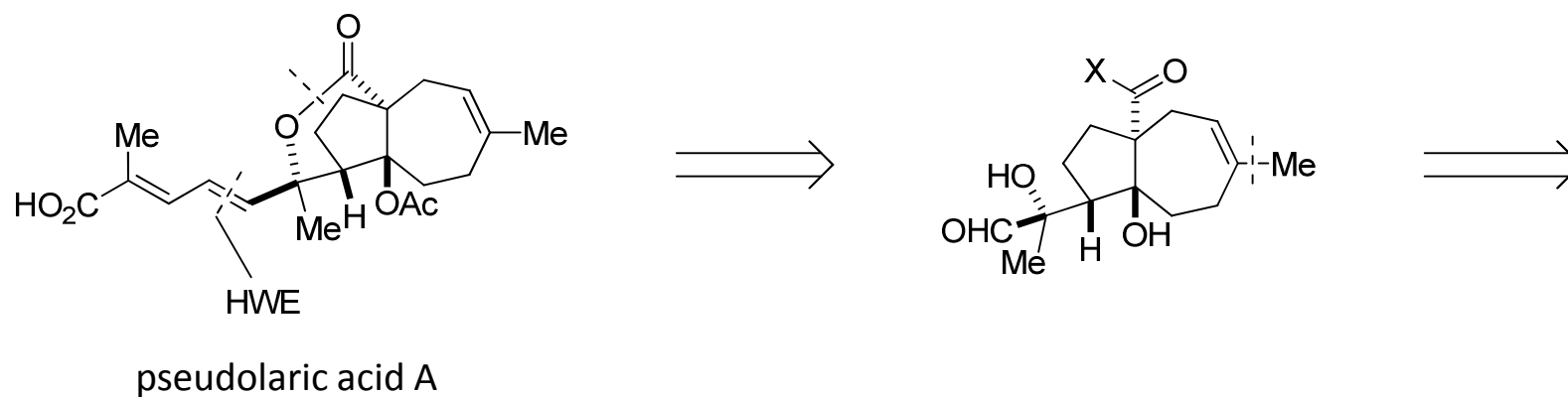
## Structural Features:

- Highly substituted tricyclic core containing 4 contiguous stereocenters
- Trans-substituted polyhydroazulene core
- Total syntheses:
  - Pseudolaric acid A: Chiu (2006),
  - Pseudolaric acid B: Trost (2008)

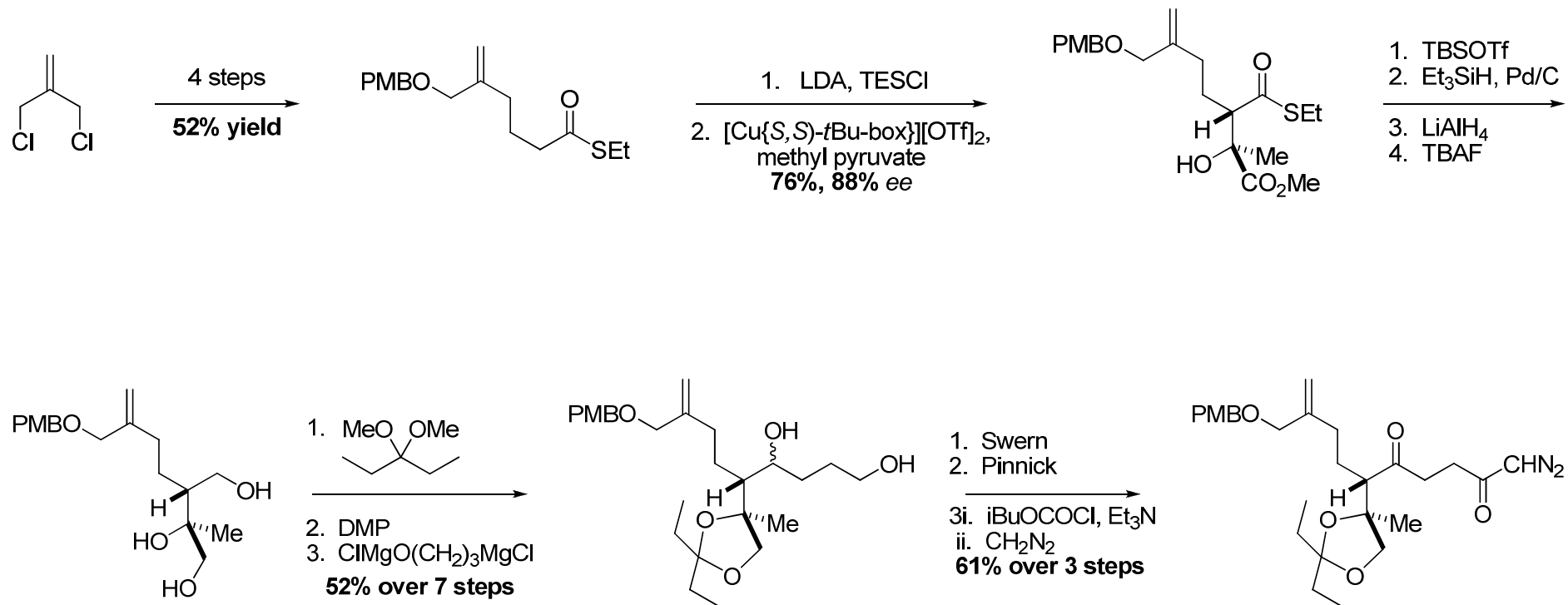


Pseudolaric acid A, R = Me  
Pseudolaric acid B, R = CO<sub>2</sub>Me

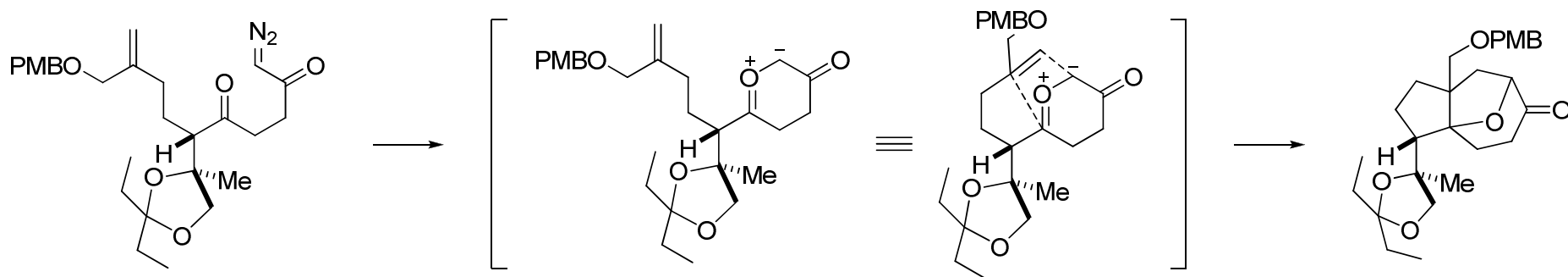
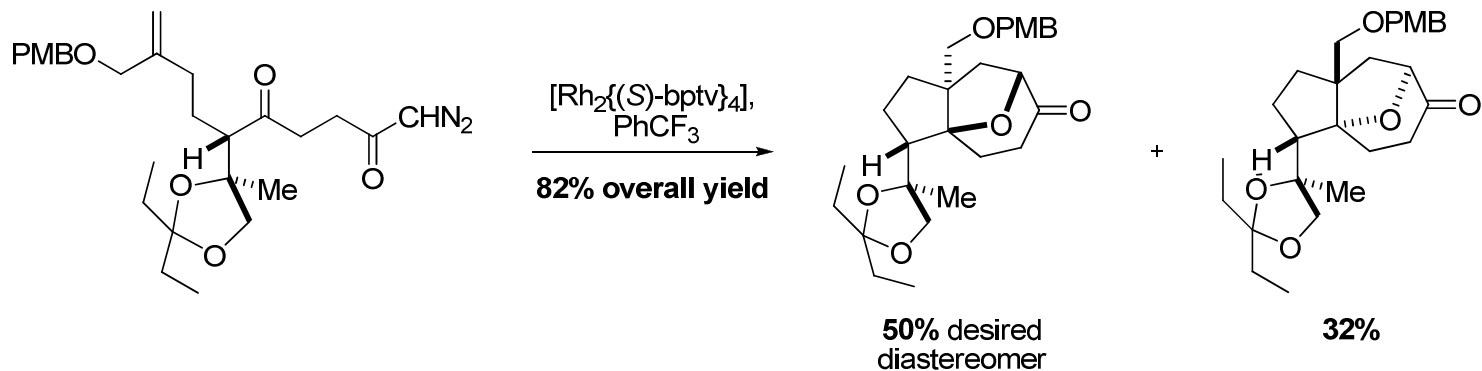
# Chiu's Retrosynthesis



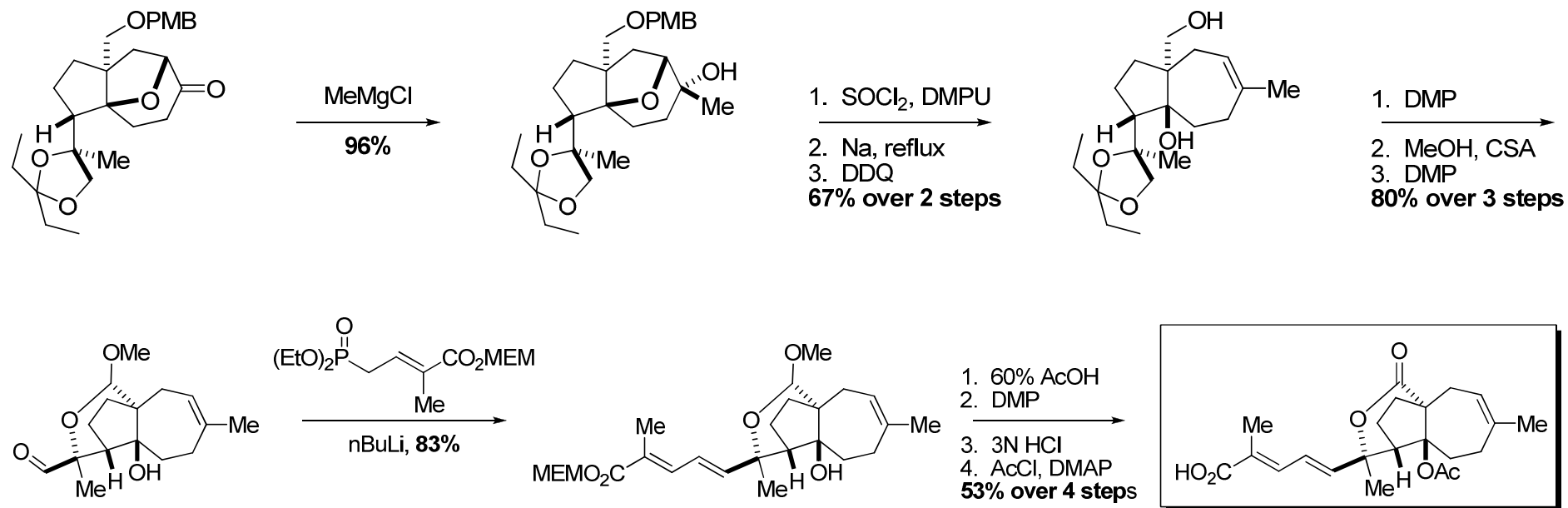
# Synthesis of the CCCC Precursor



# Cyclization Cycloaddition Cascade



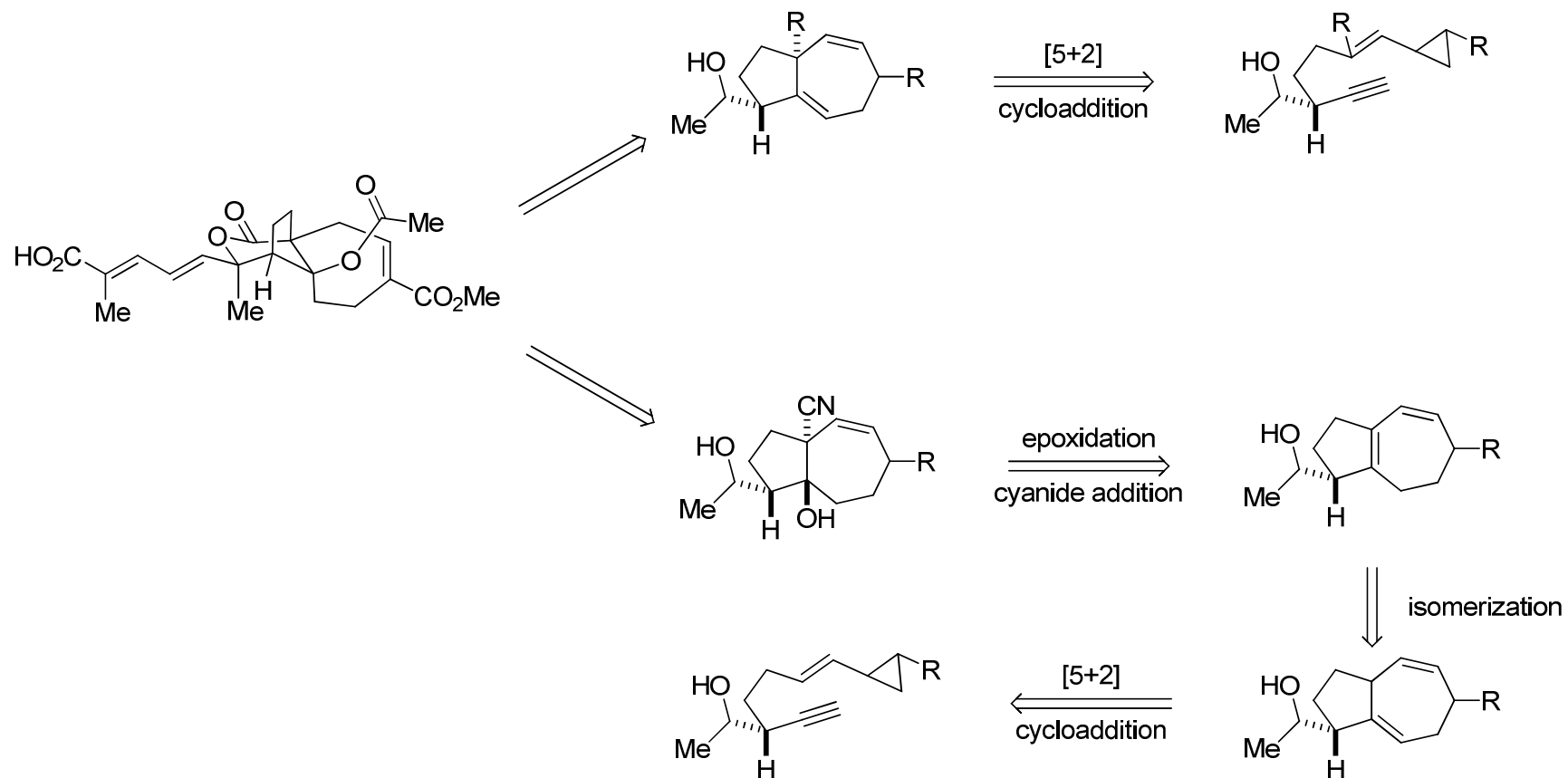
# Completion of Pseudolaric Acid A



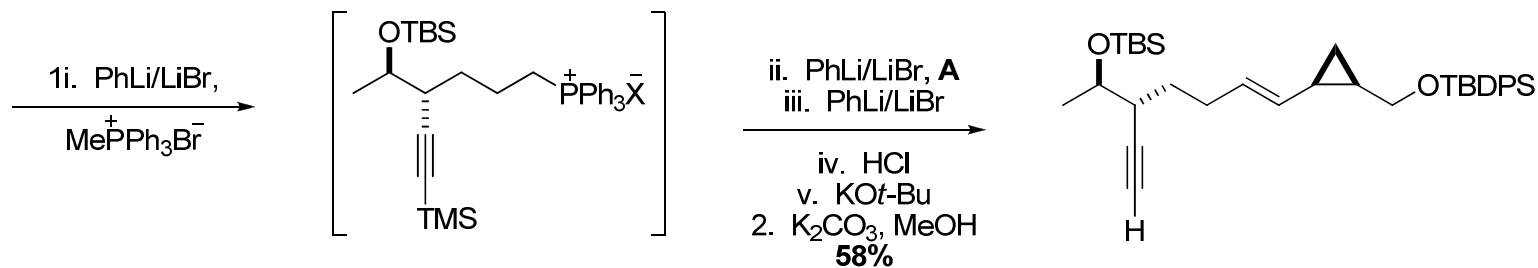
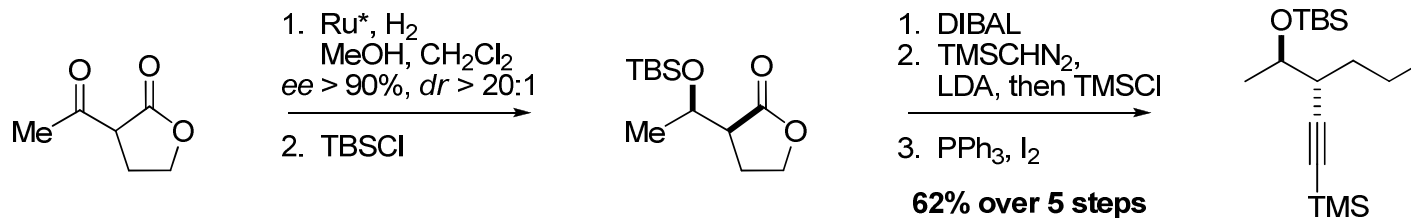
## In summary...

- Complete first total synthesis in 29 steps
- Key steps:
  - CCCC reaction
  - Cu catalyzed catalytic asymmetric aldol reaction
  - reductive elimination
- Low diastereoselectivity (1.6:1) of CCCC reaction leaves room for improvement

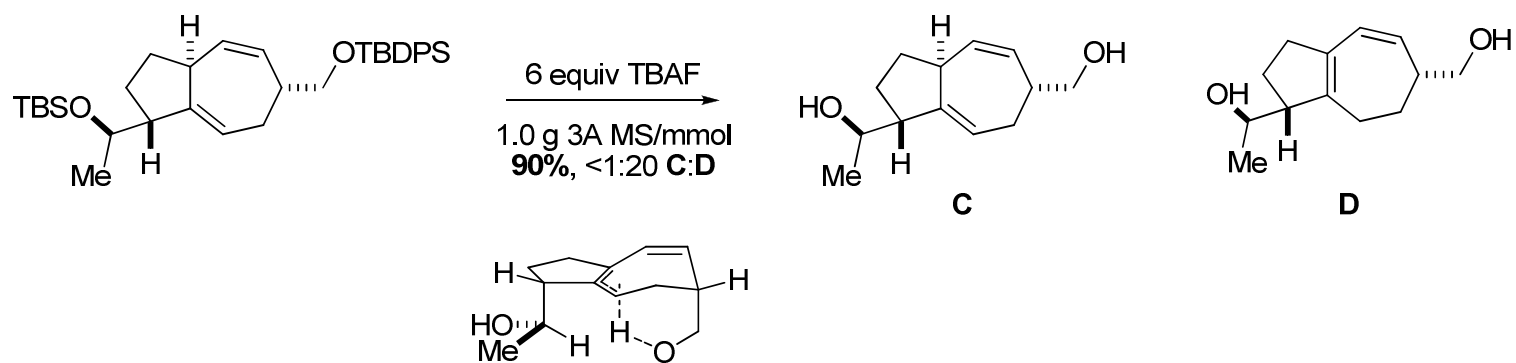
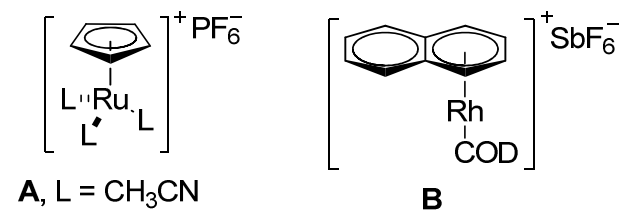
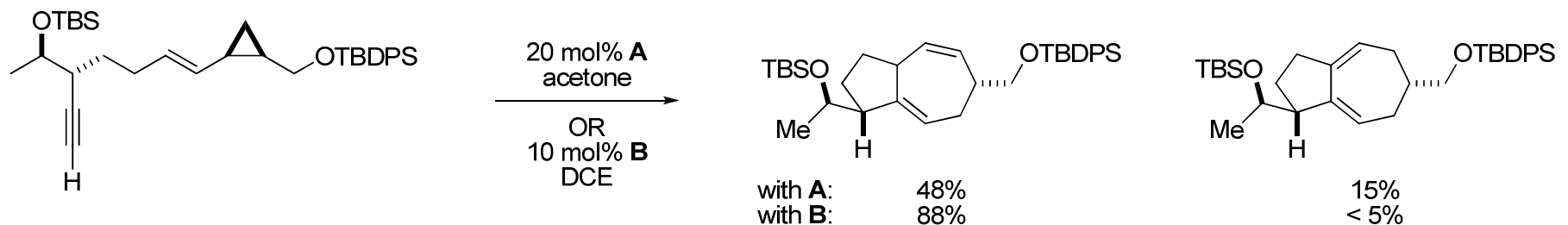
# Trost's Retrosynthesis



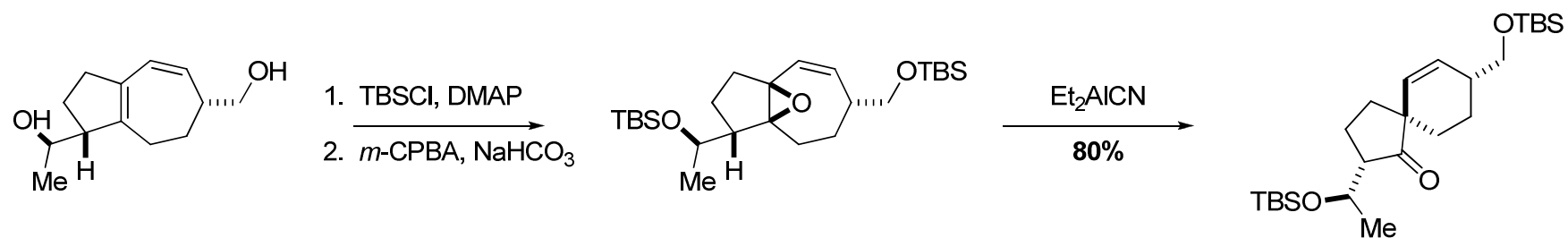
# Synthesis of the [5+2] Cyclization Precursor



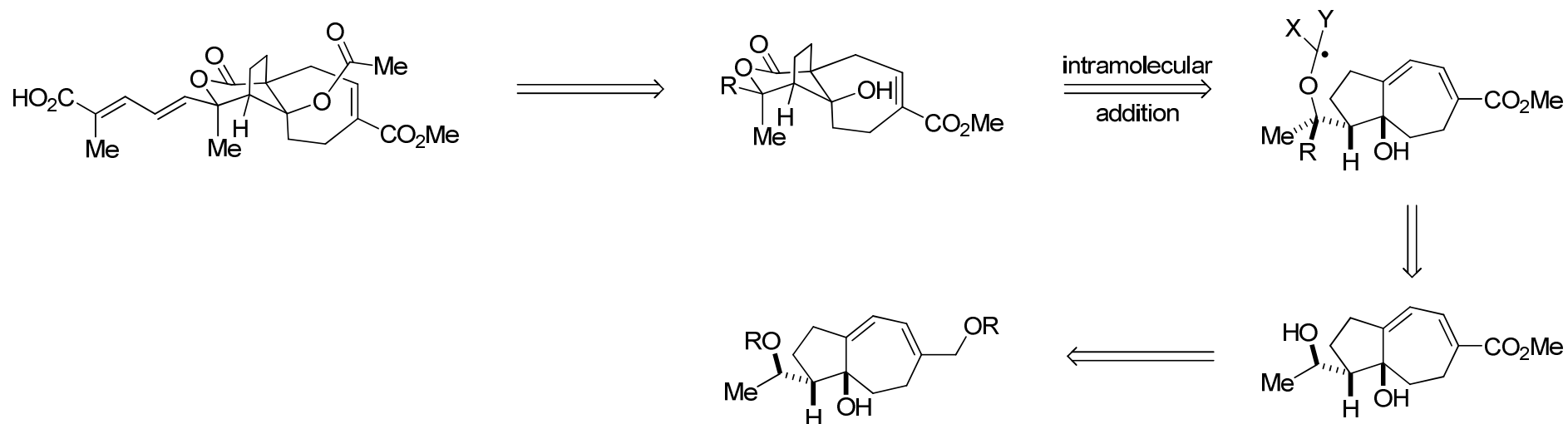
# [5+2] Cyclization and Isomerization



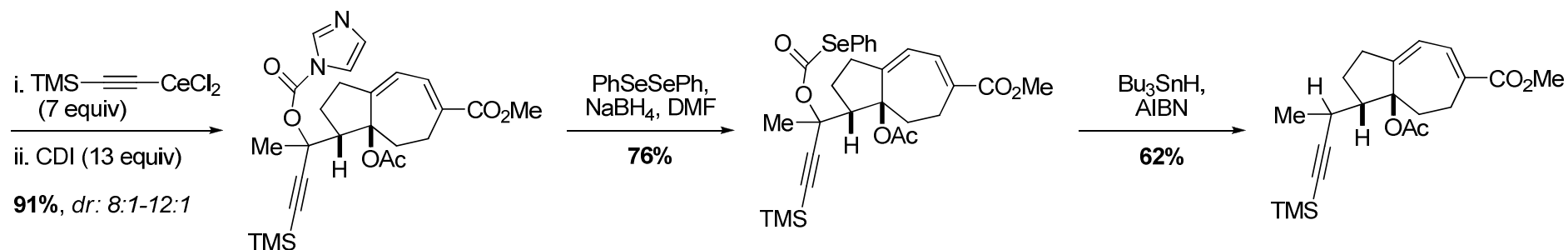
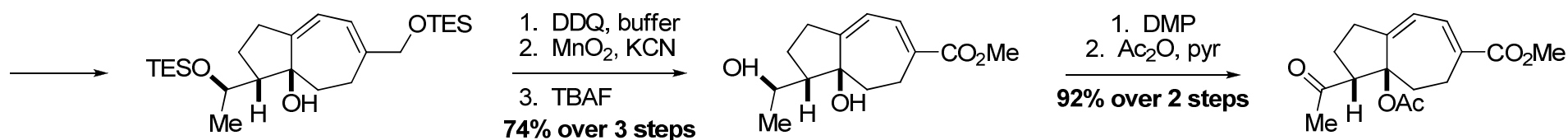
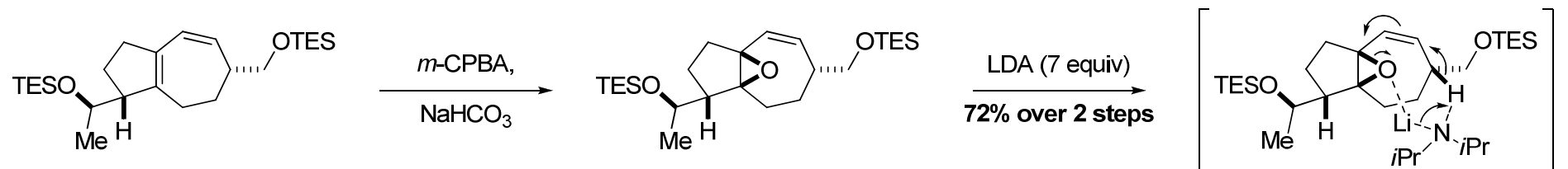
# Attempts to Install the C-10 Stereocenter via Cyanide Addition



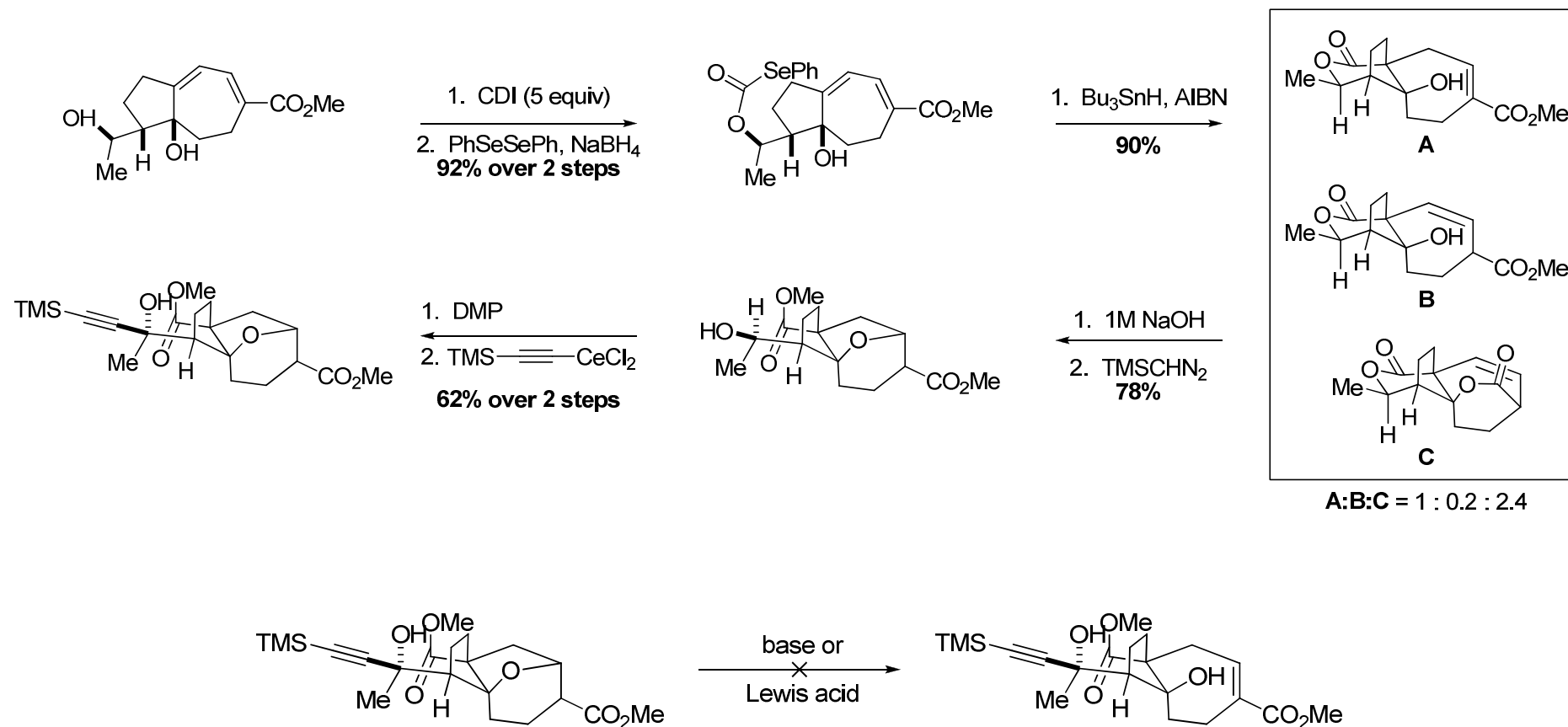
## Revised Retrosynthesis...



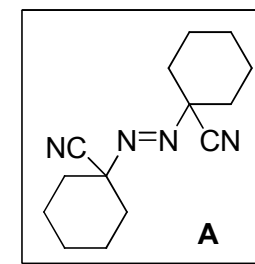
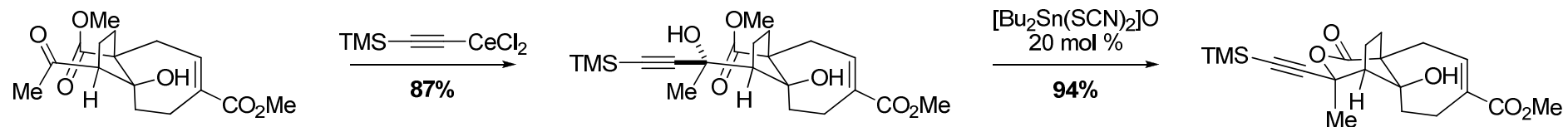
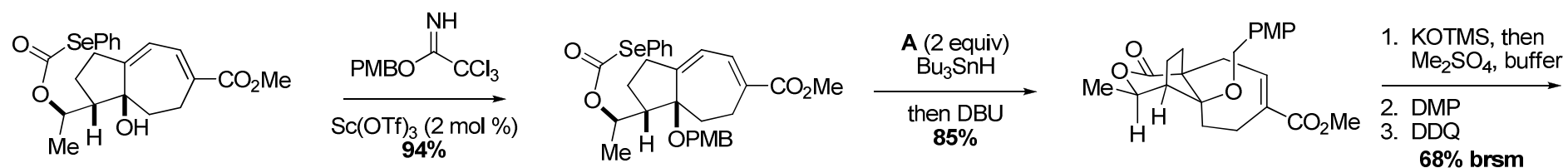
# Cyclization Attempts on the Tertiary Alkoxycarbonyl Selenide



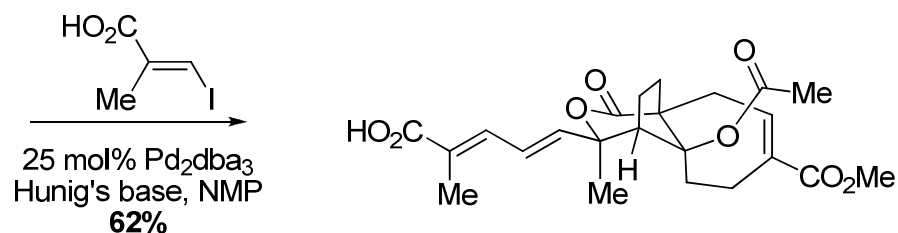
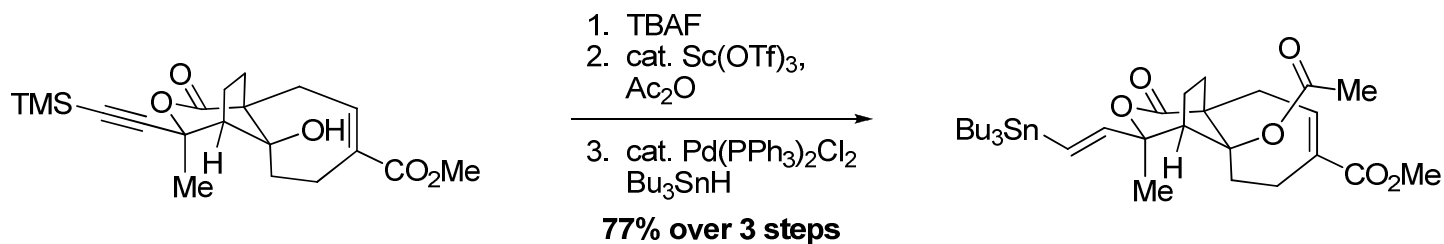
# Synthesis and Cyclization of Secondary Alkoxycarbonyl Selenide



# Synthesis and Cyclization of Secondary Alkoxycarbonyl Selenide...Take 2



# Completion of the Synthesis



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## In summary...

- Complete first total synthesis of psuedolaric acid B in 28 steps, 1.4% overall yield
- Key steps:
  - Rh catalyzed [5 +2] cyclization
  - regioselective isomerization to 1,3-diene with TBAF
  - radical cyclization