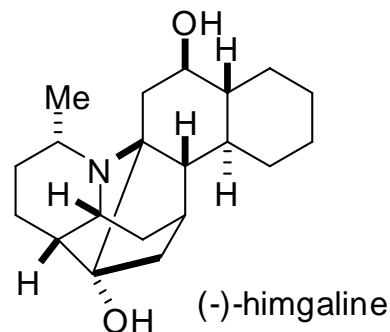




# Background

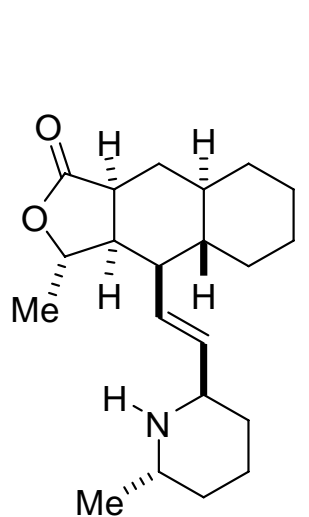
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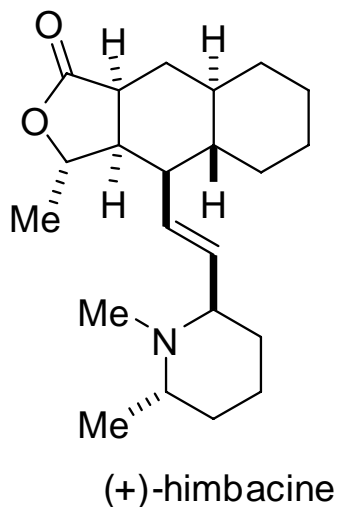
- Isolated from bark of rare rainforest tree *Galbulimima belgraveana*, found in northern Australia and Papua New Guinea (1960's)
  - Displays potent muscarinic antagonistic properties
    - Inhibition of muscarine receptors leads to increase in acetylcholine levels, possibly offsetting Alzheimer's dementia
  - SAR studies suggest *trans*-decalin substructure plays important role in the binding properties of himgaline and its congeners
-

# Congeners

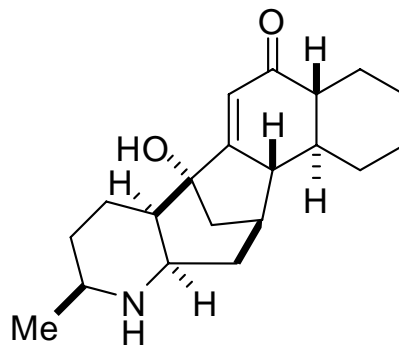
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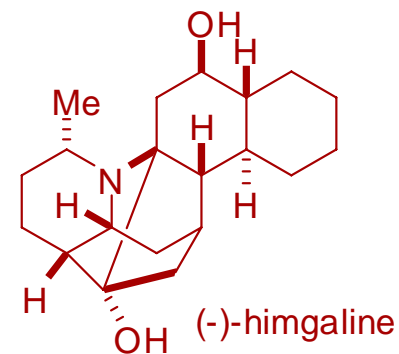
(+)-himbeline



(+)-himbacine



(-)-galbulimima alkaloid 13  
"GB 13"



(-)-himgaline

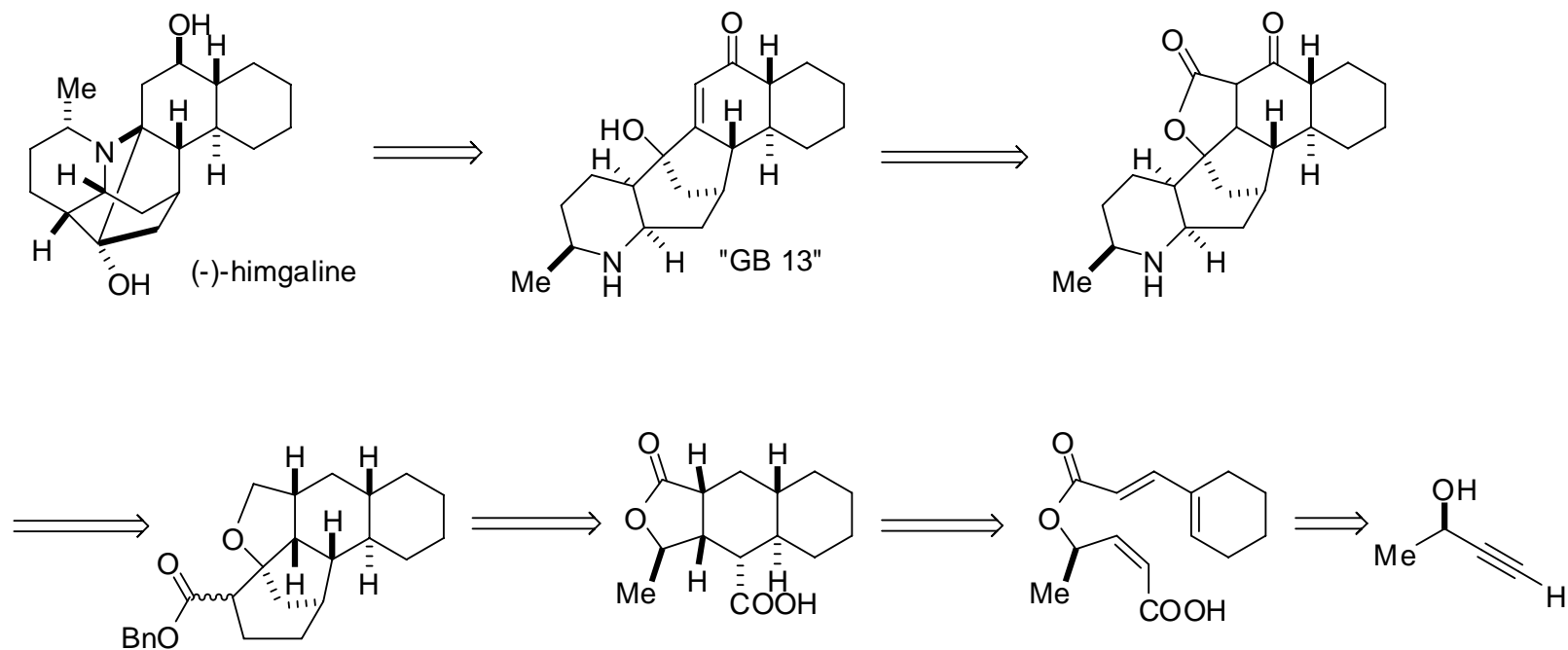
- Himbacine currently in clinical trials as an antithrombotic agent
  - "GB 13" has been used as a synthetic precursor to himgaline
-

# History of Synthetic Efforts

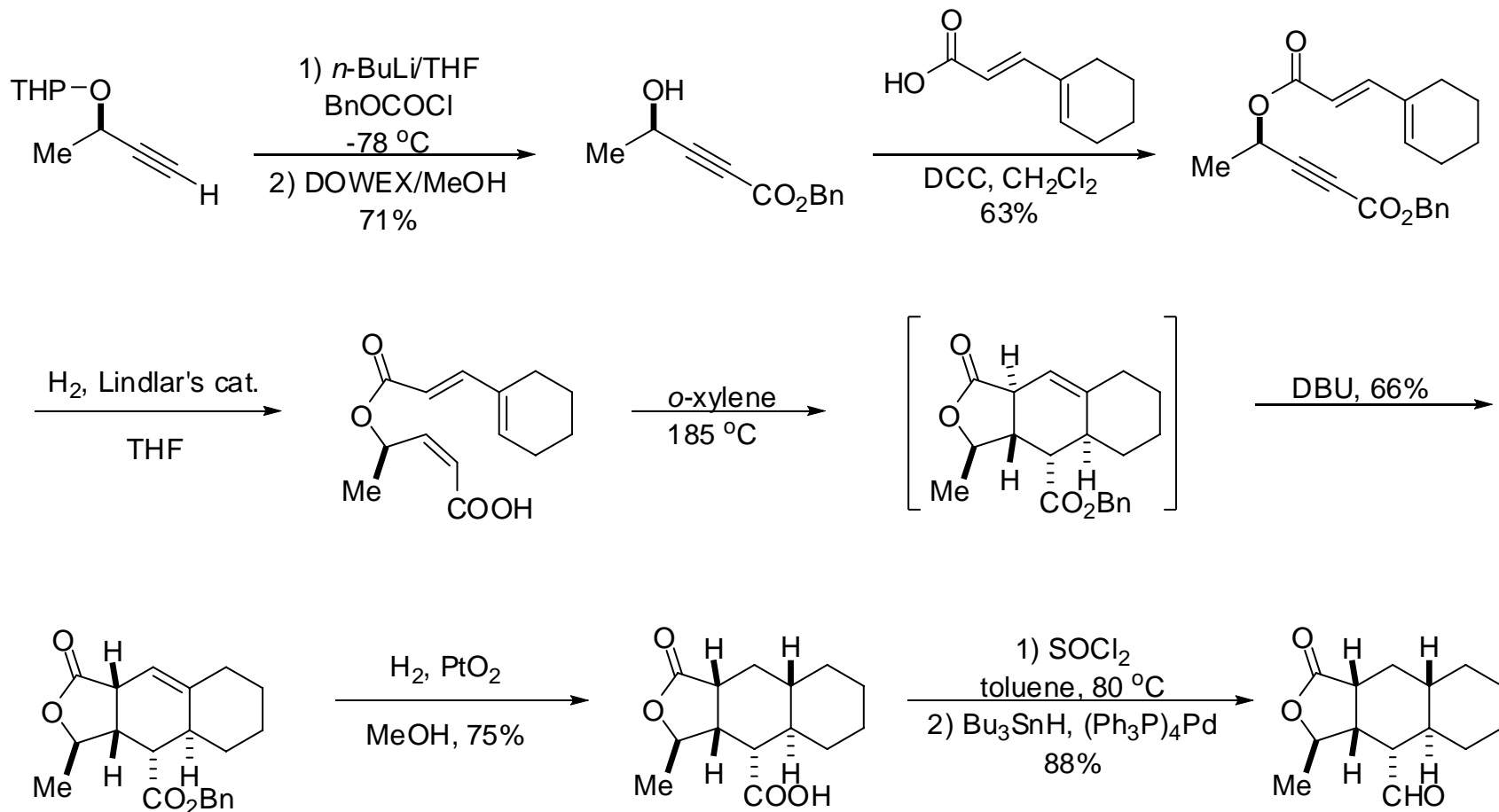
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- 1995 – First total syntheses of (+)-himbacine and (+)-himbeline (Hart and Kozikowski)
  - 2003 – Racemic synthesis of “GB 13” (Mander)
  - 2006 – Total synthesis and absolute stereochemical assignment of “(+)-GB 13” and “(-)-GB 13” (Movassaghi)
  - 2006 – Total synthesis of “(-)-GB 13” and First total synthesis of (-)-himgaline (Schering-Plough Research Institute)
  - 2007 – Total synthesis “(+)-GB 13” and (+)-himgaline (Evans)
-

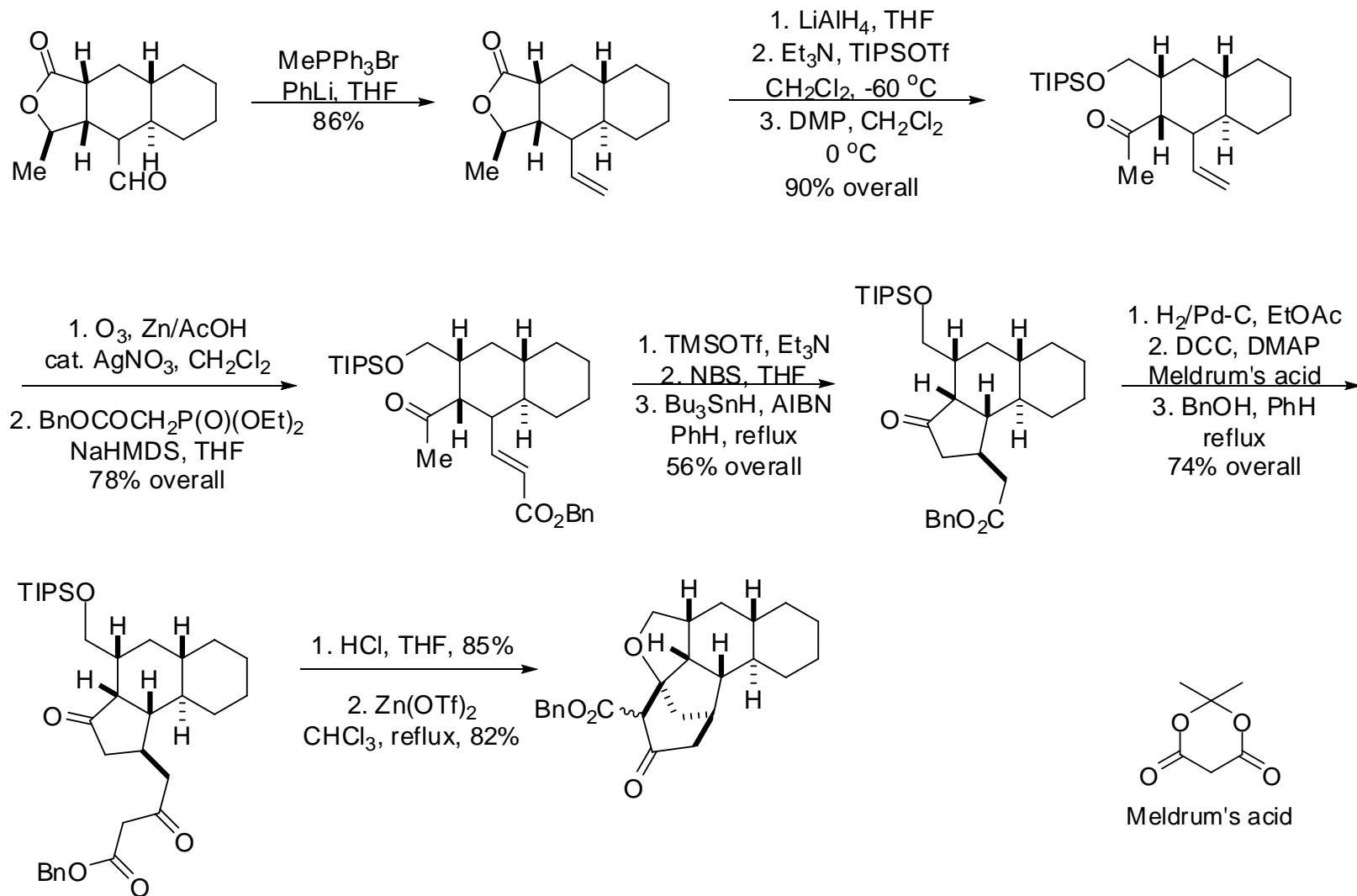
# Retrosynthesis (Schering-Plough)



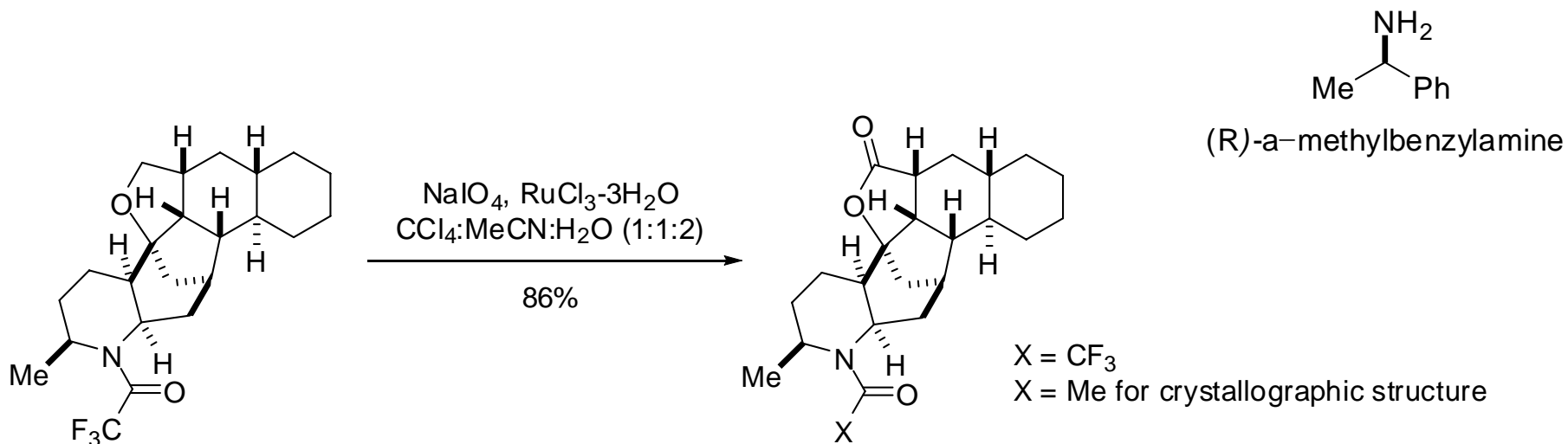
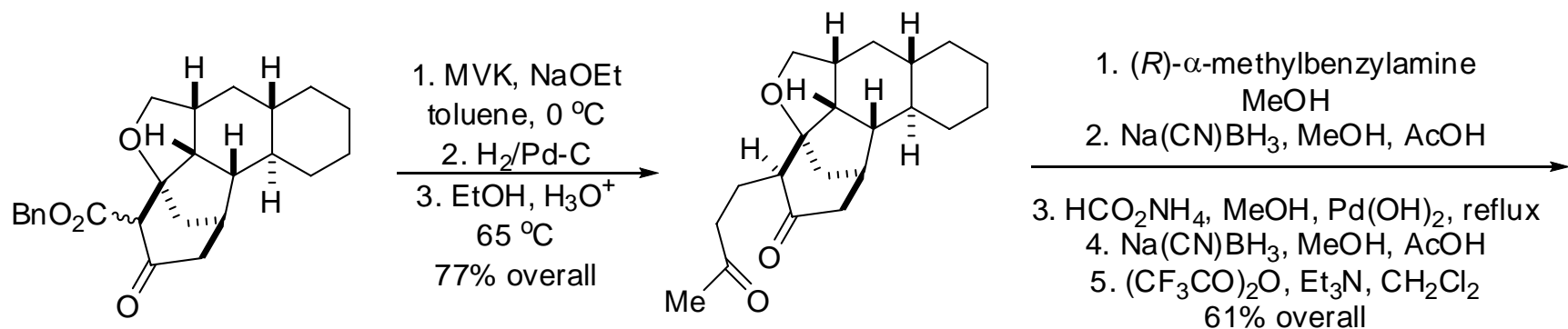
# Schering-Plough 2005



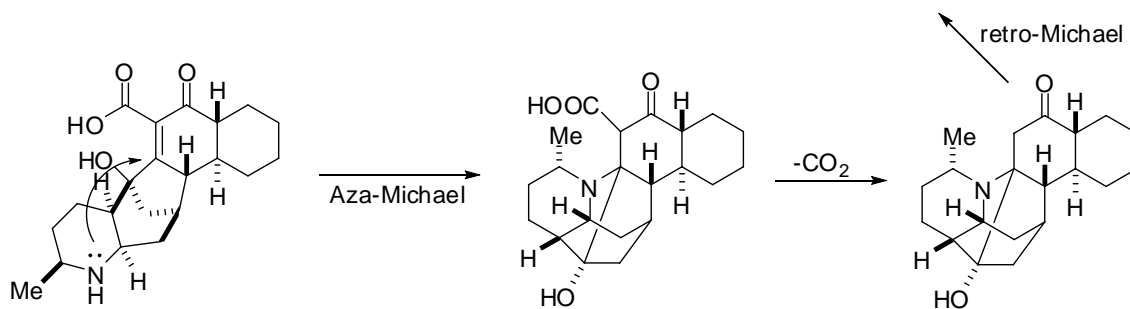
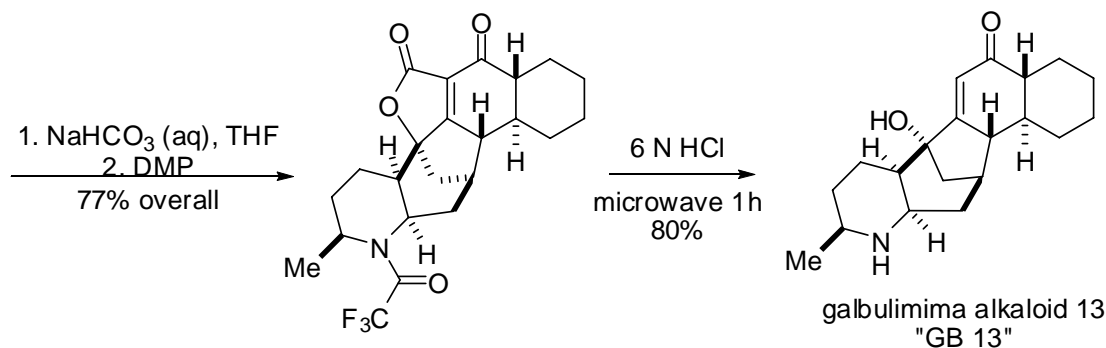
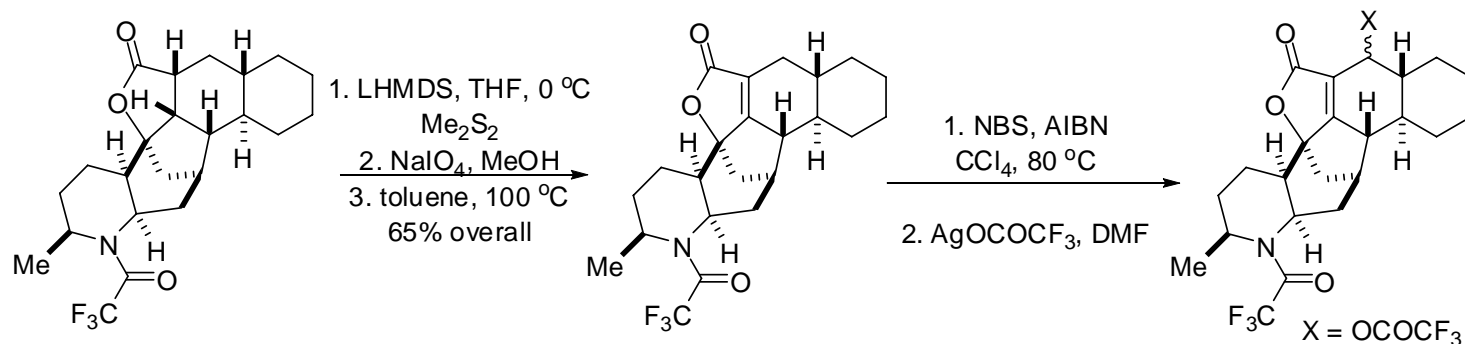
# Schering-Plough 2006



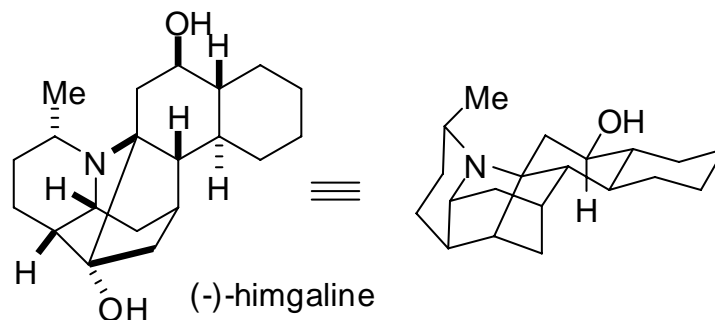
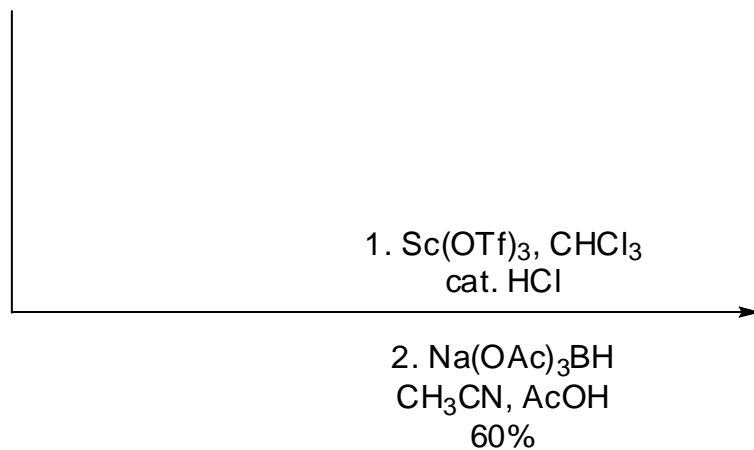
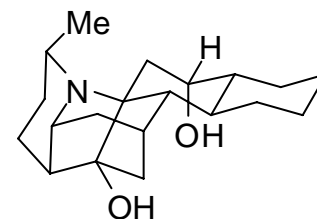
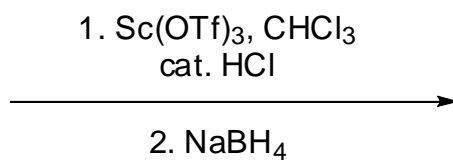
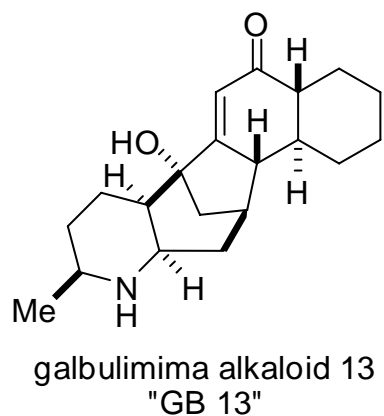
# Schering-Plough continued...



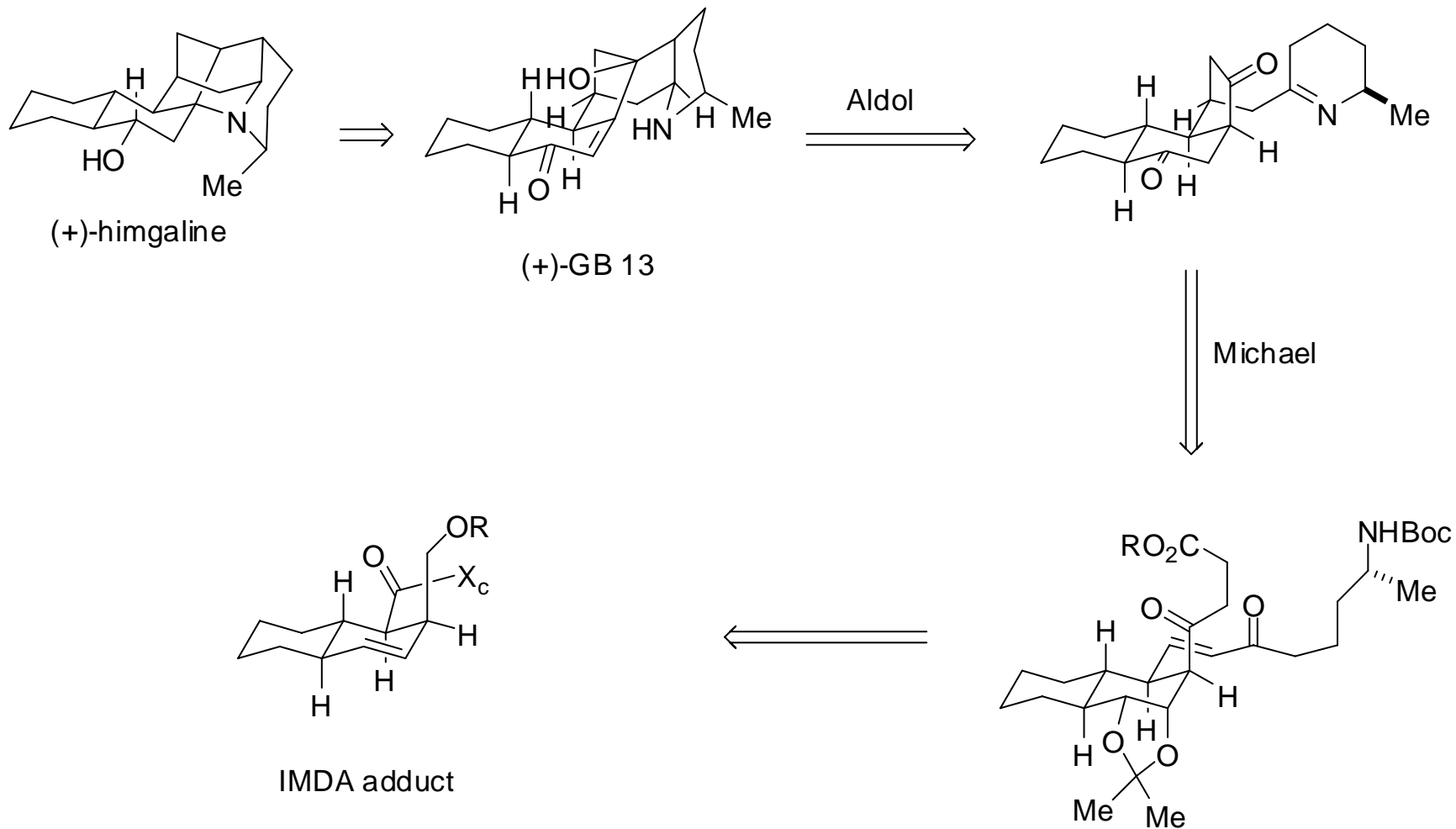
# Schering-Plough continued...



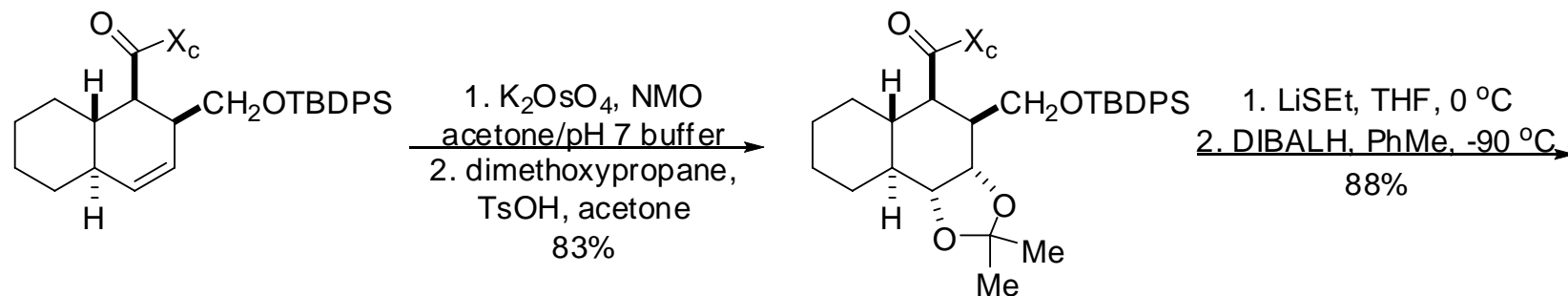
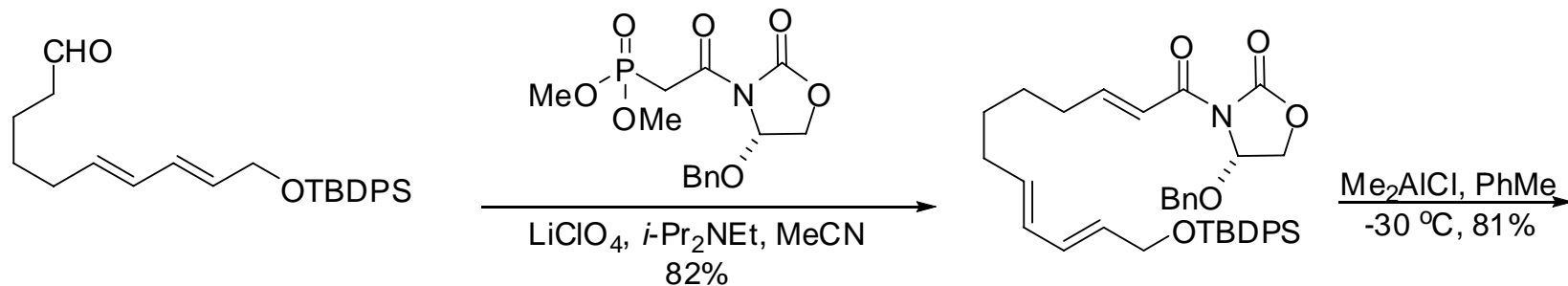
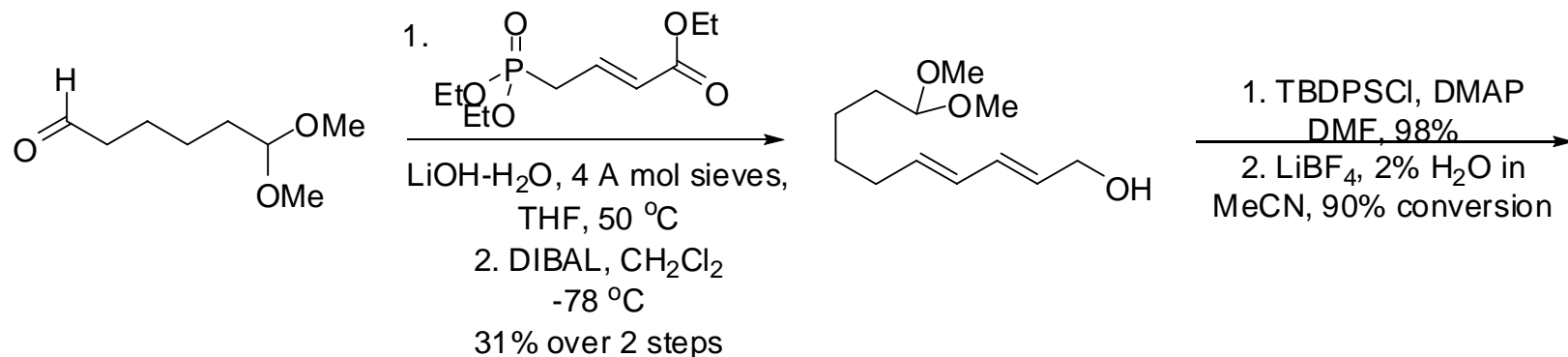
# Conversion of GB 13 to Himgaline (Schering-Plough cont'd)



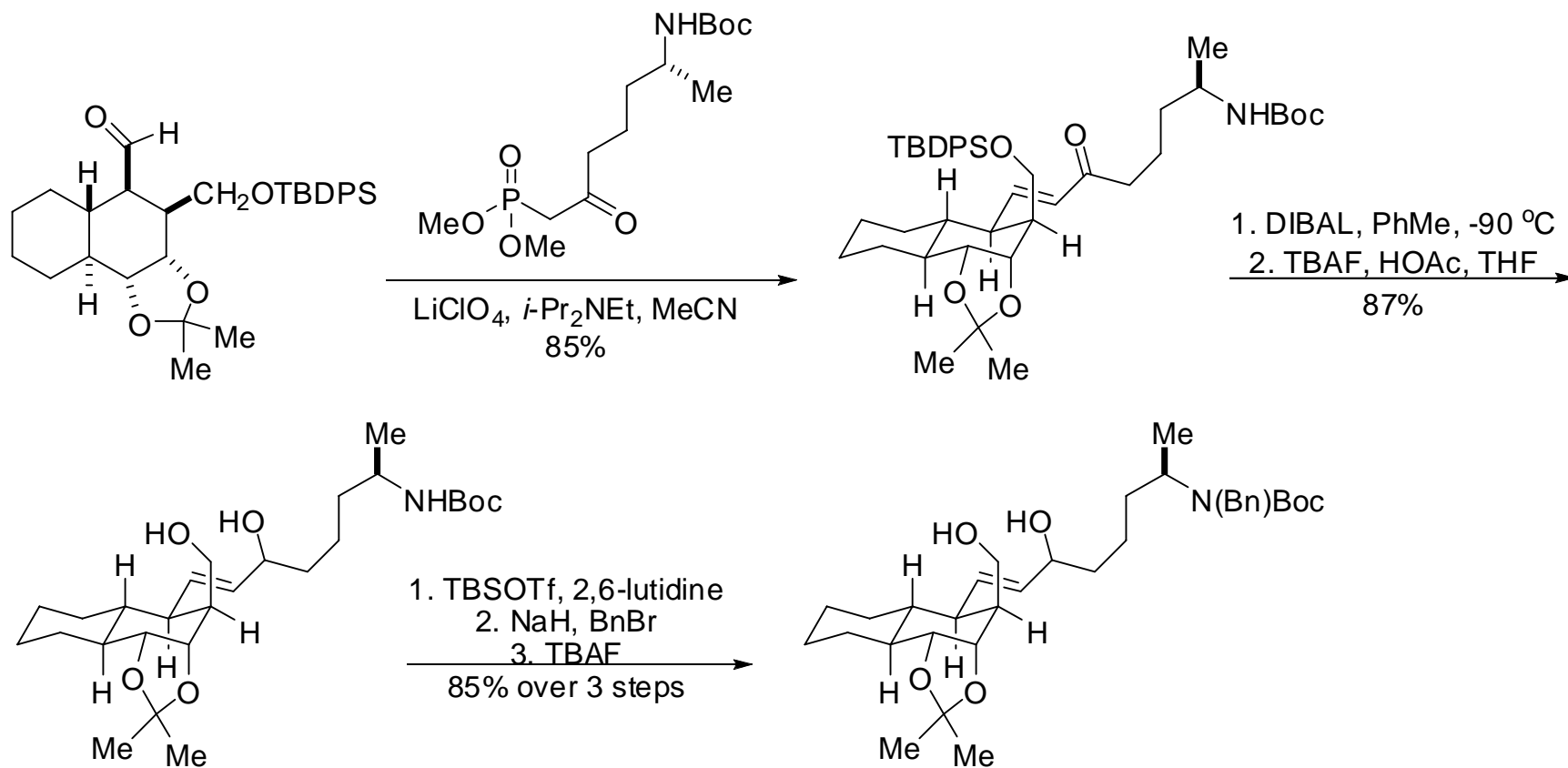
# Evans Retrosynthesis 2007



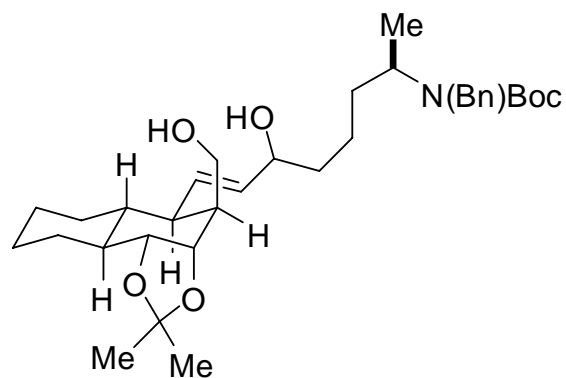
# Evans 2007 - Decalin Subunit



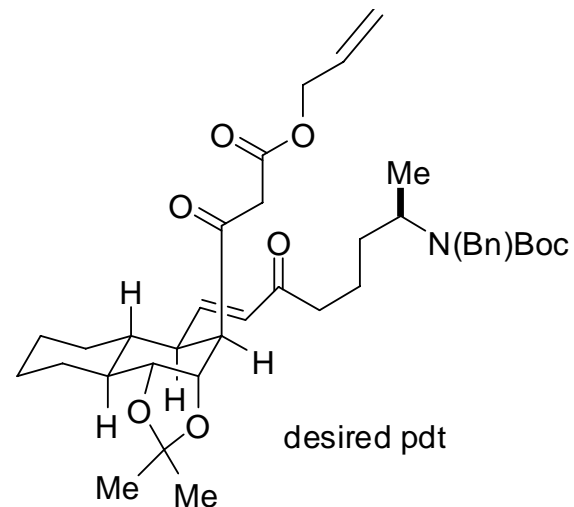
# Evans 2007 continued



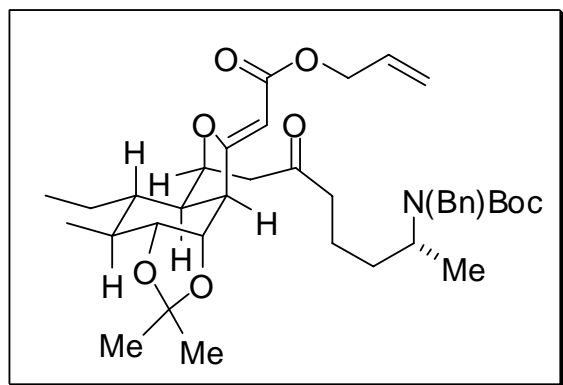
# Evans 2007 continued



1. DMP, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>  
2. allyldiazoacetate, SnCl<sub>2</sub>

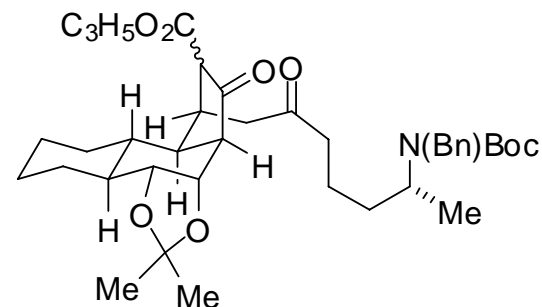


desired ptd

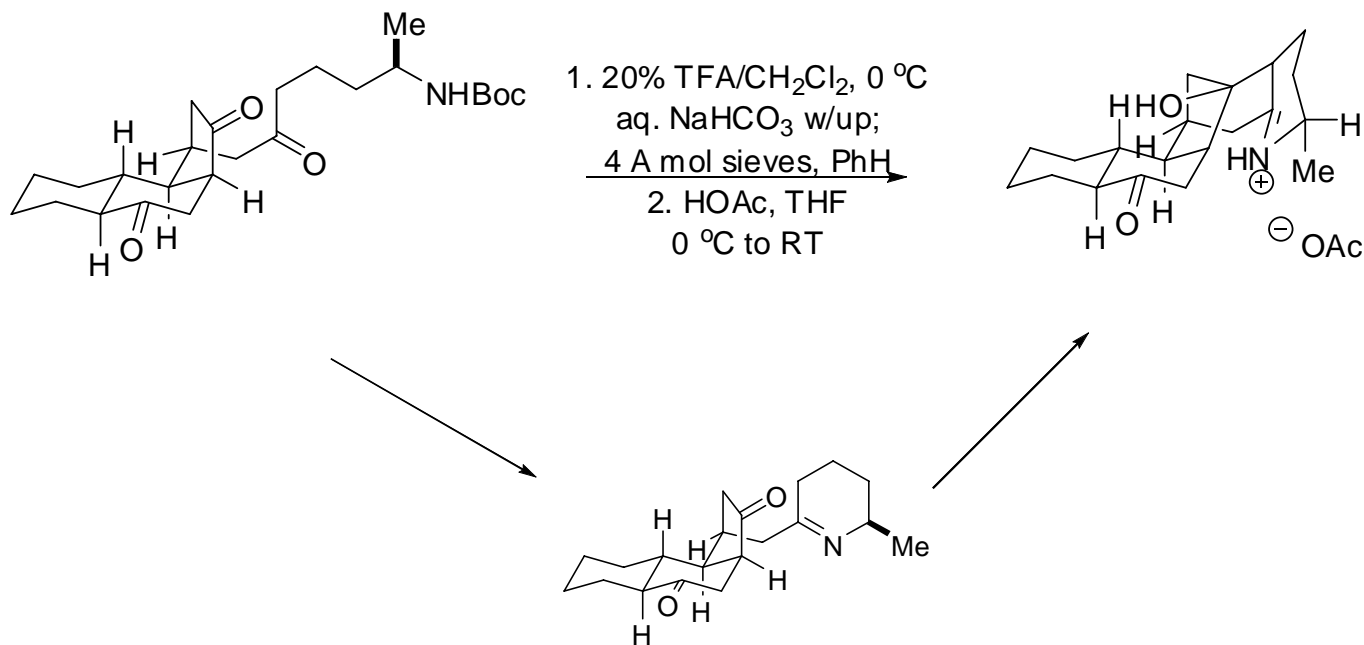
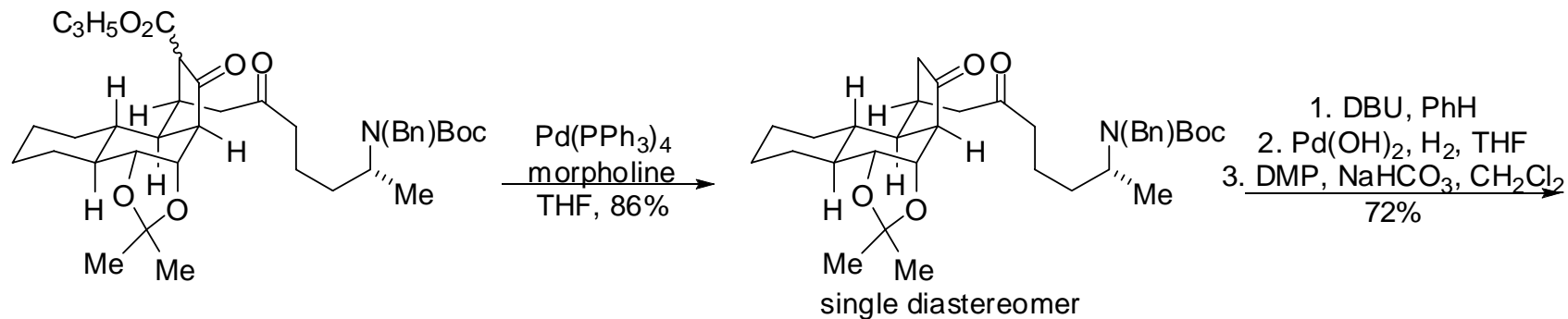


ptd obtained

LiOMe, LiClO<sub>4</sub>, Et<sub>2</sub>O  
0 °C to RT  
62% from benzyl protection

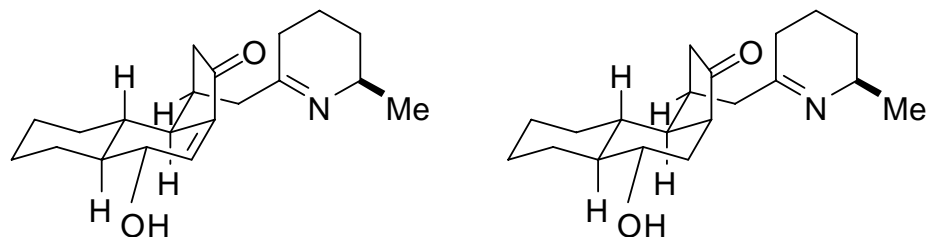


# Evans 2007 continued

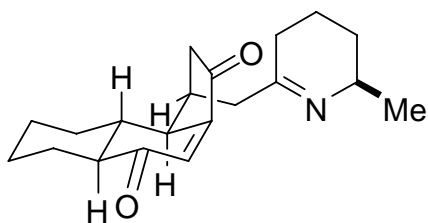


# Evans 2007- Dead Ends of Aldol Addition

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inert to a variety of reaction conditions



preference for conjugate addition over 1,2 addition

# Evans 2007 continued

