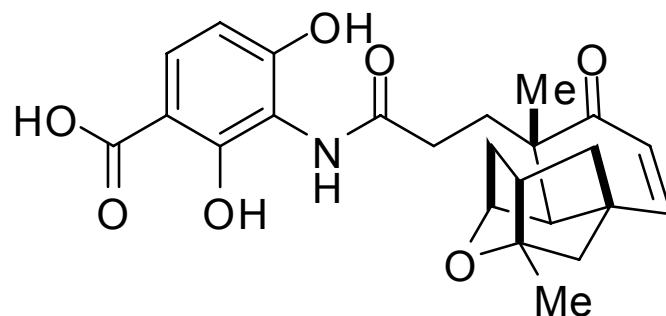


# Total Syntheses of Platensimycin

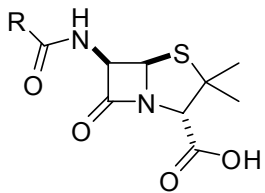


Adam M. Azman

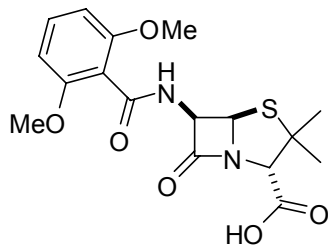
9 May 2007

# Antimicrobial Agents

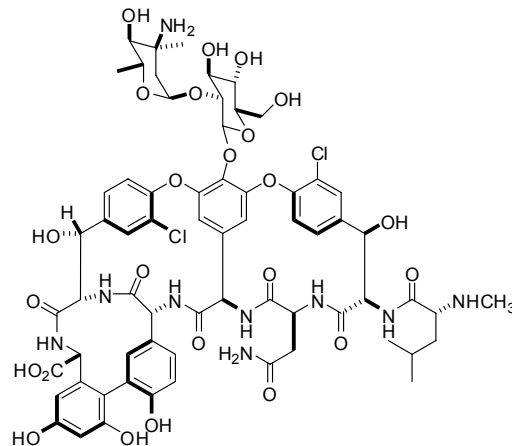
- Antibiotic refers to drugs derived wholly or partially from microorganisms
  - Antimicrobial agents can be synthetic
- 190 million doses of antimicrobials administered each day
  - 133 million courses prescribed to non-hospitalized patients each year
- First antibiotic discovered by Alexander Fleming in late 1920s (penicillin)
  - Followed by sulfonamides in late 1930s
- Penicillin not really mass produced until 1940s (WWII)
- Many new antibiotics isolated in 1940s (streptomycin, tetracycline, vancomycin)
- As resistance began to occur, synthetic antimicrobial agents prepared in 1960s (amoxicillin, ticarcillin)
- No really new classes of antimicrobial agents since cephalosporins in 1960s
- Most disrupt biosynthesis of cell wall, DNA, or proteins



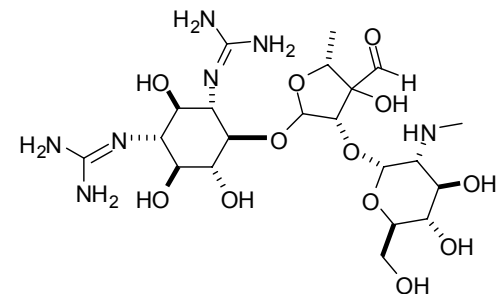
the penicillins



ticarcillin



vancomycin



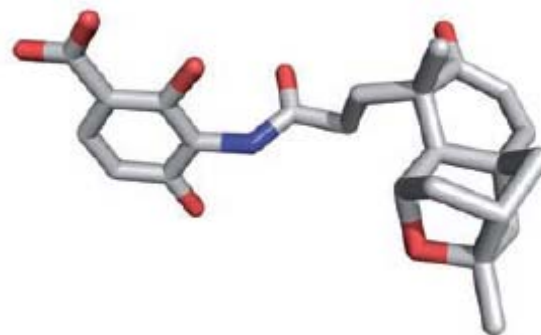
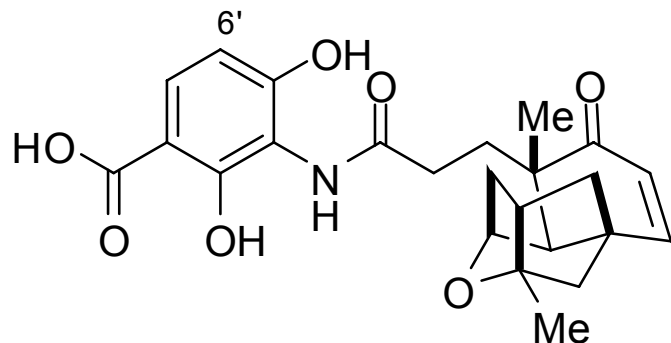
streptomycin

# Antimicrobial Resistance

- CDC: “one of the world’s most pressing public health problems”
- Causes:
  - Random mutation (bacteria can reproduce as often as every half hour)
  - Misuse of antimicrobials
    - Not taking full dosing regimen
    - Taking antimicrobials for viral infections (cold, flu, cough/sore throat (except strep throat))
- Mechanism
  - Mutation
    - Change in the antimicrobial target (i.e. DNA replication enzyme) such that bacteria can still replicate DNA, and antimicrobial agent cannot bind to enzyme
  - Destruction or Inactivation
    - Enzyme in bacteria modifies or degrades antimicrobial agent before it reaches target
  - Efflux
    - Keeps intracellular concentration of antimicrobial low by pumping antimicrobial out of cell
  - Genetic Transfer
    - DNA from a resistant bacteria are transferred into non-resistant bacteria (making them resistant, too)

# Isolation of Platensimycin

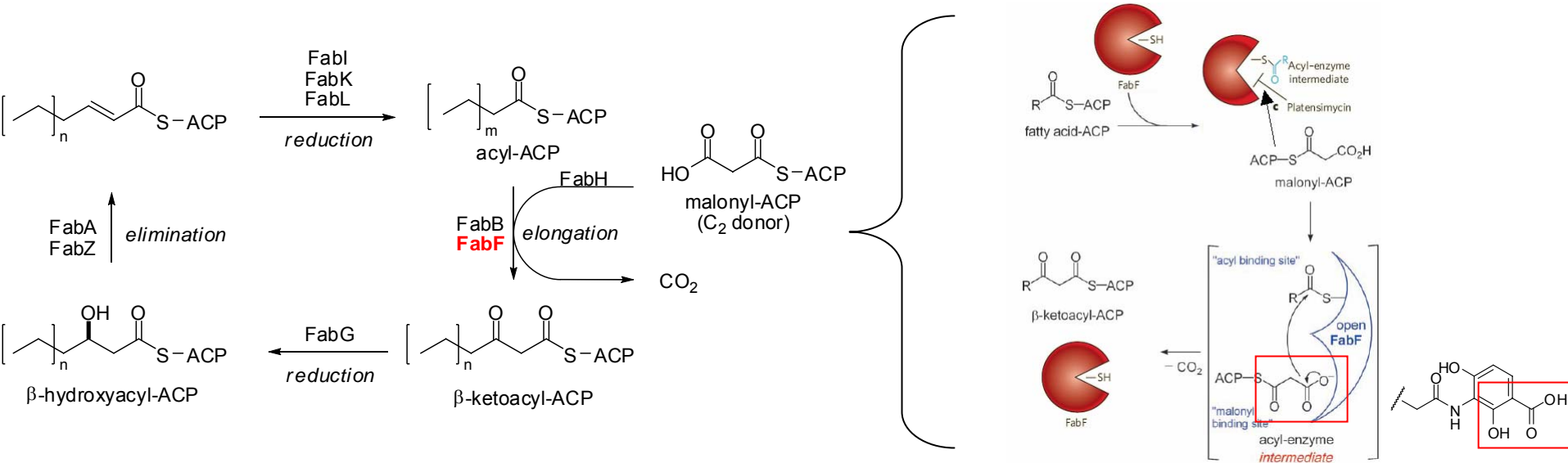
- Merck, 2006 – Antisense RNA silencing of whole-cell *Staphylococcus aureus*
  - Bacteria makes less FabF enzyme – more sensitive to chemicals targeting that enzyme
- Screen of 250,000 natural product extracts led to platensimycin
- Isolated from *Streptomyces platensis*, a bacterium recovered from South African soil sample (2-4 mg/L fermentation broth)
- Active against Meticillin Resistant *Staph. aureus* (MRSA) & Vanomycin Resistent Enterococcus (VRE)
- Various NMR, MS to determine structure
- X-ray of 6'-bromo derivative established absolute stereochemistry



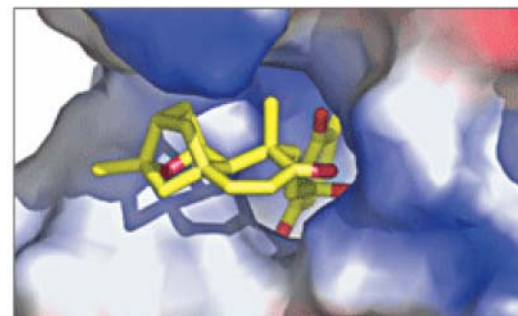
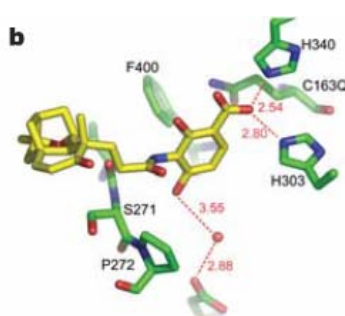
Active confirmation  
of platensimycin

# Biology

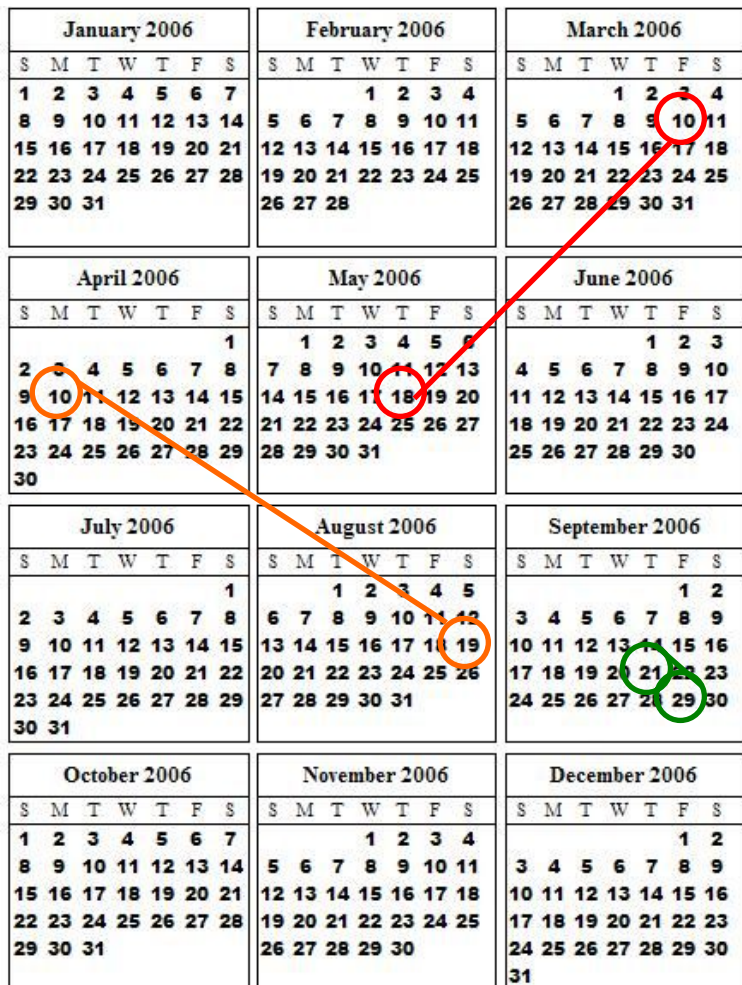
- Targets fatty-acid biosynthesis
  - FAB organized differently in bacteria (many enzymes from discrete genes) and humans (multifunctional protein encoded from single gene)
- Targets  $\beta$ -ketoacyl-ACP (acyl-carrier-protein) synthase, AKA FabF



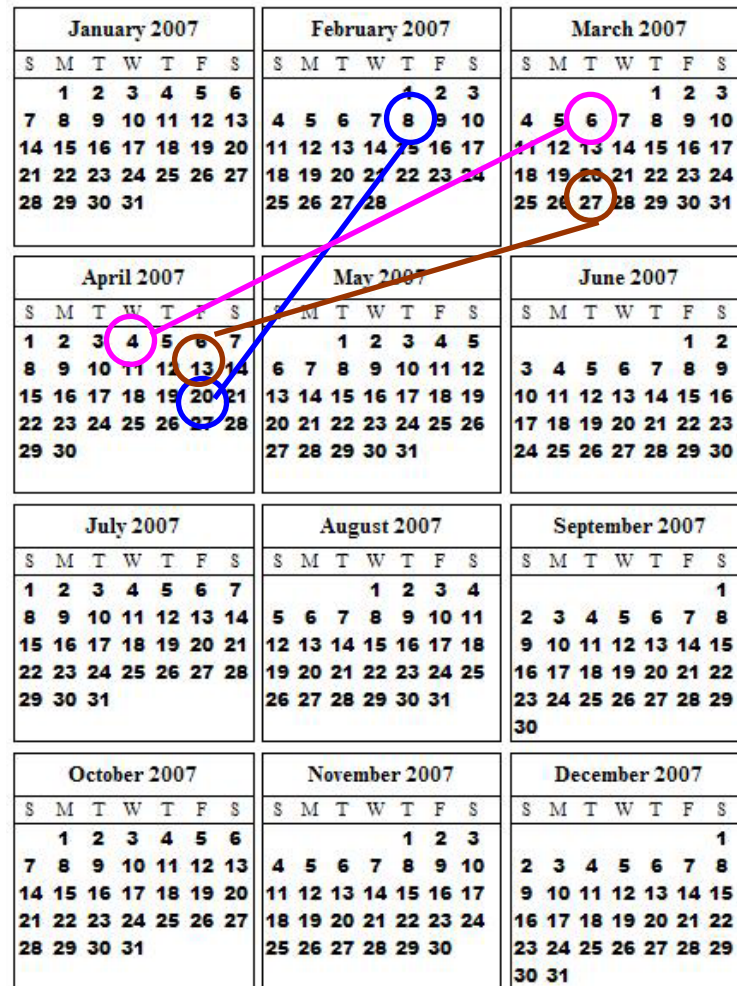
- Platensimycin binds only to enzyme w/ attached acyl group – short lived (milliseconds)
  - Merck created acyl-enzyl mimic by substituting cysteine with glutamine



# Timeline – Reception to Publication



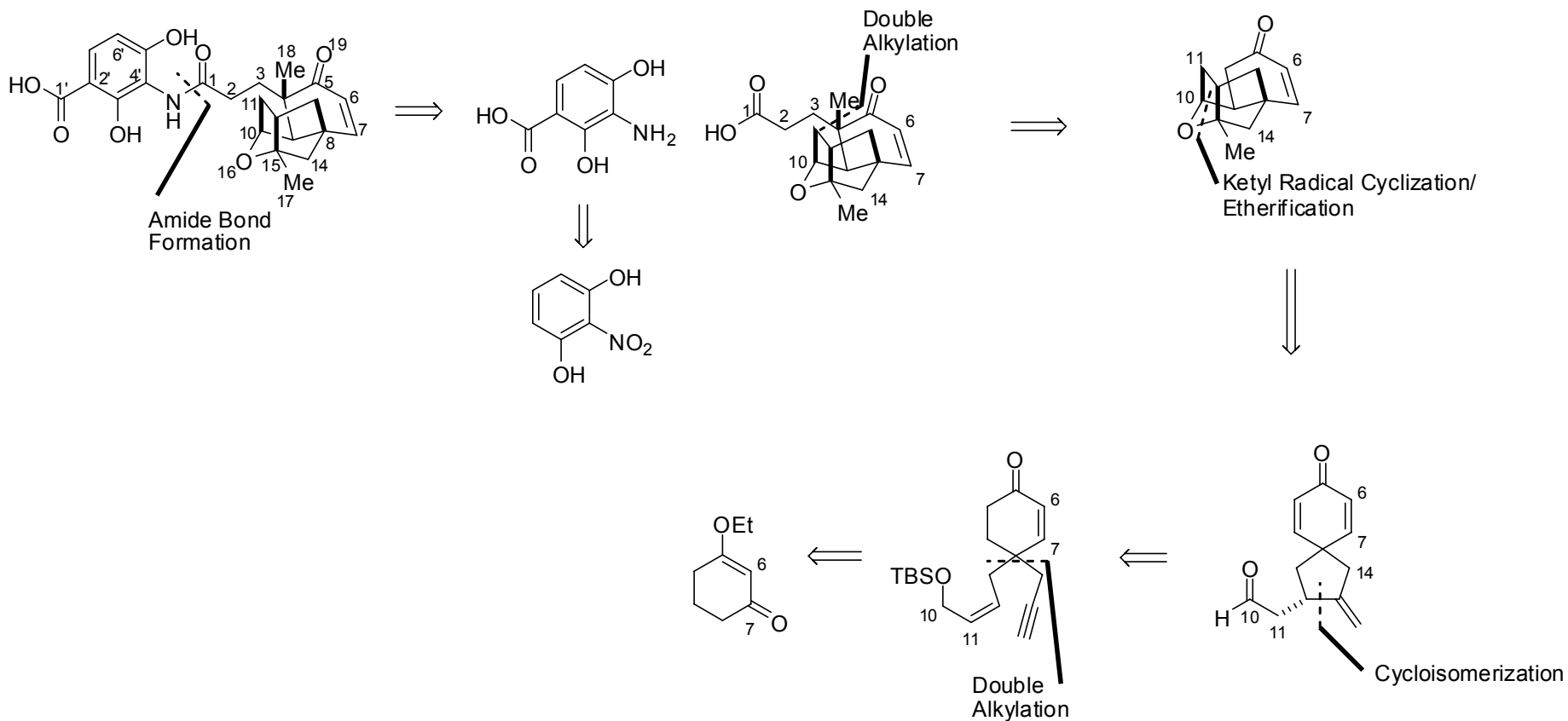
MERCK Isolation, *Nature*, 69 days  
(3 articles in this issue)  
 MERCK Isolation, *JACS*, 131 days  
 NICOLAOU Racemic Total Synthesis,  
*ACIEE*, 8 days



NICOLAOU Asymmetric Total Synthesis,  
*ACIEE*, 71 days  
 SNIDER Racemic Formal Synthesis,  
*Org. Lett.*, 29 days  
 NICOLAOU Racemic Formal Synthesis,  
*Chem. Commun.*, 17 days

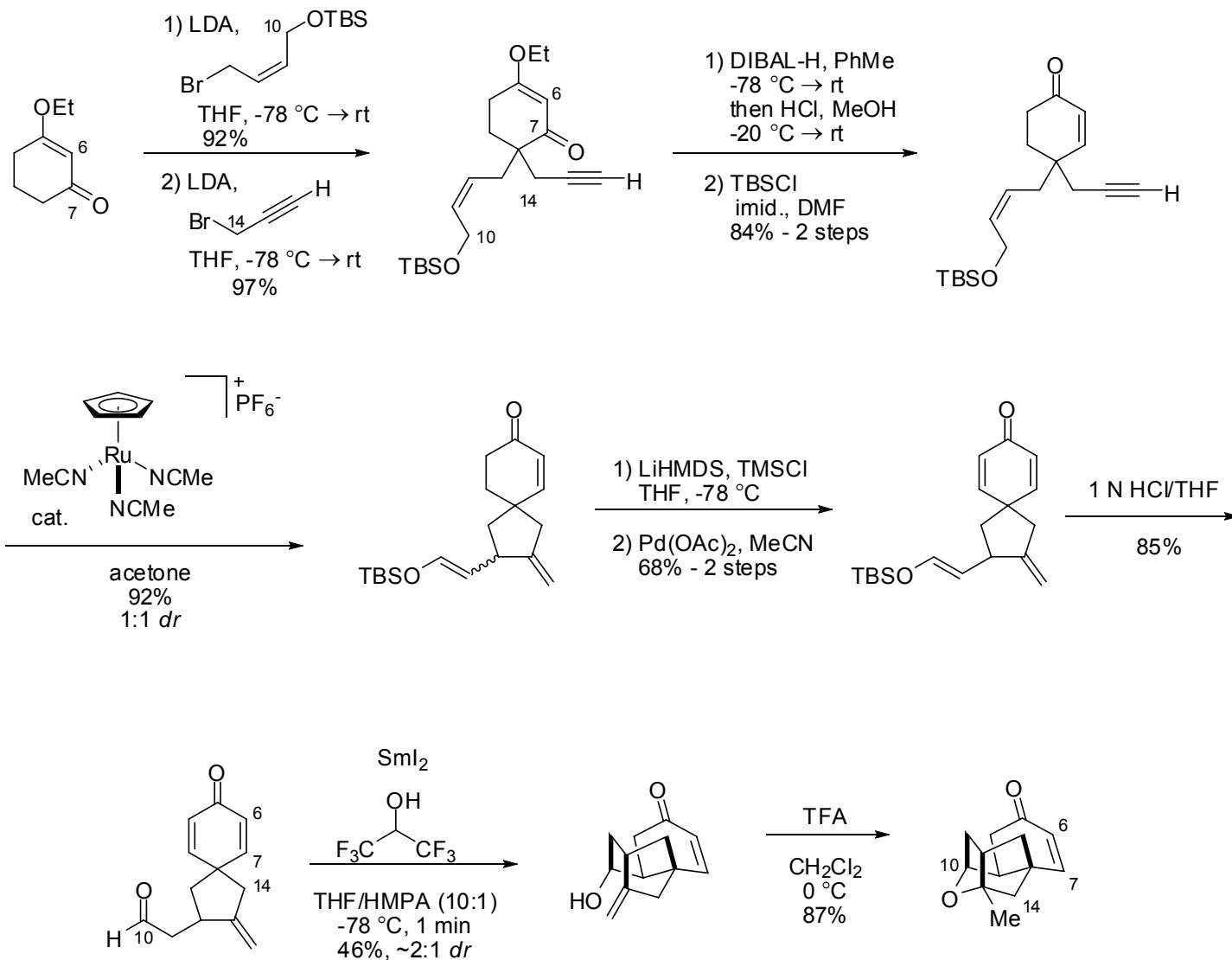
# Nicolaou's Racemic Total Synthesis

- Retro:

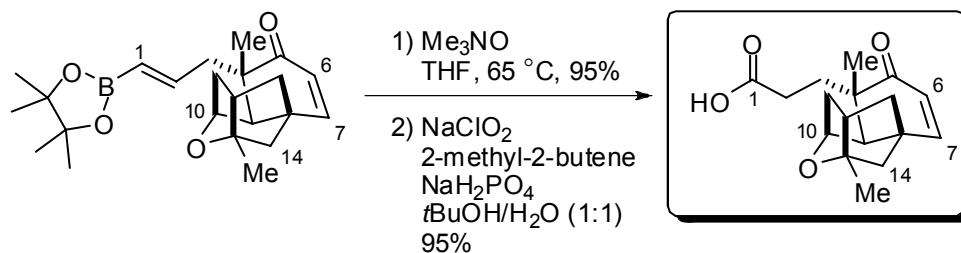
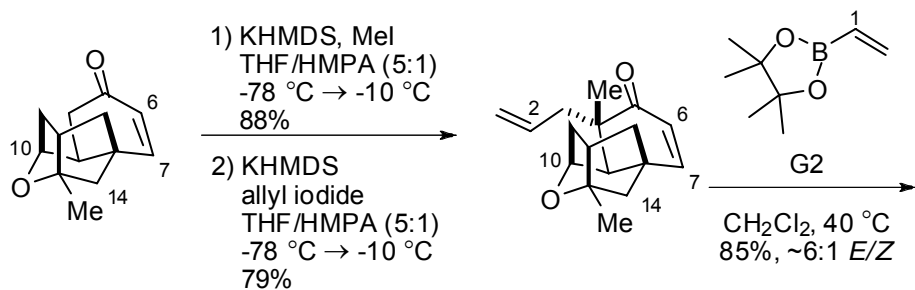


# Nicolaou's Racemic Total Synthesis

- Multi-cycle:

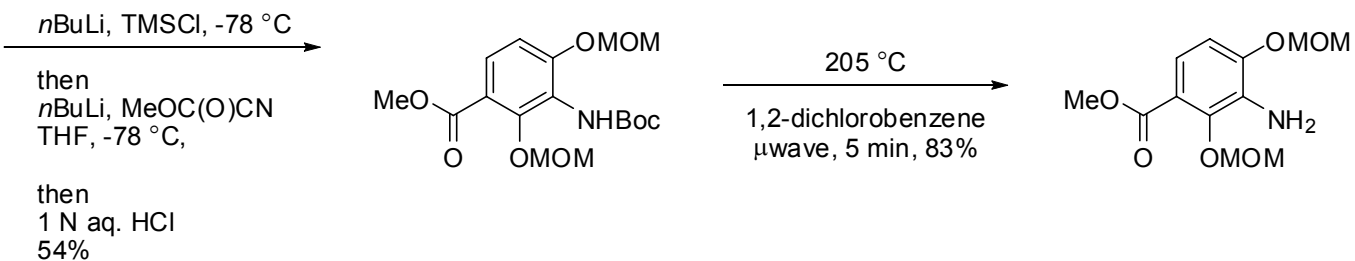
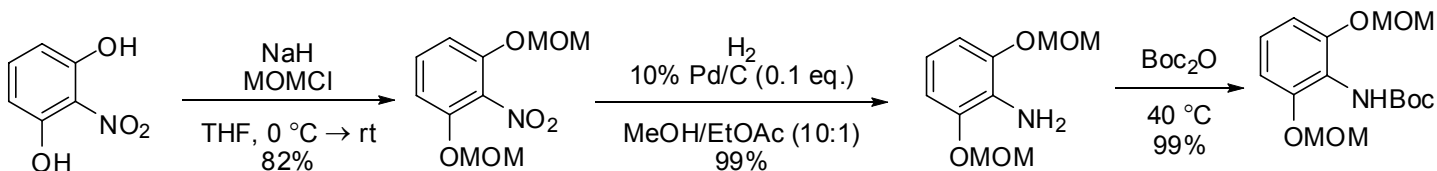


# Nicolaou's Racemic Total Synthesis



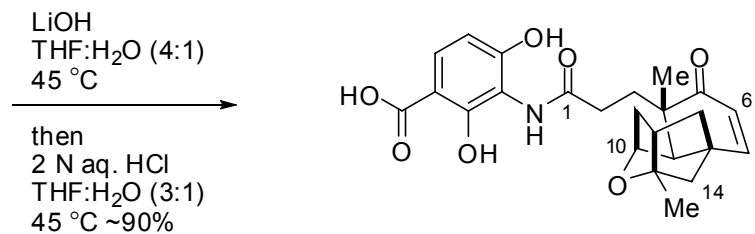
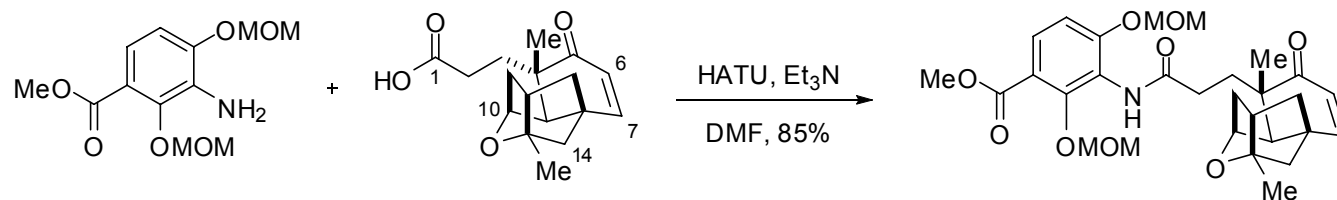
# Nicolaou's Racemic Total Synthesis

- Aromatic Amine:



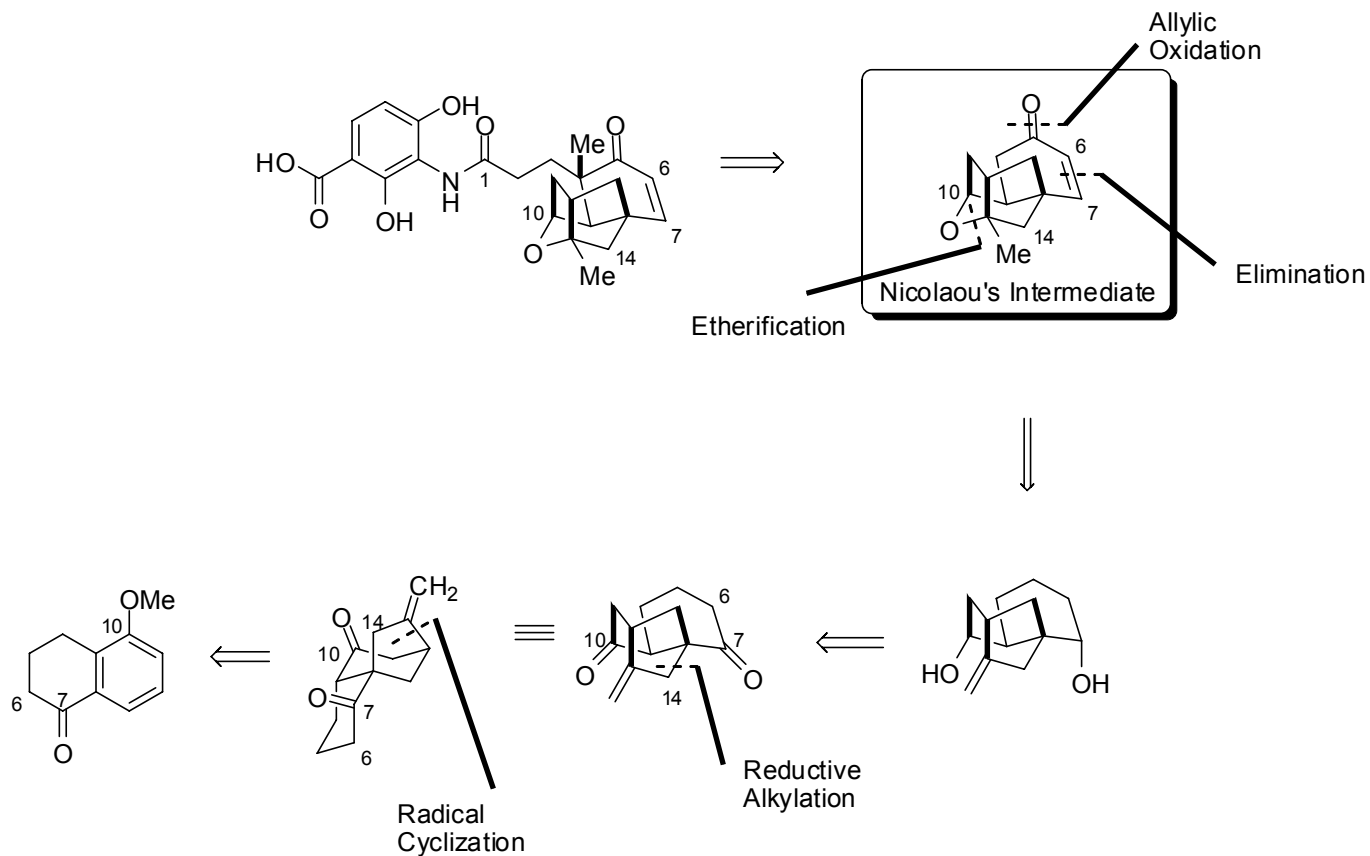
# Nicolaou's Racemic Total Synthesis

- End Game:



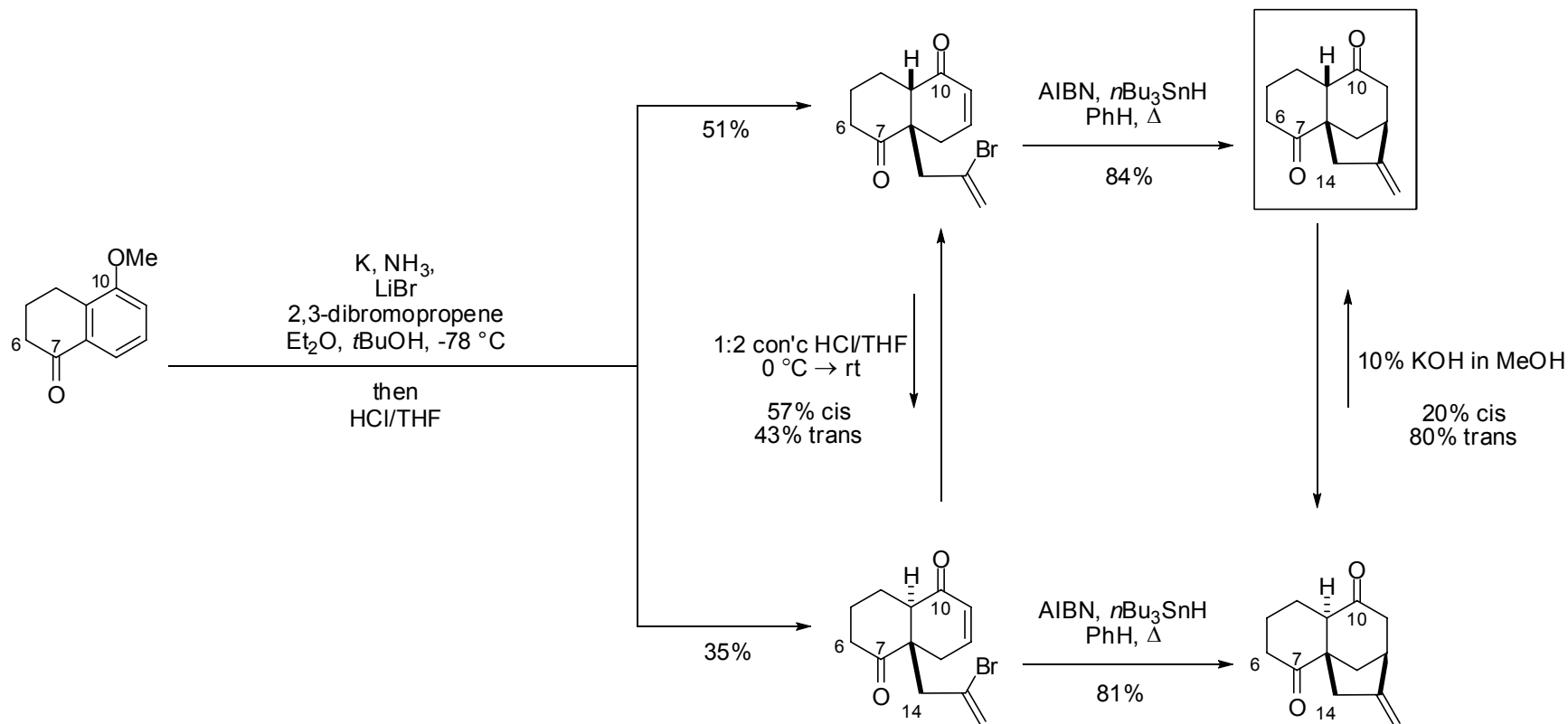
# Snider's Racemic Formal Synthesis

- Retro:



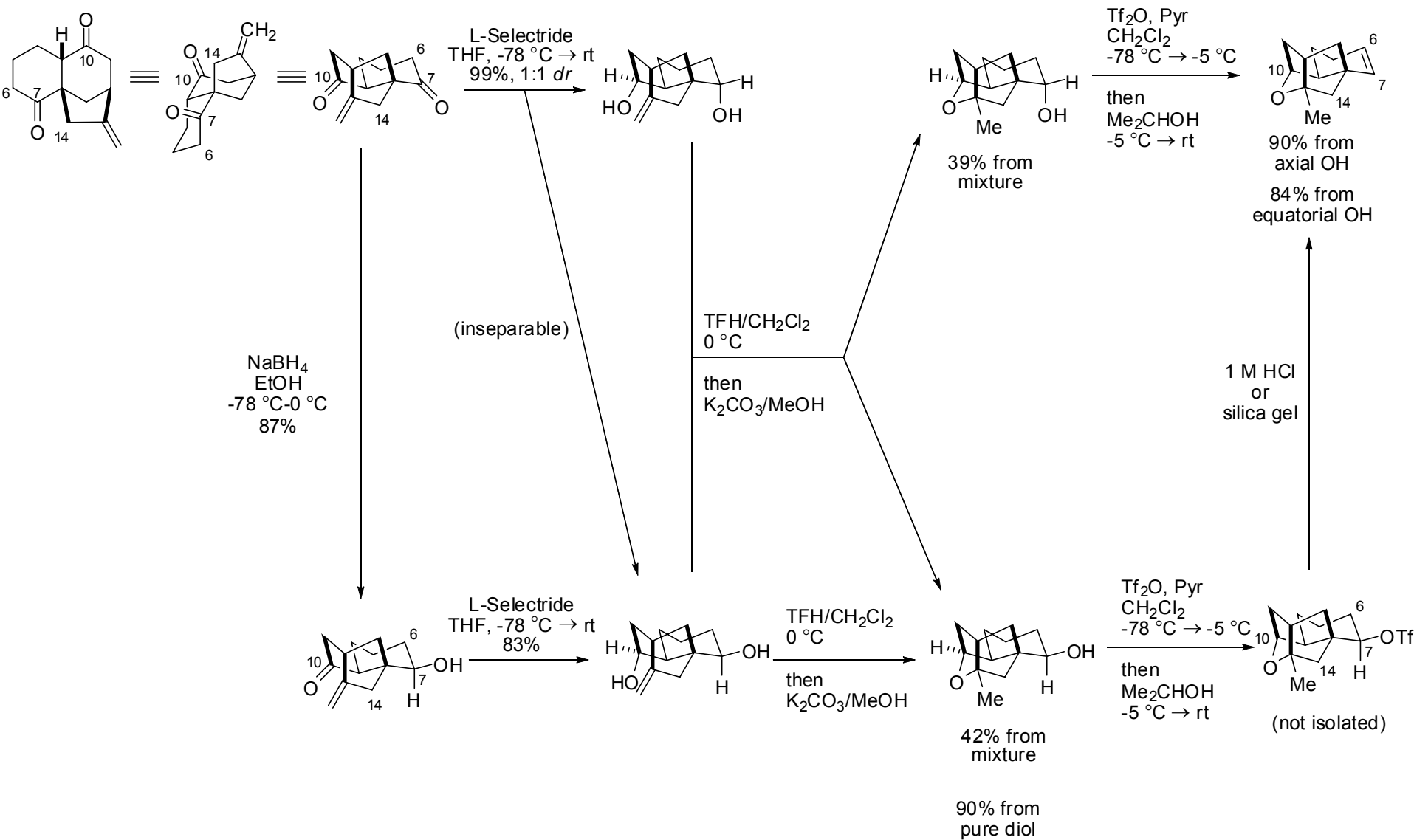
# Snider's Racemic Formal Synthesis

- Tricycle:



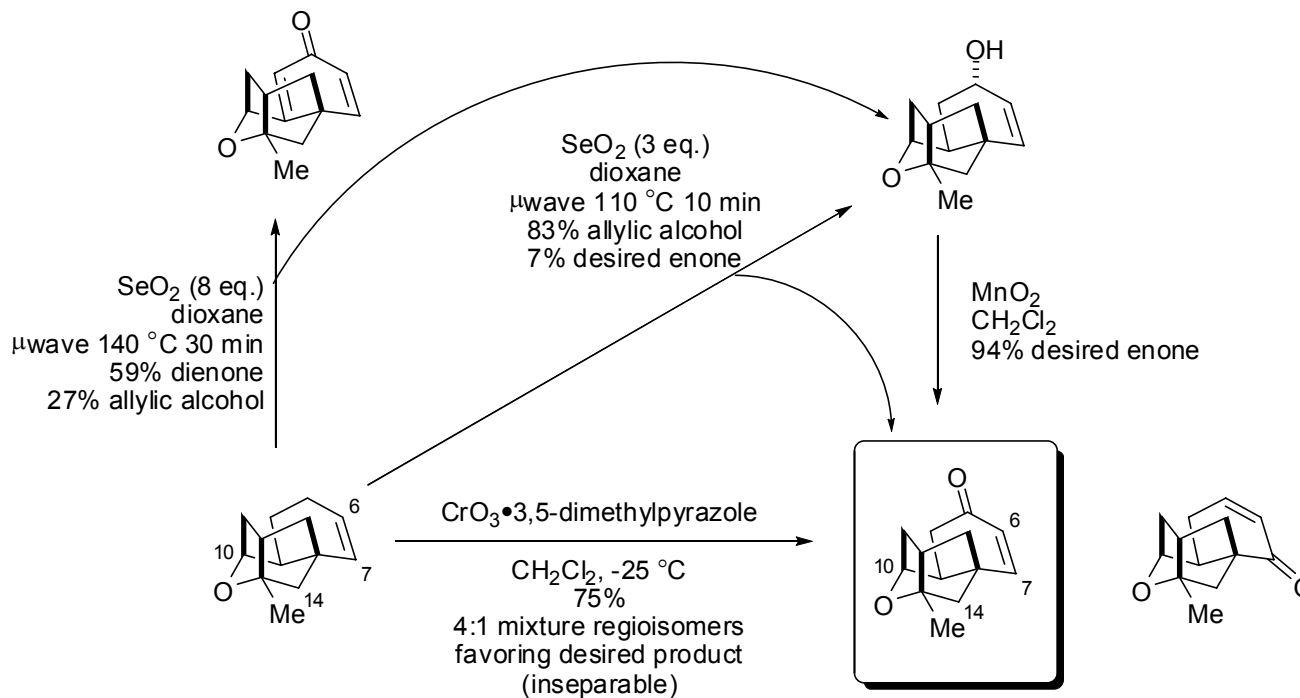
# Snider's Racemic Formal Synthesis

- Multi-cycle:



# Snider's Racemic Formal Synthesis

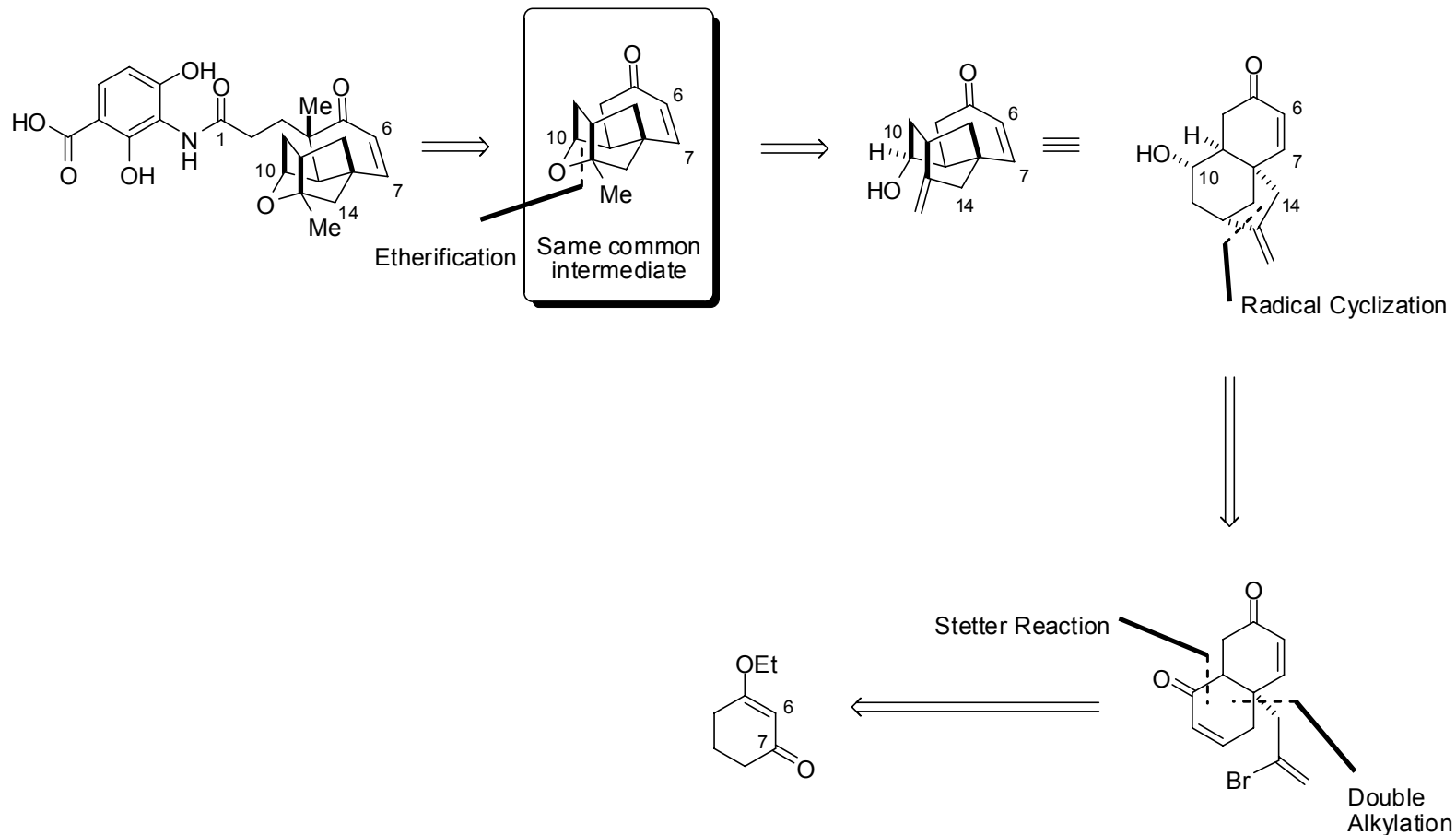
- Interception of Nicolaou's Multi-cycle:



7 steps, 32% overall yield

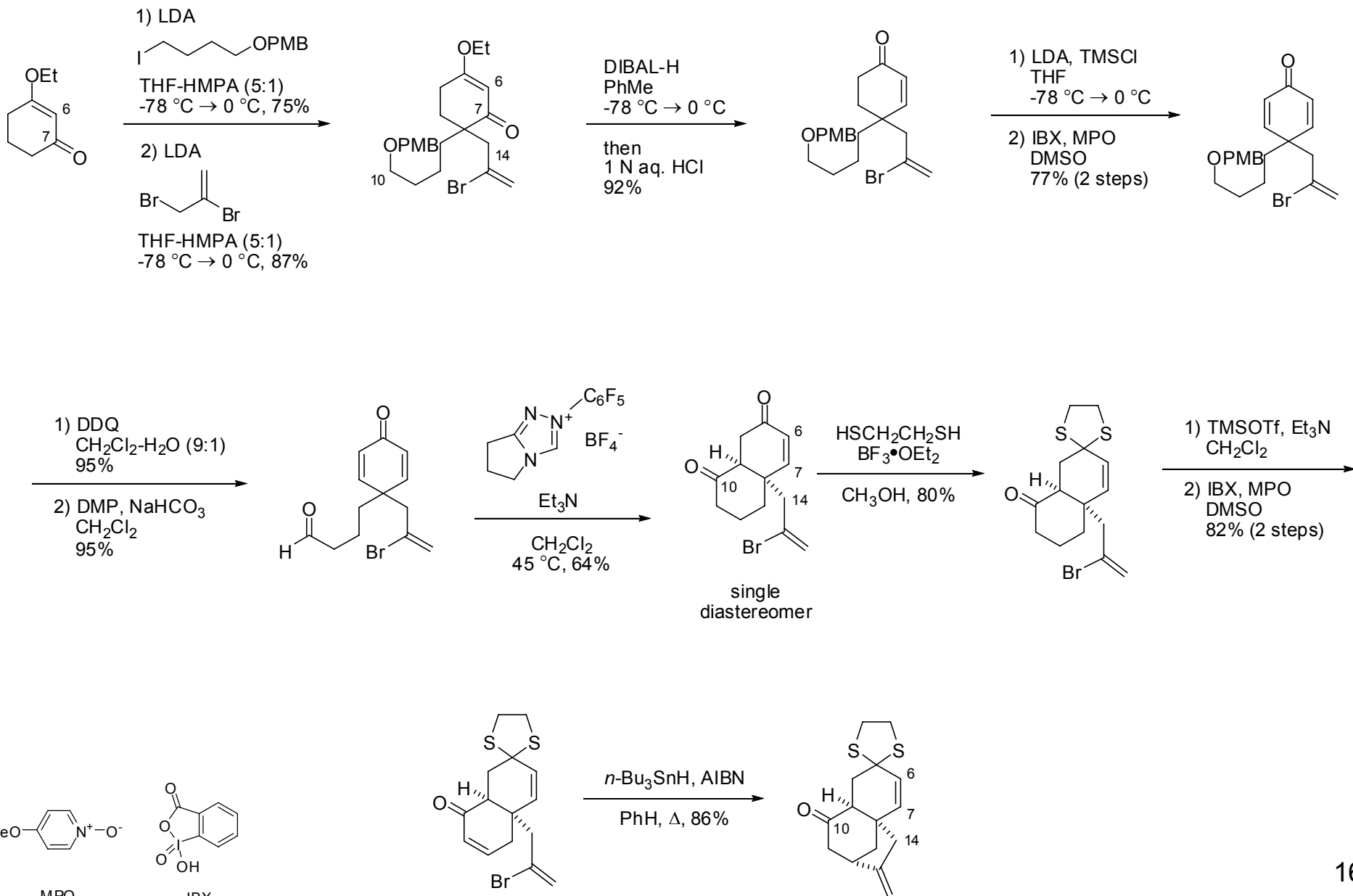
# Nicolaou's Racemic Formal Synthesis

- Retro:



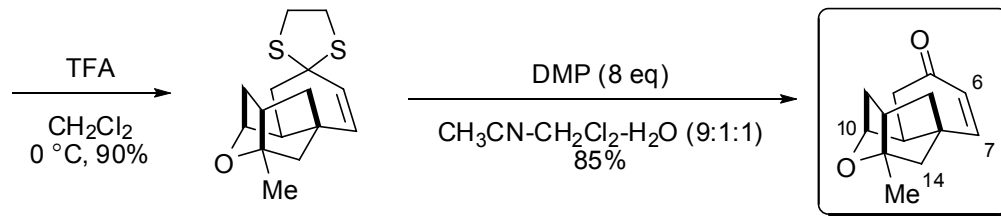
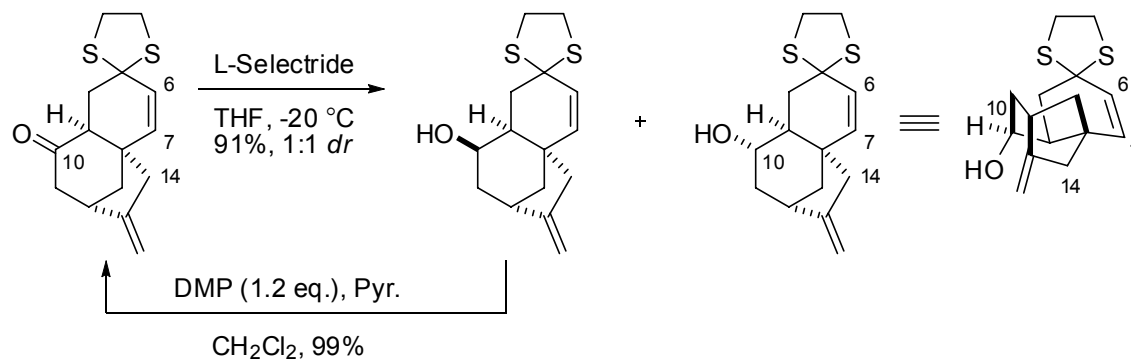
# Nicolaou's Racemic Formal Synthesis

- Tri-cycle:



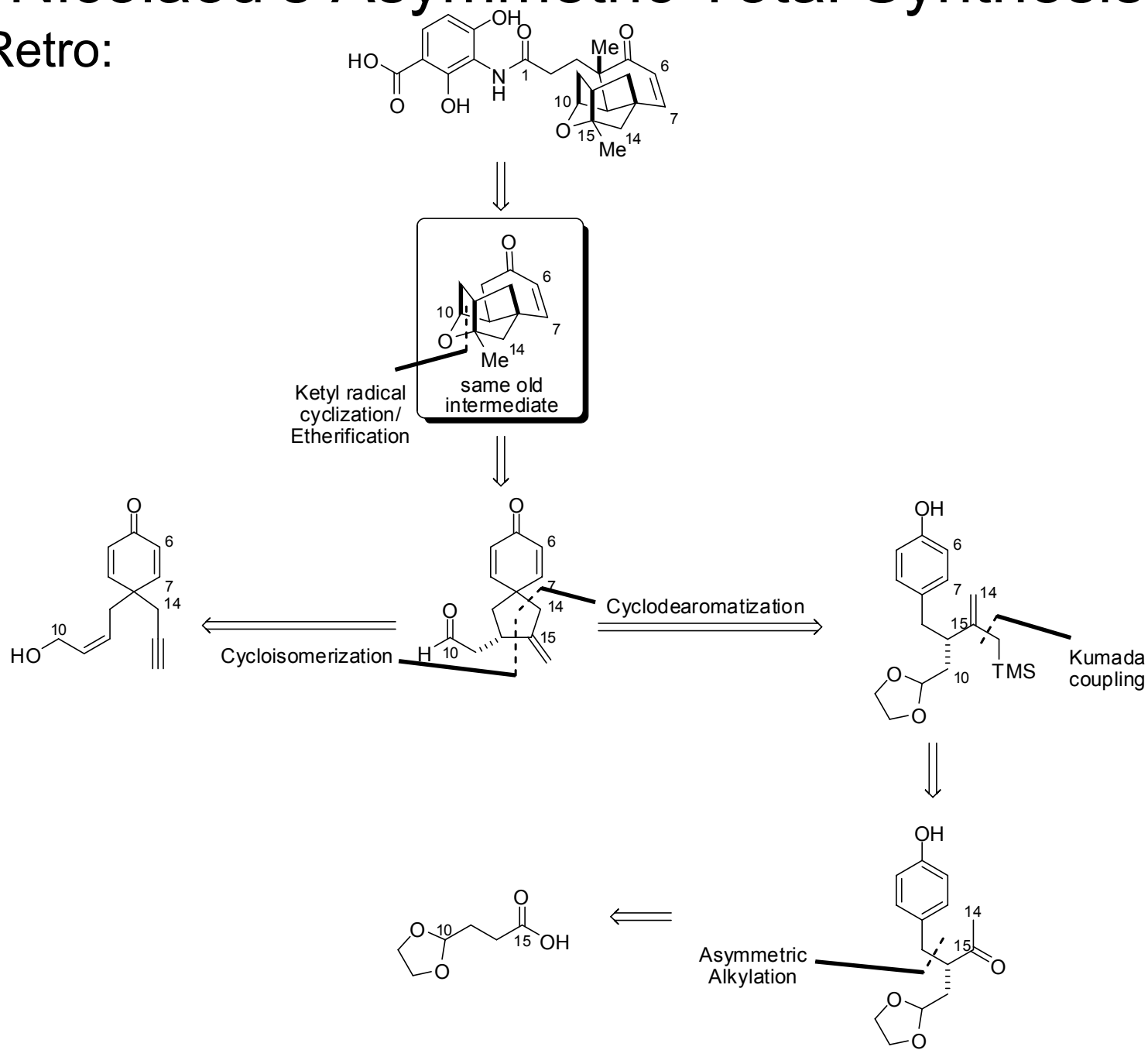
# Nicolaou's Racemic Formal Synthesis

- Interception of multi-cycle:



# Nicolaou's Asymmetric Total Synthesis

- Retro:





# Nicolaou's Asymmetric Total Synthesis

- Cyclodearomatization Strategy:

