

# Cyclopropanes as versatile intermediates in the context of total synthesis

# CYCLOPROPANES IN ORGANIC SYNTHESIS

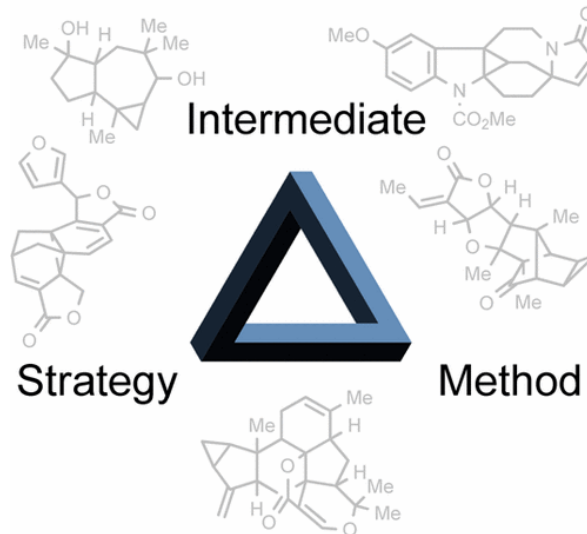
OLEG G. KULINKOVICH



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Oleg G. Kulinkovich, 2015, Wiley & Sons  
DOI:10.1002/9781118978429

## Cyclopropanes in Total Synthesis



C. Ebner & E. M. Carreira, *Chem. Rev.*, **2017**, 11651-11679

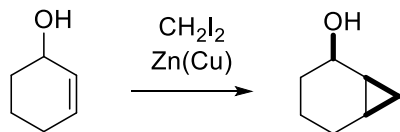
A – Introduction : Cyclopropanation methods

B – Highlights from the total synthesis literature

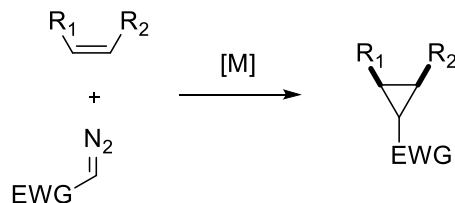
- 1 – *Cedrone* (**1973** Corey)
- 2 – *Grandisol* (**1975** Trost)
- 3 – *11-Deoxyprostaglandine E2* (**1975** Corey)
- 4 – *Strychnofoline* (**2002** Carreira)
- 5 – *Oestrone* (**2004** Pattenden)
- 6 – (+)- $\beta$ -*Araneosene* (**2005** Corey)
- 7 – *Meloscine* (**2011** Curran)
- 8 – (+)-*Lyconadin A* (**2011** Fukuyama)
- 9 – (-)-*Gelsemoxonine* (**2011** Fukuyama)
- 10 – *Steviol* (**2013** Baran)
- 11 – (-)-6-*epi-Ophiobolin N* (**2016** Maimone)
- 12 – *Piperarborenine B* (**2016** Fox)

C – Conclusion : Strategies involving cyclopropanes

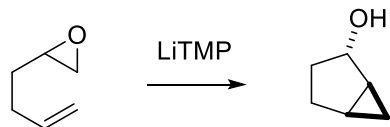
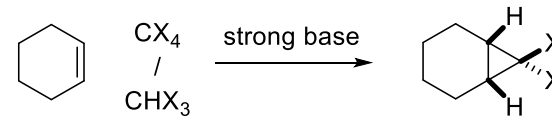
## Simmons-Smith cyclopropanation



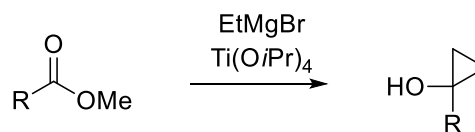
## Diazo-derived carbenoids



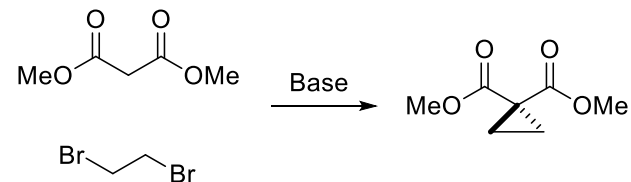
## Free carbenes



## Cycloisomerisation

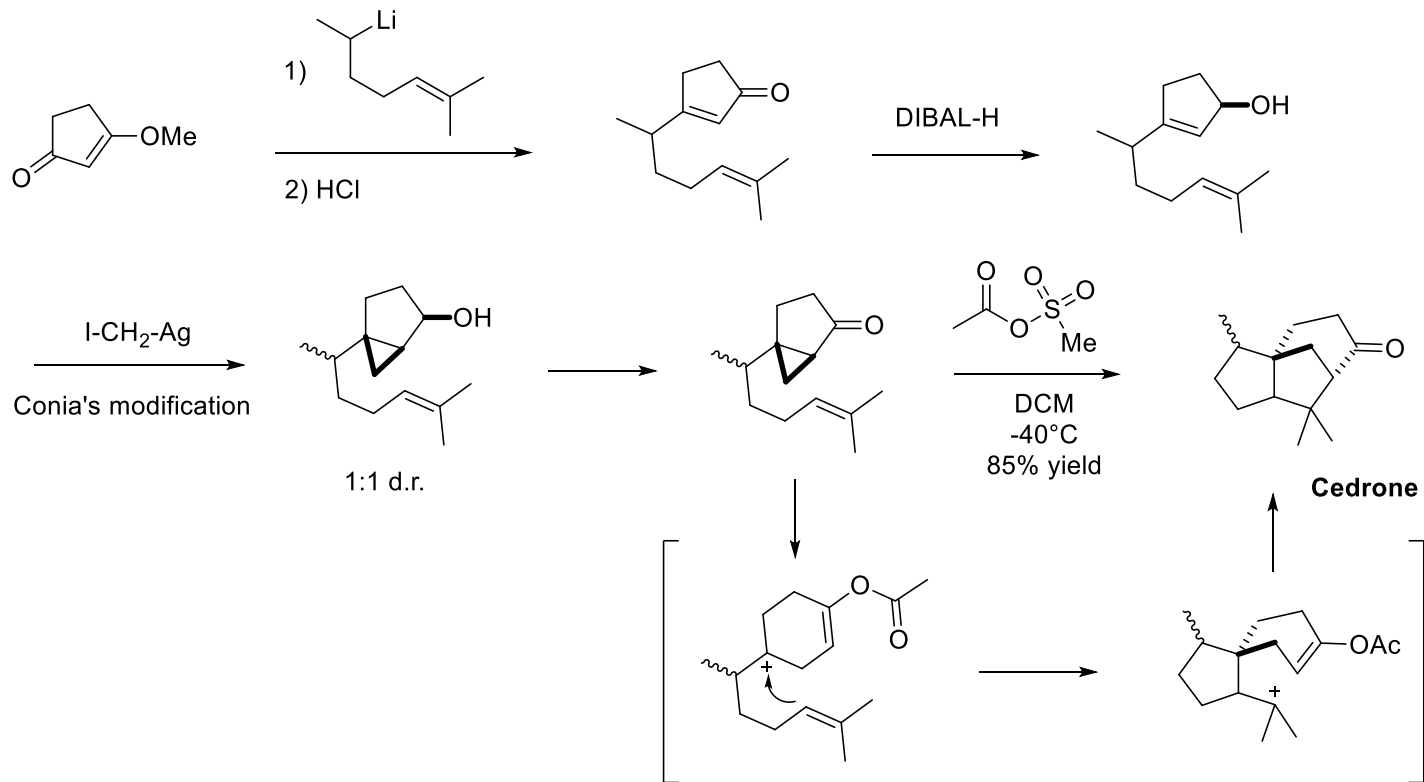


## Kulinkovich cyclopropanation

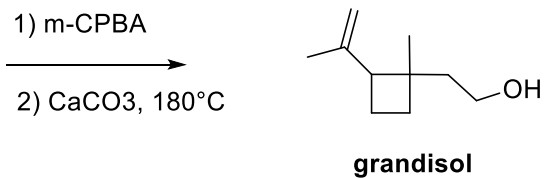
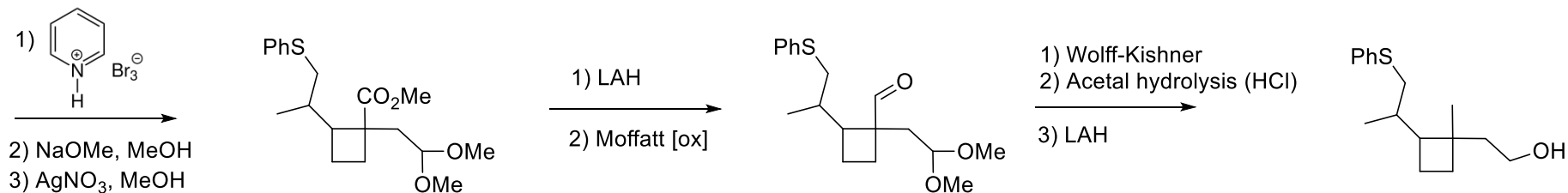
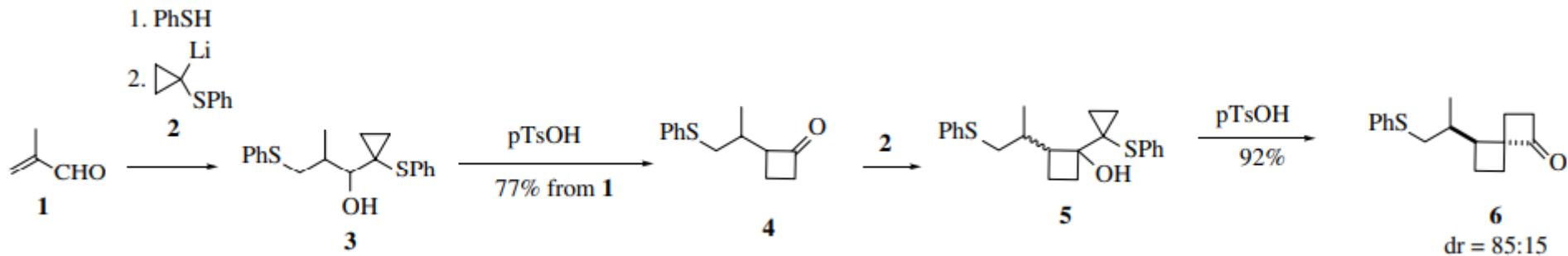


## Nucleophilic displacement

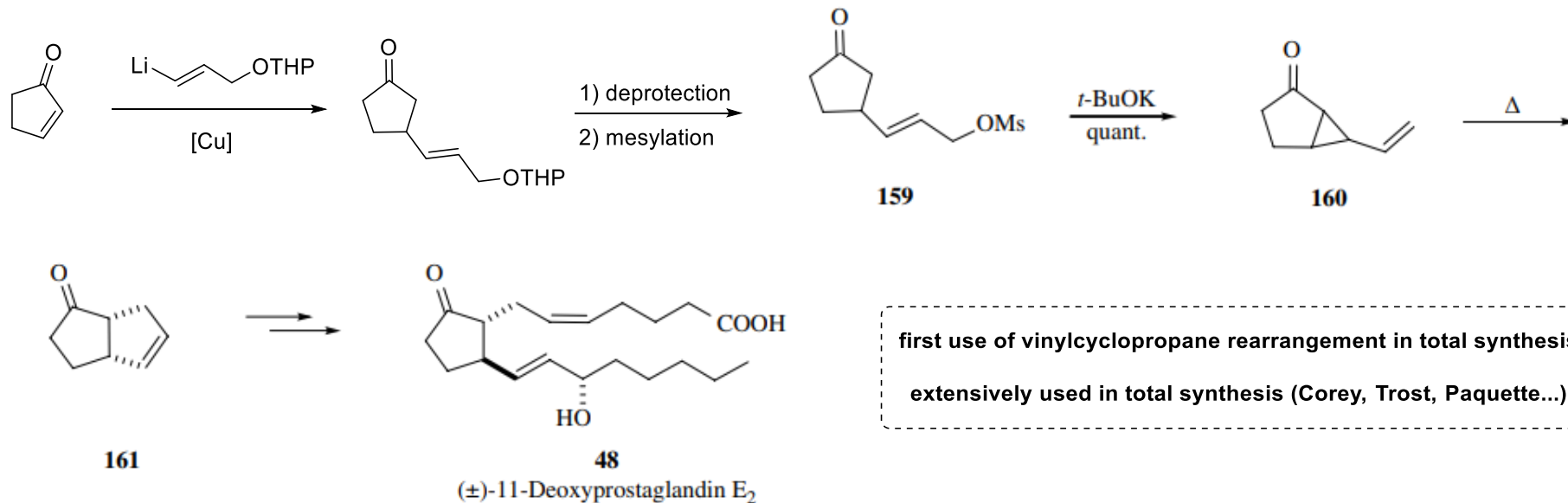
# 1 - Synthesis of rac-Cedrone



# 2 - Synthesis of rac-Grandisol

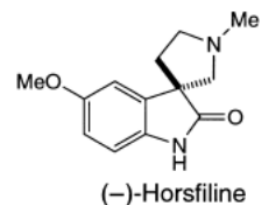
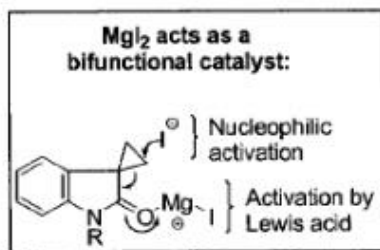
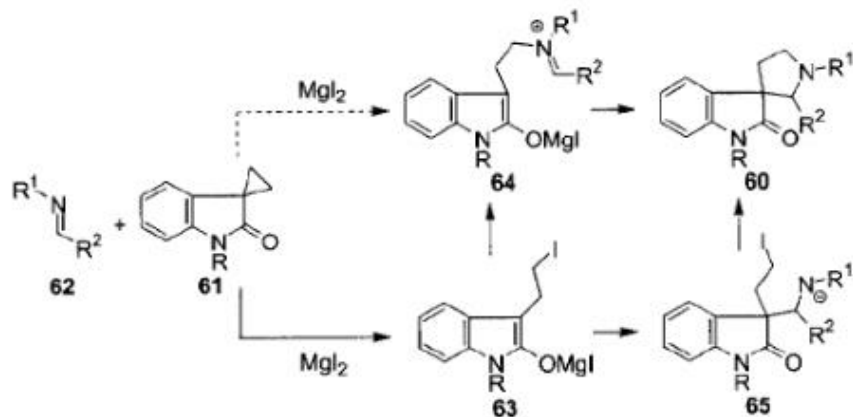


# 3 - Synthesis of rac-11-Deoxyprostaglandin E<sub>2</sub>

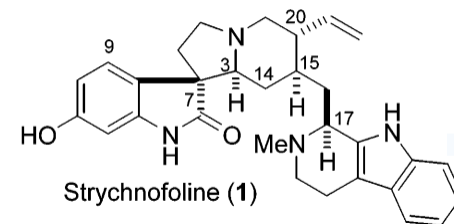


SCHEME 34

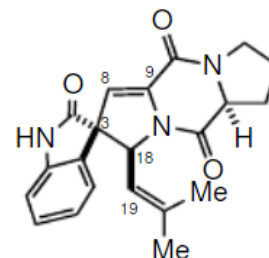
# 4 - Synthesis of Strychnofoline



*Helv. Chim. Acta* **2000** 1175-1181



*JACS* **2002** 14826-14827

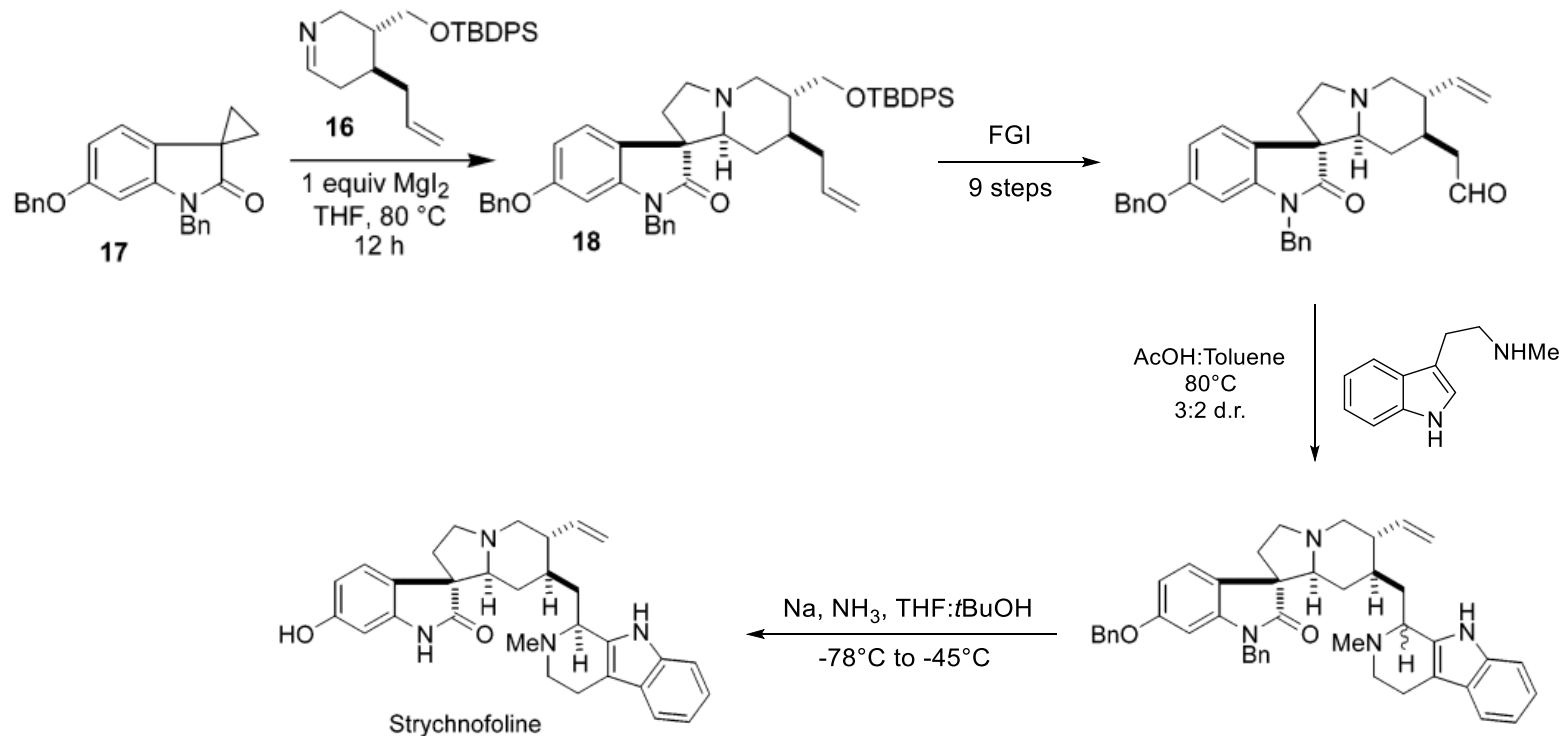


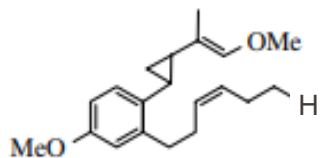
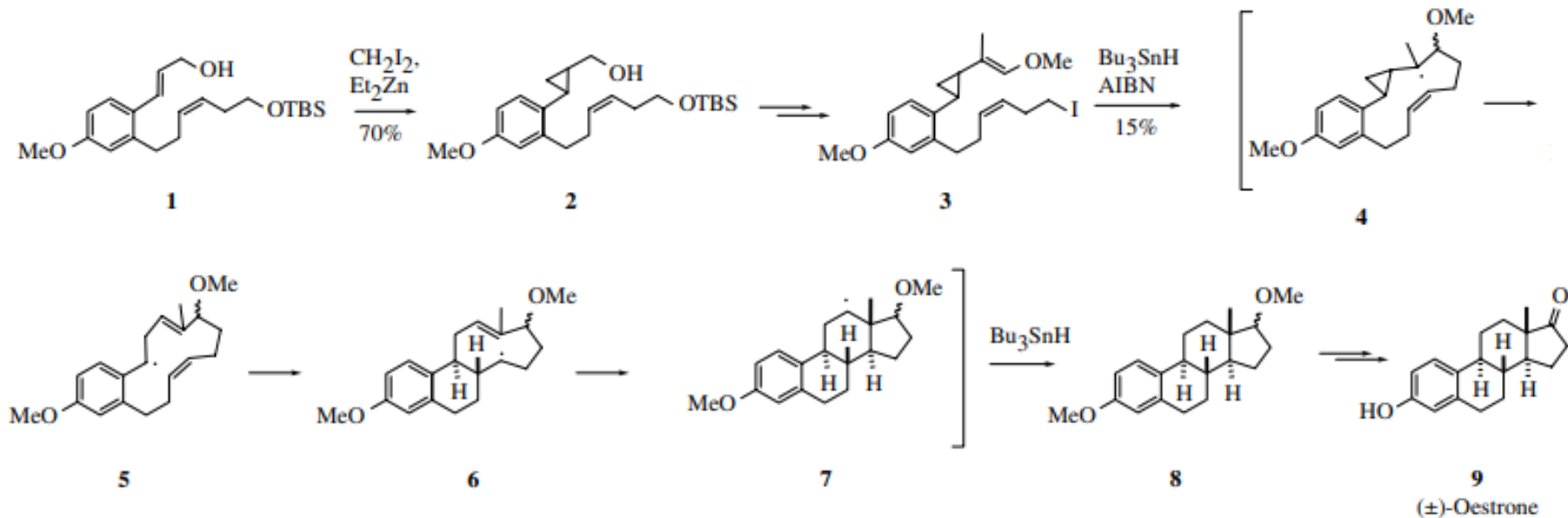
*spirotryprostatin B*

*ACIE*, **2003**, 694-696



# 4 - Synthesis of Strychnofoline

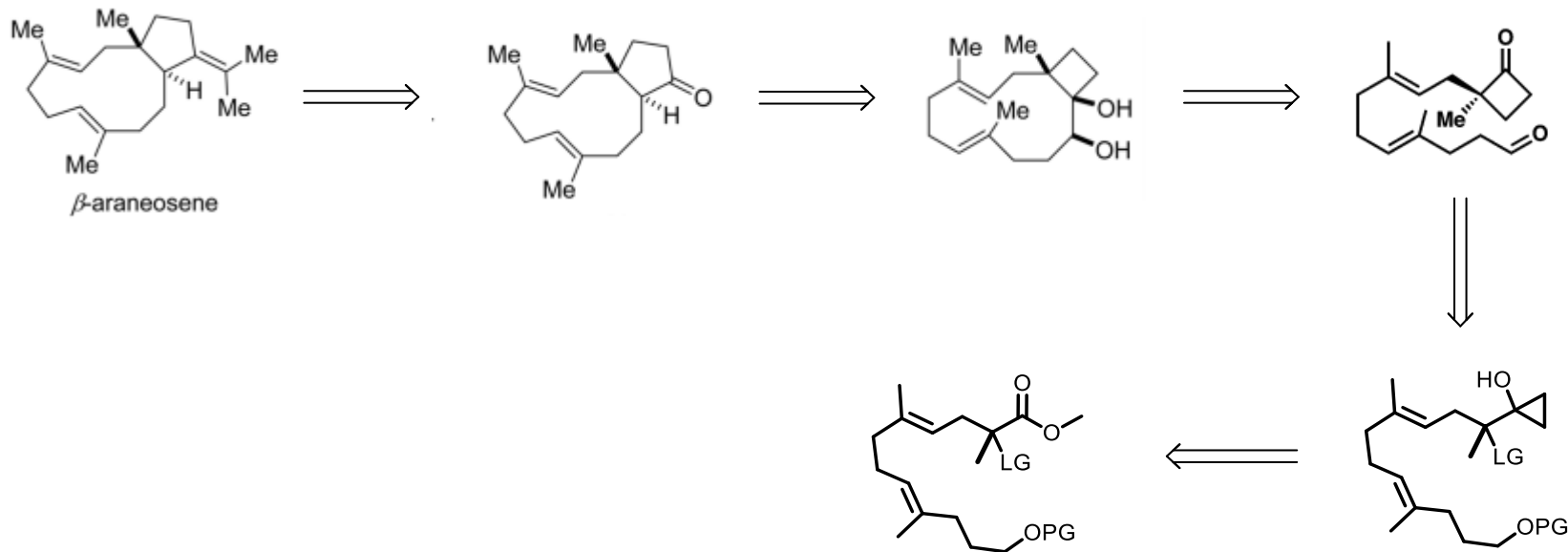




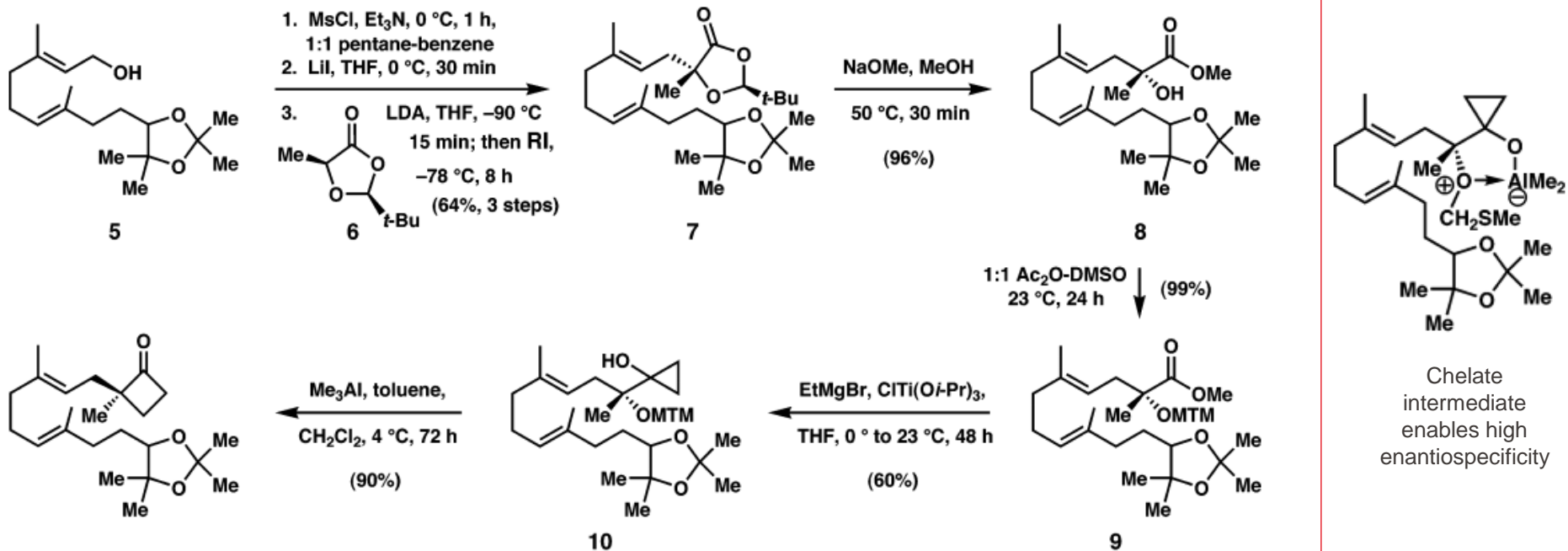
53%

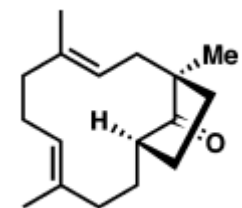
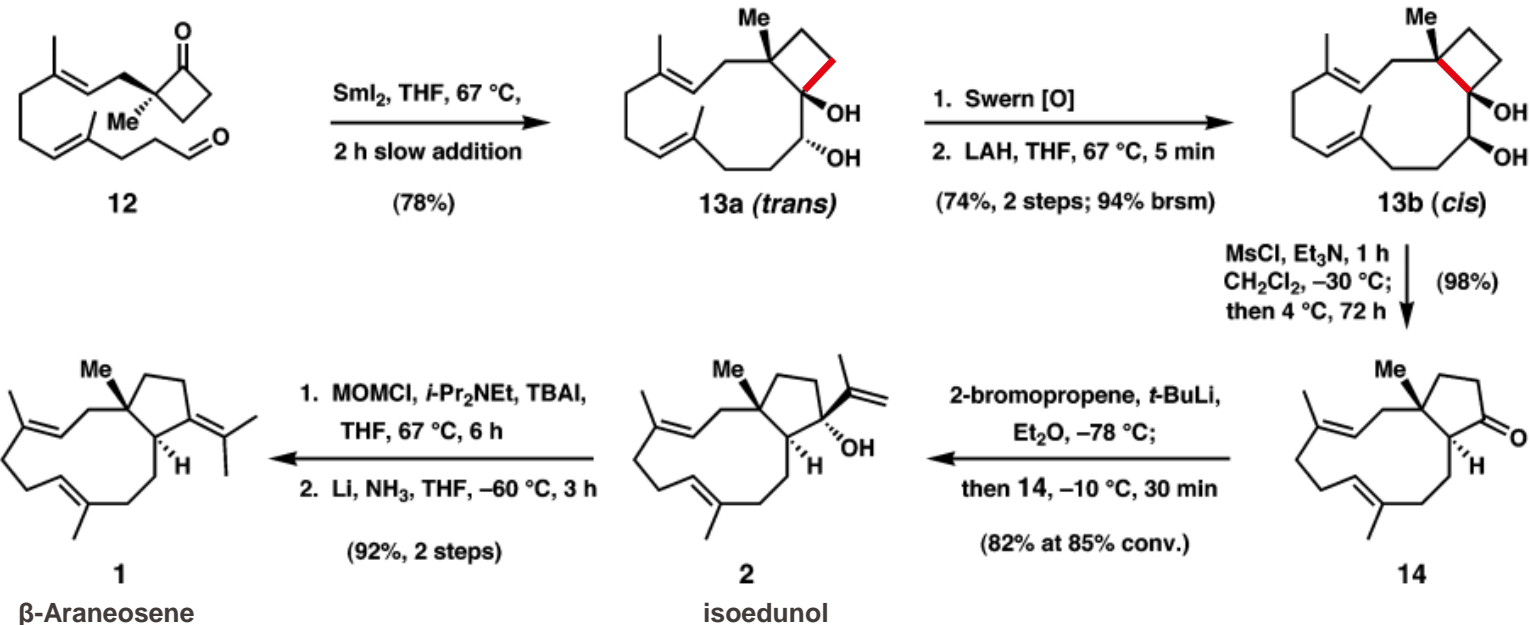
# 6 - Synthesis of (+)-B-Araneosene

Retrosynthetic analysis



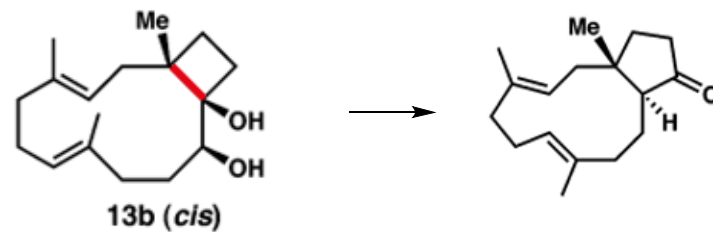
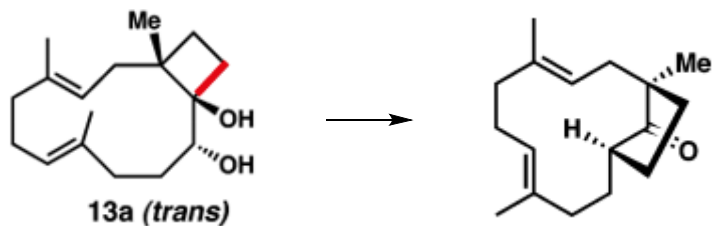
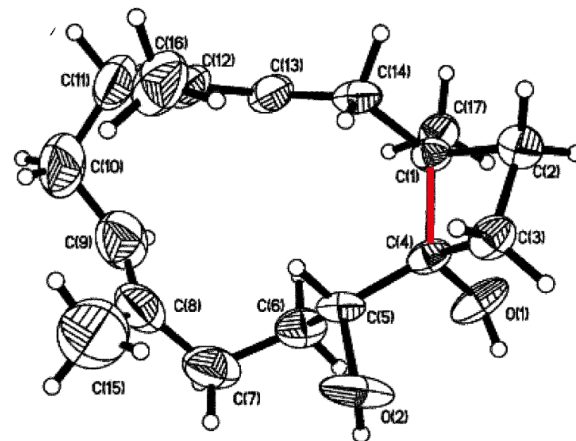
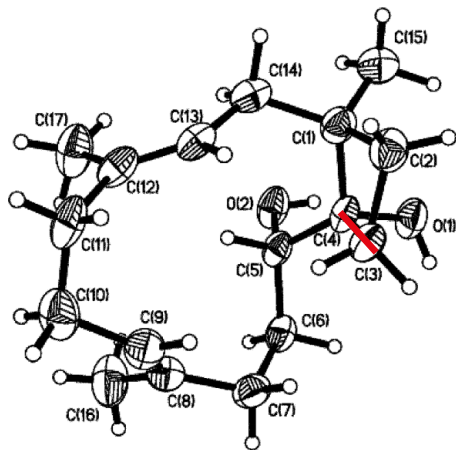
## 6 - Synthesis of (+)-B-Araneosene

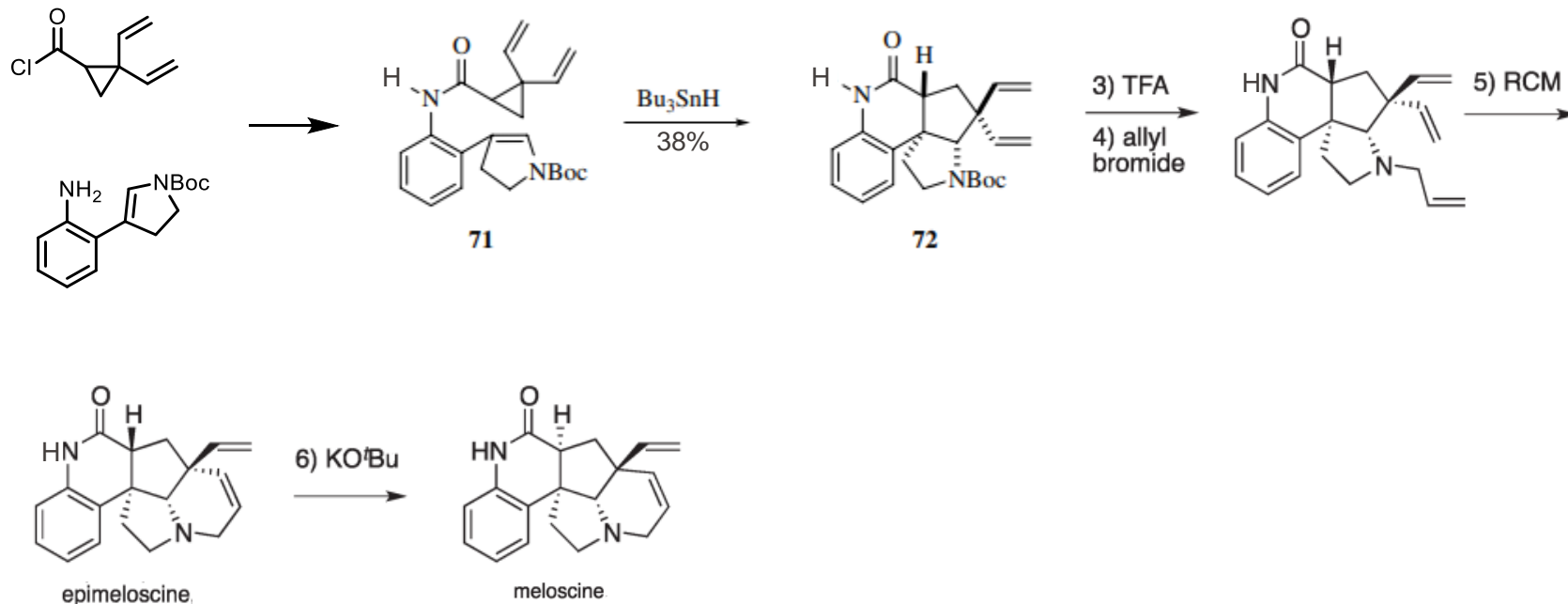


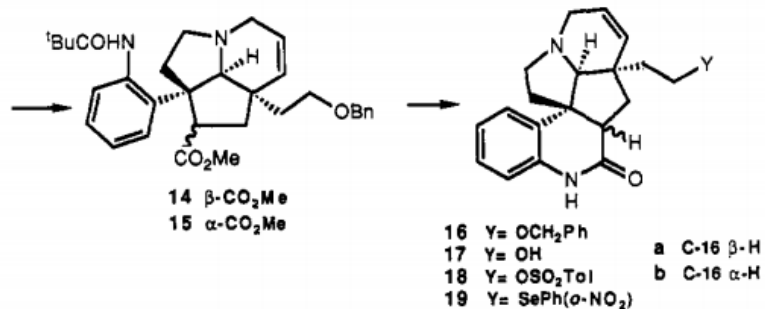
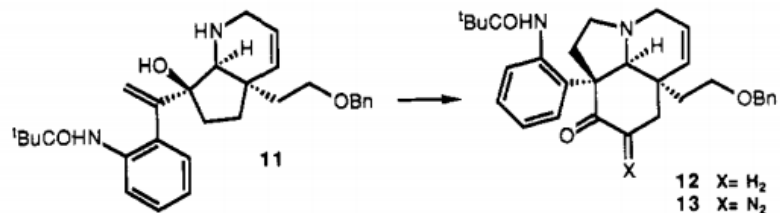


Bridged-pinnacol rearrangement product (from 13a)

# 6 - Synthesis of (+)-B-Araneosene

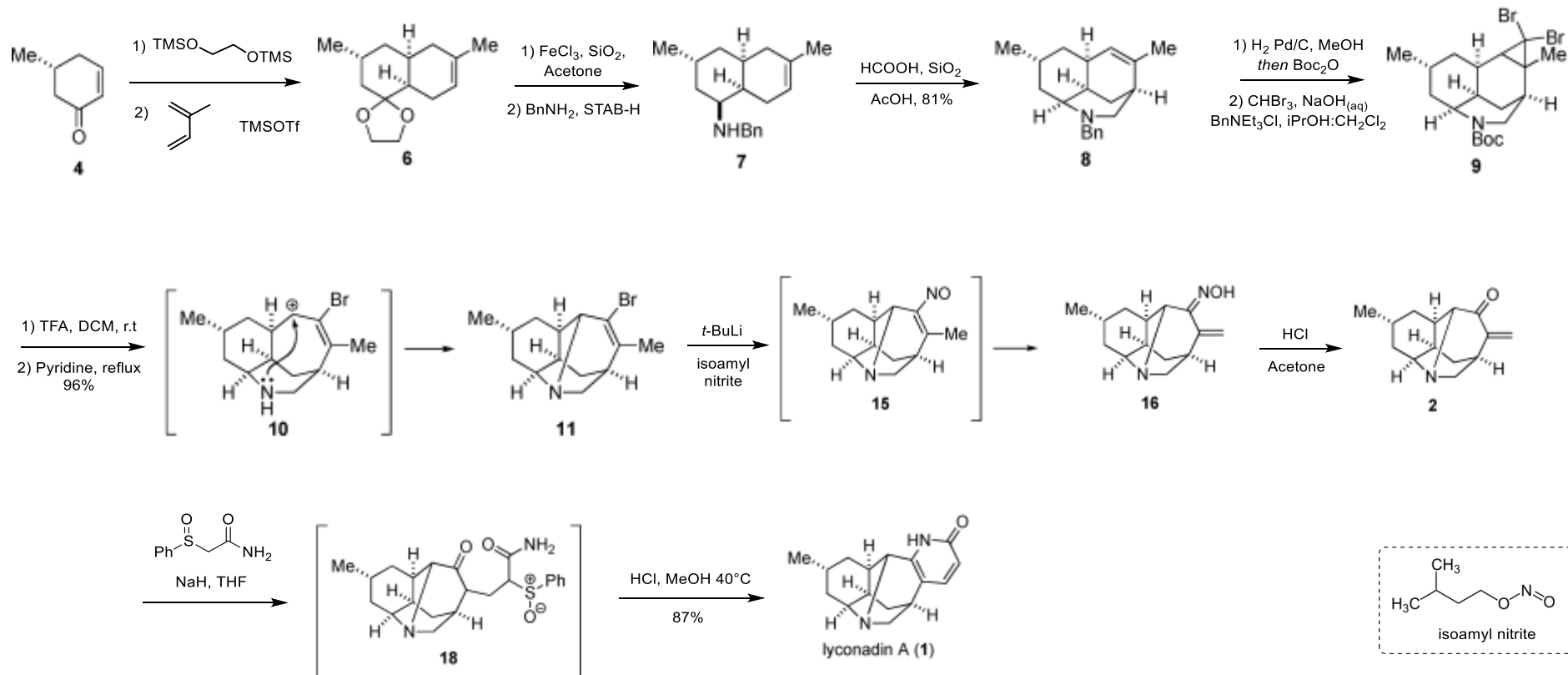


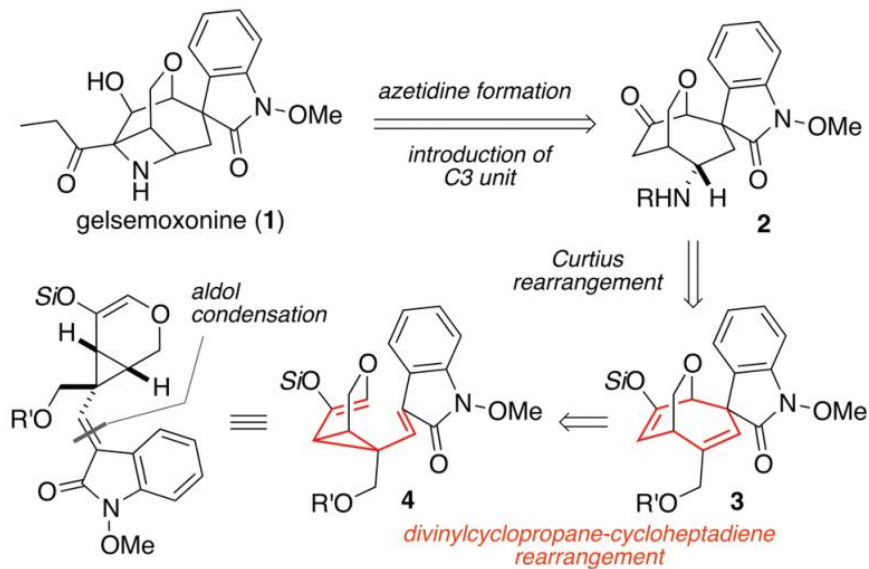






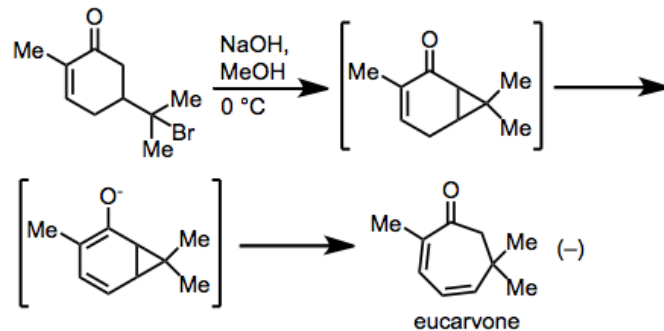
## 8 - Synthesis of (+)-Lyconadin A

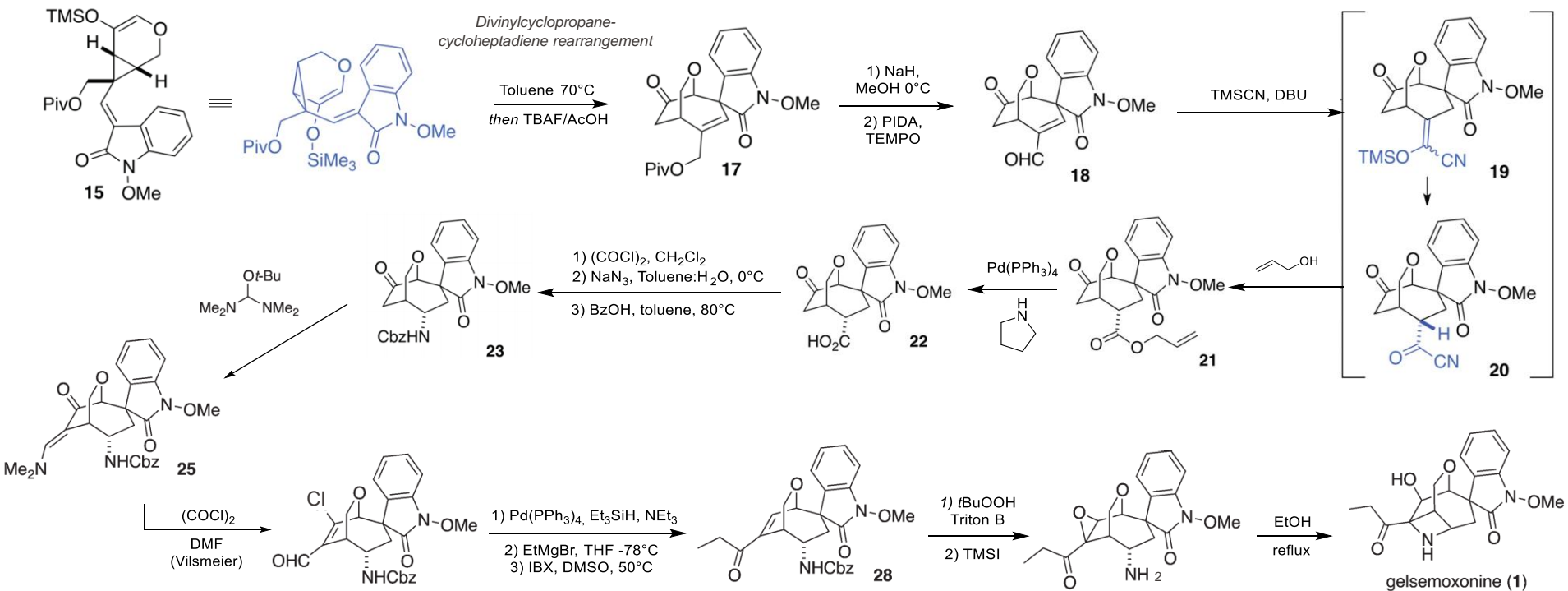


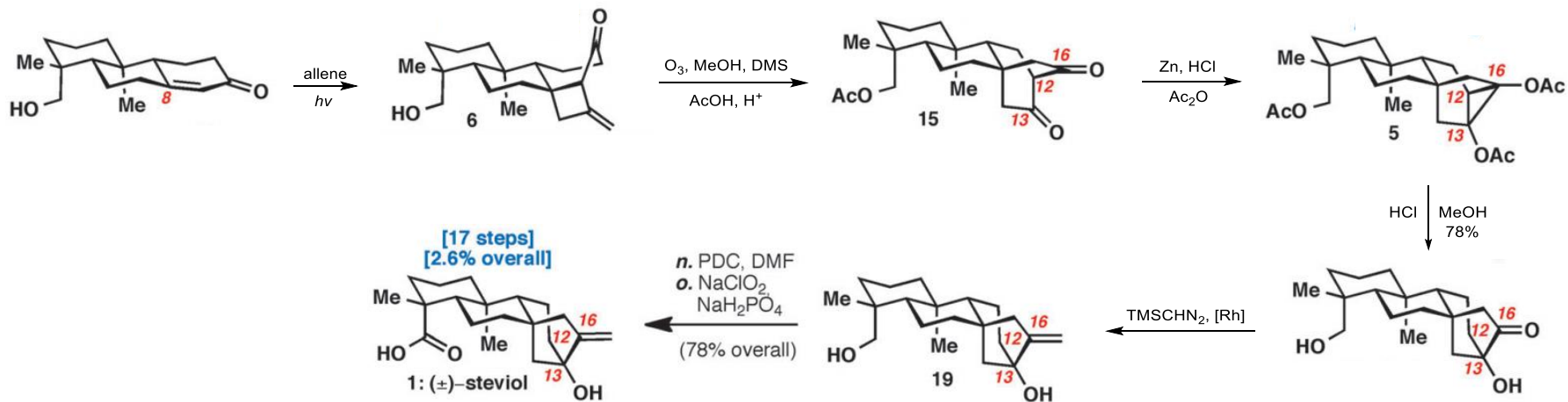


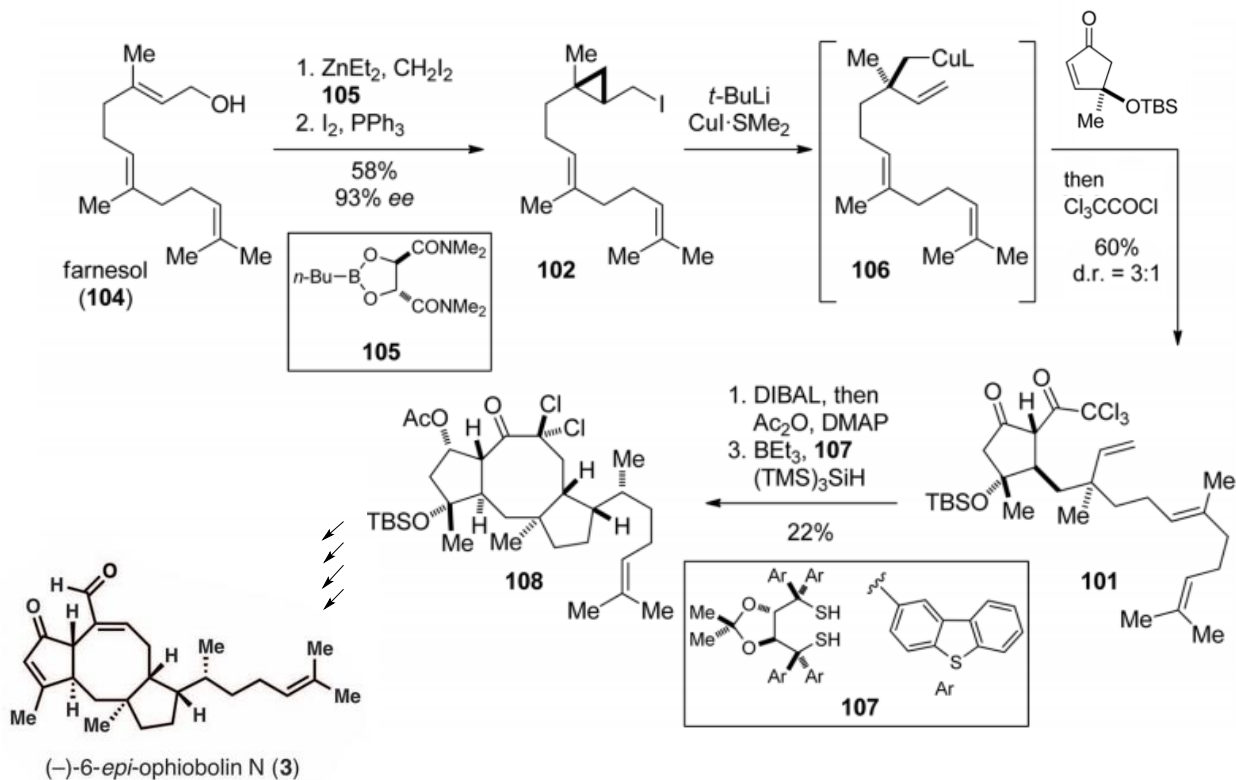
Divinylcyclopropane-cycloheptadiene rearrangement

Related to cope rearrangement

Baeyer, A. Ber. **1894**, 27, 810





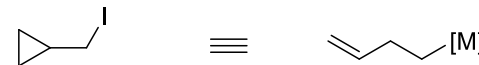


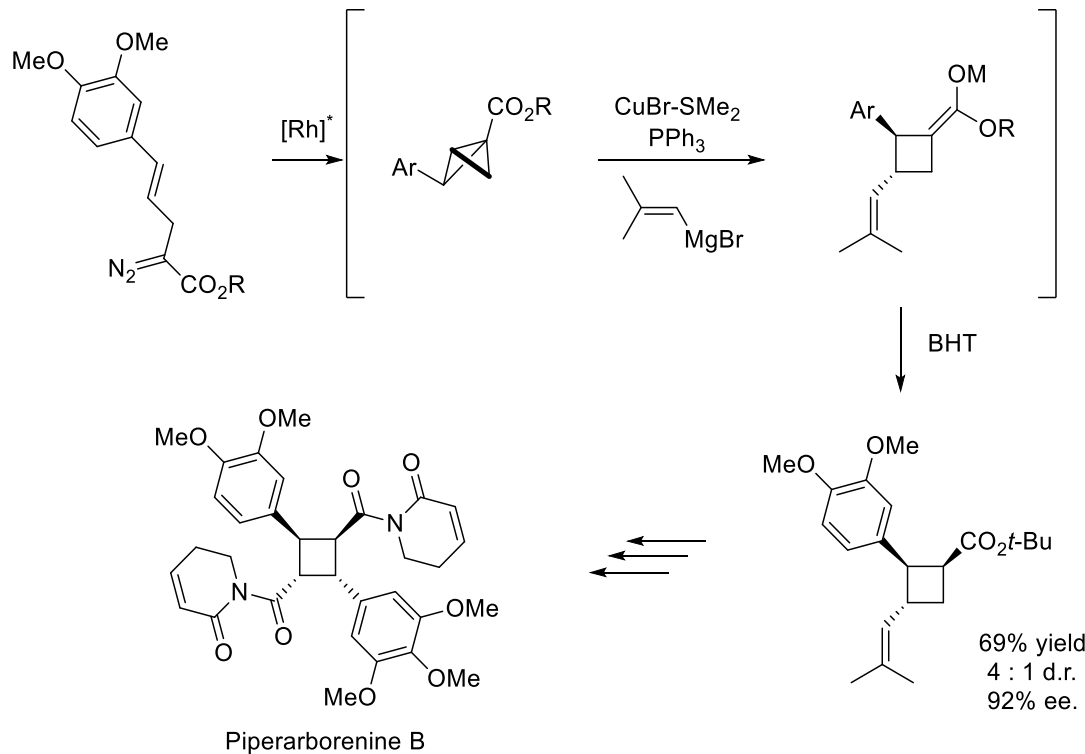
- Charette enantioselective cyclopropanation of allylic alcohols

In a single pot :

- Lithium-Halogen exchange
- Cyclopropane anionic opening
- Transmetalation with CuI-SMe<sub>2</sub>
- Conjugate addition on cyclopentenone
- Enolate trapping

-Halogenated cyclopropane = synthon for homoallylic organometal

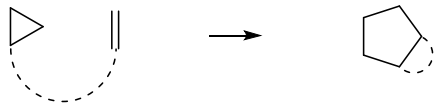




- Generation of a dicyclopropane (enantioselective)
- homoconjugate cyclopropane opening with organocopper reagent
- BHT as a sterically hindered proton source to enable good diastereoselectivity for the reprotonation step

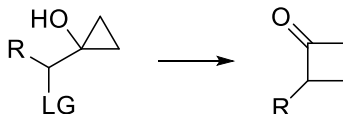
69% yield  
4 : 1 d.r.  
92% ee.

Vinylcyclopropane rearrangement  
Formal [3+2]



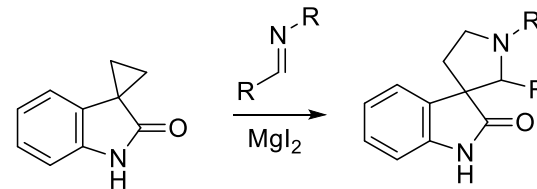
*Cedrone* **1973** Corey  
*Deoxyprostaglandine E2* **1975** Corey

Pinnacol-type ring expansion



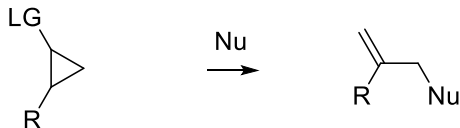
*Grandisol* **1975** Trost  
*Araneosene* **2005** Corey

MgI<sub>2</sub>-cyclopropane opening



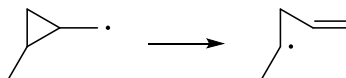
*Strychnofoline* **2002** Carreira

*Lyconadin A* **2011** Fukuyama  
*Piperarborenine B* **2016** Fox



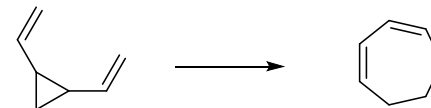
Nucleophilic opening

*Oestrone* **2004** Pattenden  
*Meloscine* **2011** Curran  
*epi-Ophiobolin N* **2016** Maimone



Radical or Anionic opening

*Gelsemoxonine* **2011** Fukuyama



Divinylcyclopropane-  
cycloheptadiene rearrangement