

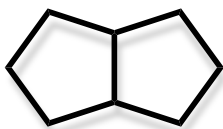
# Total Synthesis of Triquinanes



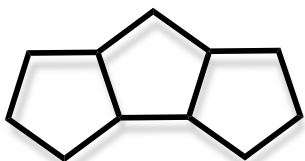
**Krishna P Kaliappan**  
*Professor of Chemistry, IIT Bombay*

**CH-588 Course on Organic Synthesis**

# Triquinanes & its classifications



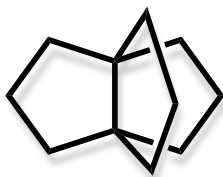
**Diquinane**



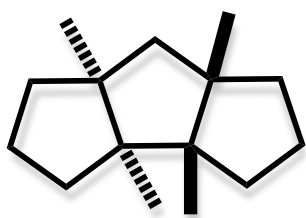
**Linear Triquinane**



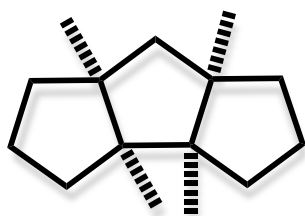
**Angular Triquinane**



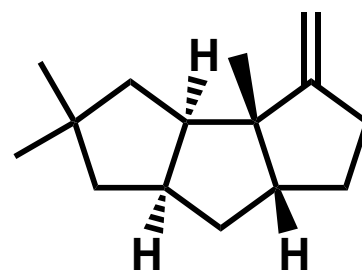
**Propellane Triquinane**



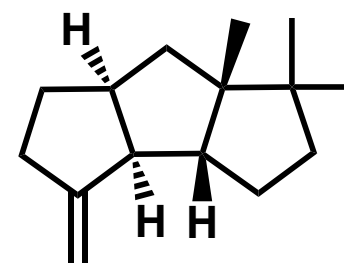
**cis:anti:cis**



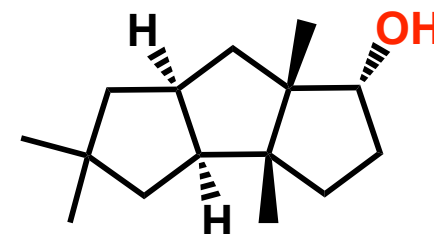
**cis:syn:cis**



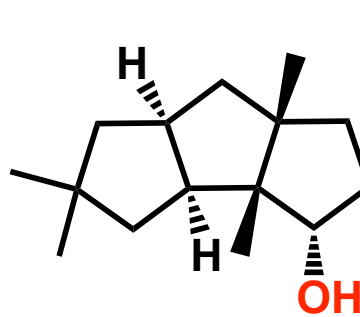
**Hirsutene**



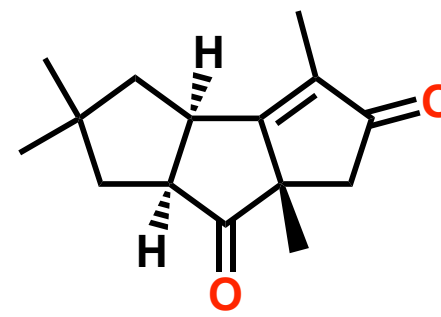
**Capnellane**



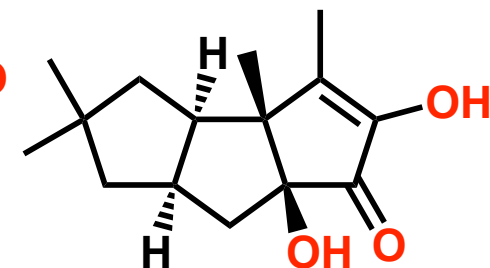
**Cerapicol**



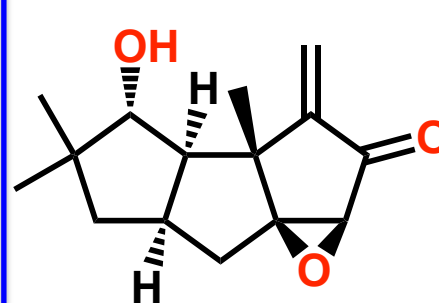
**Ceratopicanol**



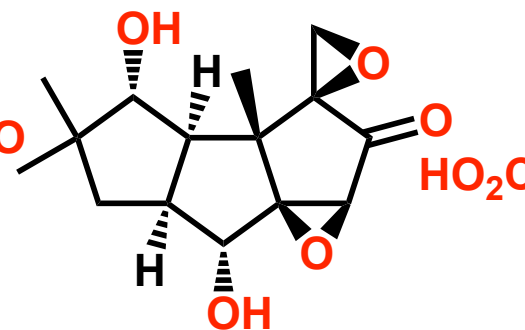
**Cucumin E**



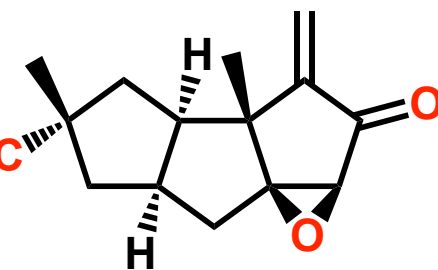
**Connatusin A**



**Hypnophyllin**

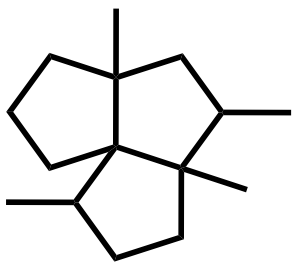


**Coriolin**

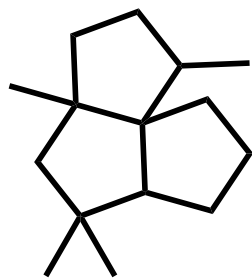


**Hirsutic acid**

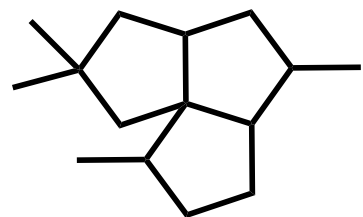
- The sesquiterpene natural products containing an **angular triquinane** moiety, isolated so far, fall into **four** different skeletal types:



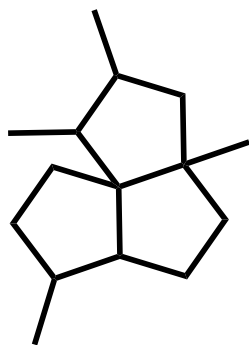
*Isocomane*



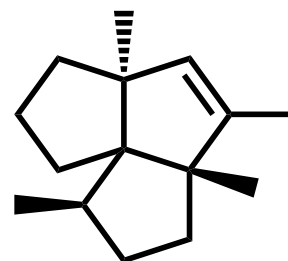
*Silphinane*



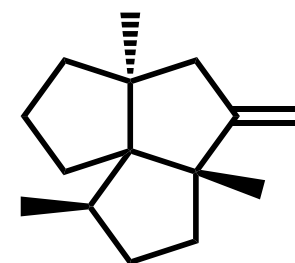
*Pentalenane*



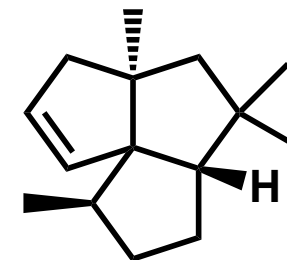
*Silphiperfolane*



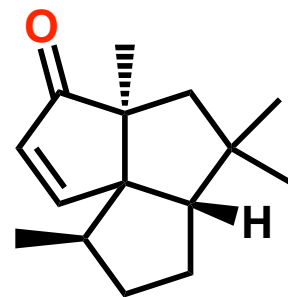
*α-Isocomene*



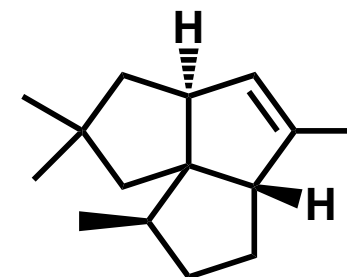
*β-Isocomene*



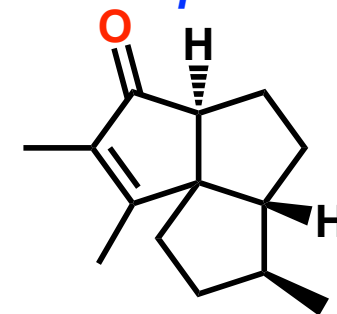
*Silphinene*



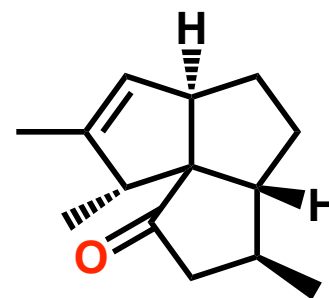
*3-Oxosilphinene*



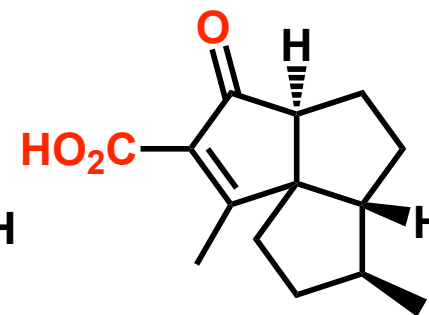
*Pentalenene*



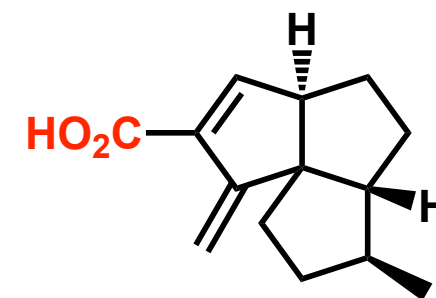
*Silphiperfoi-6-en-5-one*



*Subergorgic acid*

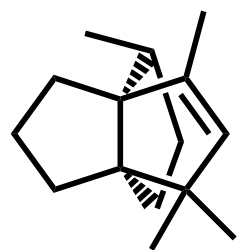


*Cantabrenic acid*

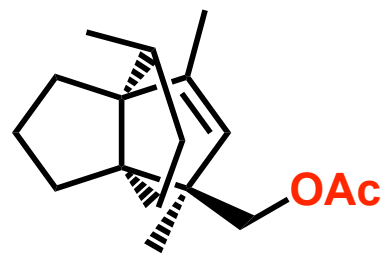


*Cantabradienoic acid*

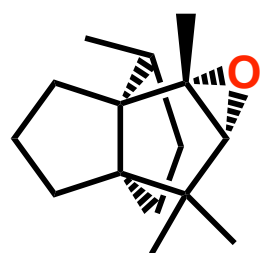
## Propellane Triquinanes



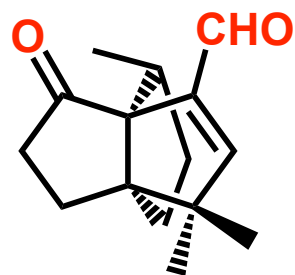
Modephane



13-OAc-modephane

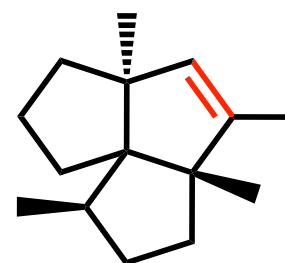


Modephane epoxide

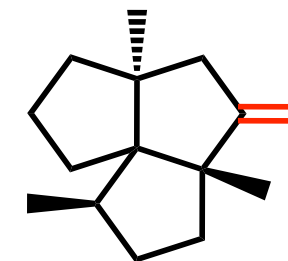


Pulicaral

## $\alpha$ - and $\beta$ - Isocomenes



*(-)*- $\alpha$ -Isocomene

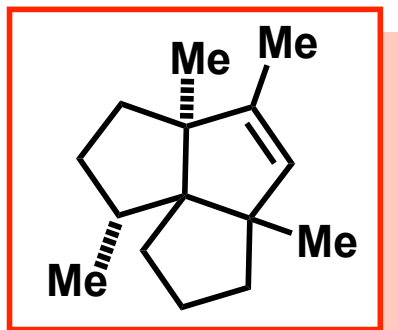


$\beta$ -Isocomene

- **Isocomenes**, isolated from *Isocoma wrightii*, are distinctive in the sense that their framework contains two angular methyl groups as part of **three contiguous quaternary carbon centers**

Bohlmann, F., *et.al.*, *J. Chem. Ber.*, **1977**, 110, 3777

Zalkow, L. H., *et.al.*, *J. Chem. Soc., Chem. Commun.*, **1977**, 456



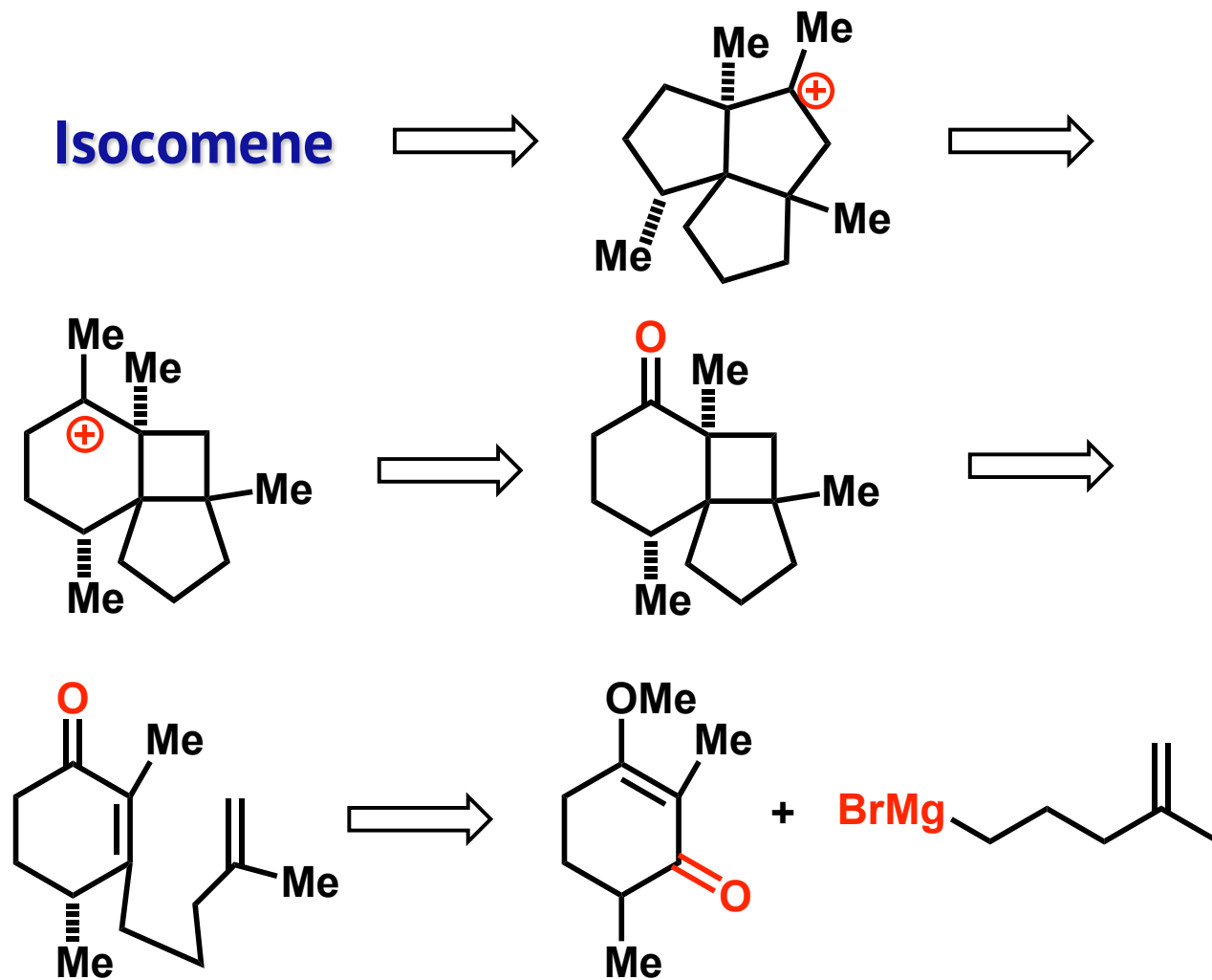
Isocomene

- Pirrung reported the total synthesis of isocomene by an efficient route in 1979.
- The key steps involved in this synthesis are (i) intramolecular [2 + 2] photocycloaddition and (ii) acid catalyzed ring expansion of 4-membered to 5-membered ring

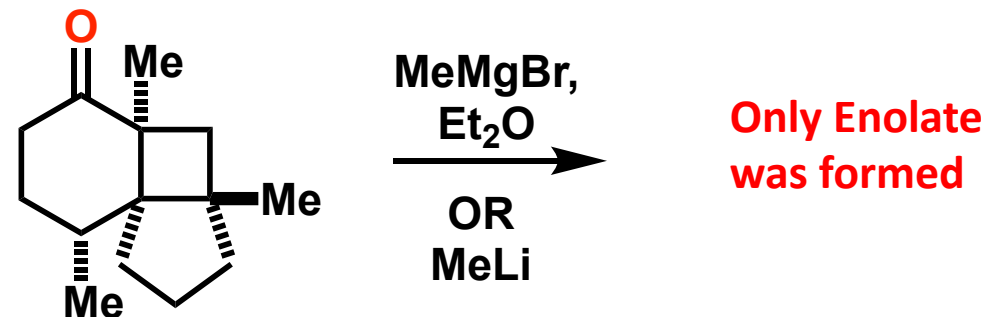
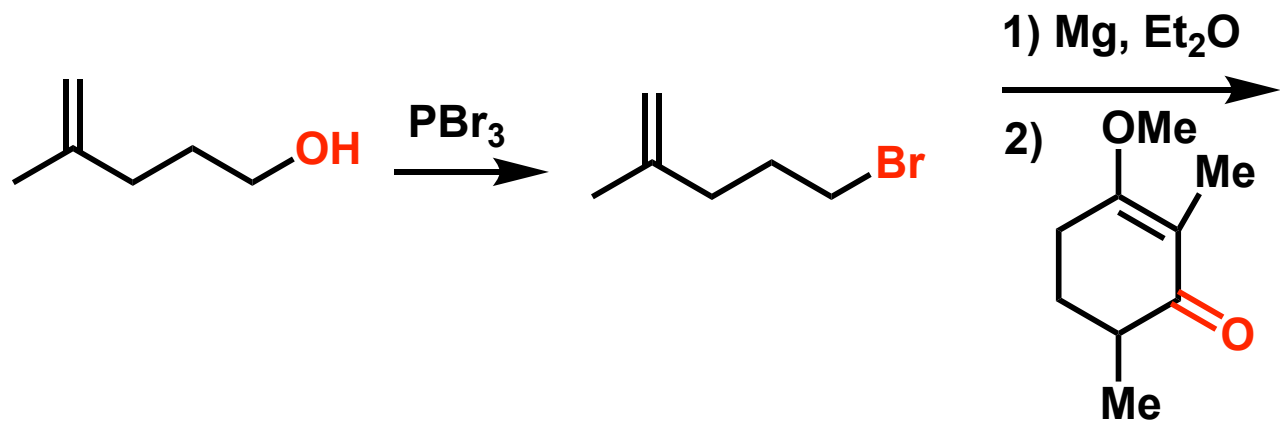
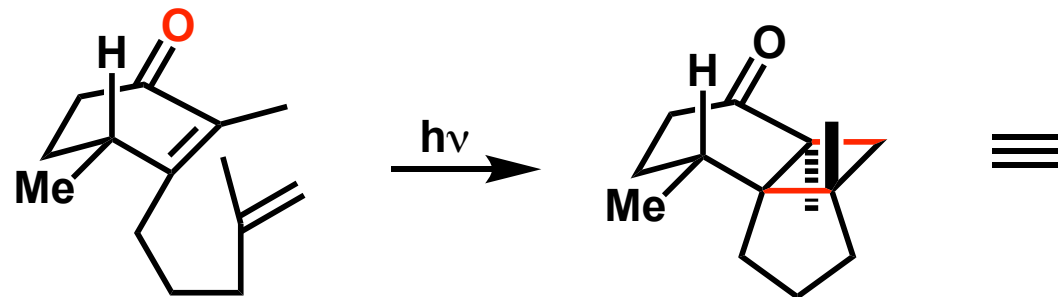
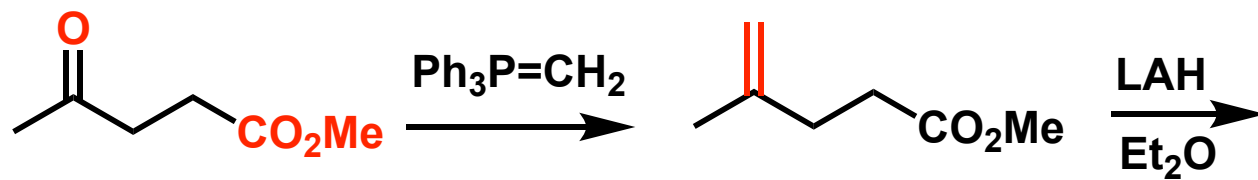
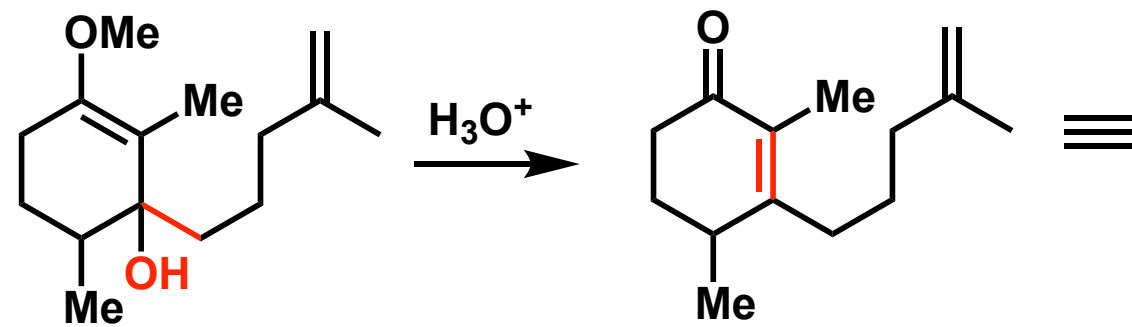
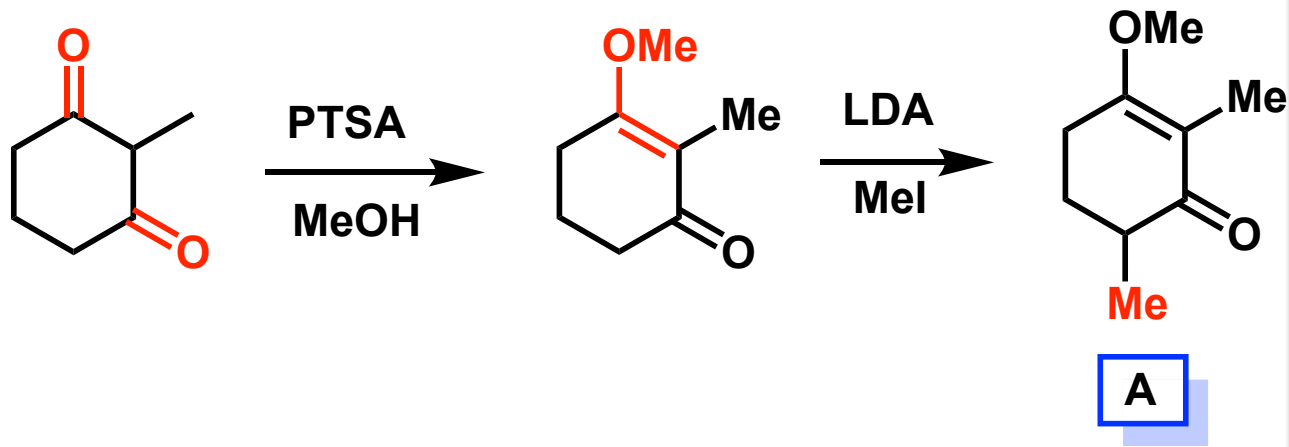
Pirrung, M. C., *J. Am. Chem. Soc.*, **1979**, *101*, 23, 7130

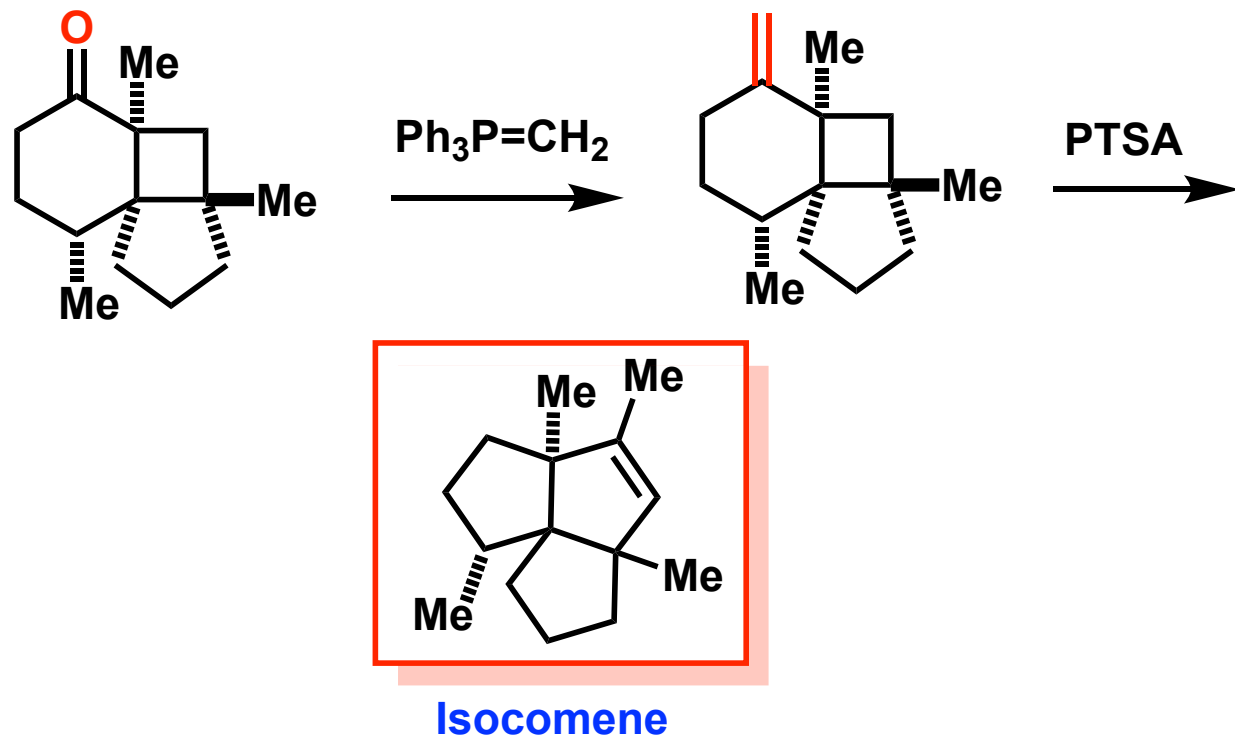
## Retrosynthesis

Isocomene



# Pirrung's Synthesis of Isocomene

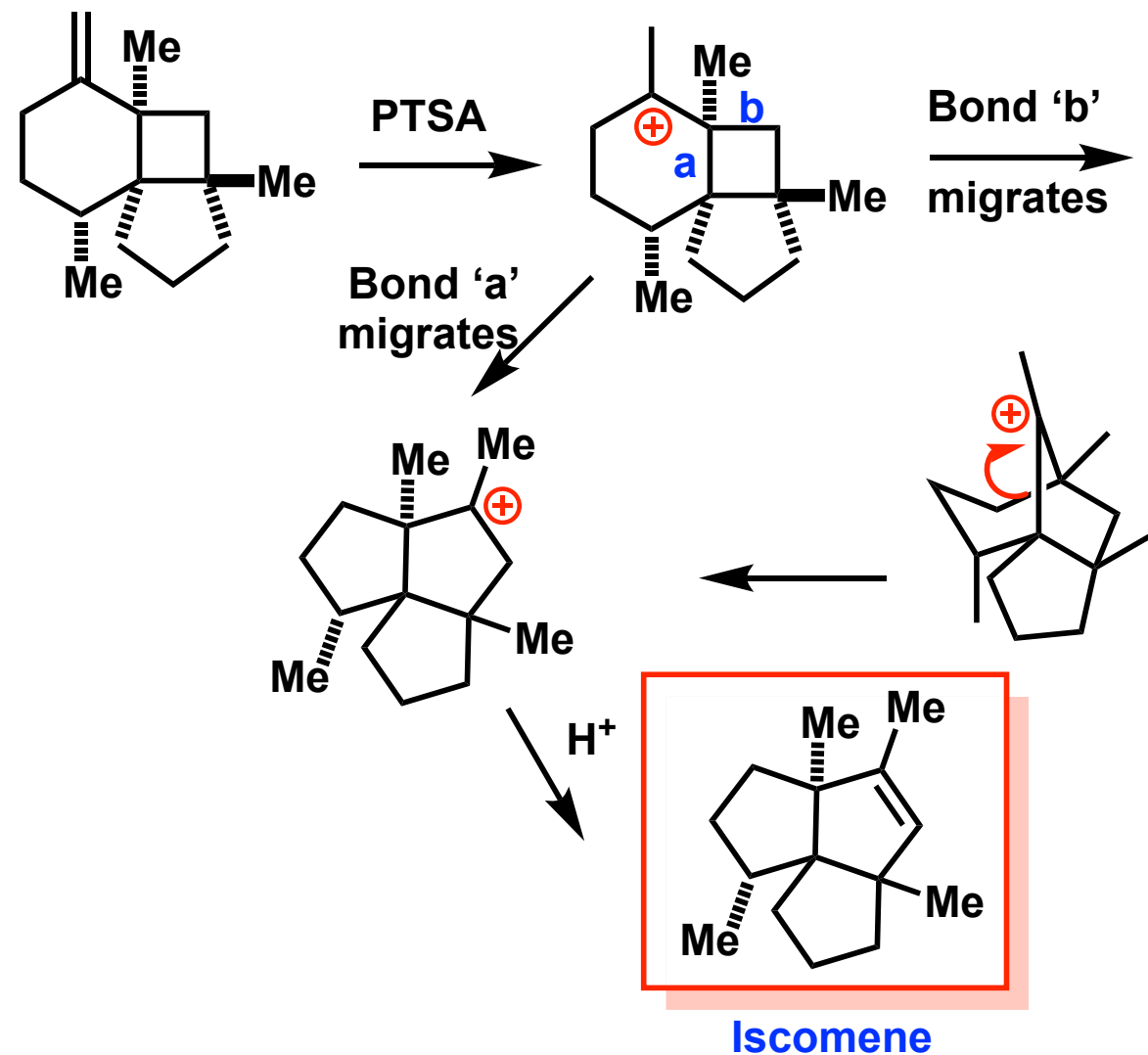




- The total synthesis of ( $\pm$ ) Isocomene was accomplished by Pirrung in 1979
- Their total synthesis was completed in 6 longest linear steps with a 42% overall yield

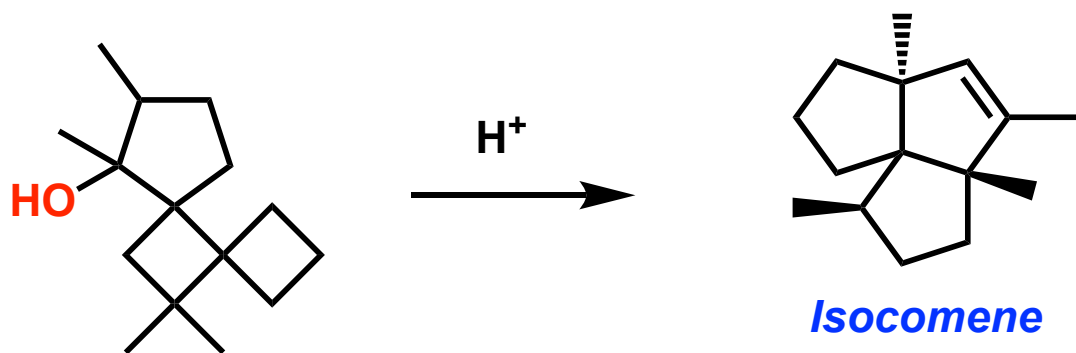
Pirrung, M. C., *J. Am. Chem. Soc.*, **1979**, *101*, 23, 7130

## Mechanism



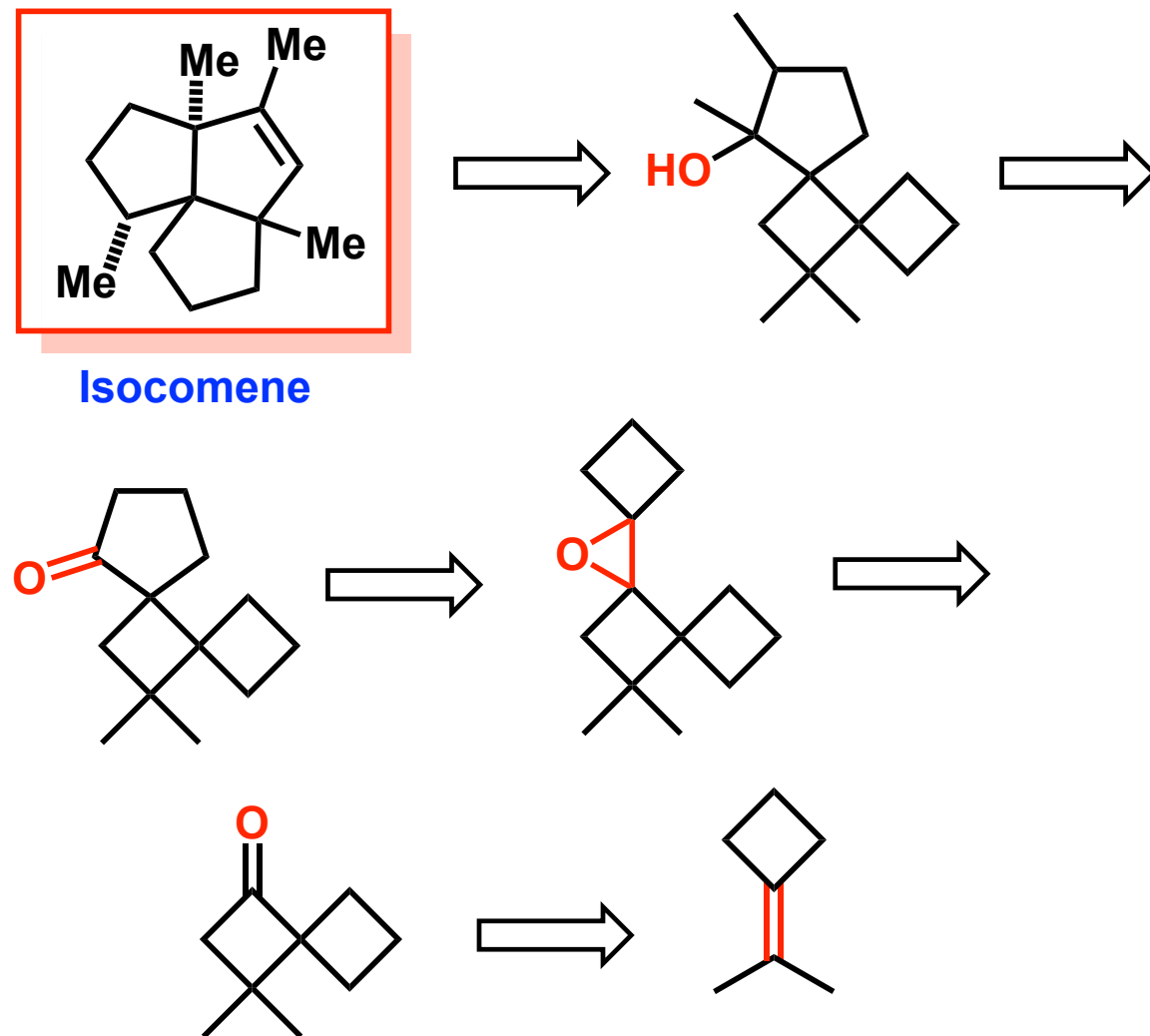
## Key Reaction

Acid catalyzed cascade rearrangement



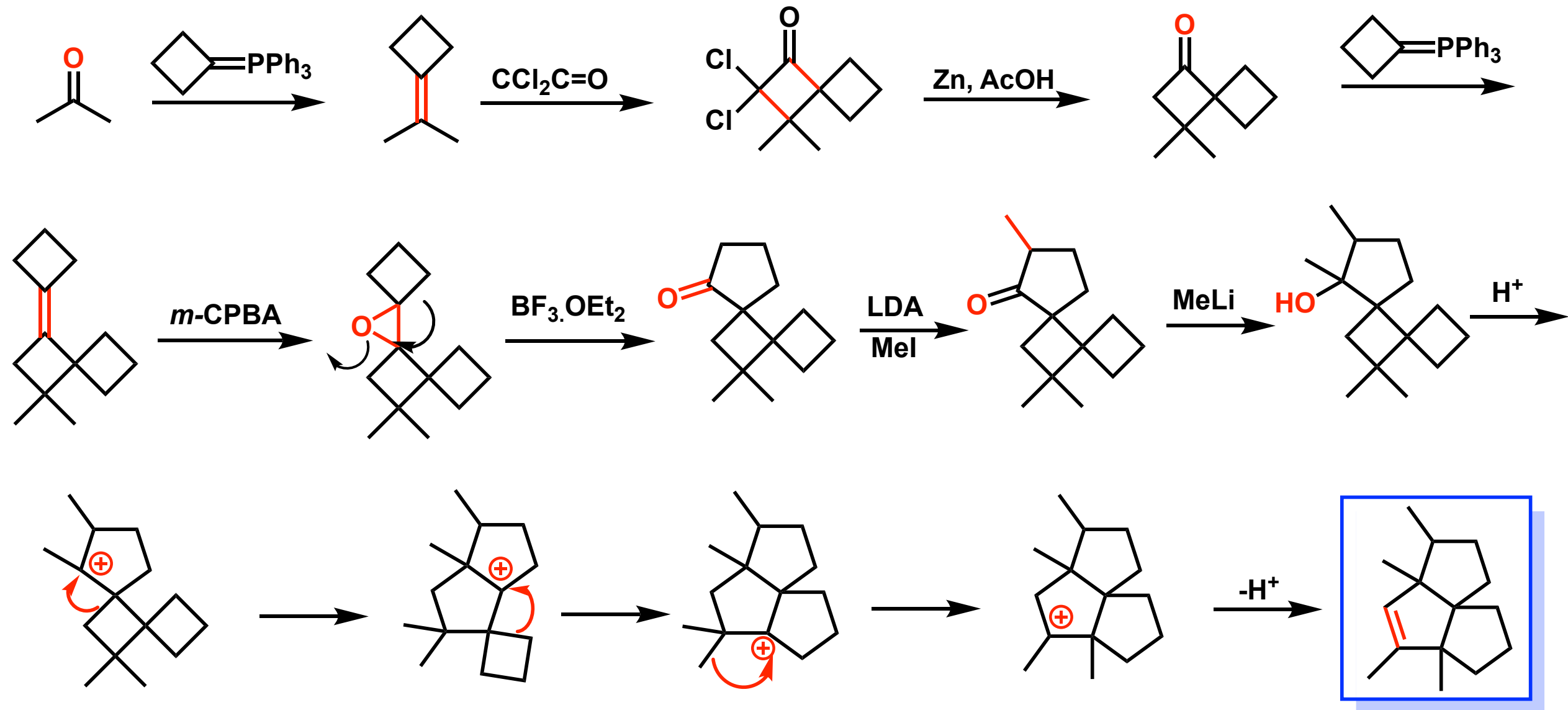
Fitjer, L., *et.al.*, *Tetrahedron Lett.*, **1988**, 29, 5525

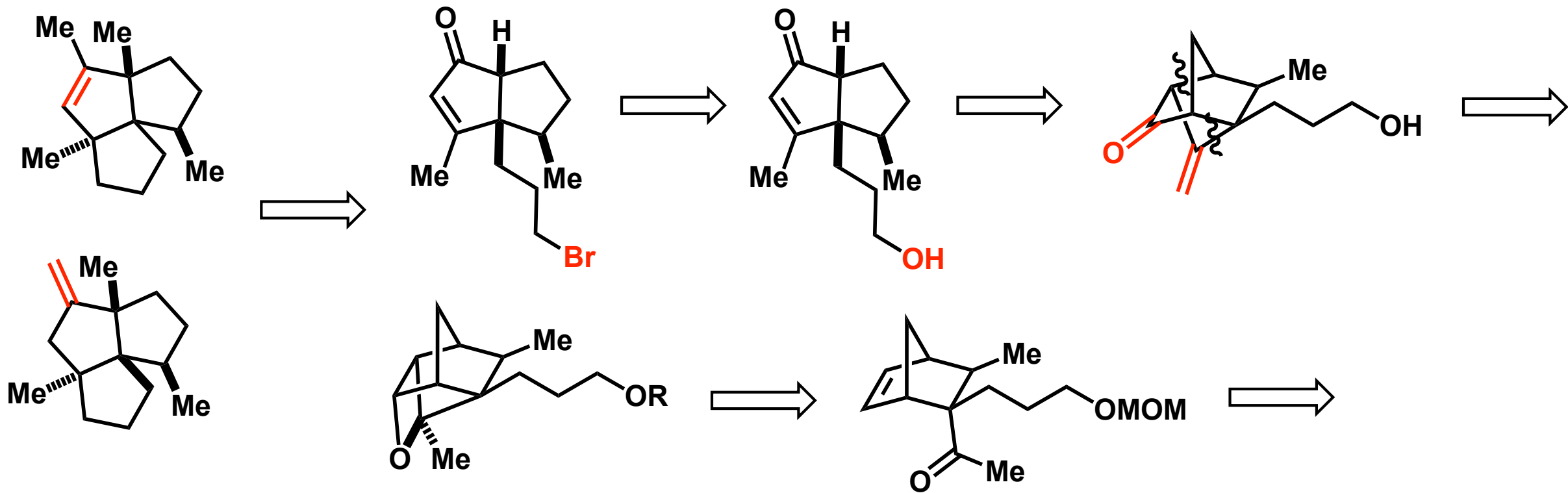
## Retrosynthesis





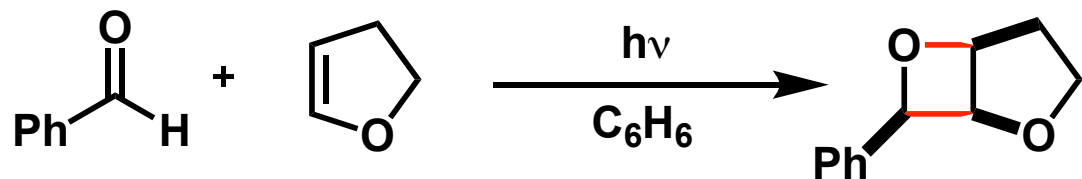
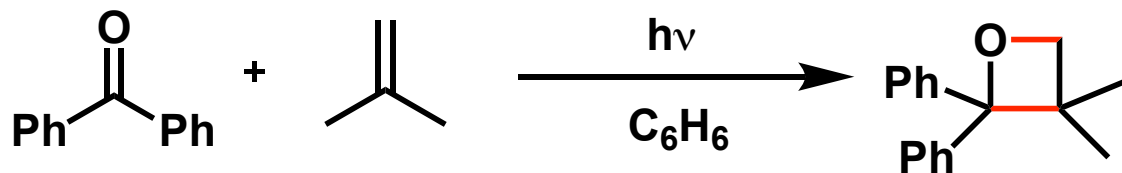
# Fitjer's Synthesis of Isocomenes



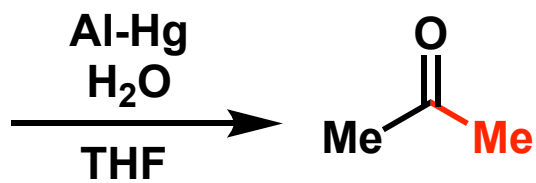
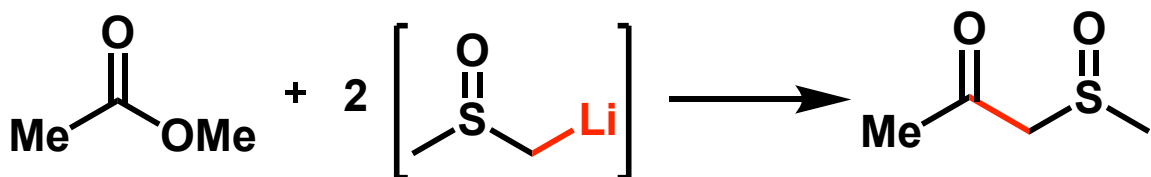


Rawal, V. H.; *et.al.*, *J. Chem. Soc. Chem. Commun.*, **1994**, 1797

## Key reactions Paterno-Buchi

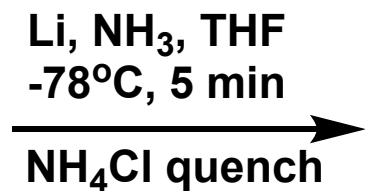
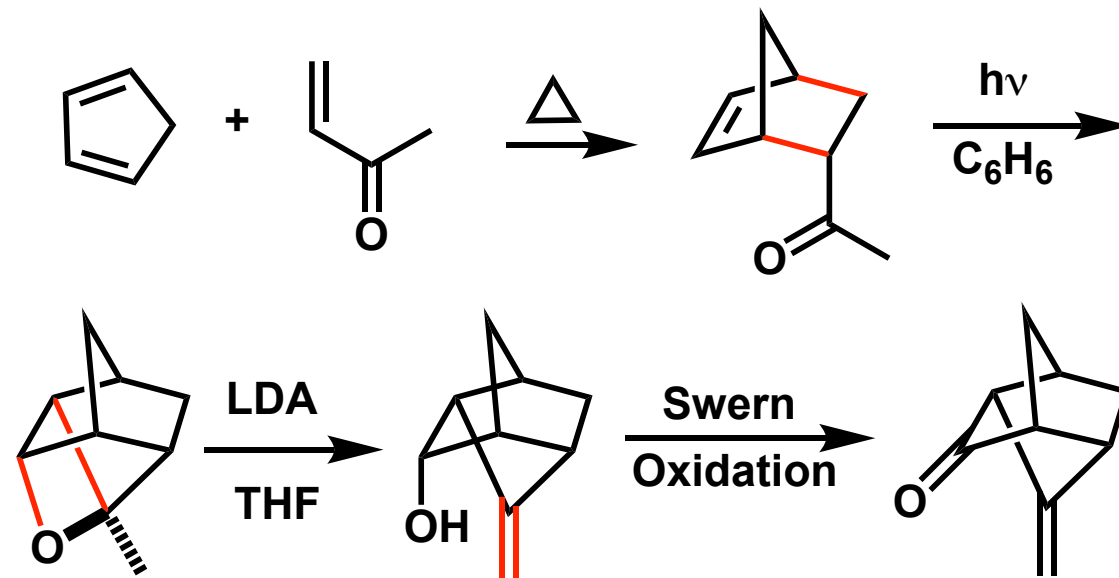


Büchi, G.; *et.al.*, *J. Am. Chem. Soc.*, 1954, 76, 4327

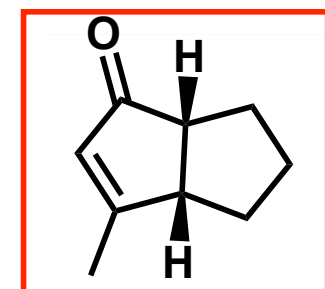


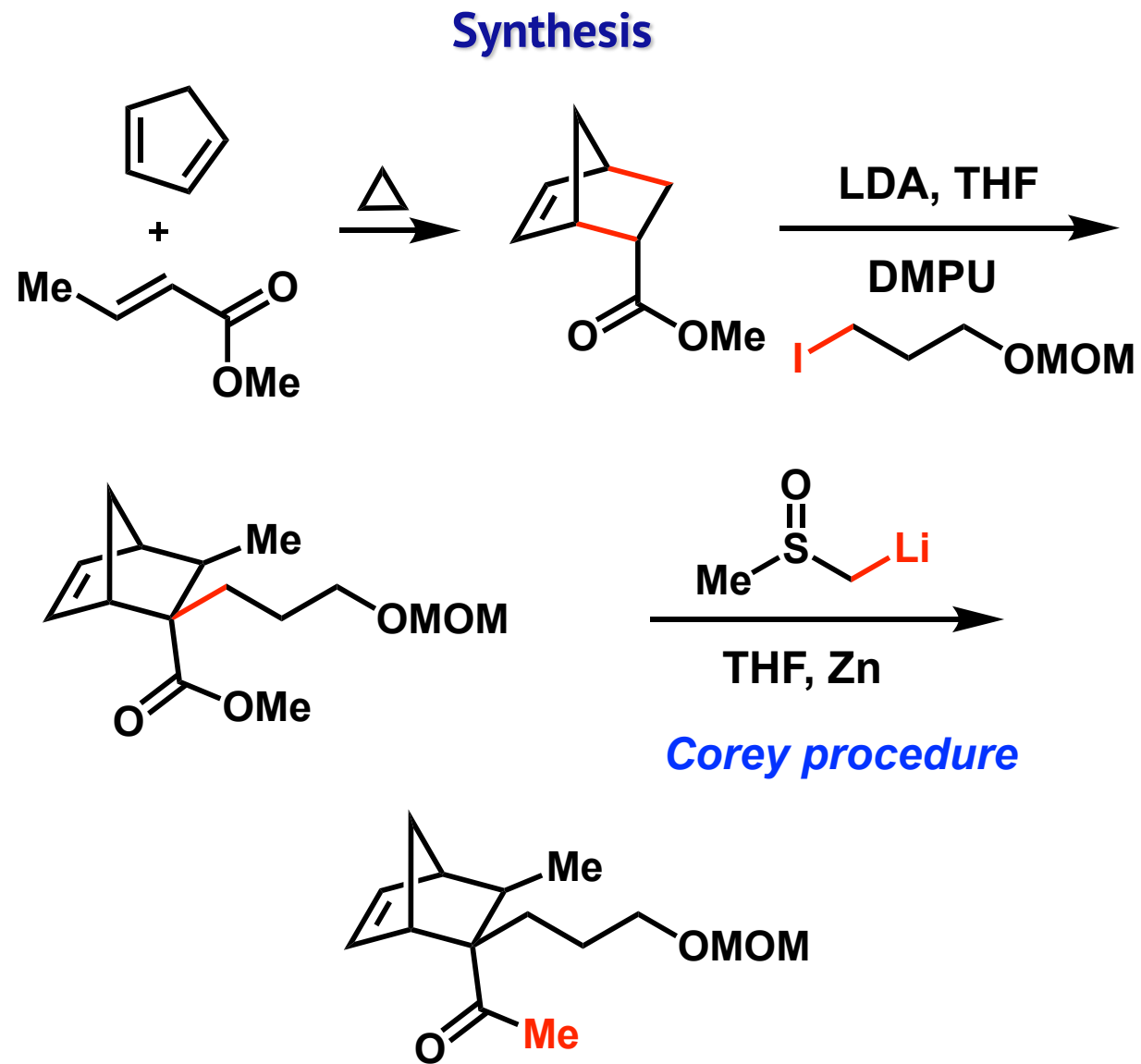
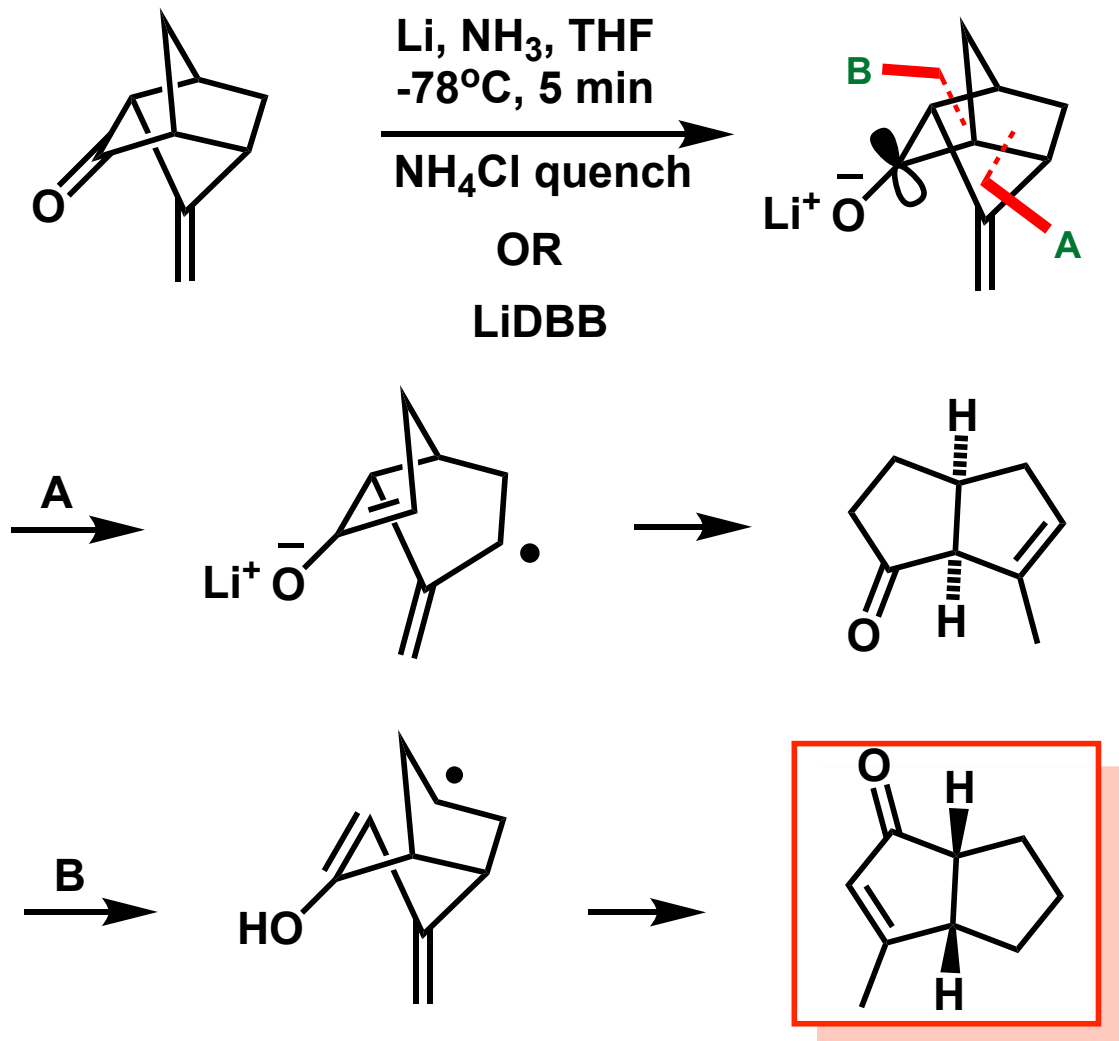
Corey, E. J., and Chaykovsky, M., *J. Am. Chem. Soc.*, 1965, 87, 1345

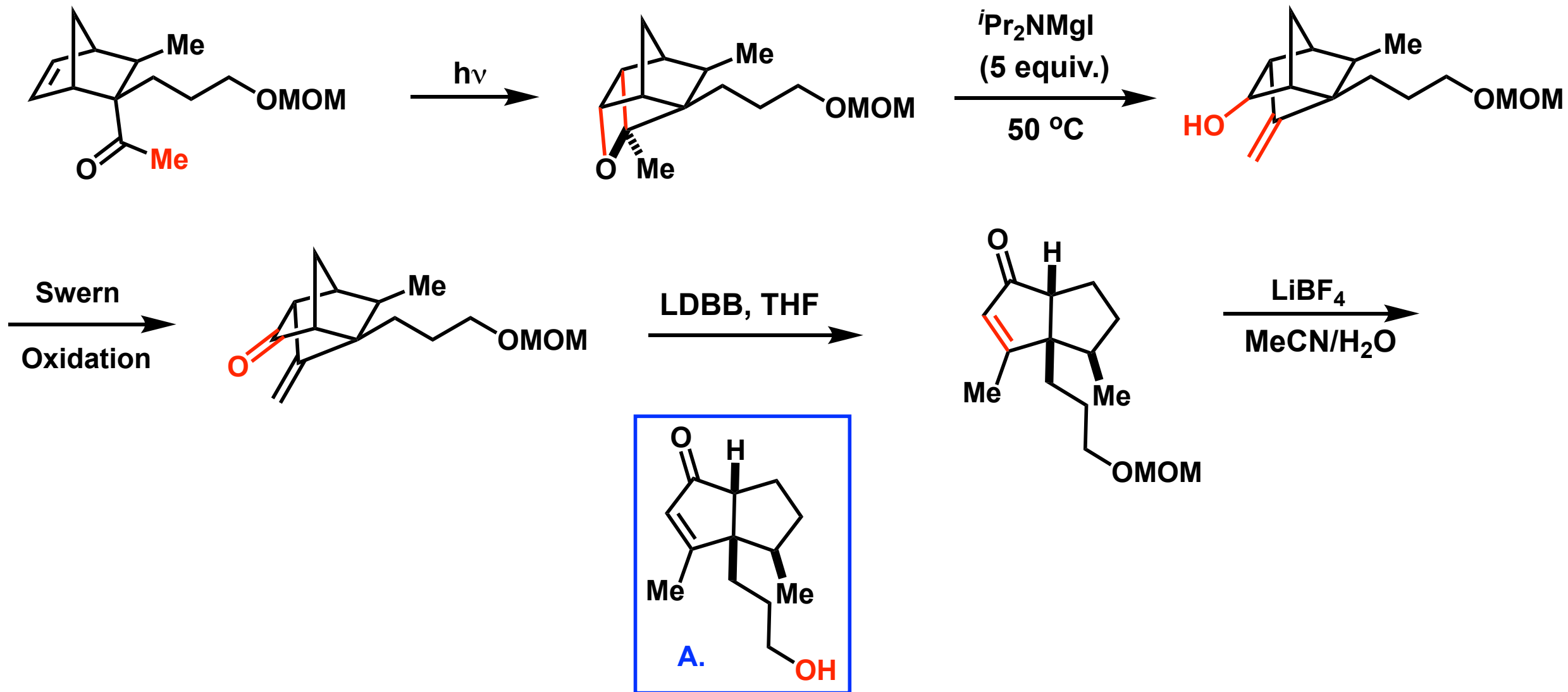
## Ring Opening of Oxetanes



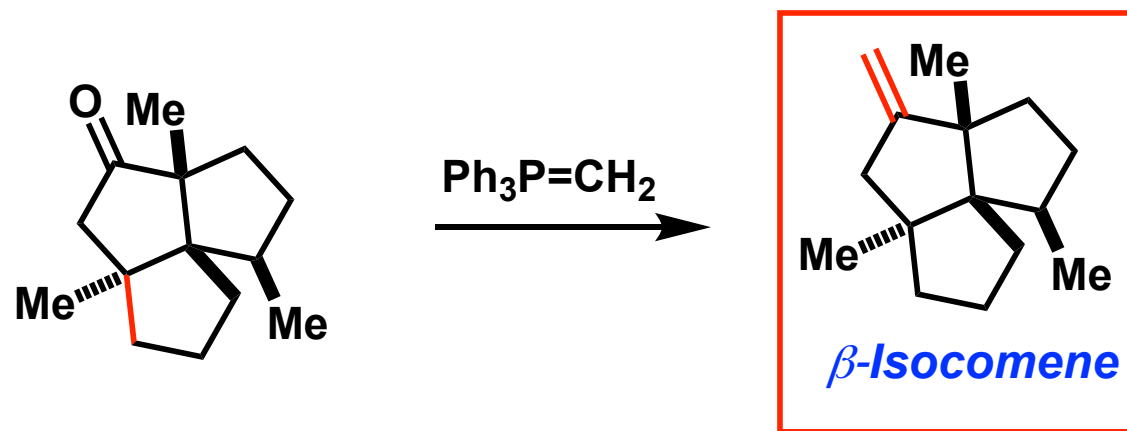
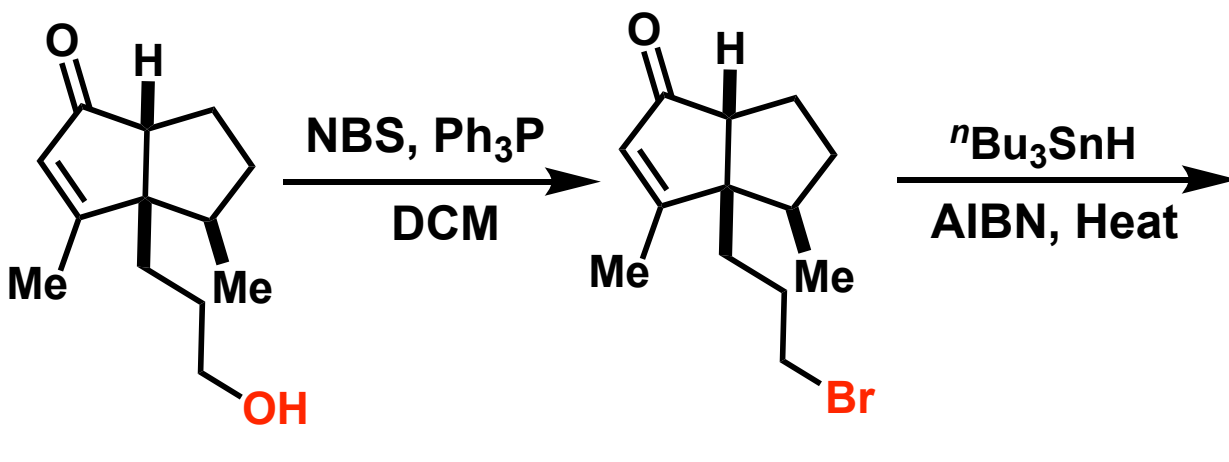
OR  
LiDBB



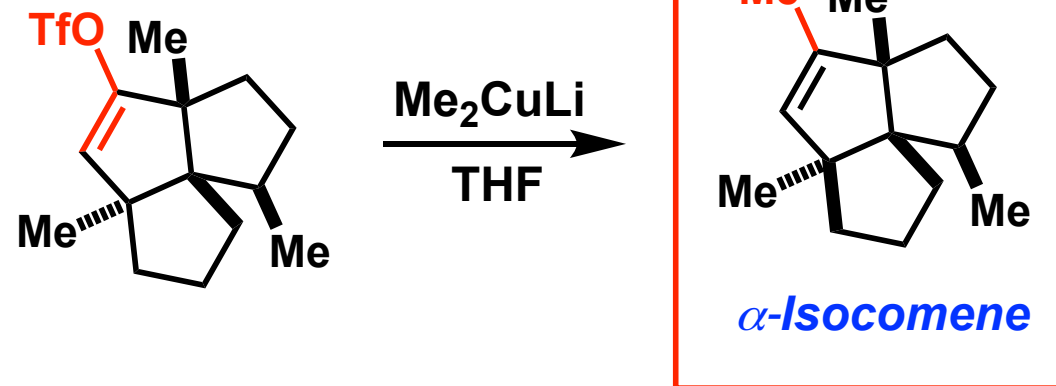
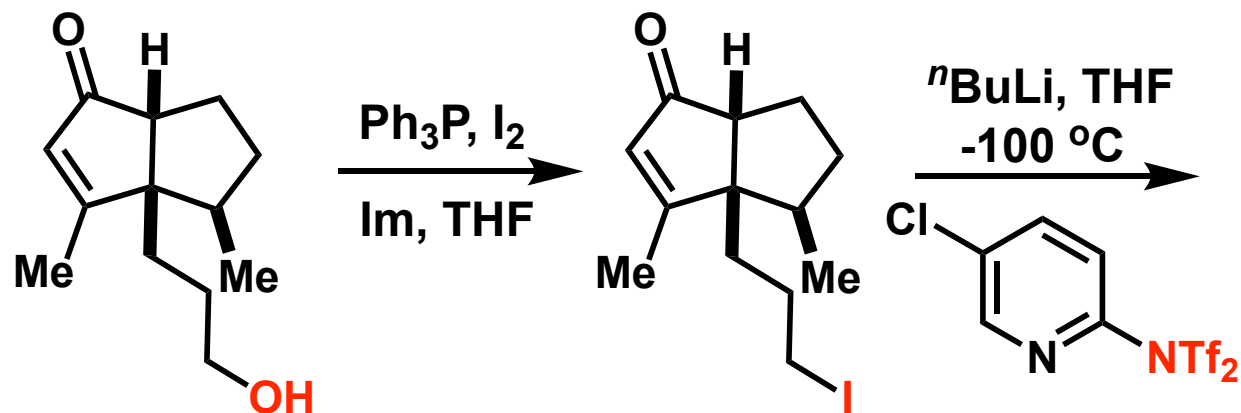




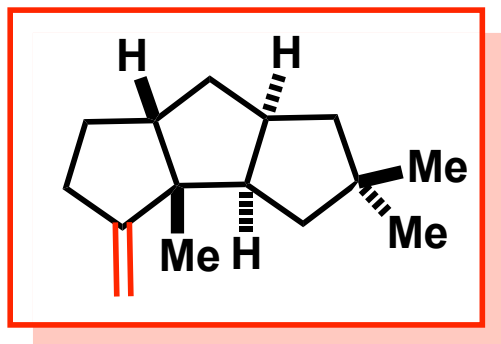
## Synthesis of $\beta$ -Isocomene



## Synthesis of $\alpha$ -Isocomene



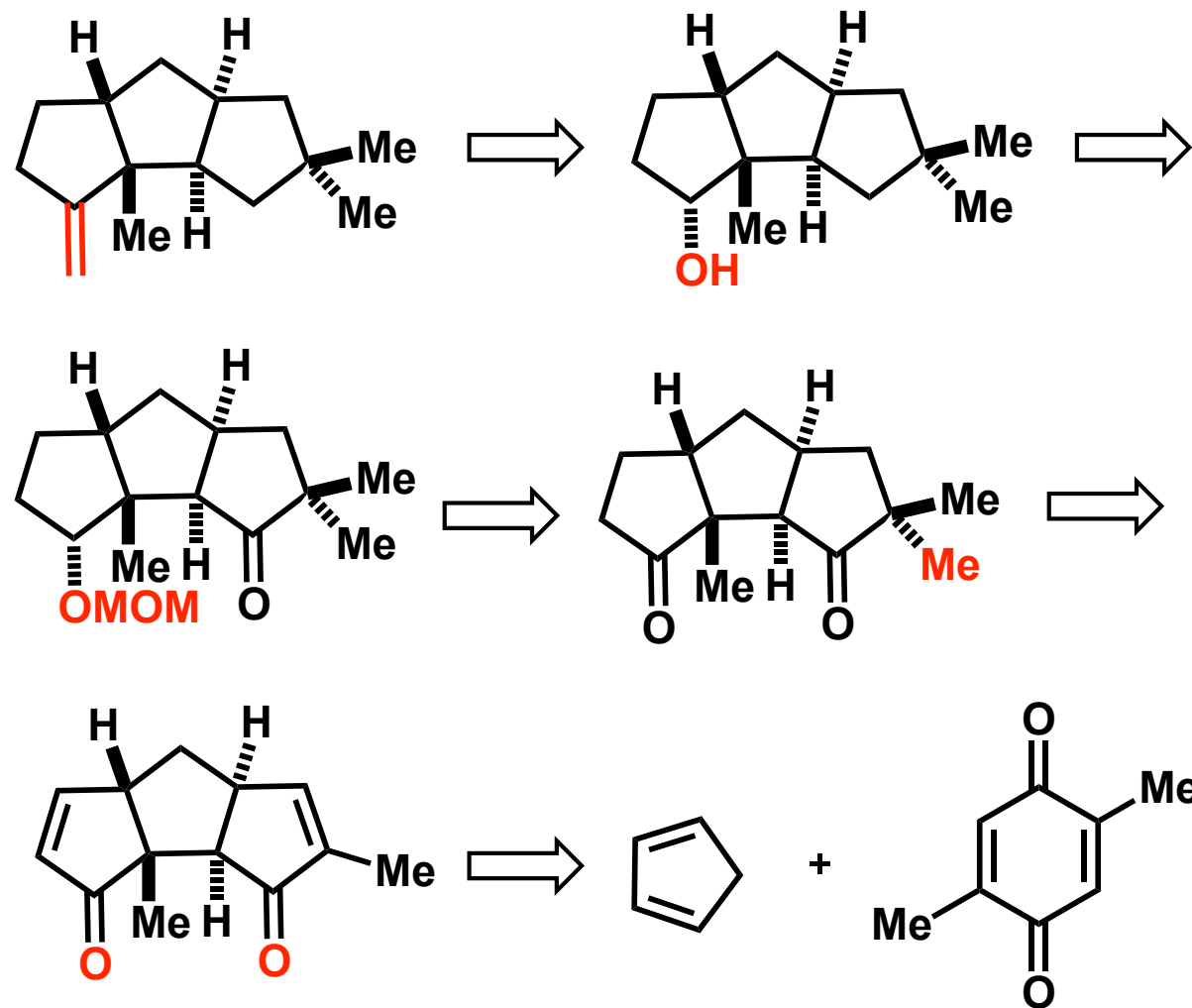
Rawal, V. H.; *et.al.*, *J. Chem. Soc. Chem. Commun.*, **1994**, 1797



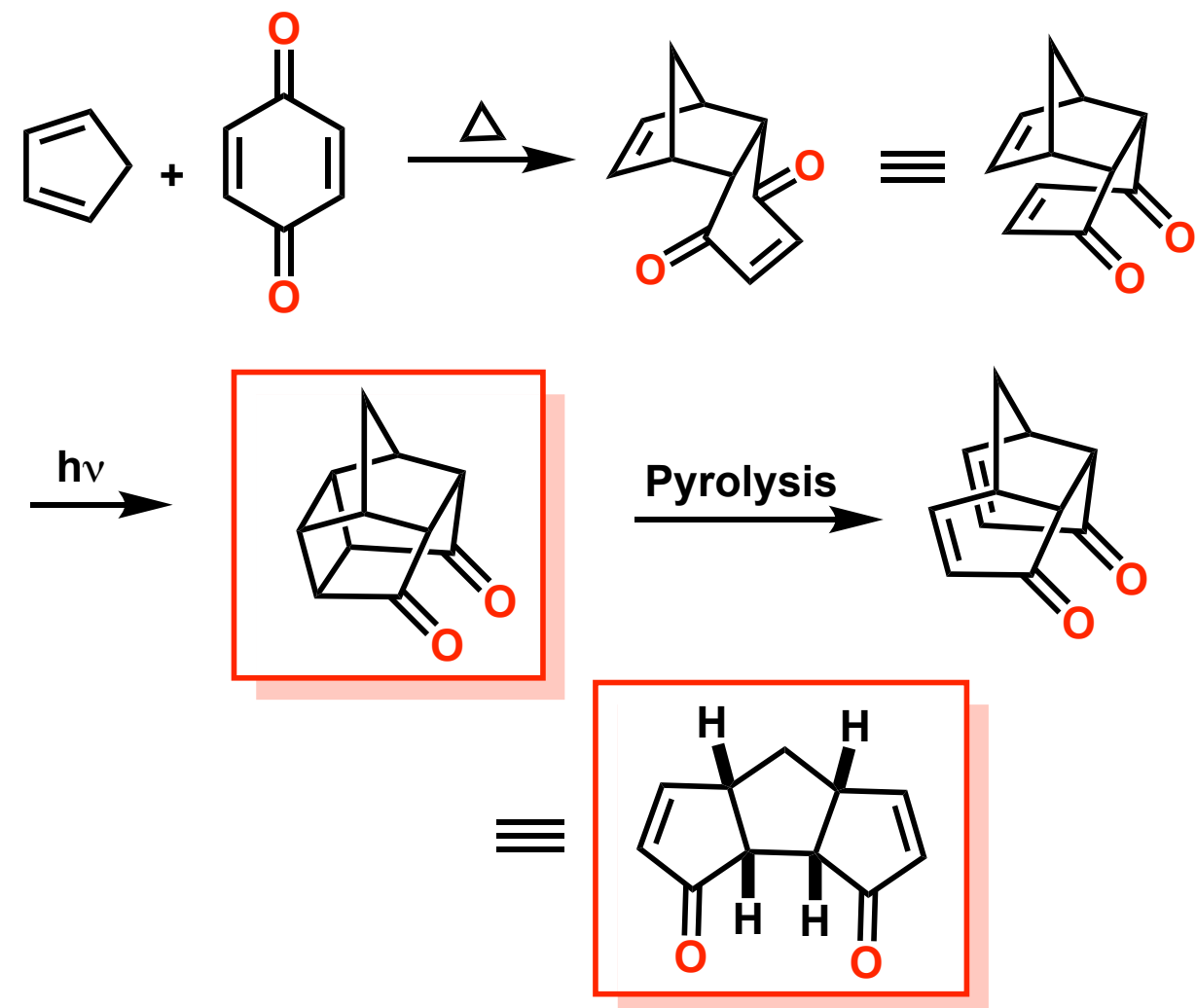
- A synthesis of the tricyclic sesquiterpene hydrocarbon ( $\pm$ ) - **hirsutene**, involving a novel **photo-thermal metathetic sequence** as the key step to generate the linearly fused tricyclopentanoid framework, was reported by **Mehta *et al.* in 1981**

Mehta, G. *et al* *J.C.S. Chem Comm*, **1981**, 756-757

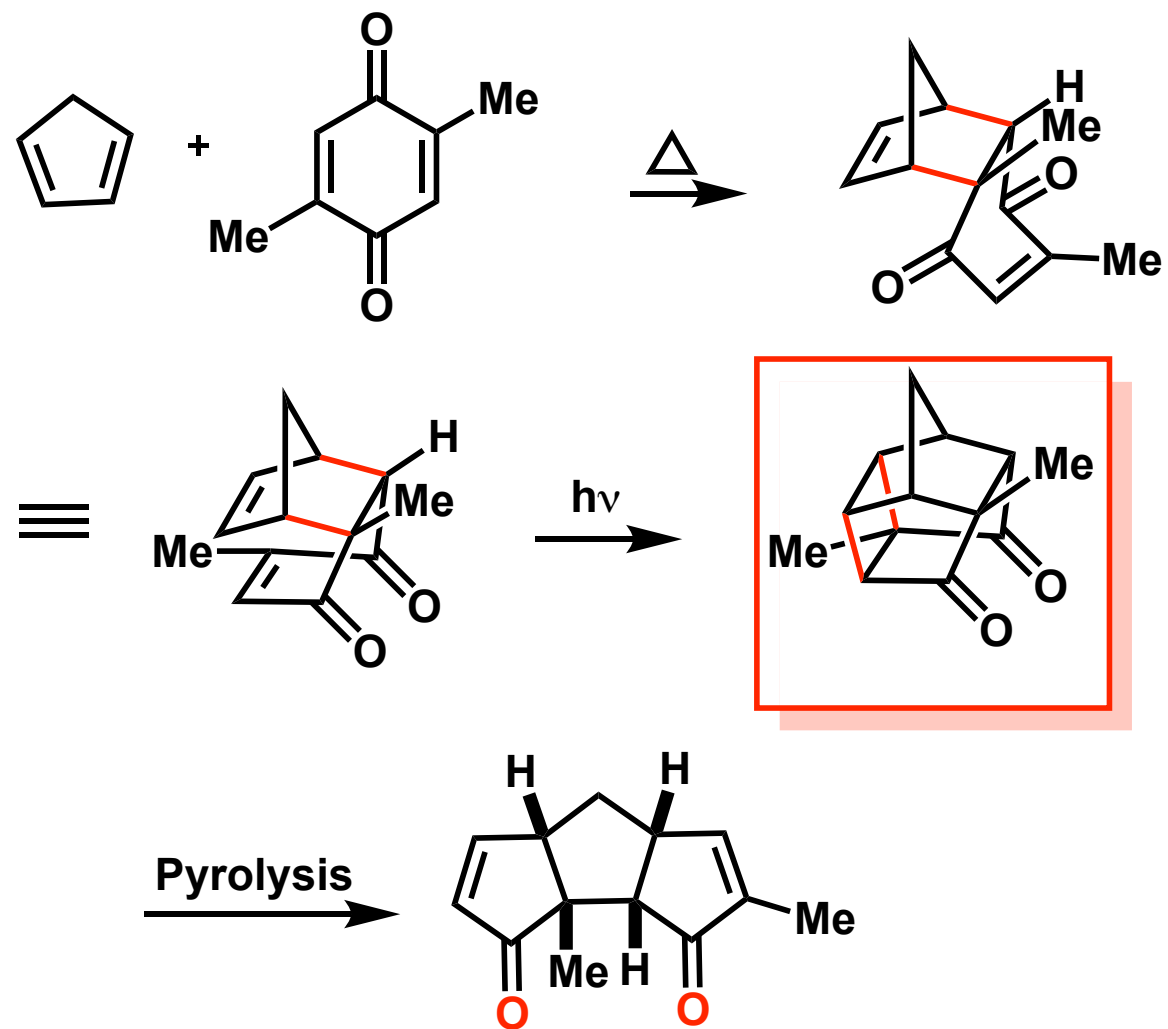
## Retrosynthetic Analysis



## Thermal Metathesis

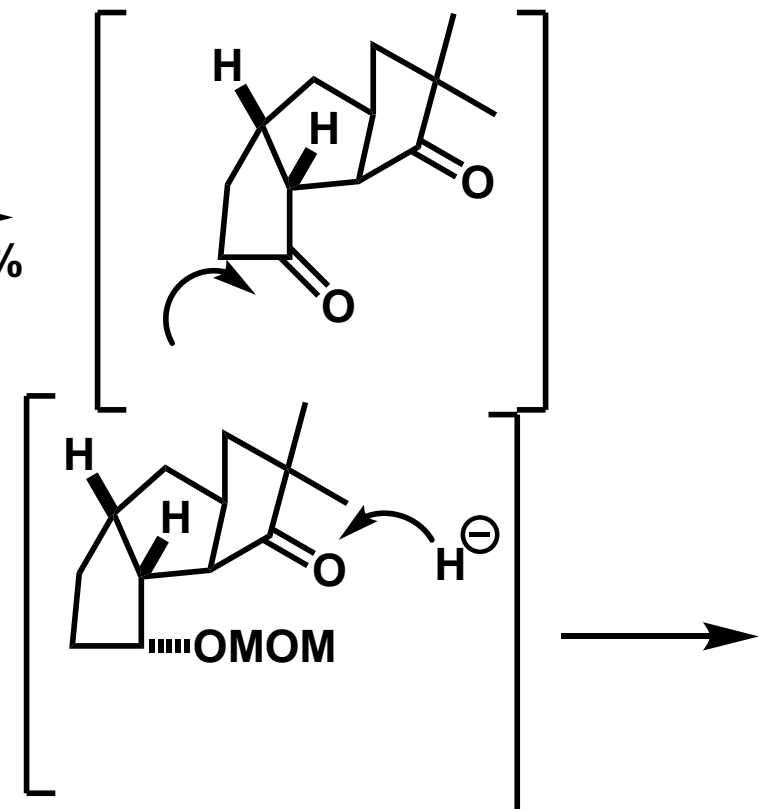
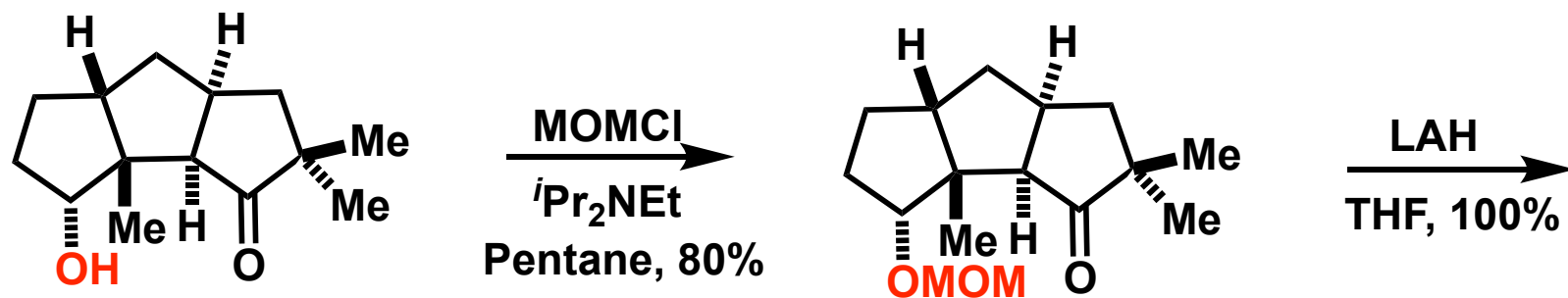
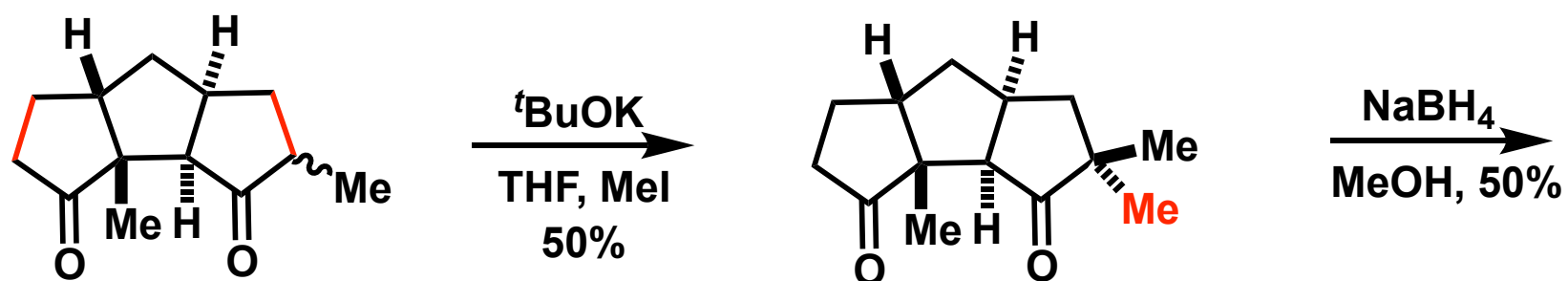
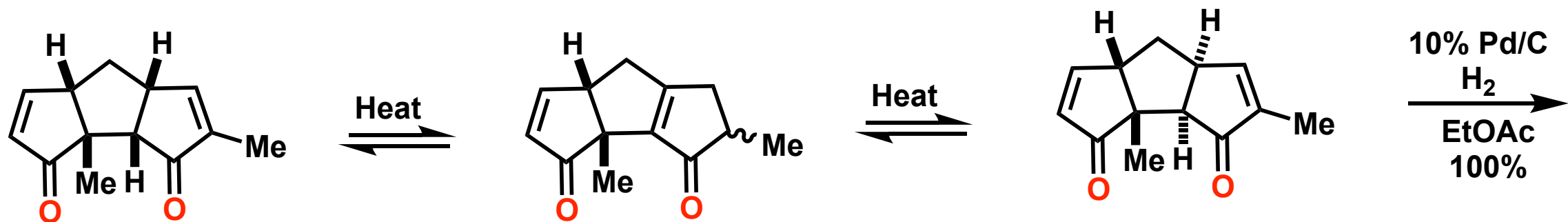


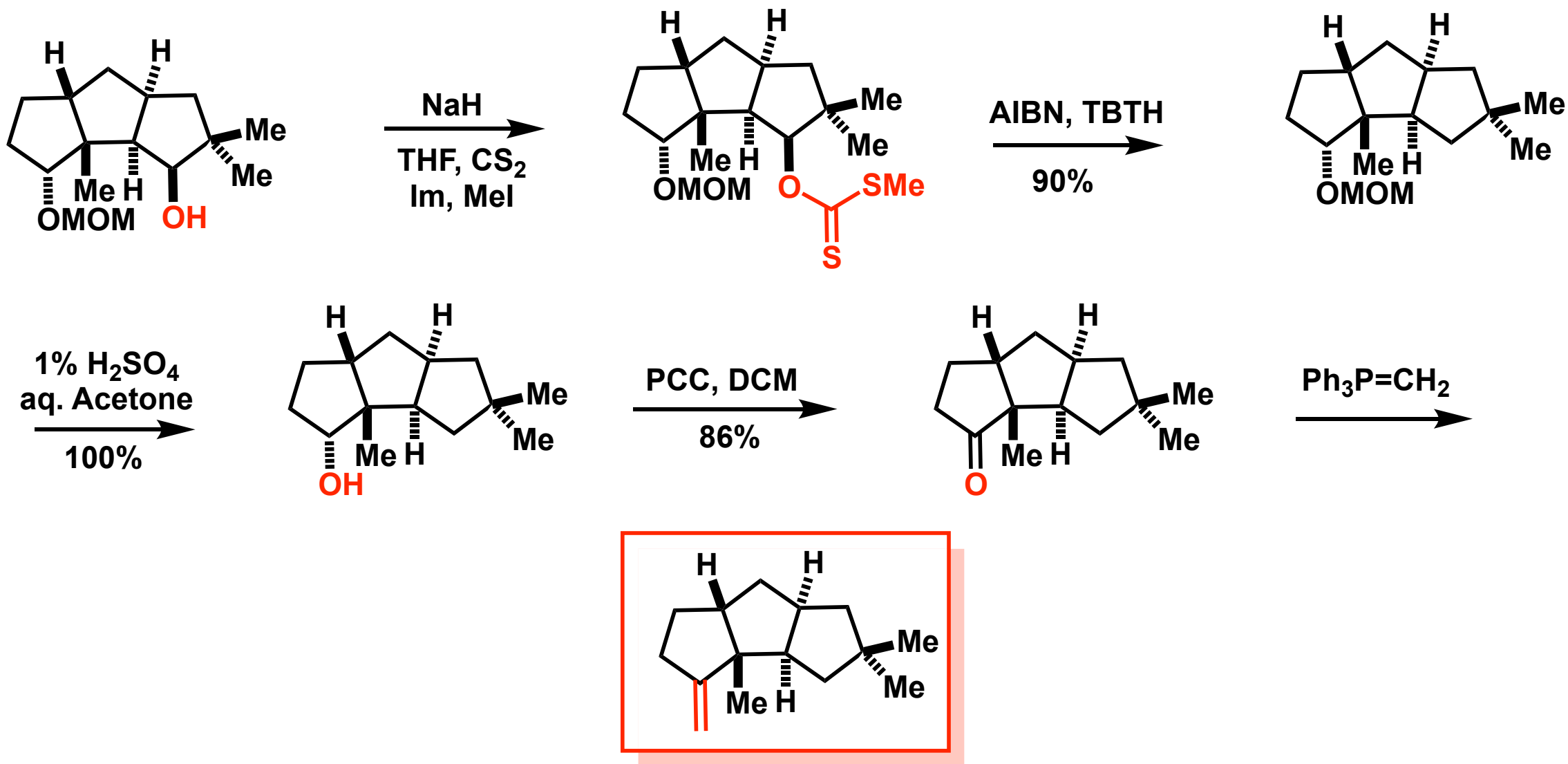
## Forward Synthesis

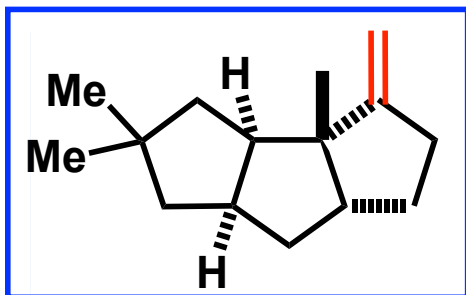




# Mehta's Synthesis of Hirsutene



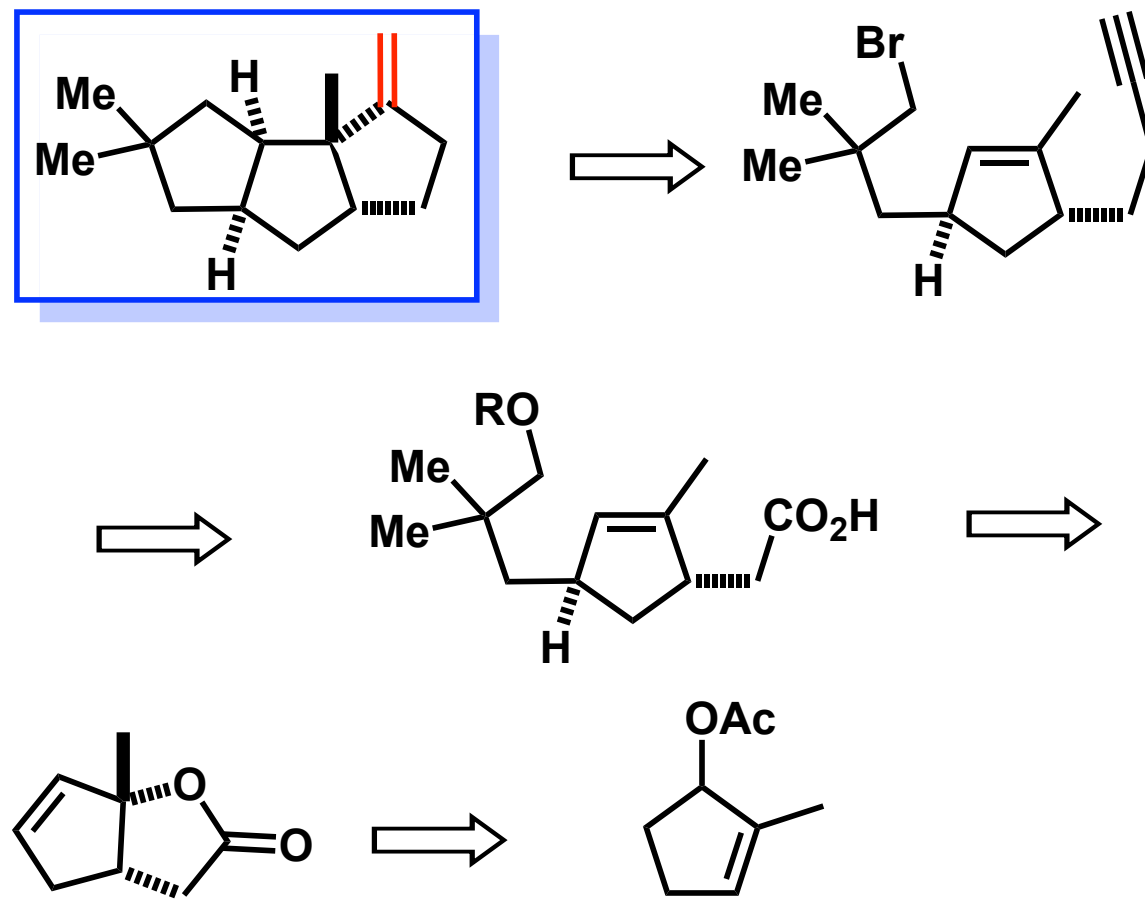




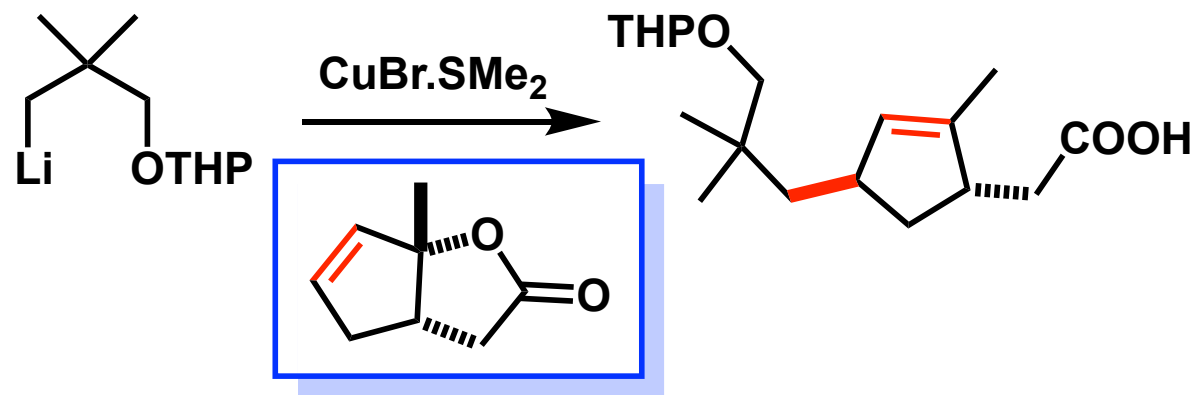
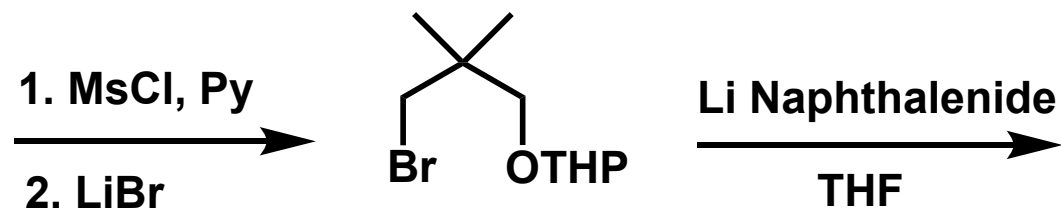
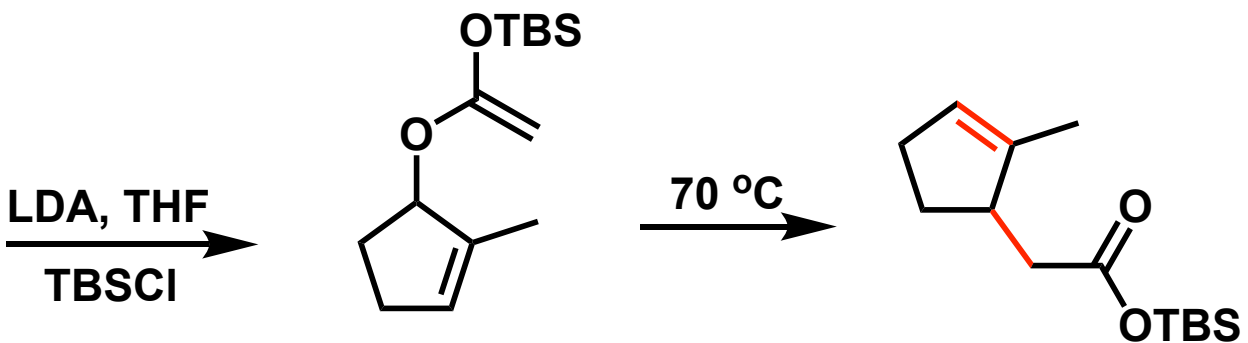
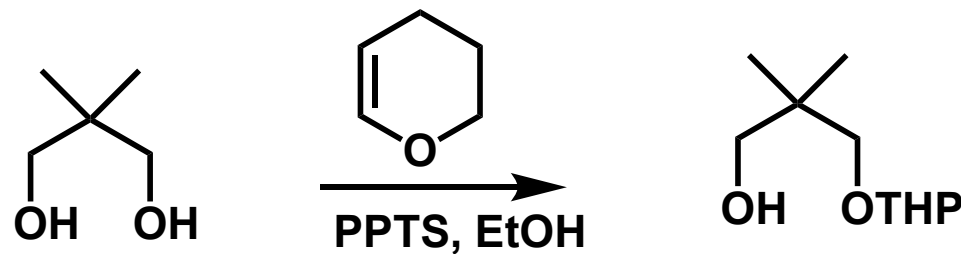
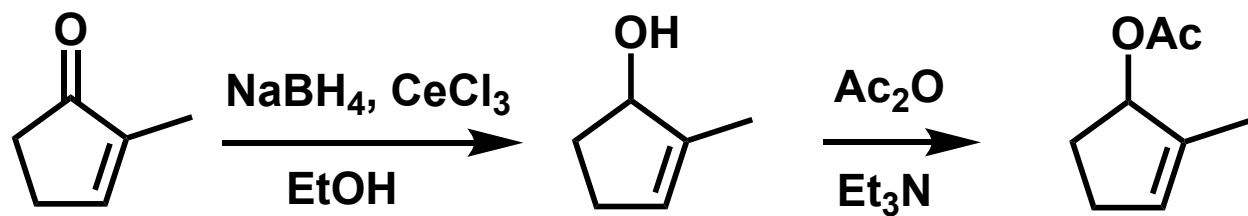
Curran, D. P and Rakiewicz, D. M, *J. Am. Chem. Soc.* **1985**, 107, 1448-1449

- Key reactions are: **Claisen rearrangement** and a **tandem radical cyclization** to construct the linear triquinane skeleton
- One of the early examples radical polyene cyclization

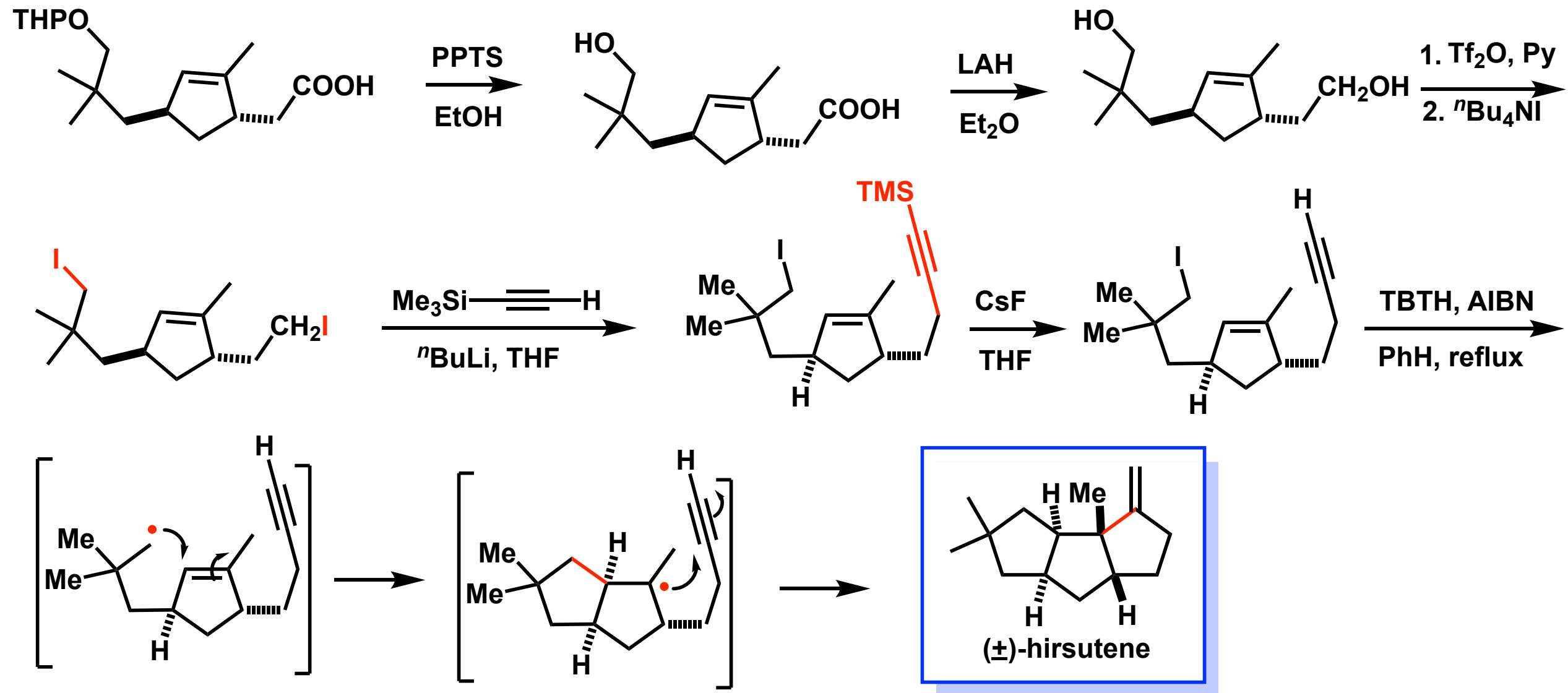
## Retrosynthetic Analysis

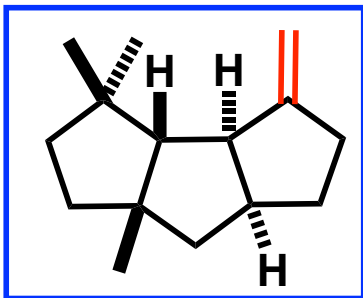


# Curran's Synthesis of Hirsutene



# Curran's Synthesis of Hirsutene





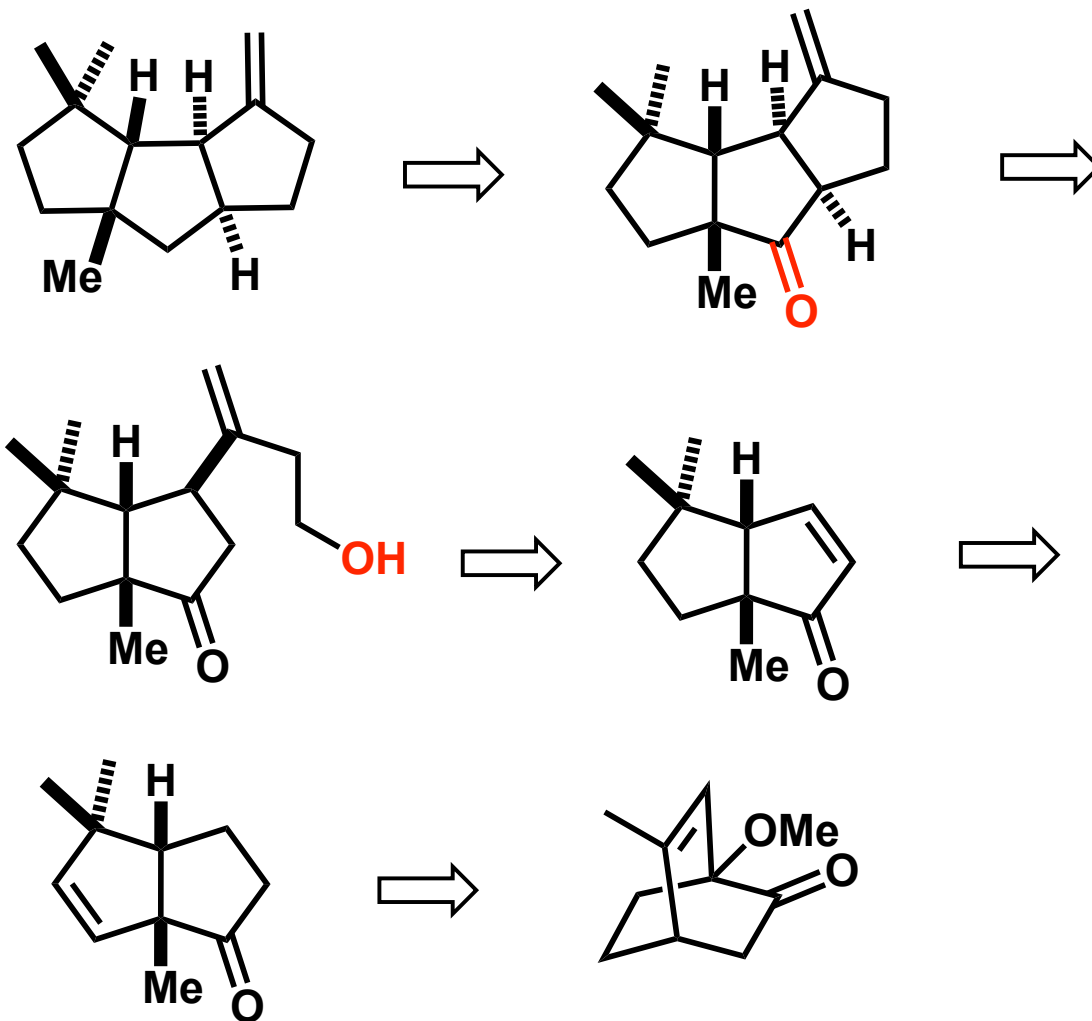
- **Capnellene** the simplest member of the capnellane group of marine sesquiterpenes, was isolated in **1978** by **Djerassi et. al.** from the soft coral *Capnella imbricata*

Ayanoglu, E., et. al, *Tetrahedron Lett.* **1978**, 1671

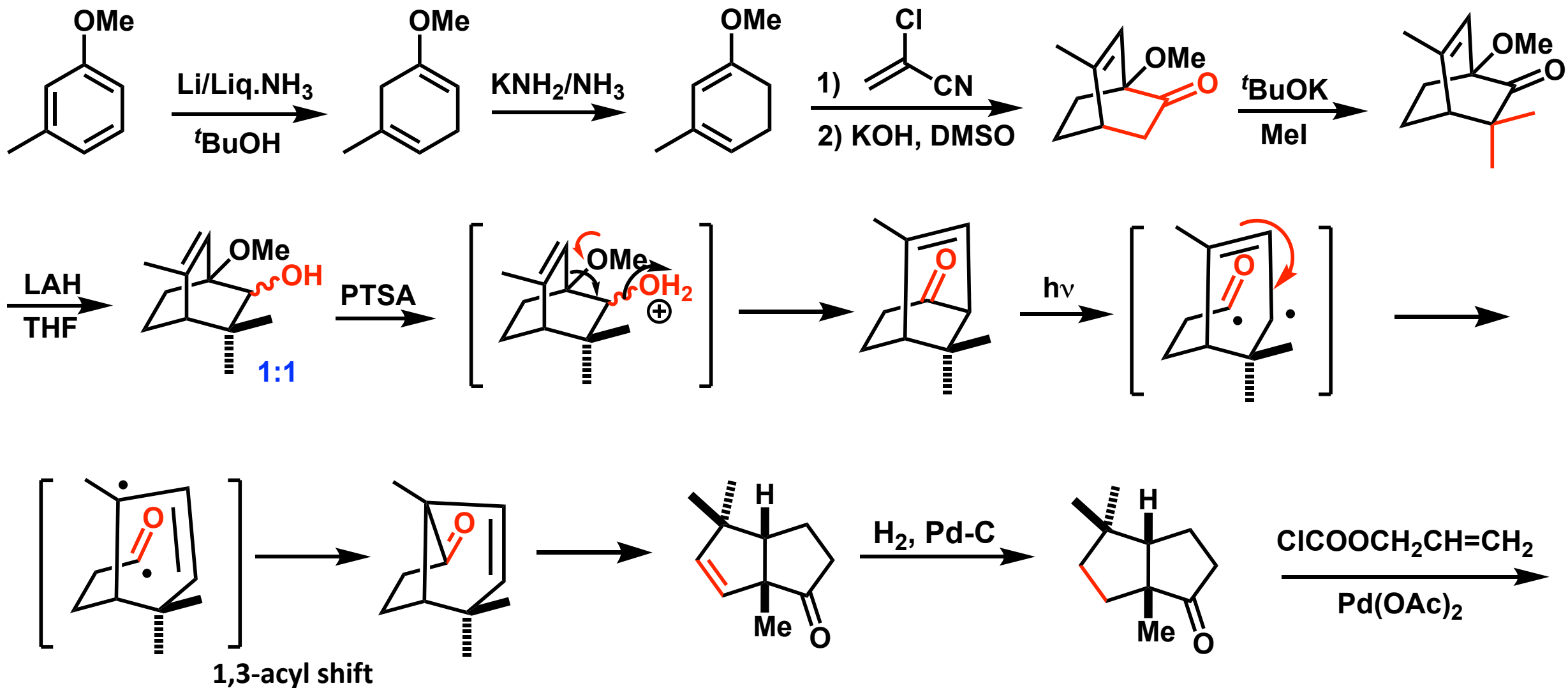
- **Uyehara** and co-workers have explored the **photochemical 1,3-acyl shift** in a bicyclo[3.2.1]oct-6-en-2-one derivative for generating the **diquinane unit of capnellane**

Uyehara, T., and co-workers, *J. Org. Chem.*, **1989**, 54, 5411

## Retrosynthetic Analysis



# Uyehara's Synthesis of Capnellene



# Uyehara's Synthesis of Capnellene

