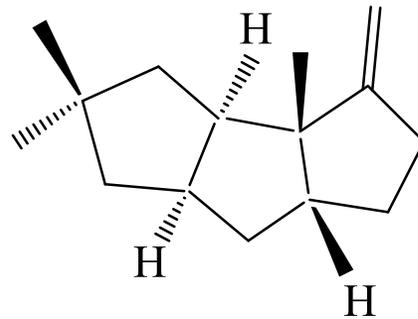


# Total Synthesis of Hirsutene



Salma Begum  
CEM 852  
1/31/2022

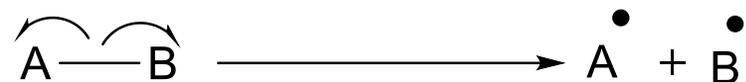
# Introduction

1. Hirsutene is a naturally occurring parent compound in class linear triquinane sesquiterpenoid (linearly fused tricyclopentanoid ring) typified by highly oxygenated Hirsutic acid and Corolin. Both of this compound have antitumor activity.
2. Dennis P. Curran synthesized Hirsutene in 1985 by using a different strategy called radical initiated tandem cyclization.
3. Hirsutene contains four stereogenic center, one of which is quaternary.
4. The key step of synthesizing this linear condensed cyclopentanoid is tandem hex-5-enyl radical cyclization.

# Radical Initiated Tandem Cyclization

Radical cyclization reactions are organic chemical transformations that yield cyclic products through radical intermediates.

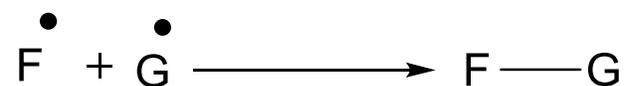
## 1. Selective radical generation



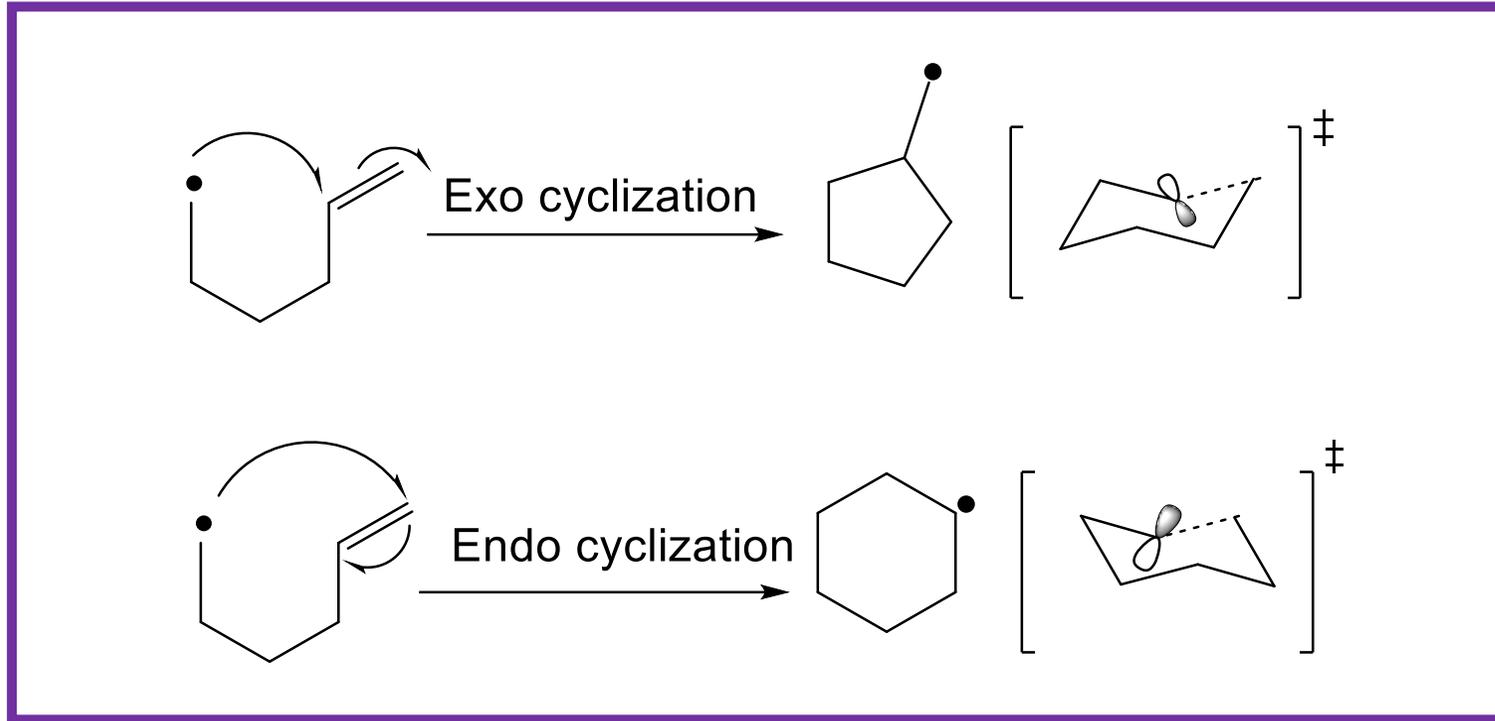
## 2. Propagation



## 3. Termination



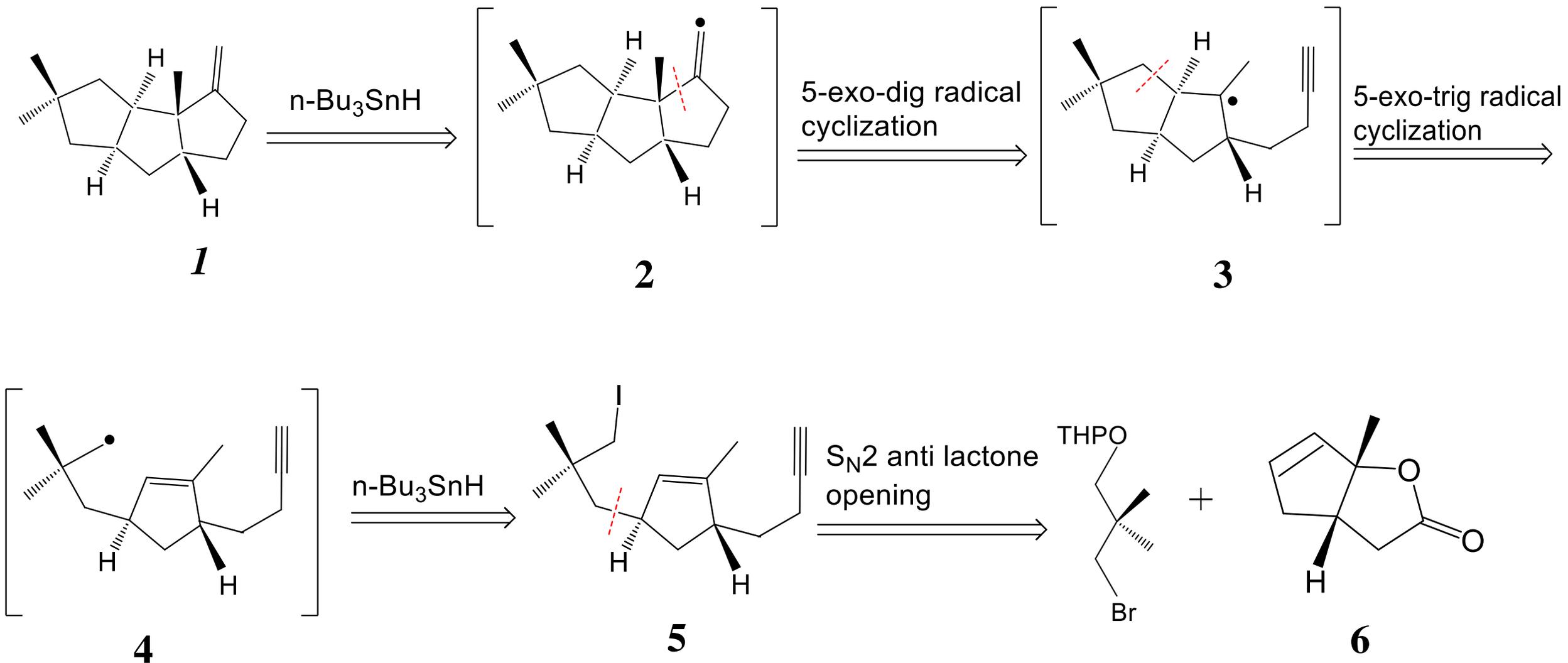
# Mechanism



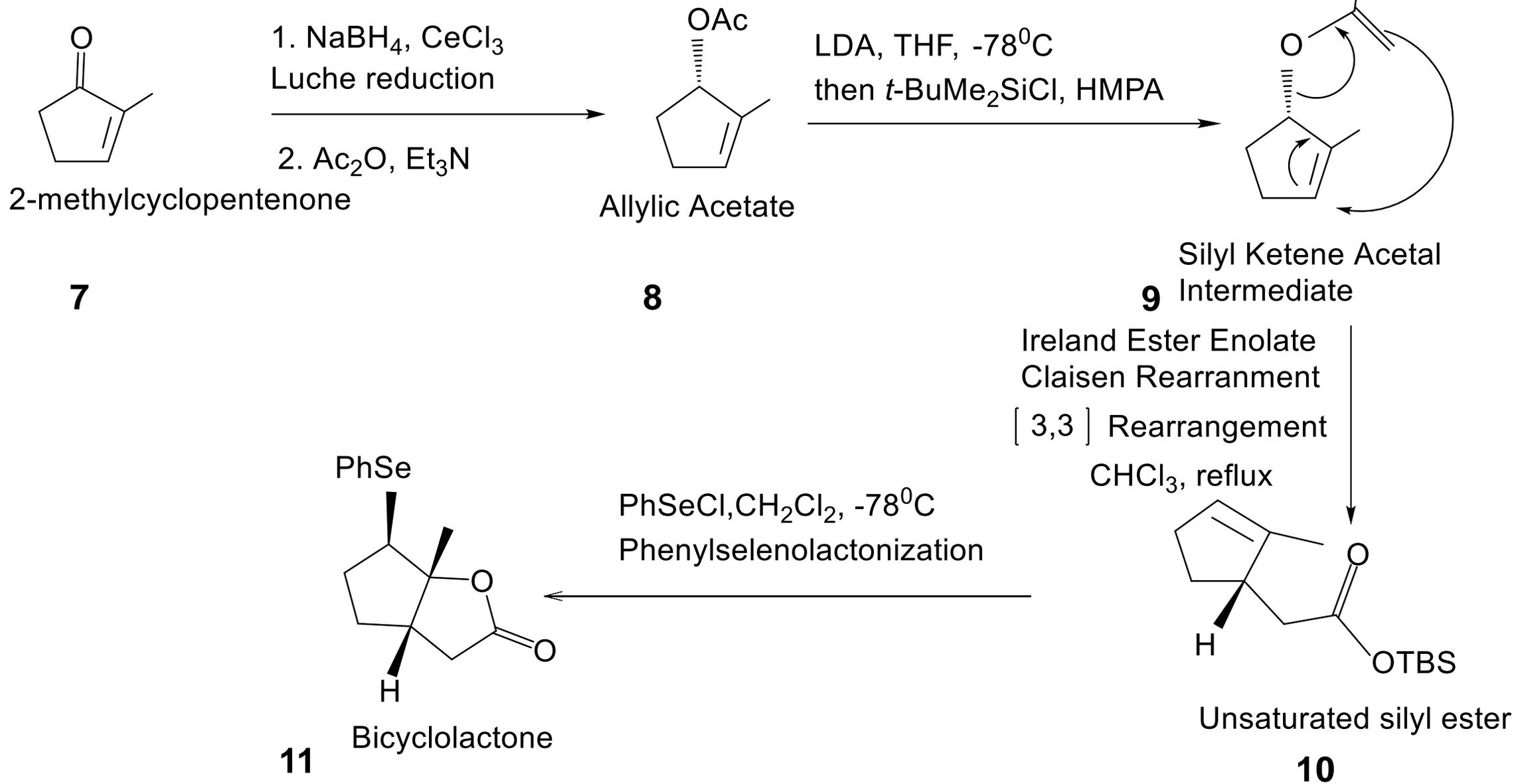
Even though exo intermediate is thermodynamically less stable than endo intermediate, exo cyclization is more common.

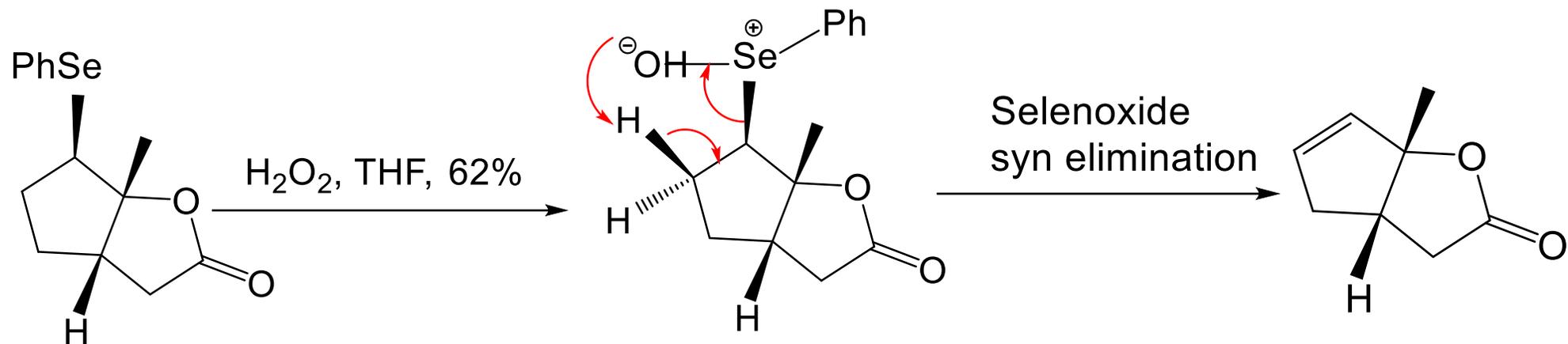
Baldwin, J.E., 1976. Rules for ring closure. *Journal of the Chemical Society, Chemical Communications*, (18), pp.734-736.

# Retrosynthesis



# Total Synthesis of Hirsutene



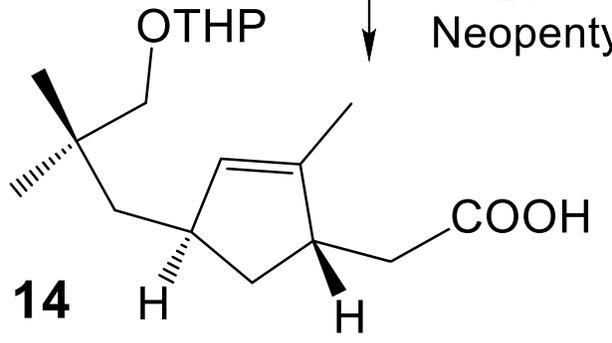
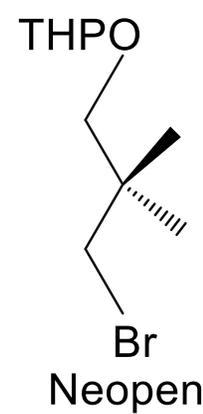


**11**

**12**

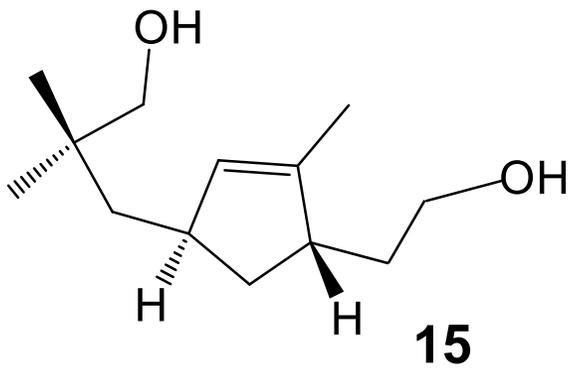
**13** Vinyl Lactone

Li naphthalenide, THF,  $-78^{\circ}\text{C}$   
 then  $\text{CuBr}\cdot\text{SMe}_2$   
 Vinyl lactone ring opening

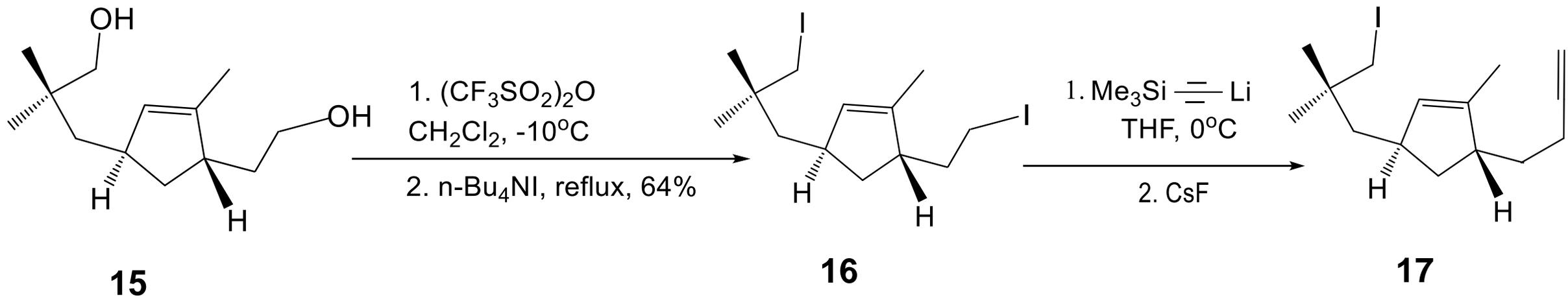


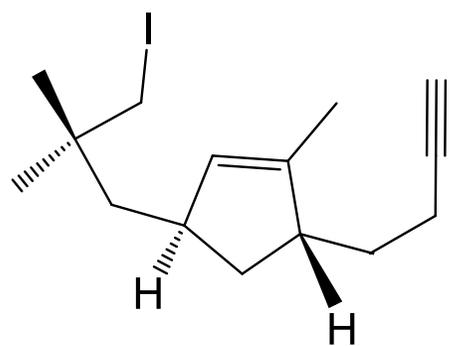
**14**

1. PPTS (ca.), EtOH  
 2.  $\text{LiAlH}_4$  (ca. 64% overall)



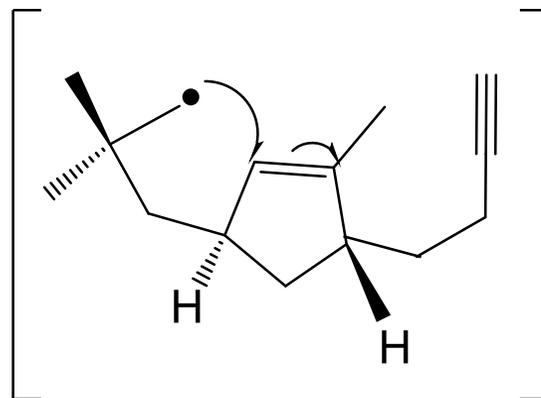
**15**





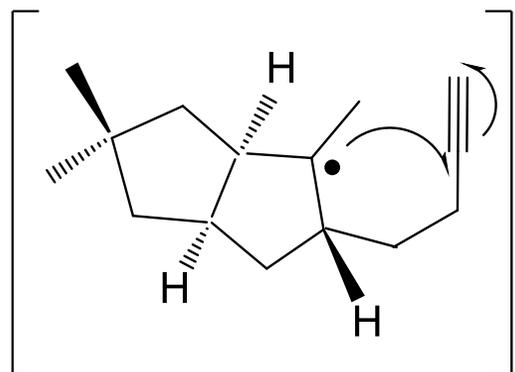
**17**

n- Bu<sub>3</sub>SnH, AIBN  
PhH(0.02M), reflux



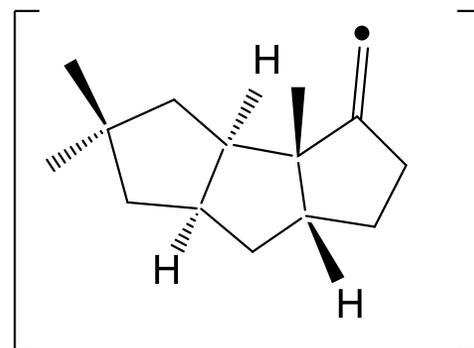
**18**

5 exo-trig radical  
cyclization



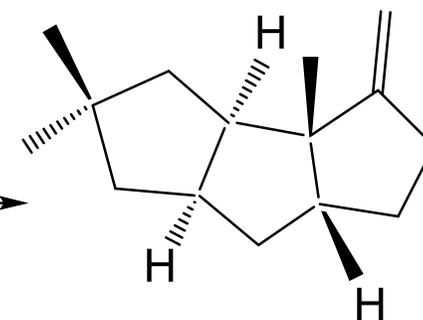
**19**

5 exo-dig radical  
cyclization



**20**

n-Bu<sub>3</sub>SnH



(±)Hirsutene

**21**

# Conclusion

1. Radical cyclization process was important strategy for this synthesis.
2. Luche reduction, Ireland ester enolate rearrangement,  $S_N2'$  anti lactone opening are some important steps.
3. 3,5 disubstituted cyclopentene is major precursor for radical cyclization process.

Thank You