CHE 535 Synthetic Organic

On the stereocontrolled
synthesis of tri-substituted alkenes

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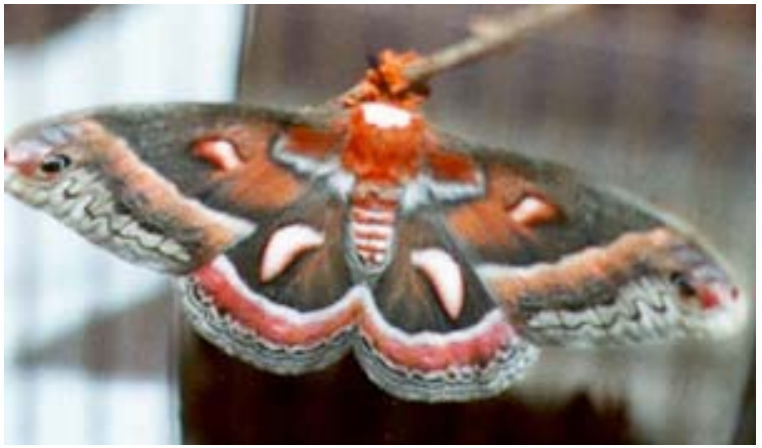
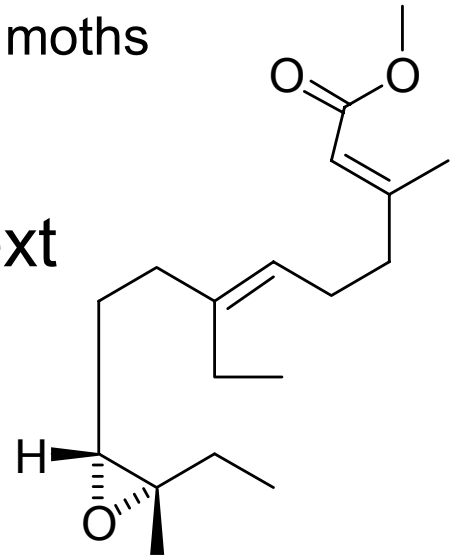
Synthesis of Cecropia-C18 Juvenile Hormone

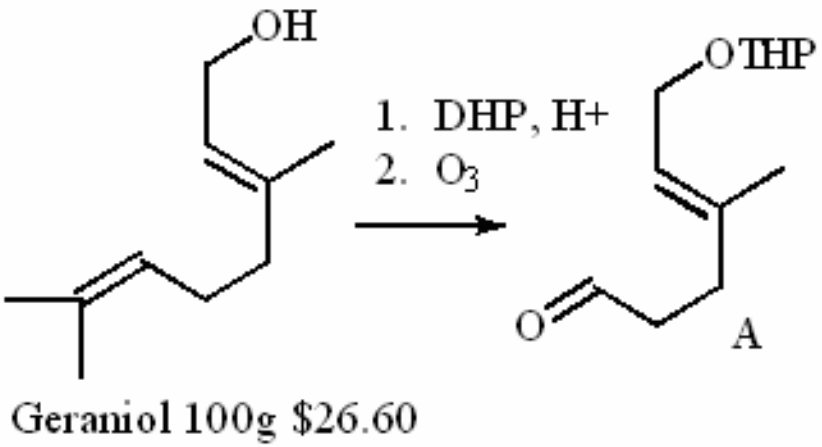


Silk moths

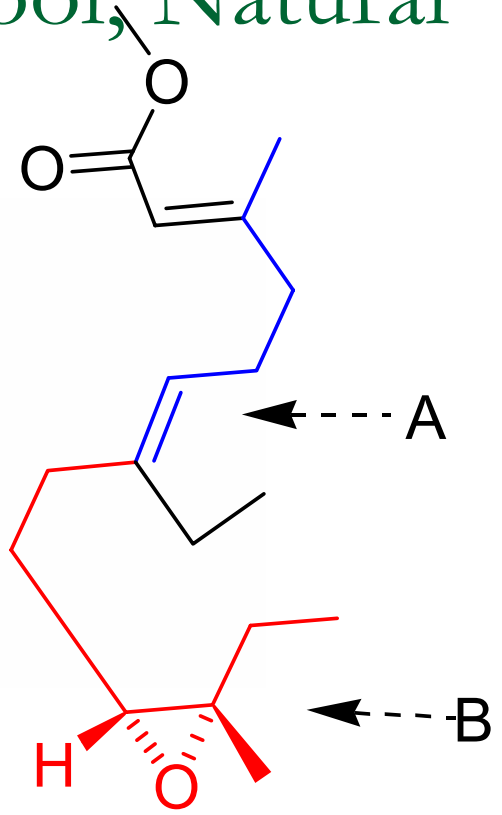
- Molecular Complexity
  - O-functionality
  - Oxirane Stereochemistry
  - Trisubstituted Alkenes
- 3 syntheses
  - Think about - general principles
  - - specific reactions in Complex context
    - -how stereochemistry was controlled
  - Evaluate syntheses, be critical
  - Don’t memorize the syntheses.



Synthesis One: The *Chiral* Pool, Natural source of stereochemistry

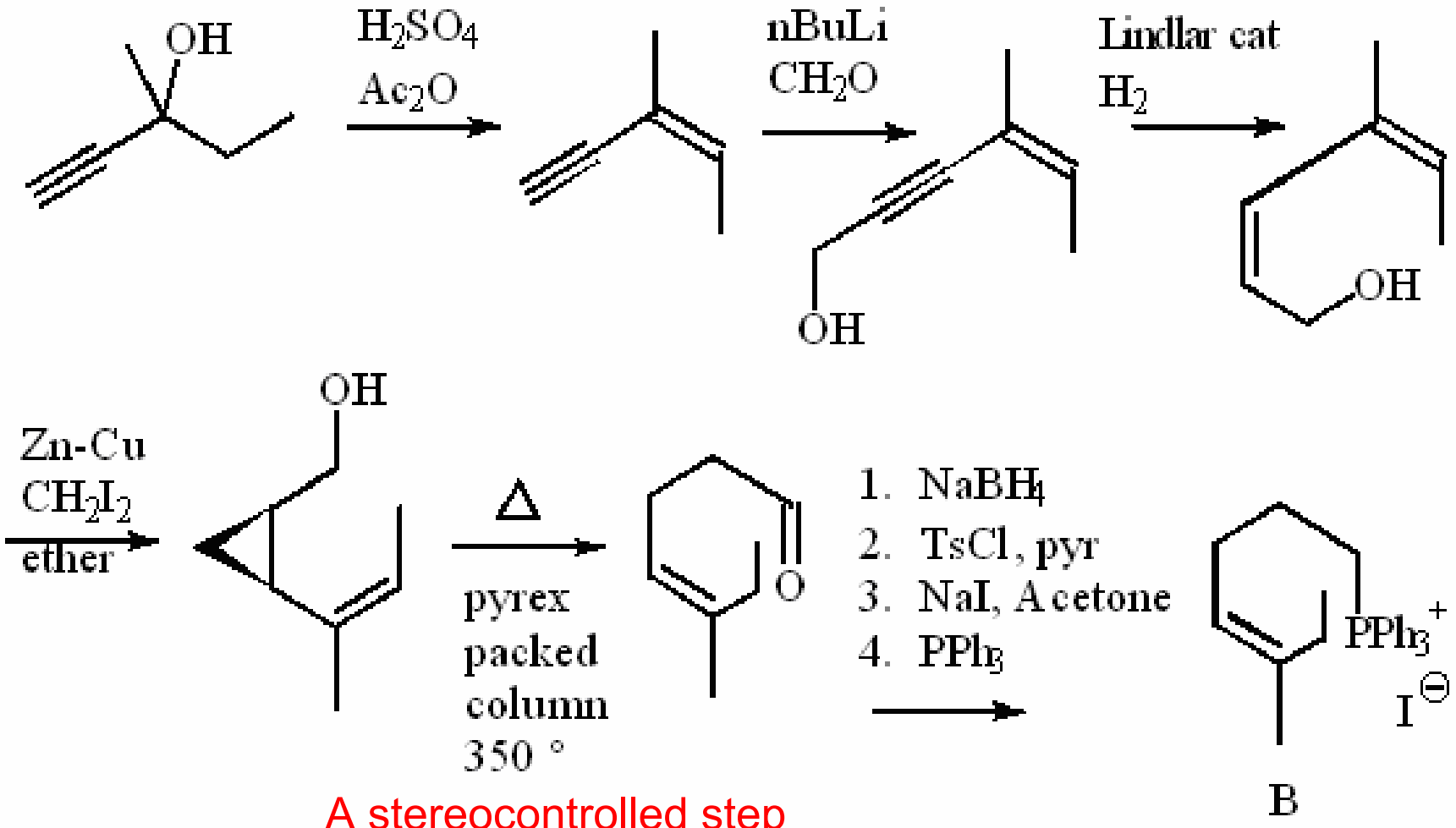


Geraniol 100g $26.60



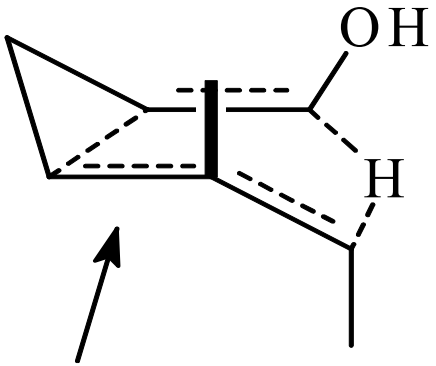
- Elias J. Corey, Hisashi Yamamoto, David K. Herron, and Kazuo Achiwa, “New stereospecific synthetic routes to trisubstituted olefins” J. Am. Chem. Soc. 1970, 92, 6635 - 6636

Another component in a convergent synthesis

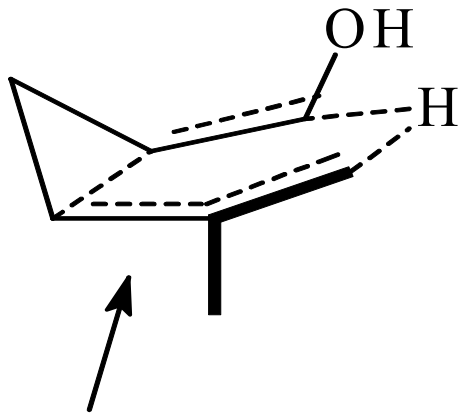


A stereocontrolled step

Retro-ene stereocontrol, a sigmatropic rearrangement



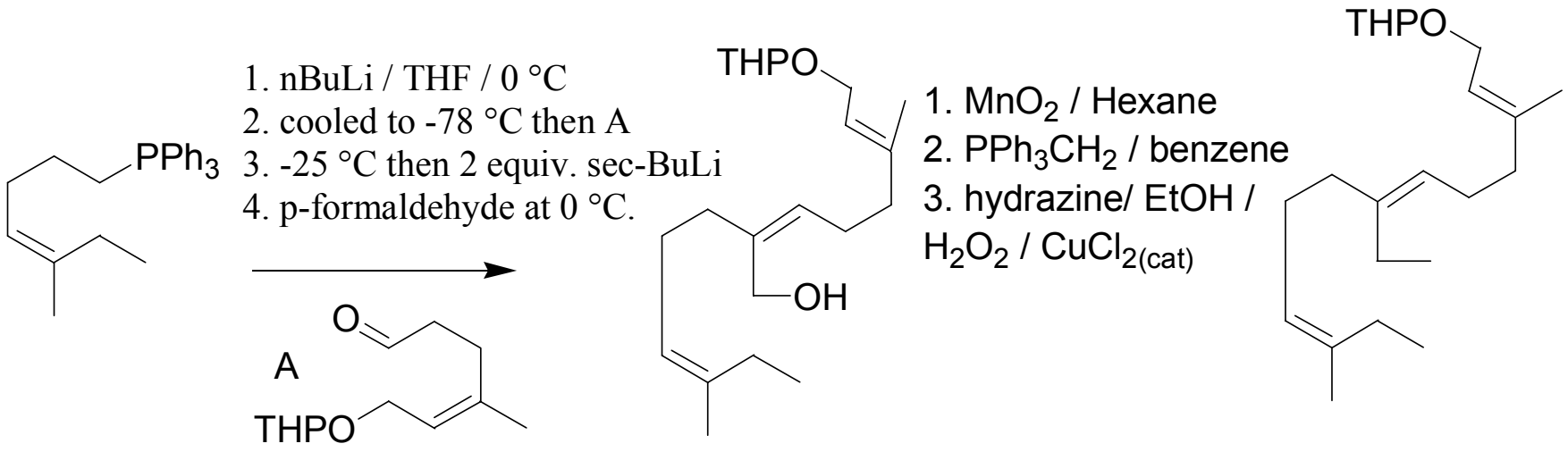
Trans double bond in pericyclic transition state



Cis double bond in pericyclic transition state
Lower energy

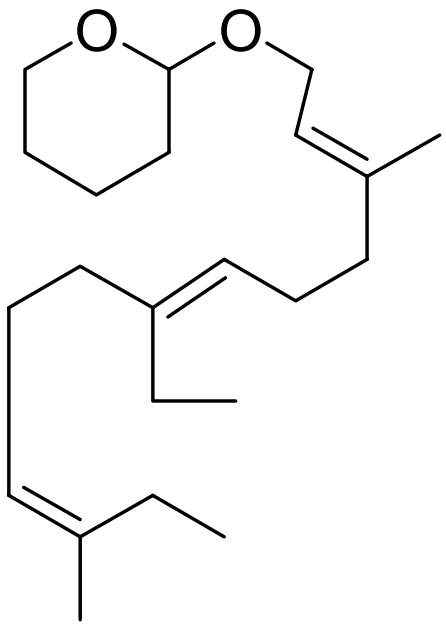
- Pseudo-axial interaction in hydro-chair destabilizes formation of the E-double bond.
- See reading assignment on the ene-reaction.

Assemblage of gross structure via synthetic intermediates A and B



- The coupling highlights the power of mechanistic information about the stability of intermediates.
- MnO_2 Corey-Ganem oxidation
- The dimide reduction is interesting. Why is the terminal alkene orthogonal to the others?

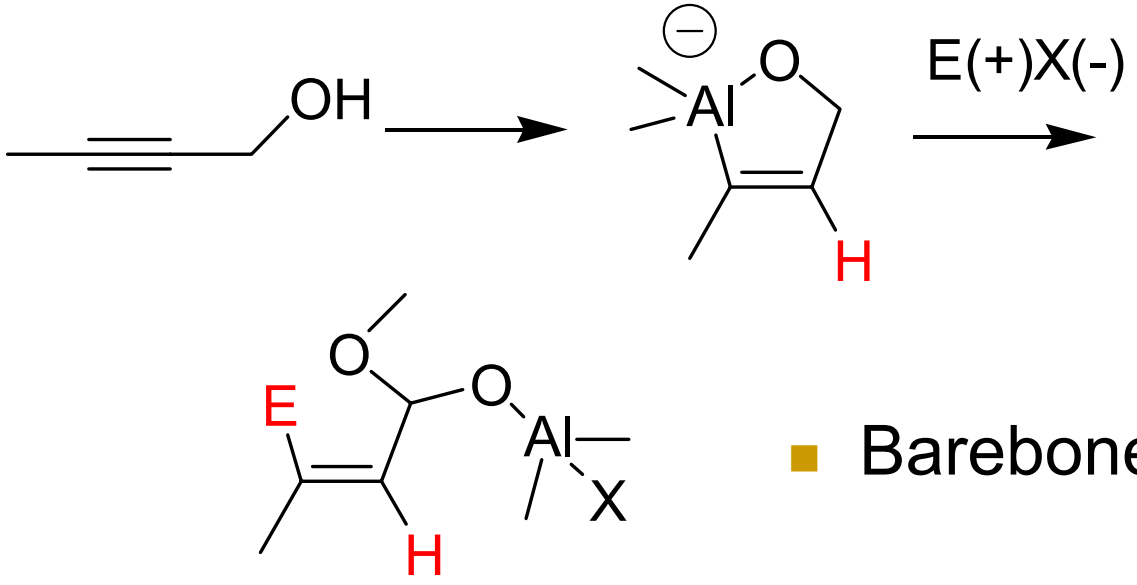
End game one



- Took a beating on the deprotection of the THP group
- Second to the last step
  - MnO_2 oxidation to the methoxyester

- Last step: HOBr/iPrOH/iPrO(-). Regiospecific for the terminal trisubstituted alkene. Results in a mixture of enantiomers.
- The biochemistry of a step after the last: *cationic cyclization*! Let's talk about it.

Synthesis Two: A general solution to stereocontrol in trisubstituted alkenes.

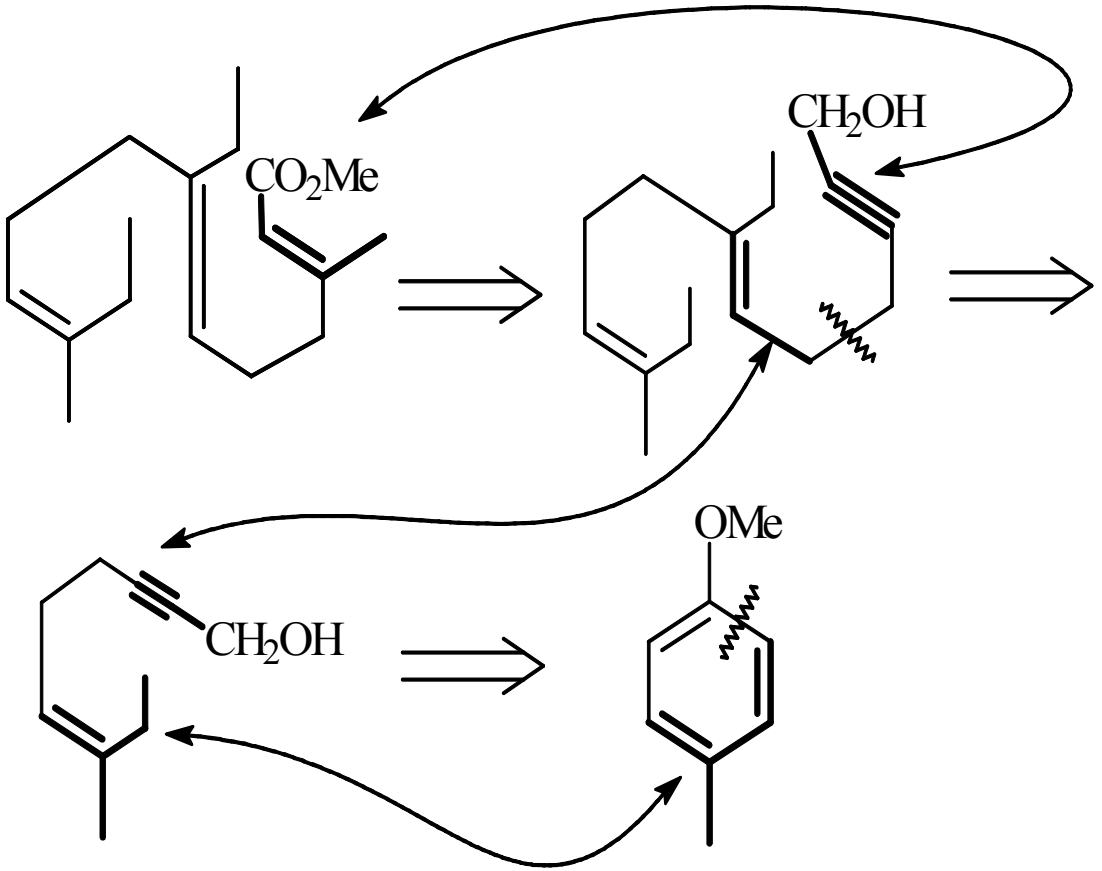


- Barebones!

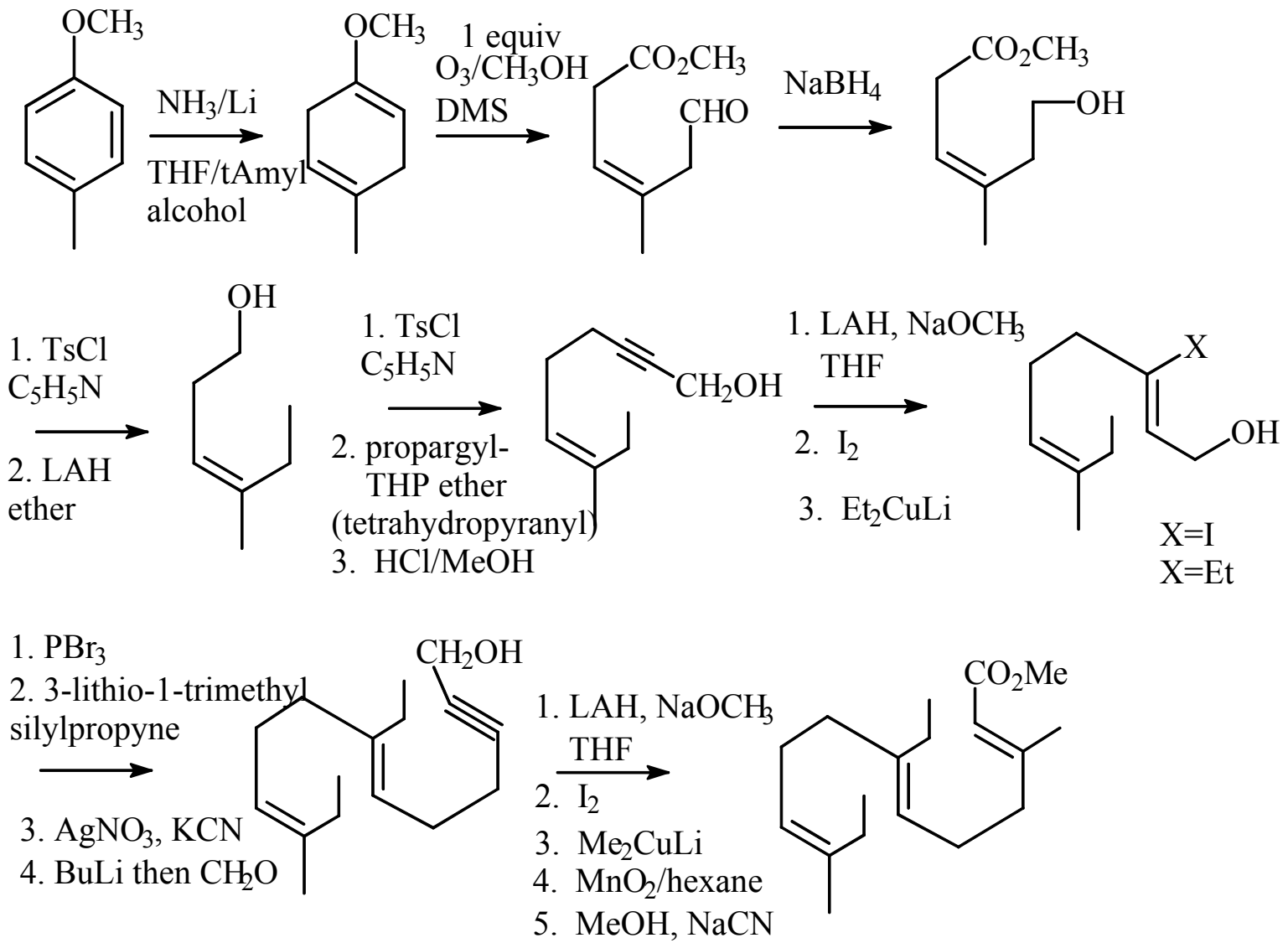
- Corey, E.J.; Katzenellenbogen, J.A.; Gilman, N.W.; Roman S.A.; Erickson,B.W. *J. Am. Chem. Soc.* **1968**, *90*, 5618-5620.

Gross construction/ Retrosynthesis

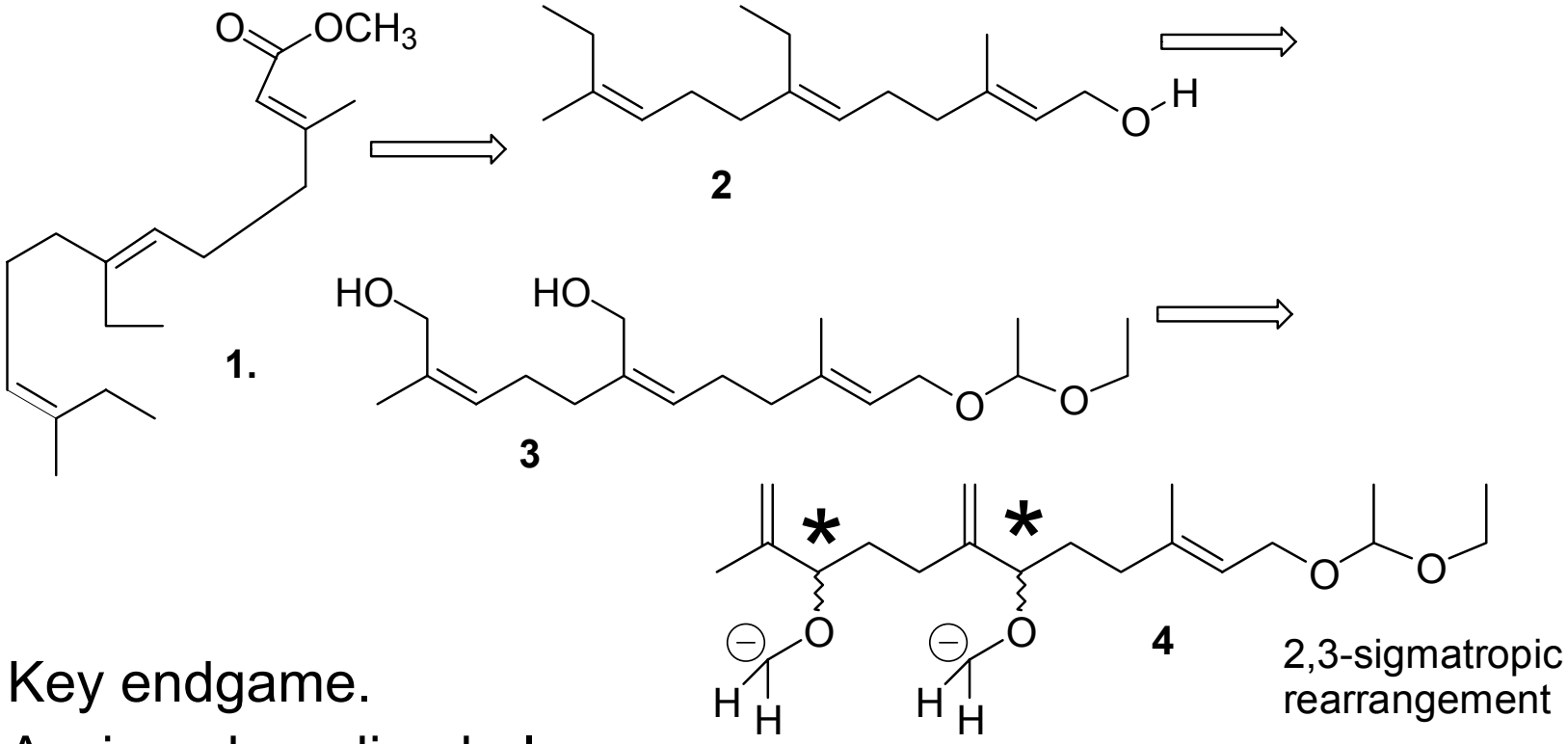
- Stereo-control via Al-H reduction of the propargyl functionality
- C-C bonds via alpha and beta acidification effect of the triple bond



For-ward

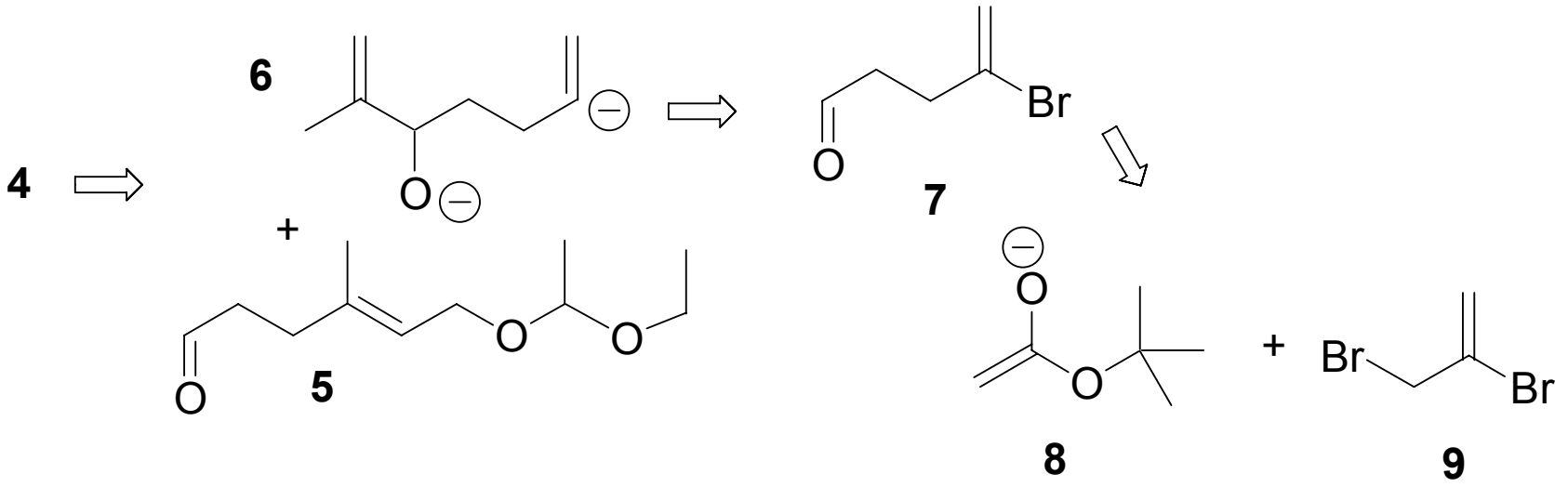

OCH3
NH3/Li
THF/tAmyl alcohol
OCH3
1 equiv O3/CH3OH
DMS
CO2CH3
CHO
NaBH4
CO2CH3
OH
1. TsCl C5H5N
2. LAH ether
OH
1. TsCl C5H5N
2. propargyl-THP ether (tetrahydropyranyl)
3. HCl/MeOH
CH2OH
1. LAH, NaOCH3 THF
2. I2
3. Et2CuLi
X
OH
X=I
X=Et
1. PBr3
2. 3-lithio-1-trimethyl silylpropyne
3. AgNO3, KCN
4. BuLi then CH2O
CH2OH
1. LAH, NaOCH3 THF
2. I2
3. Me2CuLi
4. MnO2/hexane
5. MeOH, NaCN
CO2Me

Synthesis Three: Retrosynthesis. General Stereocontrol of trisubstituted alkenes.

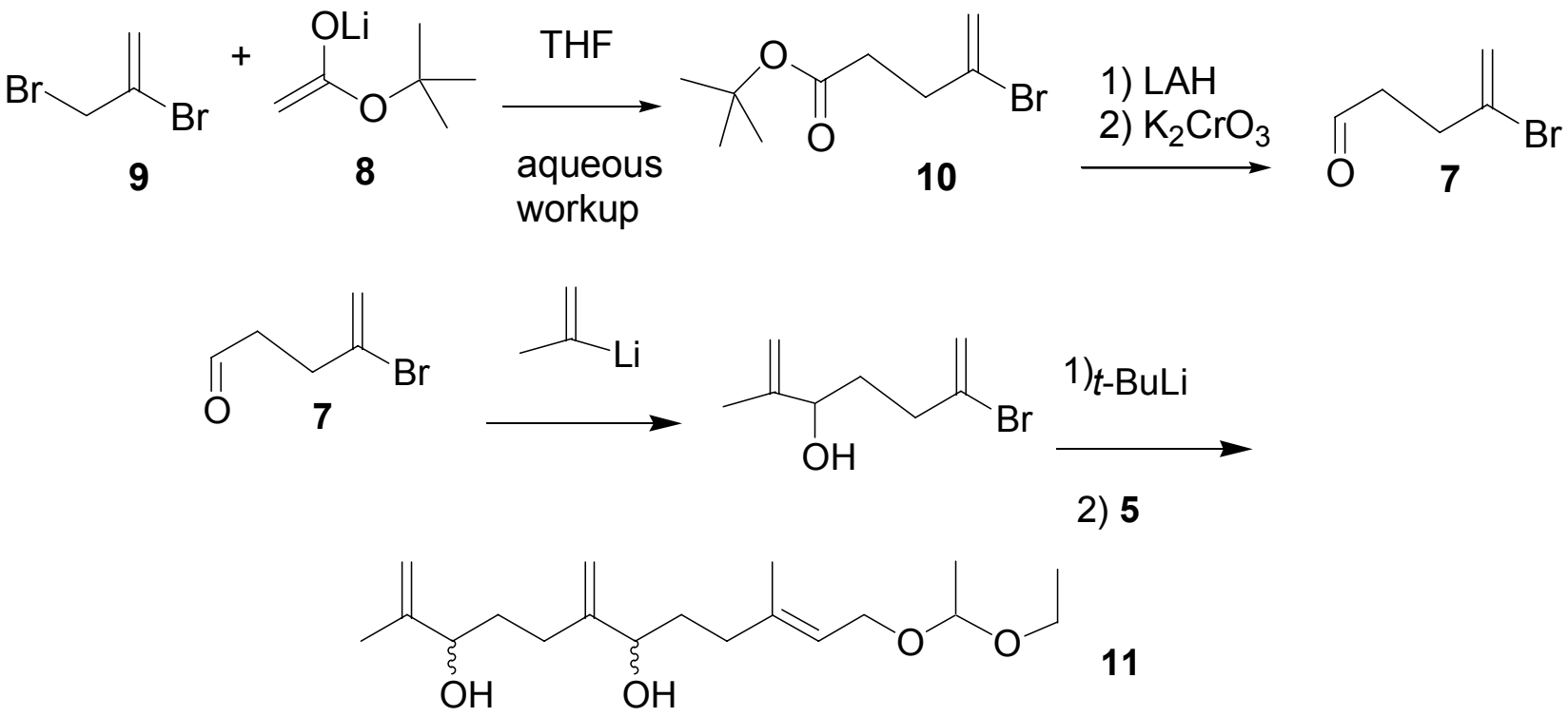


- Key endgame.
- Assigned reading below
- Still, W. C.; McDonald, J. H., III; Collum, D. B.; Mitra, A. Tetrahedron Lett. 1979, 20, 593.

Building the key intermediate

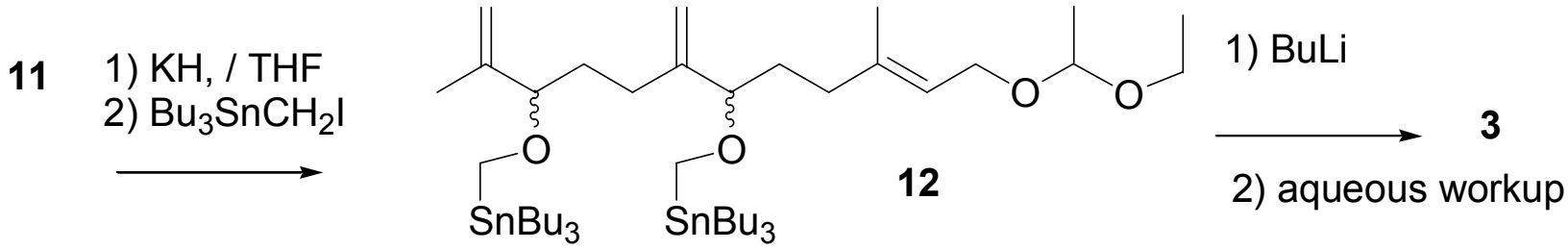


- Are the regioselectivities of the reactions above in concert with your chemical intuition?

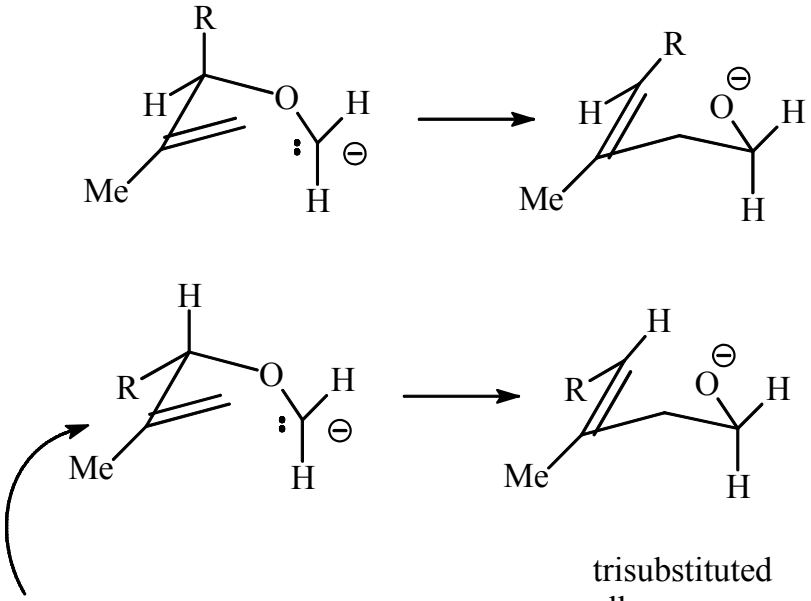


- The absolute configuration of the carbinol carbon atoms in **11** did not matter in the stereochemistry of the alkene.

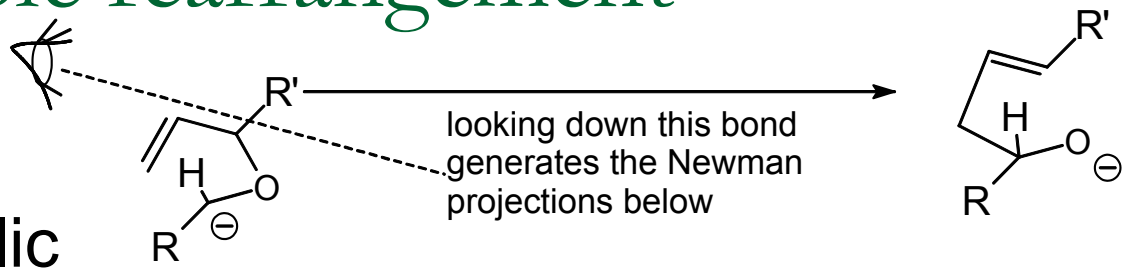
Key step: 2,3-sigmatropic rearrangement



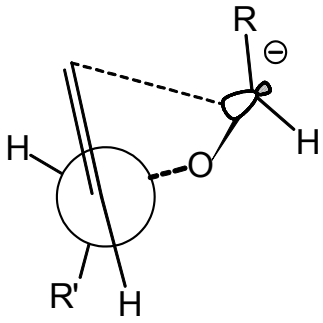
- 1,2-allylic strain controls the stereochemistry
- When thinking mechanism and stereochem evaluate the possibilities



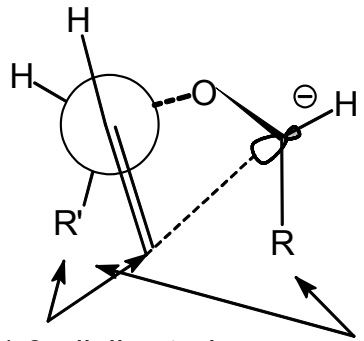
General stereocontrol in the 2,3-sigmatropic rearrangement



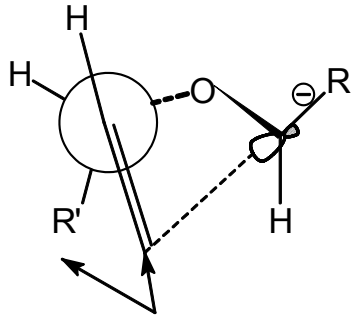
- More allylic strain
- In terms of bare bones



Strain-Minimized t-State



1,3-allylic strain



1,3-allylic strain
1,3-tranannular interactio

- Required reading: Bruckner, R. 2,3-Sigmatropic Rearrangements; *Comprehensive Synthetic Organic Chemistry* Trost and Flemming Eds.; Pergamon Press: Oxford, **1991**; Vol. 6, pp 873.