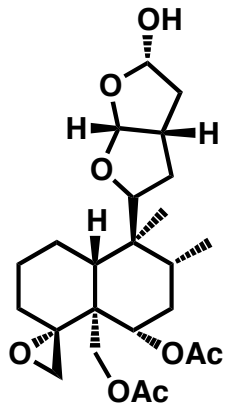




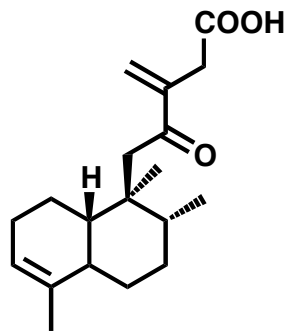
Clerodane diterpenes



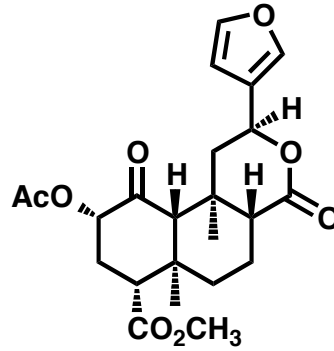
Match the molecule!



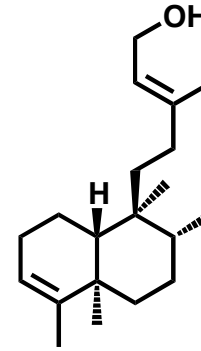
derivative of
lupulin D



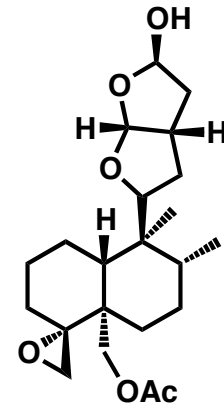
(5R,8R,9S,10R)-12-oxo-
ent-3,13(16)-clerodien-
15- oic acid



salvinorin A



(-)-kolavenol



scuteceprol A



antifeedant



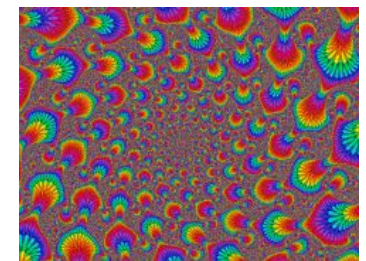
antileishmanial



extremely potent
antitumor activity



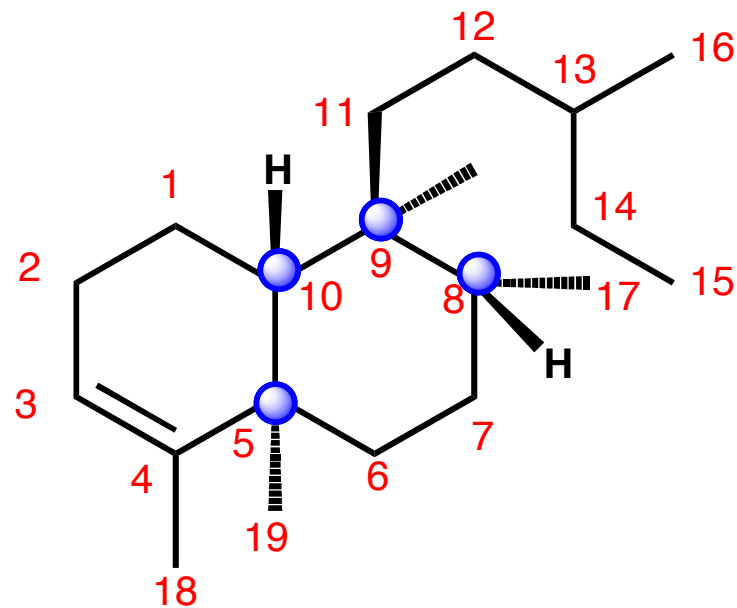
antibacterial



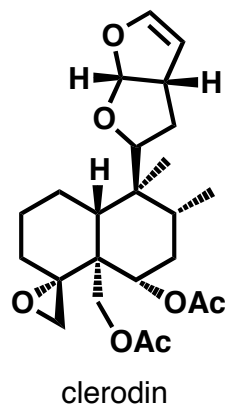
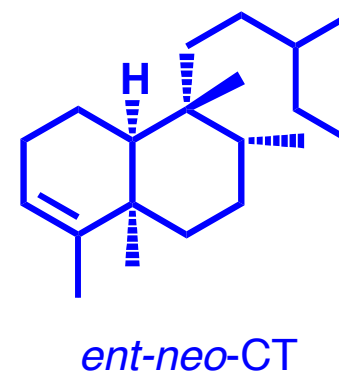
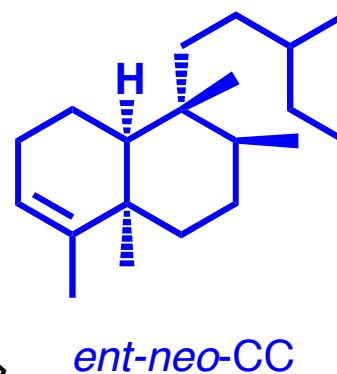
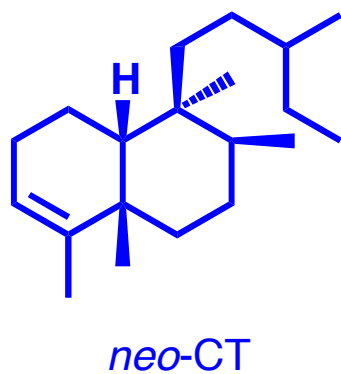
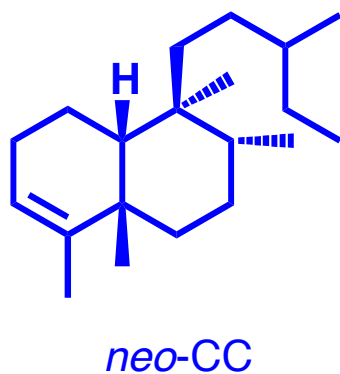
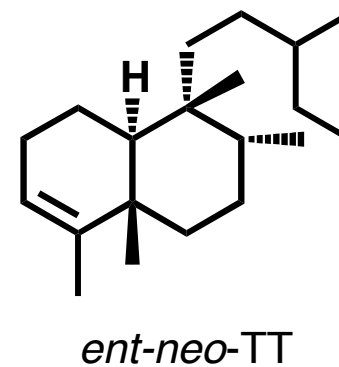
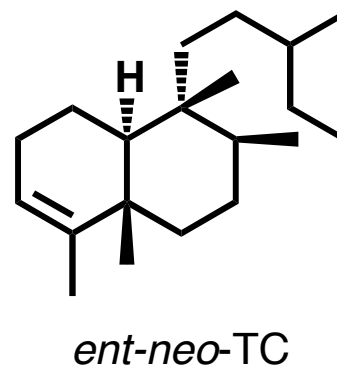
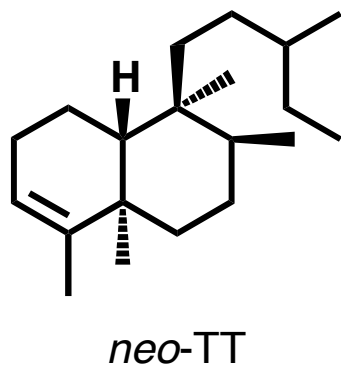
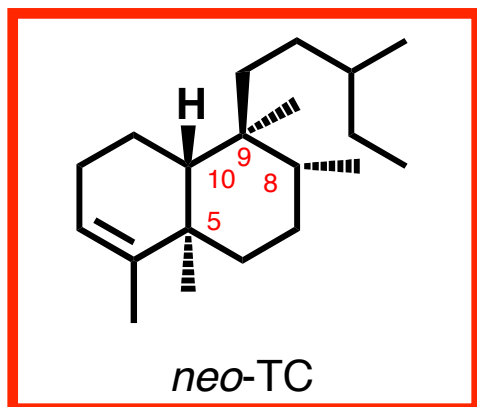
most potent
naturally occurring
hallucinogen

Clerodane diterpenoids

- Large group of secondary metabolites
- interesting biological activities

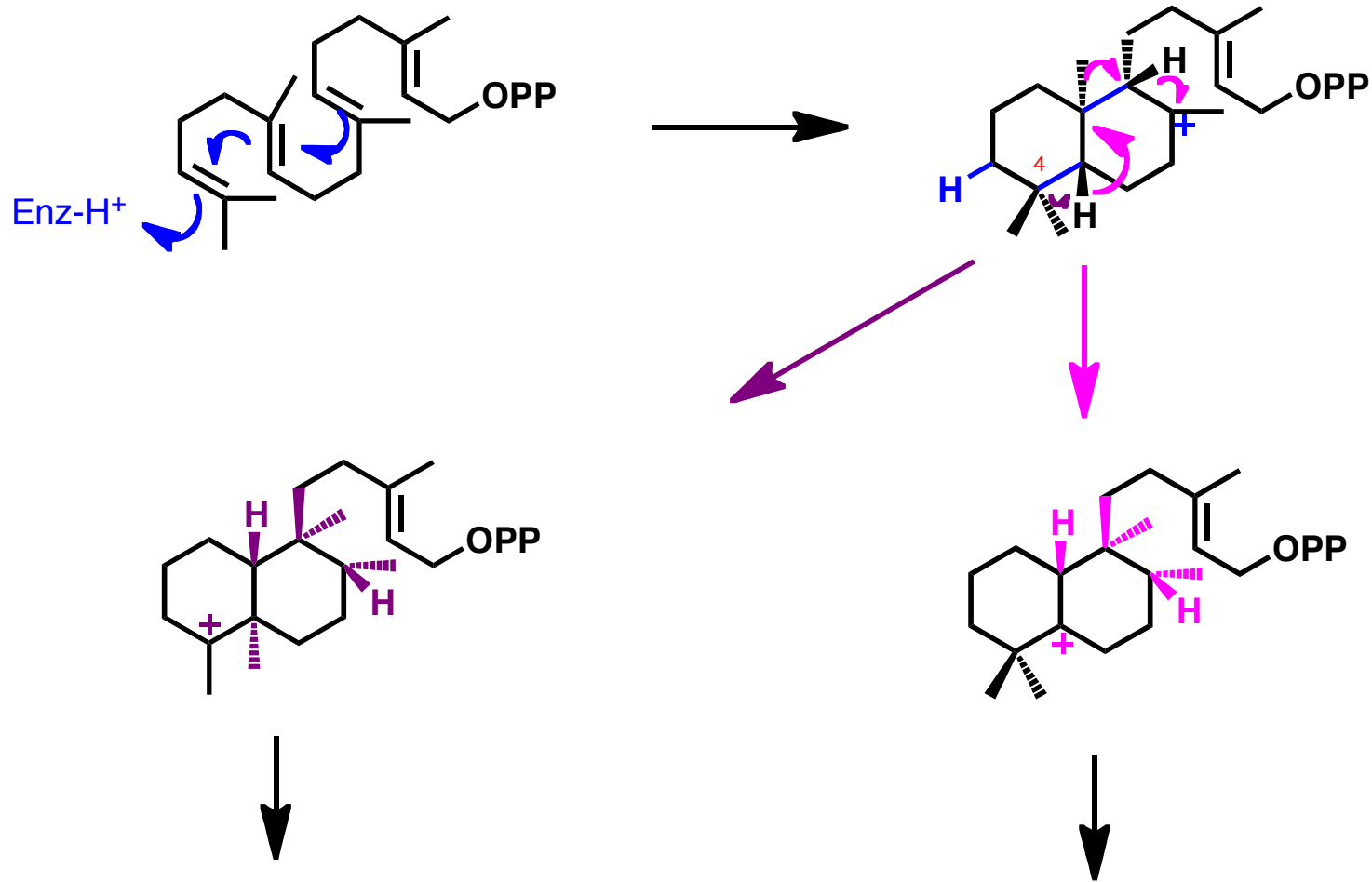


Stereochemical variety



Biosynthesis

- formed via the backbone rearrangement of labdadienyl cation produced by cyclization of geranylgeranyl pyrophosphate



trans-clerodane diterpenoids

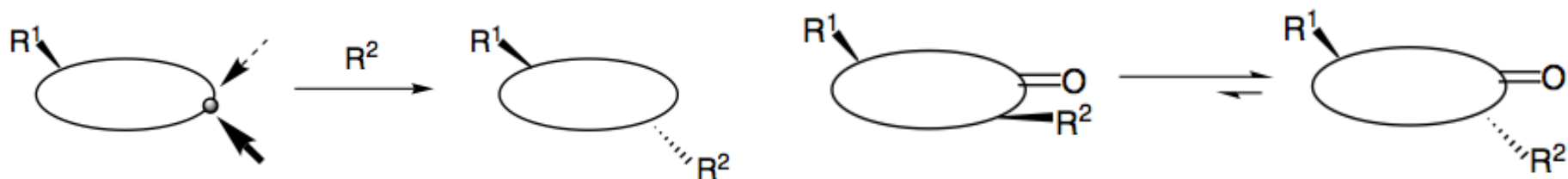
cis-clerodane diterpenoids

Challenges in clerodane synthesis

- Classical stereochemical problems:
 - diastereoselective ring formation
 - diastereoselective reactions on the ring

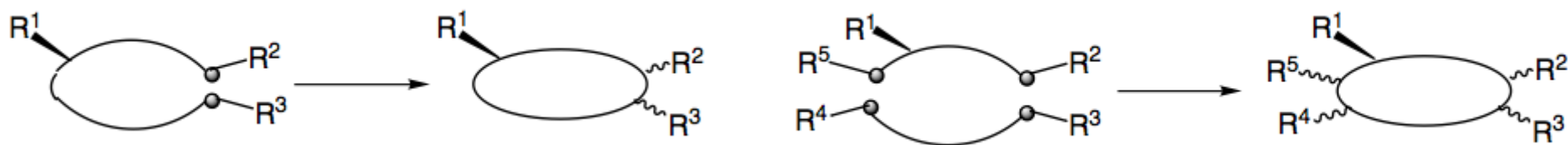
Traditional methods for clerodane synthesis

-Diastereoface-selective reactions on rigid ring/ thermodynamic equilibration



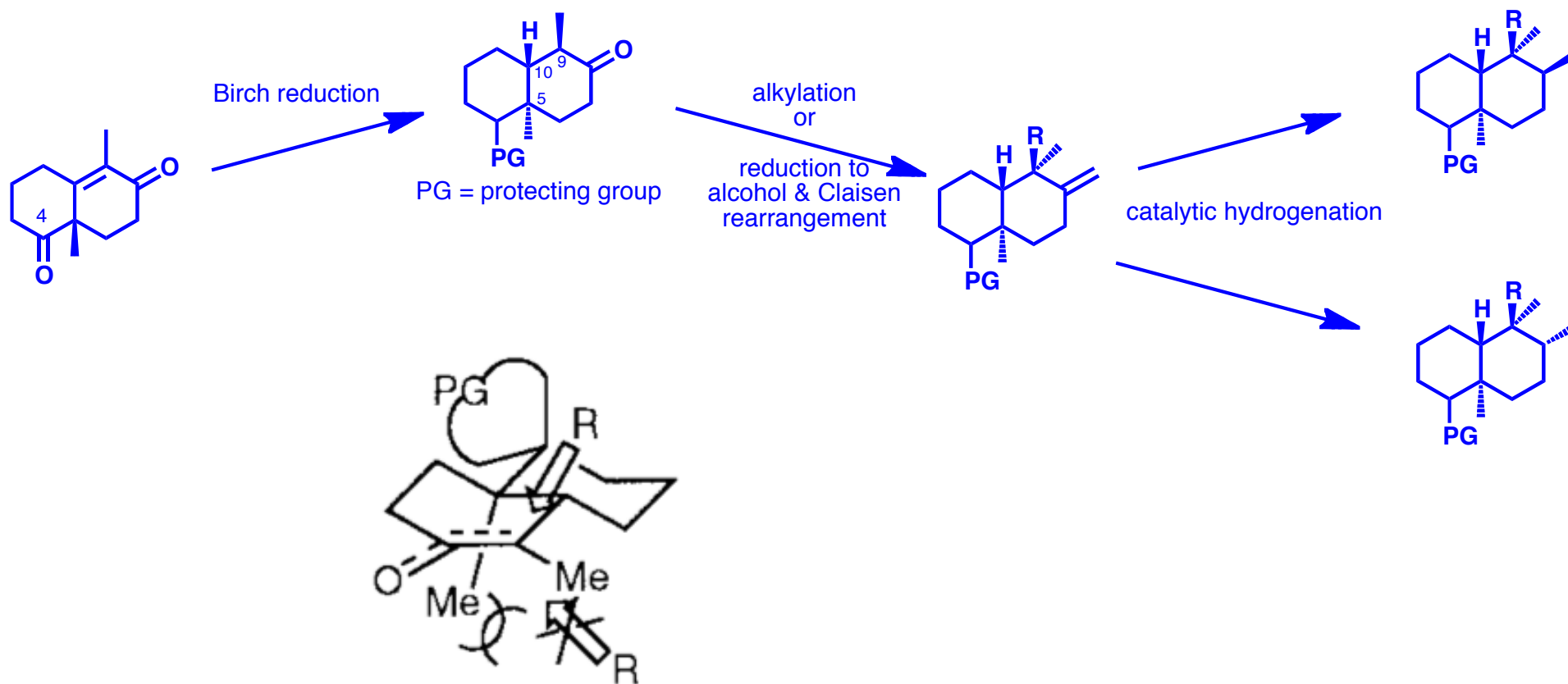
- Wieland-Miescher ketone analog
- Cyclohexane derivatives

-Multiple stereocontrolled ring formation

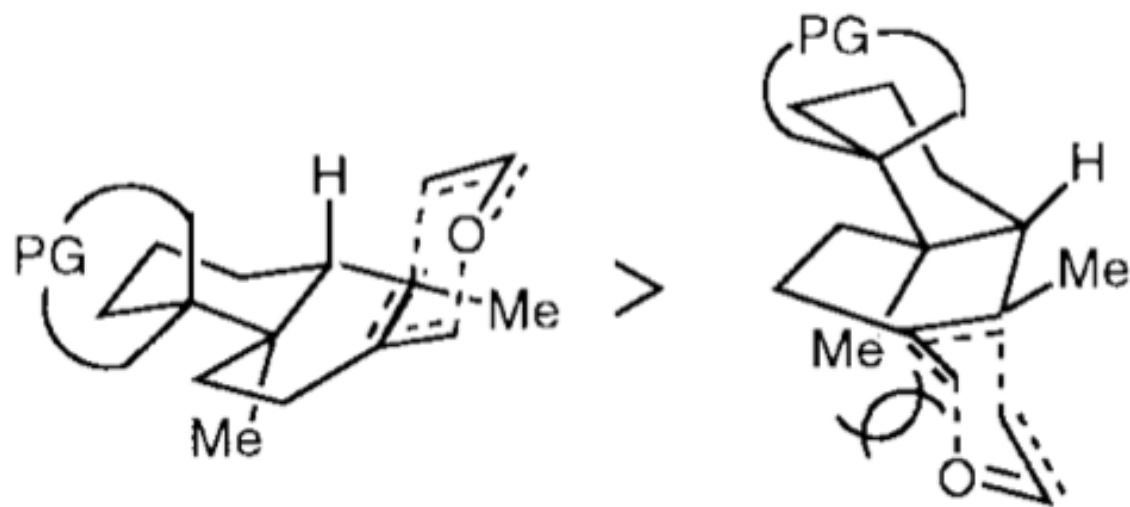
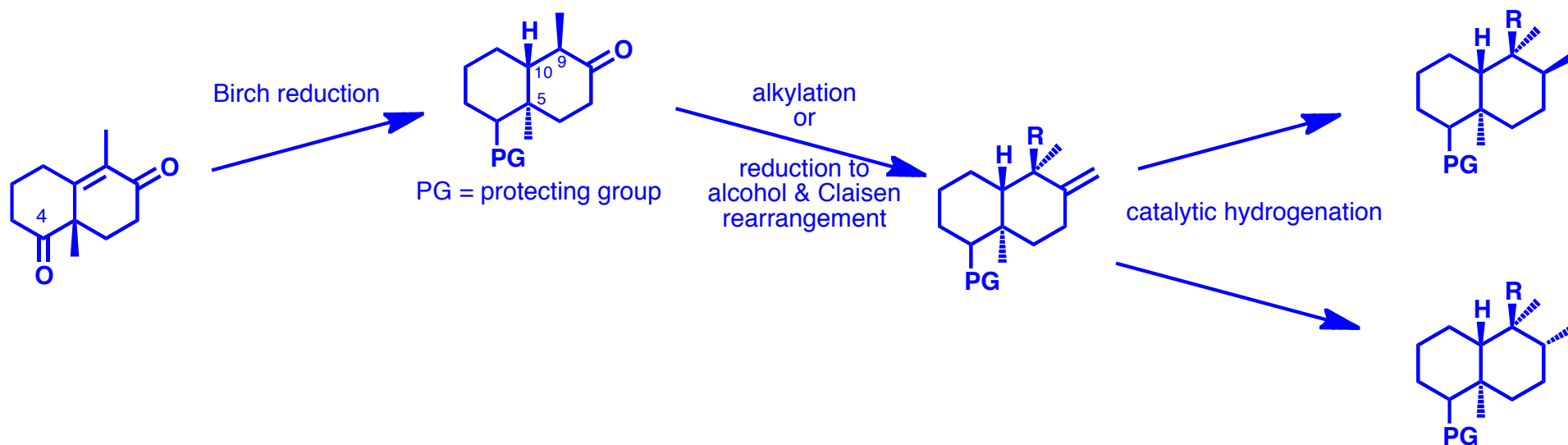


- Diels-Alder reactions
- Ring closure reaction

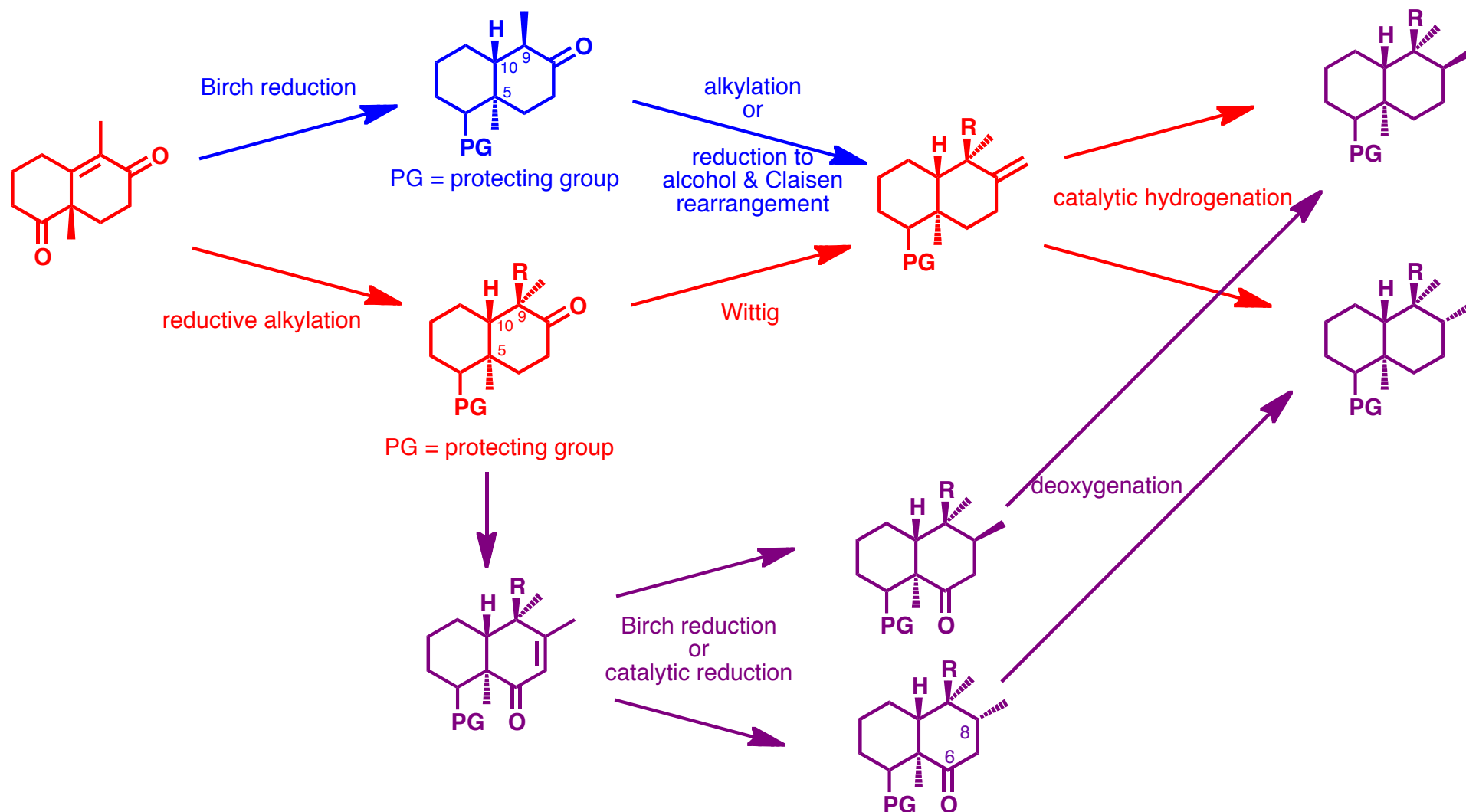
Diastereoface selective/ thermodynamic equilibration



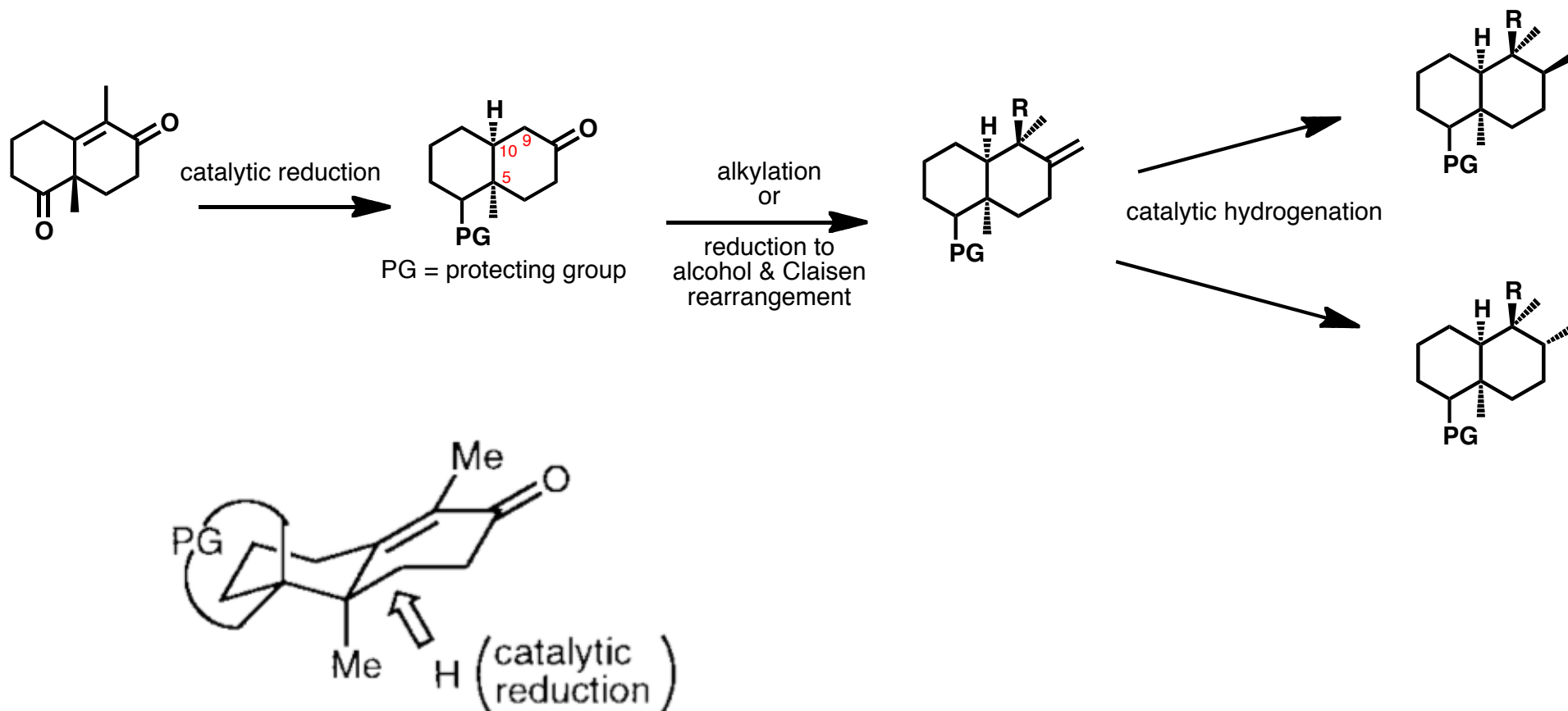
Diastereoface selective/ thermodynamic equilibration



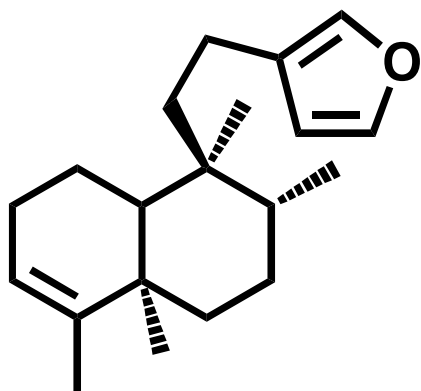
Diastereoface selective/ thermodynamic equilibration



Diastereoface selective/ thermodynamic equilibration



Example #1: annonene

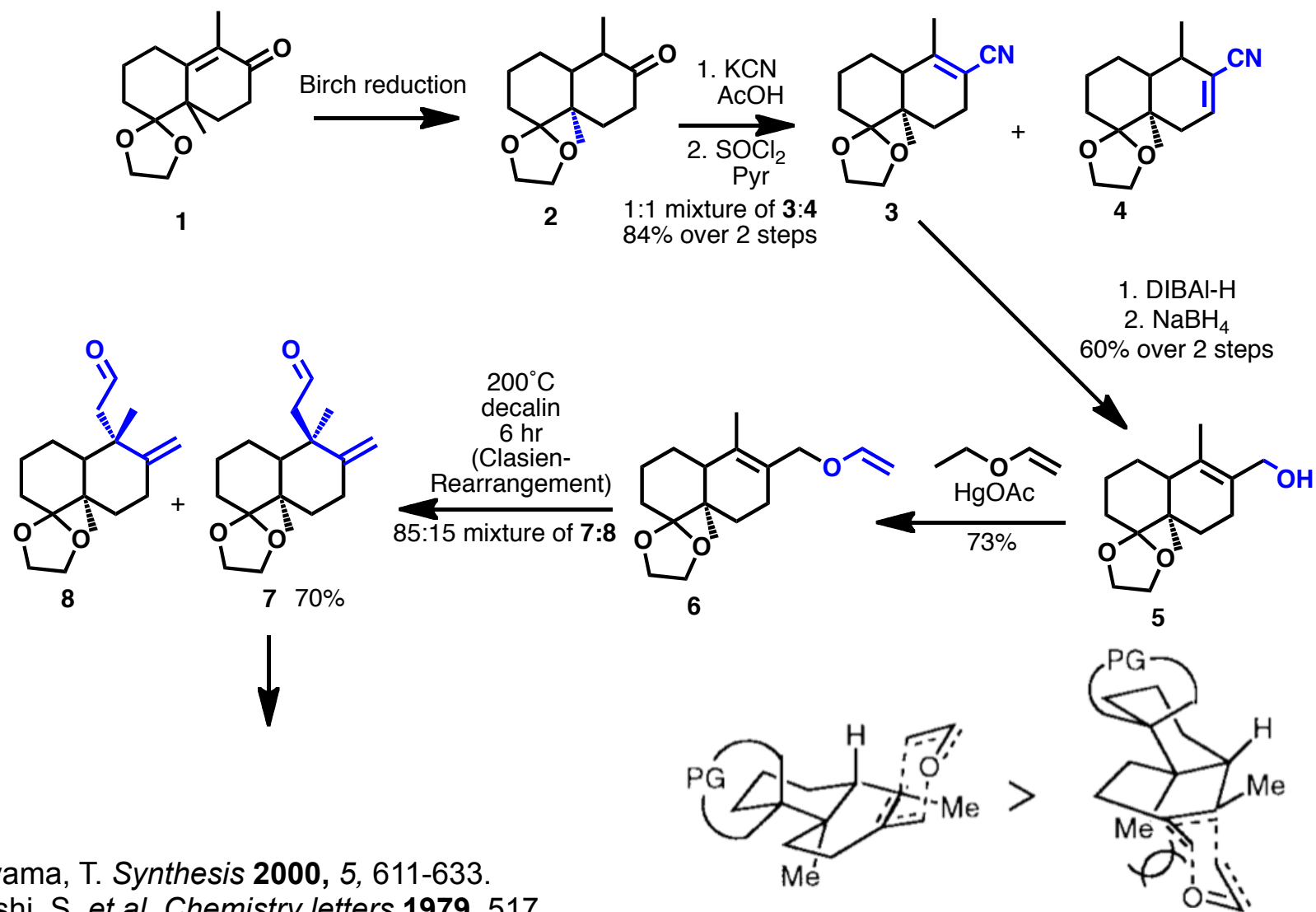


- Satoru Takahashi, Takenori Kusumi, Hiroshi Kakisawa
- Chemistry Letters (Chemical Society of Japan)
- 1979
- first synthesis of *trans*-clerodane diterpene

Tokoroyama, T. *Synthesis* **2000**, 5, 611-633.

Takahashi, S. *et al. Chemistry letters* **1979**, 517.

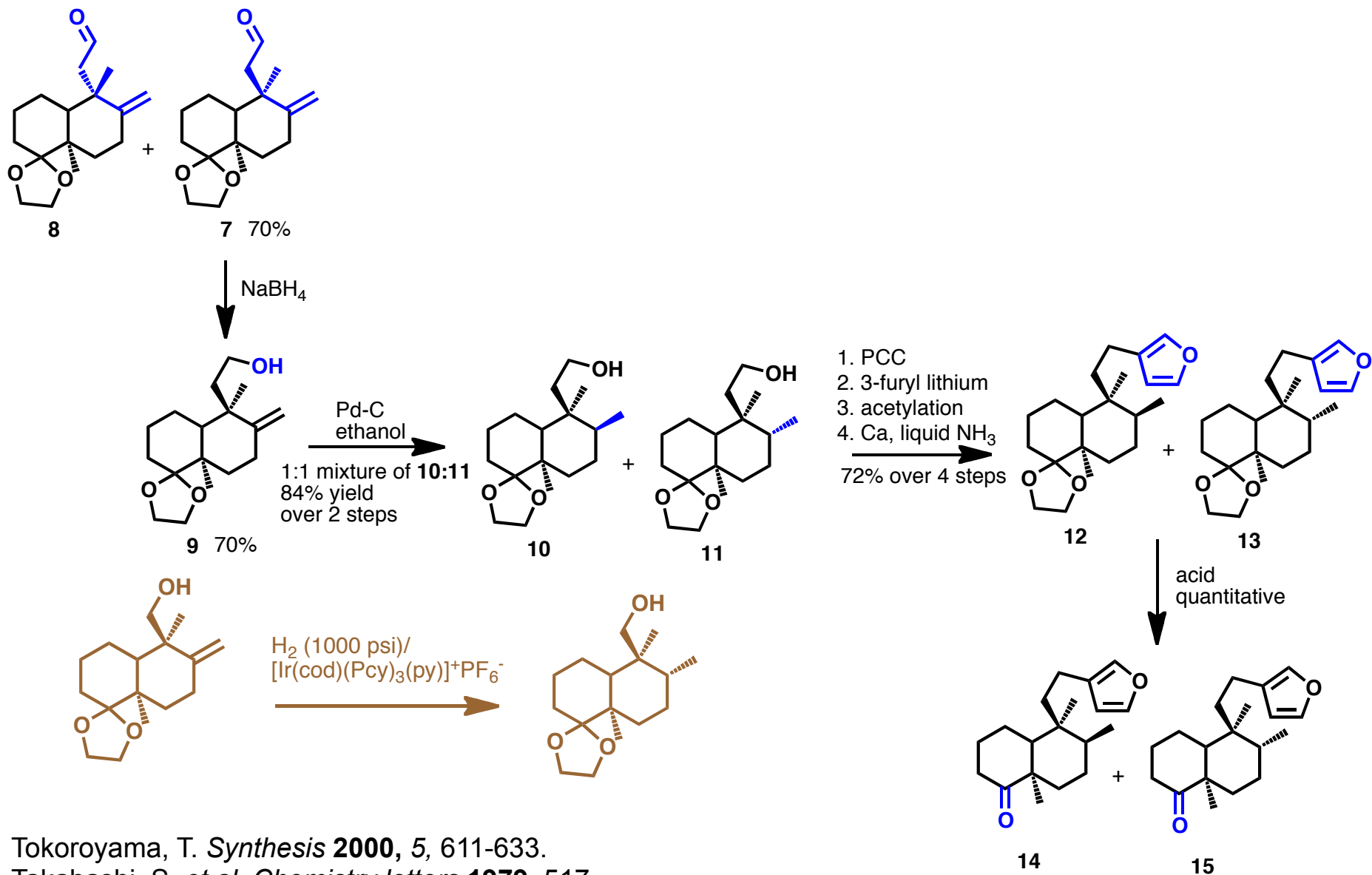
Example #1: annonene



Tokoroyama, T. *Synthesis* **2000**, 5, 611-633.

Takahashi, S. *et al. Chemistry letters* **1979**, 517.

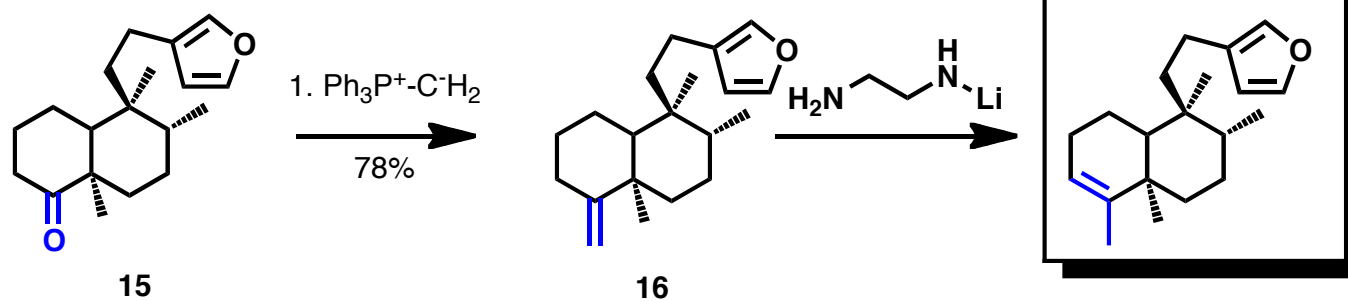
Example #1: annonene



Tokoroyama, T. *Synthesis* **2000**, 5, 611-633.

Takahashi, S. *et al. Chemistry letters* **1979**, 517.

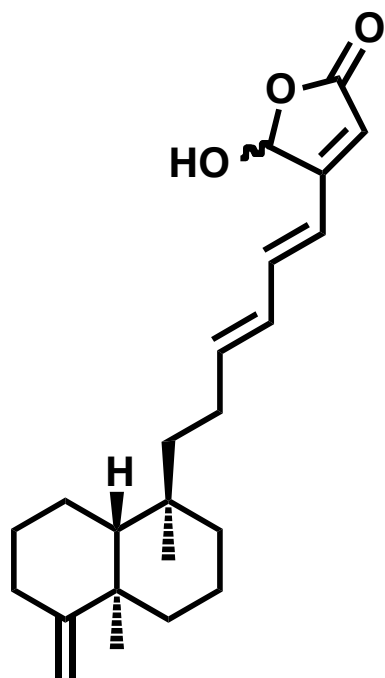
Example #1: annonene



Tokoroyama, T. *Synthesis* **2000**, 5, 611-633.

Takahashi, S. *et al. Chemistry letters* **1979**, 517.

Example #2: palauolide

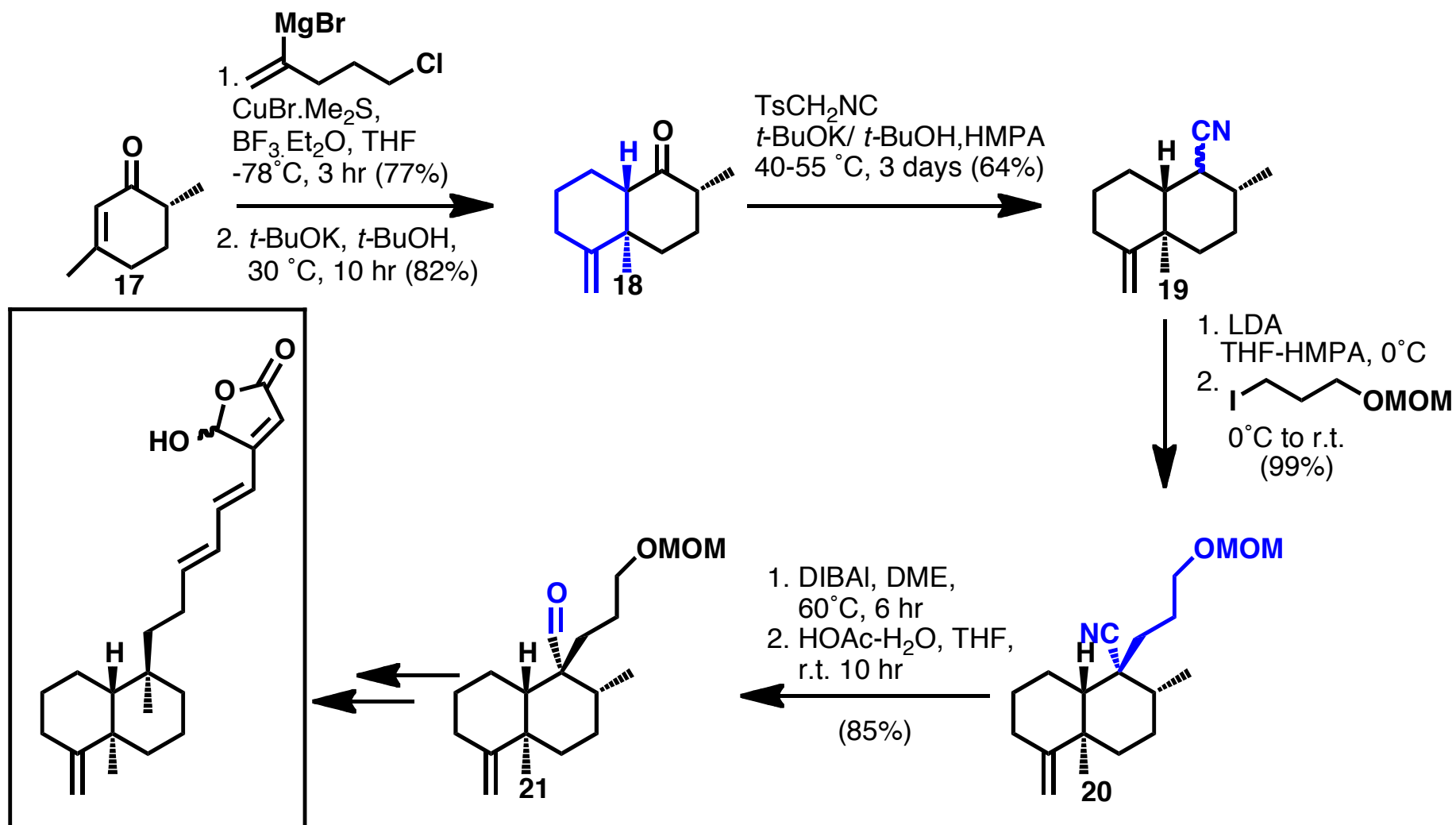


- Edward Piers & John S. M. Wai
- University of B.C.
- 1987

Tokoroyama, T. *Synthesis* **2000**, 5, 611-633.

Piers, E. *et al. J. Chem. Soc., Chem. Commun.* **1987**, 1342.

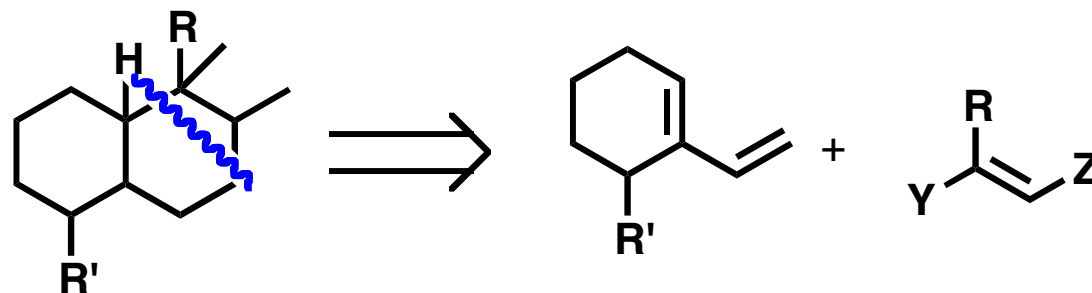
Example #2: palauolide



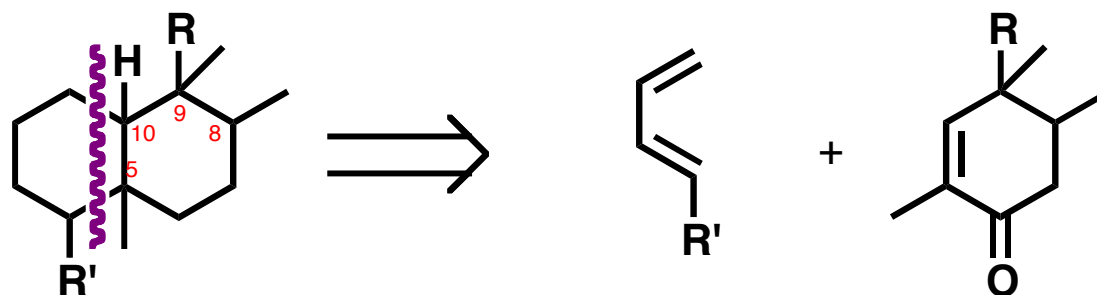
Tokoroyama, T. *Synthesis* **2000**, 5, 611-633.

Piers, E. *et al.* *J. Chem. Soc., Chem. Commun.* **1987**, 1342.

Intermolecular Diels-Alder strategy

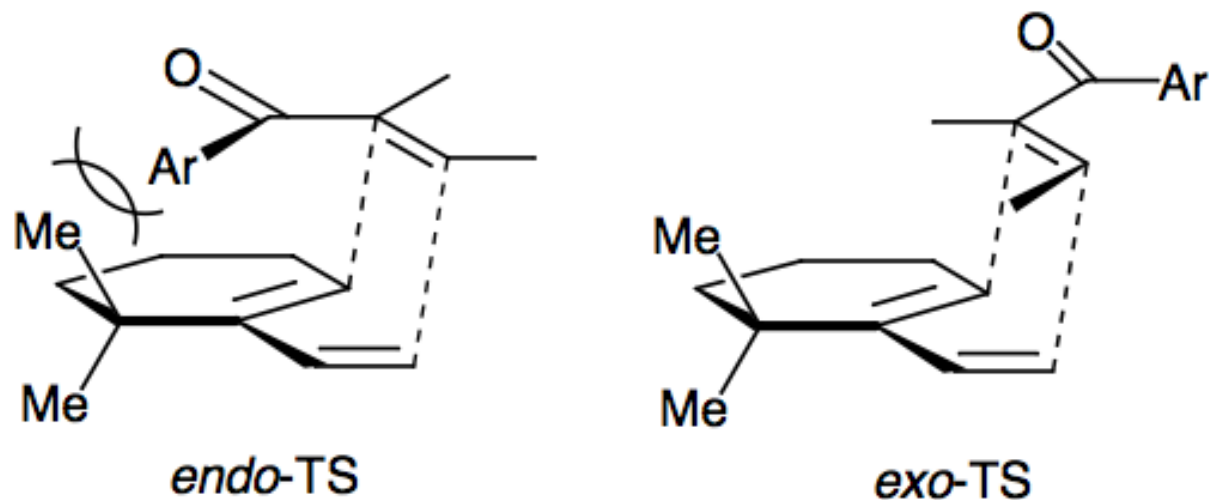
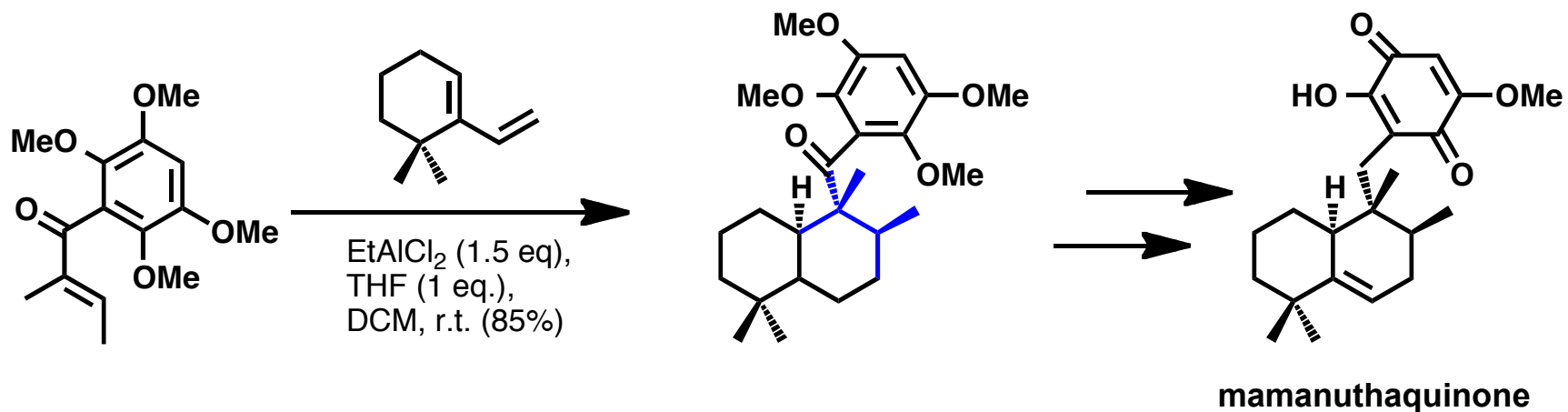


- simultaneous establishment of 3 stereocenters: C-8, C-9, C-10
- can't easily attach substituents to C-5



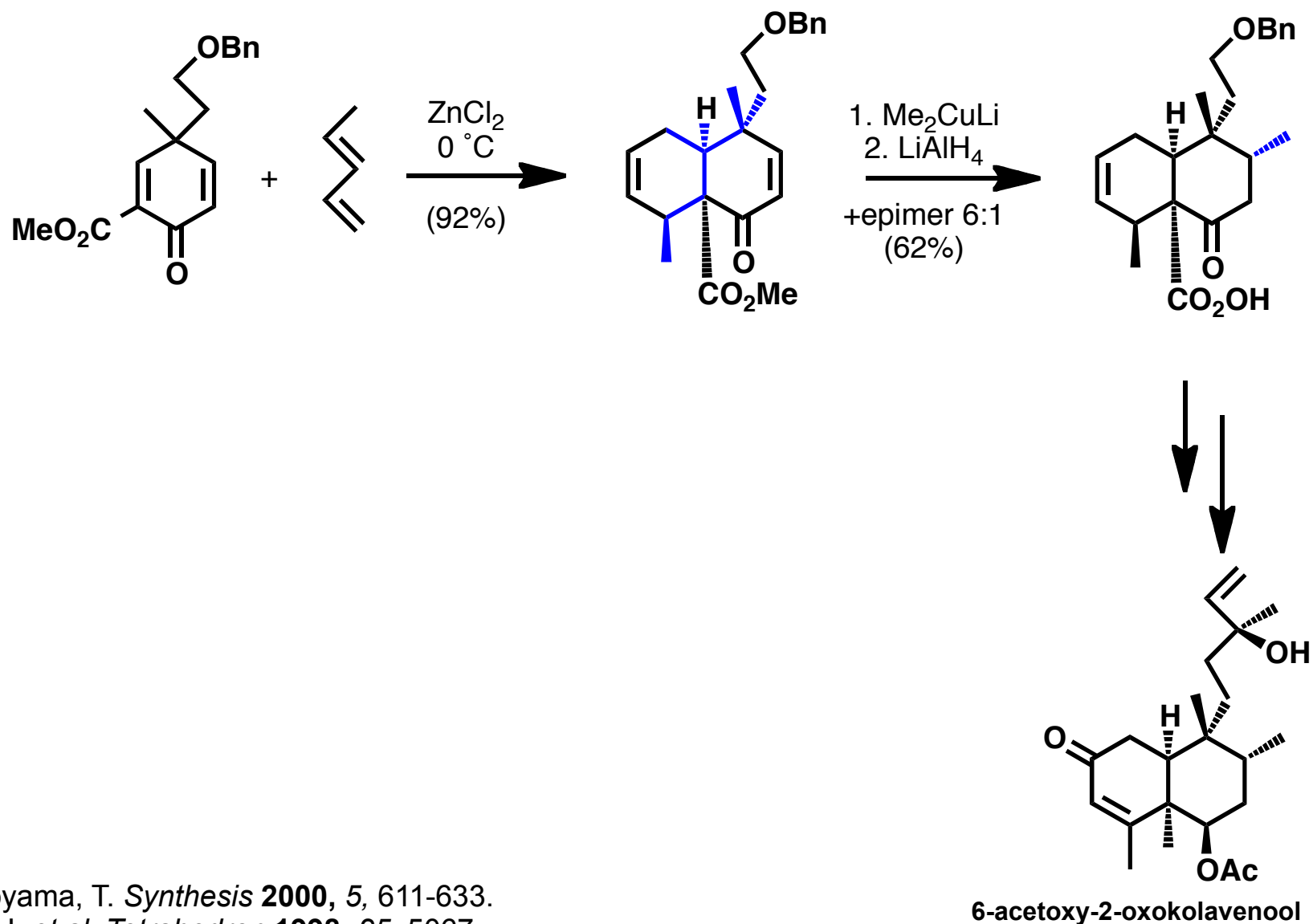
- establishment of C-5 and C-10 simultaneously
- need to construct C-8 and C-9 separately

Example #3: mamanuthaquinone



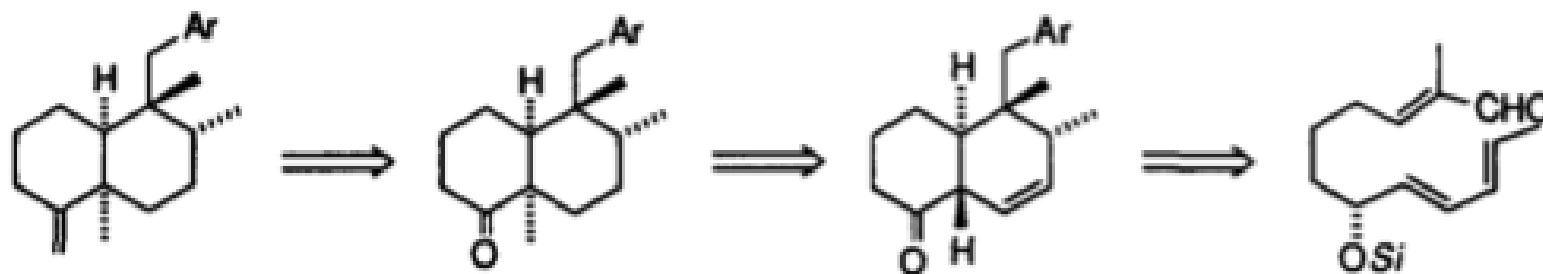
Tokoroyama, T. *Synthesis* **2000**, 5, 611-633.
Yoon, T. *et al. Angew. Chem. Int. Ed. Engl.* **1994**, 33, 853.

Example #4: 6-acetoxy-2-oxokolavenool



Tokoroyama, T. *Synthesis* **2000**, 5, 611-633.
Liu, H-J. *et al. Tetrahedron* **1998**, 25, 5067.

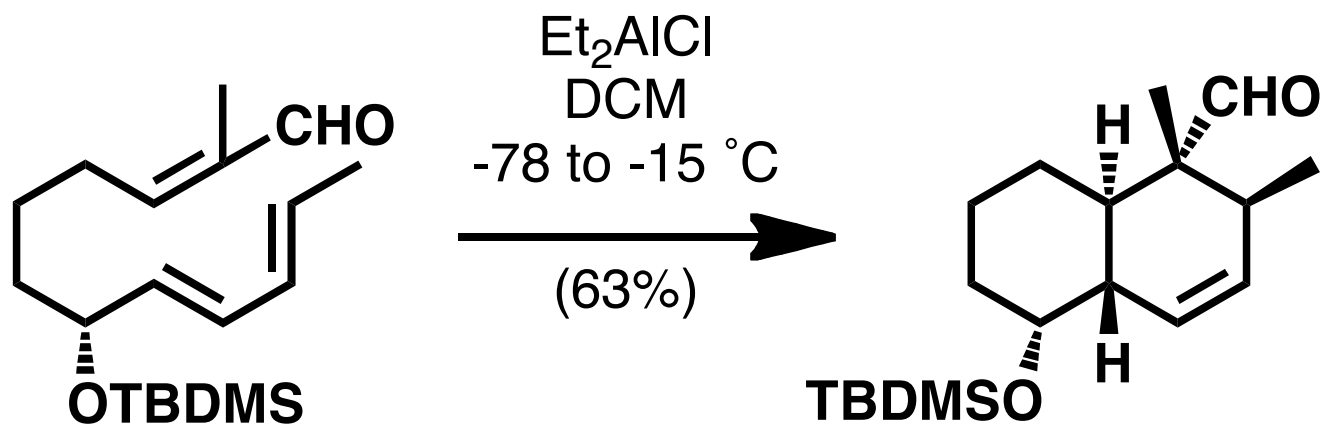
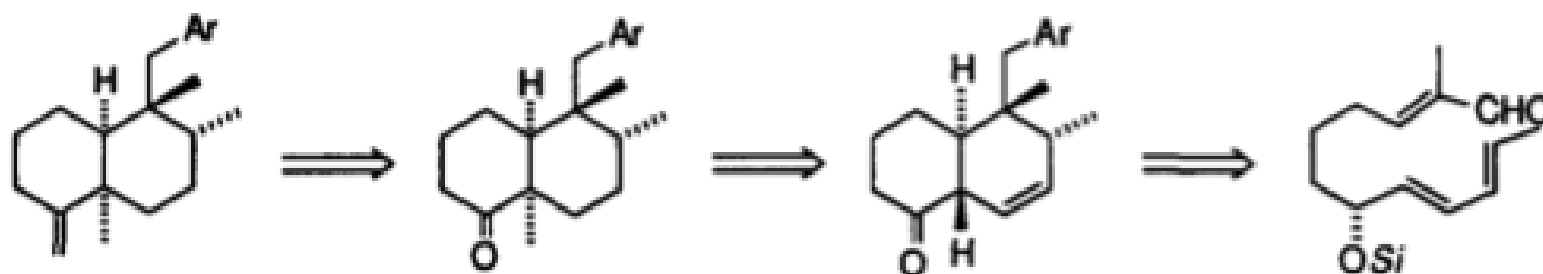
Intramolecular Diels-Alder example



Tokoroyama, T. *Synthesis* **2000**, 5, 611-633.

Kawai, N. *et al. Tetrahedron Lett.* **1999**, 40, 4193.

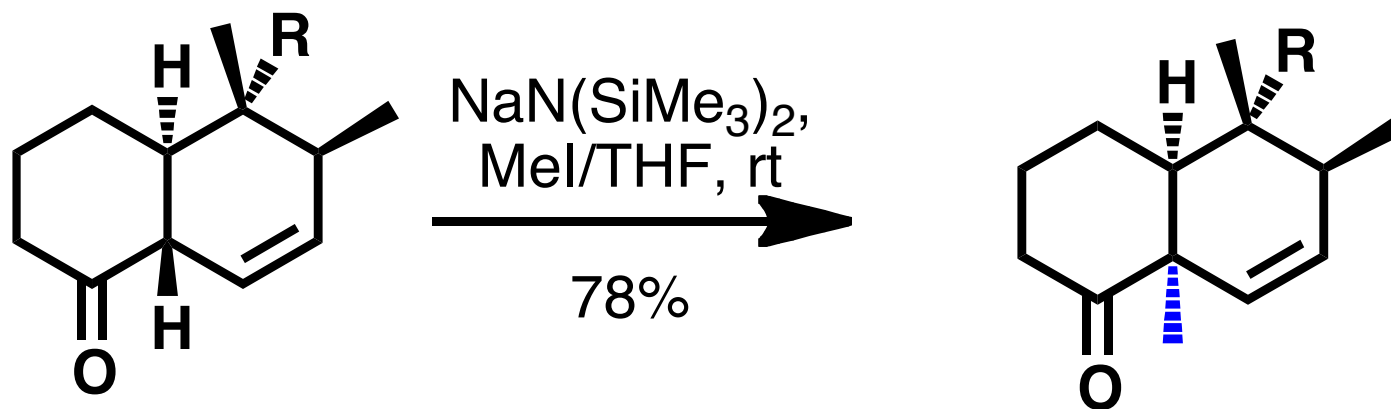
Intramolecular Diels-Alder example



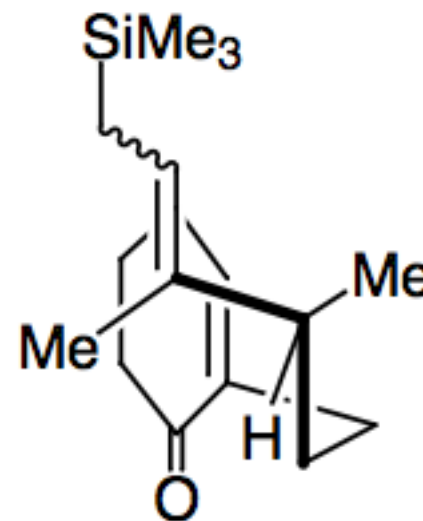
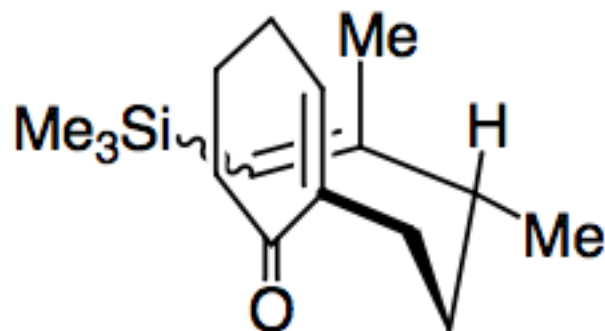
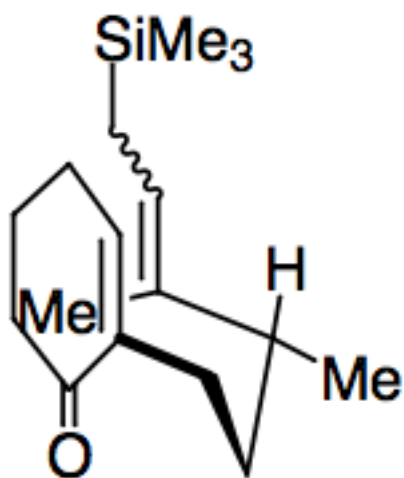
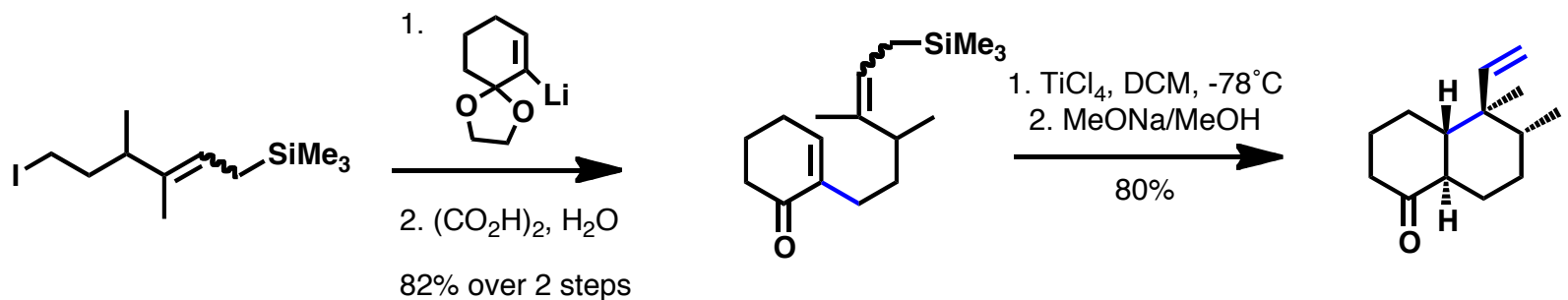
Tokoroyama, T. *Synthesis* **2000**, 5, 611-633.

Kawai, N. *et al.* *Tetrahedron Lett.* **1999**, 40, 4193.

Intramolecular Diels-Alder example



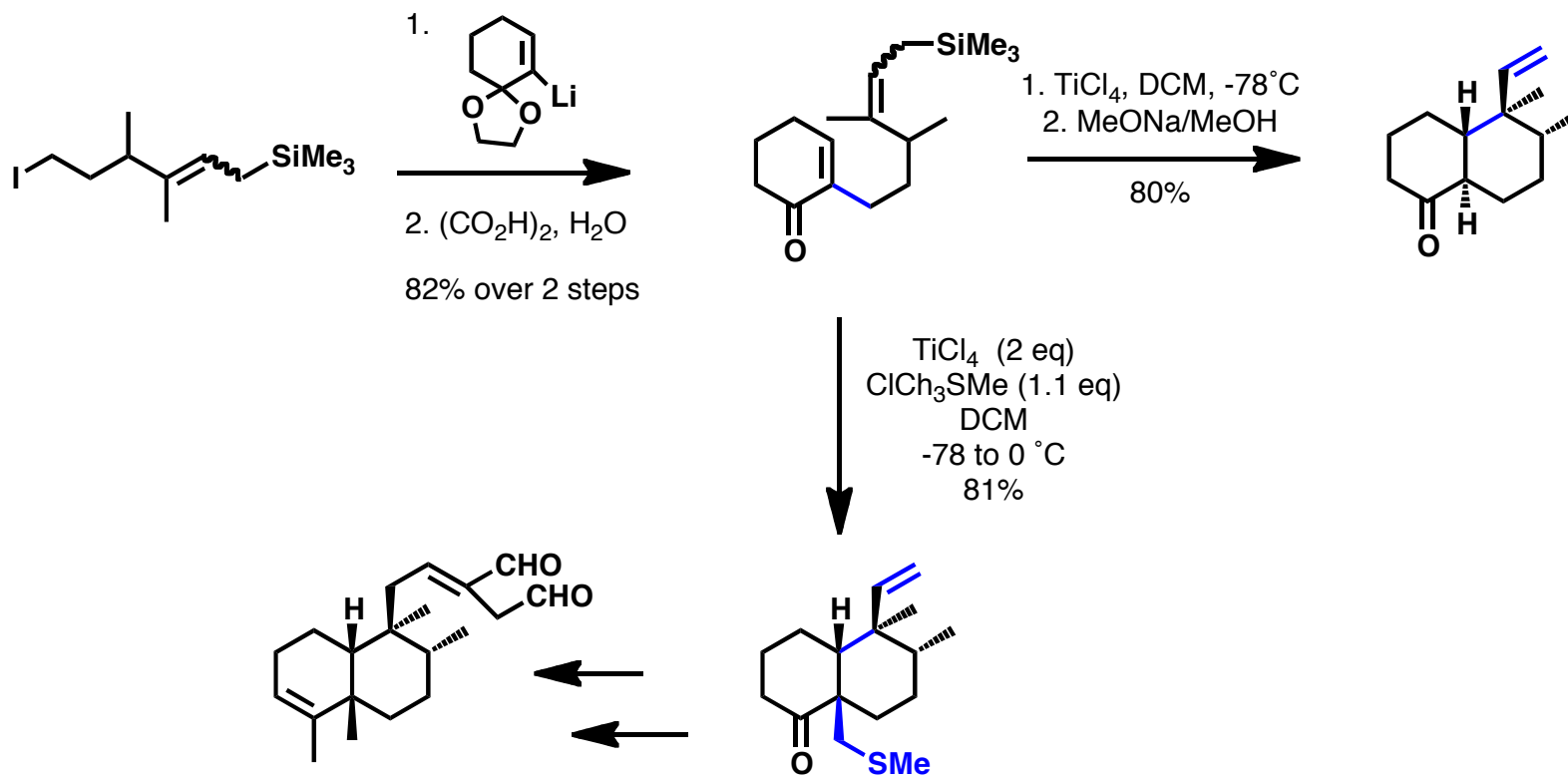
Example #6: ring closure reaction



Tokoroyama, T. *Synthesis* **2000**, 5, 611-633.

Tokoroyama, T. *Tetrahedron Lett.* **1984**, 25, 5067.

Example #6: ring closure reaction



Tokoroyama, T. *Synthesis* **2000**, 5, 611-633.
Tokoroyama, T. *Tetrahedron Lett.* **1984**, 25, 5067.