Natural Products Chemistry: Koji Nakanishi

David Lin

Professor Koji Nakanishi

- Born 1925 in Hong Kong
- B.S., Nagoya University, 1947
- Ph.D., Nagoya University, 1954 (Fujio Egami)
- Studied at Harvard (Louis Fieser), 1950-1952
- Asst. Professor, Nagoya University, 1955-1958
- Professor, Tsukuba University (Tokyo), 1958-1963
- Professor, Tohoku University (Sendai), 1963-1969
- Professor, Columbia University, 1969-present
- Married to Yasuko
- Two children, Keiko and Jun

"A Wandering Natural Products Chemist"

Natural Products Isolation and Characterization:

- Elucidated the structures of over 180 natural products
- Highlights include: the ginkgolides, brevetoxin A & B, the illudins, periplanone B, the taxcins, the ecdysteroids

Spectroscopic Methods in Structure Determination

- First discovered phenomenon of NOE in natural products
- Development of exciton chirality method for determining absolute stereochemistry

Bioorganic Chemistry

- Studies into the bioactivity of the ginkgolides
- Synthesis and study of the activity of retinal chromophores
- Determining the cause of macular degeneration, the primary form of blindness in the elderly

Magic

Notorious for his magic tricks at conferences
My personal favorite is the magic bag trick, where a person climbs into a bag which is tied up. After the magician performs his charm, the person appears from behind a nearby curtain. Nakanishi has performed this trick on Raymond Lemieux, Gilbert Stork, Jack Baldwin, Ron Breslow, and others.

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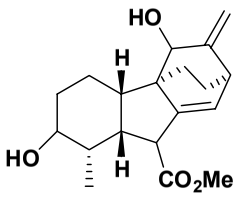
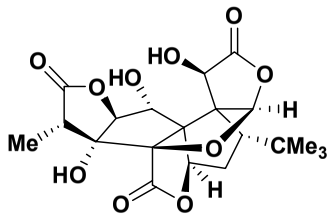
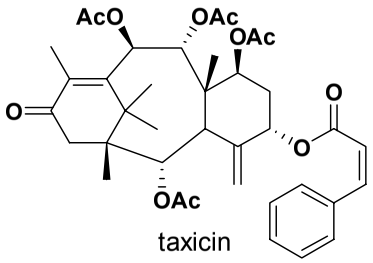


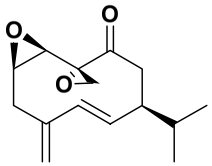
antheridiogen



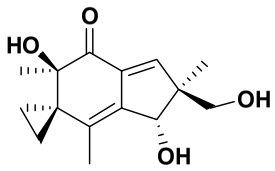
ginkgolide B



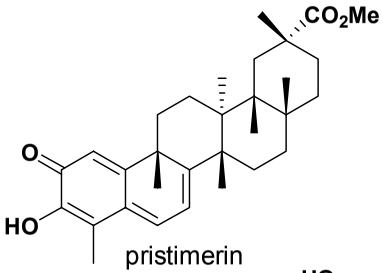
taxicin



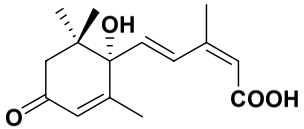
periplanone B



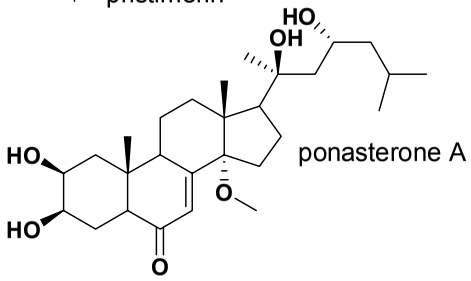
illudin



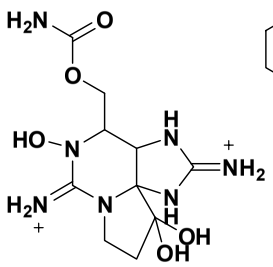
pristimerin



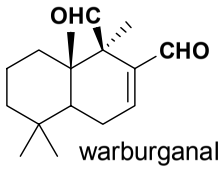
abscisic acid



ponasterone A

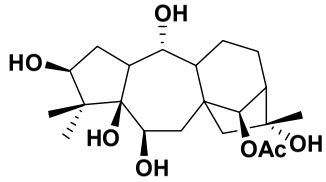


neosaxitoxin

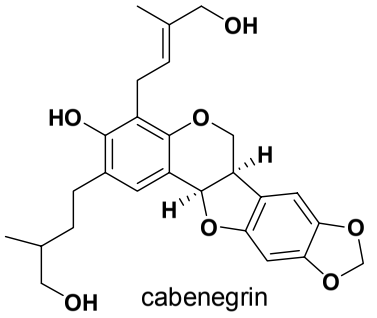


warburganal

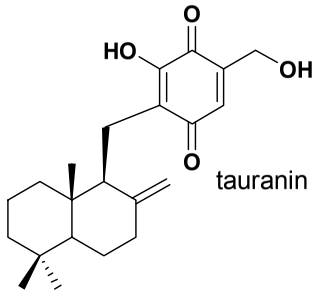
tunichrome B



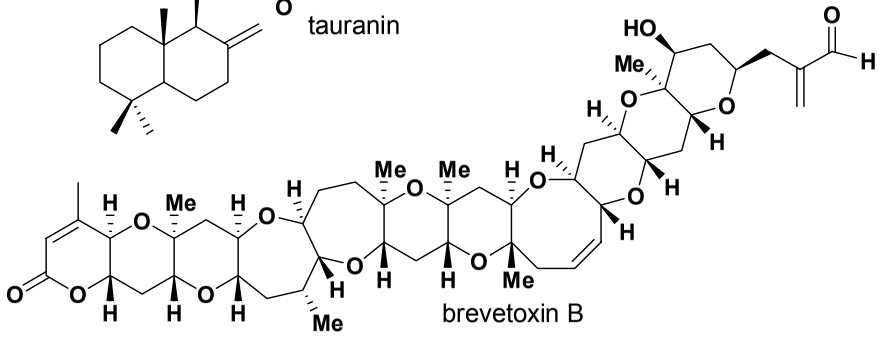
grayanotoxin I



cabenegrin



tauranin



brevetoxin B

The Exciton Chirality Method

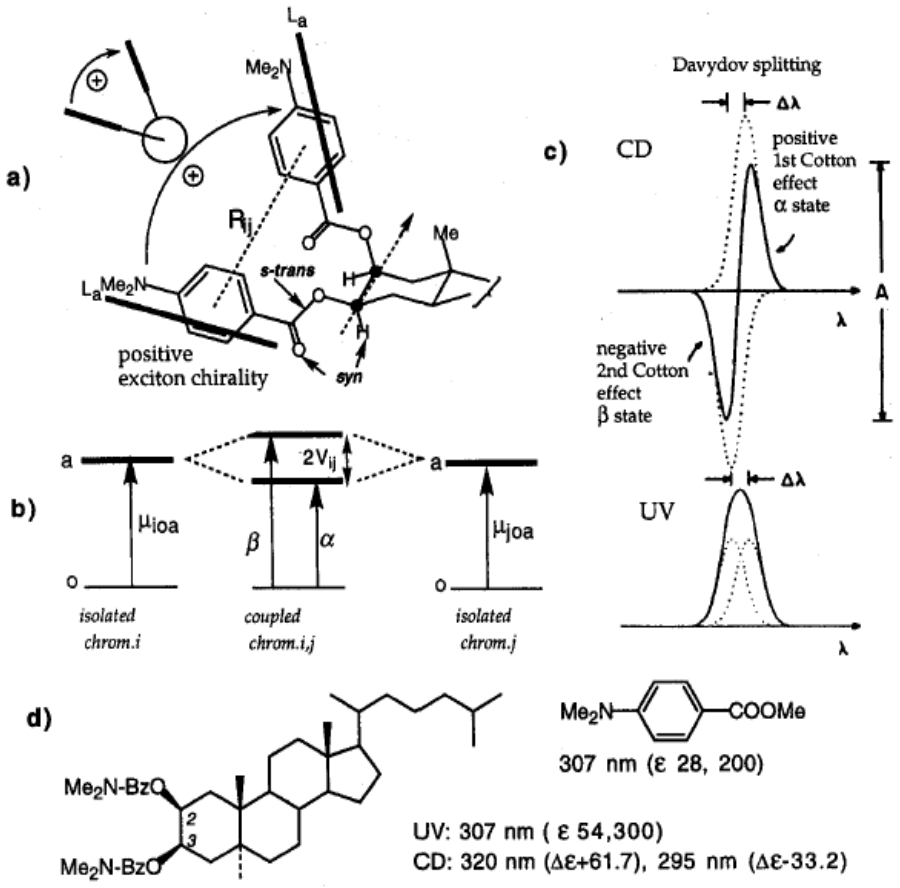


Figure 12.1 (*a*) Exciton coupling of two identical chromophores (*i* and *j*) of steroidal 2,3-bis-*p*-diemthylaminobenzoate with positive chirality and interchromophoric distance R_{ij}; the carbinyl hydrogens are represented *syn* to the ester carbonyl and the ester group is in *s*-trans conformation; (*b*) the splitting of the excited states of isolated chromophores into α and β states with Davydov split $2V_{ij}$; (*c*) summation CD and UV curves (solid line) of two component curves (dotted line) and amplitude *A* of bisignate CD curve; (*d*) CD and UV data of 5α-cholestane-2β,3β-diol-bis-*p*-dimethylaminobenzoate in EtOH.

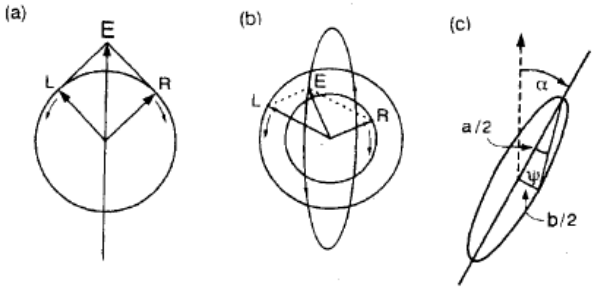
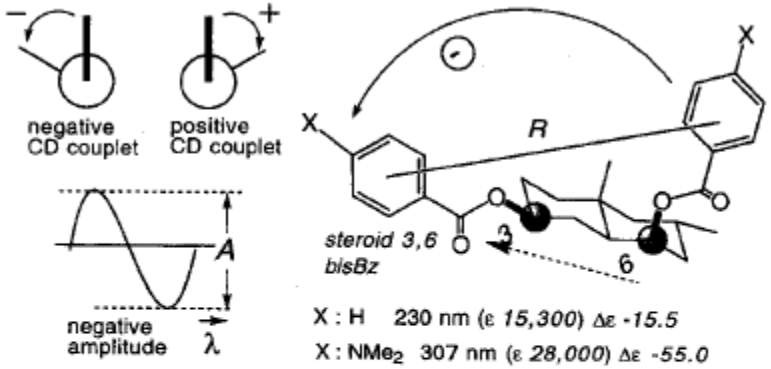


Figure 1.17 (*a*) Plane-polarized light resolved into two circularly polarized components, R and L. As long as the intensities and phases of the two circularly polarized components remain the same, their resultant will lie in a plane and oscillate in magnitude. (*b*) If the right circularly polarized component is less intense (absorbed more) than the left circularly polarized component, the electric vector of the light follows an elliptical path, as shown, corresponding to elliptically polarized light. (*c*) The semimajor and semiminor axes of the ellipse form a triangle and the angle opposite the semiminor axis is the angle, ψ, the ellipticity. The angle is proportional to the circular dichroism. The major axis of the ellipse has been rotated through the angle α, corresponding to the optical rotation.



1. Sample amount : microgram scale
2. Solvent : MeCN, sometimes methylcyclohexane with acyclics.
3. Chromophore : any chrom. with large ε and known direction of μ.
4. Sign of *split CD* : determined by chirality of chromophores.
5. *A* value (amplitude) is maximal at projection angle of ca. 70°, proportional to ε^2, inversely proportional to R^2.

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Characterization of the Ginkgolides: Serendipity Rocks!

Problem: Ginkgolide extracted from the root bark of the ginkgo tree, removal of which kills the tree.

Serendipity: Typhoon hits Sendai, Japan and uproots many ginkgo trees. Nakanishi group members rush to Sendai to obtain material.

Characterization of the Ginkgolides: Serendipity Rocks!

Problem: NMR spectra of ginkgolide not very helpful in structure elucidation.

Serendipity: Undergraduate contaminates sample of LAH-reduced ginkgolide with acid and leaves it in drying oven while he goes off to play baseball. Sample goes to tar in oven. However, chromatography of the tar produces ginkgolide triether derivative which provides more useful NMR data and…

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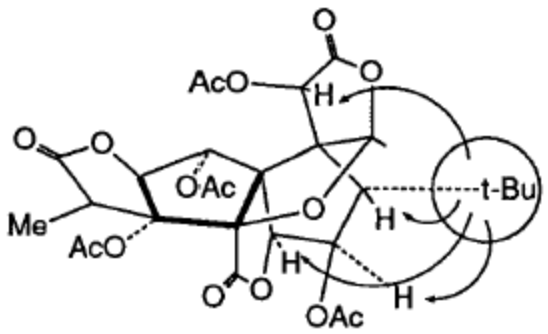
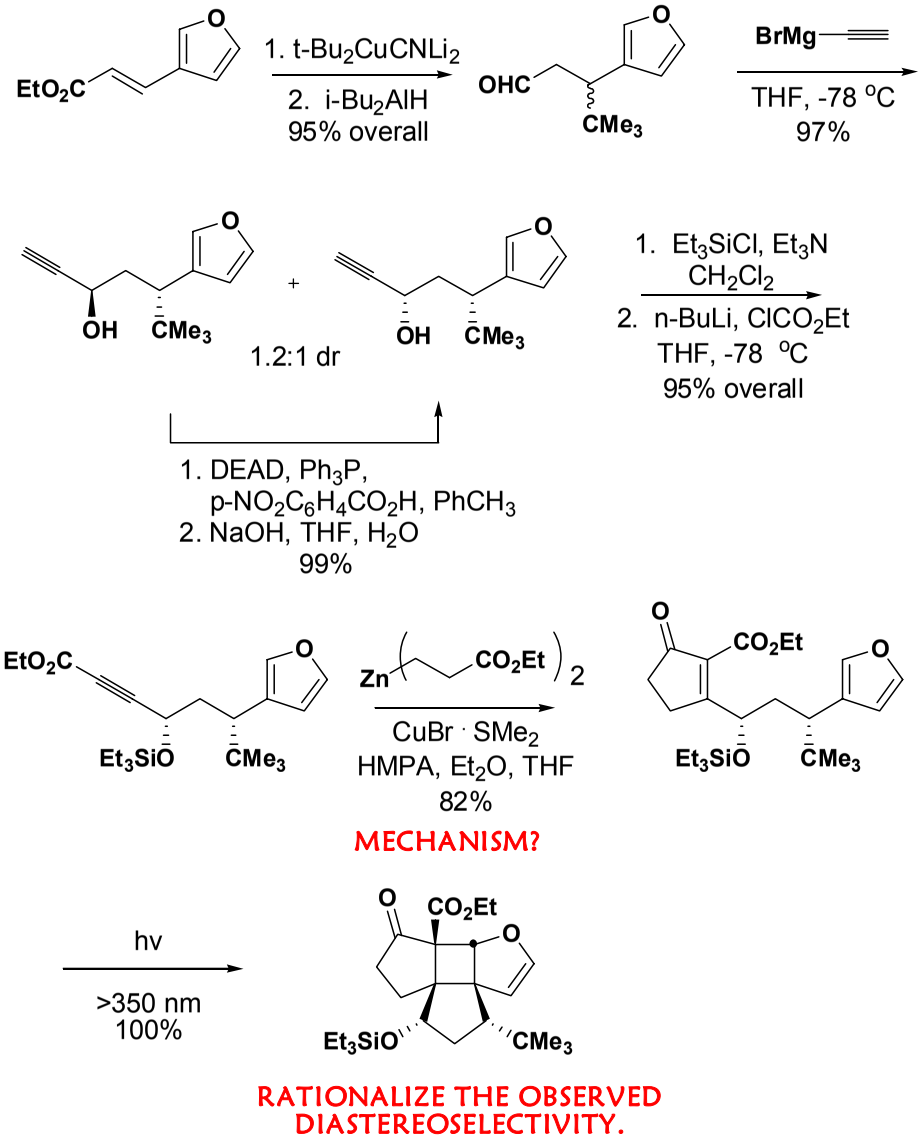
…The Discovery of NOE



NOE's observed upon irradiation of t-Bu in ginkgolide A.

NOTE: For a comprehensive review of the biology and chemistry of the ginkgolides and the related bilobalides, see Nakanishi's recent review: *Angew. Chem. Intl. Ed.* **2004**, *43*, 1640.

Crimmins synthesis of ginkgolide B: *J. Am. Chem. Soc.* **1999**, *121*, 10249; *J. Am. Chem. Soc.* **2000**, *122*, 8453.



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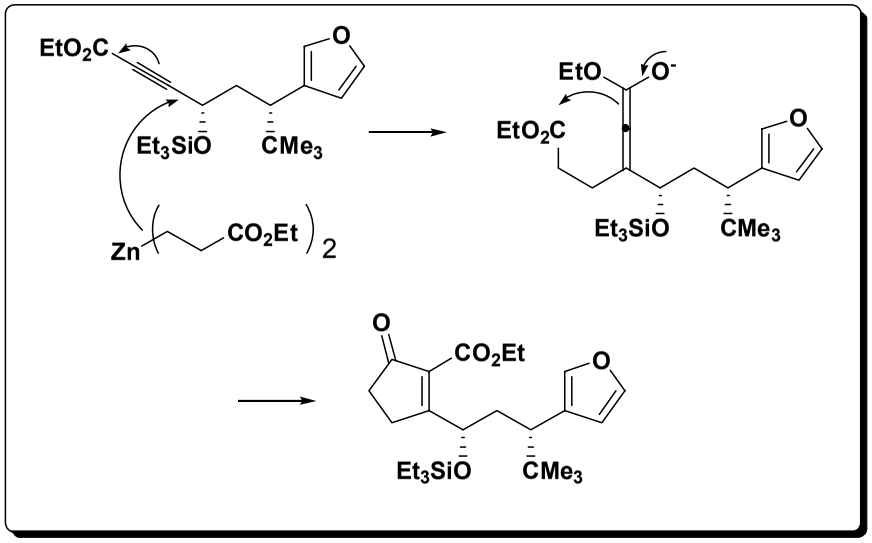
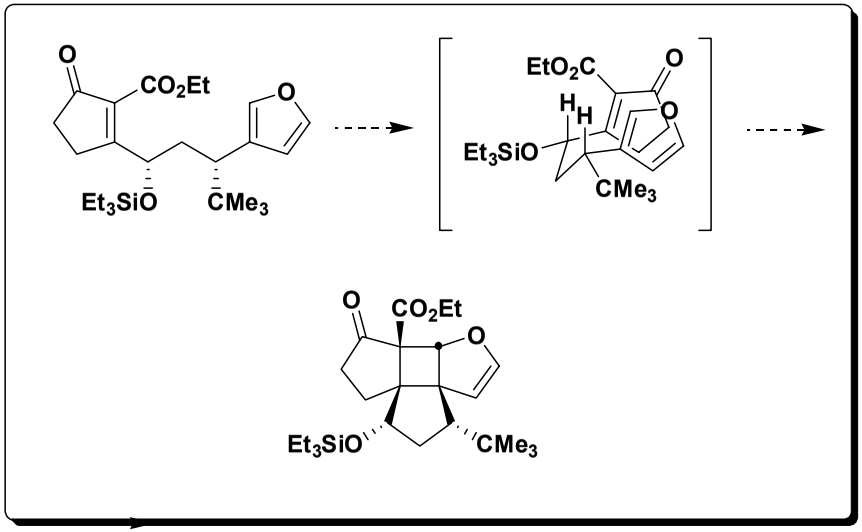
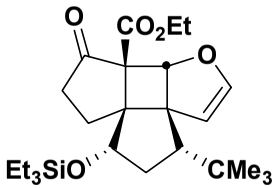
mechanism of Crimmins' homoenolate cyclopentenone formation:



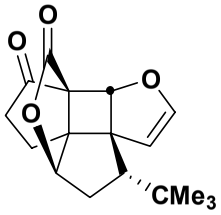
rationalizing diastereoselectivity of the [2+2]:





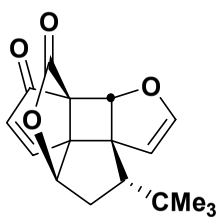
1. HF/CH_3CN
2. MsCl, Et_3N
3. EtOH, H_2O, reflux
4. PPTS, PhH, reflux

63% over four steps



Notice that a stereocenter has been inverted. This route was taken to improve the diastereoselectivity of the [2+2] cycloaddition, which was poorer with the trans stereochemistry.

PhSeCl, HCl, then $NaIO_4$

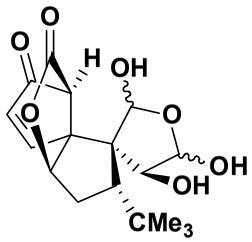


DMDO, then p-TsOH

H_2O, acetone

94%

MECHANISM?

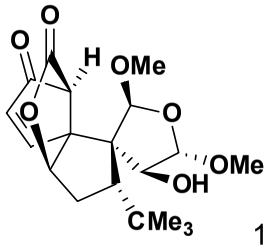


MeOH

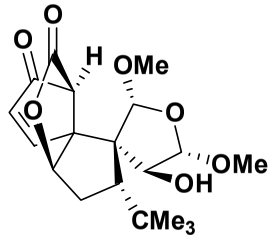
$HC(OMe)_3$

p-TsOH

95%overall



\+



1:5.5 de

6 N HCl, acetone

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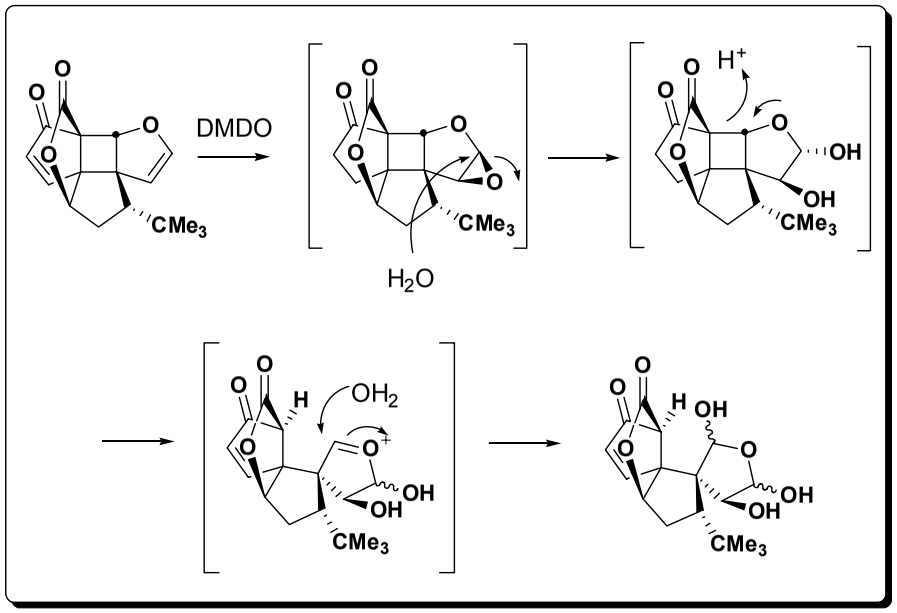
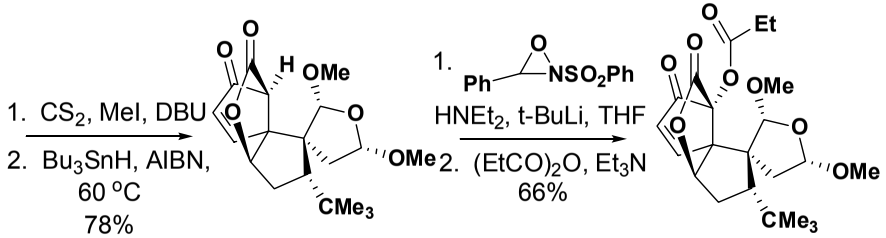
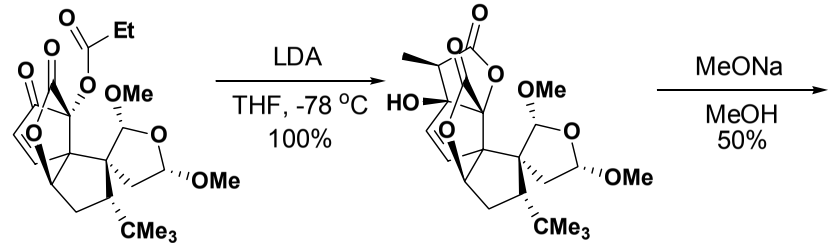
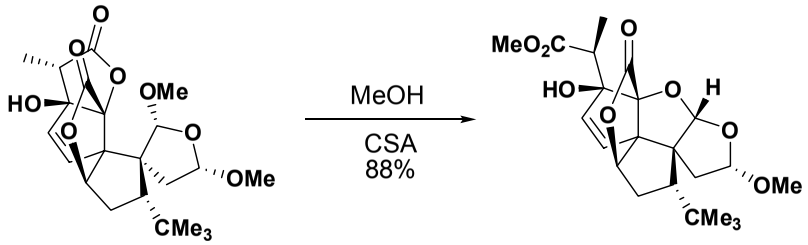
mechanism for cyclobutane ring rupture:



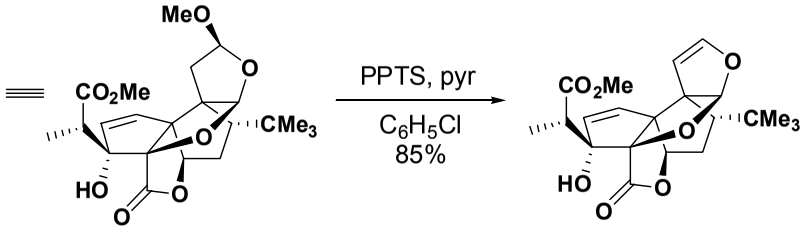


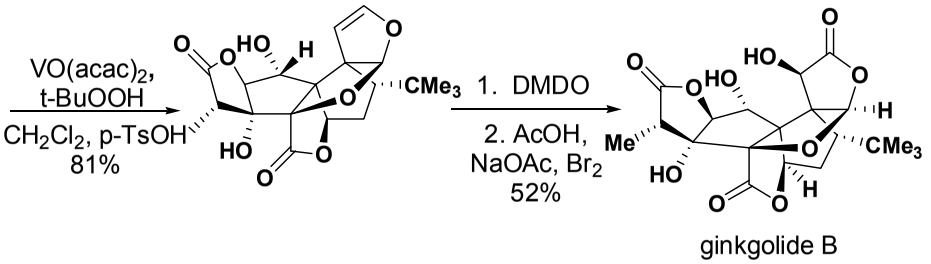
This somewhat curious deoxygenation temporarily removes a hydroxyl which proved troublesome in the upcoming ring-closing step.





Here they racemize a troublesome stereocenter to achieve the poor 50% yield, but the undesired diastereomer was easily recovered and recycled.





ginkgolide B

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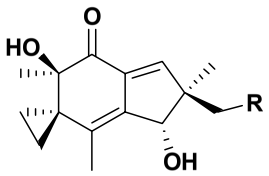
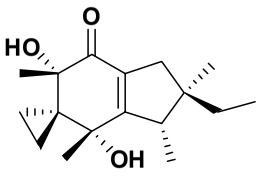
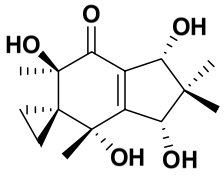
The Illudins, Illudanes, and Protoilludanes



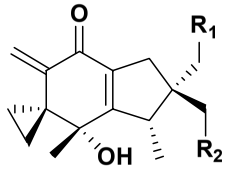
Illudin M (R=H)
Illudin S (R=OH)



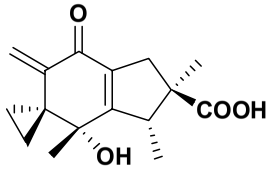
Illudin A



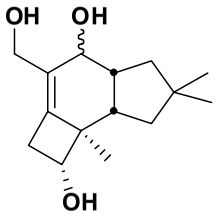
Illudin B



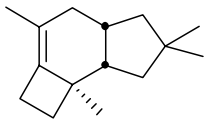
R_1, R_2 = H: Illudin C
R_1 = OH, R_2 = H: Illudin C_2
R1 = H, R_2 = OH: Illudin C_3



Illudinic Acid



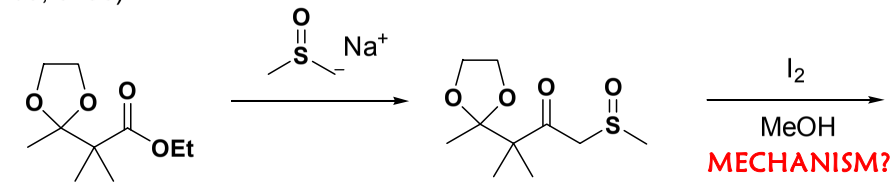
α-OH: illudol
β-OH: epi-illudol

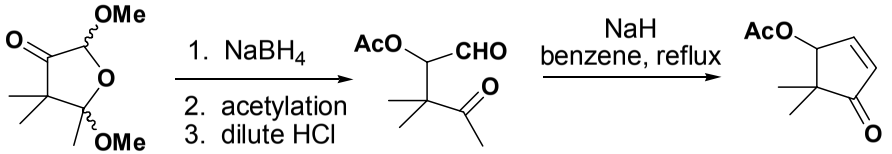


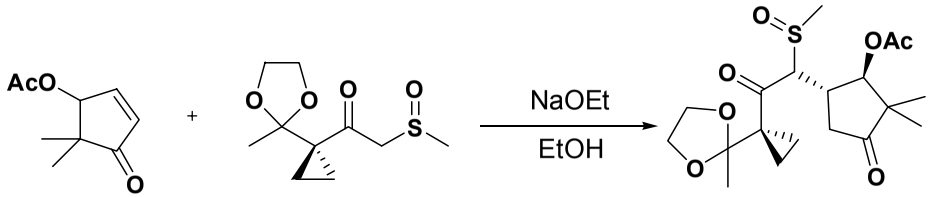
illudene

- Highly toxic sesquiterpene first isolated from the bioluminescent mushroom *tsuki-yo-take*
- Possesses potent antitumor activity, probably by cross-linking DNA base pairs
- Subject of intense medicinal chemistry/SAR studies

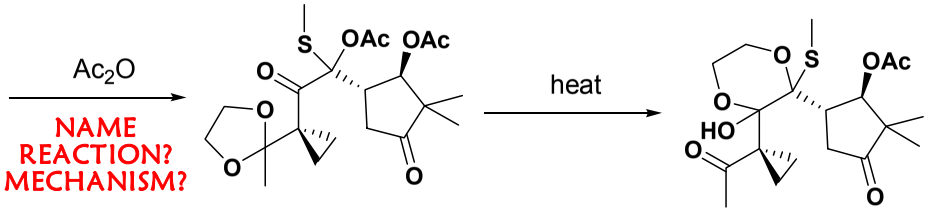
The First Synthesis, Illudin M: Matsumoto et al (*J. Am. Chem. Soc.* **1968**, *90*, 3280)

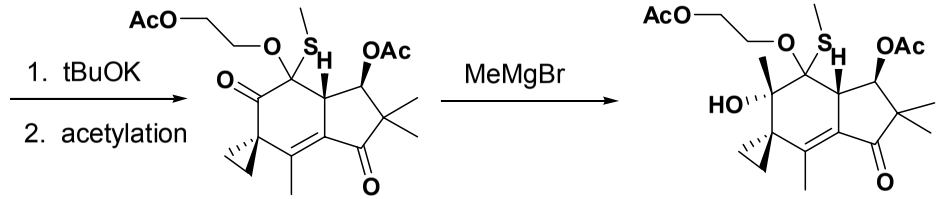






stereoselective; other diastereomer not observed





selective for ketone shown, and stereoselective as well!

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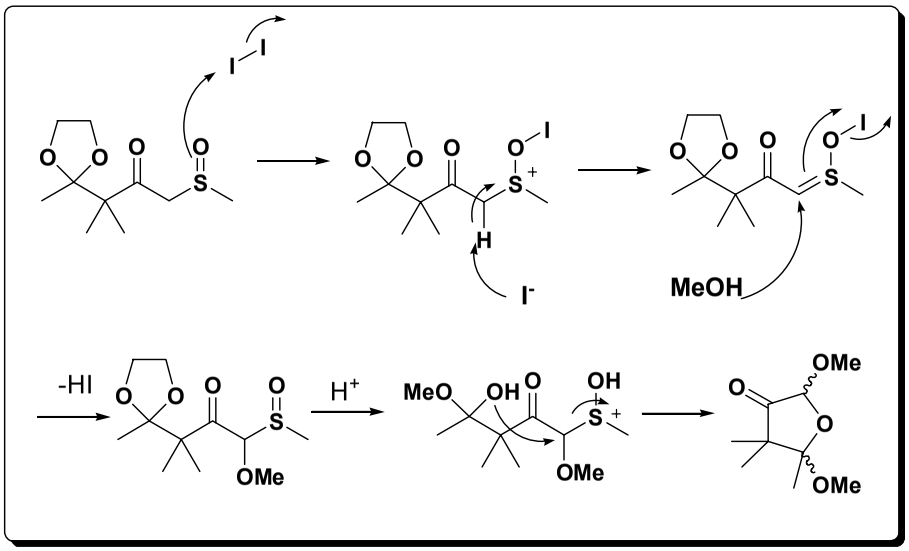
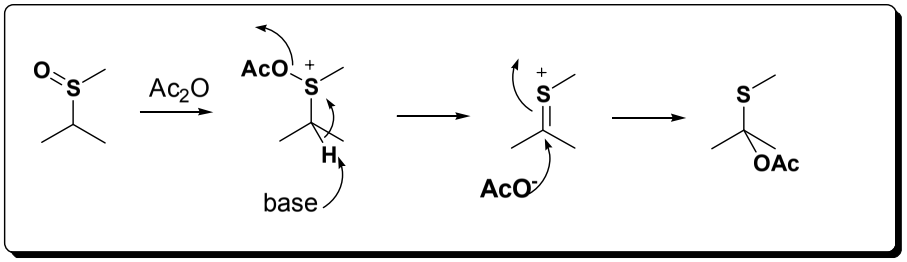
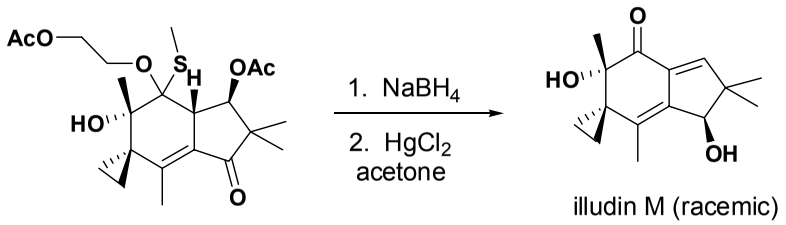
mechanism of oxidative cyclization:



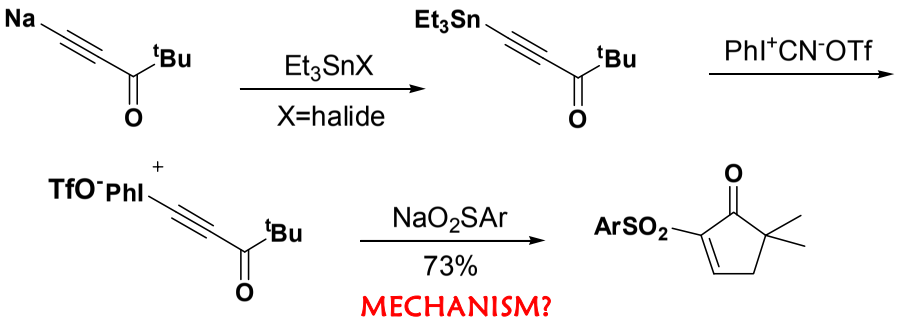
the Pummerer rearrangement:



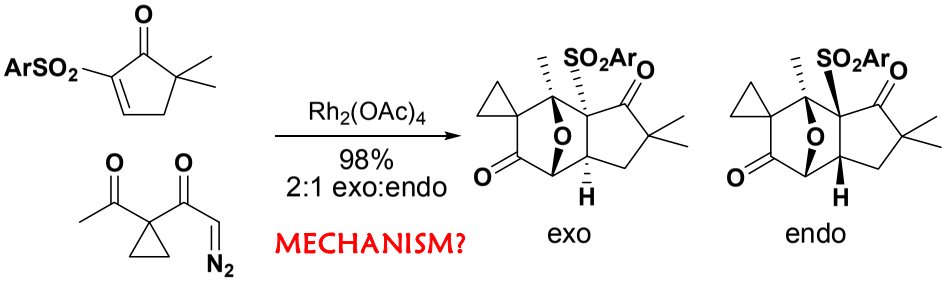


illudin M (racemic)

Padwa et al, *J. Org. Chem.* 1997, ***62*, 1317.**



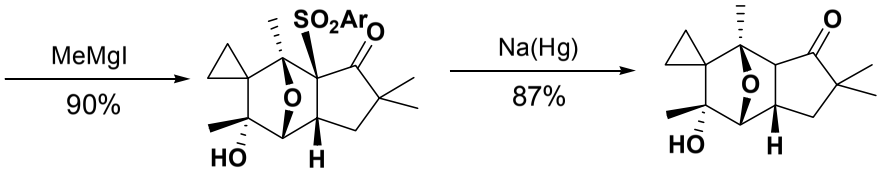
MECHANISM?

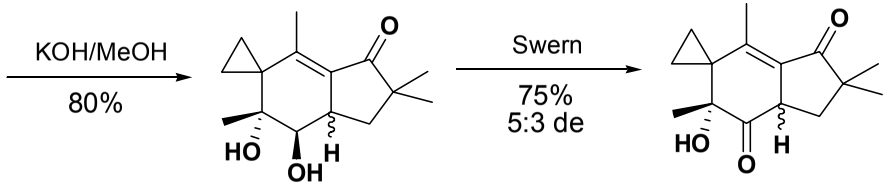


MECHANISM?

exo endo

Note that stereoconfiguration at bridgehead carbons ultimately do not matter, so both isomers carried forward.





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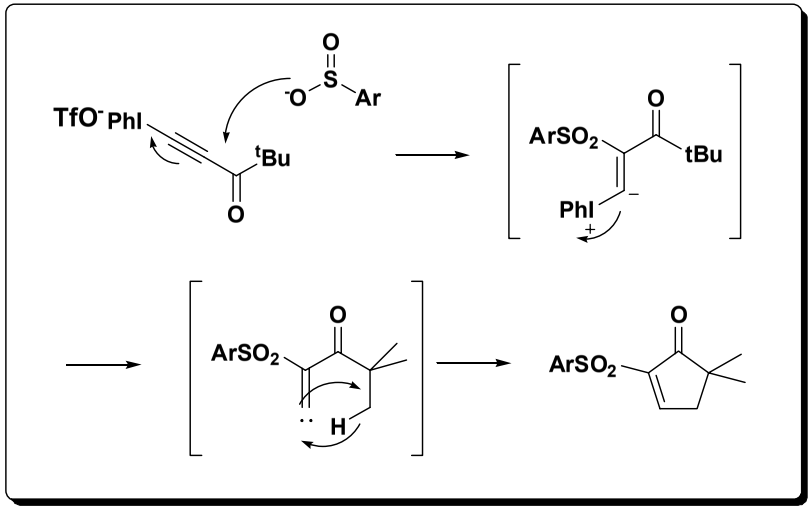
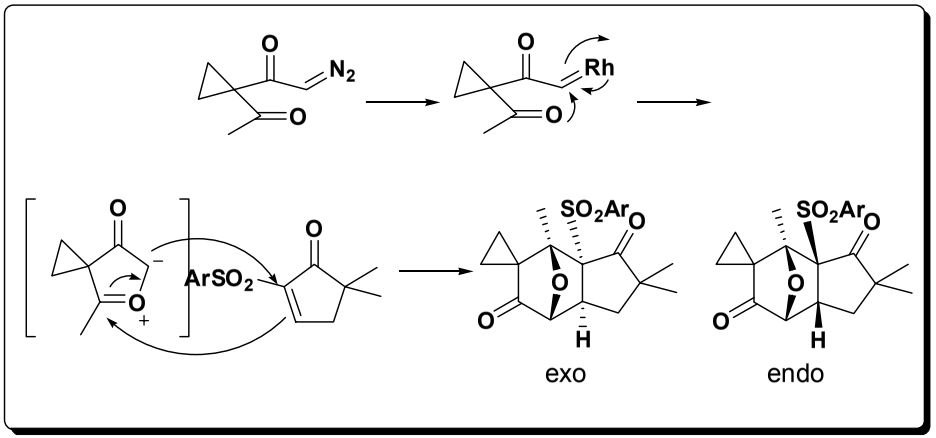
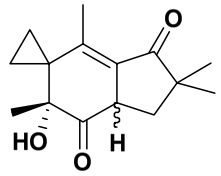
mechanism of cyclization:

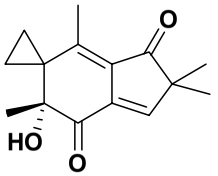


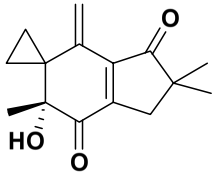
Padwa's Rh(II)-catalyzed 1,3-dipolar cycloaddition:





DDQ



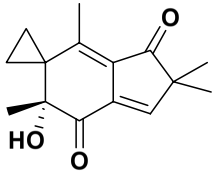


Here Padwa intercepts a known intermediate from another total synthesis.

14% (desired)

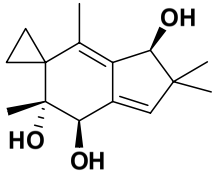
56% (undesired)

Completion of the Padwa synthesis: Kinder and Bair, *J. Org. Chem.* **1994**, *59*, 6965.



$LiAlH_4$

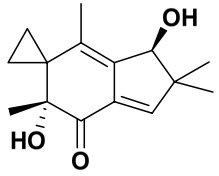
74%



NBS

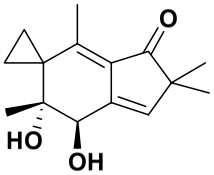
pyridine

$LiAlH_4$



illudin-M
30%

+



undesired isomer
23%

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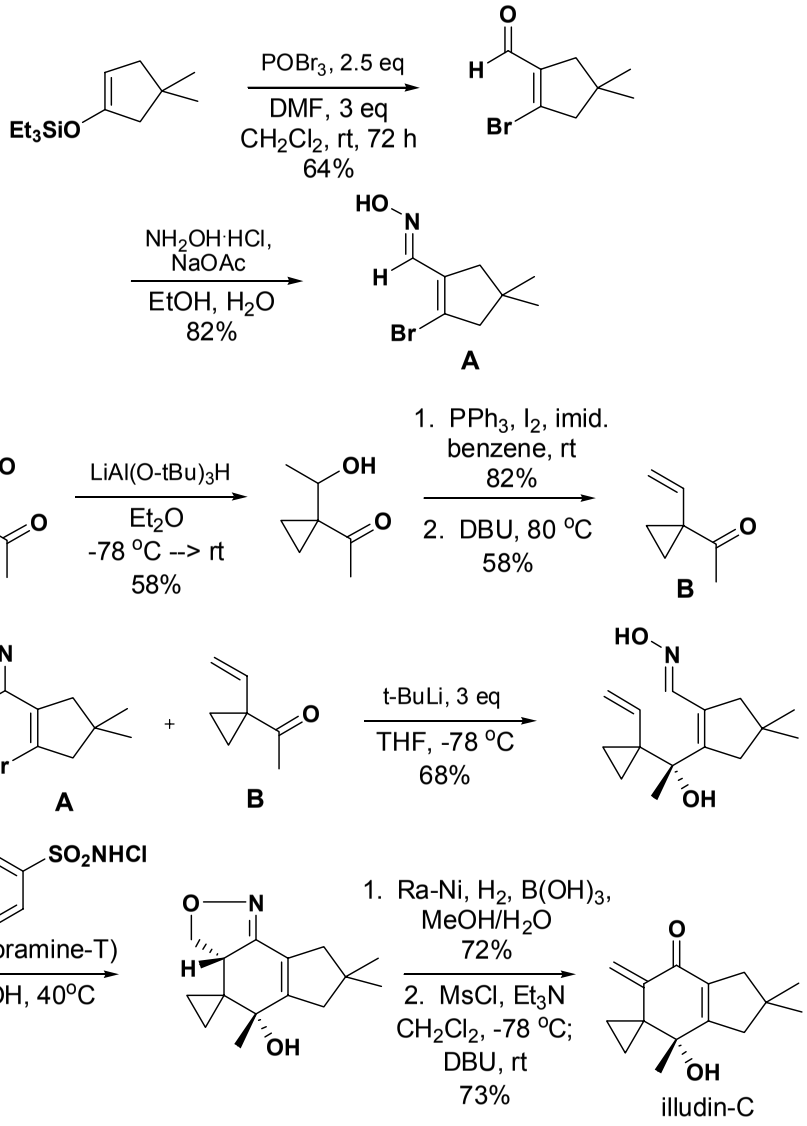
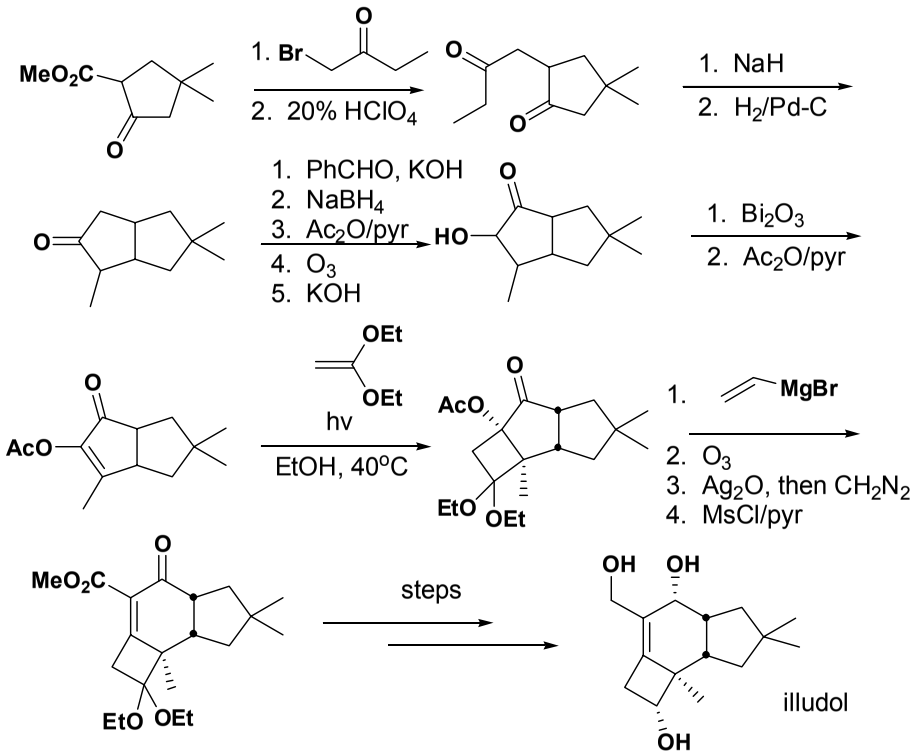
Funk's synthesis of illudin-C (*Org. Lett.* **2001**, *3*, 2611):



Illudol: Matsumoto et al (*TL* **1969**, 3913; *TL* **1971**, 3521):



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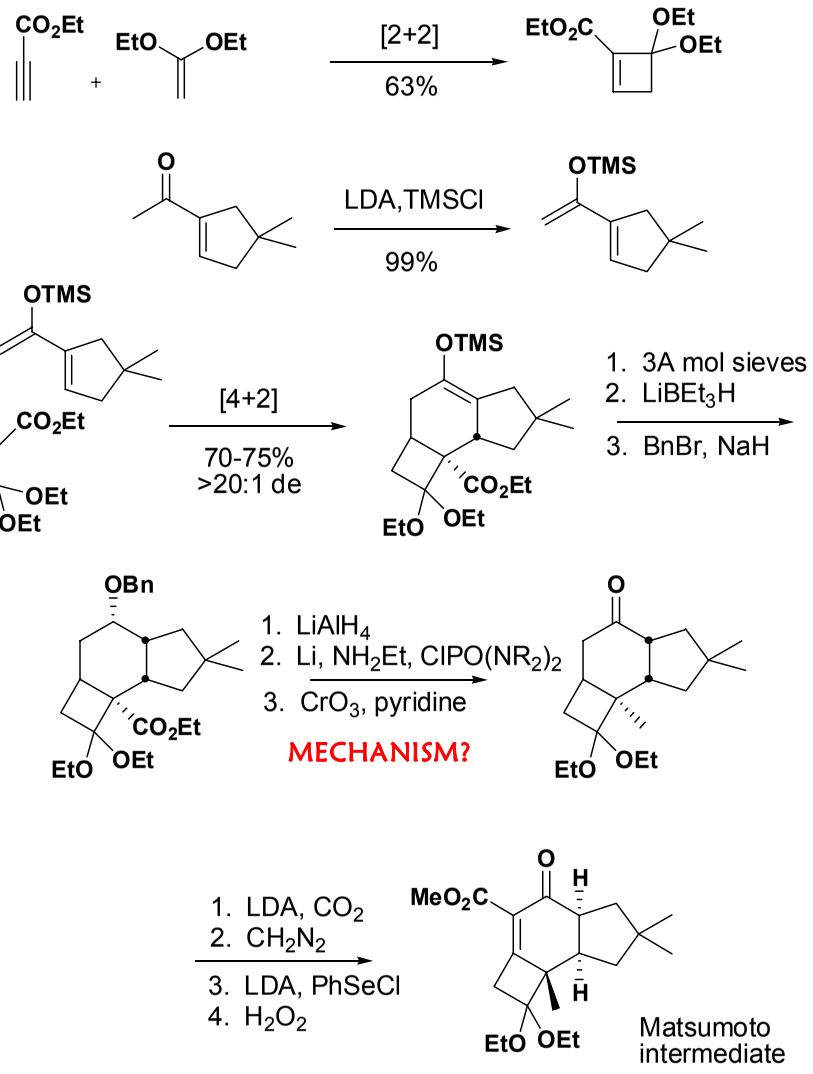
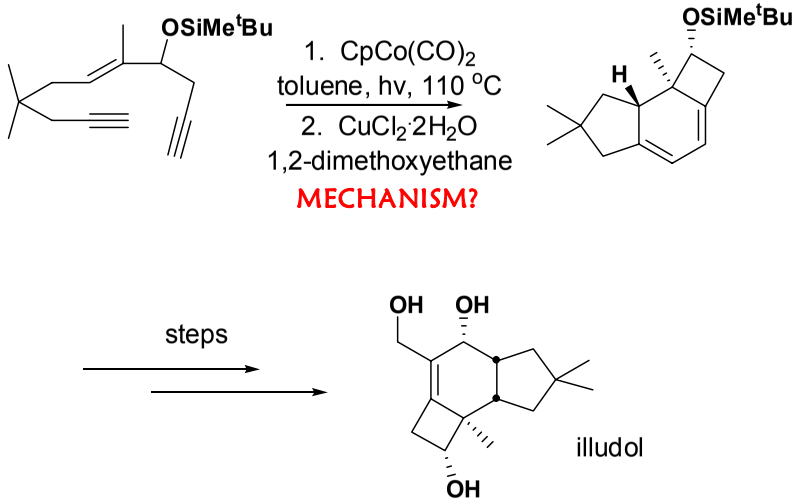
Illudol: Semmelhack (*J. Am. Chem. Soc.* **1982**, *104*, 747):



Illudol: Vollhardt (*J. Am. Chem. Soc.* **1991**, *113*, 381):



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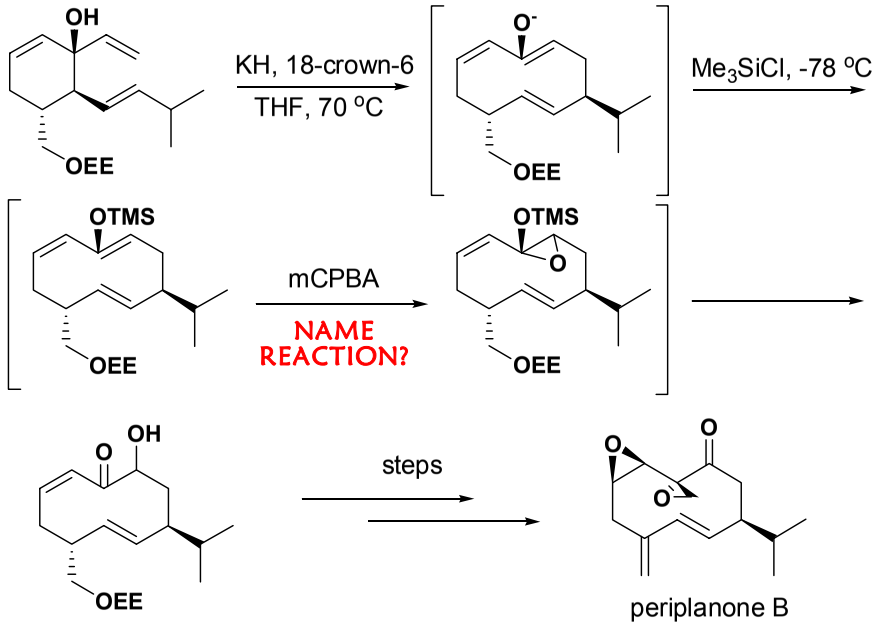
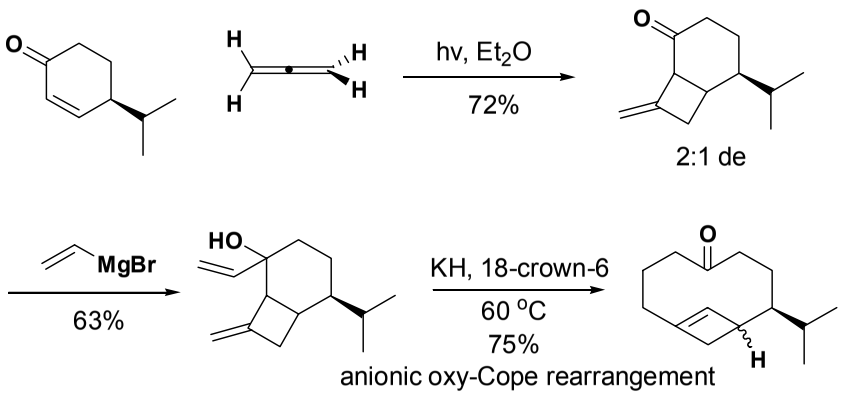
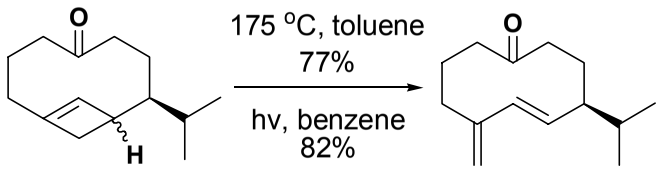
Periplanone B: W.C. Still (*J. Am. Chem. Soc.* **1979**, *101*, 2493.

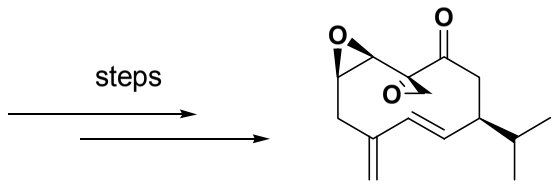


Periplanone B: S.L. Schreiber (*J. Am. Chem. Soc.* **1984**, *106*, 4038):





[2+2] electrocyclic ring opening



periplanone B

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Additional References

•*Circular Dichroism: Principles and Applications*. 2nd Ed. Berova, N., K. Nakanishi, R.W. Woody, eds. New York: Wiley-VCH, 2000.
•Nakanishi, K. *A Wandering Natural Products Chemist.* J.I. Seeman, ed. Washington, D.C.: American Chemical Society, 1991.
•Nicoloau, K.C., E.J. Sorensen. *Classics in Total Synthesis*. New York: VCH Publishers, 1996.
•A complete list of Nakanishi's publications may be found at his group's website:
http://www.columbia.edu/cu/chemistry/groups/nakanishi/