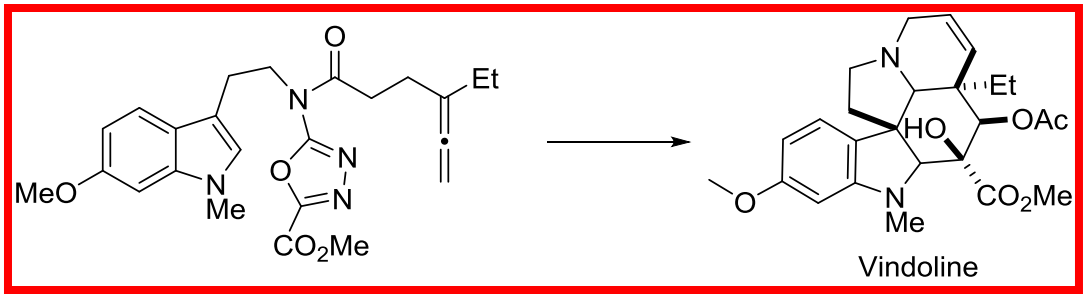
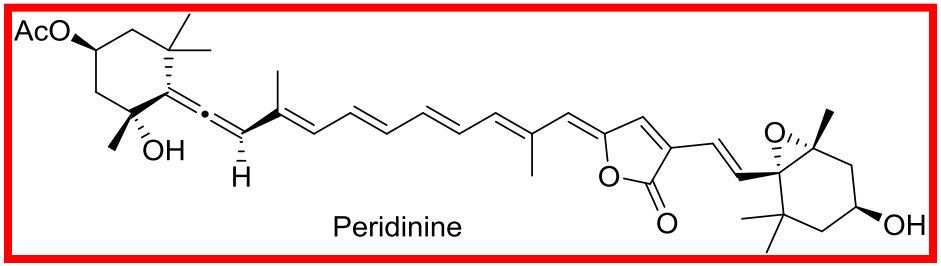
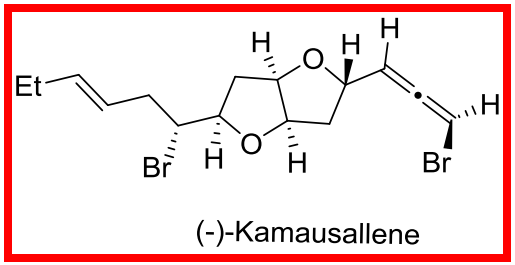
Allenes in Total Synthesis



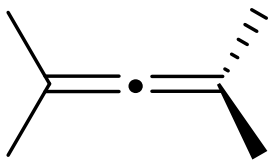




Mohammad Mujahid
EAA Group, University of Oxford
2nd June 2016

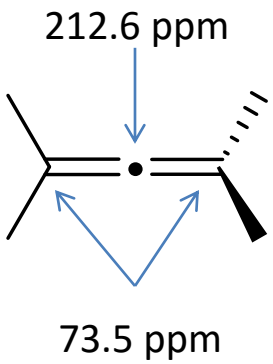
Introduction

Structural properties



- Molecules with chiral axis leading to “extended tetrahedral” shape.
- Two sigma and two pi bonds with central C being sp-hybridised.
- Has hybrid character of an olefin and an alkyne thus show reactions of both olefin and alkyne.

Spectroscopic properties



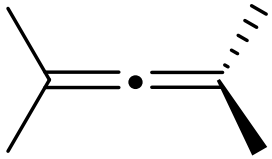
$HC{\equiv}CH$

73.8 ppm

$H_2C{=}CH_2$

122.8 ppm

Spectroscopic properties



ν = 1960 cm $^{-1}$ and 1050 cm $^{-1}$

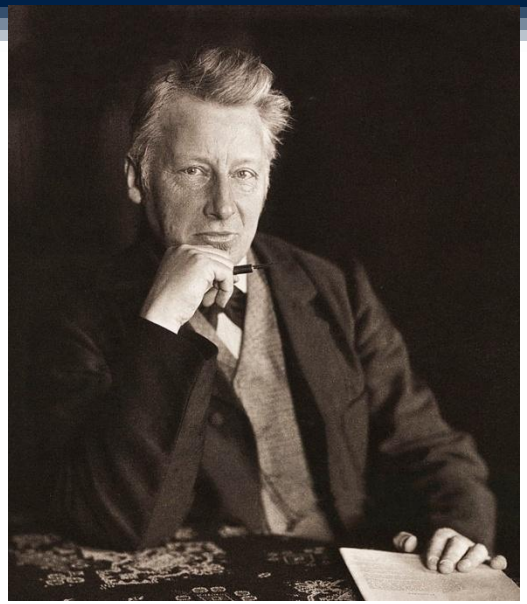
$HC{\equiv}CR$

2260-2100 cm $^{-1}$

$H_2C{=}CHR$

1620-1680 cm $^{-1}$

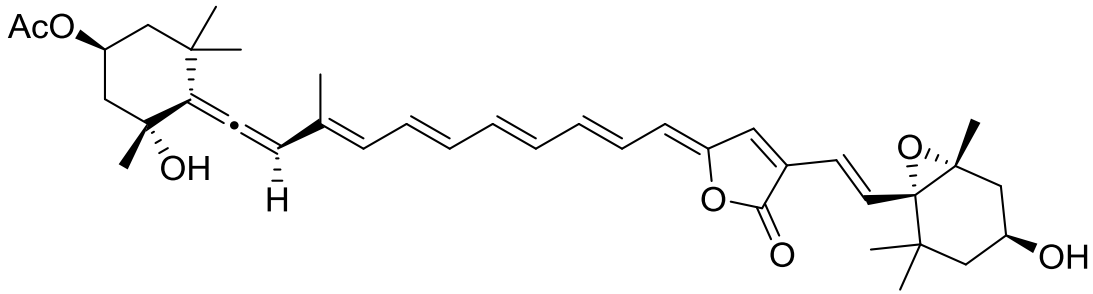
Allene in synthesis



- Considered a chemical curiosity for a long time.
- van't Hoff predicted the correct tetrahedral structure of allenes and higher cumulenes in 1875[1] but most chemist had their doubts.
- First reported synthesis was in 1890 and was initially an attempt to disprove the existence of this class of compound.[2]

1) J. H. van't Hoff, La Chimie dans l'Espace, Bazendijk: Rotterdam, 1875
2) B. S. Burton, H. von Pechmann, *Ber. Dtsch. Chem. Ges.* **1887**, 20, 145

Allene in synthesis



Peridinine

- More than 150 natural products have allene functionality.
- All allenic natural products isolated until now are chiral and have been isolated in non-racemic form.
- Structures of many natural products having allenes were wrongly assigned which were corrected once IR and Raman spectroscopy became prominent.
- From 1984−2004, more than 8000 papers have been published on allenes.

1) J. H. van't Hoff, La Chimie dans l'Espace, Bazendijk: Rotterdam, 1875; 2) B. S. Burton, H. von Pechmann, Ber. Dtsch. Chem. Ges. 1887, 20, 145. Modern Allene Chemistry- N. Krause, A. S. K. Hashmi

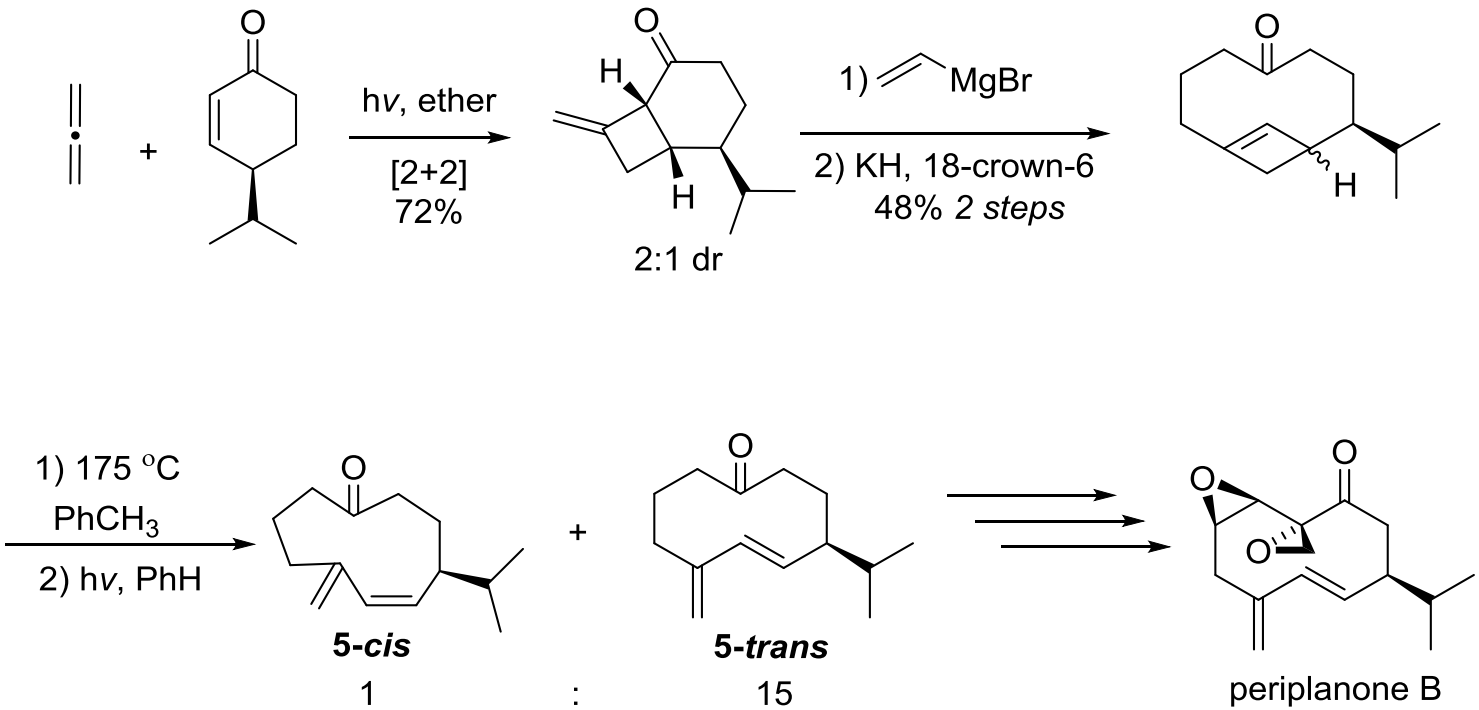
Allenes as precursors in total synthesis

Allenes as precursors in total synthesis

- Cycloaddition reactions: [2+2], [4+2] and miscellaneous
- Transition metal-catalysed cycloadditions
- Transition metal-promoted cyclisations
- Acid-catalysed rearrangements
- Allenoates

Cycloaddition reactions

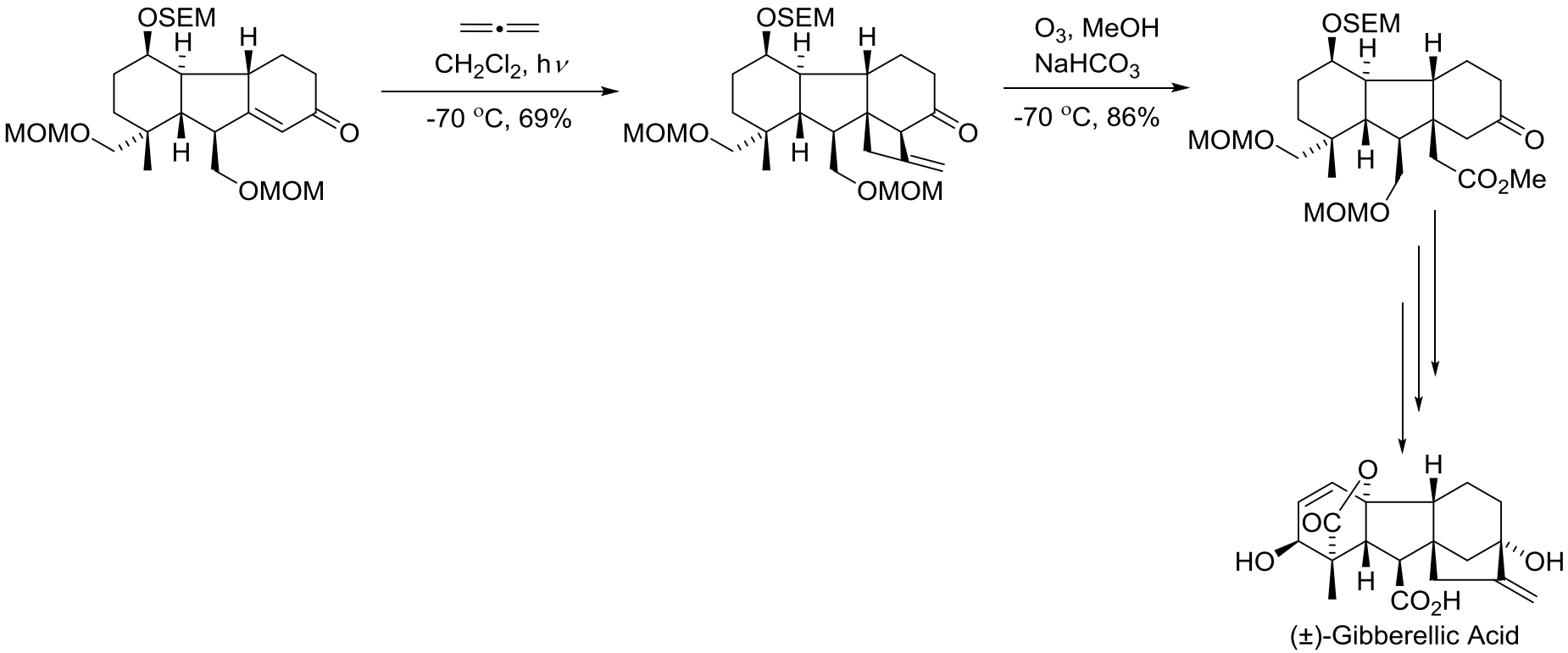
- [2+2] cycloaddition
  Periplanone B: American Cockroach pheromone



S. L. Schreiber, C. Santini. *J. Am. Chem. Soc.* **1984**, 106, 4038

Cycloaddition reactions

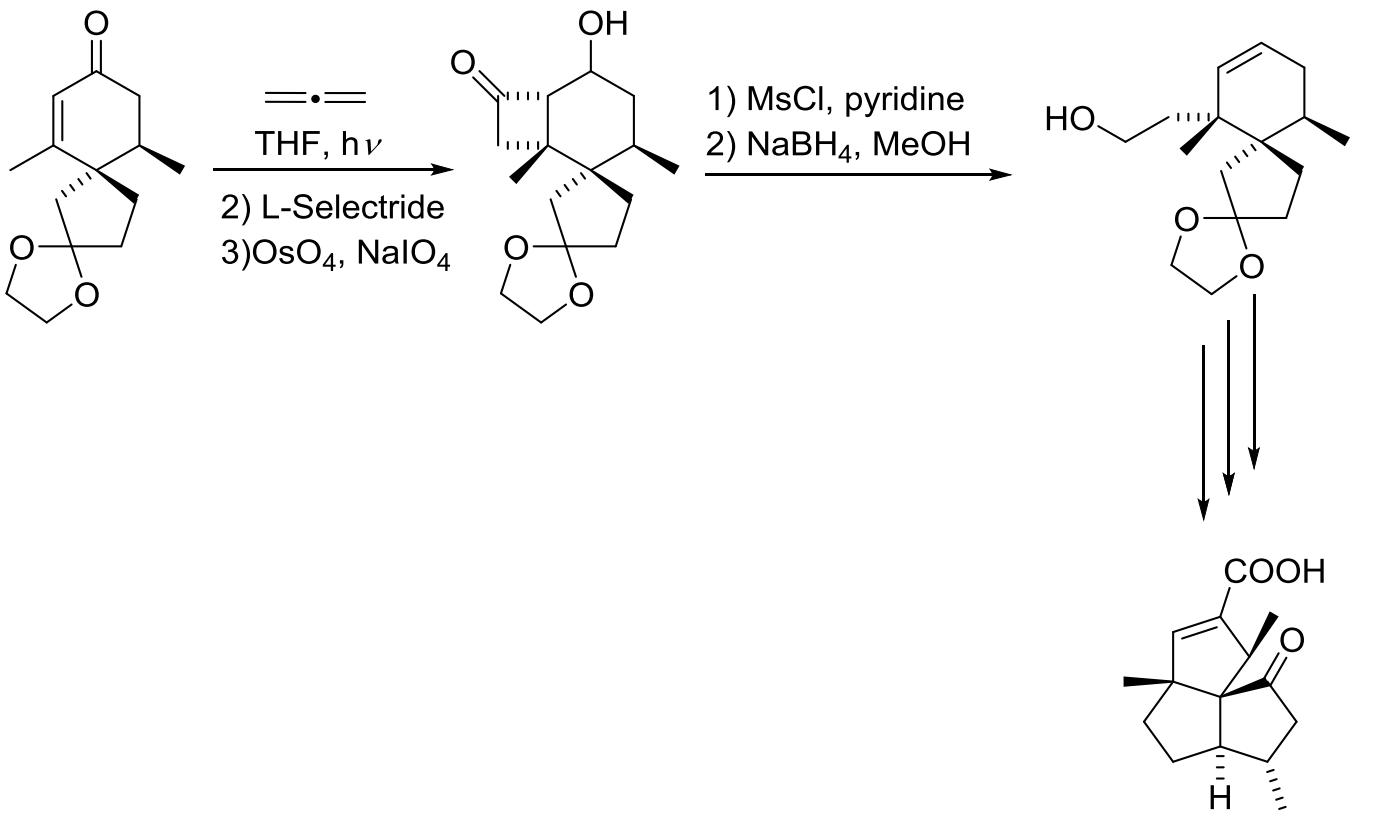
- [2+2] cycloaddition
  (±)-Gibberellic Acid: Plant growth hormone synthesised industrially.



K. Kanematsu. *Tetrahedron Lett.* **1989**, 30, 971

Cycloaddition reactions

- [2+2] cycloaddition
  (±)-Subergorgic Acid: Isolated from Gorgonian coral, show cardiotoxic properties.

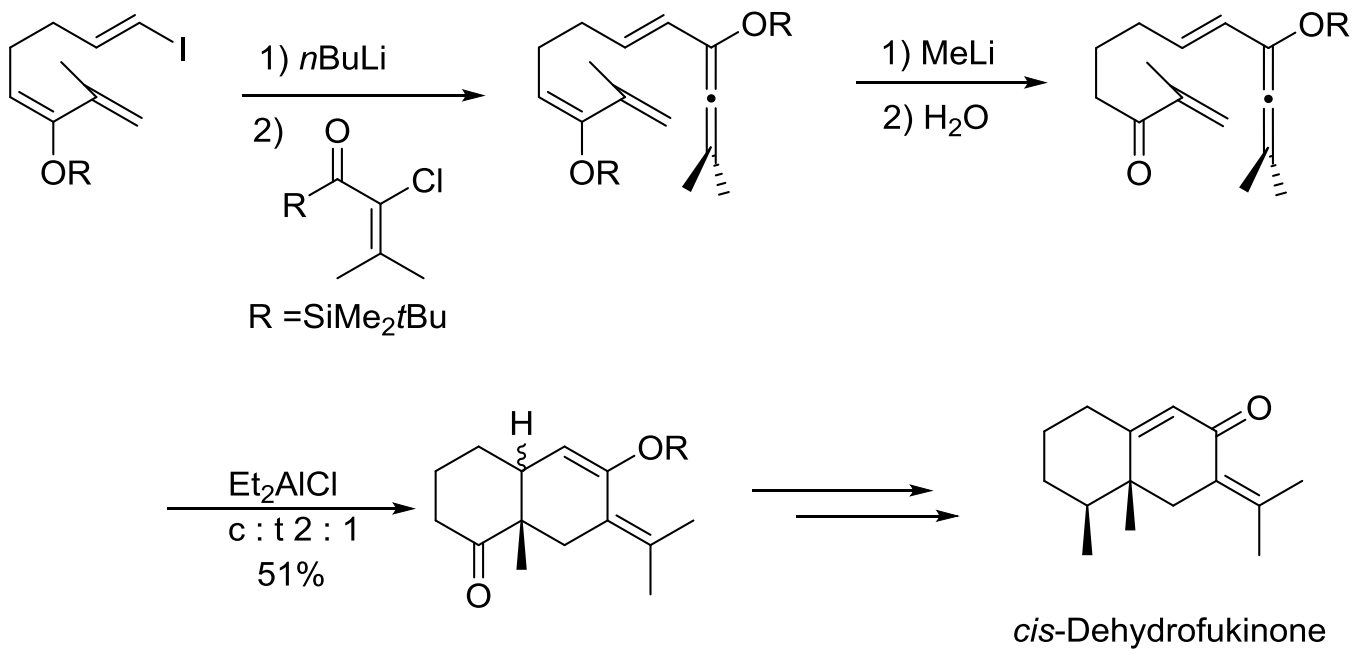


(±)-Subergorgic Acid

C. Iwata. *J. Org. Chem.* **1988**, 53, 1623

Cycloaddition reactions

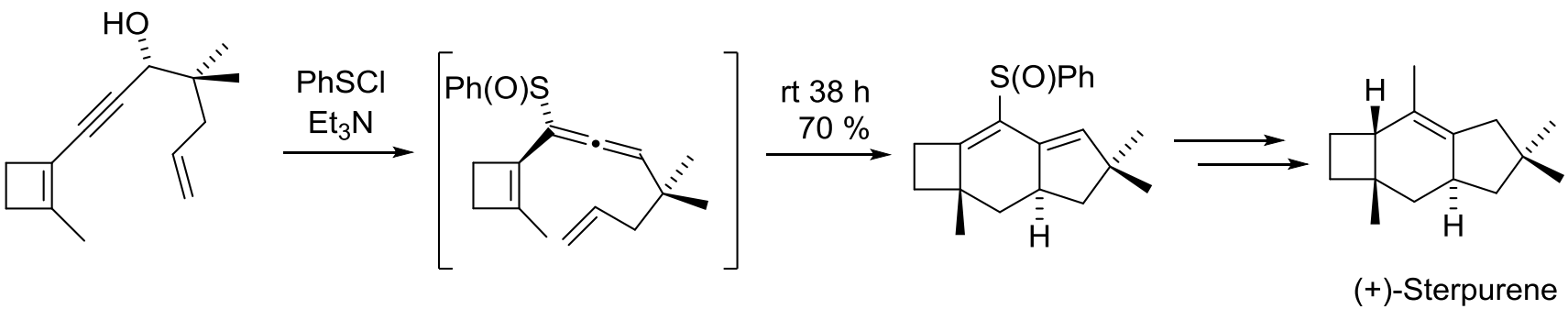
- [4+2] cycloaddition: Allene as diene component
  cis-Dehydrofukinone



H. Riech. *J. Am. Chem. Soc.* **1986**, 108, 7791

Cycloaddition reactions

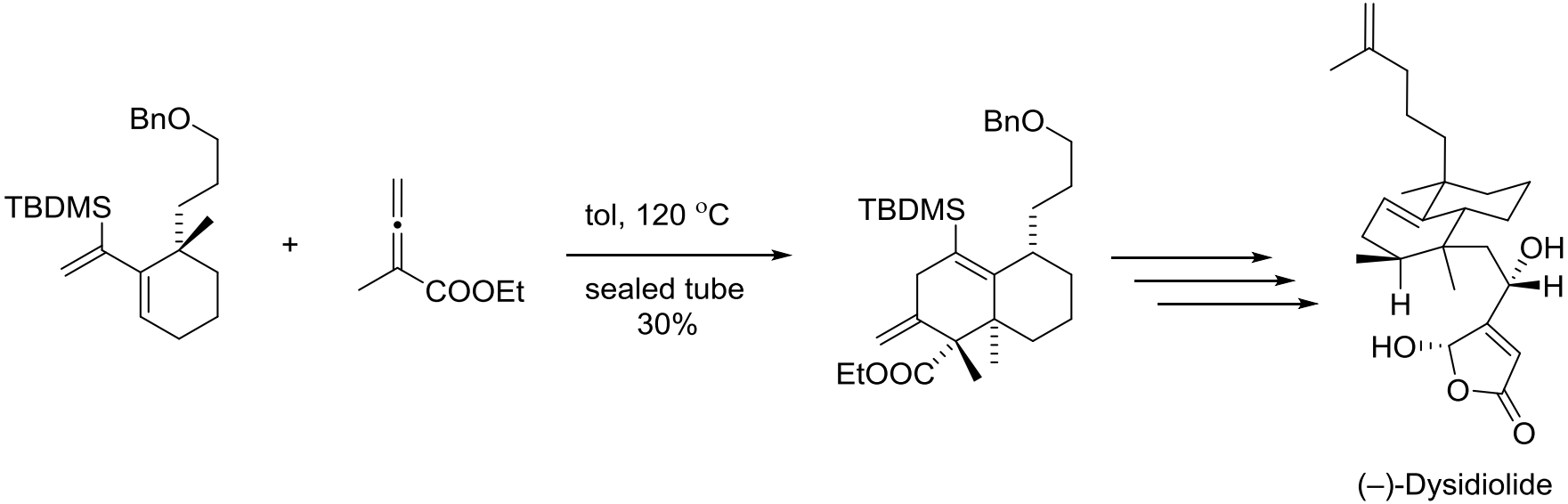
- [4+2] cycloaddition: Allene as diene component
  (+)-Sterpurene: A metabolite of fungus responsible for silver leaf disease in trees.



W. H. Okamura. *J. Am. Chem. Soc.* **1989**, 111, 3717

Cycloaddition reactions

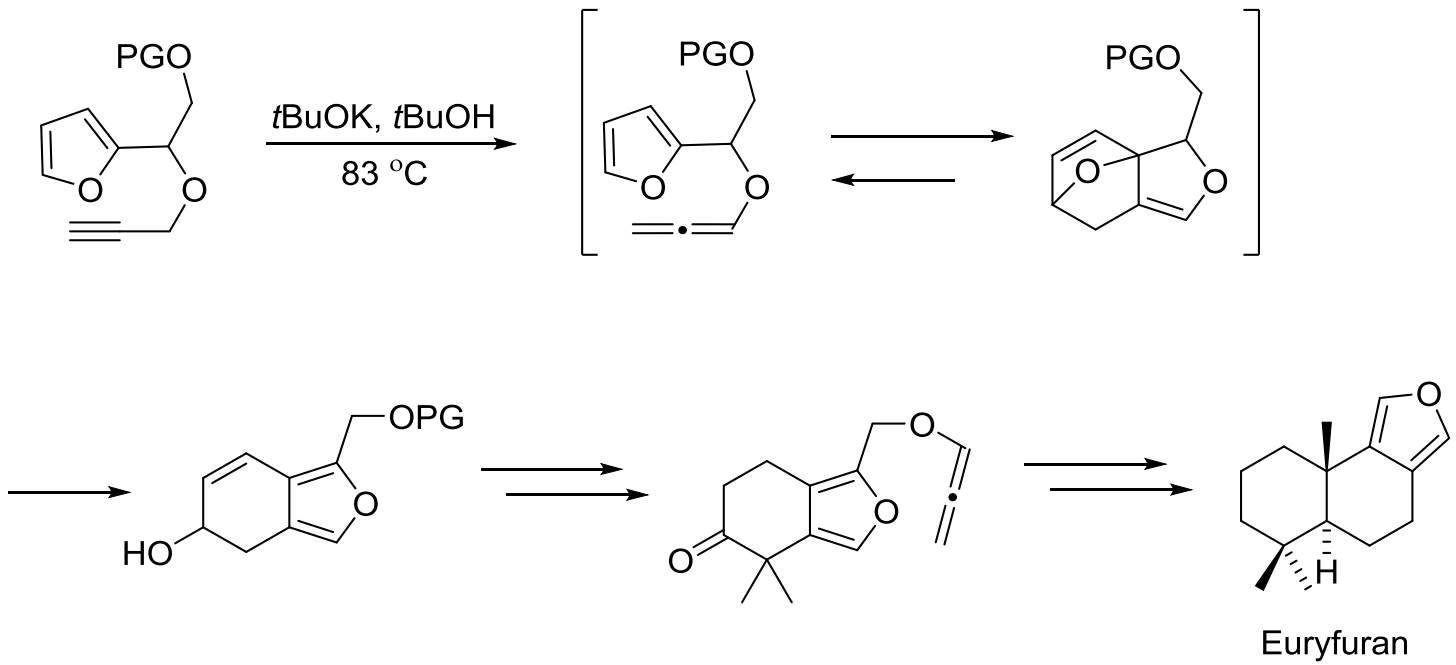
- [4+2] cycloaddition: Allene as dienophile component
  (–)-Dysidiolide: Phosphatase inhibitor



M.E. Jung. *J. Am. Chem. Soc.* **1999**, 121, 3529

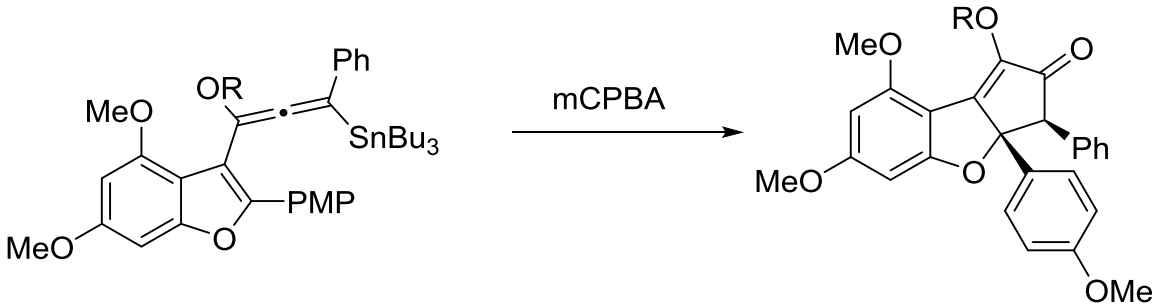
Cycloaddition reactions

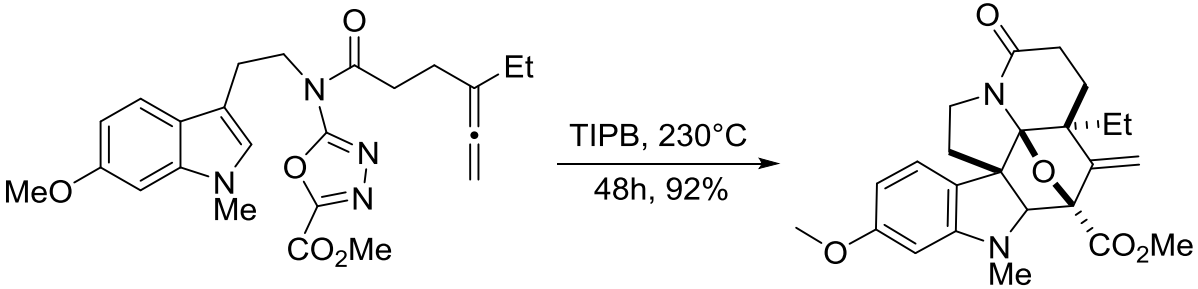
- [4+2] cycloaddition: Allene as dienophile component
  Euryfuran: isolated from marine sponges.



S. Soejima. *Heterocycles*, **1991**, 32, 1483

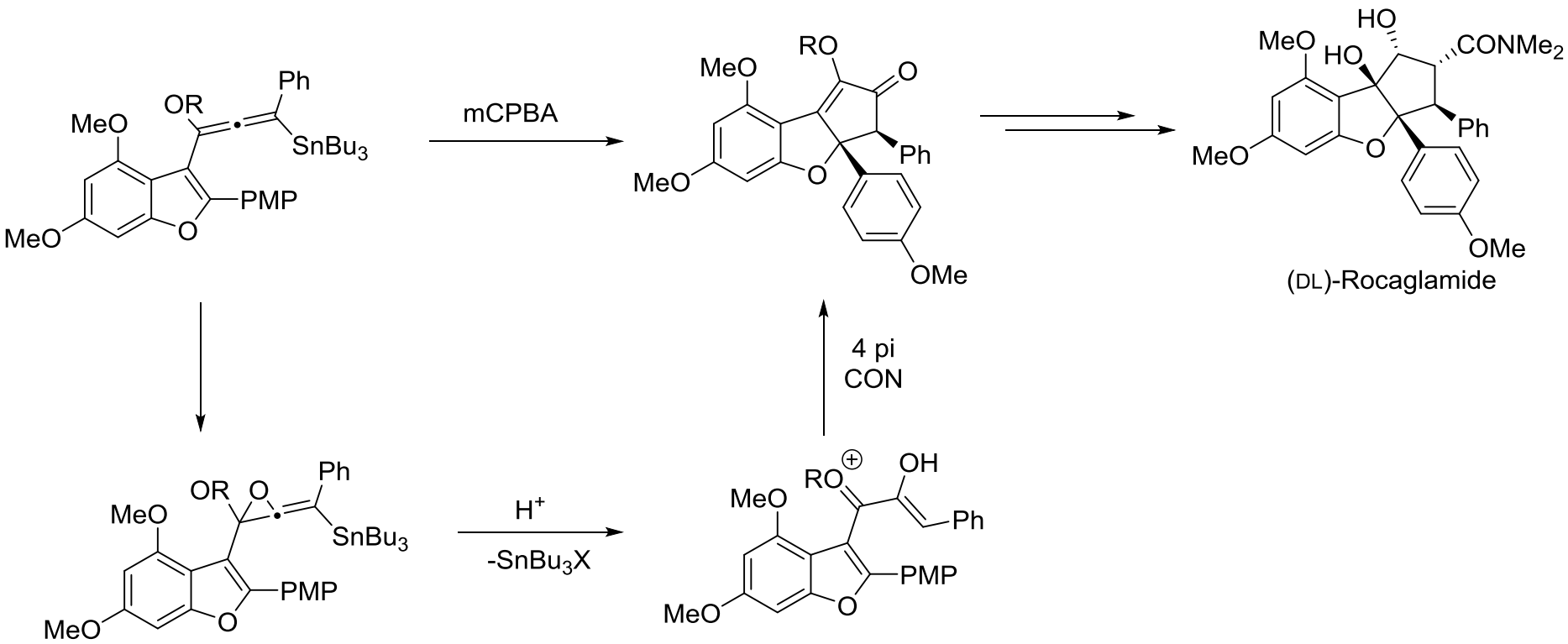
Quiz Time


MeO
OR
Ph
SnBu3
PMP
MeO
O
mCPBA
RO
MeO
O
Ph
MeO
O
OMe


O
N
Et
MeO
N
Me
O
N
N
CO2Me
TIPB, 230°C
48h, 92%
O
N
Et
O
O
N
Me
CO2Me

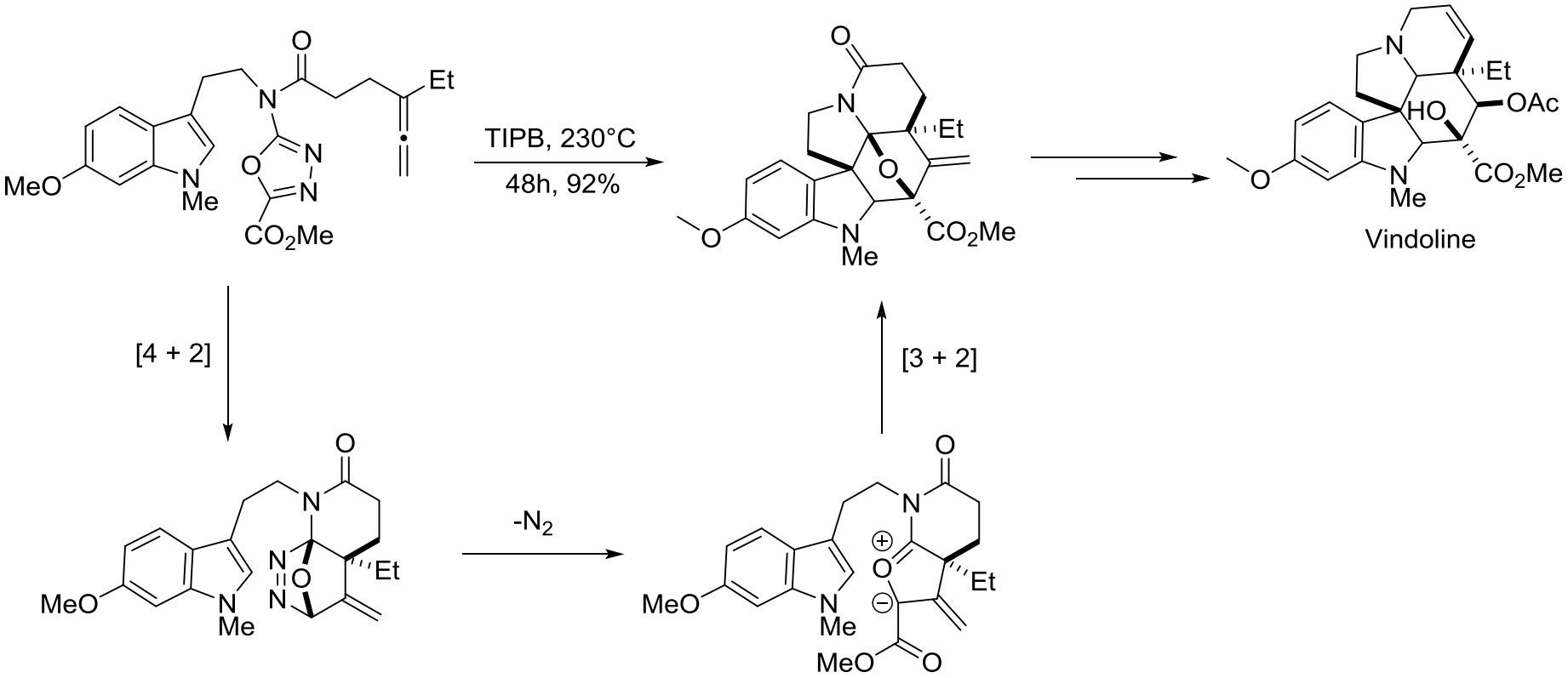
Cycloaddition reactions

- Miscellaneous cyclisation/cycloaddition
  (DL)-Rocaglamide: Potent insecticidal, anti-fungal, anti-inflammatory and anti-cancer activities.



Cycloaddition reactions

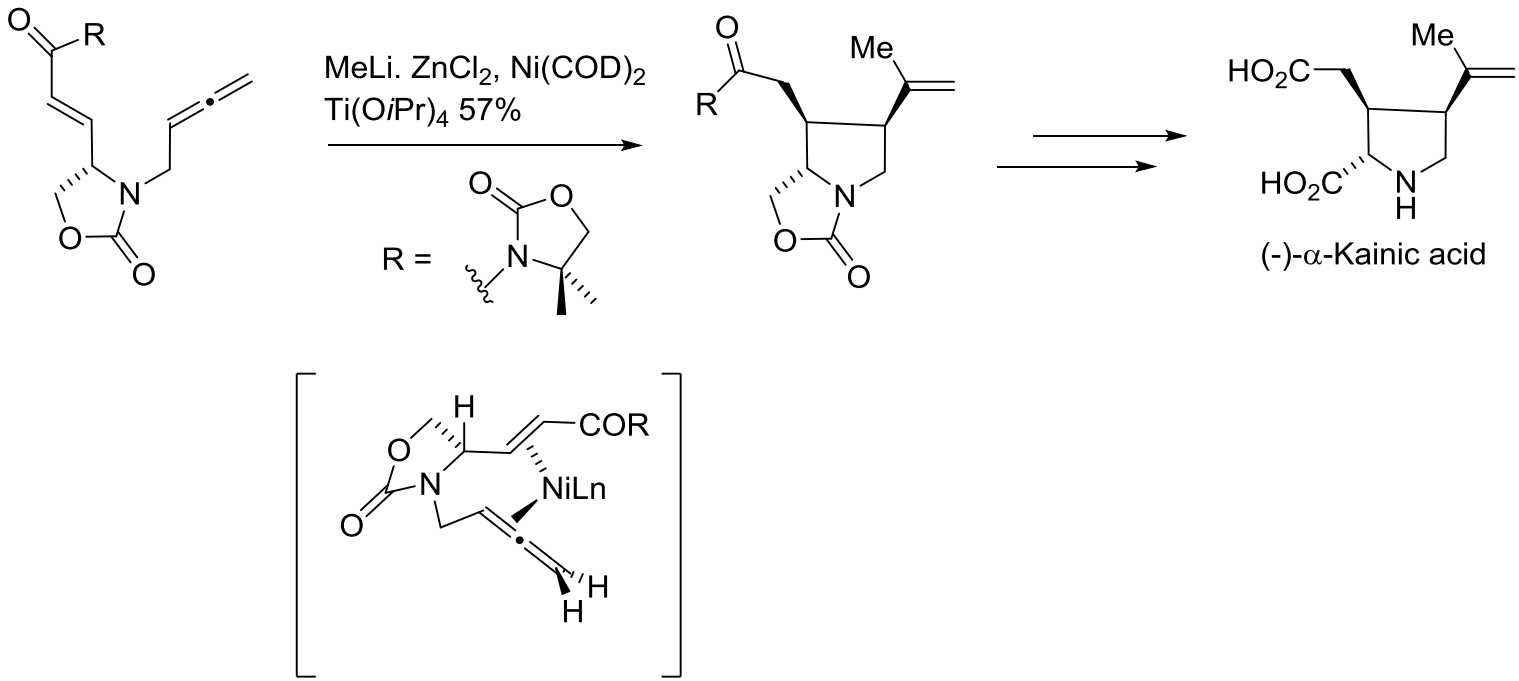
- Miscellaneous cyclisation/cycloaddition
  Vindoline: Precursor to anti-cancer drug Vinblastine



D. L. Boger. *Org. Lett.* **2015**, 17, 5460

Transition−Metal Catalysed Cycloadditions

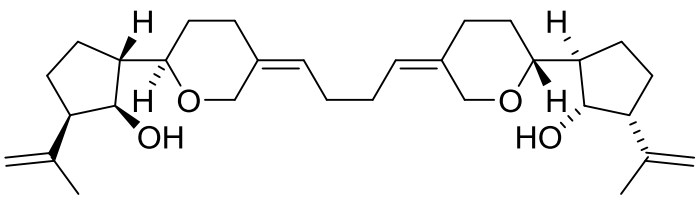
- (-)-α-Kainic acid: Possesses neuroexcitatory properties.



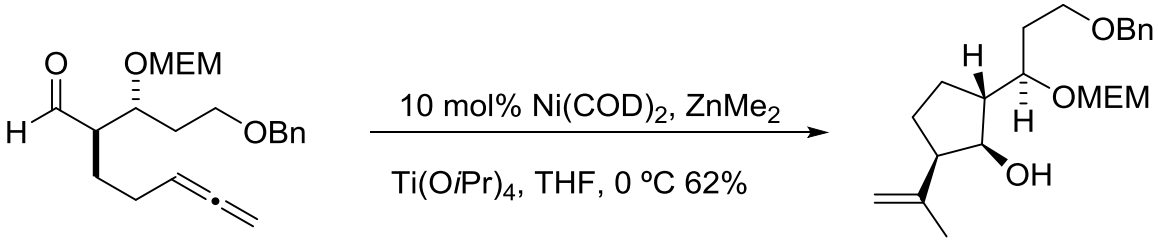
J. Montgomery. *J. Am. Chem. Soc.* **1999**, 121, 11139

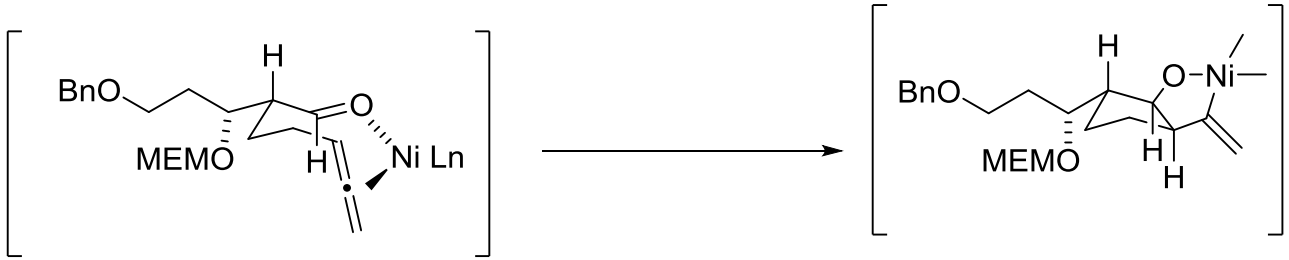
Transition Metal Catalysed Cycloadditions

- Testudinariol A: Isolated from skin and mucus of marine mollusc.



Testudinariol A

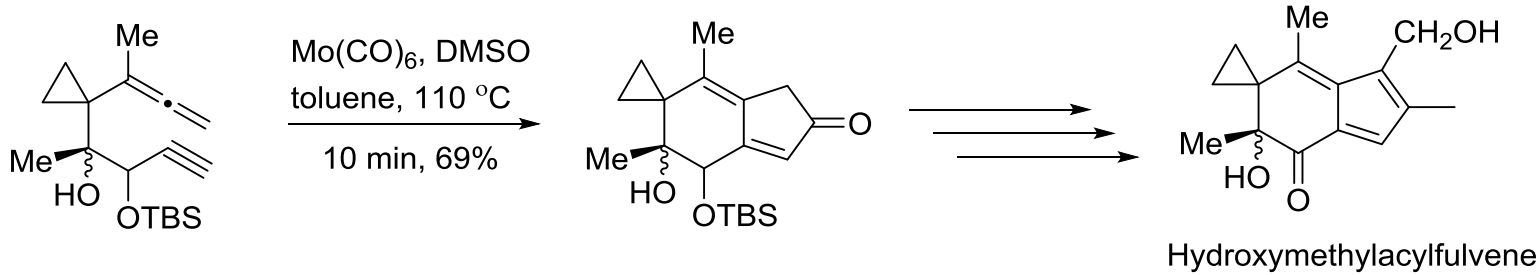




J. Montgomery. *J. Am. Chem. Soc.* **2002**, 124, 9366

Transition Metal Catalysed Cycloadditions

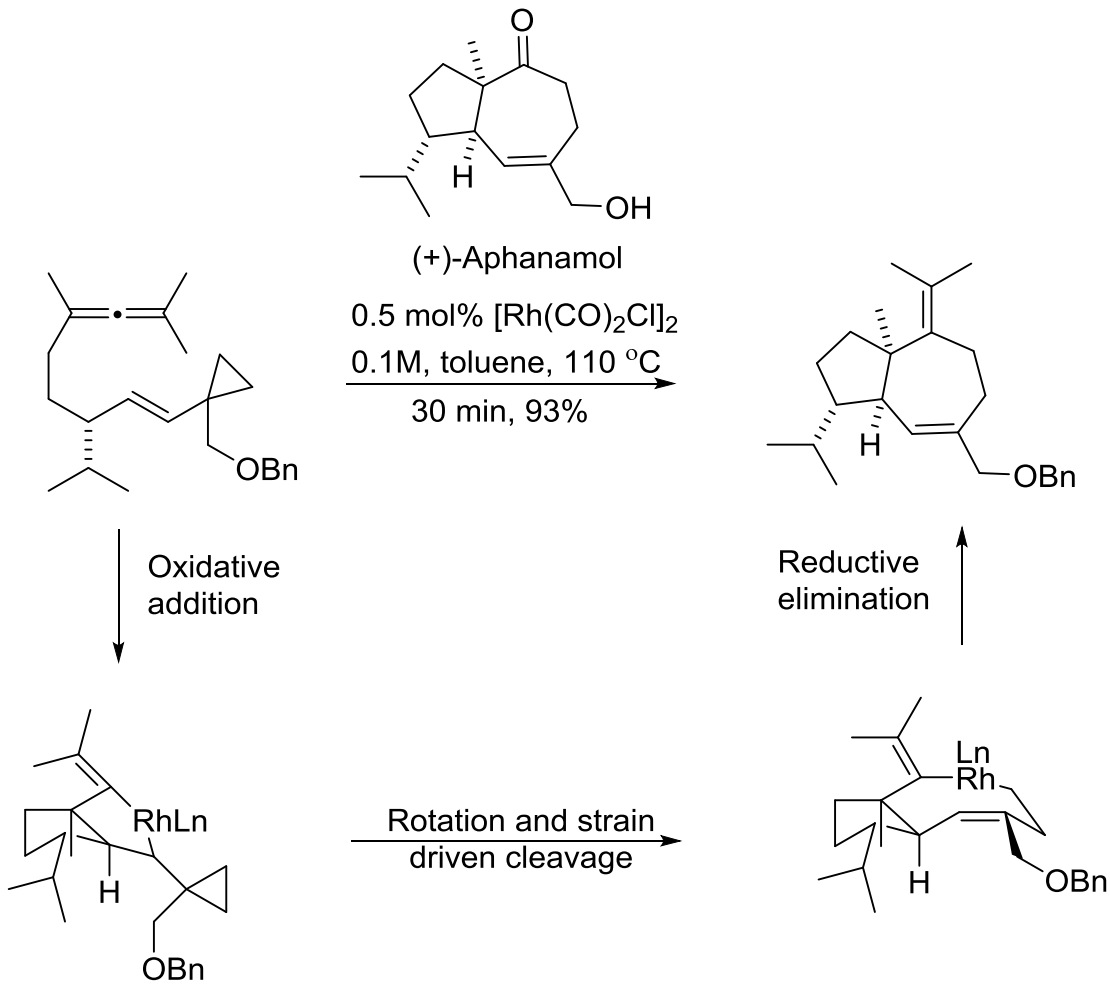
- Hydroxymethylacylfulvene: Potent anti-tumor agent.



J. Petersen. *J. Am. Chem. Soc.* **2000**, 122, 4915

Transition Metal Catalysed Cycloadditions

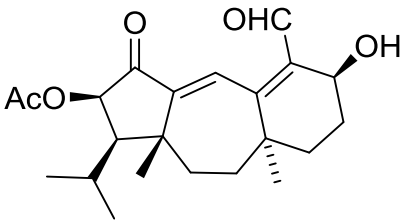
- (+)-Aphanamol:



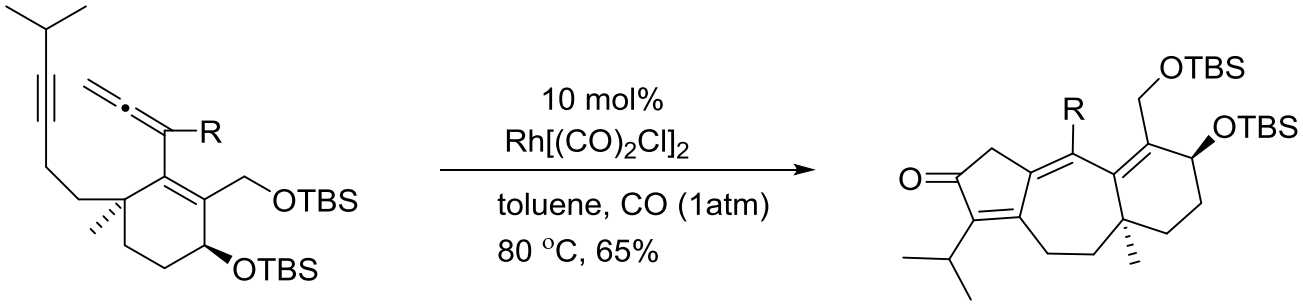
P. A. Wender. *Org. Lett.* **2000**, 2, 2323

Transition Metal Catalysed Cycloadditions

- Guanacastepene A: Good activity for vancomycin resistant pathogens



Guanacastepene A

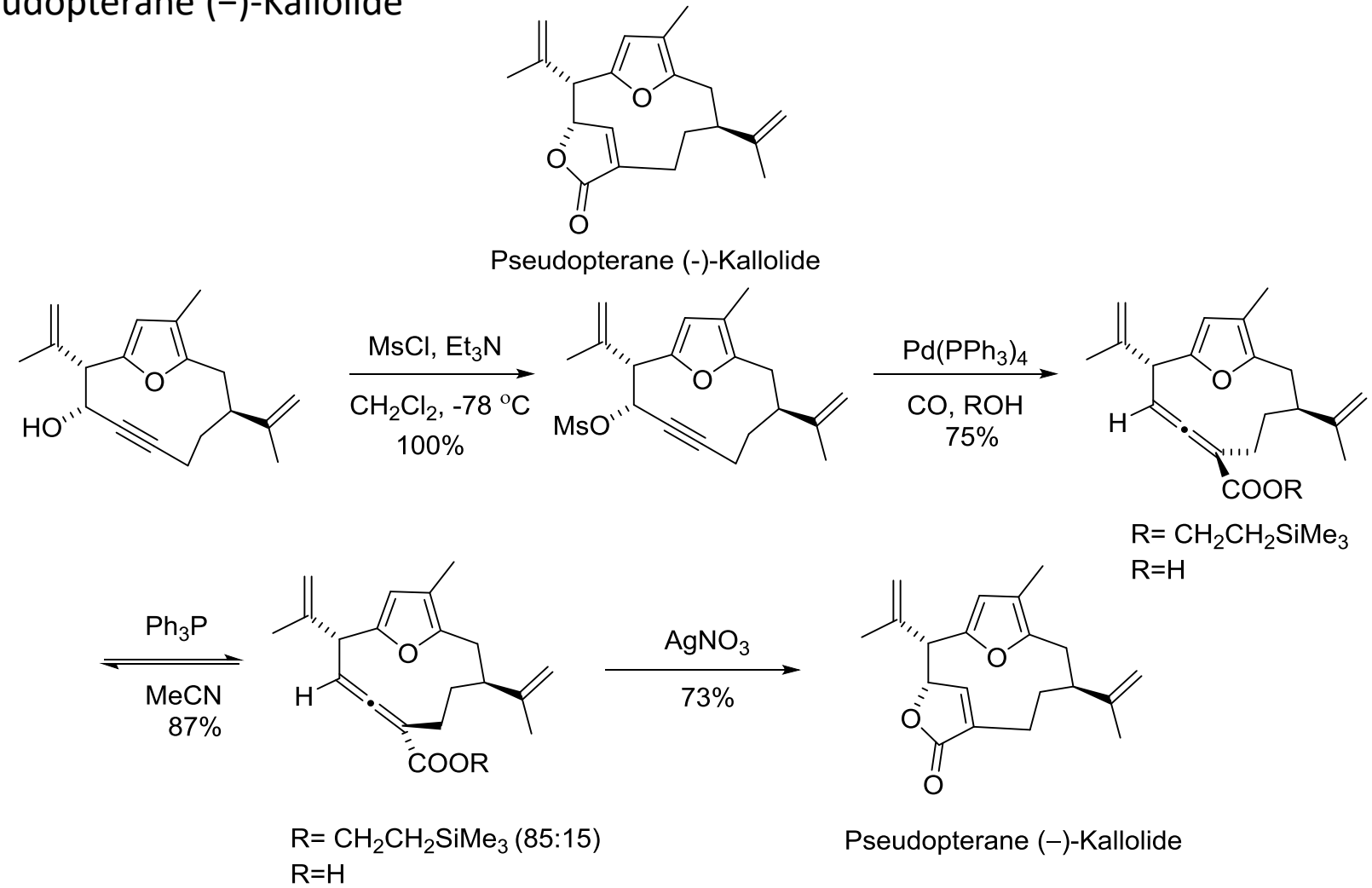


R = $SiMe_2Ph$

K. M. Brummond. *Org. Lett.* **2003**, 5, 3491

Transition Metal promoted cyclisations

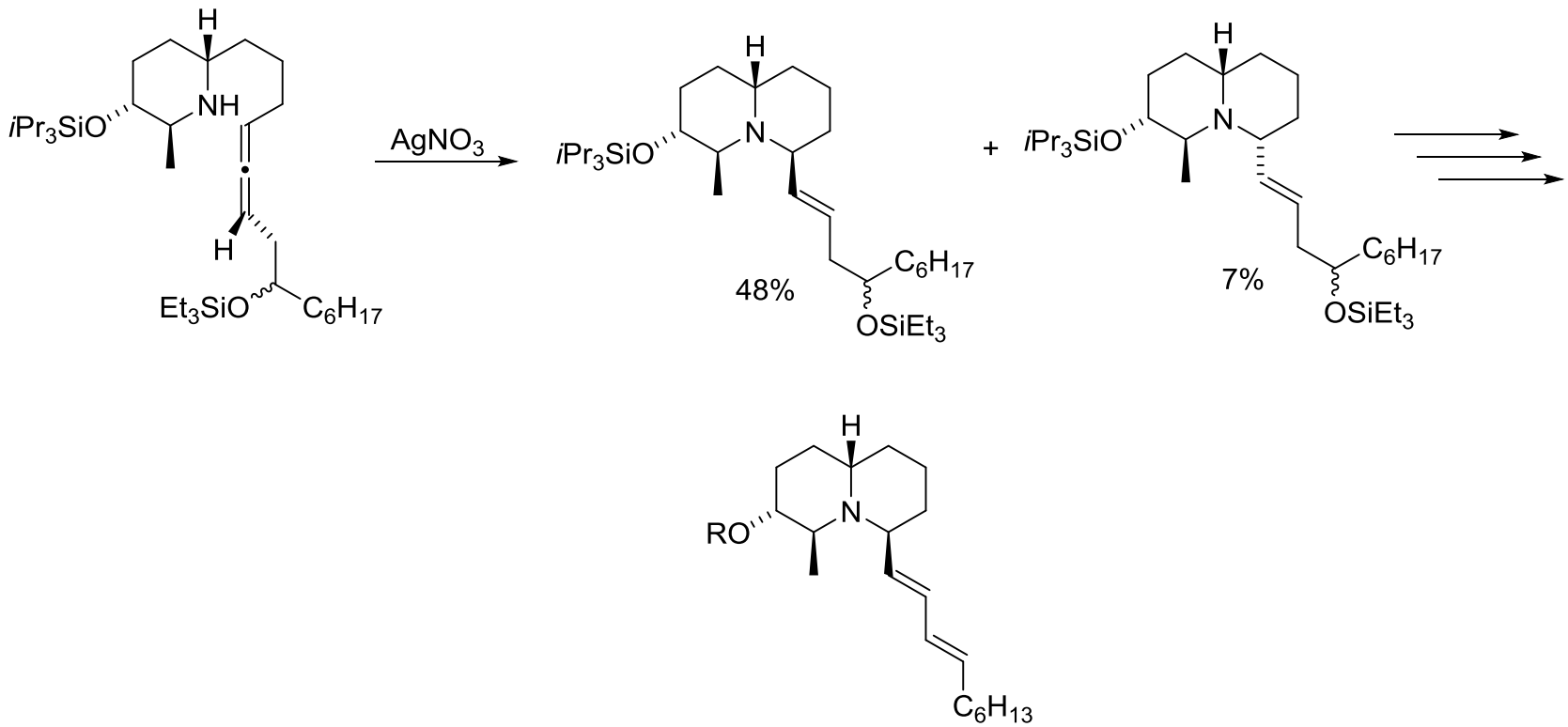
- Pseudopterane (−)-Kallolide



J.A. Marshall. *J. Org. Chem.* **1996**, 61, 5729

Transition Metal promoted cyclisations

- Clavepictines: Show anti-fungal, anti-cancer and anti-tumor properties

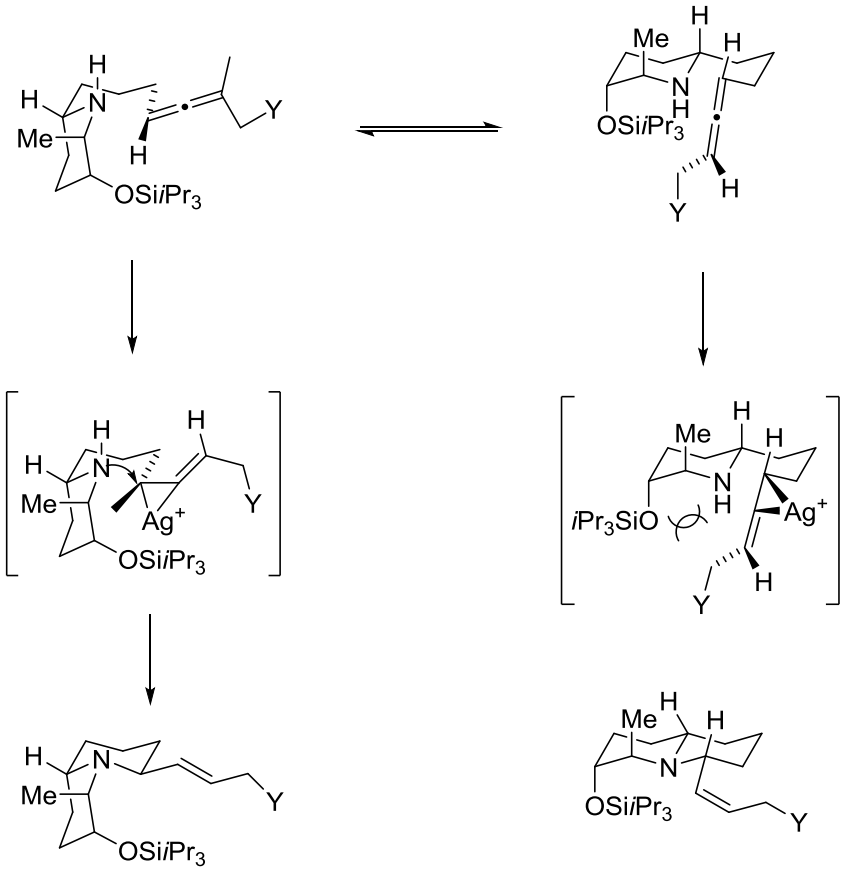


R= Ac (Clavepictine A)
R= H (Clavepictine B)

J.K. Cha. *J. Am. Chem. Soc.* **1999**, 121, 10012

Transition Metal promoted cyclisations

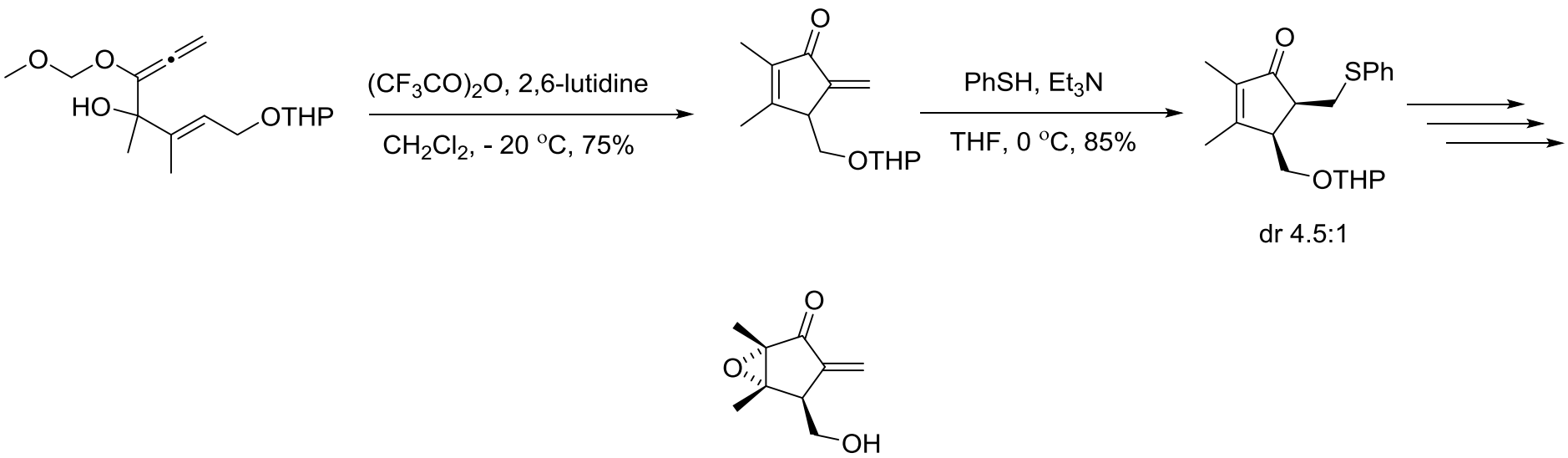
- Clavepictines:



J.K. Cha. *J. Am. Chem. Soc.* **1999**, 121, 10012

Acid Catalysed Rearrangement

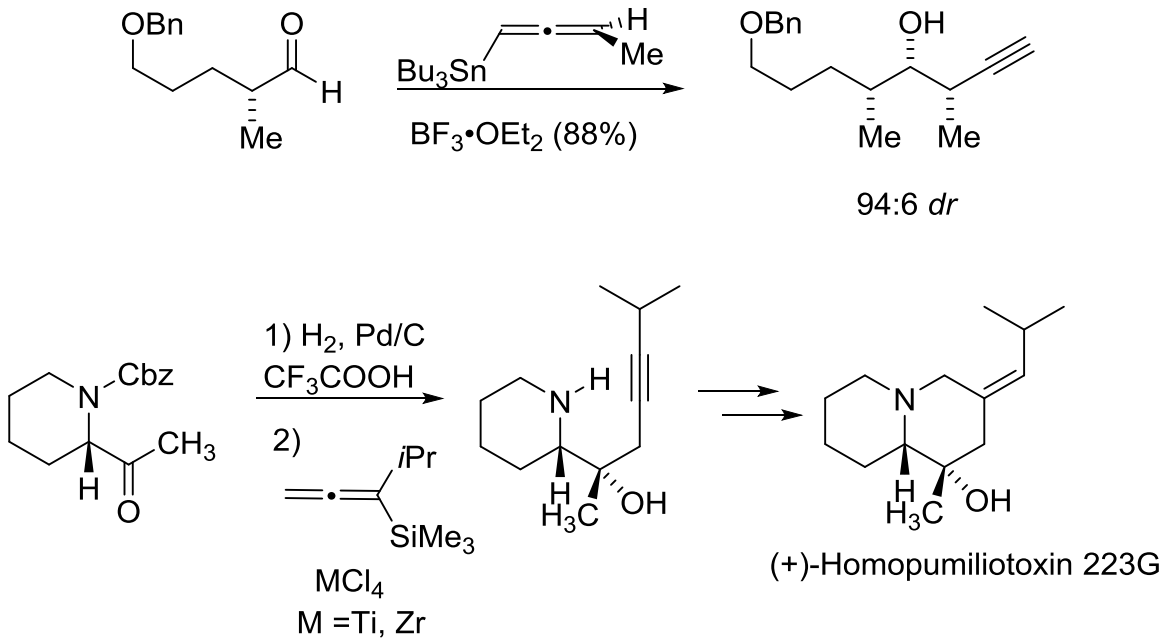
- (+)-Methylenomycin: Active against Gram-positive and Gram-negative bacteria



(±)-Methylenomycin

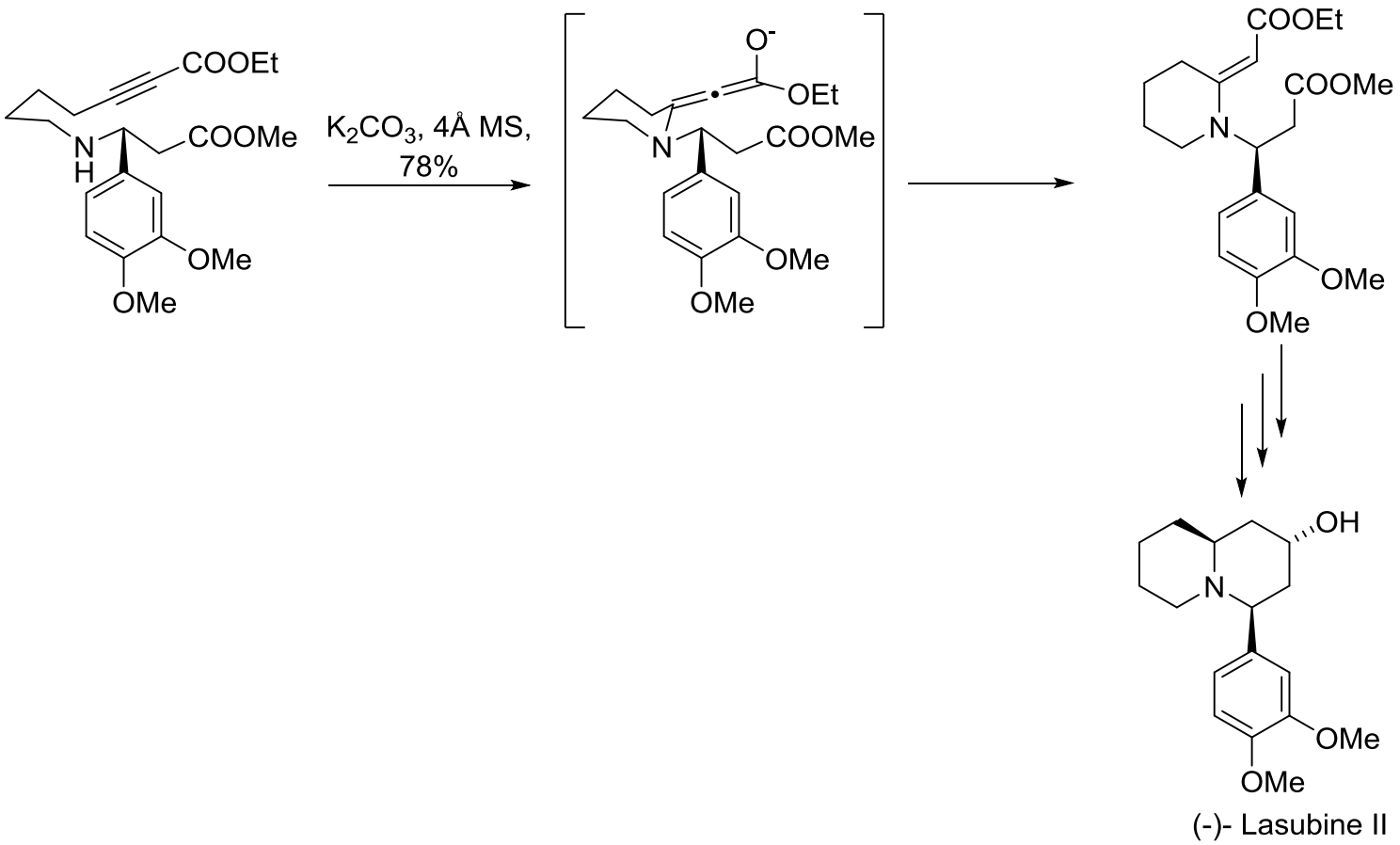
S. Trehan. *J. Org. Chem.* **1989**, 54, 46

Allenyl Organometallic intermediates



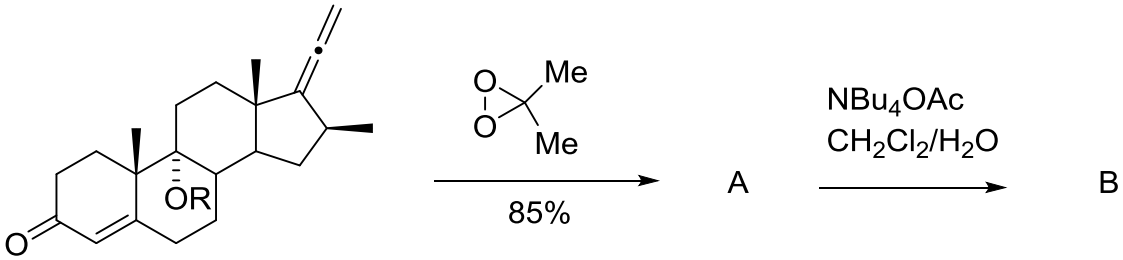
J. A. Marshall. *J. Org. Chem.* **2002**, 67, 2751; C. Kibayashi. *Tetrahedron Lett*. **1998**, 39, 2149

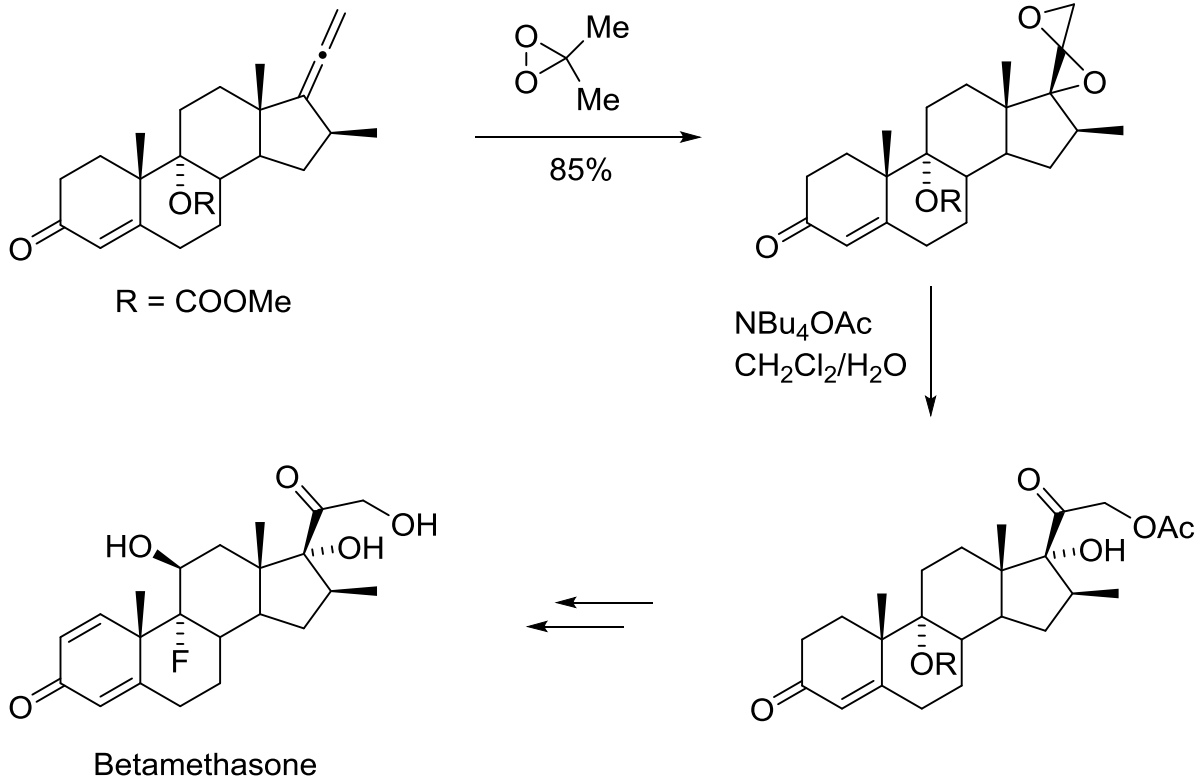
Allenoates



W. Zhu. *Org. Lett.* **2001**, 3, 3927

Quiz Time



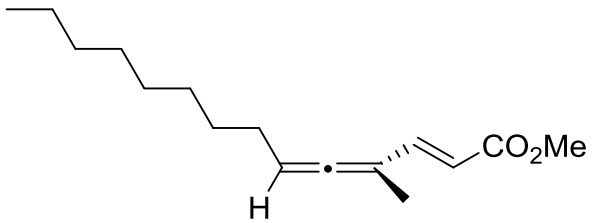


D. R. Andrews. *Tetrahedron Lett.* **1996**, 37, 3417

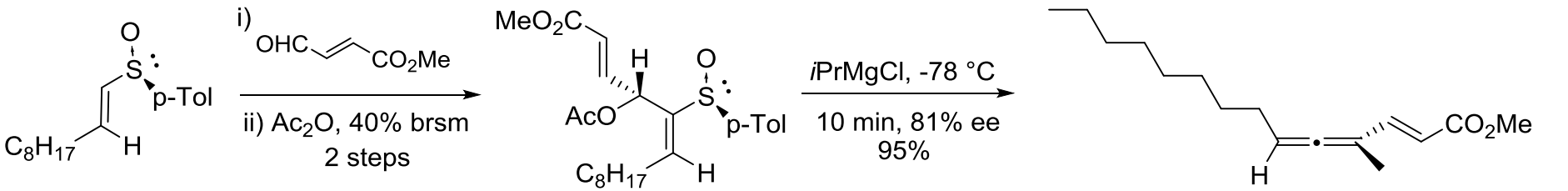
Allenes in natural products

Synthesis of methyl (R,E)-4-methyltetradeca-2,4,5-trienoate

- Insect pheromone from dry bean beetle



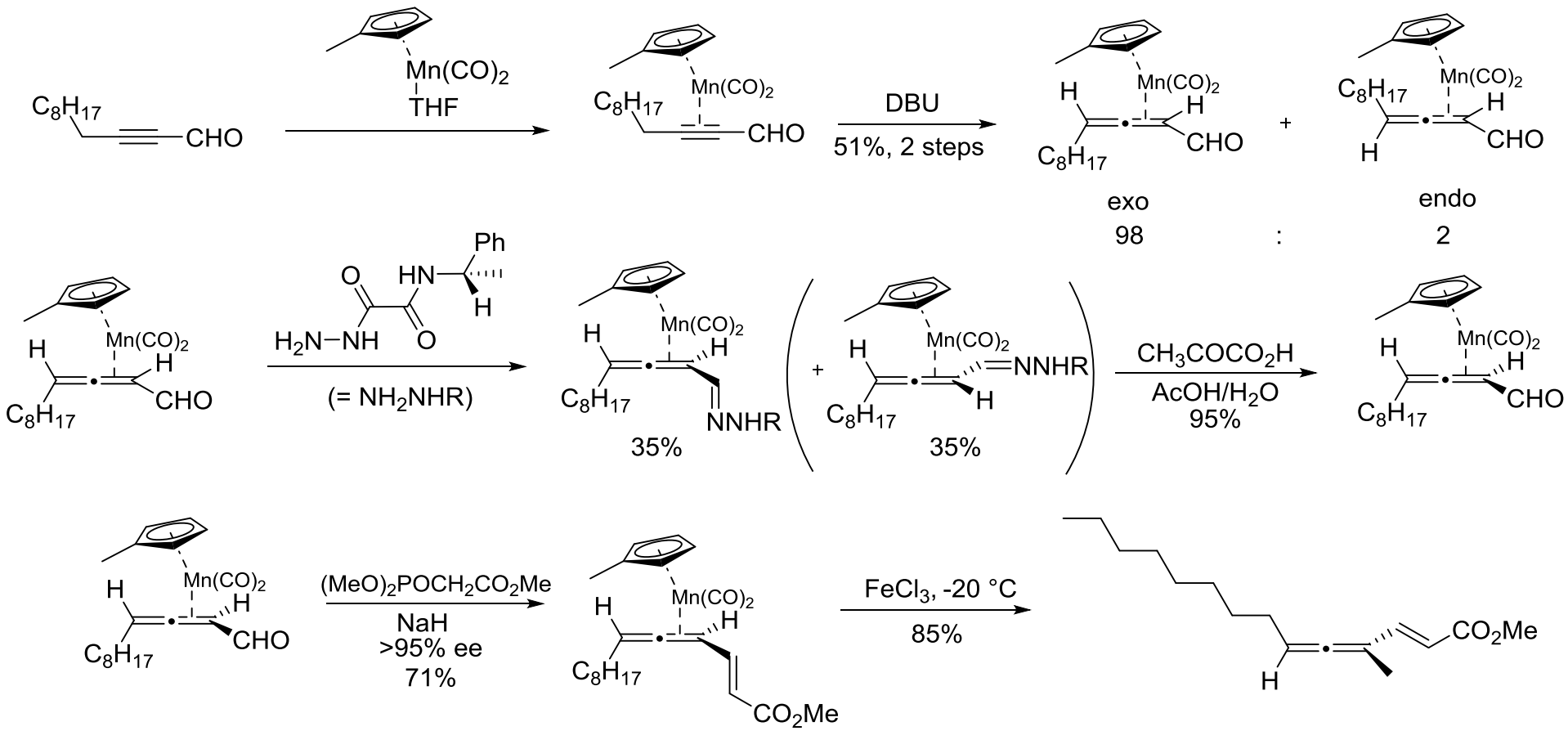
methyl (*R*,*E*)-4-methyltetradeca-2,4,5-trienoate



methyl (*R*,*E*)-4-methyltetradeca-2,4,5-trienoate

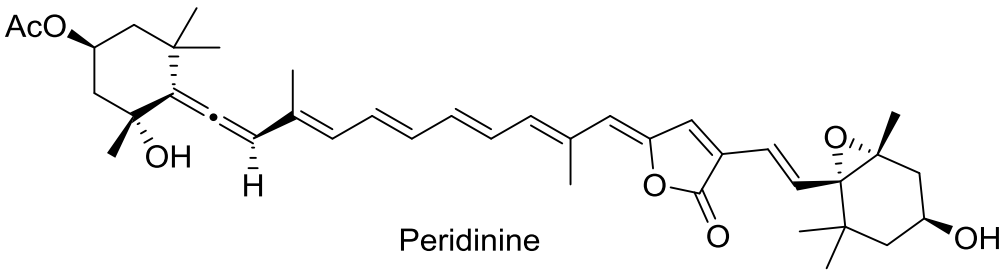
K. Sakai, *Tetrahedron*, **2002**, 58, 2533

Synthesis of methyl (*R*,*E*)-4-methyltetradeca-2,4,5-trienoate



M. Franck Neumann, *Tetrahedron Asymmetry*, **1998**, 697

Synthesis of Peridinine

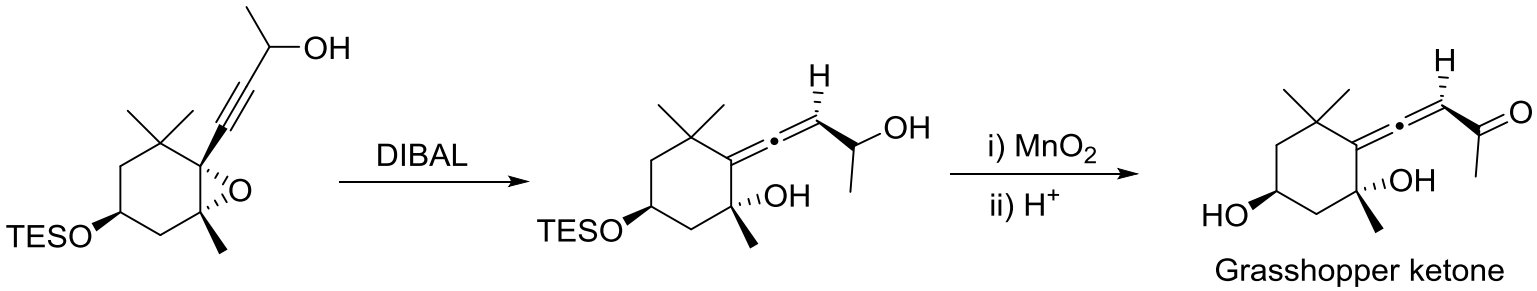


Peridinine

- Highly oxidised C-37 nor-carotenoid.
- isolated from the planktonic algae dinoflagellates which causes red tides.
- It has an allene and a ylidenebutenolide function in the main conjugated polyene chain.
- Isolated in 1890. However correct structure assigned in 1971 and first total synthesis in 1993.

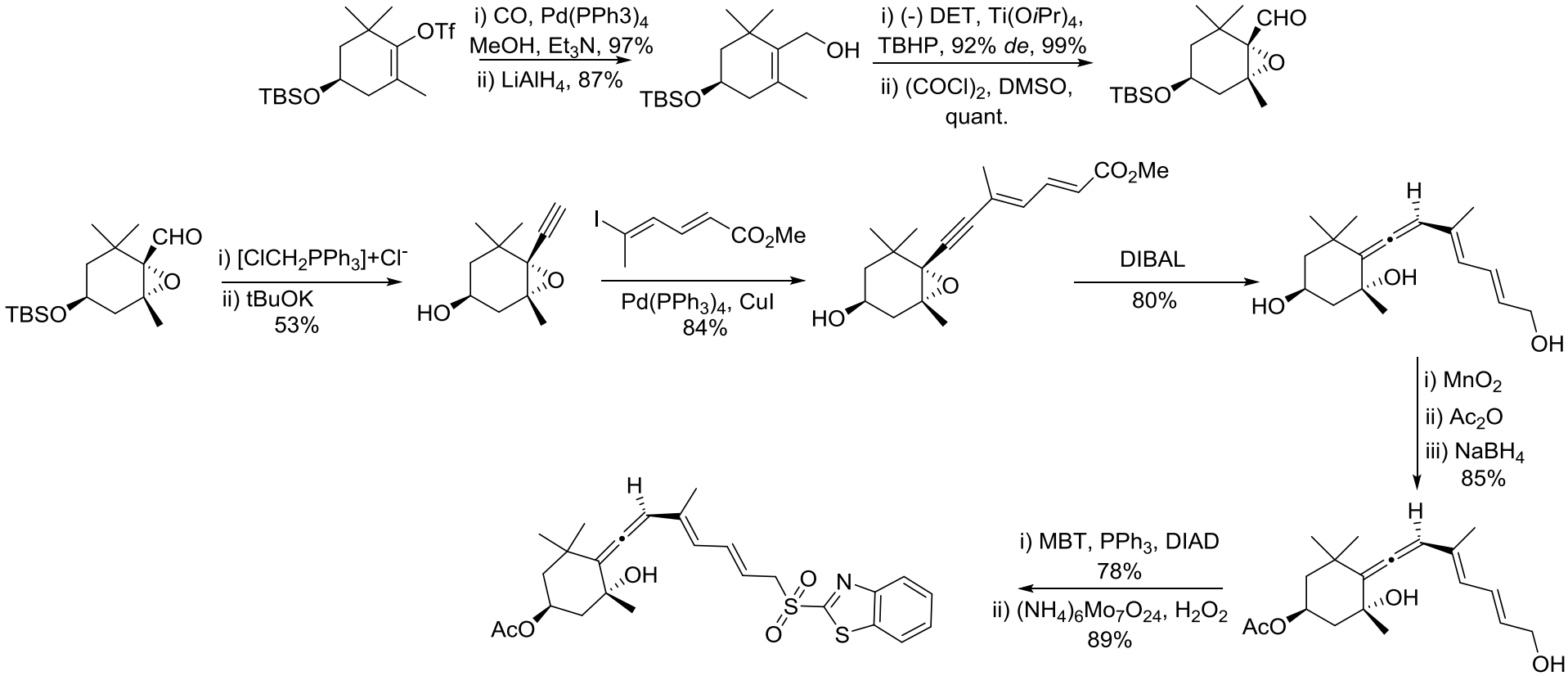
S. Katsumura. *Angew. Chem. Int. Ed.* **2002**, 41, 1023

Synthesis of Grasshopper ketone.



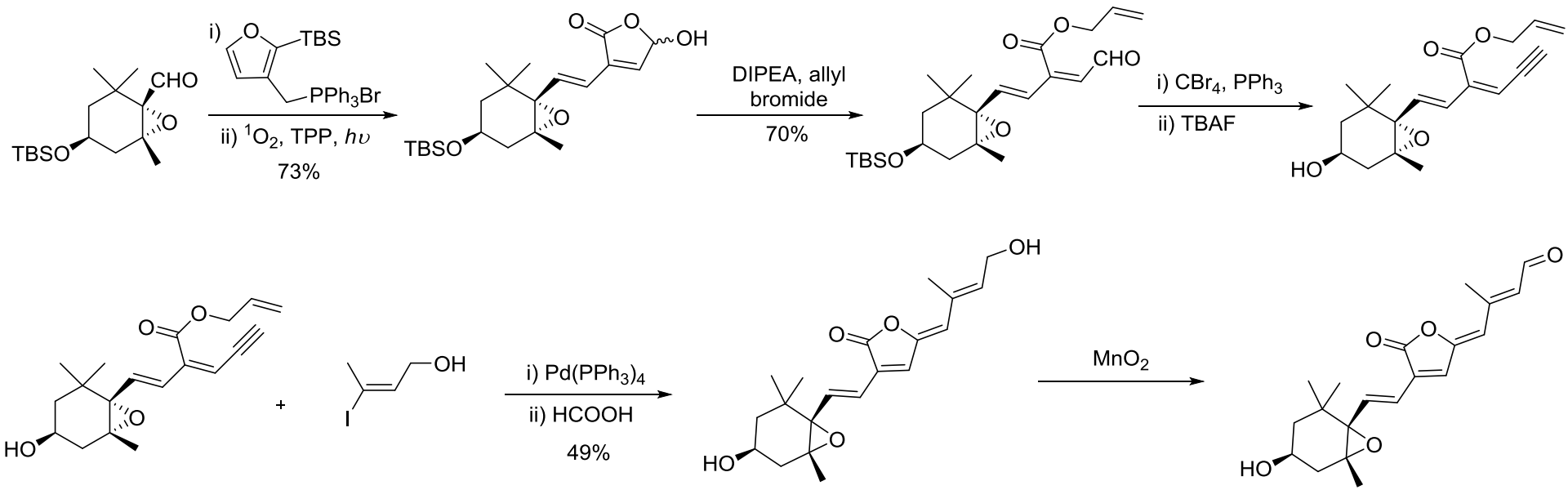
C. H. Eugster. *Helvetica Chimica Acta*, **1990**, 700

Synthesis of Peridinine



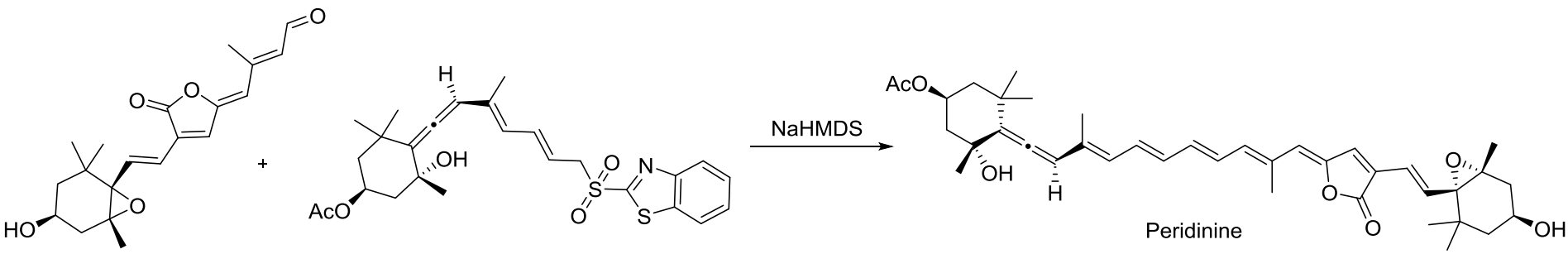
S. Katsumura. *Angew. Chem. Int. Ed.* **2002**, 41, 1023

Synthesis of Peridinine



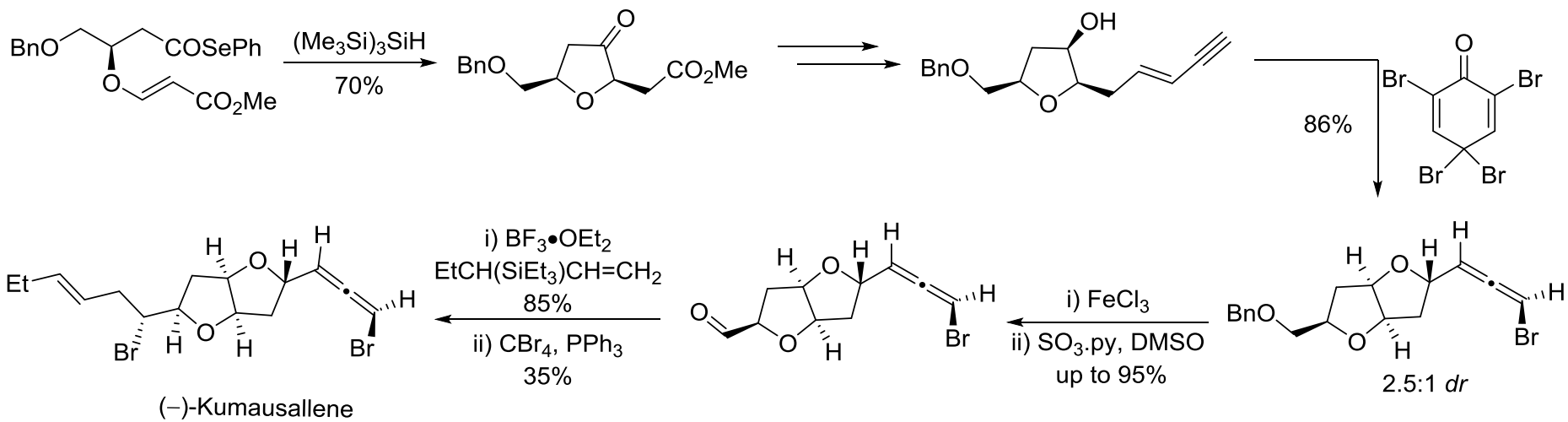
S. Katsumura. *Angew. Chem. Int. Ed.* **2002**, 41, 1023

Synthesis of Peridinine



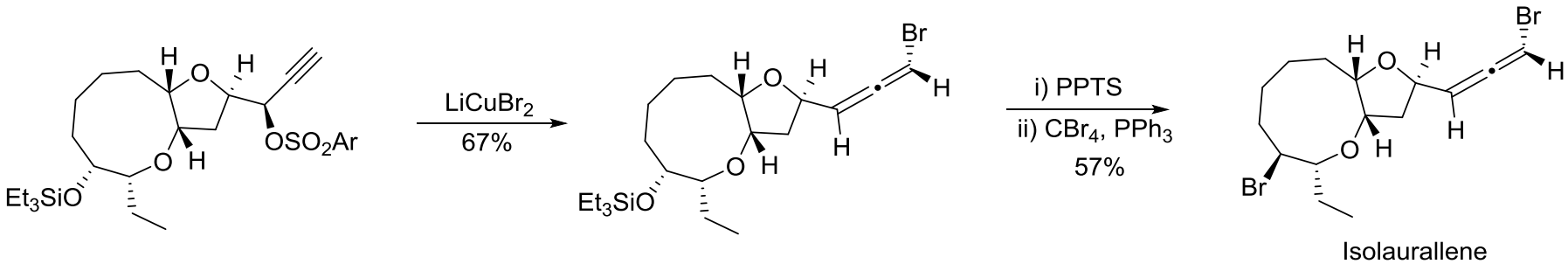
S. Katsumura. *Angew. Chem. Int. Ed.* **2002**, 41, 1023

Synthesis of (−)-Kumausallene



P. A. Evans *Angew. Chem Int. Ed.* **1999**, 38, 3175

Synthesis of Isolaurallene



M. T. Crimmins. *J. Am. Chem. Soc.*, **2001**, 123, 1533

UNIVERSITY OF OXFORD

Thank You…
Questions or Suggestions???