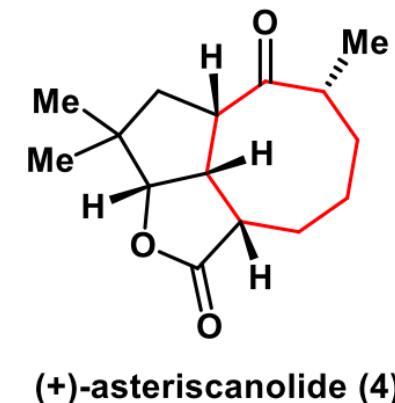
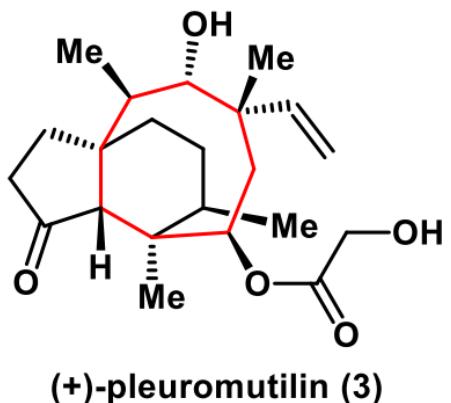
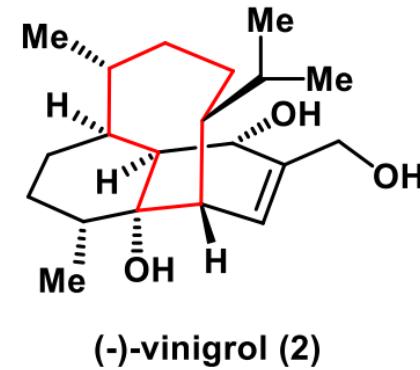
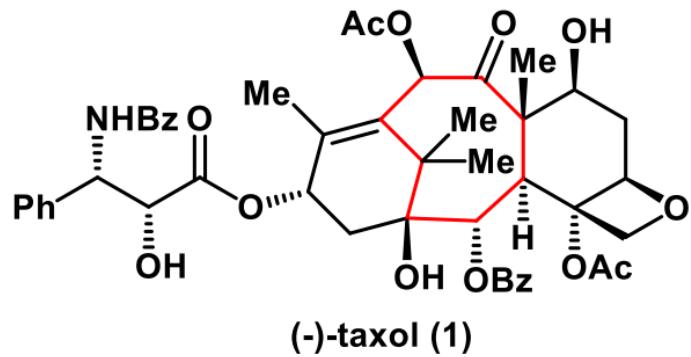


# *Constructing Eight-Membered Carbocycles in Natural Products*

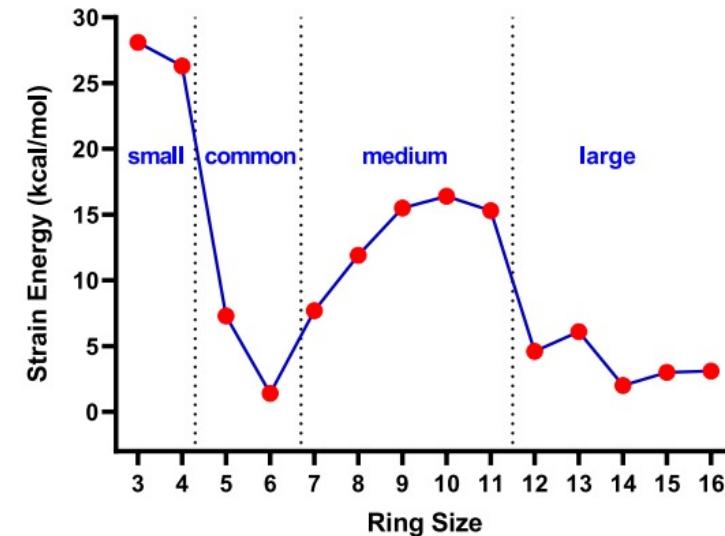


Sam He  
Literature Presentation  
11/18/22



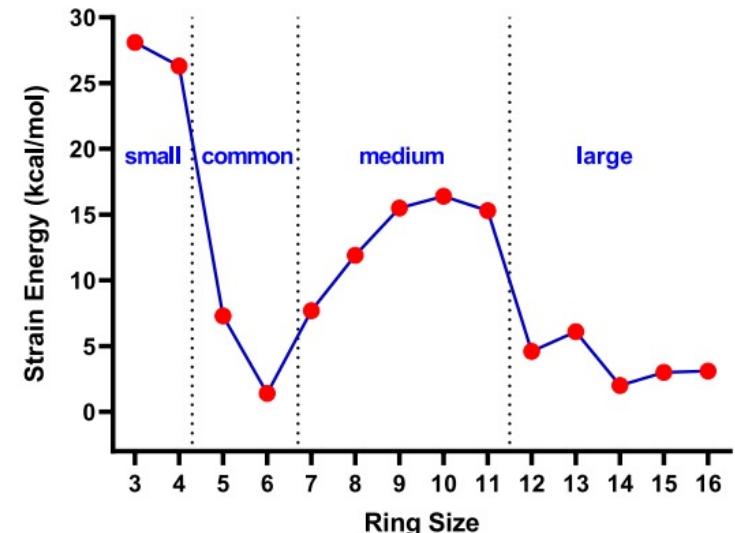
## *Cyclooctane – The Challenges*

- Molecular mechanics calculated 8-membered carbocycles to have relatively high strain energy

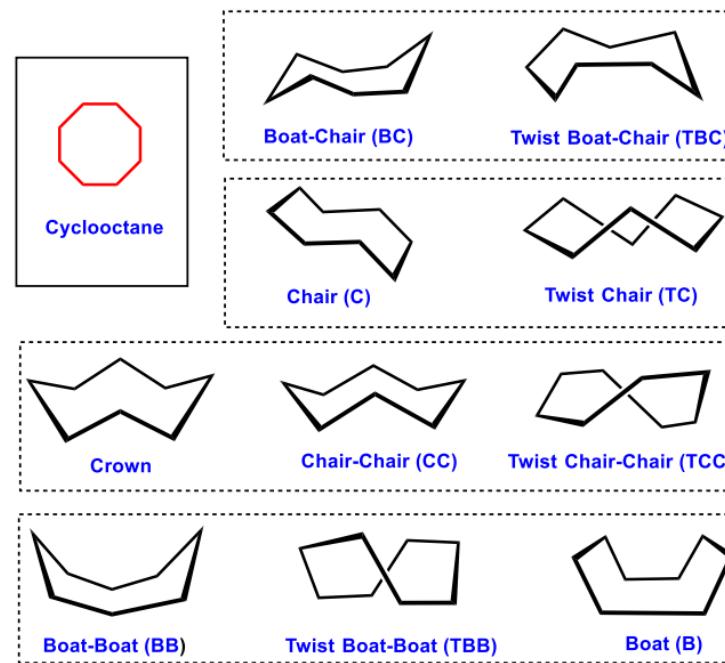


# Cyclooctane – The Challenges

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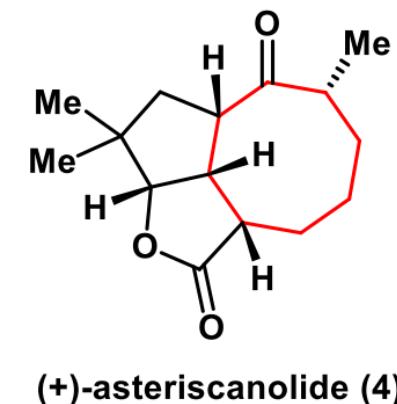
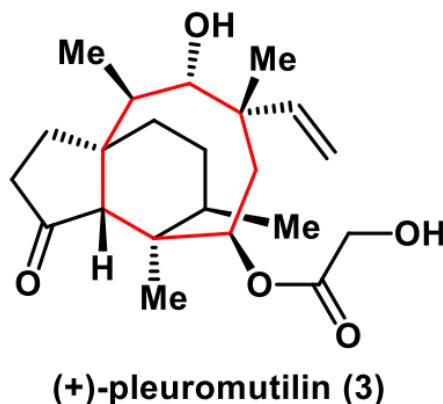
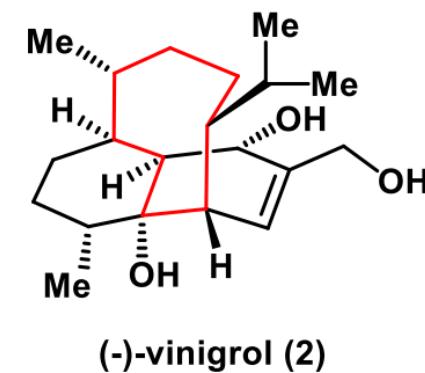
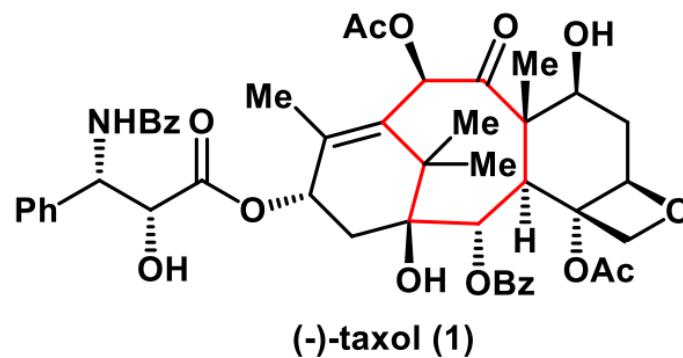


- 8-membered rings are **flexible**
  - 10 different conformations!
  - can interconvert readily depending on nature of substituents



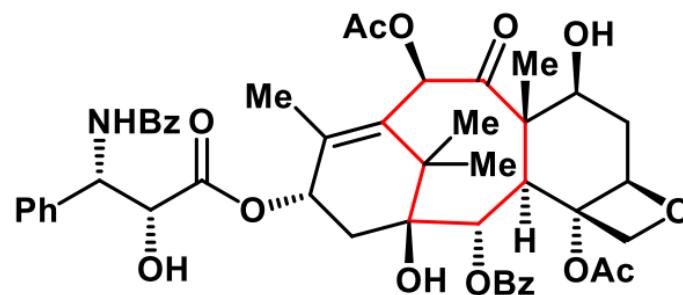
# Cyclooctanoids – The Challenges

- Cyclooctanoid natural products typically consist of fused/bridged skeletons
  - hard to predict which methods will give what regio/stereo/chemo-selective control

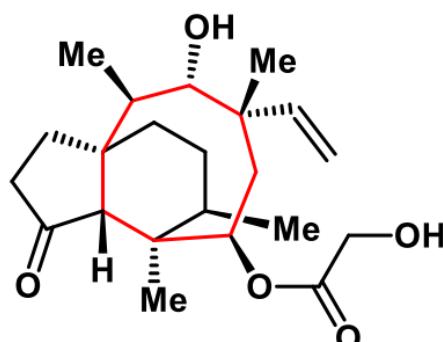


# Cyclooctanoids – The Appeal

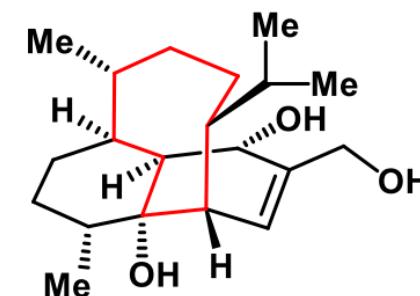
- Cyclooctanoid natural products do exhibit important bioactivities and thus are interesting targets for total synthesis
  - Many strategies have been developed to construct the 8-membered ring systems



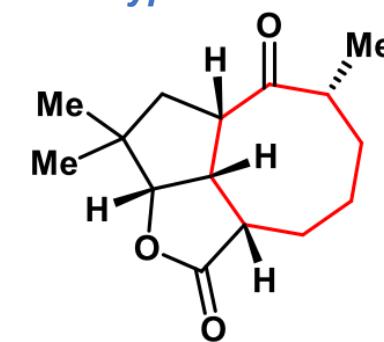
(-)taxol (1)  
anti-cancer



(+)-pleuromutilin (3)  
anti-bacterial

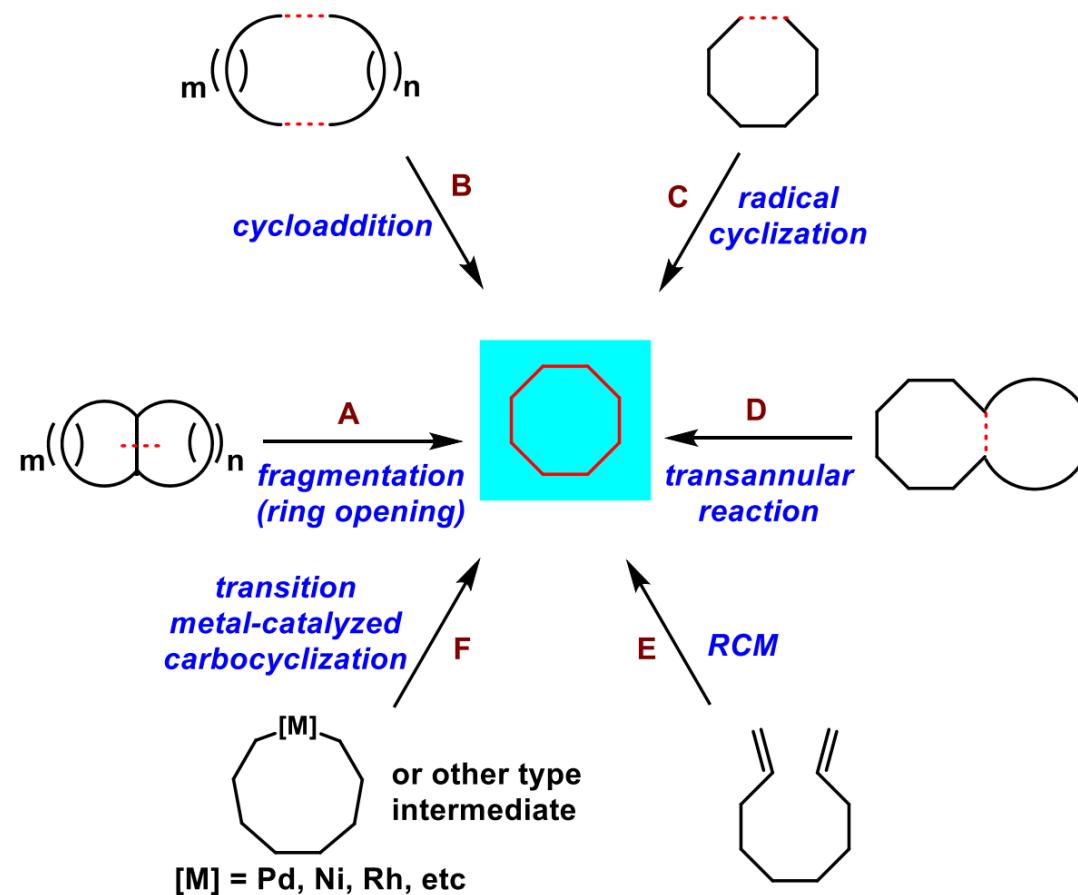


(-)vinigrol (2)  
anti-hypertension

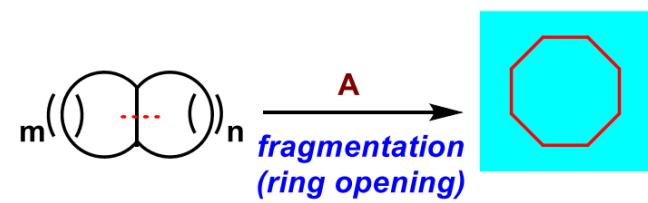


(+)-asteriscanolide (4)

# *Different Strategies*

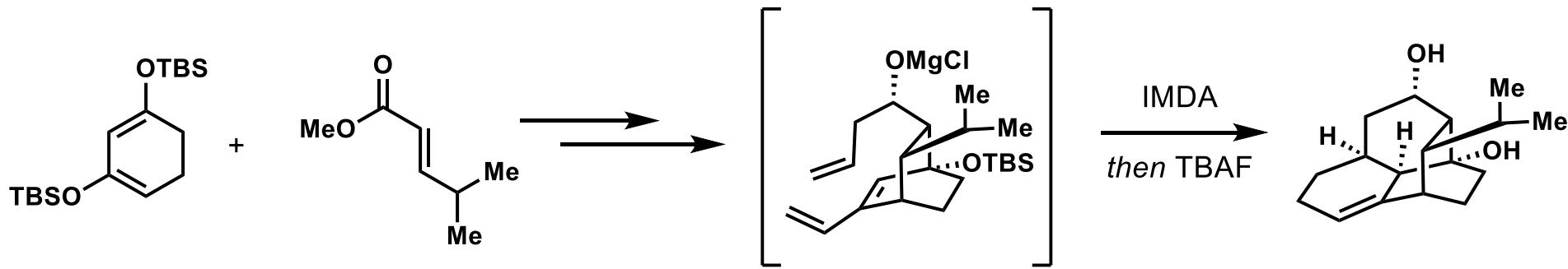


## *Different Strategies*



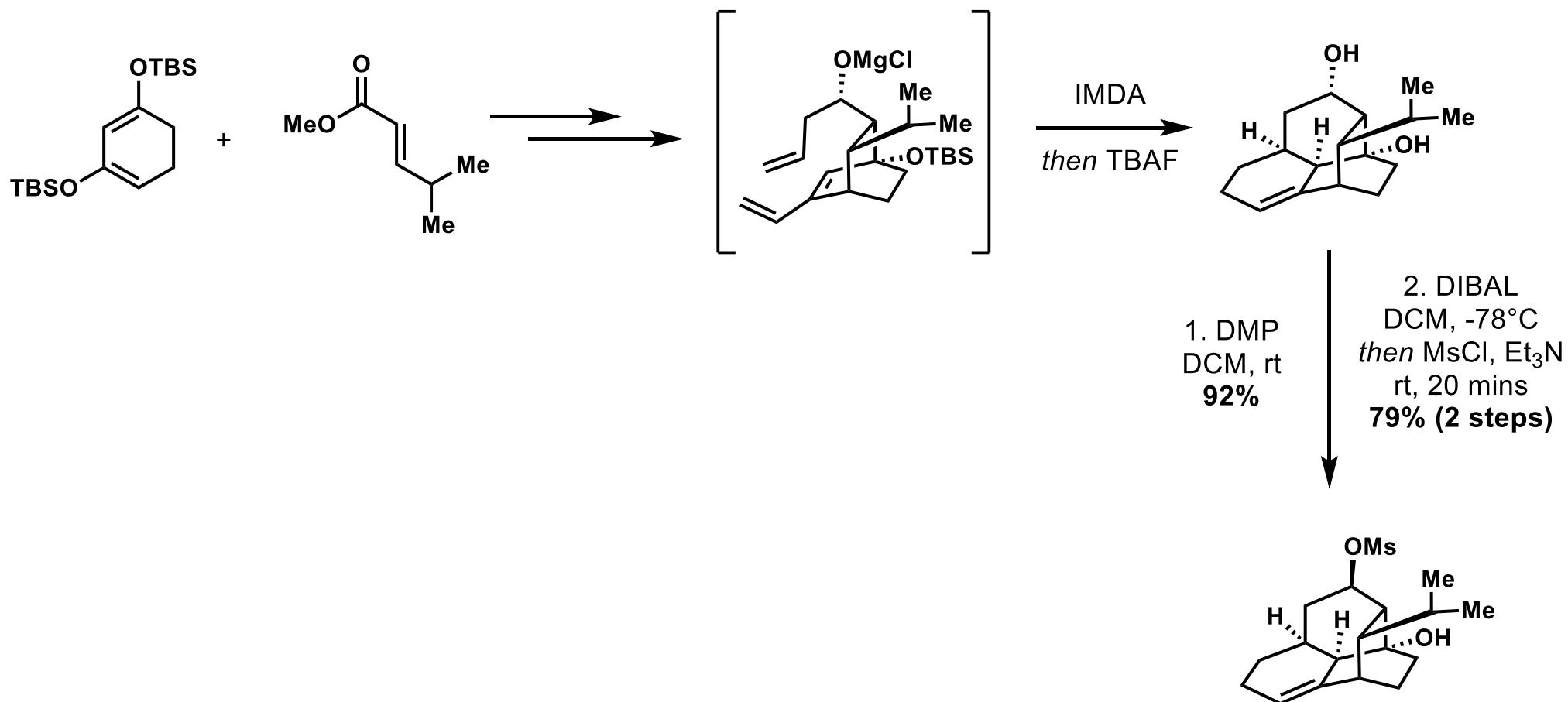
# *Fragmentation*

Vinigrol (Baran, 2009)



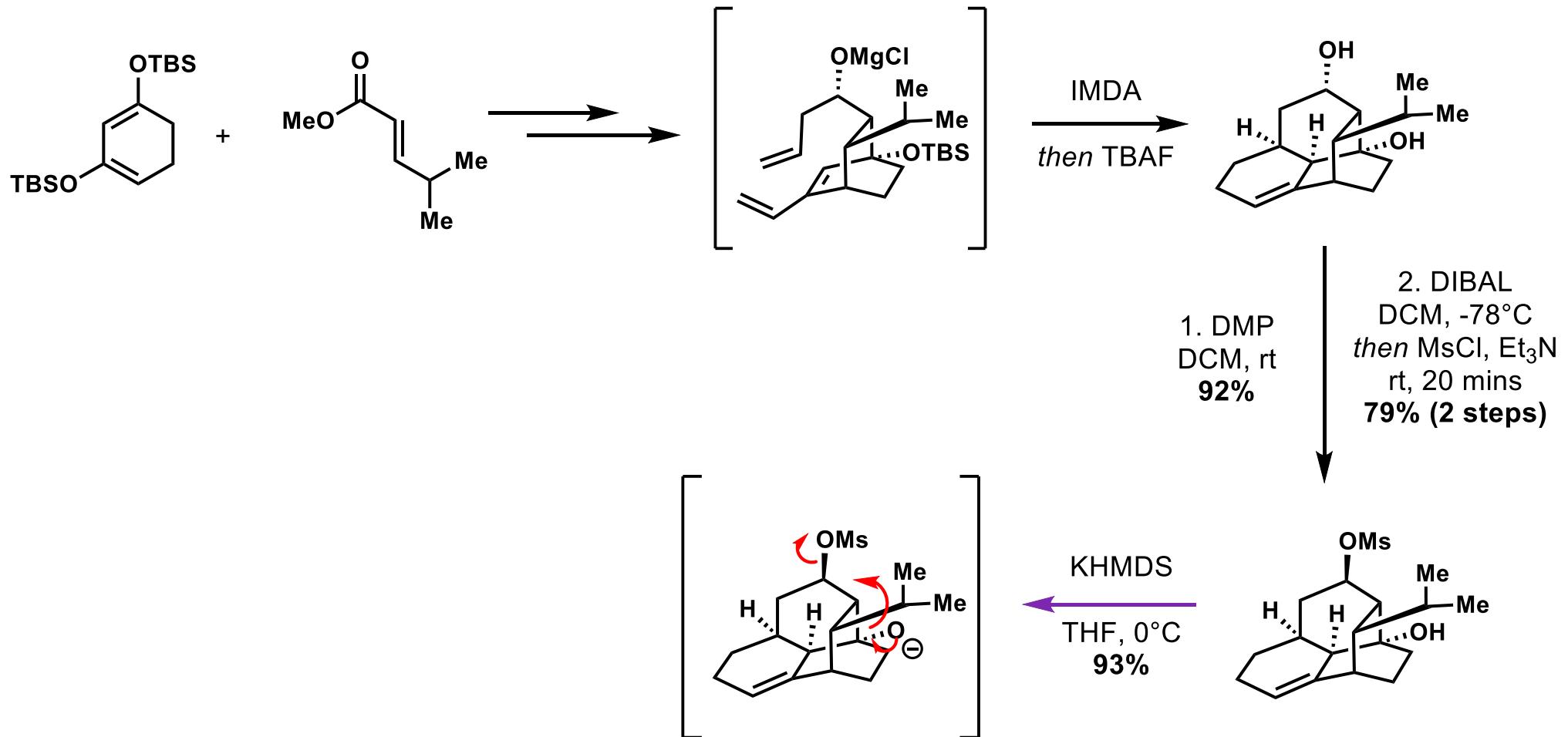
# *Fragmentation*

Vinigrol (Baran, 2009)



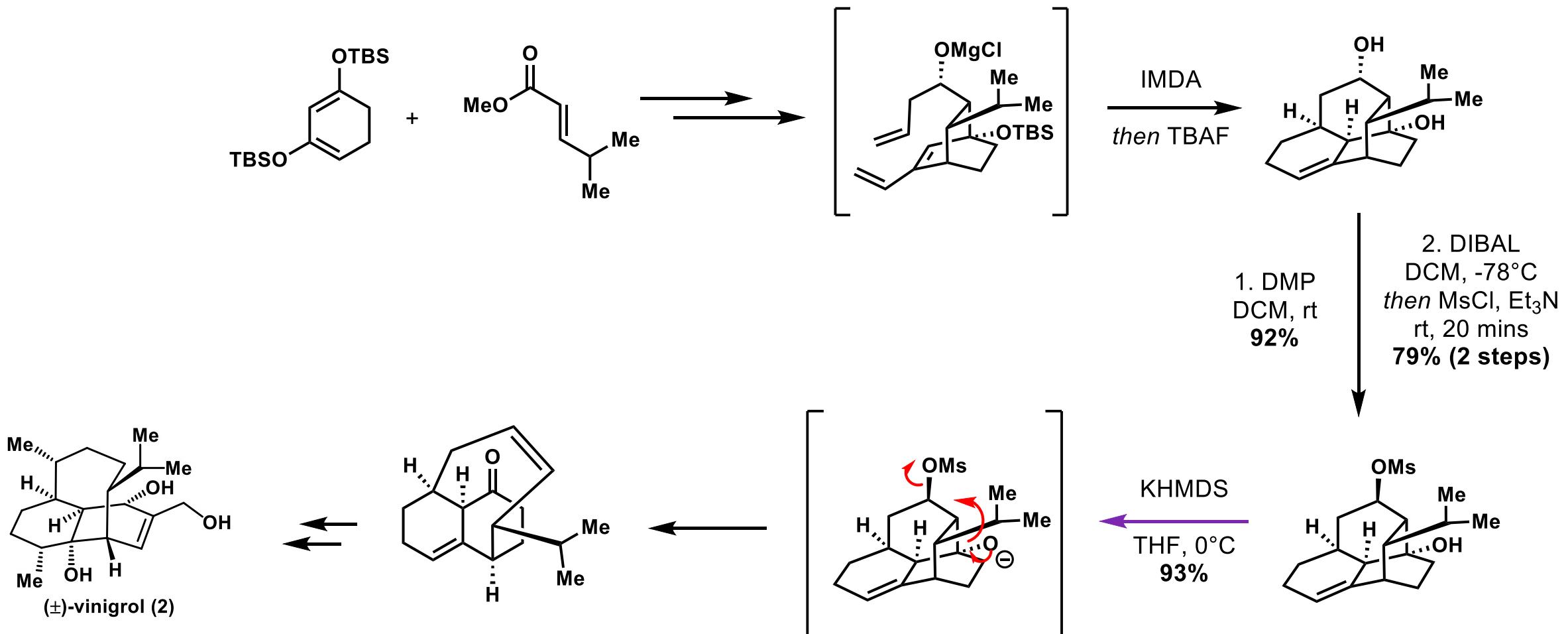
# Fragmentation

Vinigrol (Baran, 2009)

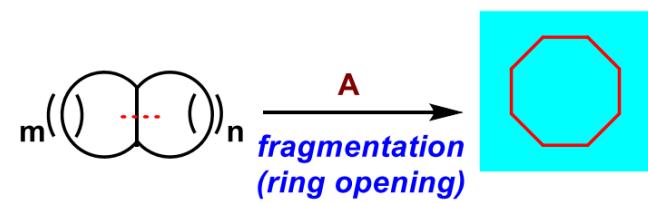


# Fragmentation

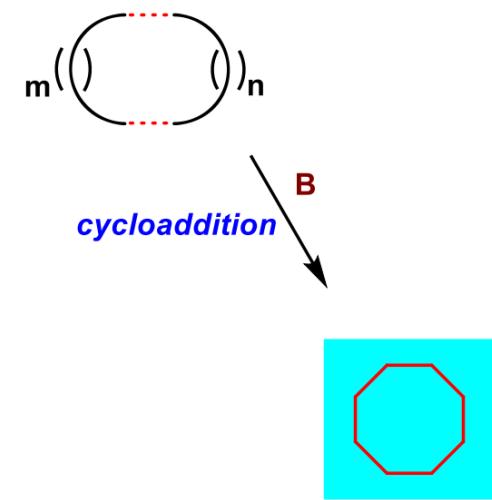
Vinigrol (Baran, 2009)



## *Different Strategies*

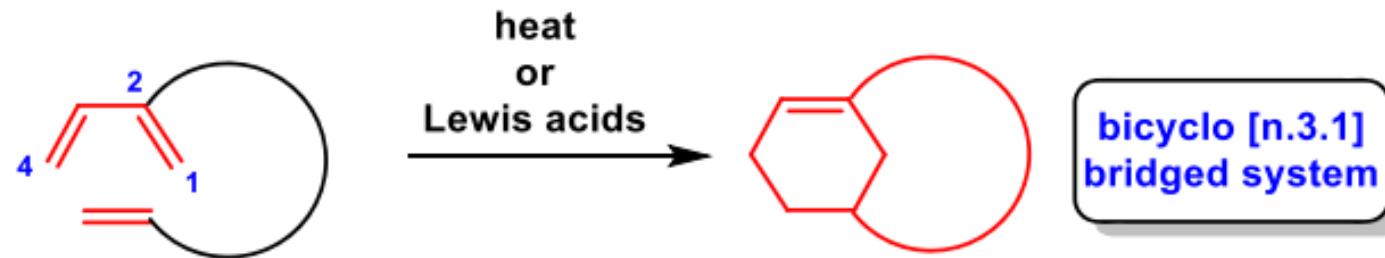


## *Different Strategies*



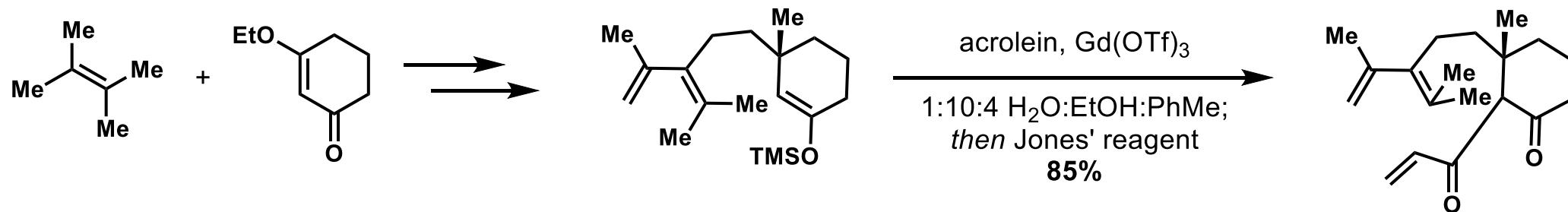
## *Intramolecular Cycloaddition*

b) Shea's type II Diels-Alder cycloaddition



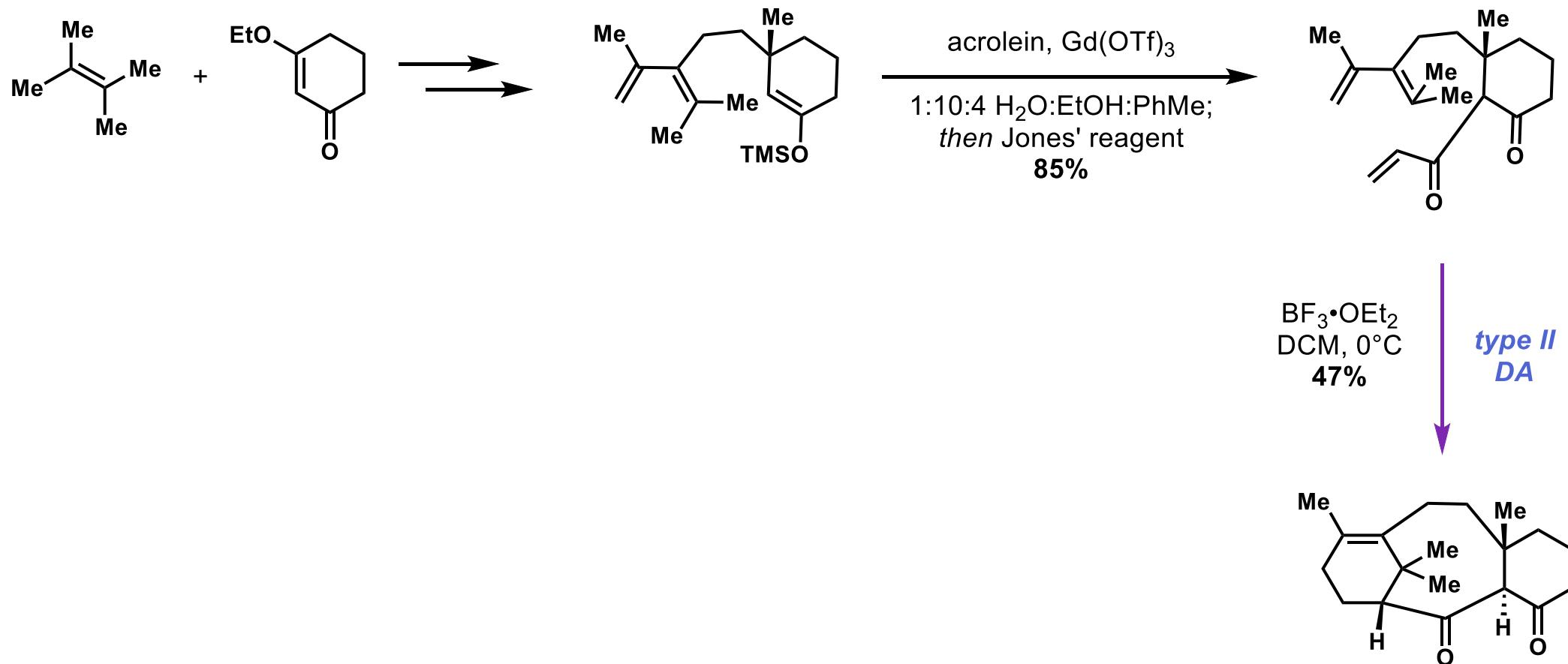
# *Intramolecular Cycloaddition*

Taxanes (Baran, 2012)



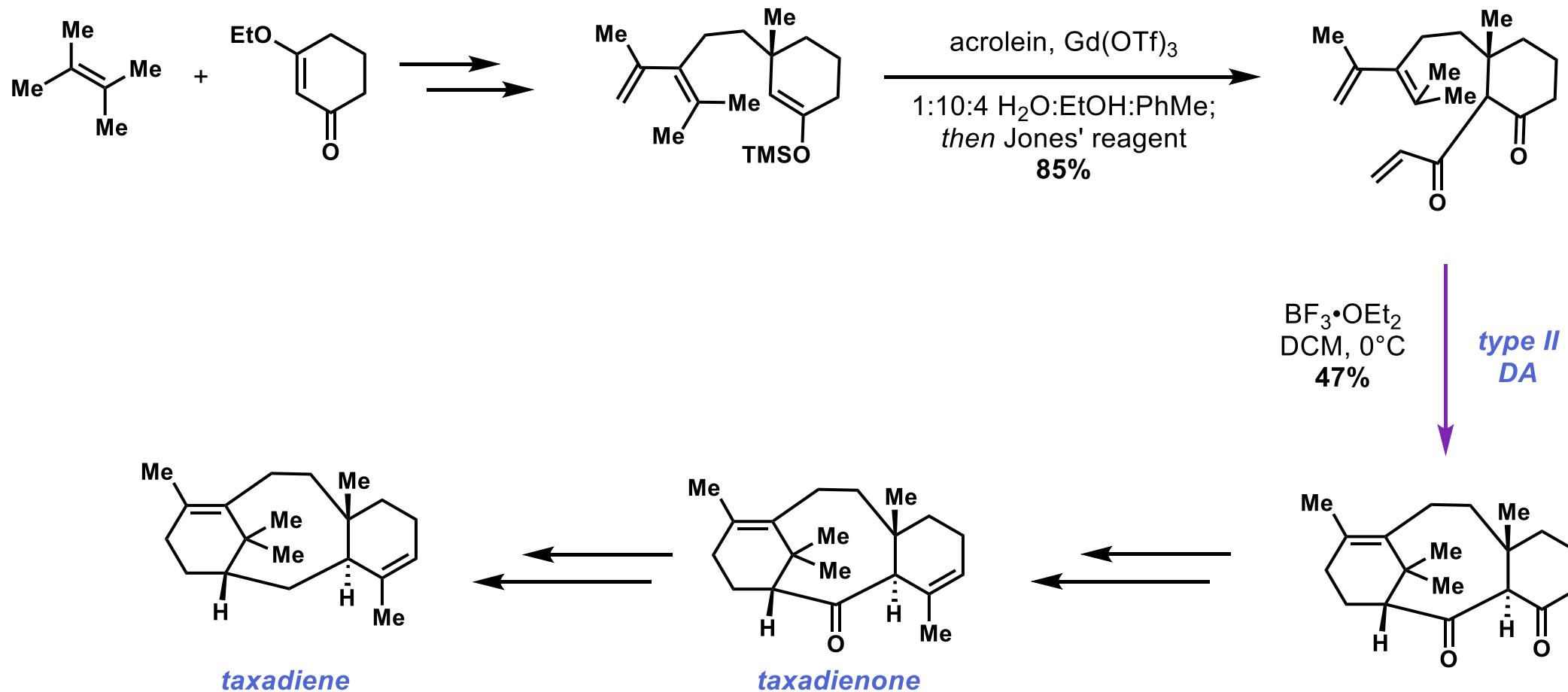
# Intramolecular Cycloaddition

Taxanes (Baran, 2012)



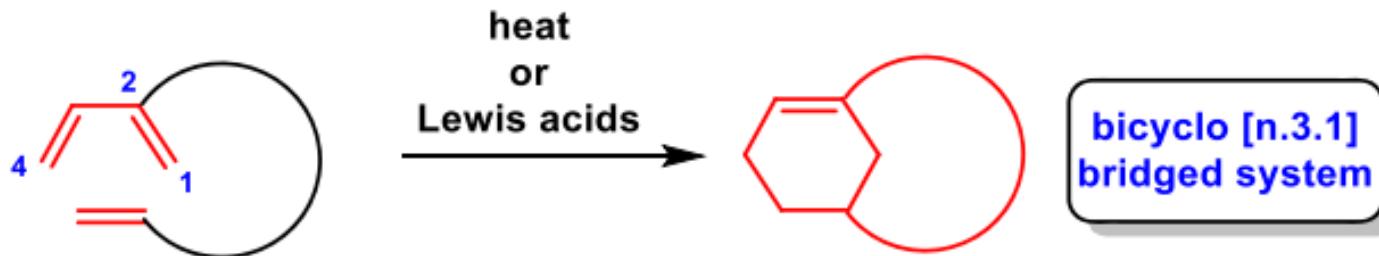
# Intramolecular Cycloaddition

Taxanes (Baran, 2012)

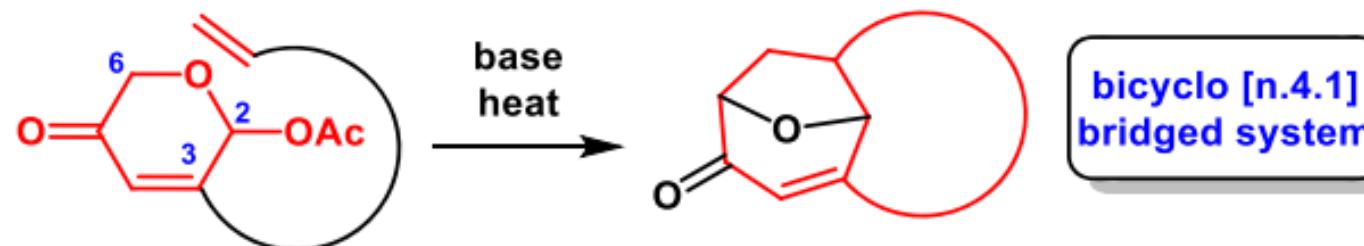


## *Intramolecular Cycloaddition*

b) Shea's type II Diels-Alder cycloaddition

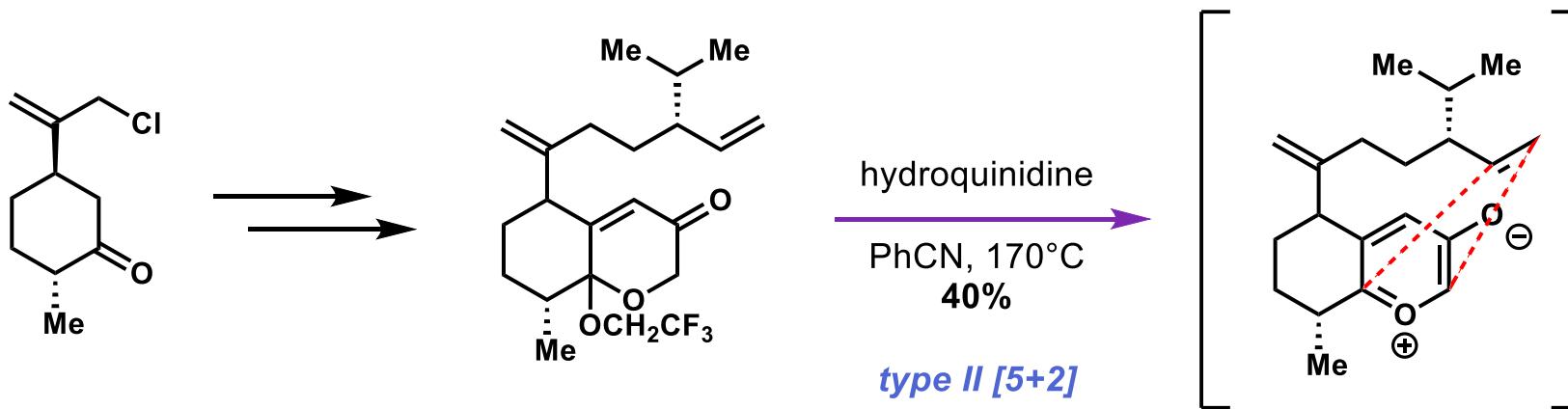


c) Li's type II [5+2] cycloaddition



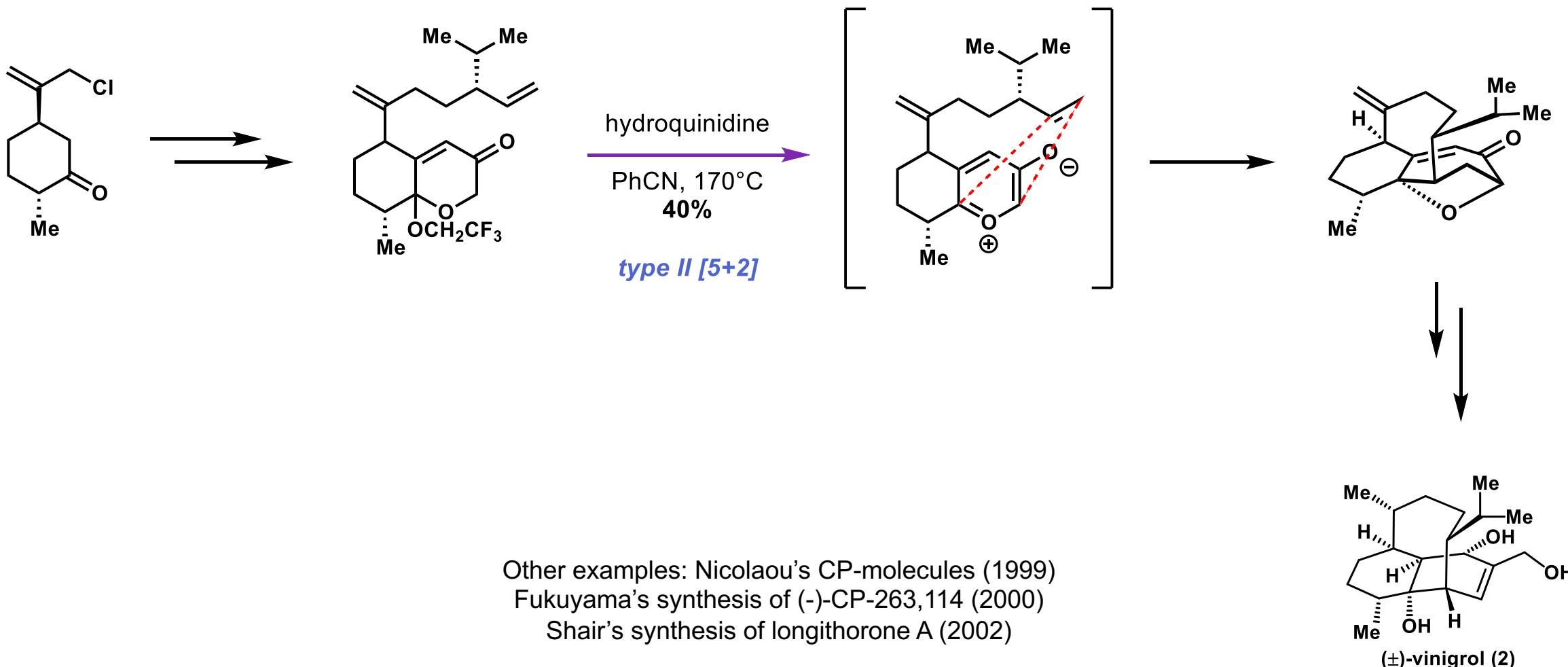
# *Intramolecular Cycloaddition*

Vinigrol (Li, 2019)

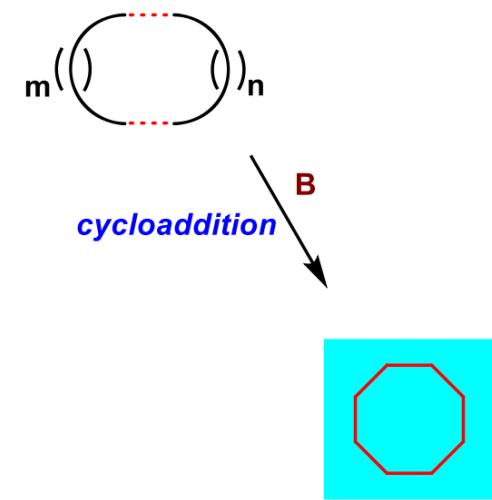


# Intramolecular Cycloaddition

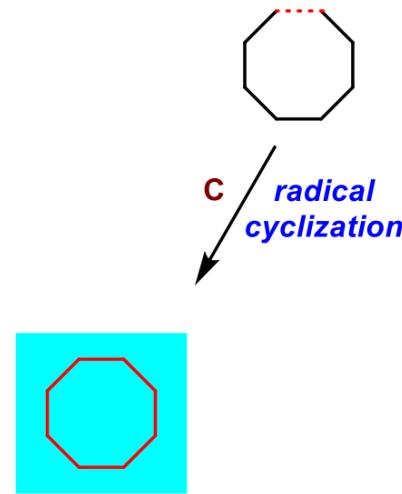
Vinigrol (Li, 2019)



## *Different Strategies*

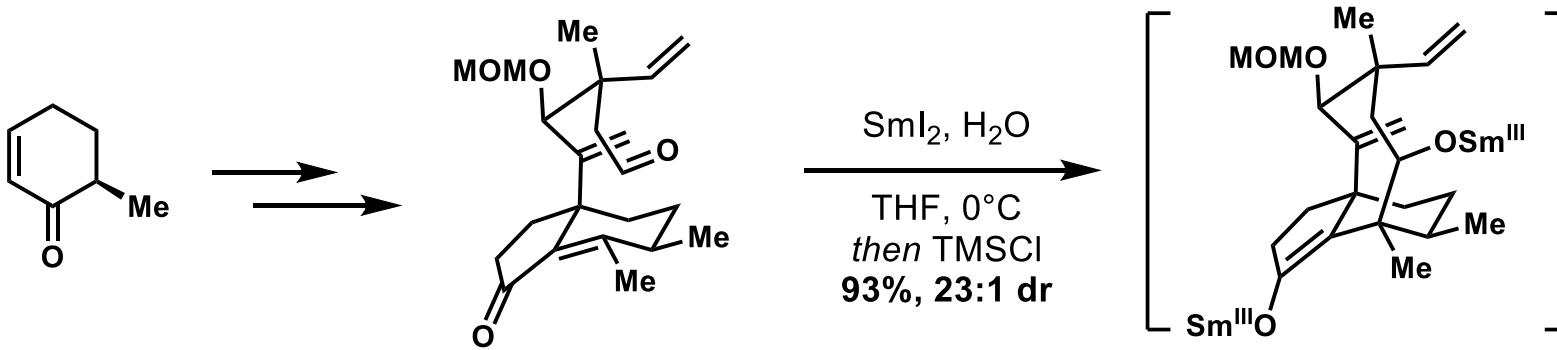


## *Different Strategies*



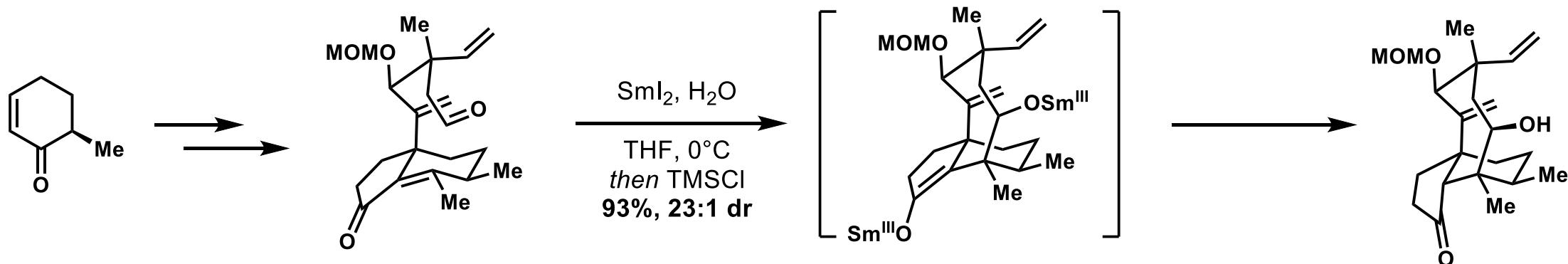
# *Radical-Mediated Cyclization*

*Sml<sub>2</sub> – Pleuromutilin (Reisman, 2018)*

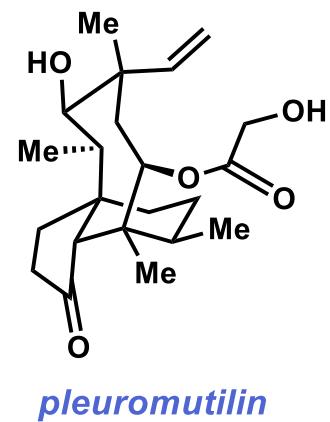


# *Radical-Mediated Cyclization*

*Sml<sub>2</sub> – Pleuromutilin (Reisman, 2018)*



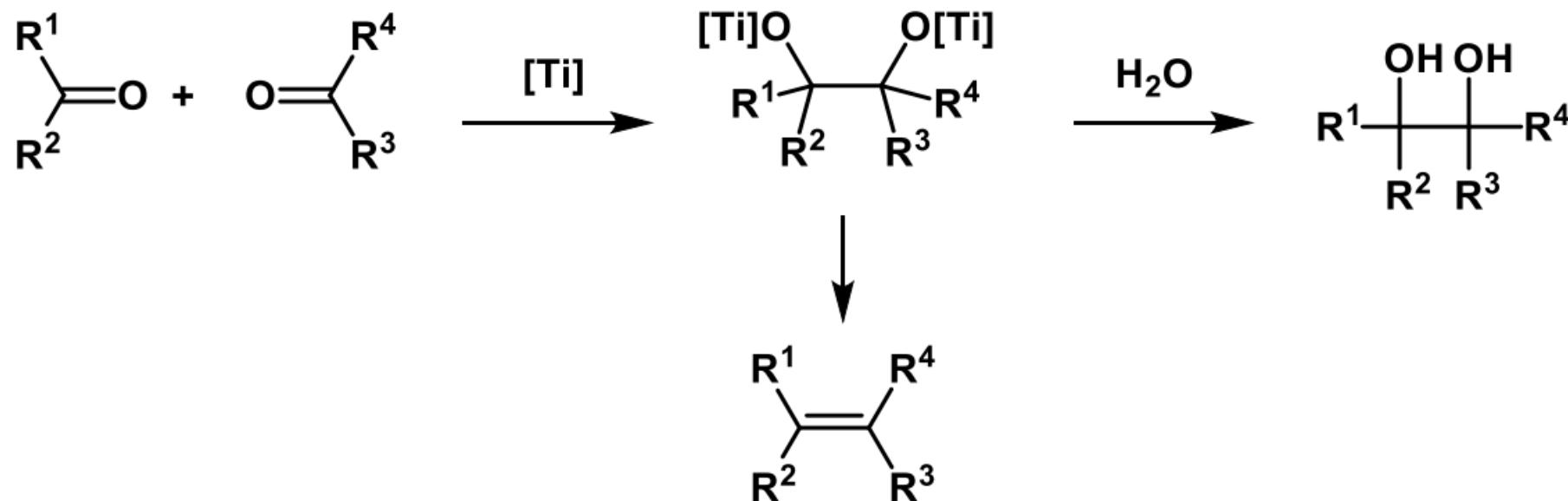
Other examples:  
Mukaiyama's synthesis of taxol (1999)  
Molander's synthesis of iso-schizandrin (2003)  
Procter's synthesis of pleuromutilin (2013)



*pleuromutilin*

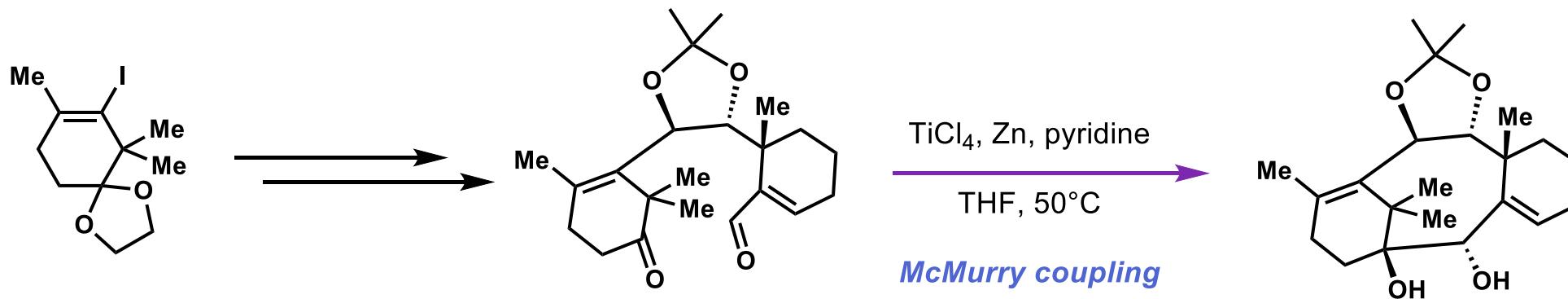
## ***Radical-Mediated Cyclization***

*McMurry Coupling – 1-Hydroxytaxinine (Inoue, 2019)*



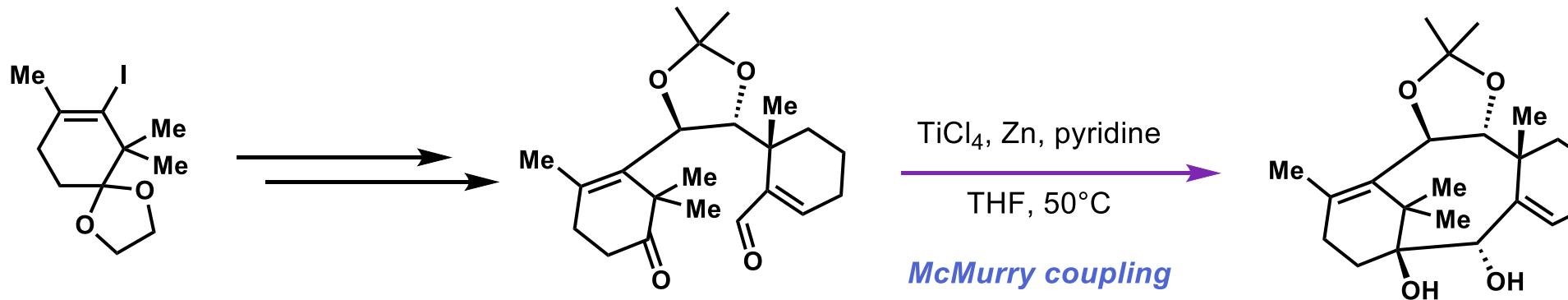
# **Radical-Mediated Cyclization**

McMurry Coupling – 1-Hydroxytaxinine (Inoue, 2019)

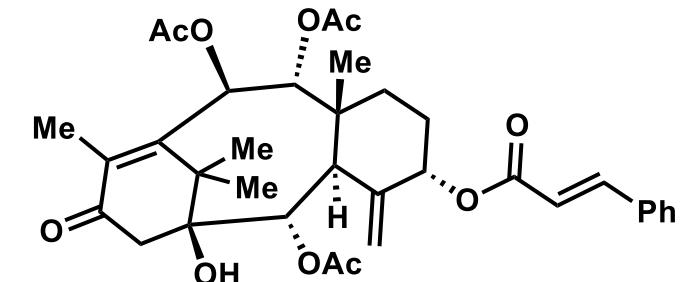


# **Radical-Mediated Cyclization**

McMurry Coupling – 1-Hydroxytaxinine (Inoue, 2019)



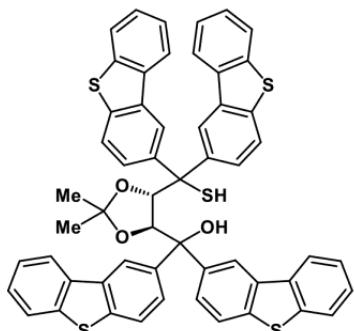
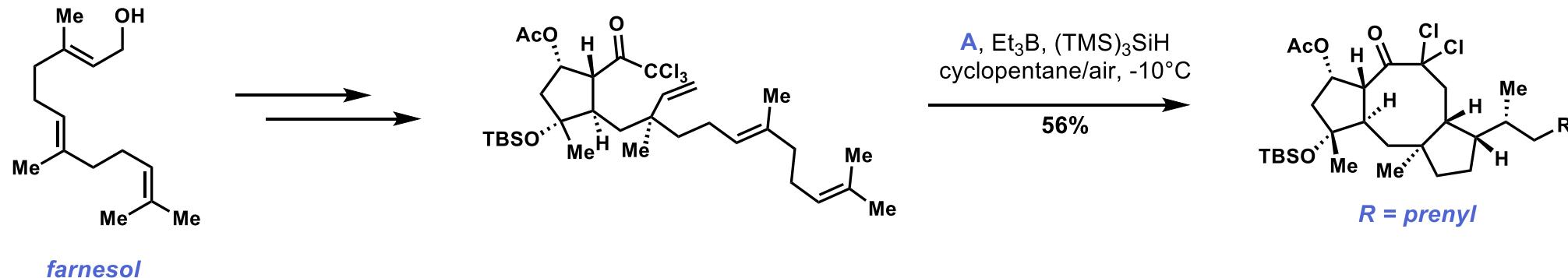
Other examples: *Nature*. **1994**, 367, 630–634  
(Nicolaou's taxol)



**(+)-1-hydroxytaxinine**

# *Radical-Mediated Cyclization*

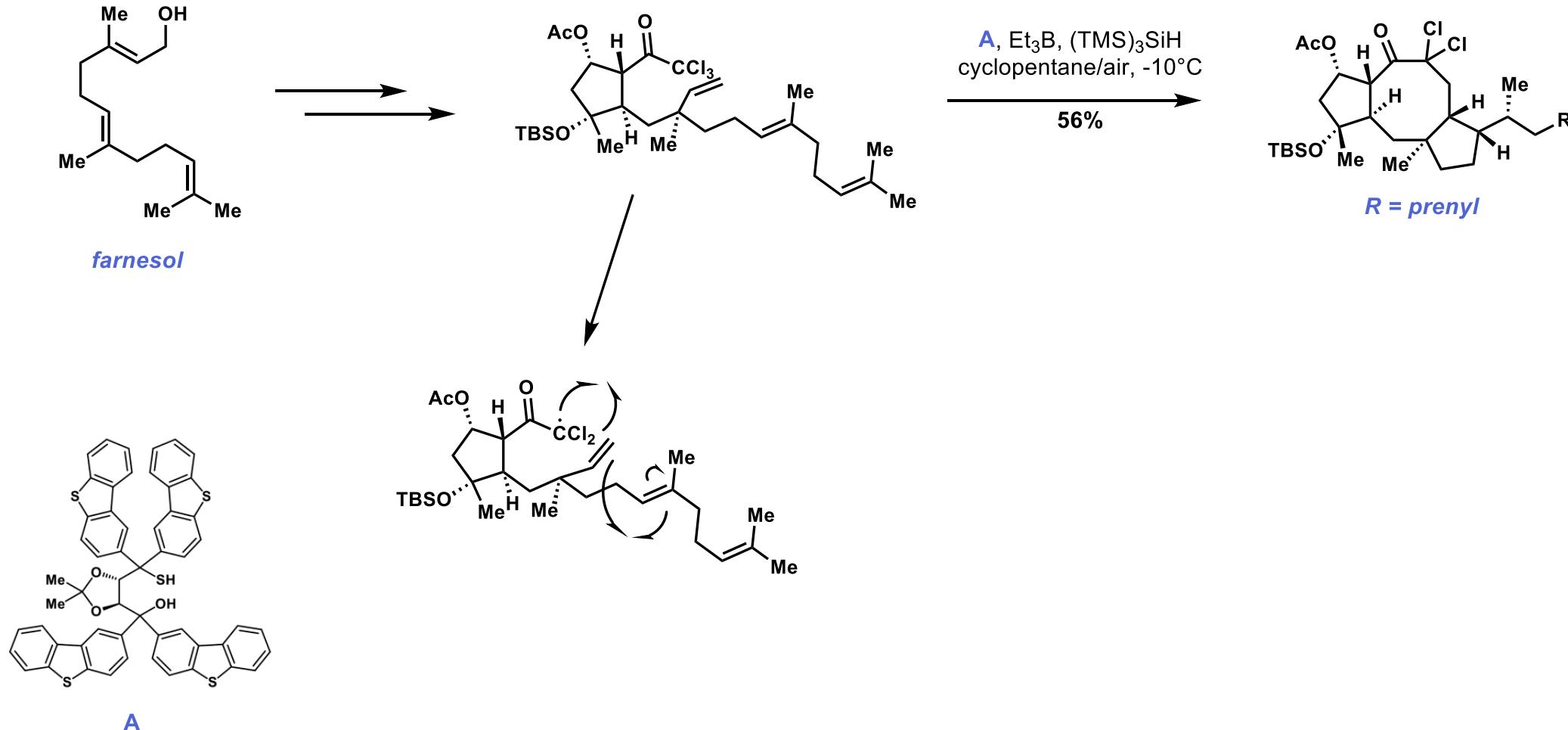
*Radical cascade –6-epi-Ophiobolin N (Maimone, 2016)*



A

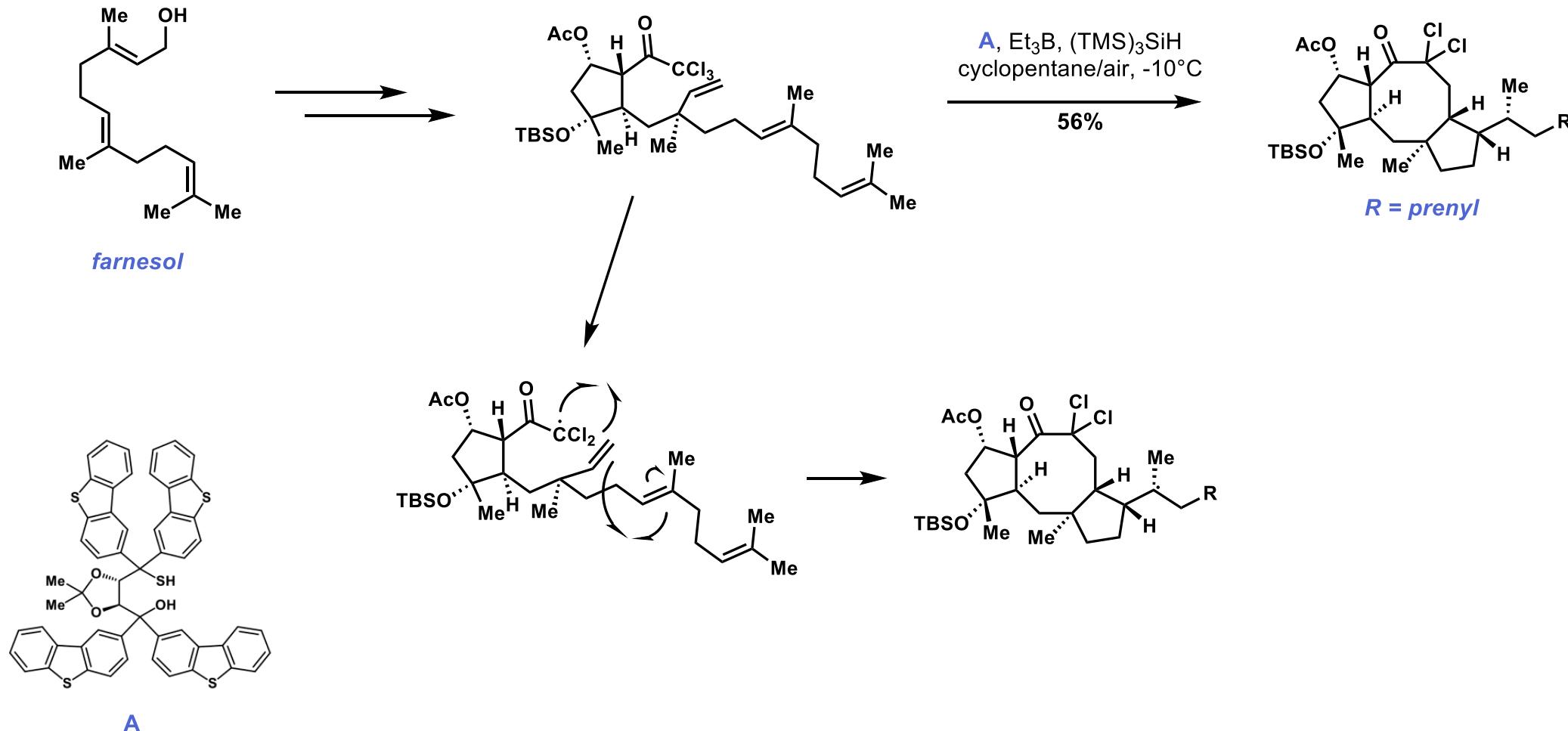
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Radical cascade –6-*epi*-Ophiobolin N (Maimone, 2016)



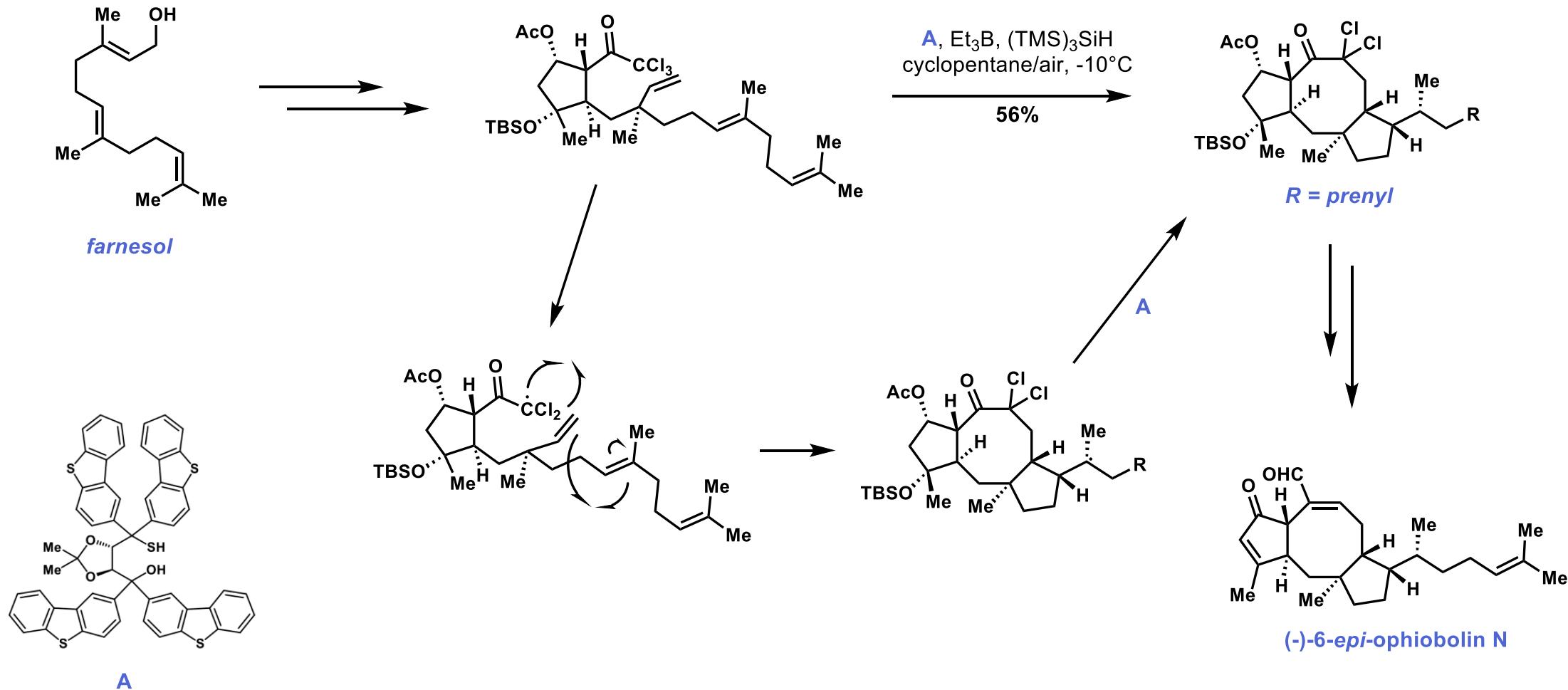
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Radical cascade –6-*epi*-Ophiobolin N (Maimone, 2016)

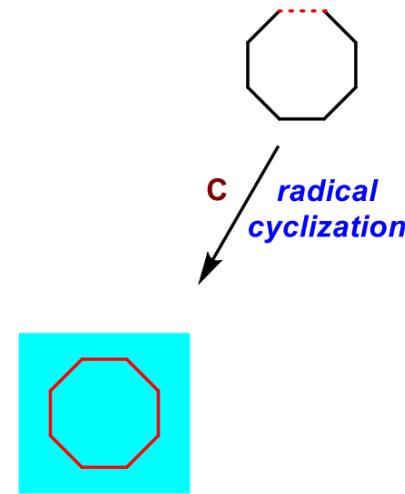


# Radical-Mediated Cyclization

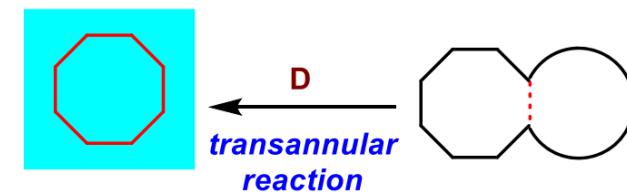
Radical cascade –6-*epi*-Ophiobolin N (Maimone, 2016)



## *Different Strategies*

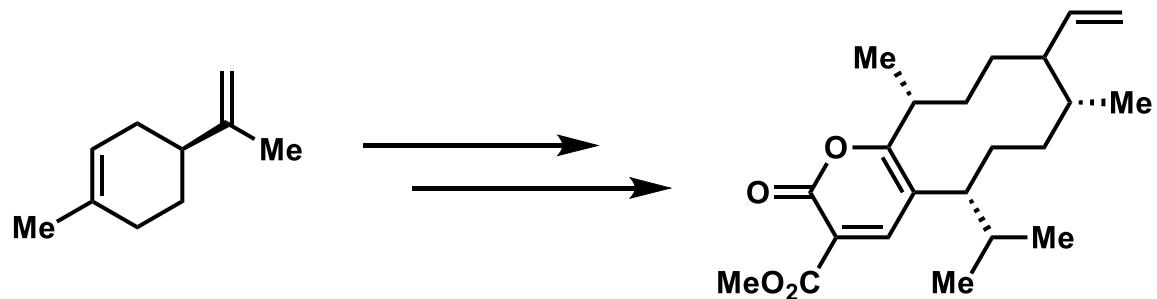


## *Different Strategies*



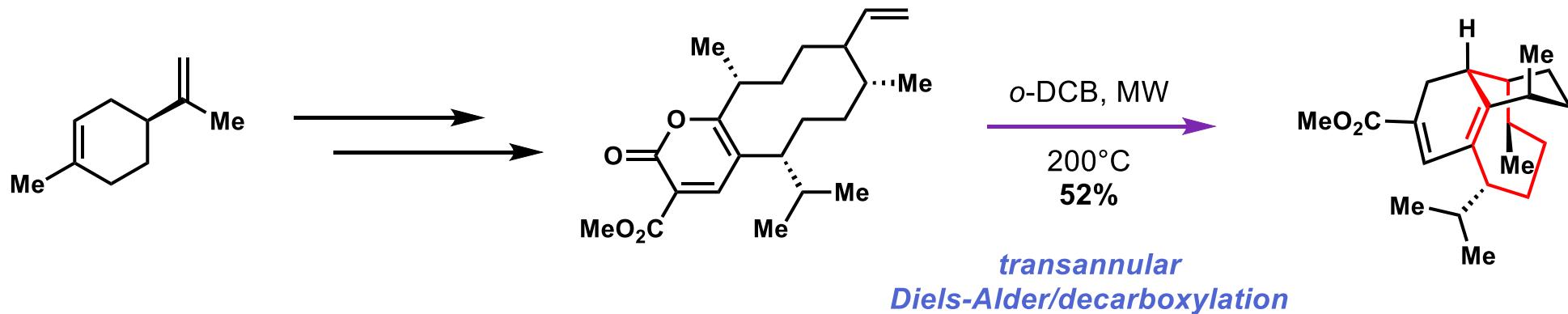
# *Transannular Reactions*

Vinigrol (Luo, 2019)



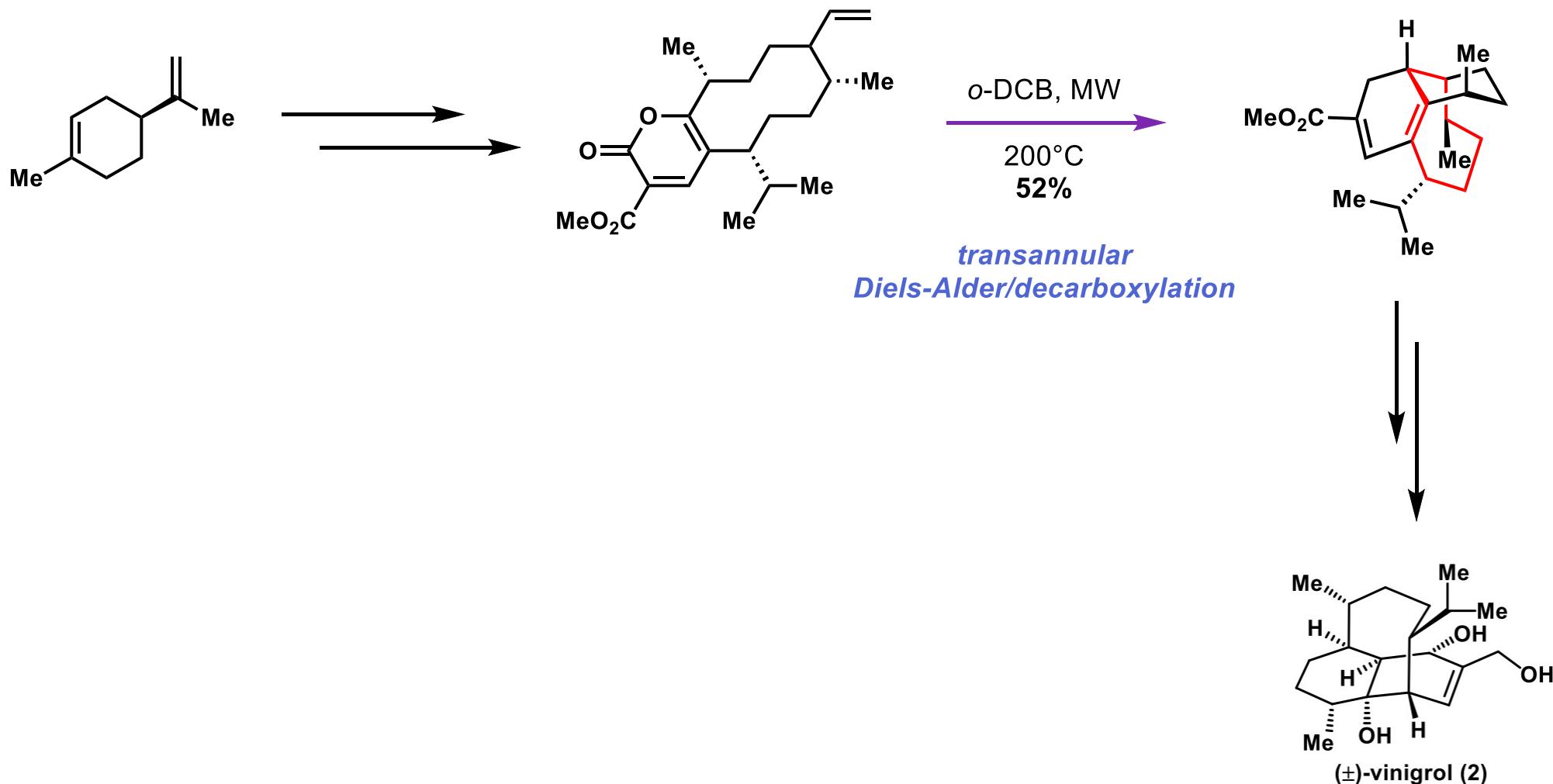
# *Transannular Reactions*

Vinigrol (Luo, 2019)



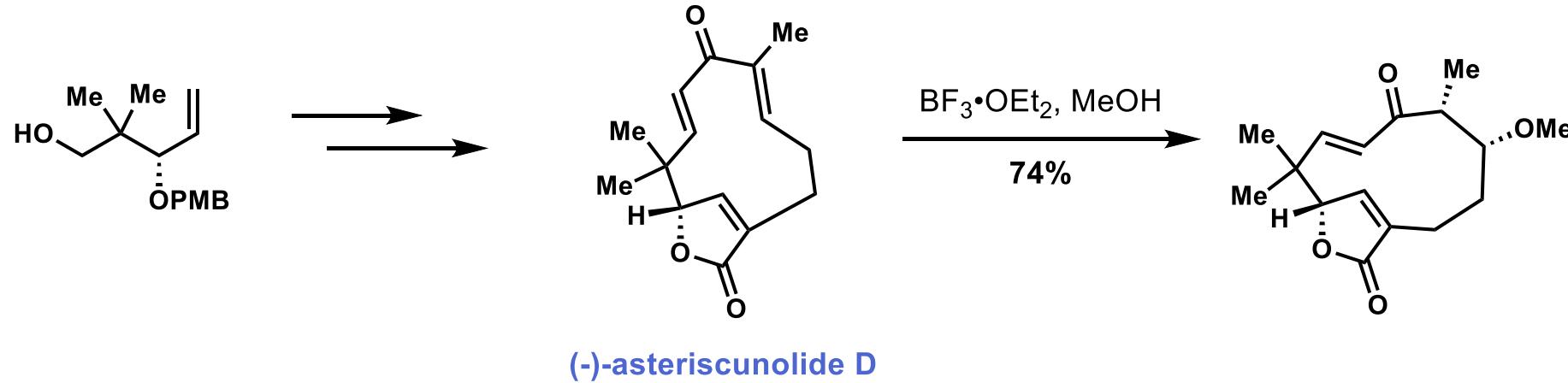
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Vinigrol (Luo, 2019)



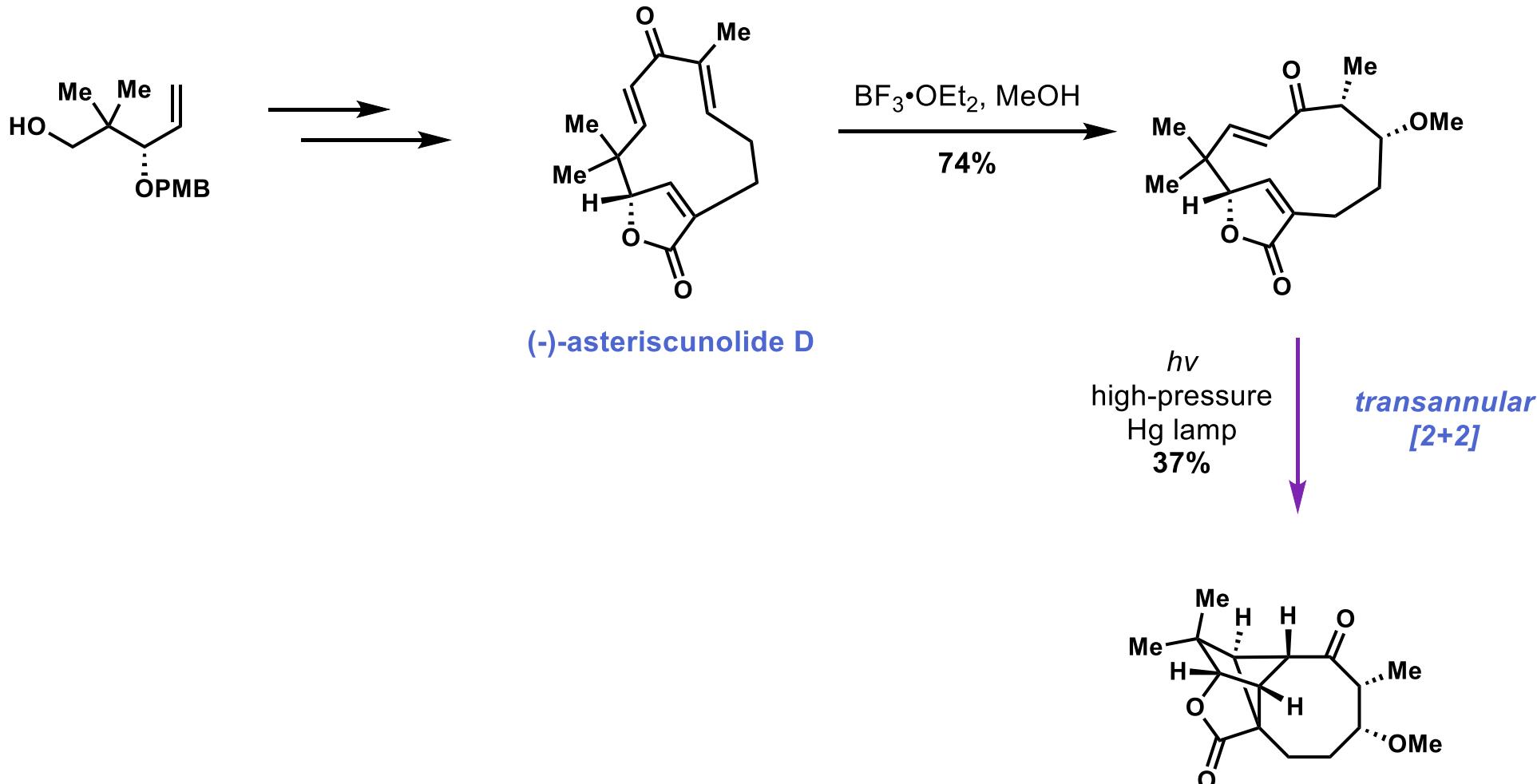
# *Transannular Reactions*

Aquatolide (Takao, 2019)



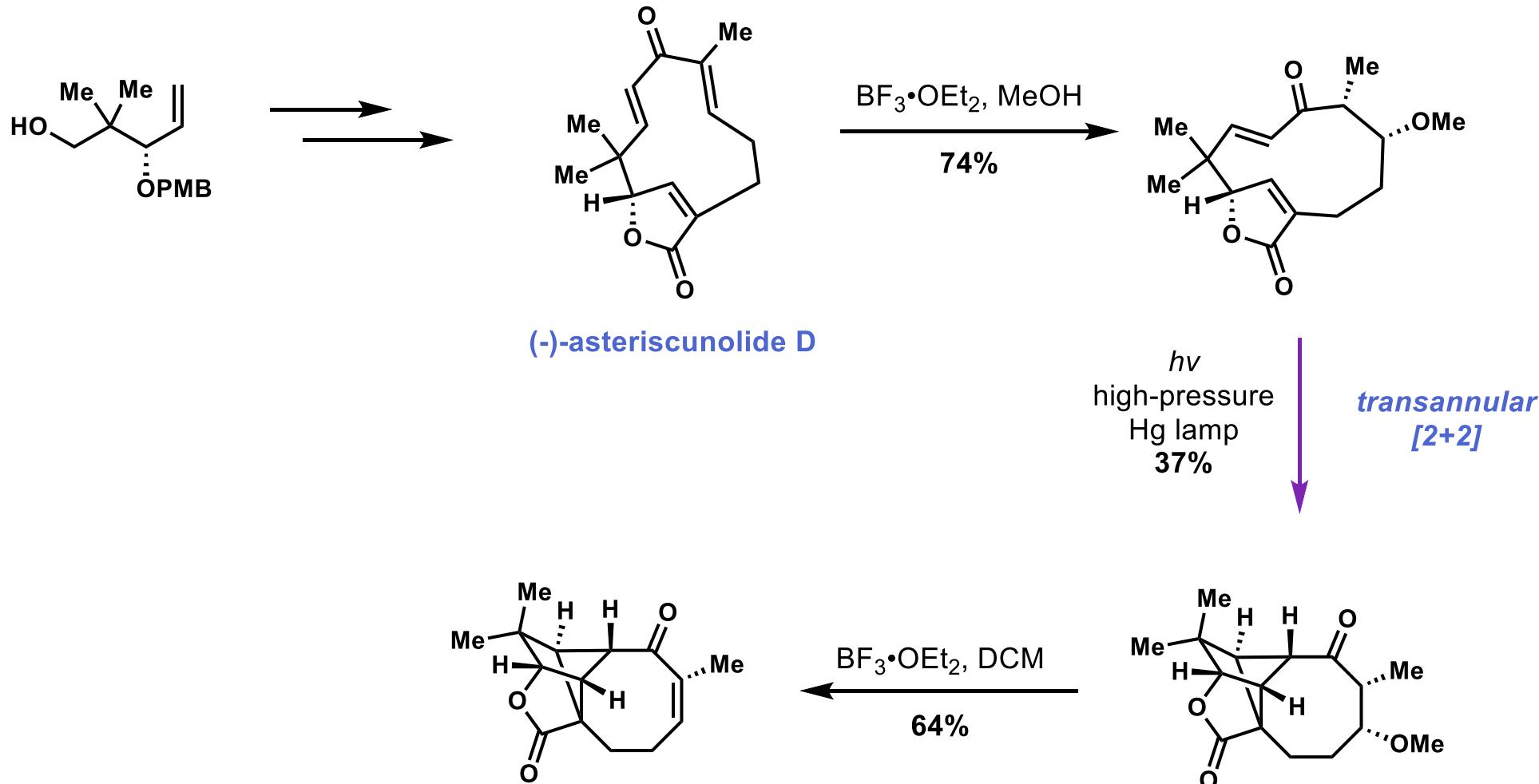
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Aquatolide (Takao, 2019)



# *Transannular Reactions*

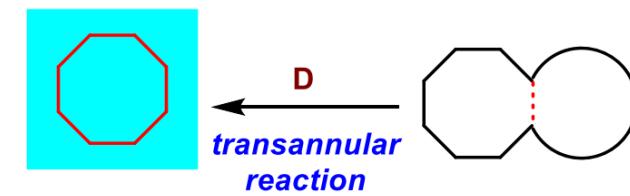
Aquatolide (Takao, 2019)



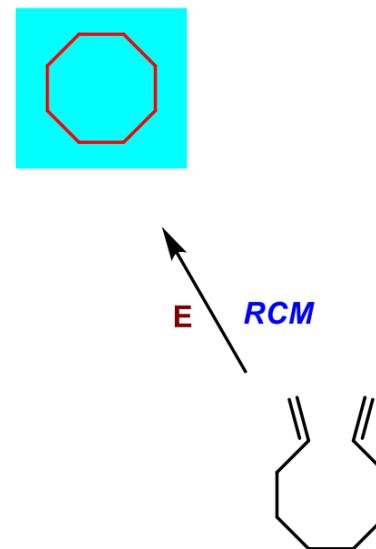
Other examples: (+)-FR182877 (Sorensen, 2002)  
(-)-FR182877 (Evans, 2002)

(+)-aquatolide

## *Different Strategies*

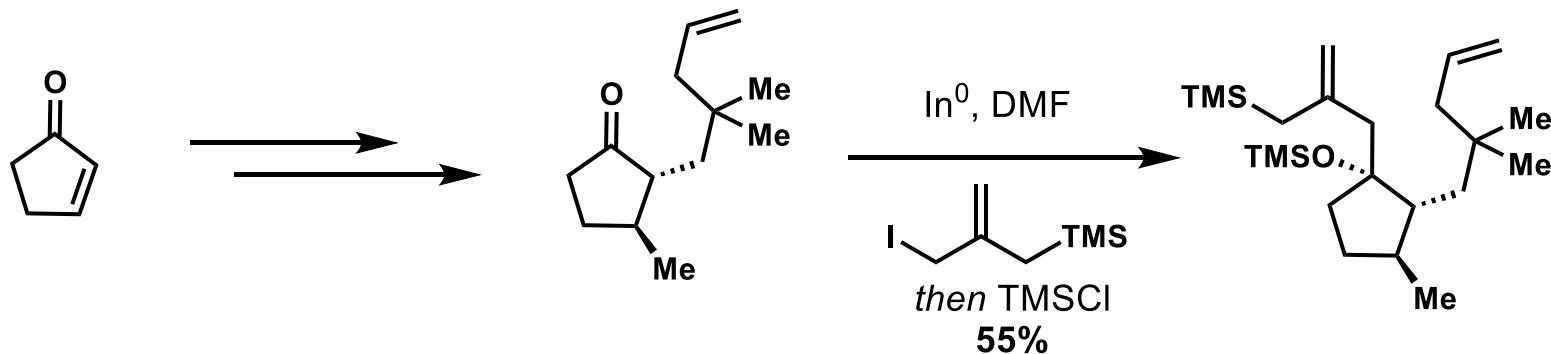


## *Different Strategies*



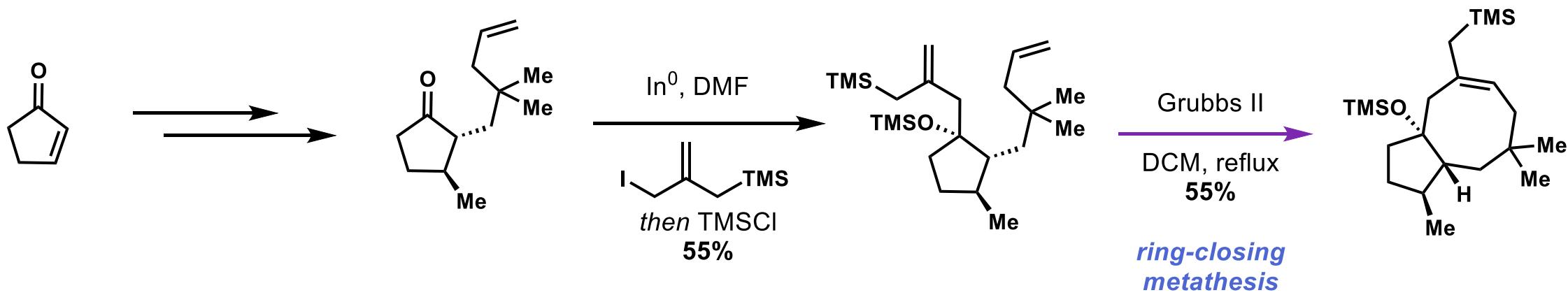
# *Ring Closing Metathesis*

Poitediol (Vanderwal, 2010)



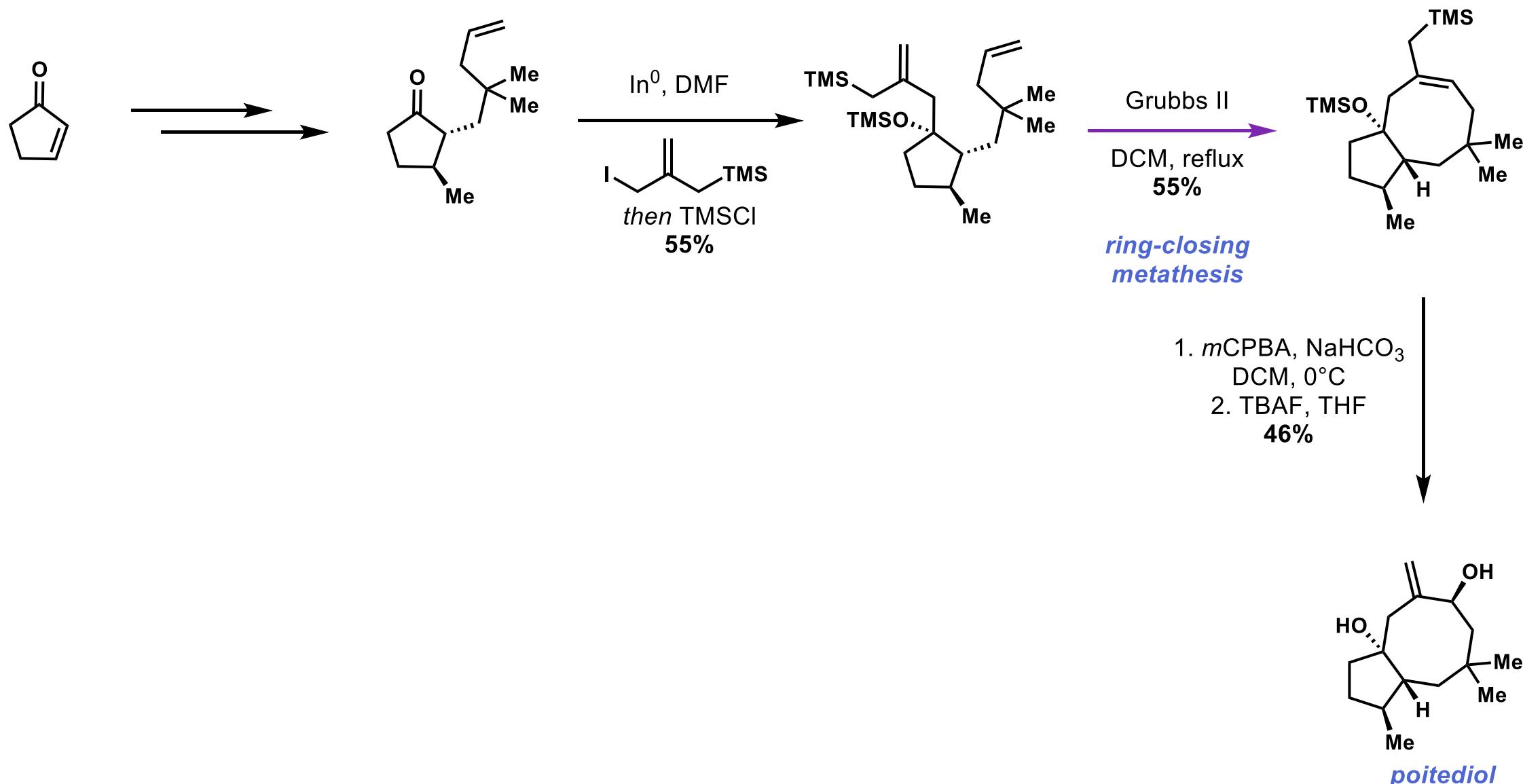
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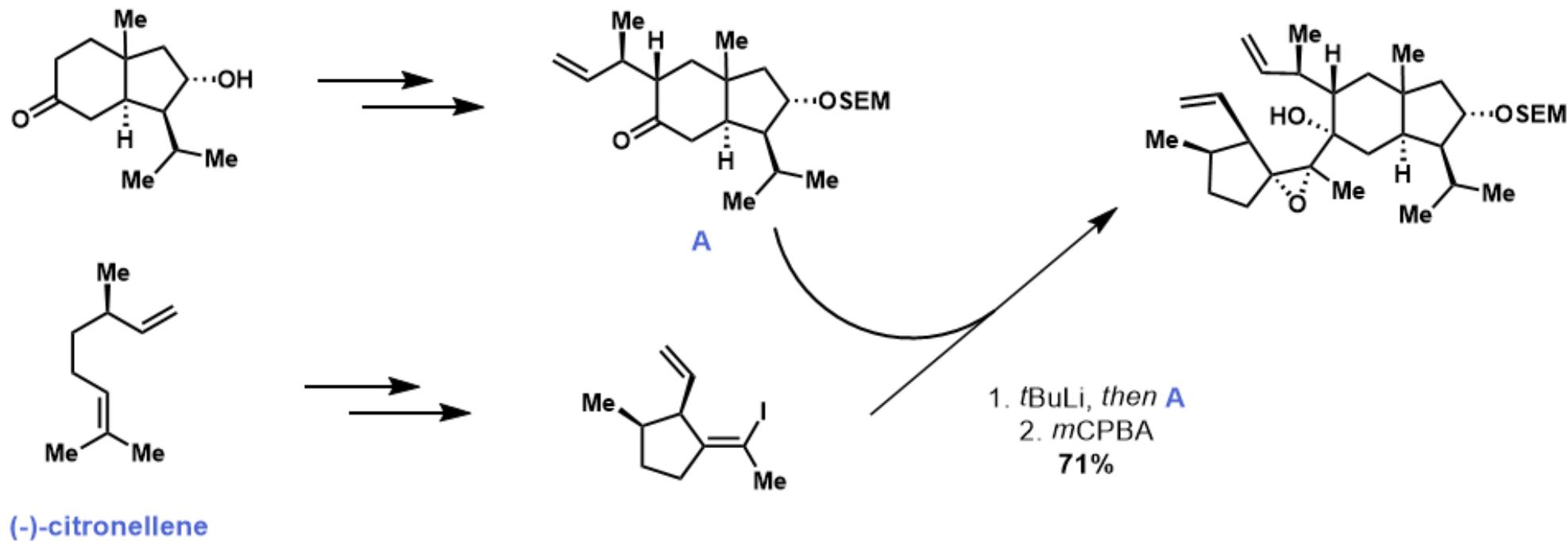
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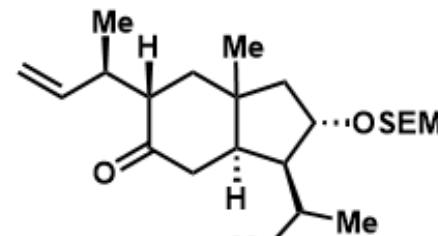
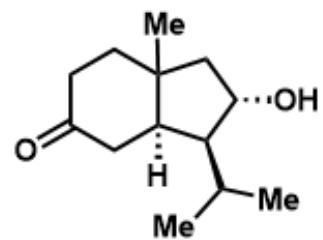
# *Ring Closing Metathesis*

*Nitidasin (Trauner, 2014)*

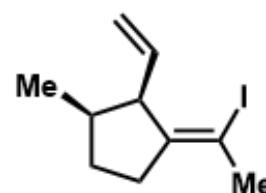
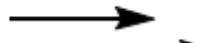
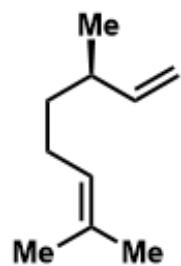


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*Nitidasin (Trauner, 2014)*

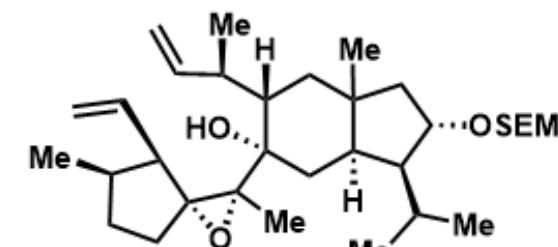


A

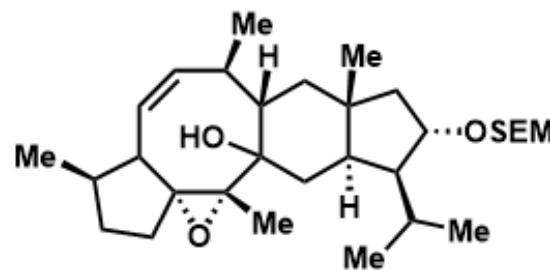


(-)citronellene

1. *t*BuLi, then A  
2. *m*CPBA  
71%

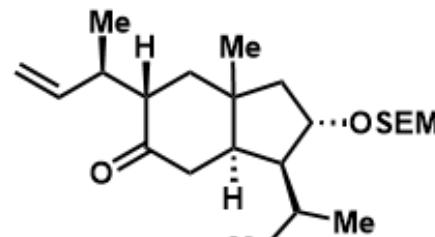
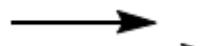
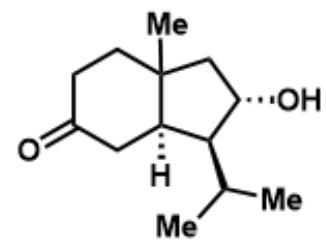


Grubbs II  
benzene, reflux  
86%  
RCM

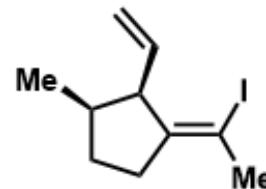
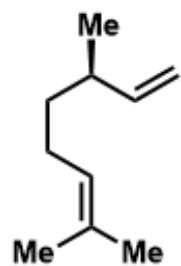


# *Ring Closing Metathesis*

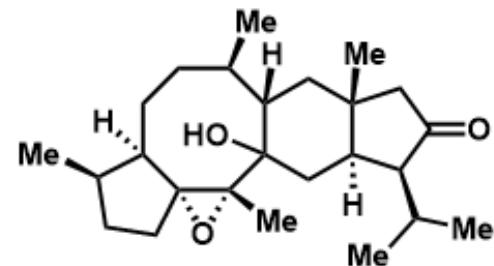
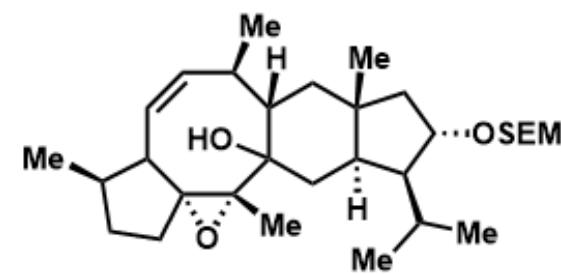
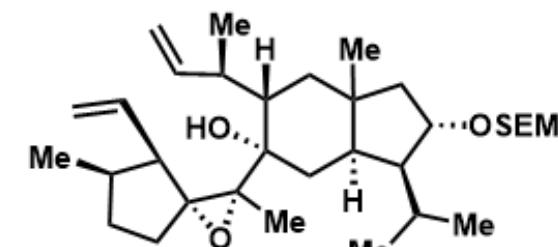
*Nitidasin (Trauner, 2014)*



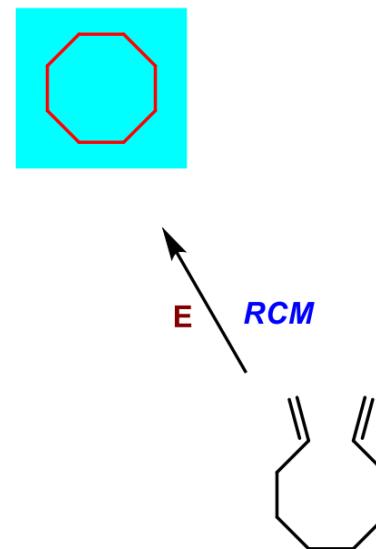
A



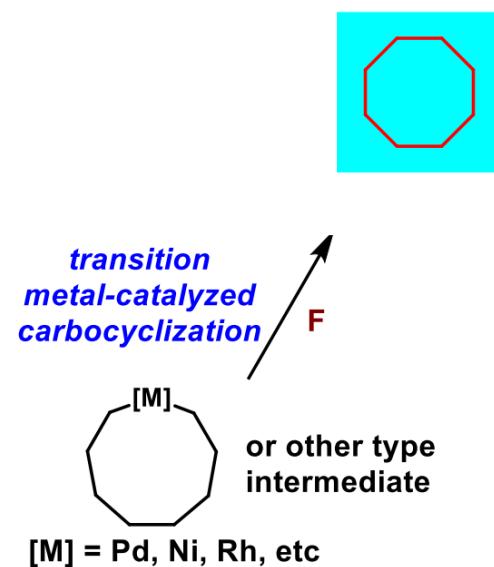
1. *t*BuLi, then A  
2. *m*CPBA  
71%



## *Different Strategies*

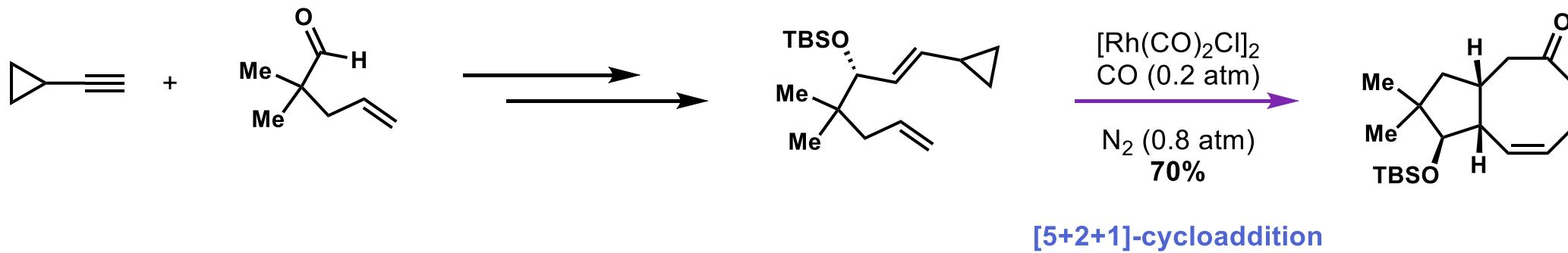


# *Different Strategies*



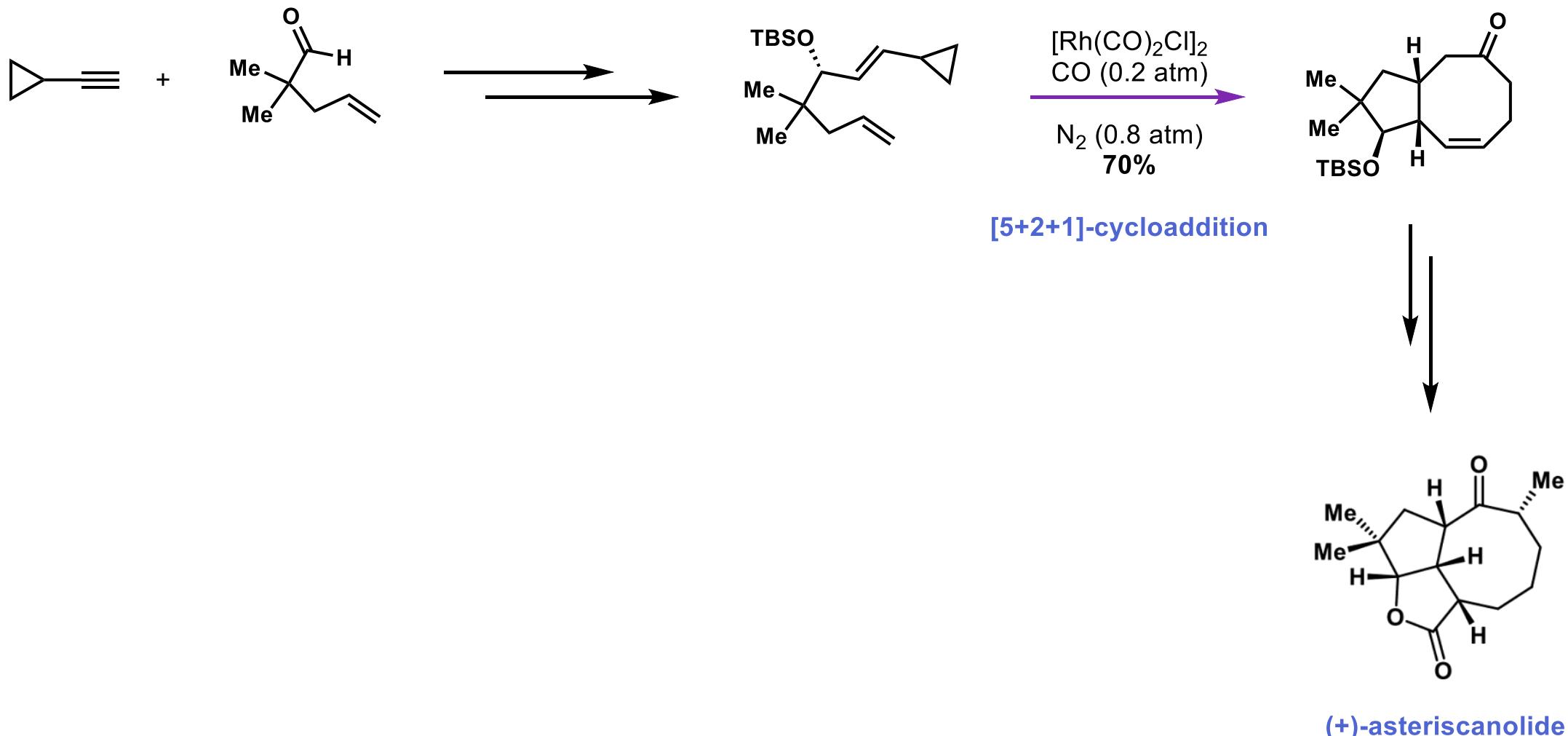
# *Transition Metal-Catalyzed Carbocyclization*

Asteriscanolide (Yu, 2011)



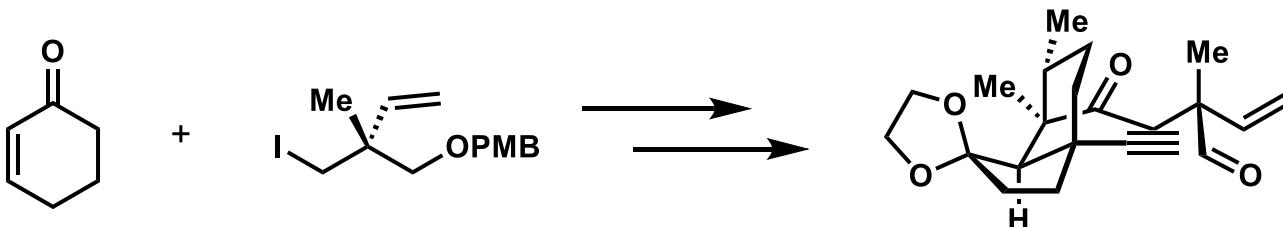
# *Transition Metal-Catalyzed Carbocyclization*

Asteriscanolide (Yu, 2011)



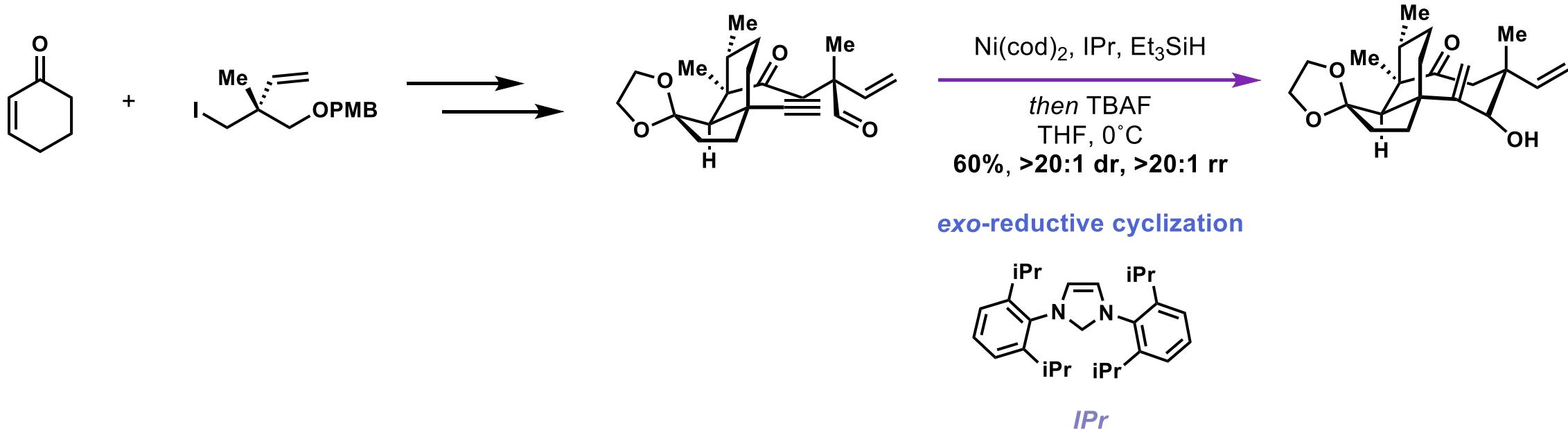
# *Transition Metal-Catalyzed Carbocyclization*

Pleuromutilin (Herzon, 2017)



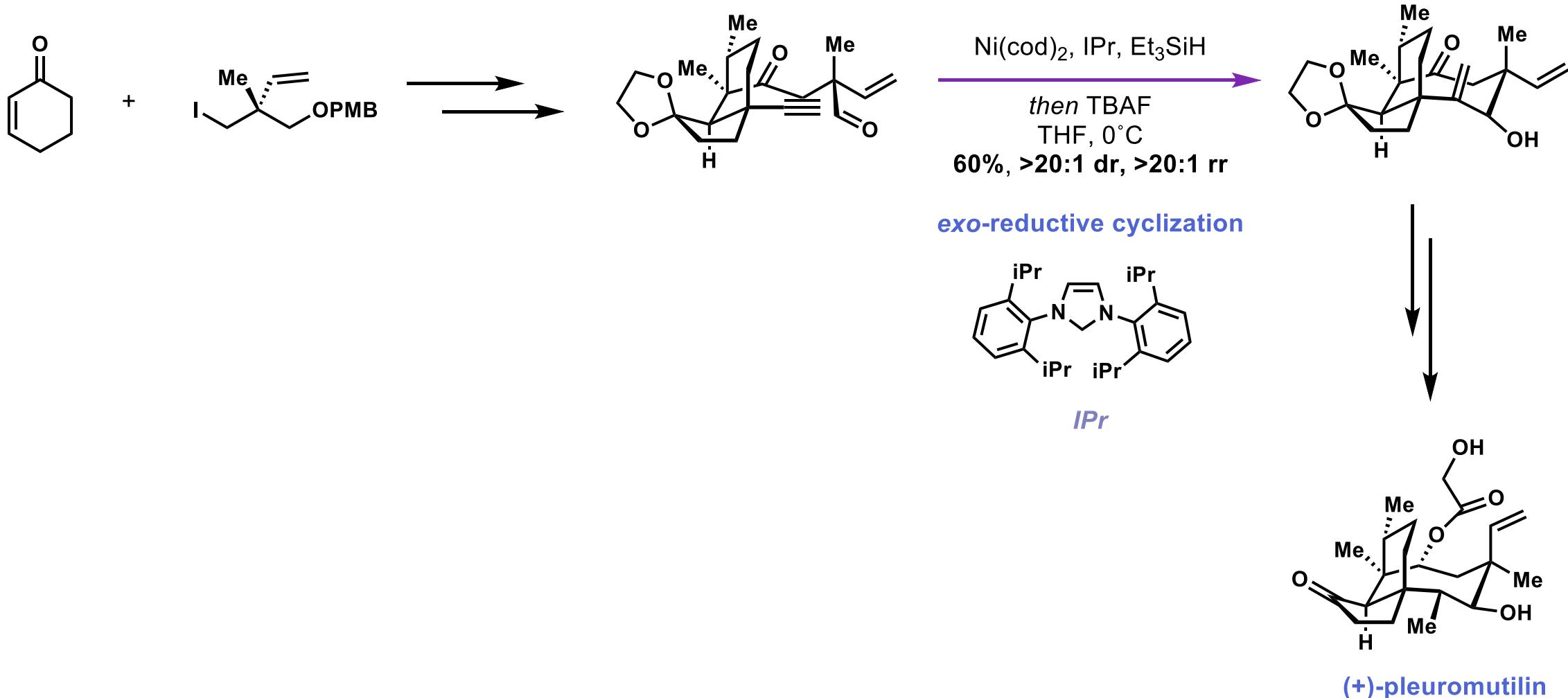
# *Transition Metal-Catalyzed Carbocyclization*

Pleuromutilin (Herzon, 2017)



# *Transition Metal-Catalyzed Carbocyclization*

Pleuromutilin (Herzon, 2017)



## *Different Strategies*

