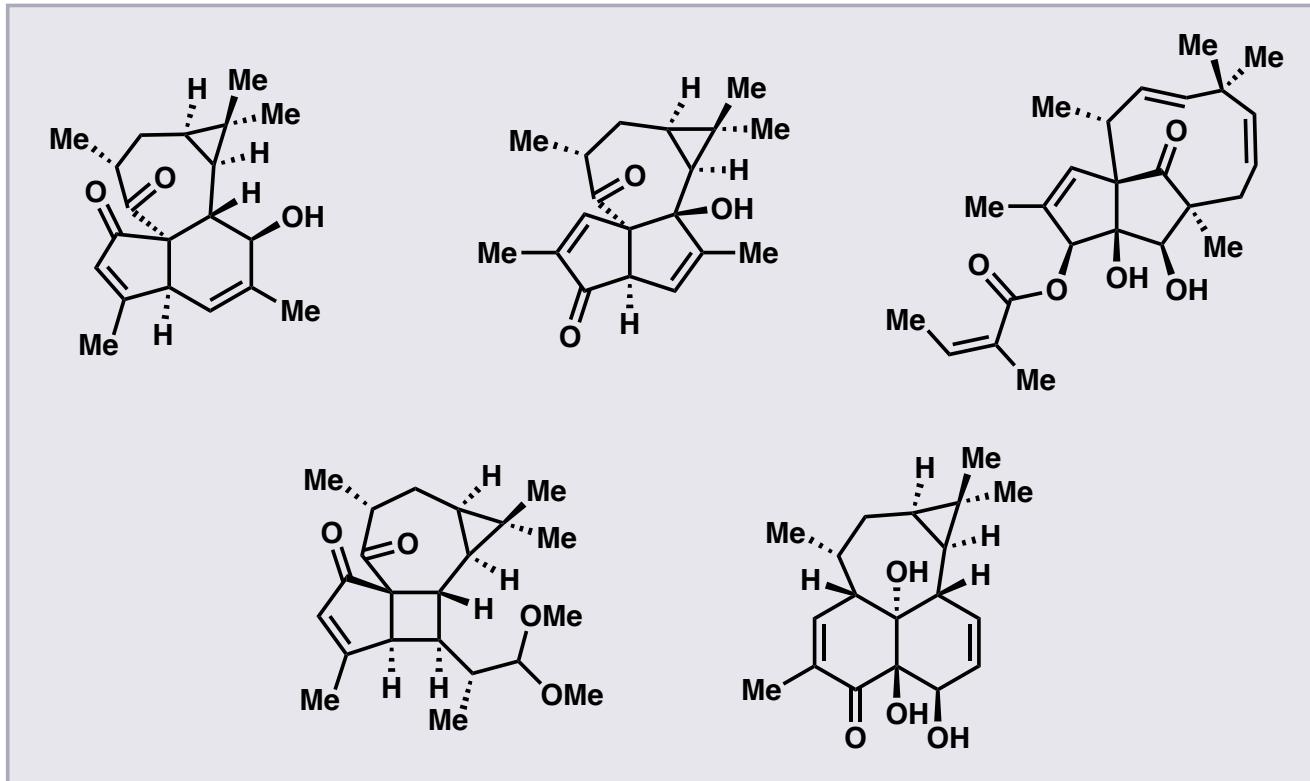
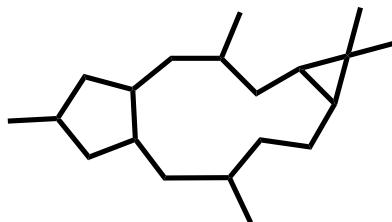


# *Synthetic Approaches to the Pepluanol Natural Products*

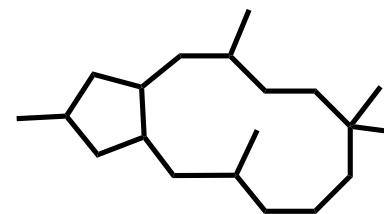


Nicholas A. Falcone  
Literature Group Meeting  
November 19<sup>th</sup>, 2021

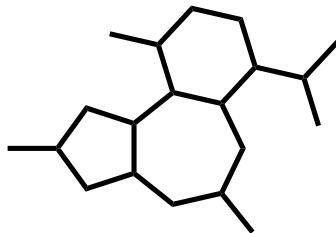
# *Euphorbia* Diterpenes: Featured Classes



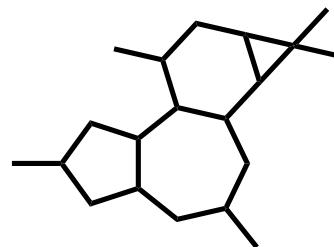
lathyrane



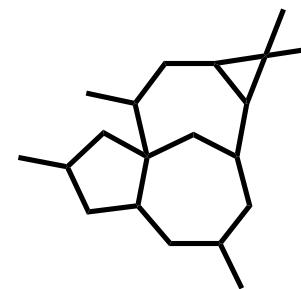
jatrophane



daphnane



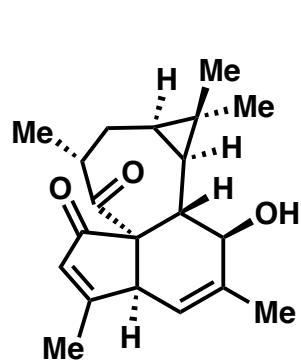
tigliane



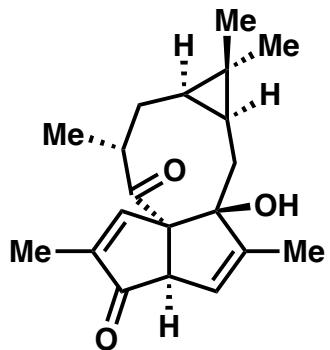
ingenane

> 750 members across more than 2000 species

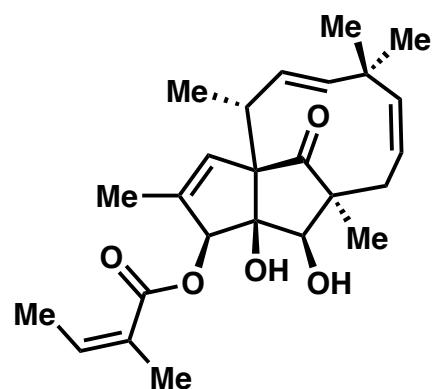
# Pepluanol Natural Products



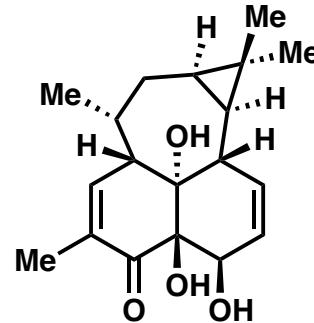
pepluanol A



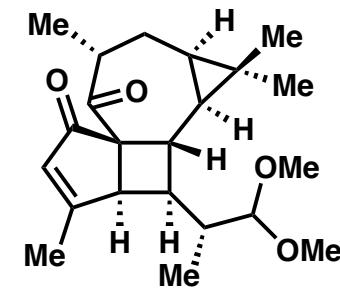
pepluanol B



pepluanol C

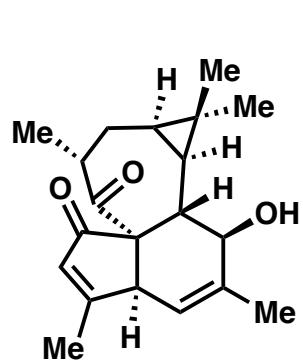


pepluanol D

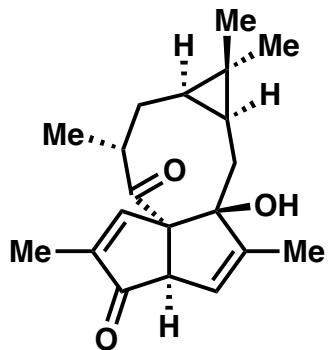


pepluacetal

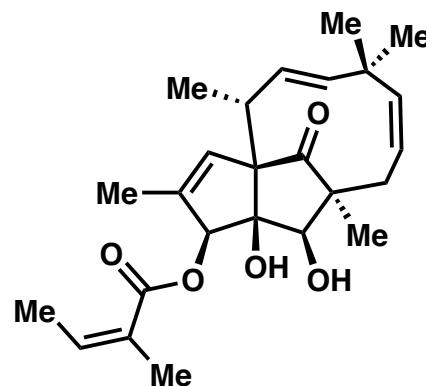
# Pepluanol Natural Products



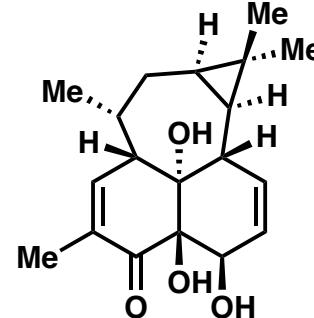
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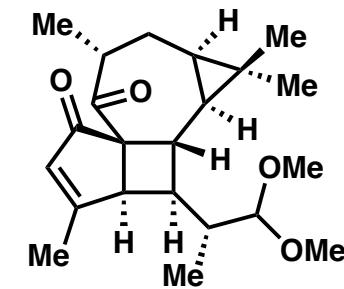
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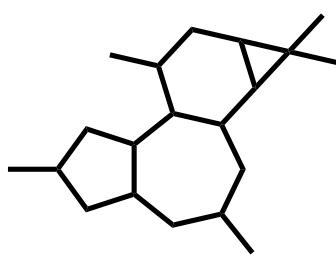
pepluanol C



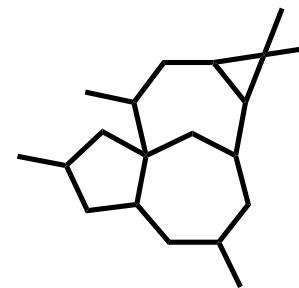
pepluanol D



pepluacetal

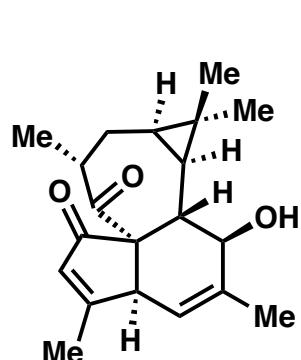


tigliane

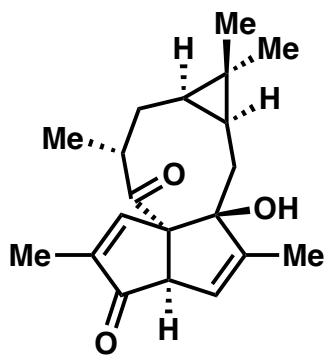


ingenane

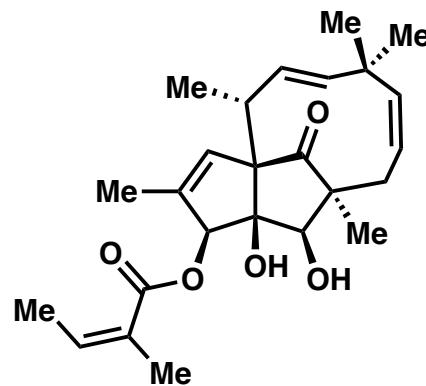
# Pepluanol Natural Products



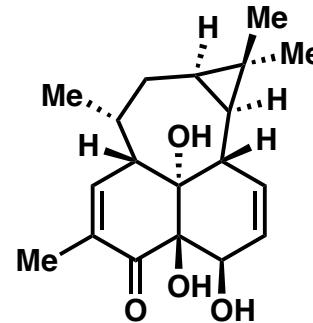
pepluanol A



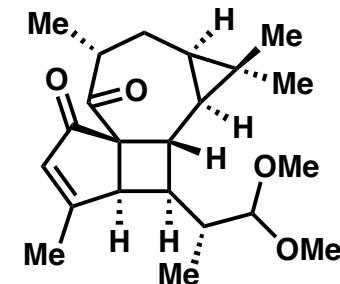
pepluanol B



pepluanol C



pepluanol D



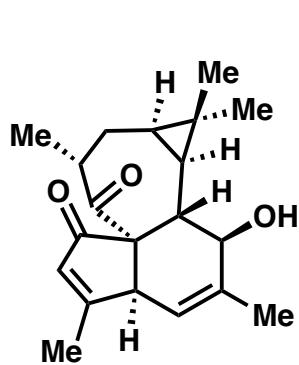
pepluacetal

- Unprecedented polycyclic ring systems

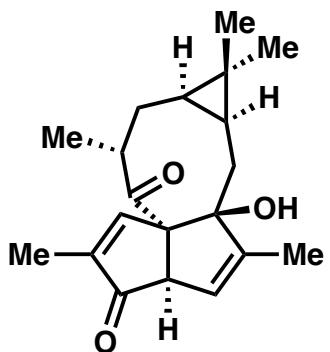
- Inhibit voltage-gated potassium channel  $K_v$  1.3

- Potential application as immunosuppressants

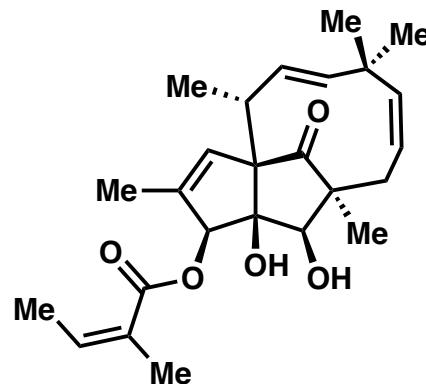
# Pepluanol Natural Products



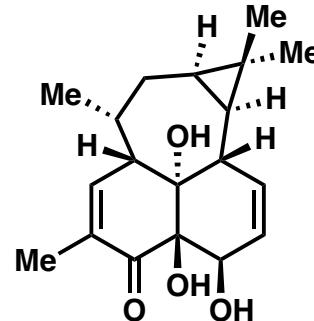
pepluanol A



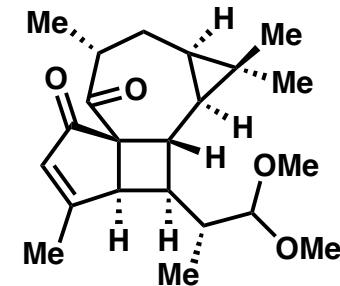
pepluanol B



pepluanol C



pepluanol D



pepluacetal

## Pepluanol A:

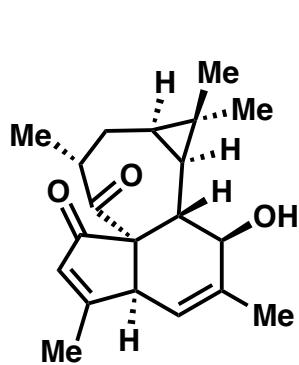
Xuan, J.; Lio, Z.; Zhu, A.; Rao, P.; Yu, L.; Ding, H.  
Zhejiang University  
*Angew. Chem. Int. Ed.* **2017**, 56, 8898–8901.

Yuan, P.; Gerlinger, C. K. G.; Herberger, J.; Gaich, T.  
University of Konstanz  
*J. Am. Chem. Soc.* **2021**, 143, 11934–11938.

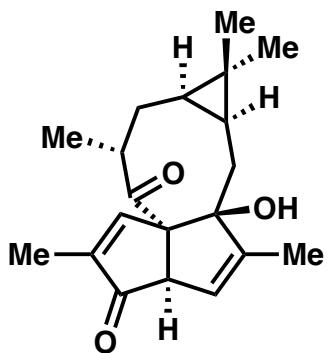
## Pepluanol B:

Zhang, J.; Liu, M.; Wu, C.; Zhao, G.; Chen, P.; Zhou, L.; Xie, X.; Fang, R.; Li, H.; She, X.  
Lanzhou University  
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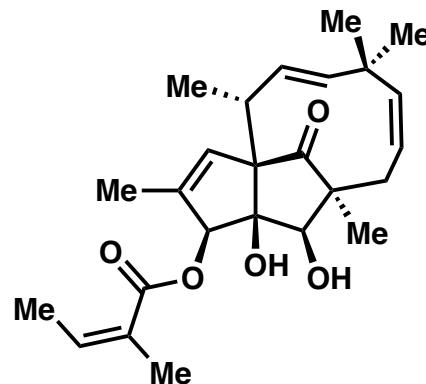
# Pepluanol Natural Products



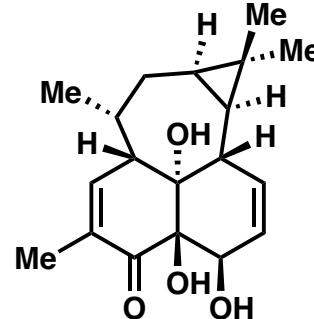
pepluanol A



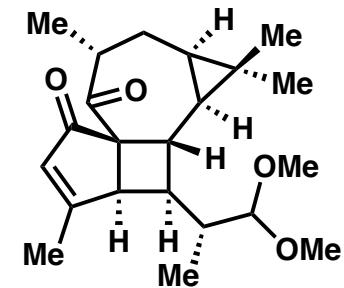
pepluanol B



pepluanol C



pepluanol D



pepluacetal

## Pepluanol A:

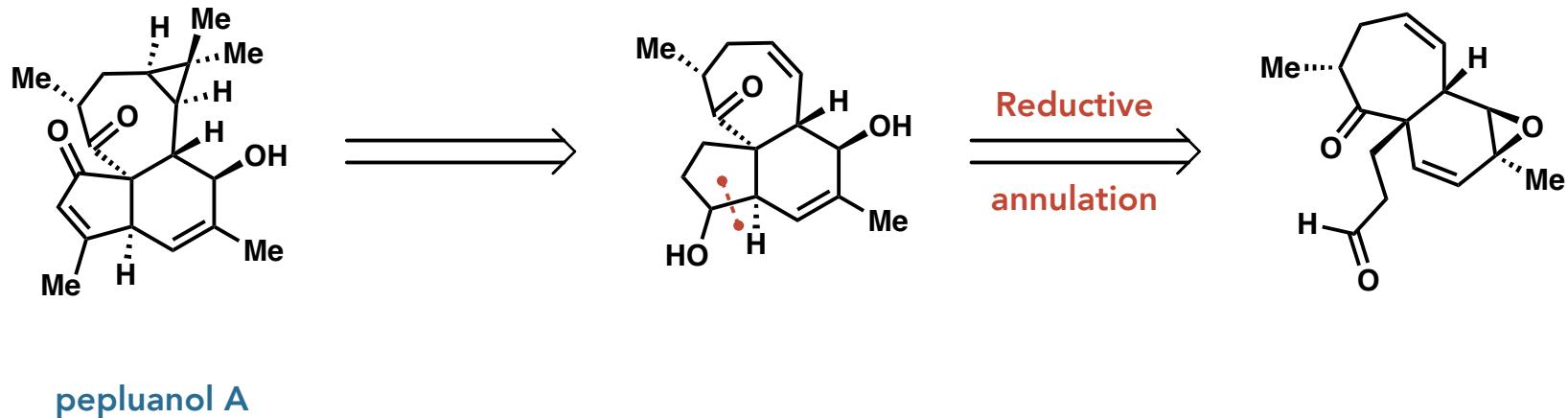
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University of Konstanz  
*J. Am. Chem. Soc.* **2021**, 143, 11934–11938.

## Pepluanol B:

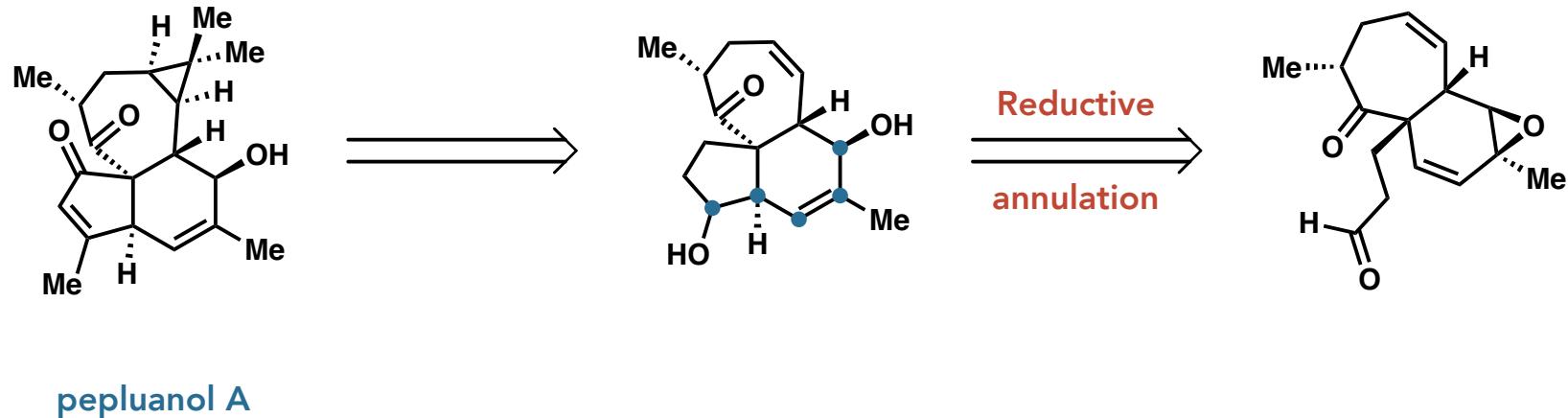
Zhang, J.; Liu, M.; Wu, C.; Zhao, G.; Chen, P.; Zhou, L.; Xie, X.; Fang, R.; Li, H.; She, X.  
Lanzhou University  
*Angew. Chem. Int. Ed.* **2020**, 59, 3966–3970.

# Ding's Reductive Annulation Strategy



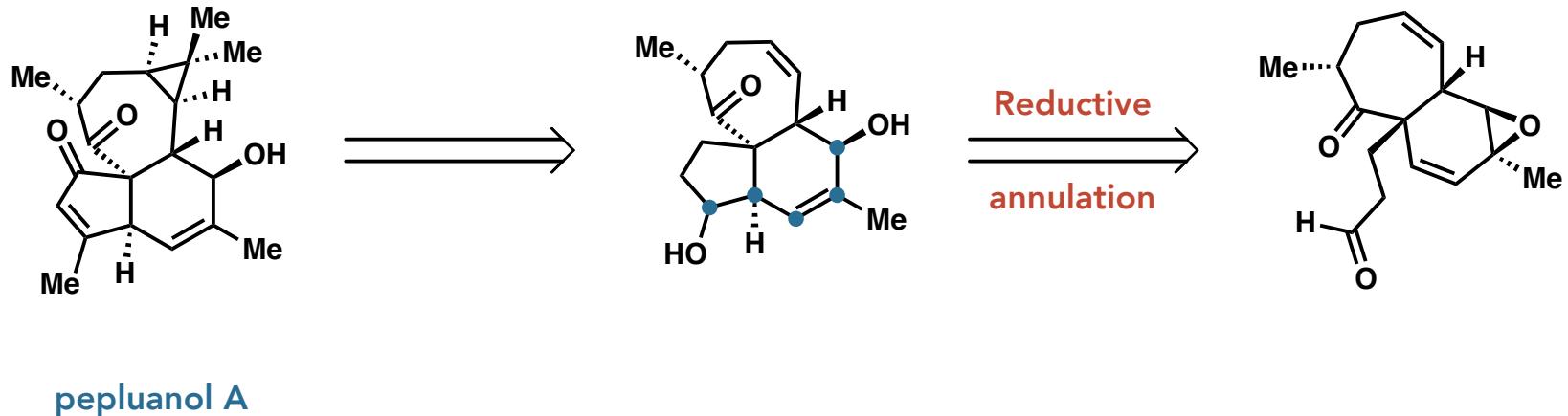
Molander, G. A.; Shakya, S. R. *J. Org. Chem.* **1996**, *61*, 5885.  
Aurrecochea, J. M.; Iztueta, E. *Tetrahedron Lett.* **1995**, *36*, 7129.  
Ding, H. et al. *Angew. Chem. Int. Ed.* **2017**, *56*, 8898.

# Ding's Reductive Annulation Strategy

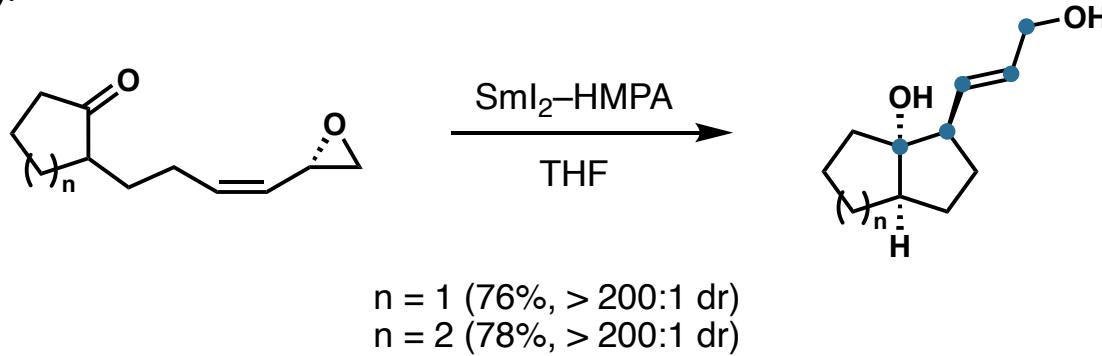


Molander, G. A.; Shakya, S. R. *J. Org. Chem.* **1996**, 61, 5885.  
Aurrecoechea, J. M.; Iztueta, E. *Tetrahedron Lett.* **1995**, 36, 7129.  
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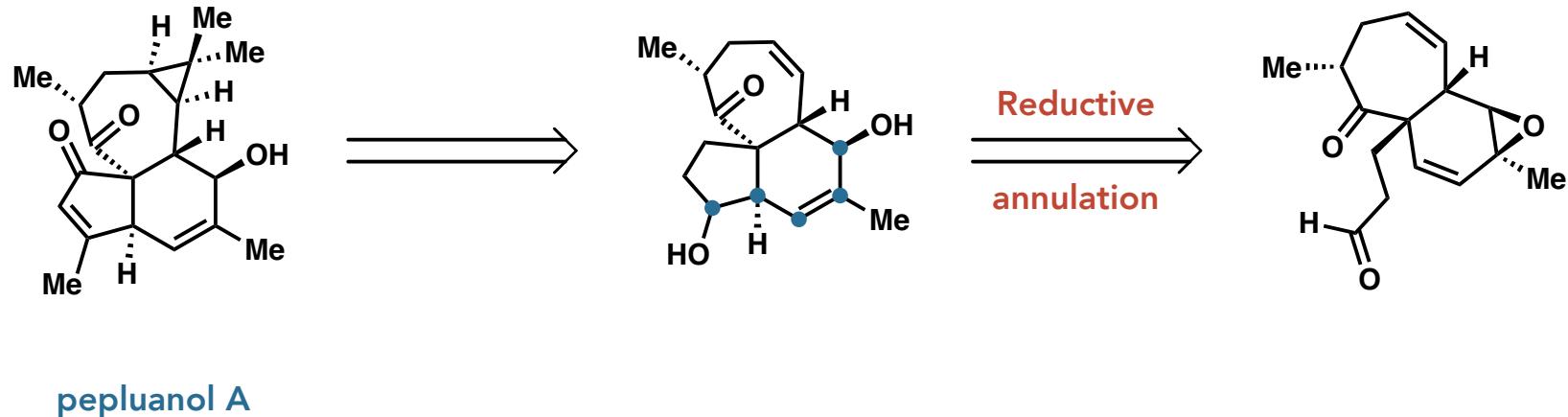
# Ding's Reductive Annulation Strategy



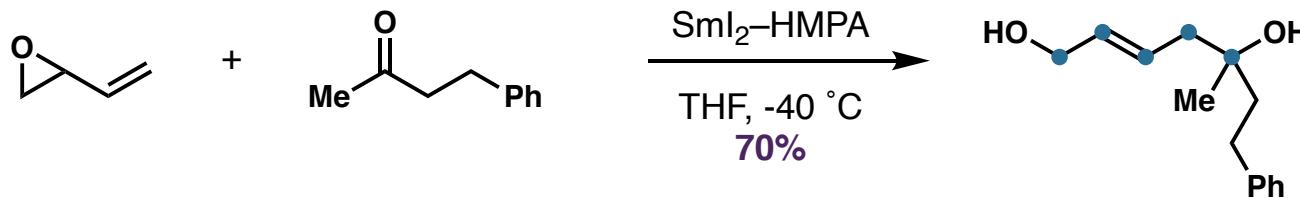
Molander (1996):



# Ding's Reductive Annulation Strategy



Aurrecoechea (1995):

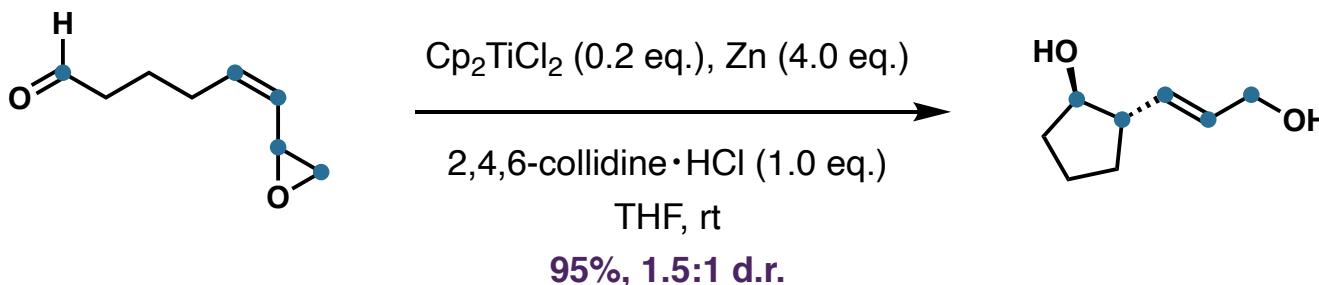


Molander, G. A.; Shakya, S. R. *J. Org. Chem.* **1996**, *61*, 5885.

Aurrecoechea, J. M.; Iztueta, E. *Tetrahedron Lett.* **1995**, *36*, 7129.

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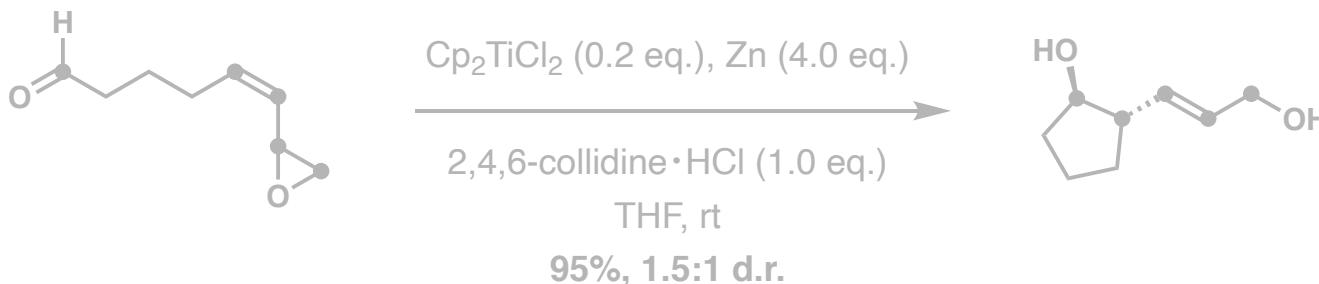
# Ding's Reductive Annulation Strategy



**Other conditions:** SmI<sub>2</sub>-HMPA; *n*-Bu<sub>3</sub>SnH/AIBN; *n*-Bu<sub>3</sub>SnH/Et<sub>3</sub>B/O<sub>2</sub>; Pd(PPh<sub>3</sub>)<sub>4</sub>/SmI<sub>2</sub>, CrCl<sub>2</sub>/Lil; SnCl<sub>2</sub>/*n*-Bu<sub>4</sub>NBr; LiDBB

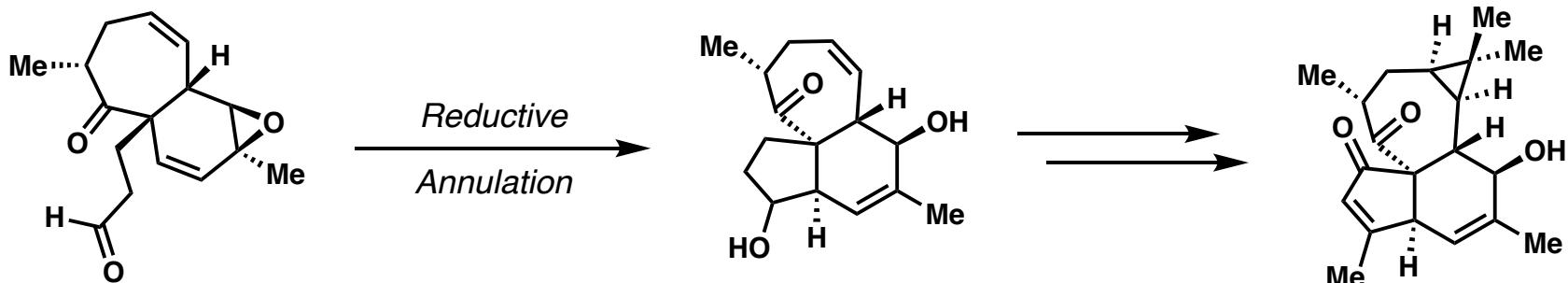
9 examples  
73–93%, up to 8:1 dr

# Ding's Reductive Annulation Strategy



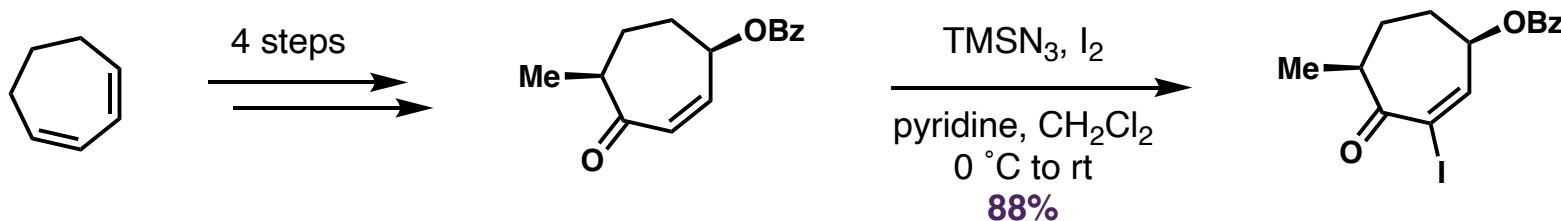
Other conditions:  $\text{SmI}_2$ -HMPA;  $n\text{-Bu}_3\text{SnH}/\text{AIBN}$ ;  $n\text{-Bu}_3\text{SnH}/\text{Et}_3\text{B}/\text{O}_2$ ;  $\text{Pd}(\text{PPh}_3)_4/\text{SmI}_2$ ,  $\text{CrCl}_2/\text{LiI}$ ;  $\text{SnCl}_2/n\text{-Bu}_4\text{NBr}$ ; LiDBB

9 examples  
73–93%, up to 8:1 dr



- Molander, G. A.; Shakya, S. R. *J. Org. Chem.* **1996**, *61*, 5885.  
Aurrecoechea, J. M.; Iztueta, E. *Tetrahedron Lett.* **1995**, *36*, 7129.  
Ding, H. et al. *Angew. Chem. Int. Ed.* **2017**, *56*, 8898.

# Assembling the [5.4.0]-Ring System



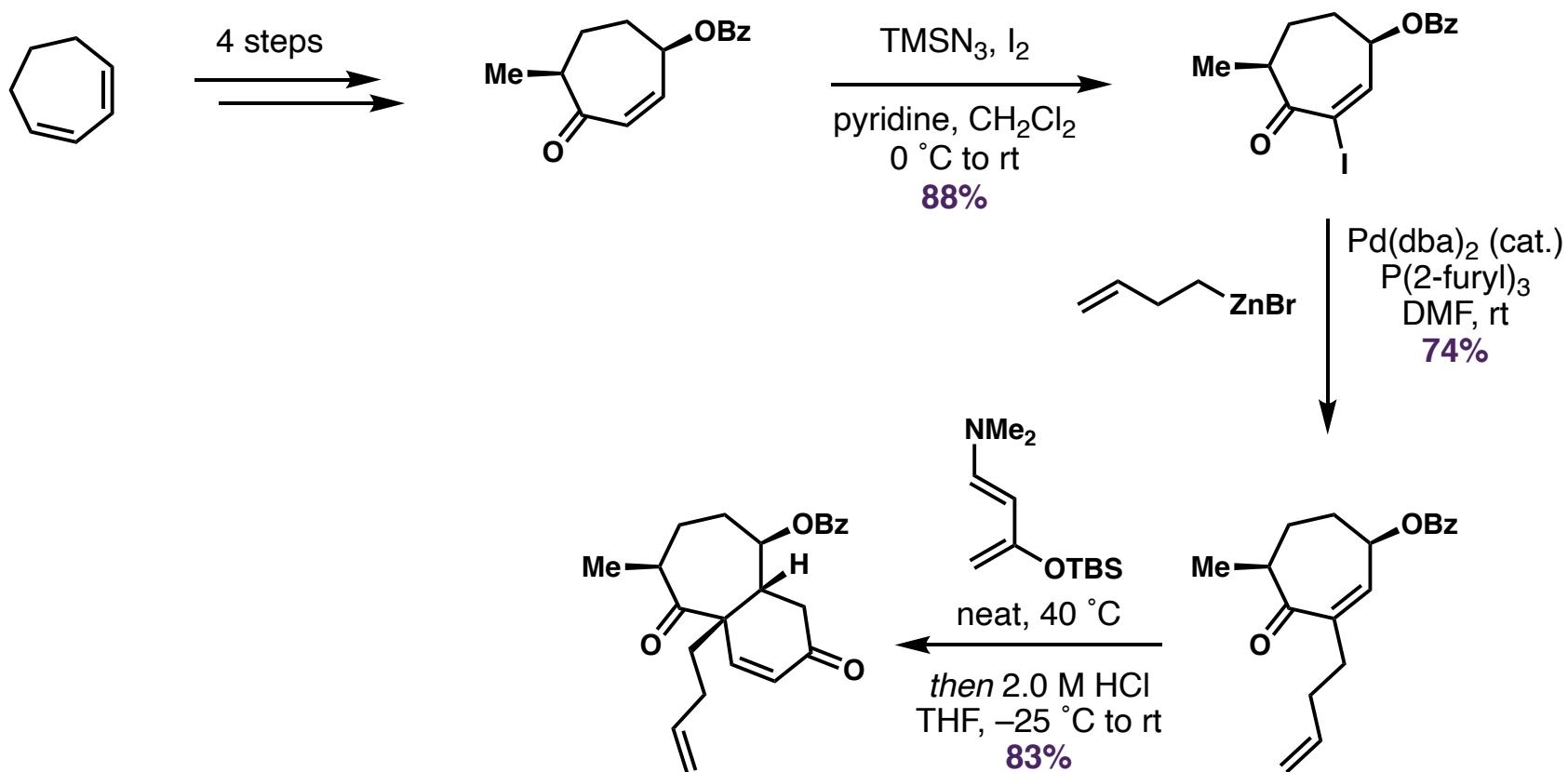
Pearson, A. J.; Bansal, H. S. *Tetrahedron Lett.* **1986**, 27, 283.

Danishefsky, S. J. et al. *J. Am. Chem. Soc.* **2008**, 130, 13765.

Rawal, V. H. et al. *Angew. Chem. Int. Ed.* **2008**, 47, 4373.

Ding, H. et al. *Angew. Chem. Int. Ed.* **2017**, 56, 8898.

# Assembling the [5.4.0]-Ring System



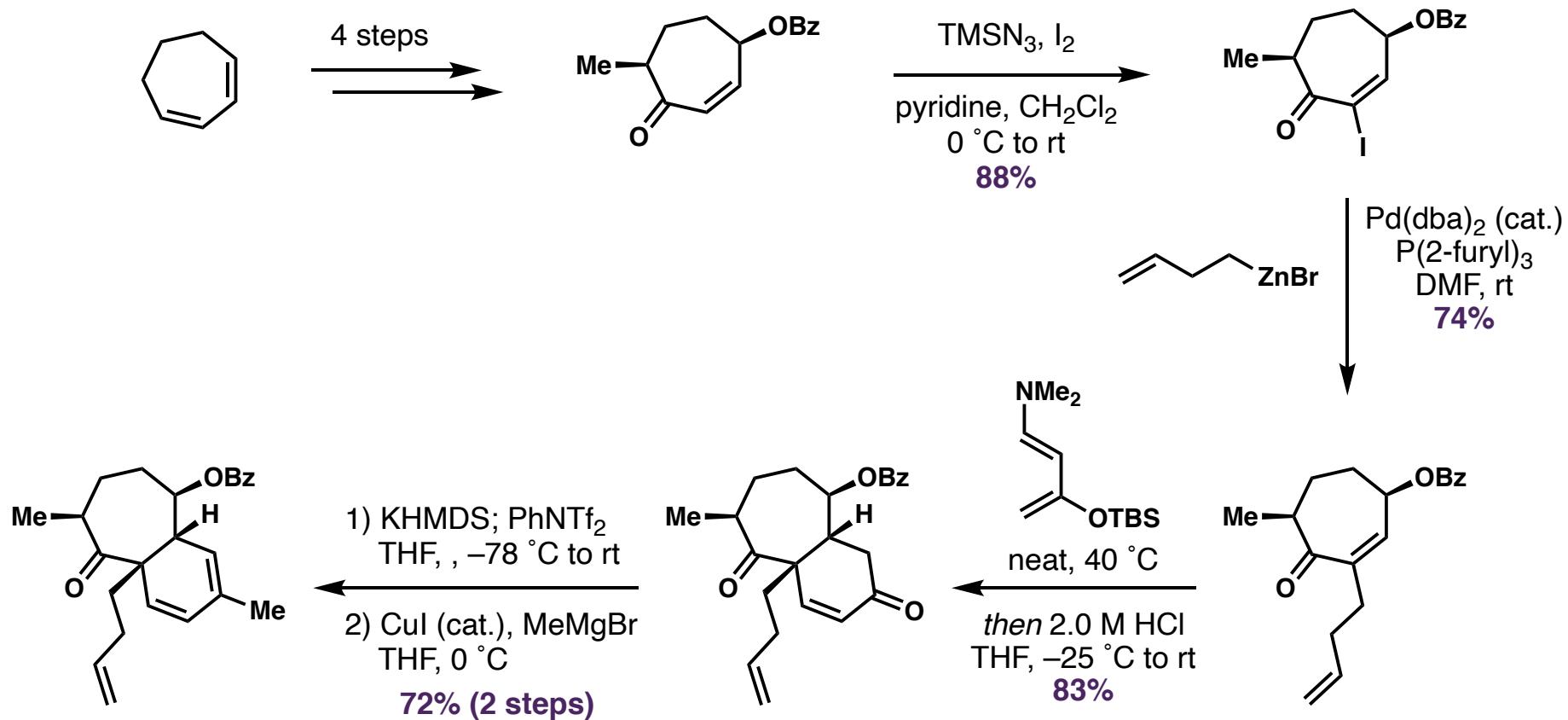
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# Assembling the [5.4.0]-Ring System



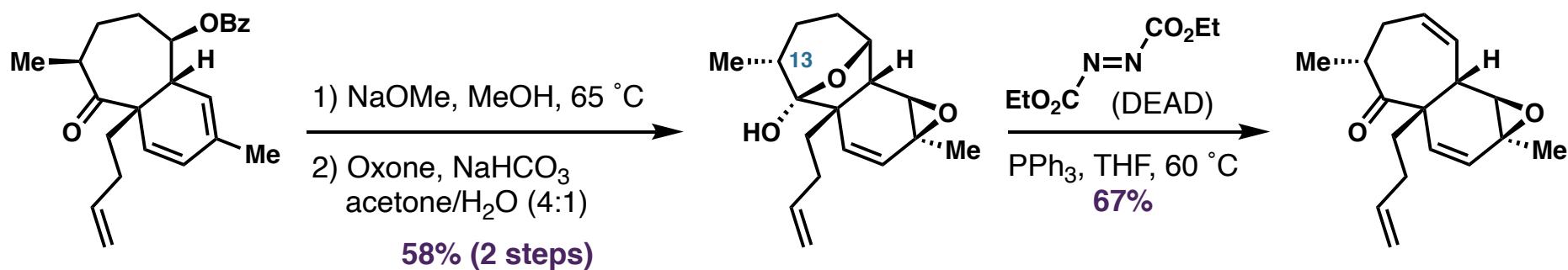
Pearson, A. J.; Bansal, H. S. *Tetrahedron Lett.* **1986**, 27, 283.

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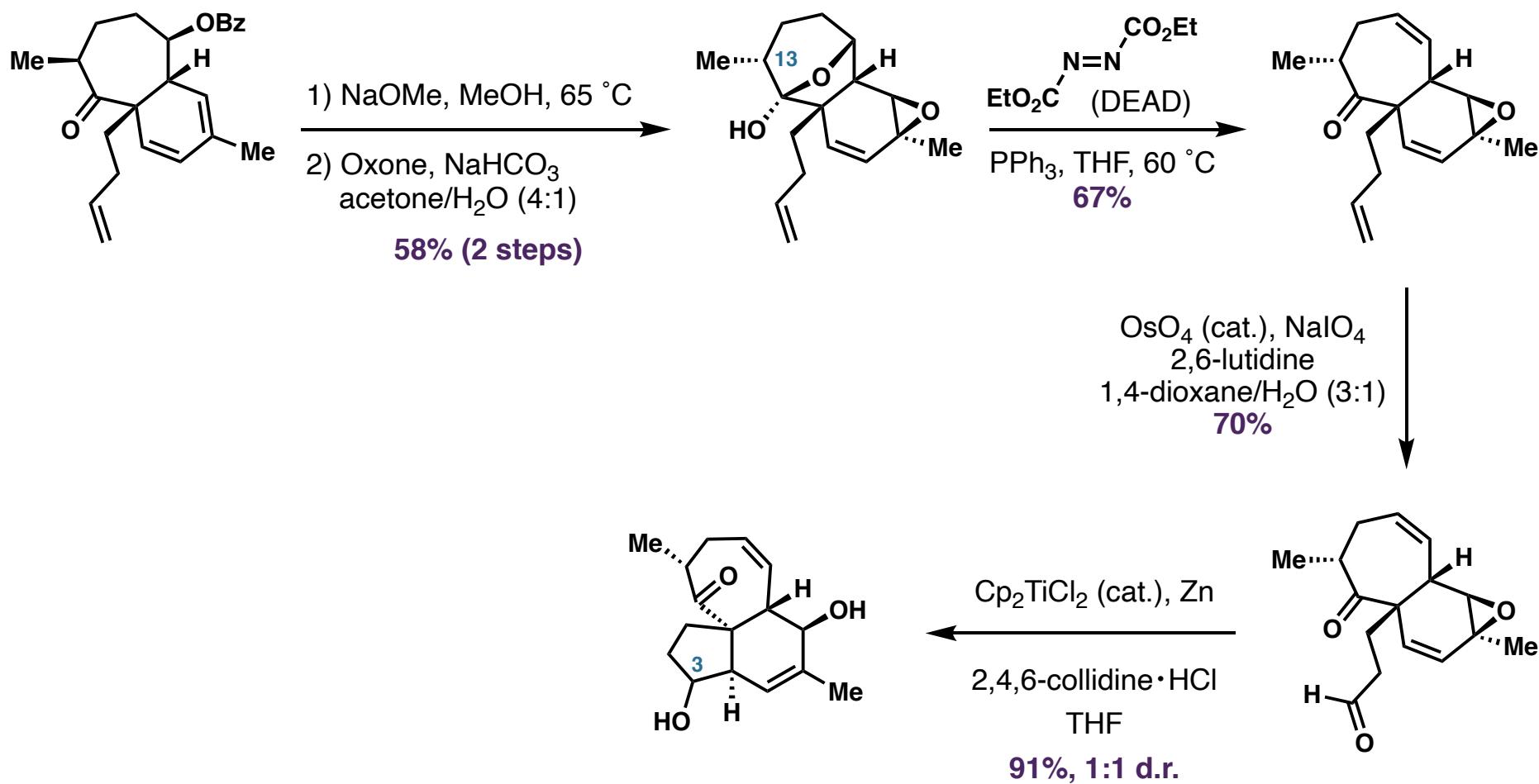
Rawal, V. H. et al. *Angew. Chem. Int. Ed.* **2008**, 47, 4373.

Ding, H. et al. *Angew. Chem. Int. Ed.* **2017**, 56, 8898.

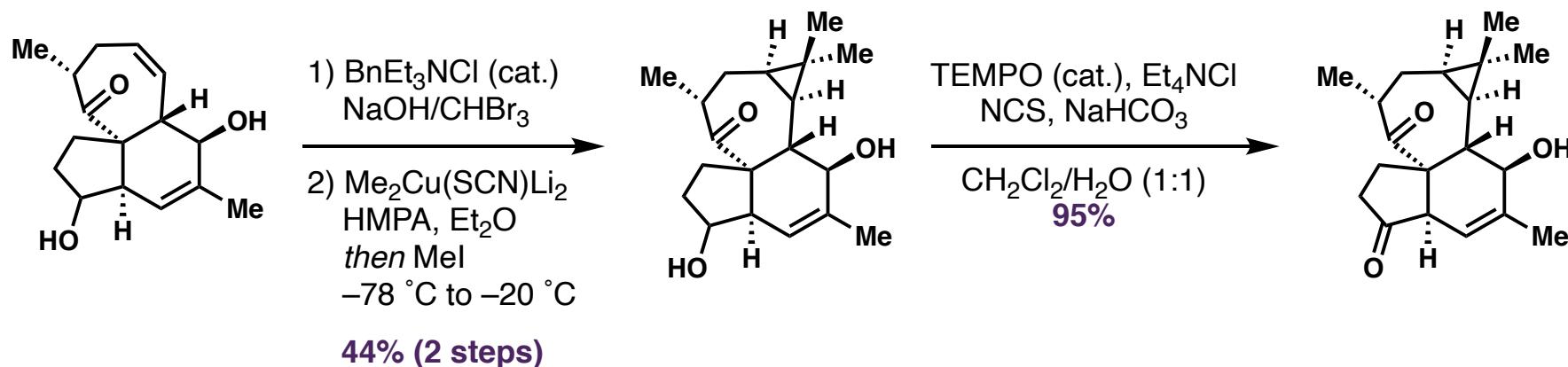
# Advancing to the Reductive Annulation



# Advancing to the Reductive Annulation



# Completing the Synthesis of Pepluanol A

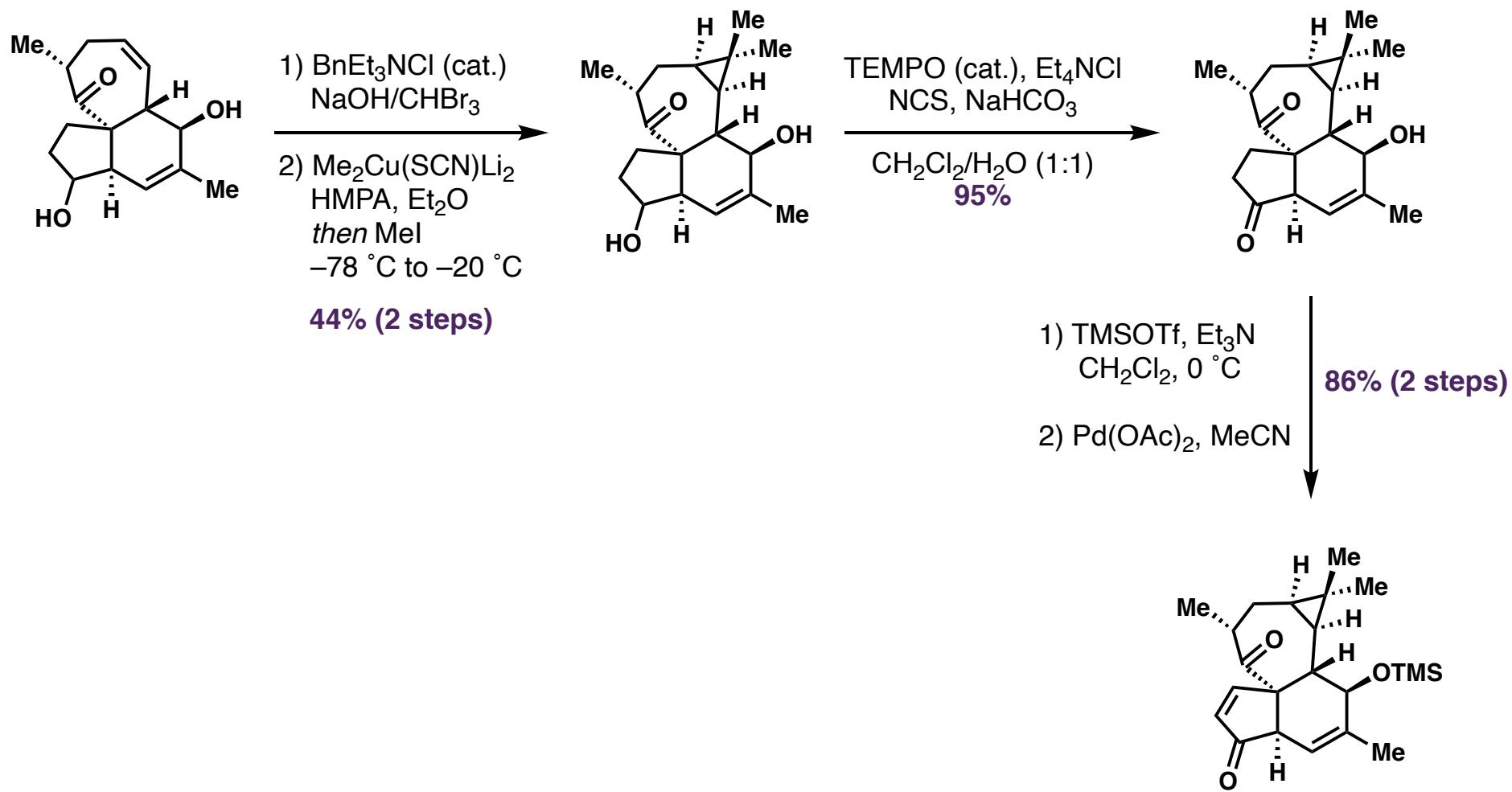


Winkler, J. D. et al. *J. Am. Chem. Soc.* **2002**, 124, 9726.

Einhorn, J. et al. *J. Org. Chem.* **1996**, 61, 7452.

Ding, H. et al. *Angew. Chem. Int. Ed.* **2017**, 56, 8898.

# Completing the Synthesis of Pepluanol A

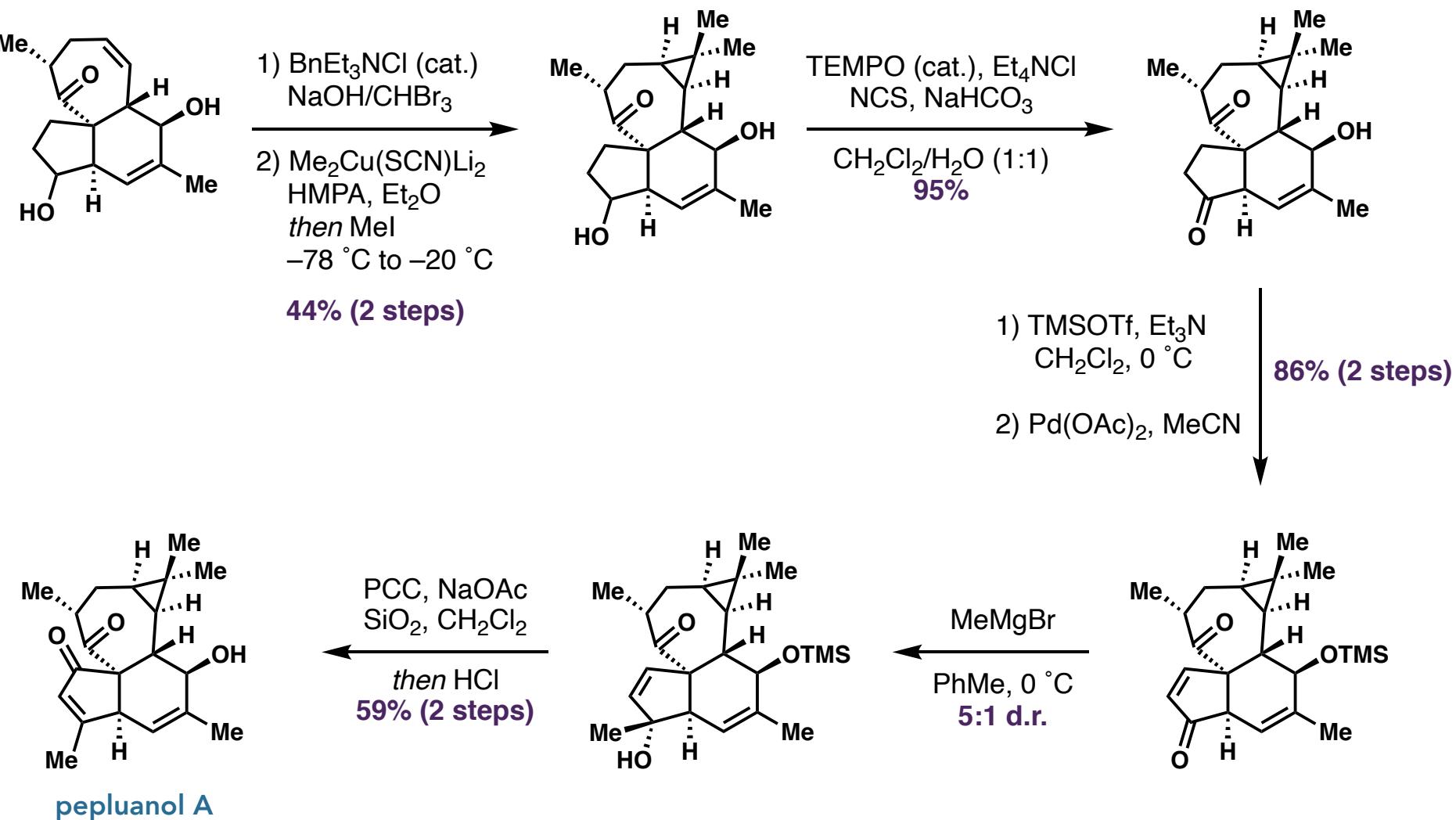


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# Completing the Synthesis of Pepluanol A

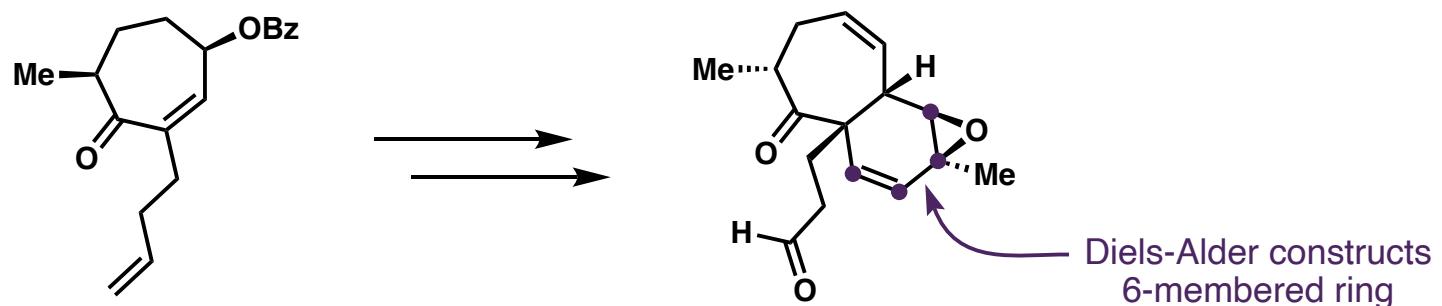


Winkler, J. D. et al. *J. Am. Chem. Soc.* **2002**, 124, 9726.

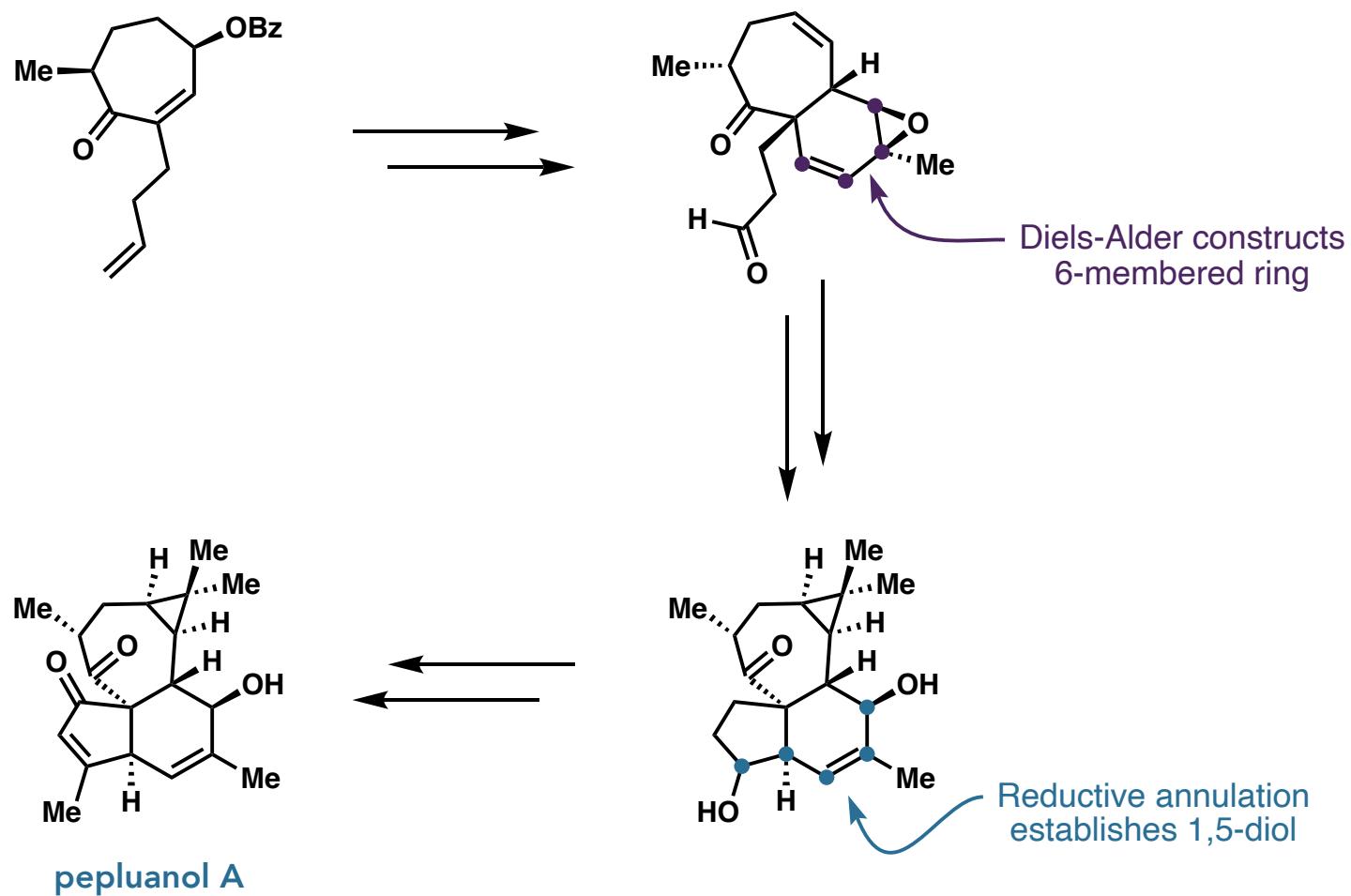
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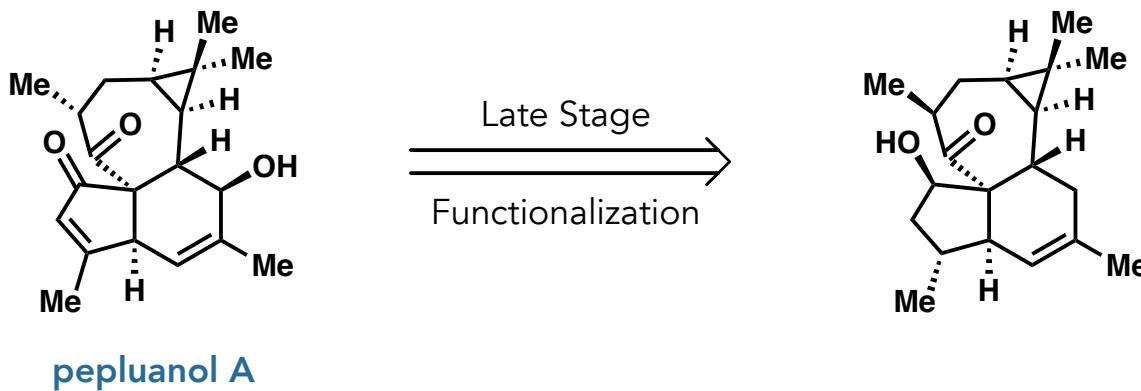
# Completing the Synthesis of Pepluanol A



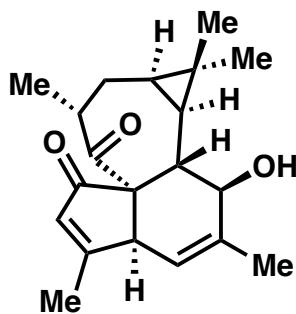
# Completing the Synthesis of Pepluanol A



# Gaich's IMDA Strategy

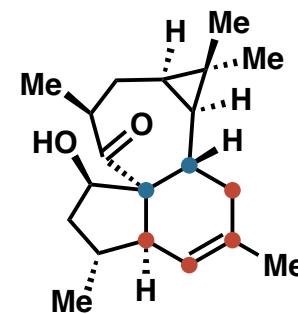


# Gaich's IMDA Strategy

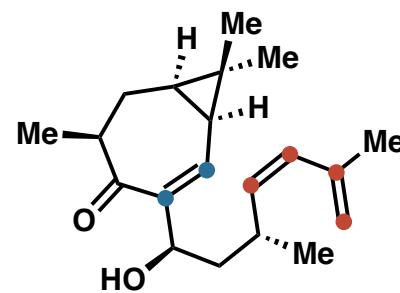


pepluanol A

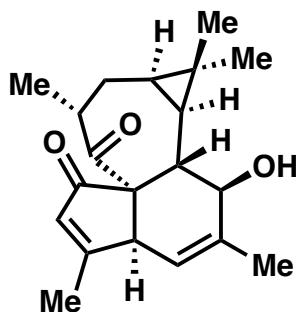
Late Stage  
Functionalization



Diels-Alder

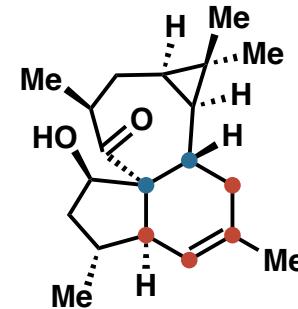


# Gaich's IMDA Strategy

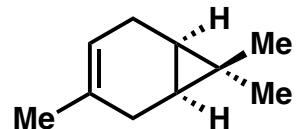


pepluanol A

Late Stage  
Functionalization

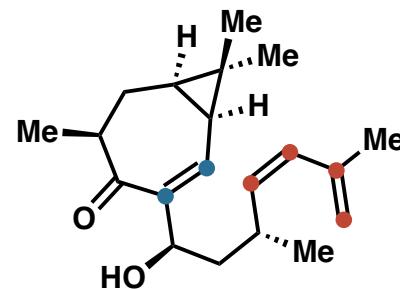


Diels-Alder

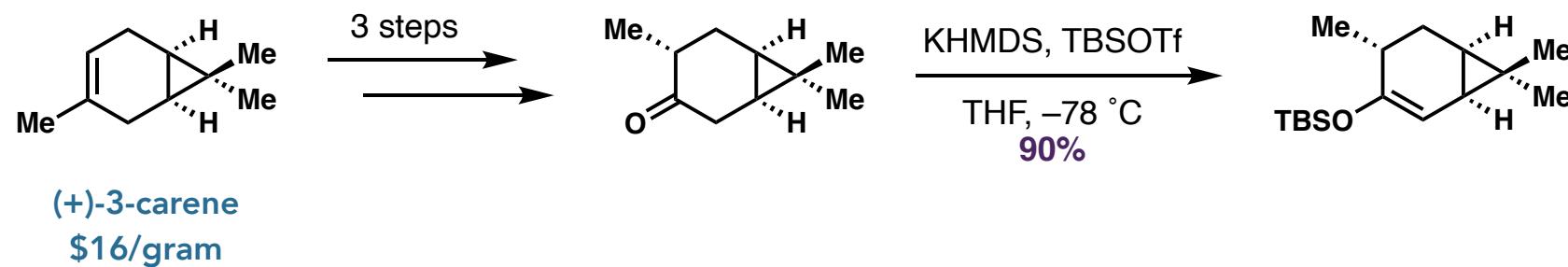


(+)-3-carene  
\$16/gram

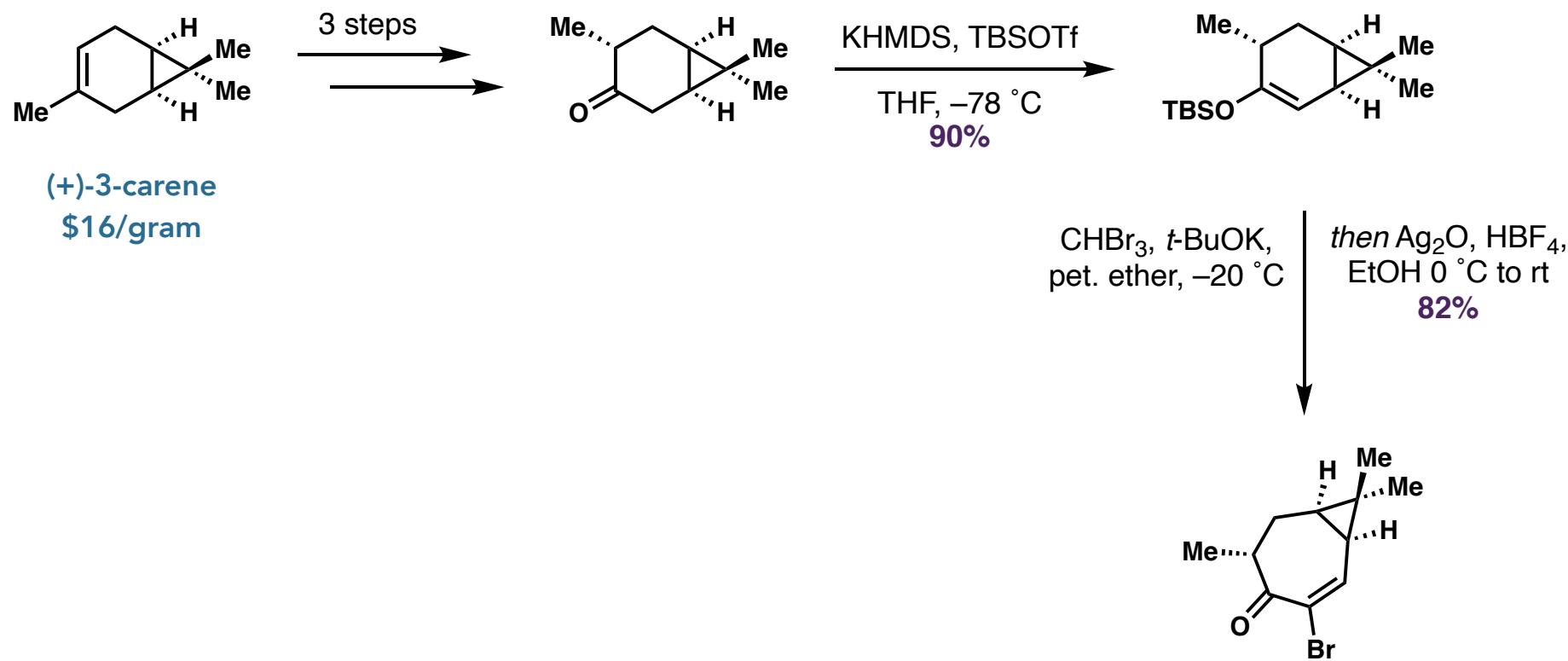
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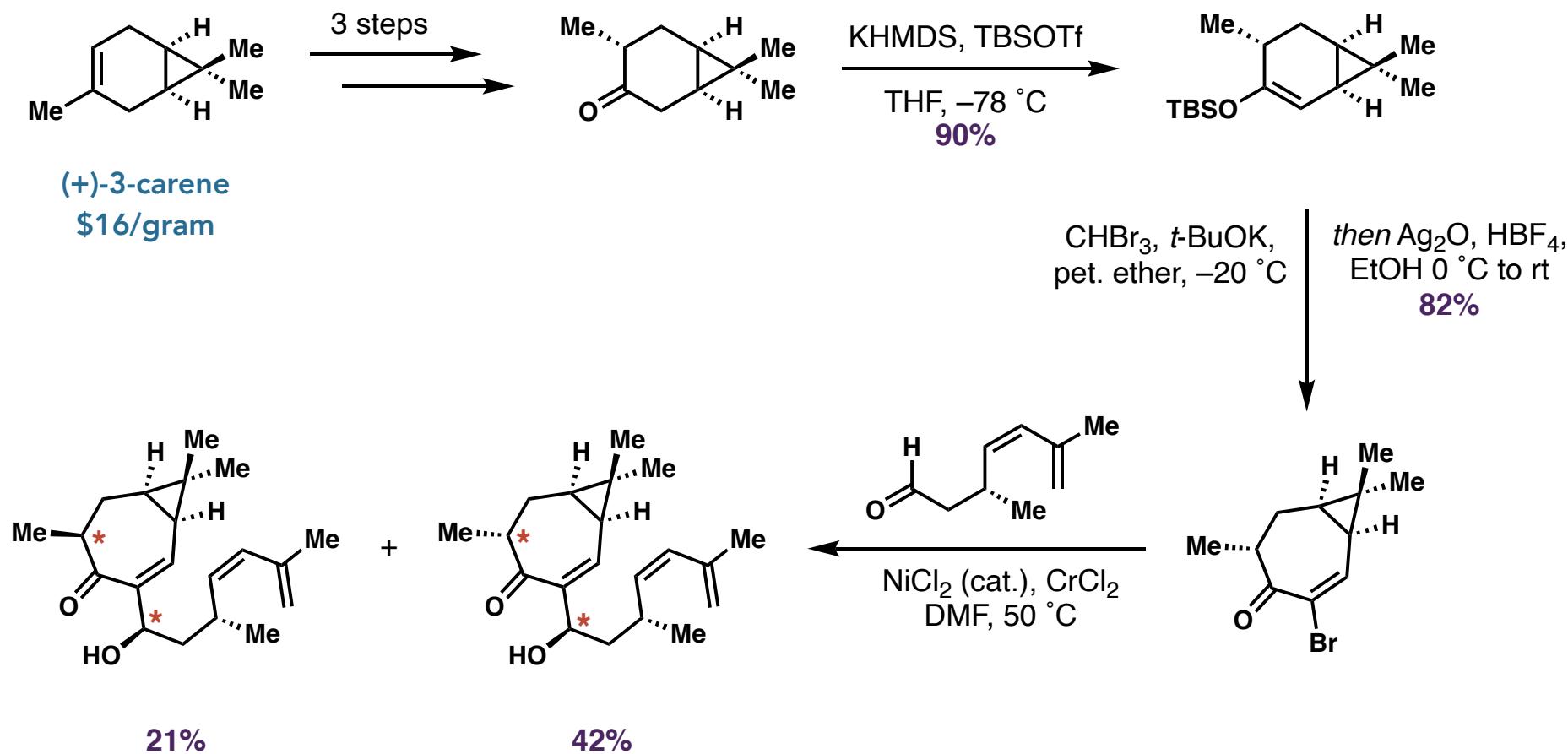
# Accessing a Functionalized Cycloheptenone



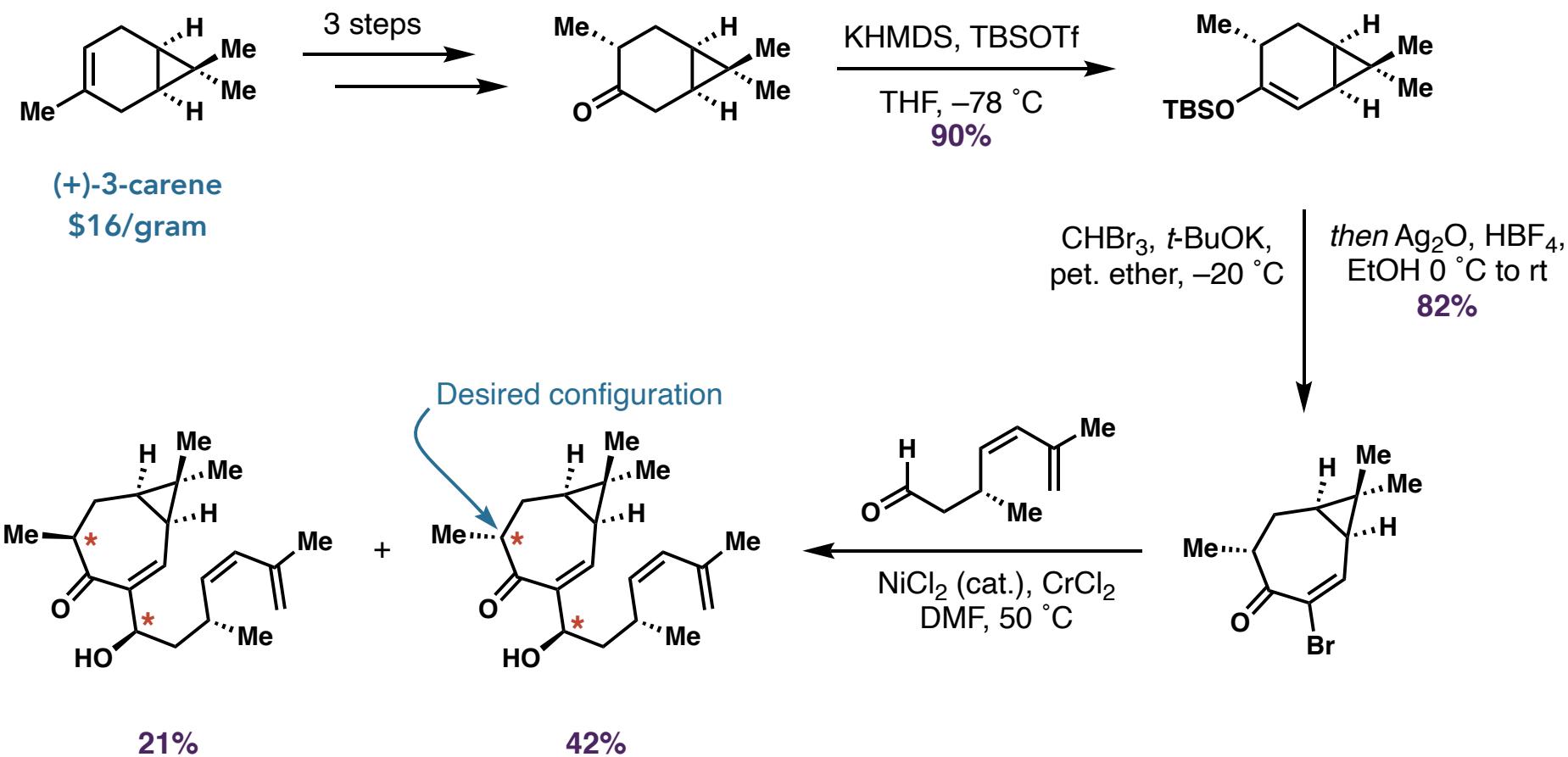
# Accessing a Functionalized Cycloheptenone



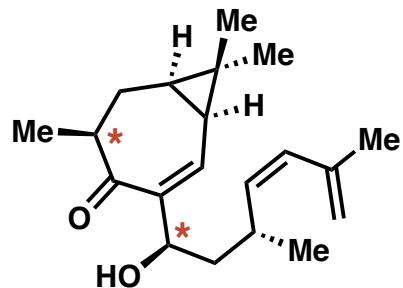
# Accessing a Functionalized Cycloheptenone



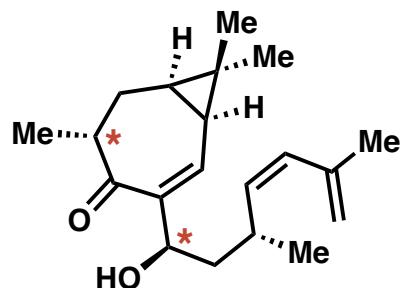
# Accessing a Functionalized Cycloheptenone



# Diels-Alder Attempts with the C-13 Epimers

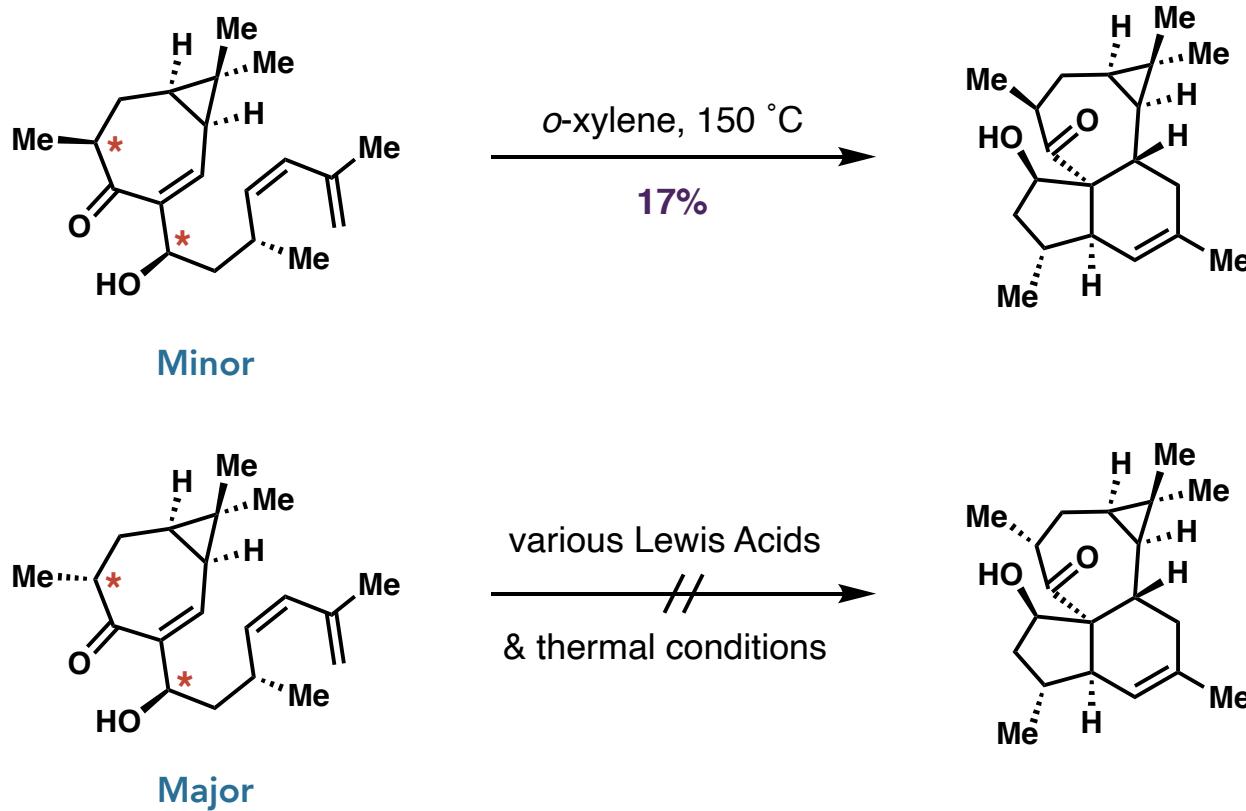


Minor



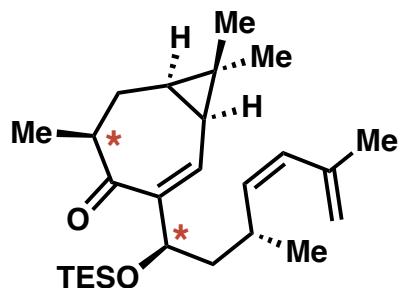
Major

# Diels-Alder Attempts with the C-13 Epimers

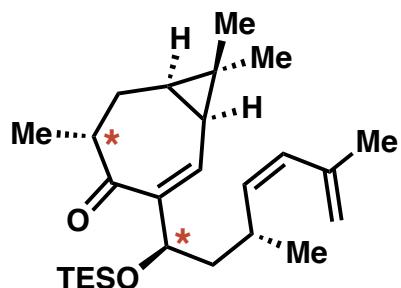


Only the minor isomer shows reactivity under various conditions

# Diels-Alder Attempts with the C-13 Epimers

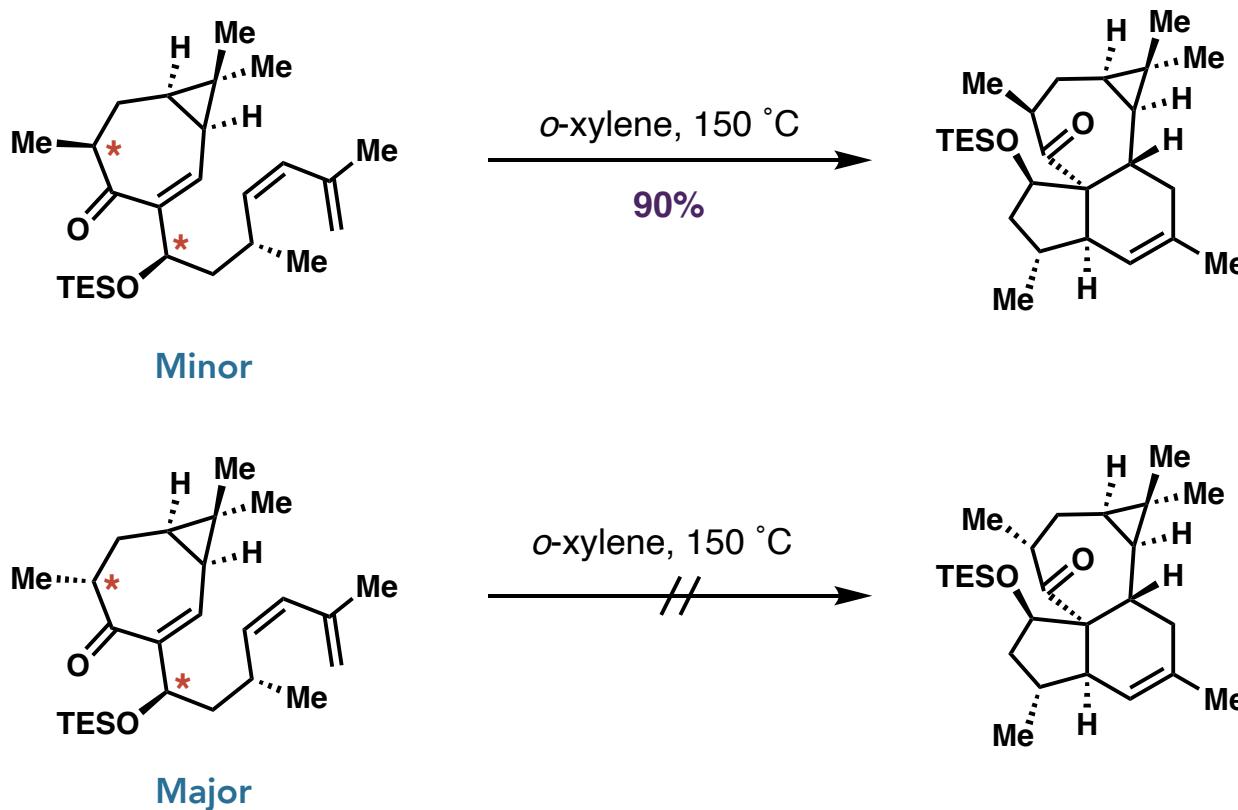


Minor



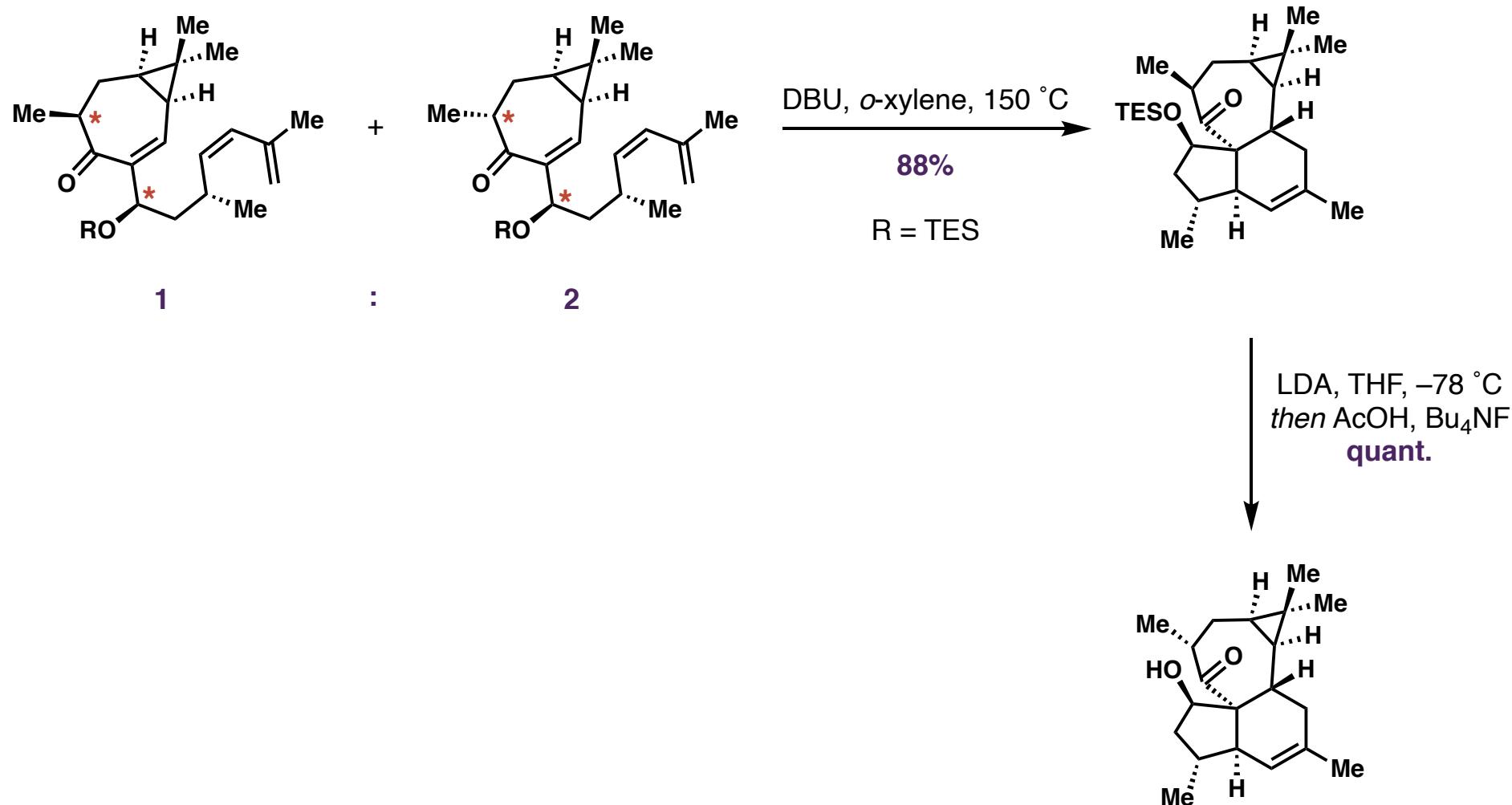
Major

# Diels-Alder Attempts with the C-13 Epimers

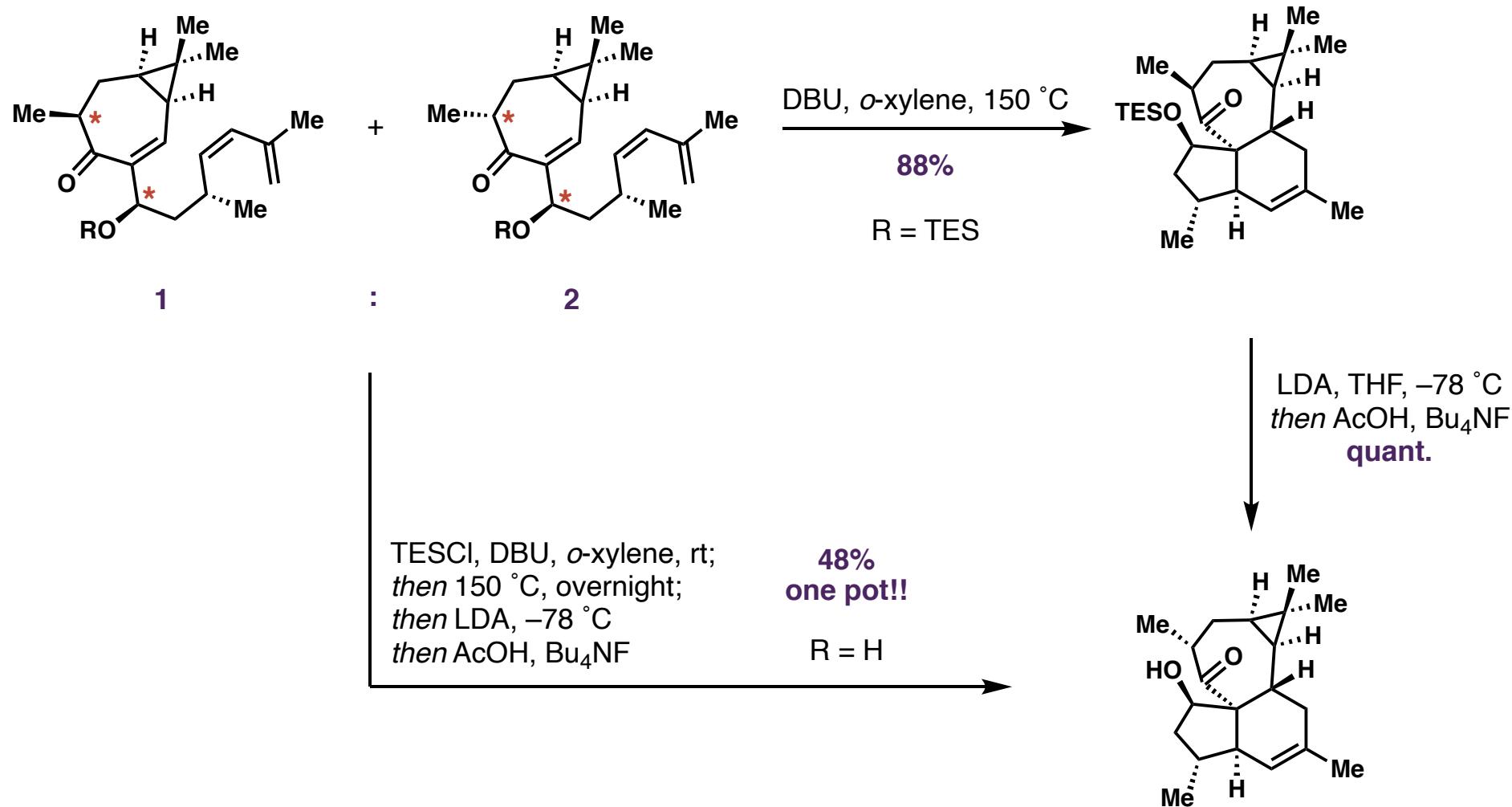


Only the minor isomer shows reactivity under thermal conditions  
DFT studies suggest the possibility of a Curtin–Hammett-driven stereoconvergent IMDA

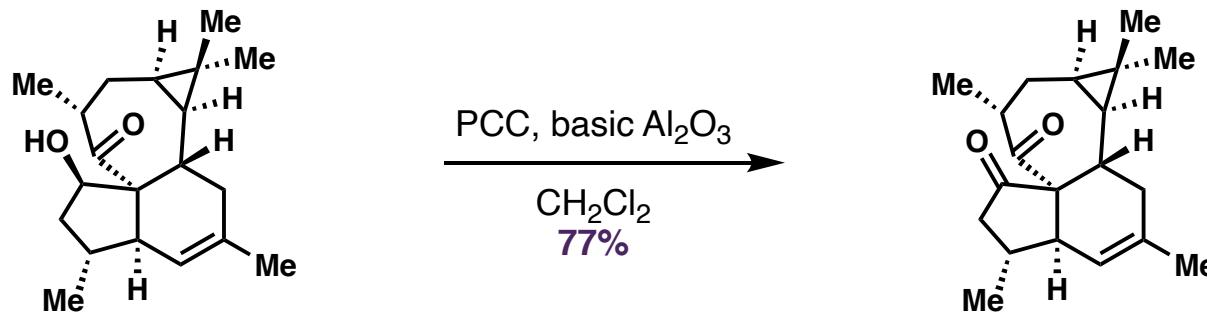
# Diels-Alder Attempts with the C-13 Epimers



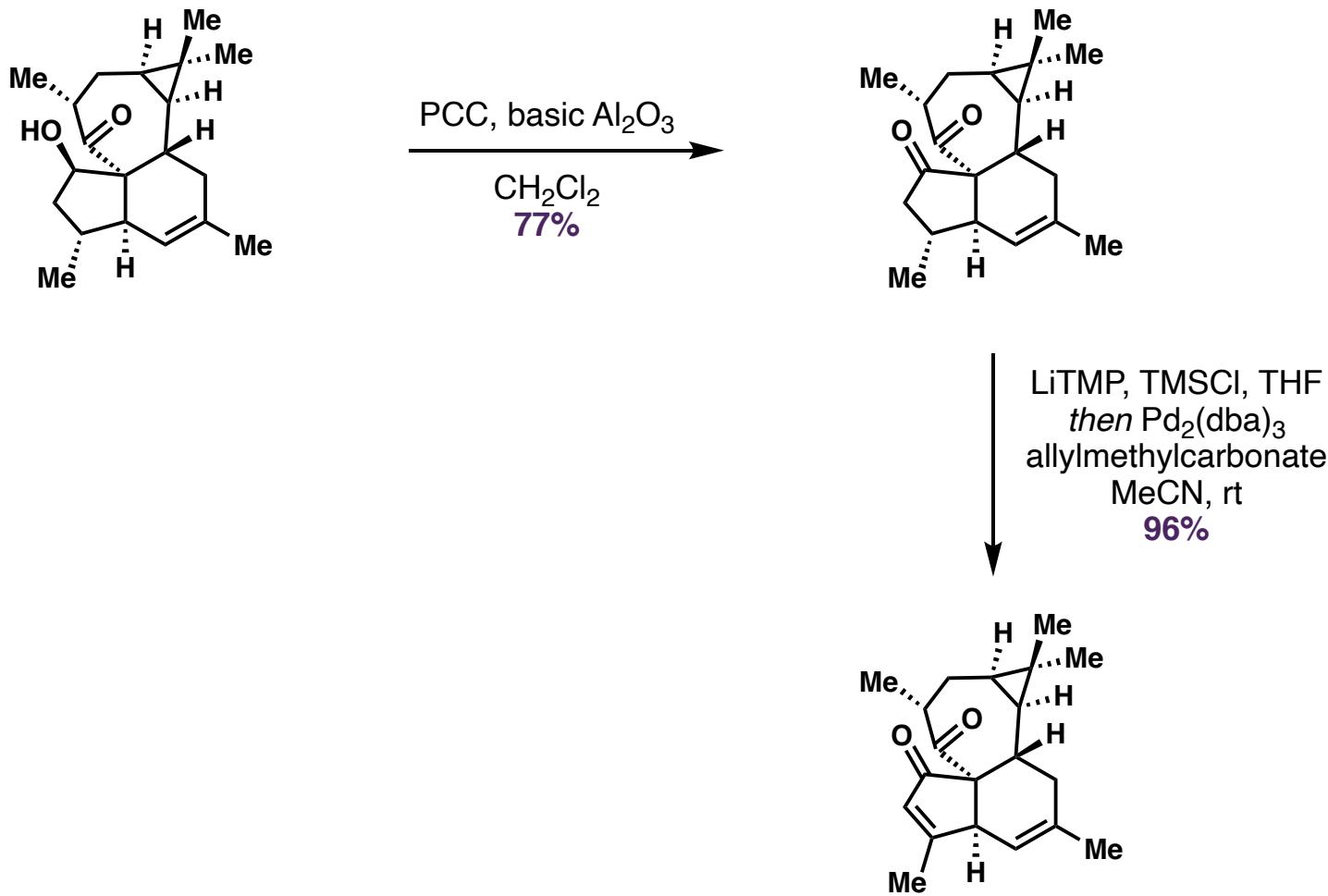
# Diels-Alder Attempts with the C-13 Epimers



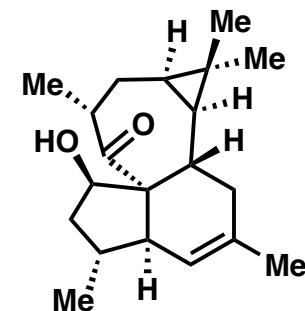
# Completing the Synthesis of (+)-Pepluanol A



# Completing the Synthesis of (+)-Pepluanol A

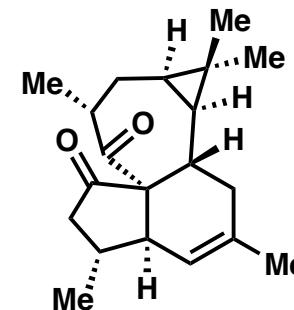


# Completing the Synthesis of (+)-Pepluanol A

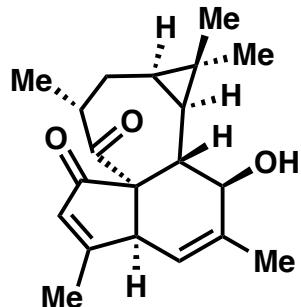


PCC, basic  $\text{Al}_2\text{O}_3$

$\text{CH}_2\text{Cl}_2$   
77%

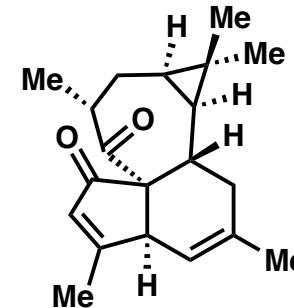


LiTMP, TMSCl, THF  
*then*  $\text{Pd}_2(\text{dba})_3$   
allylmethylcarbonate  
 $\text{MeCN}$ , rt  
96%



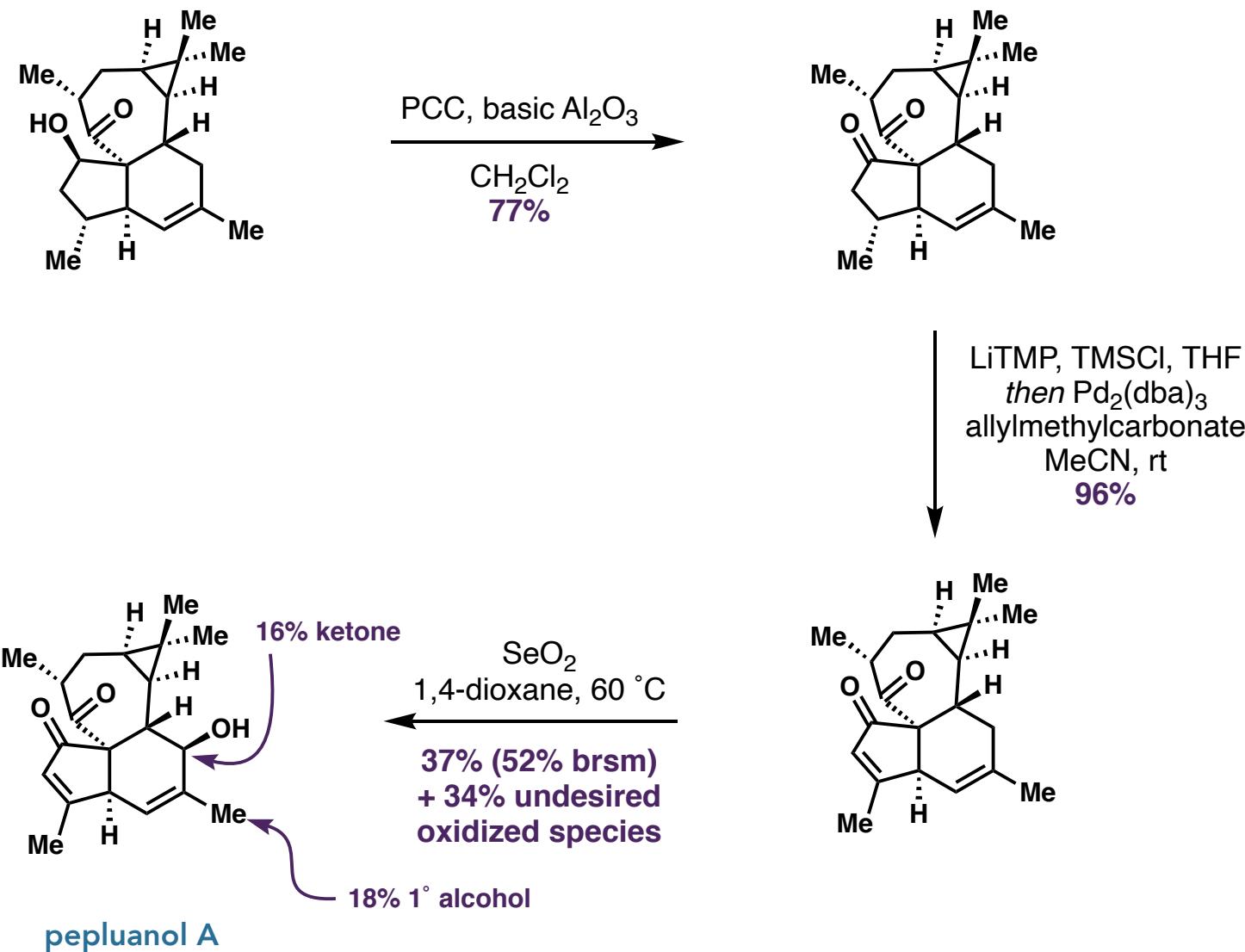
$\text{SeO}_2$   
1,4-dioxane, 60 °C

37% (52% brsm)  
+ 34% undesired  
oxidized species

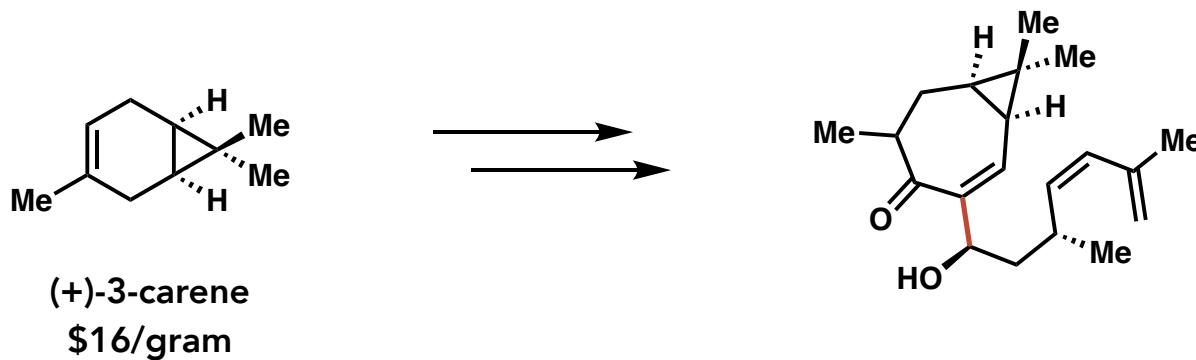


pepluanol A

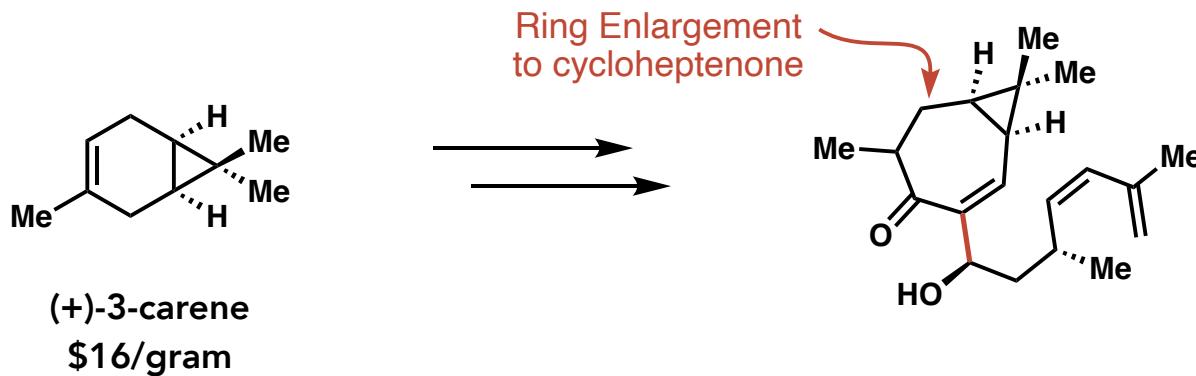
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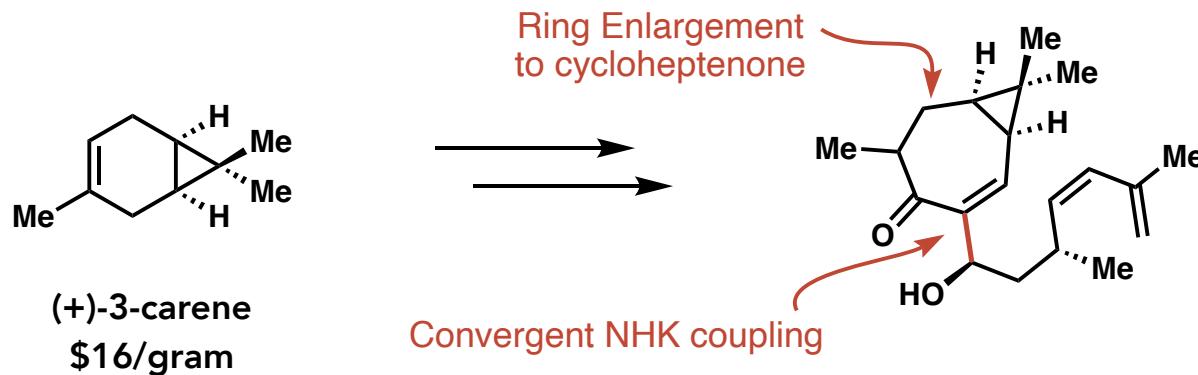
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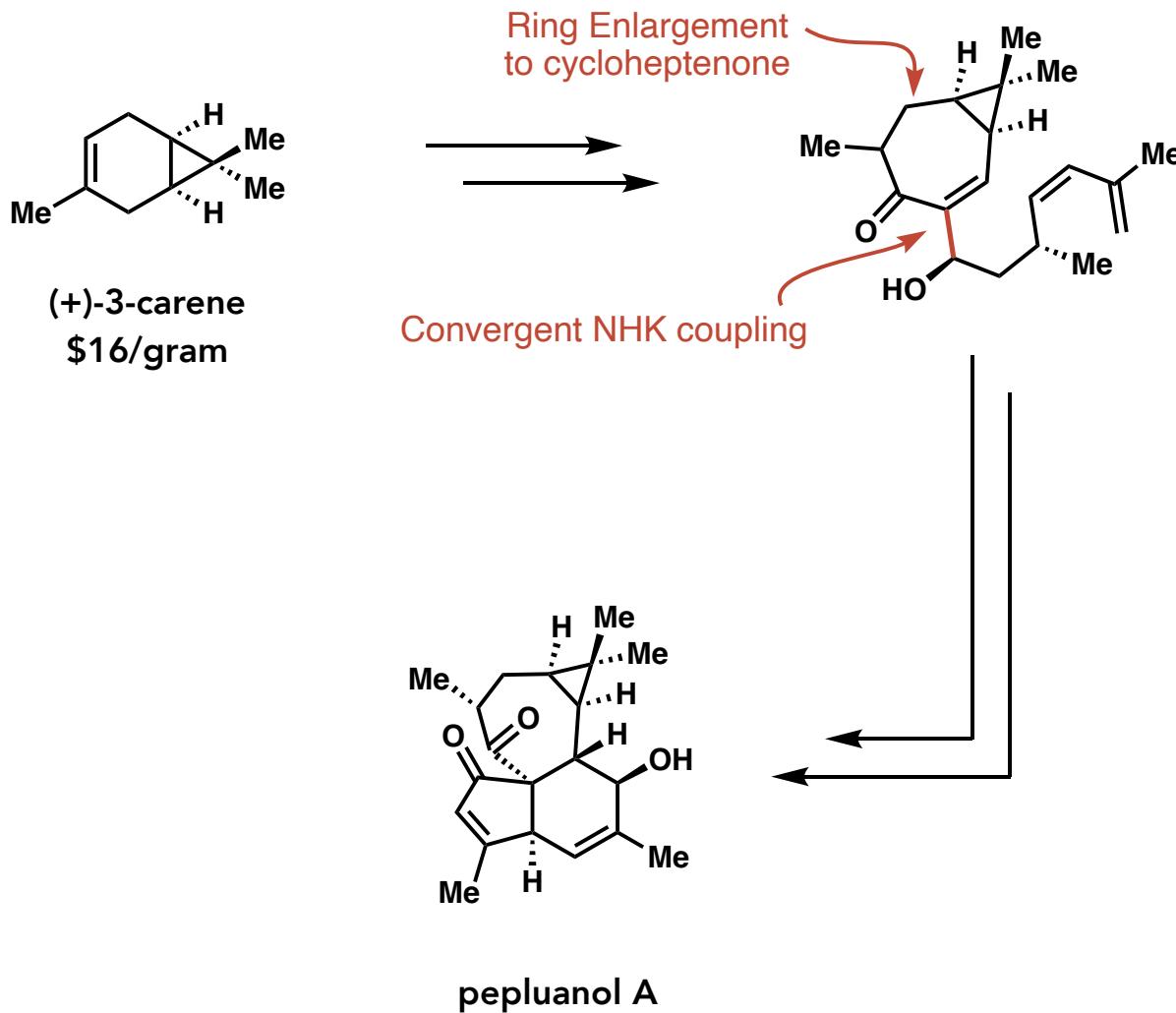
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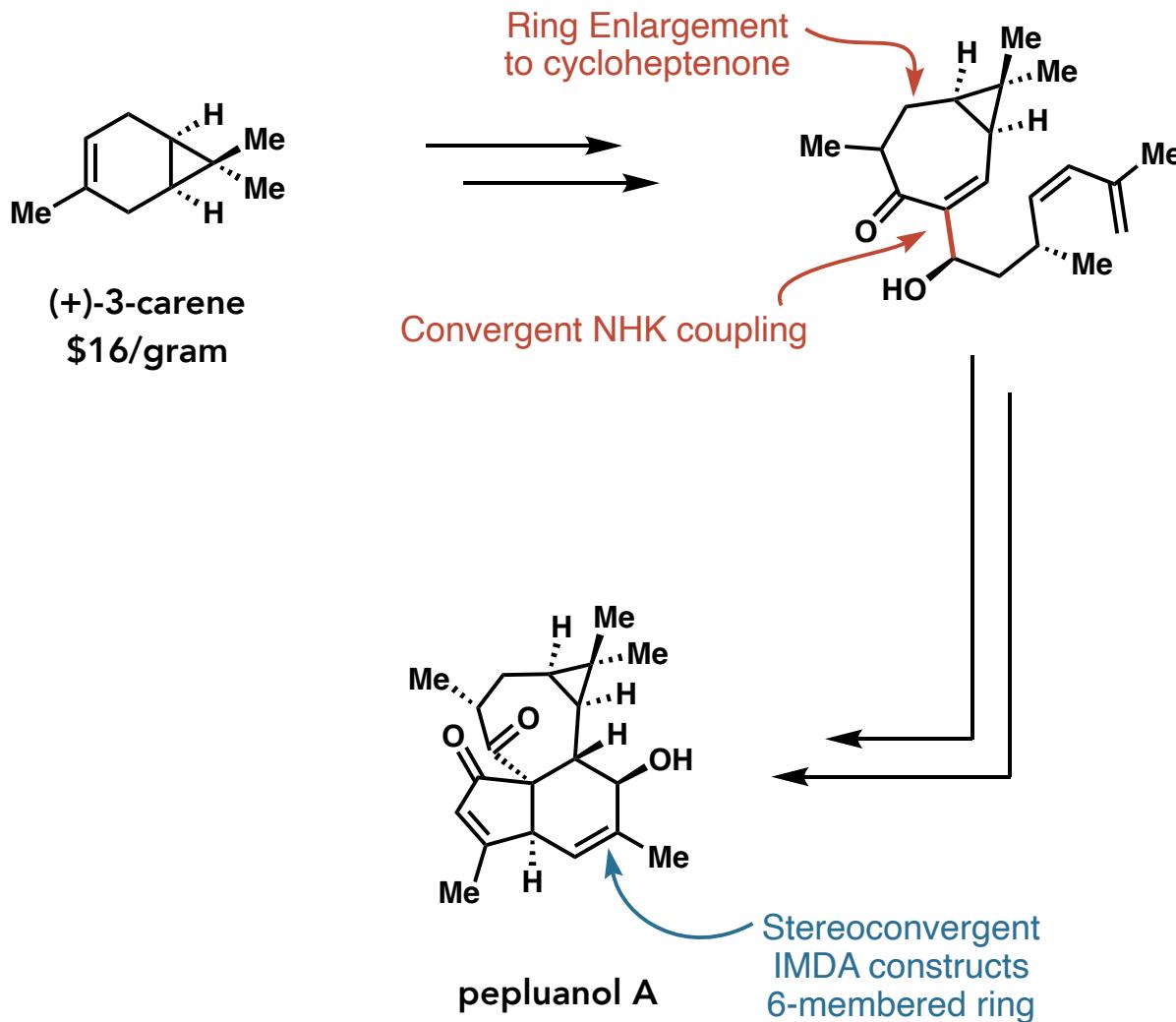
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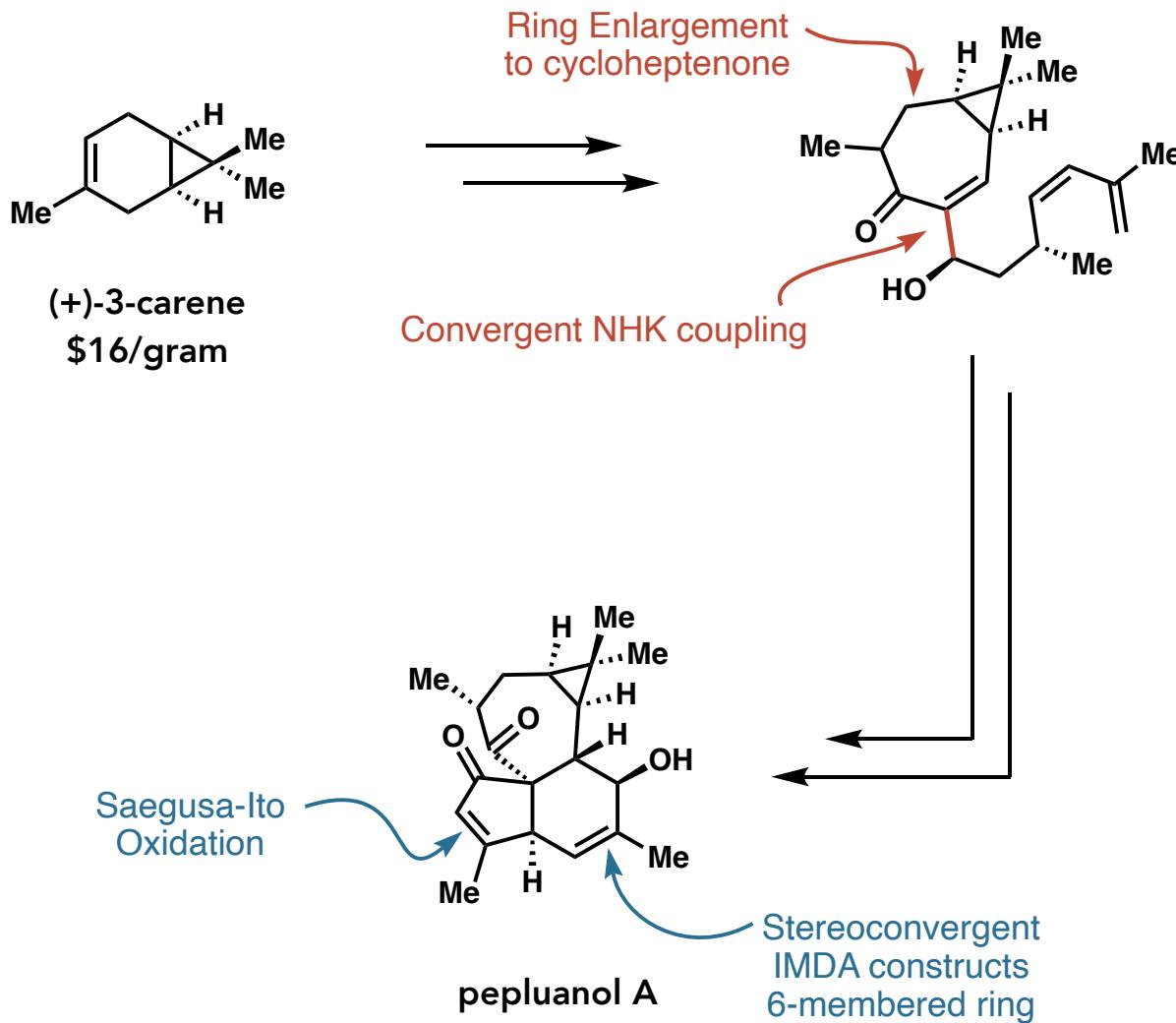
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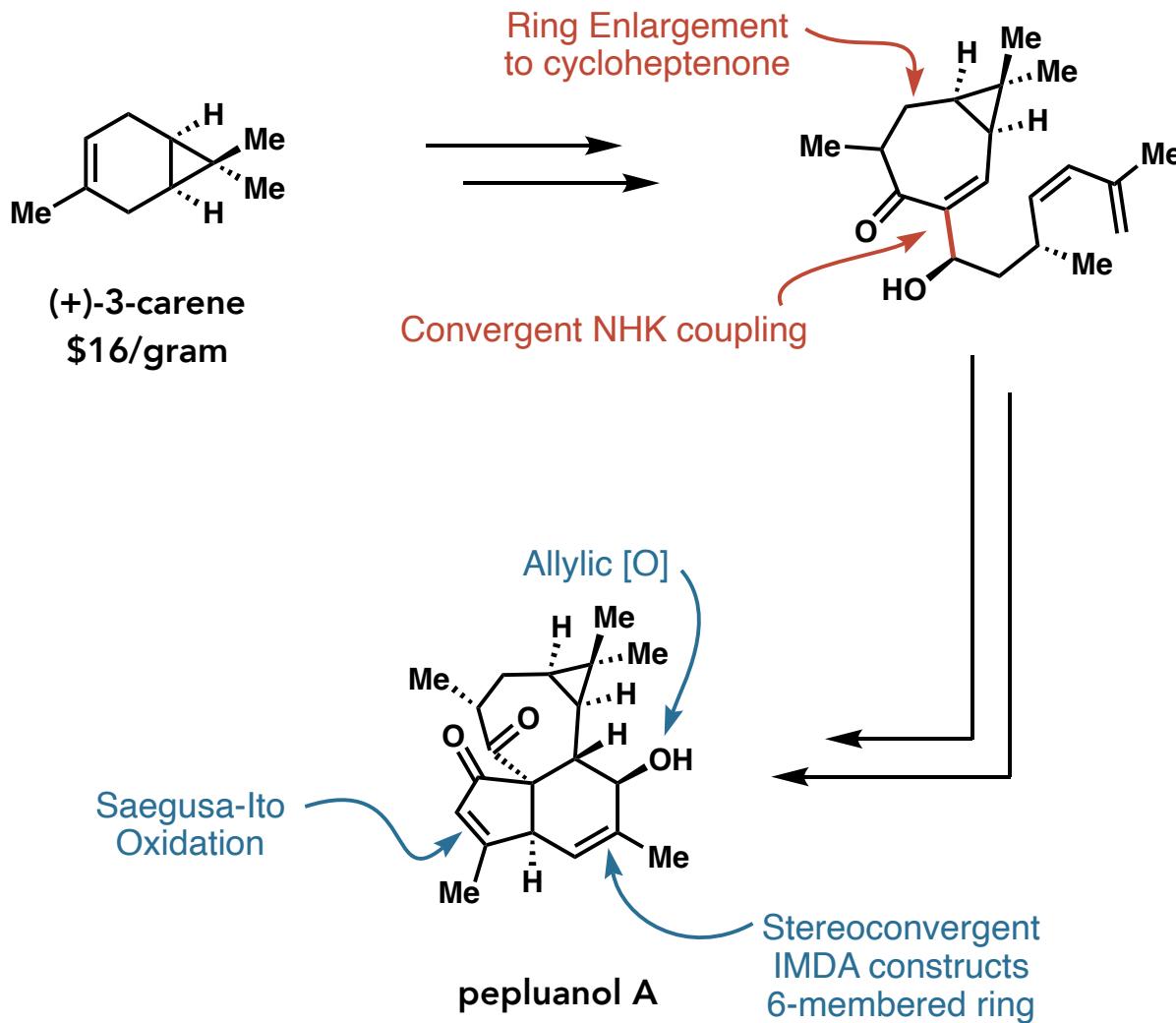
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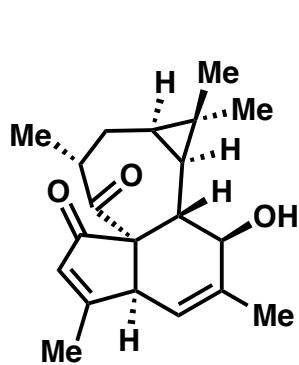
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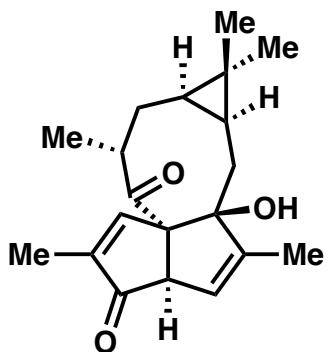
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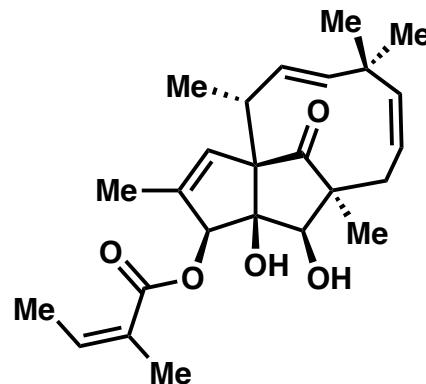
# Pepluanol Natural Products



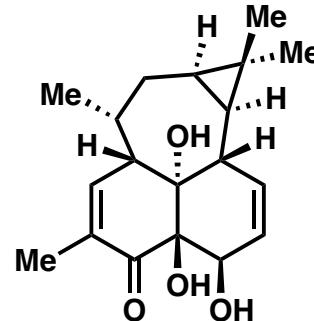
pepluanol A



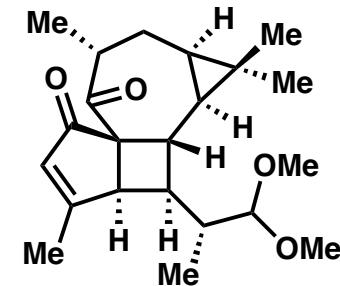
pepluanol B



pepluanol C



pepluanol D



pepluacetal

## Pepluanol A:

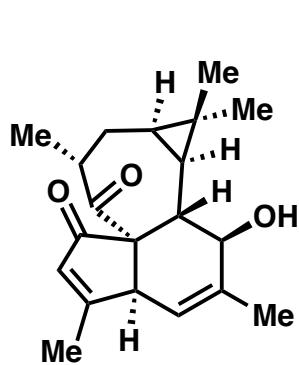
Xuan, J.; Lio, Z.; Zhu, A.; Rao, P.; Yu, L.; Ding, H.  
Zhejiang University  
*Angew. Chem. Int. Ed.* **2017**, 56, 8898–8901.

Yuan, P.; Gerlinger, C. K. G.; Herberger, J.; Gaich, T.  
University of Konstanz  
*J. Am. Chem. Soc.* **2021**, 143, 11934–11938.

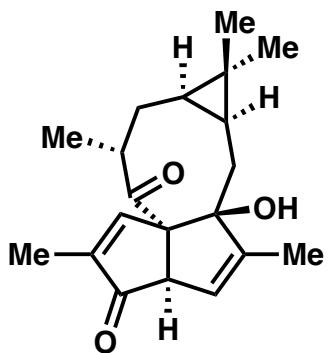
## Pepluanol B:

Zhang, J.; Liu, M.; Wu, C.; Zhao, G.; Chen, P.; Zhou, L.; Xie, X.; Fang, R.; Li, H.; She, X.  
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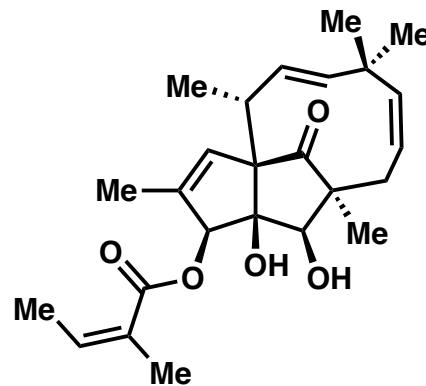
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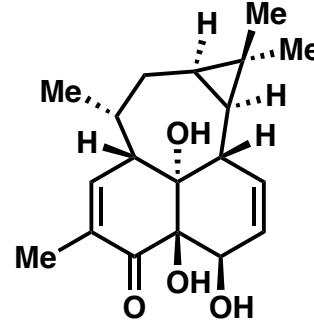
pepluanol A



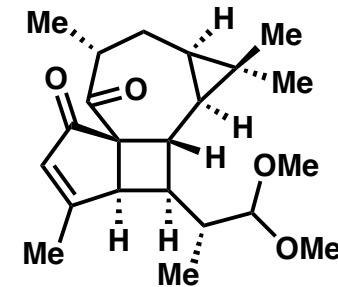
pepluanol B



pepluanol C



pepluanol D



pepluacetal

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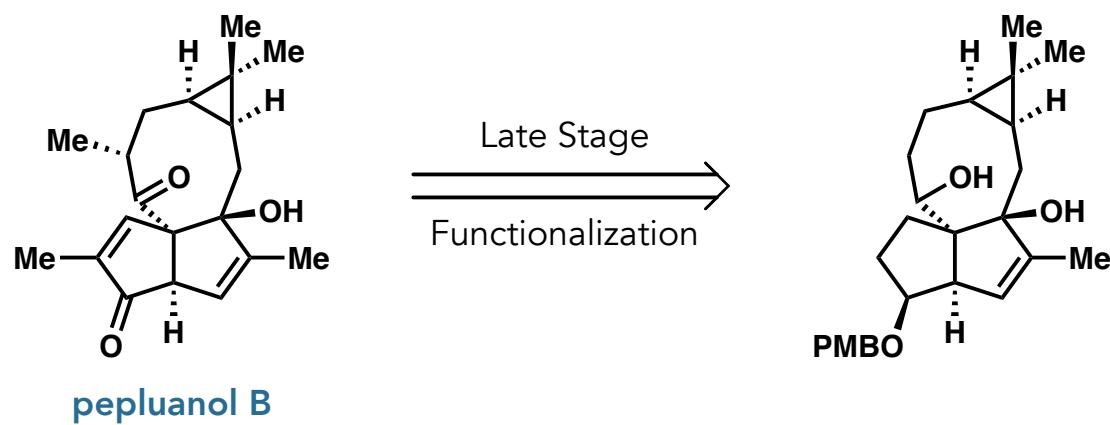
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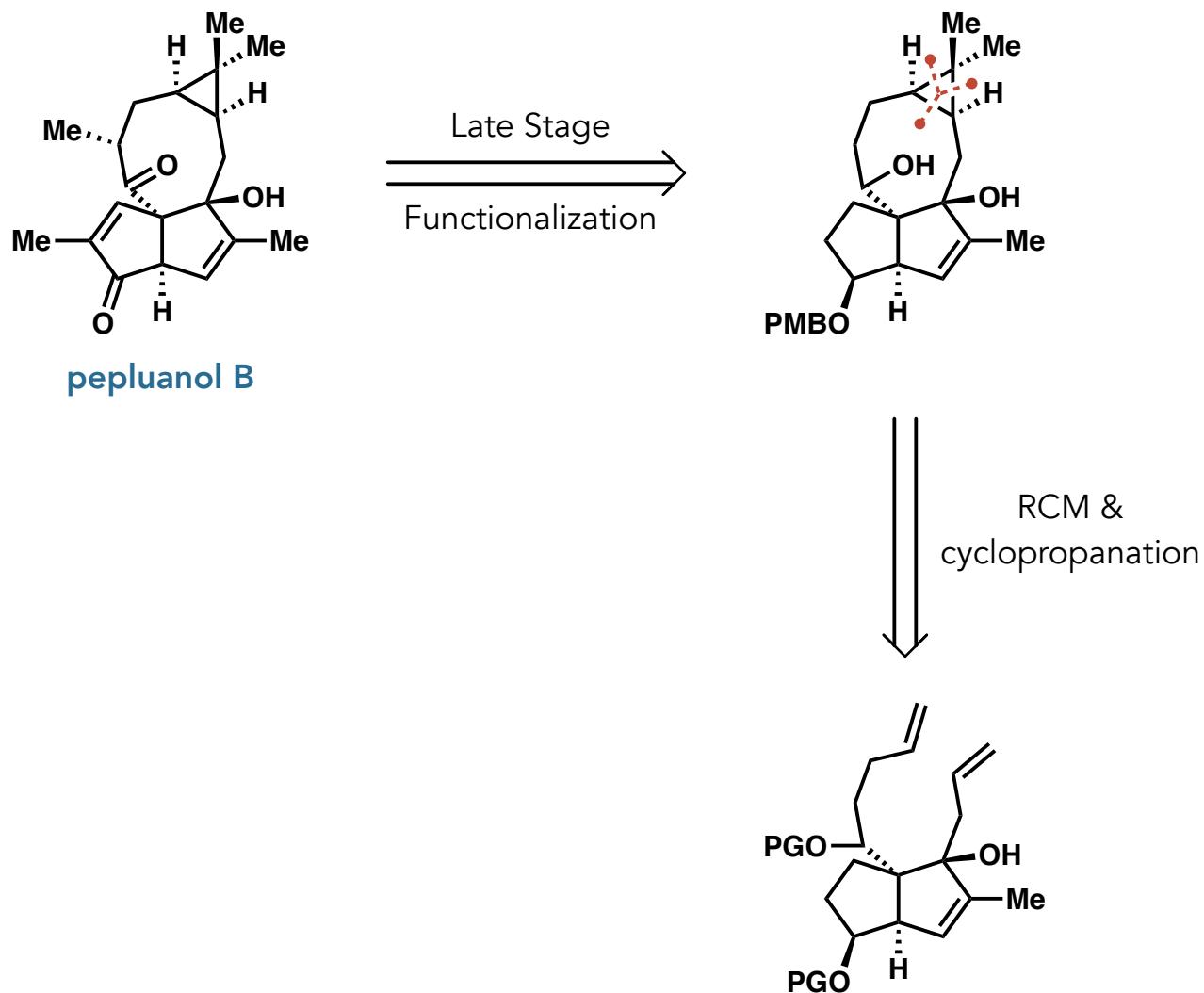
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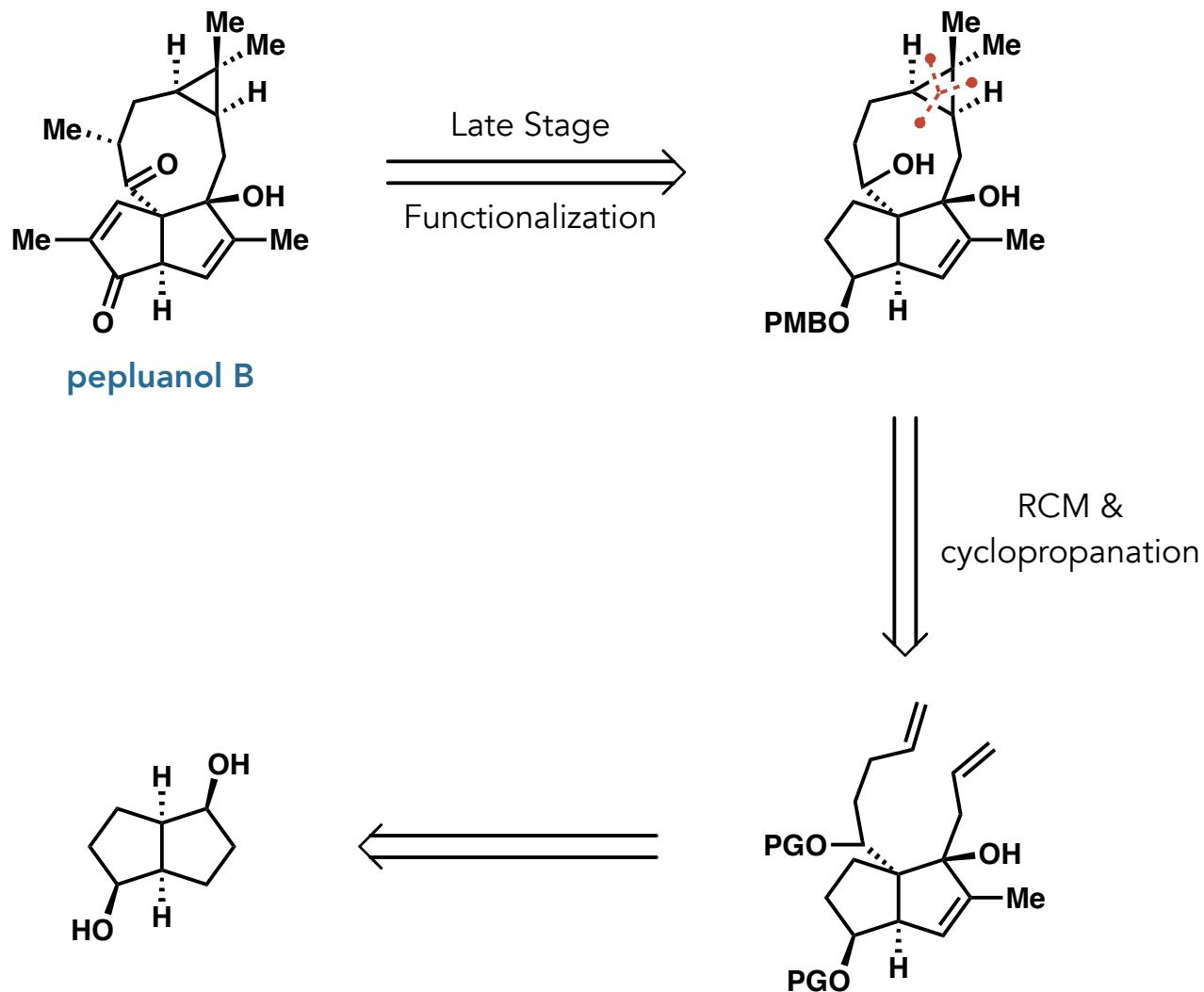
# Synthesis of (-)-Pepluanol B



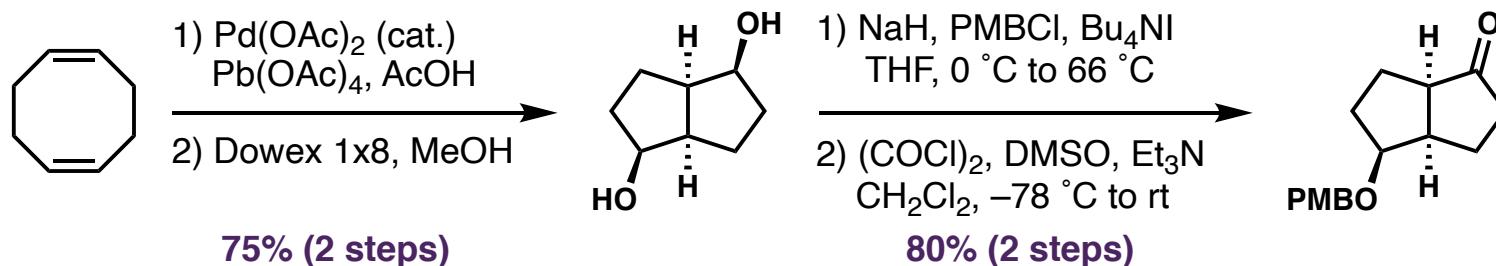
# Synthesis of (-)-Pepluanol B



# Synthesis of (-)-Pepluanol B



# Assembling a Functionalized [3.3.0] System

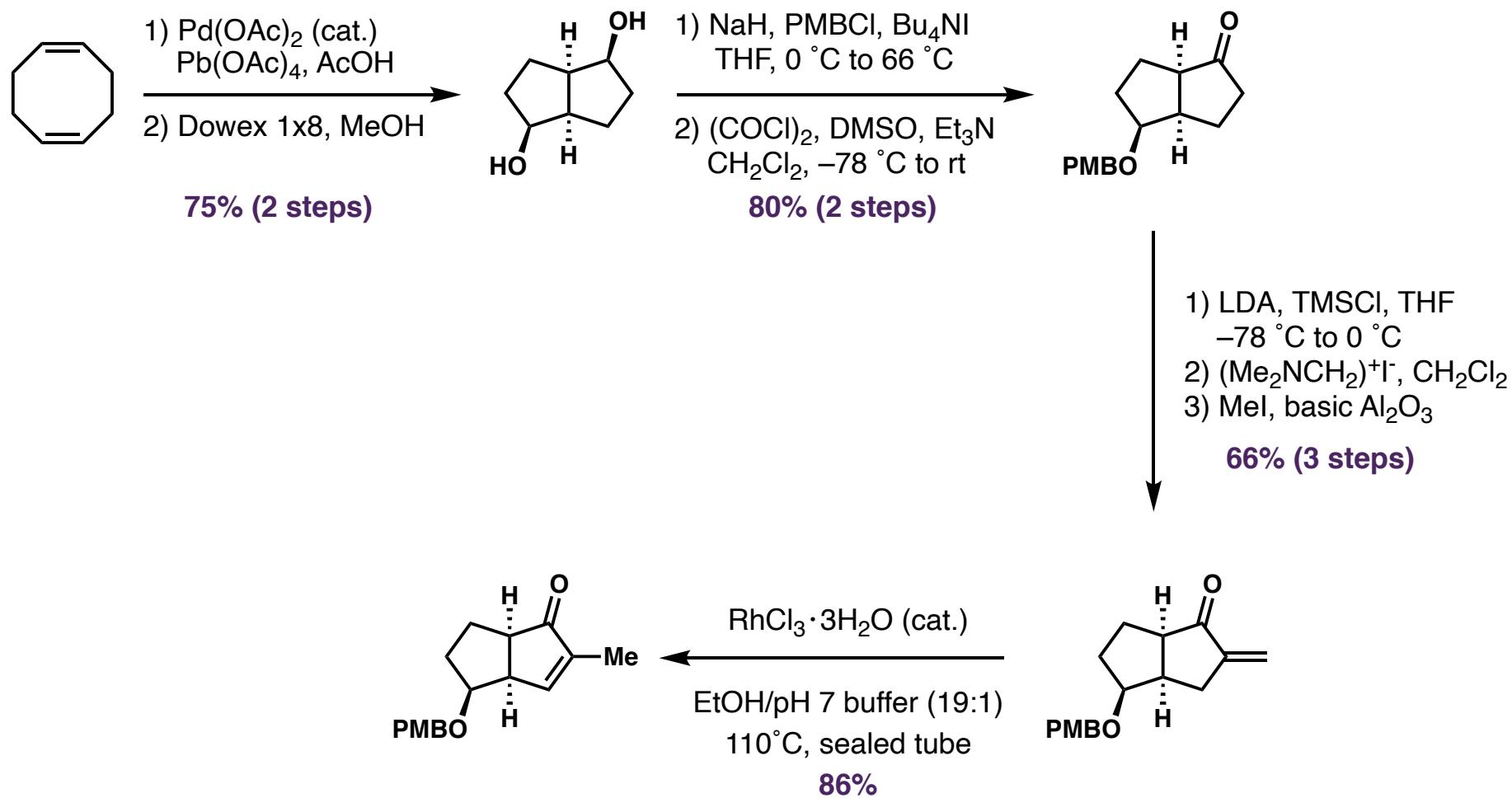


Henry, P. J. et al. *J. Chem. Soc., Chem. Commun.* **1974**, 112–113.

Disanayaka, B. W.; Weedon, A. C. *Synthesis* **1983**, 952.

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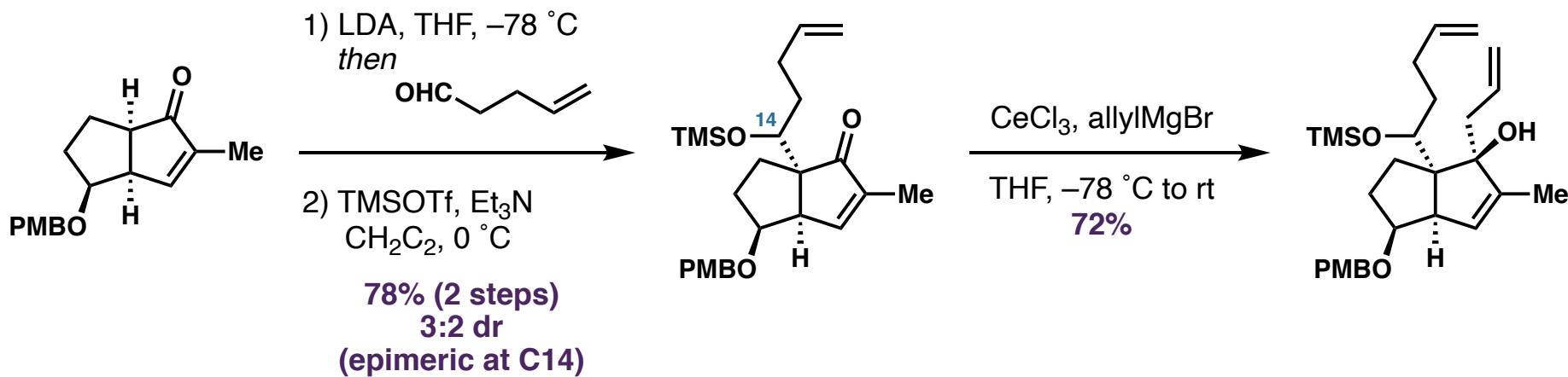


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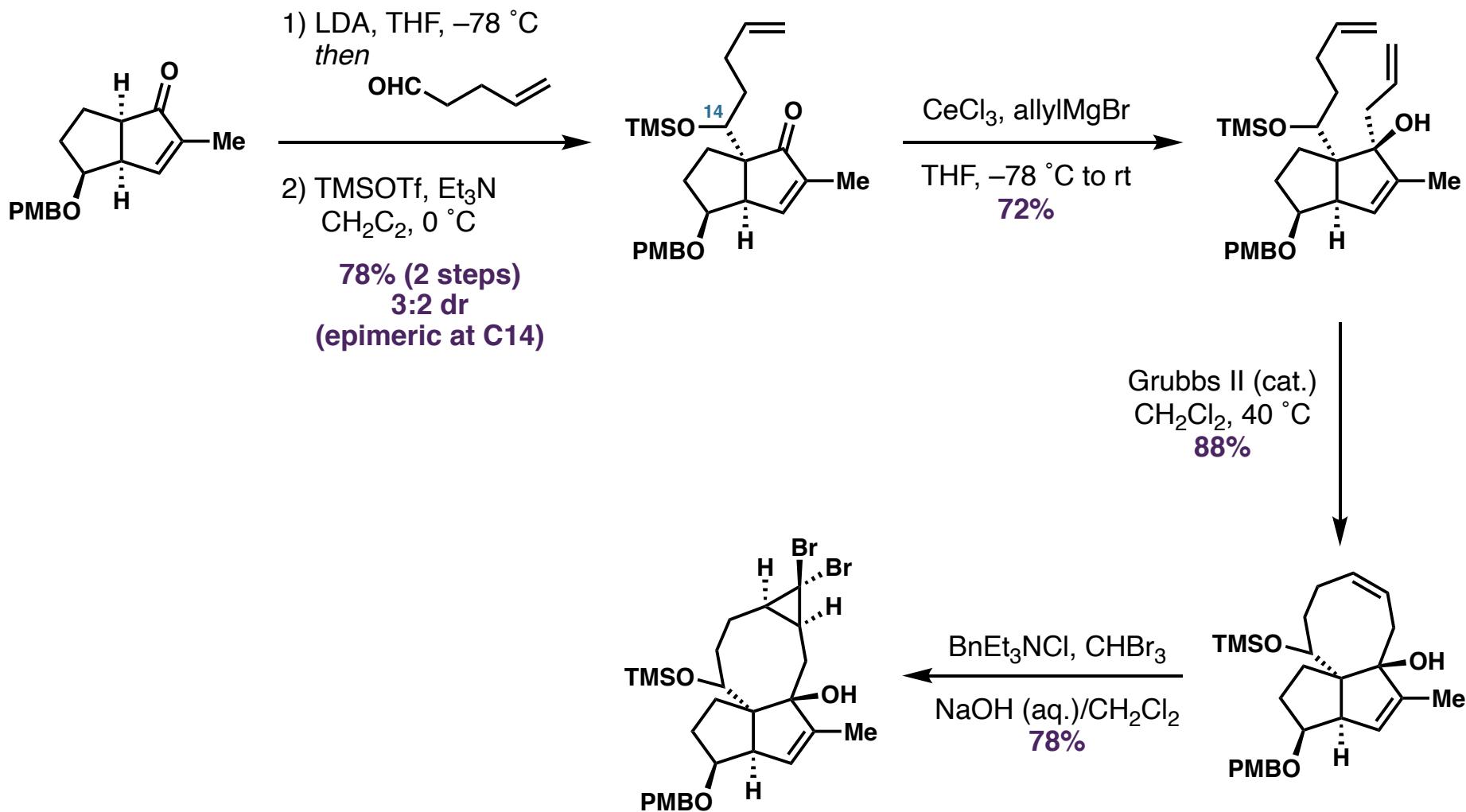
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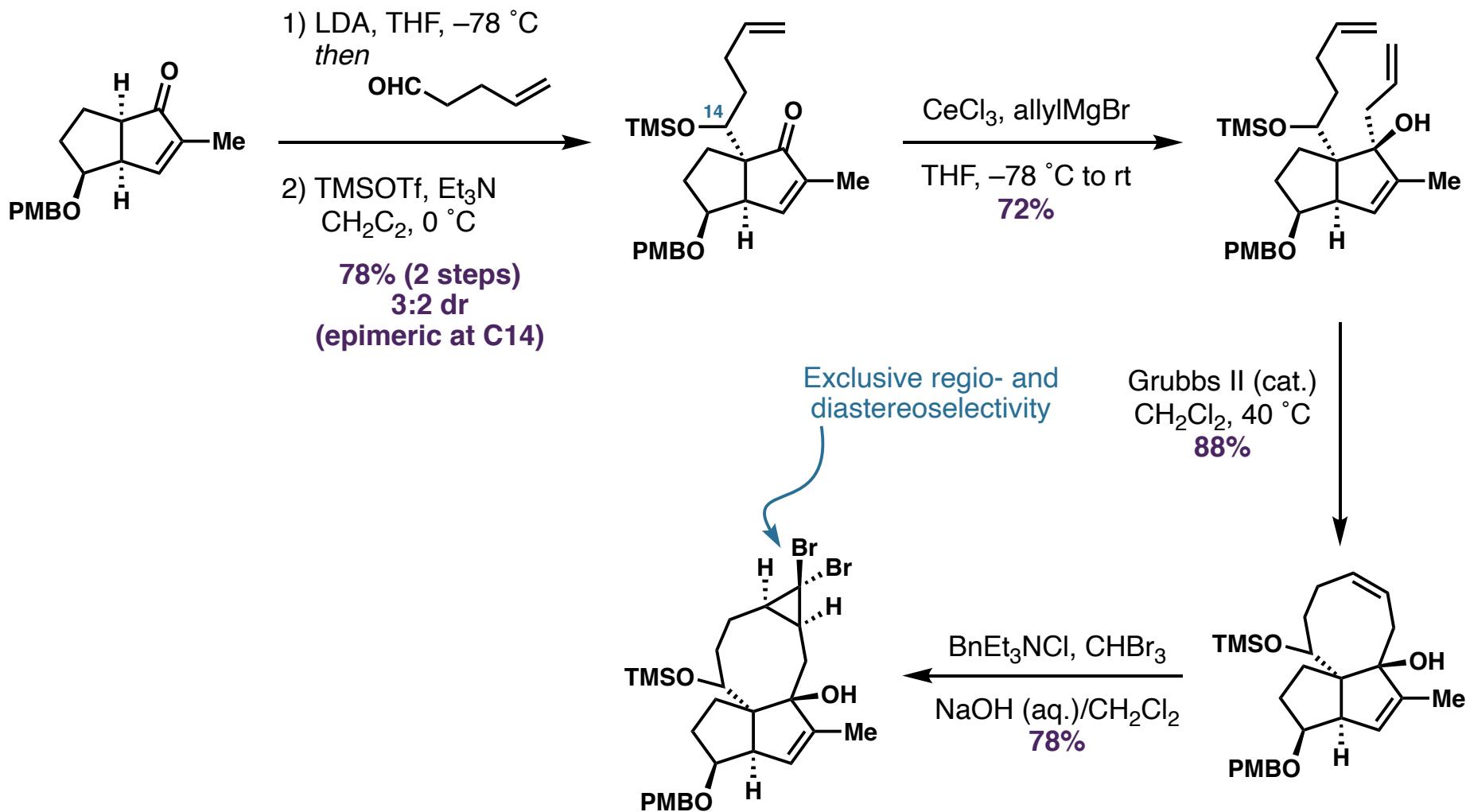
# Constructing the Eight-Membered Ring



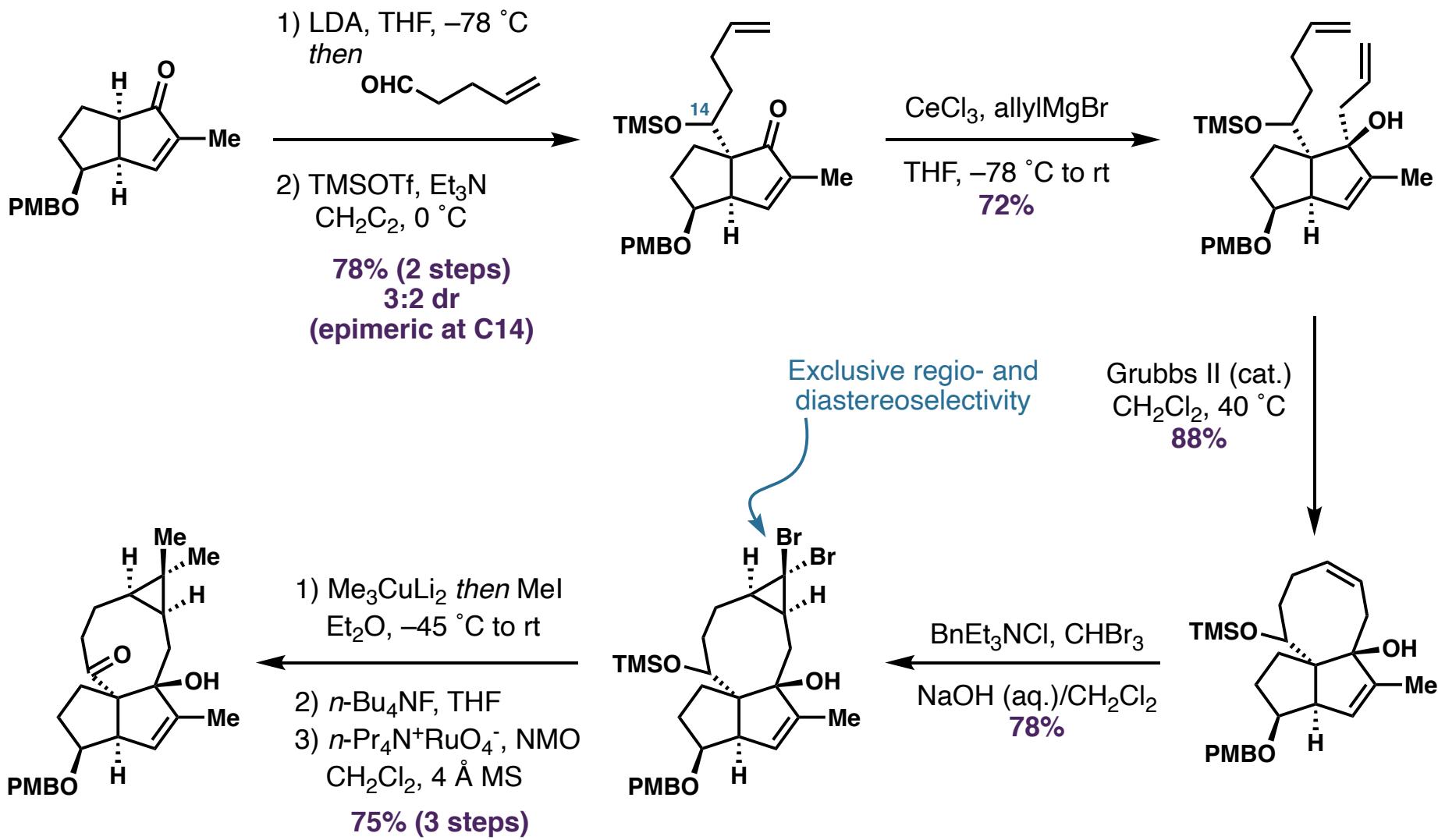
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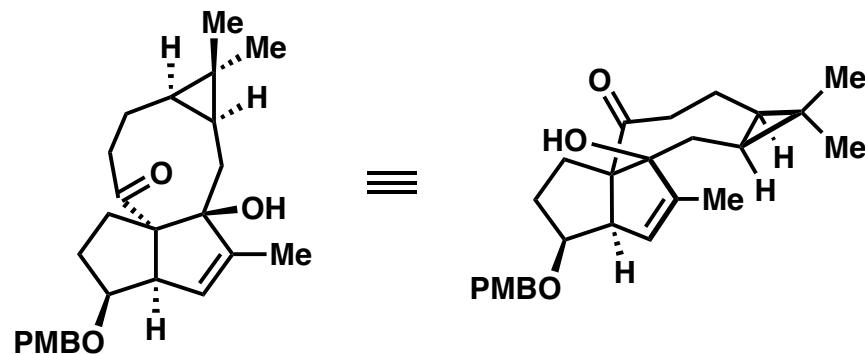
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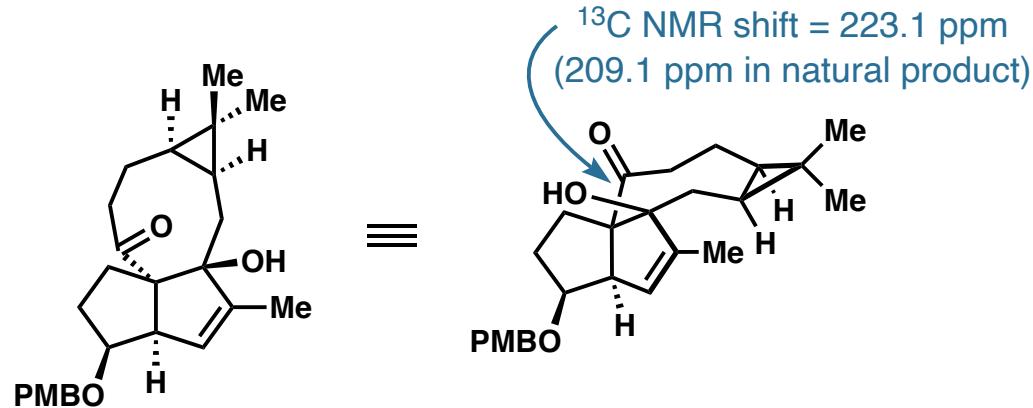
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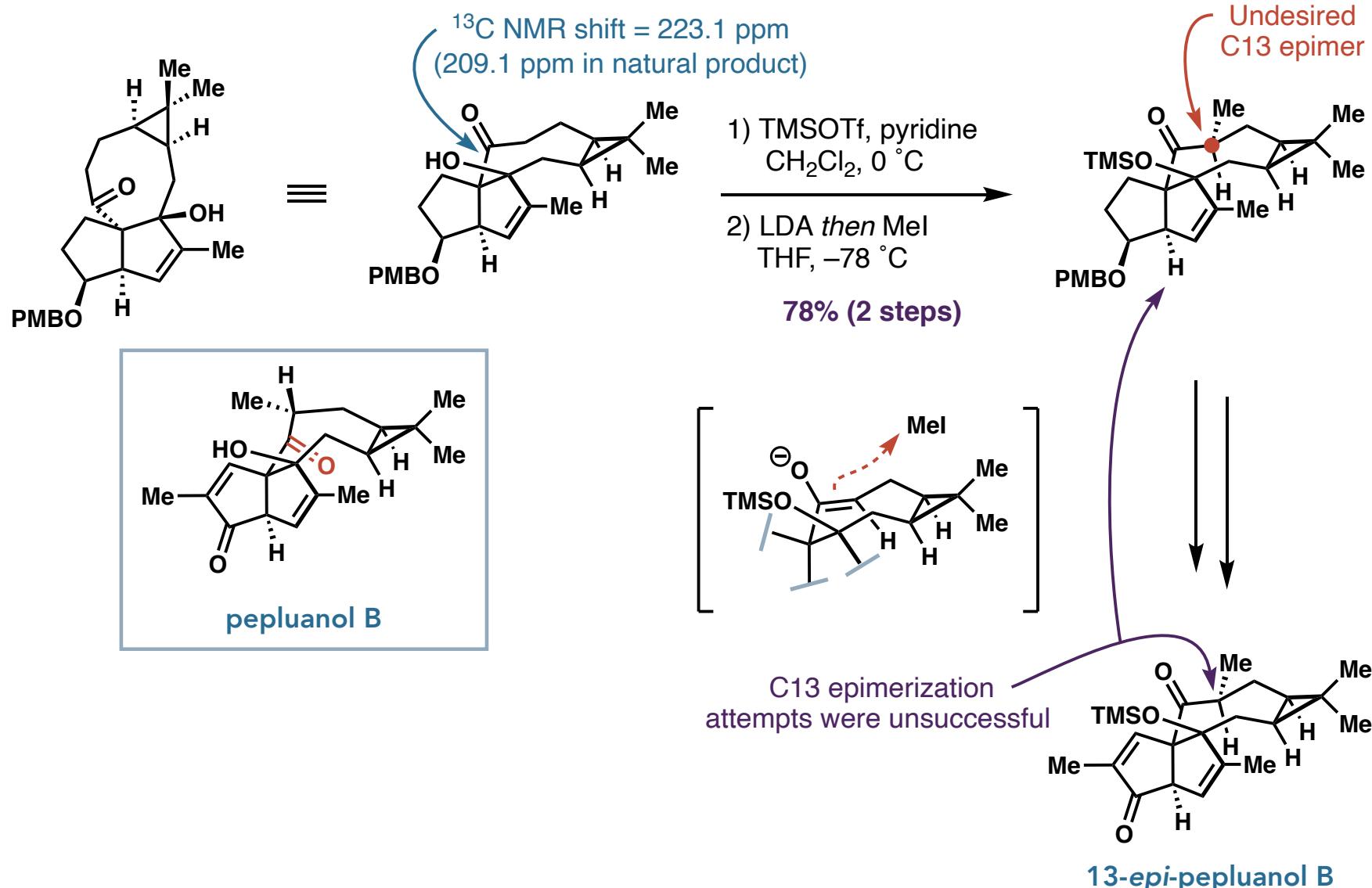
# A Conformational Conundrum



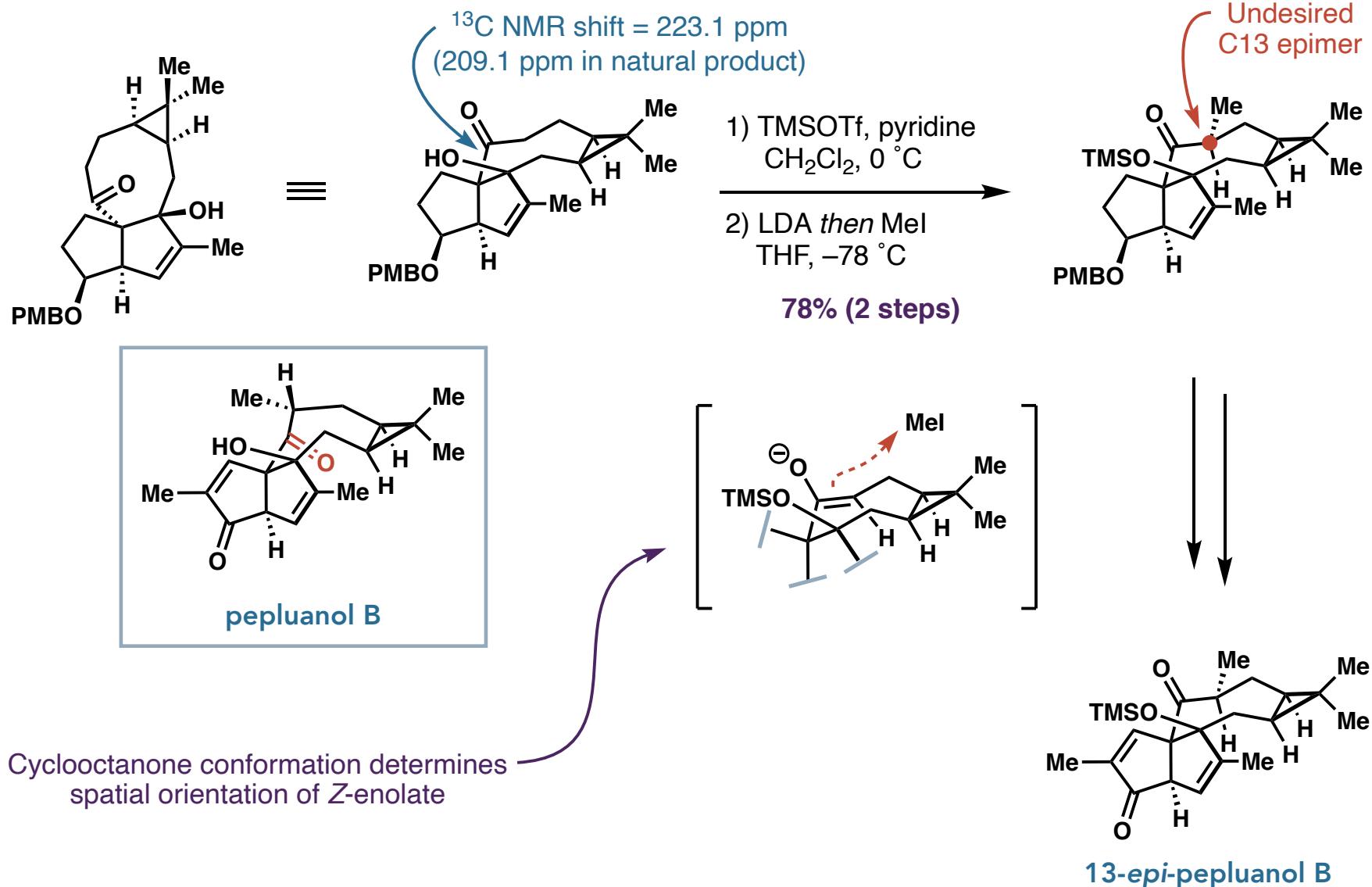
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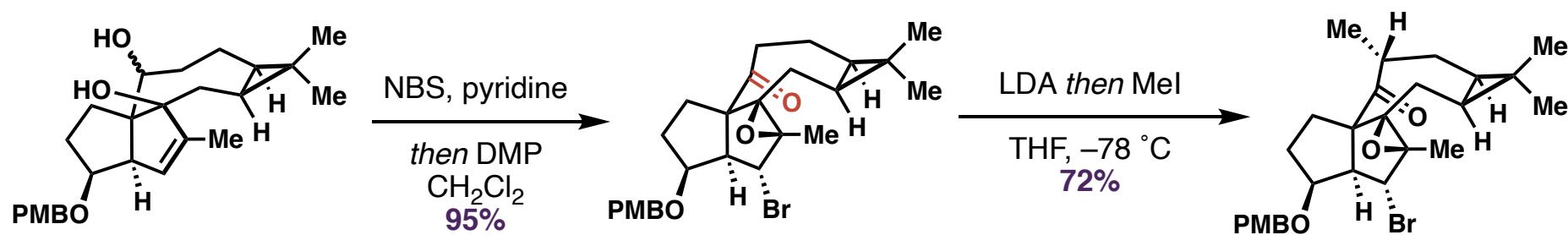
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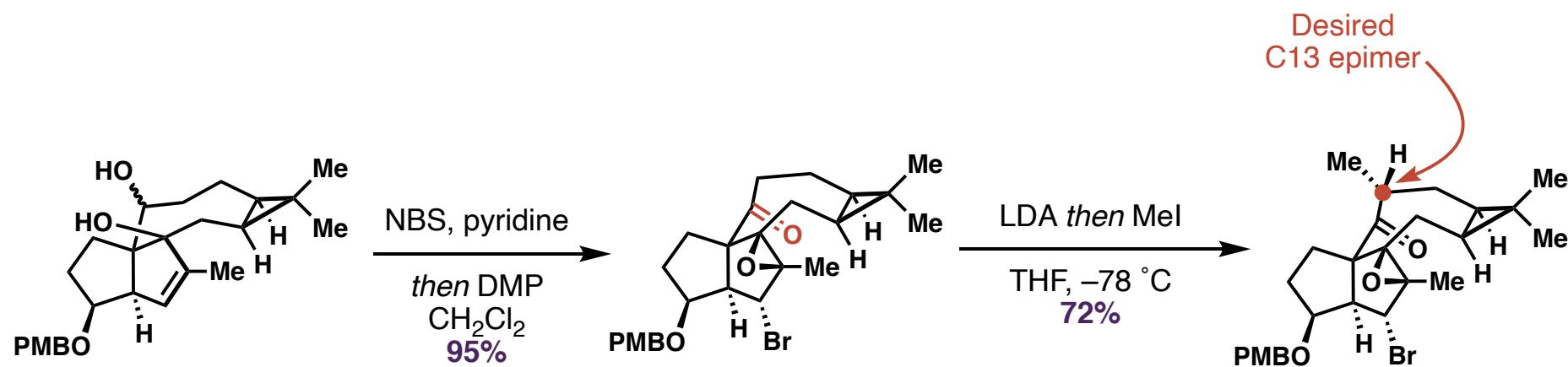
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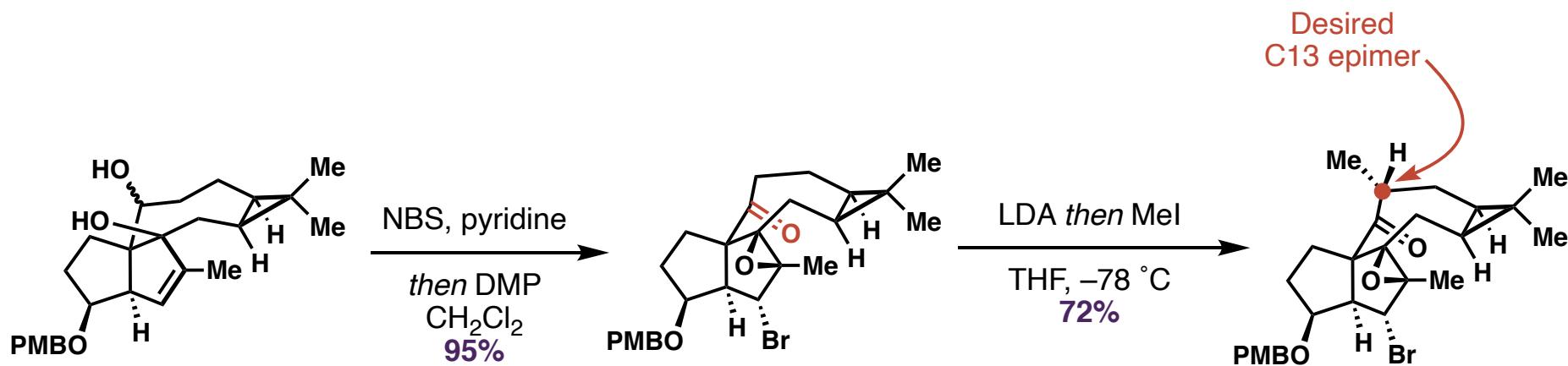
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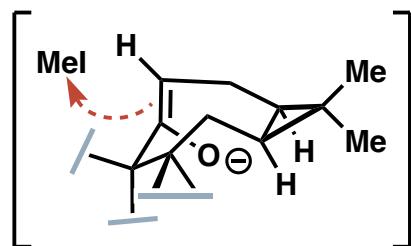
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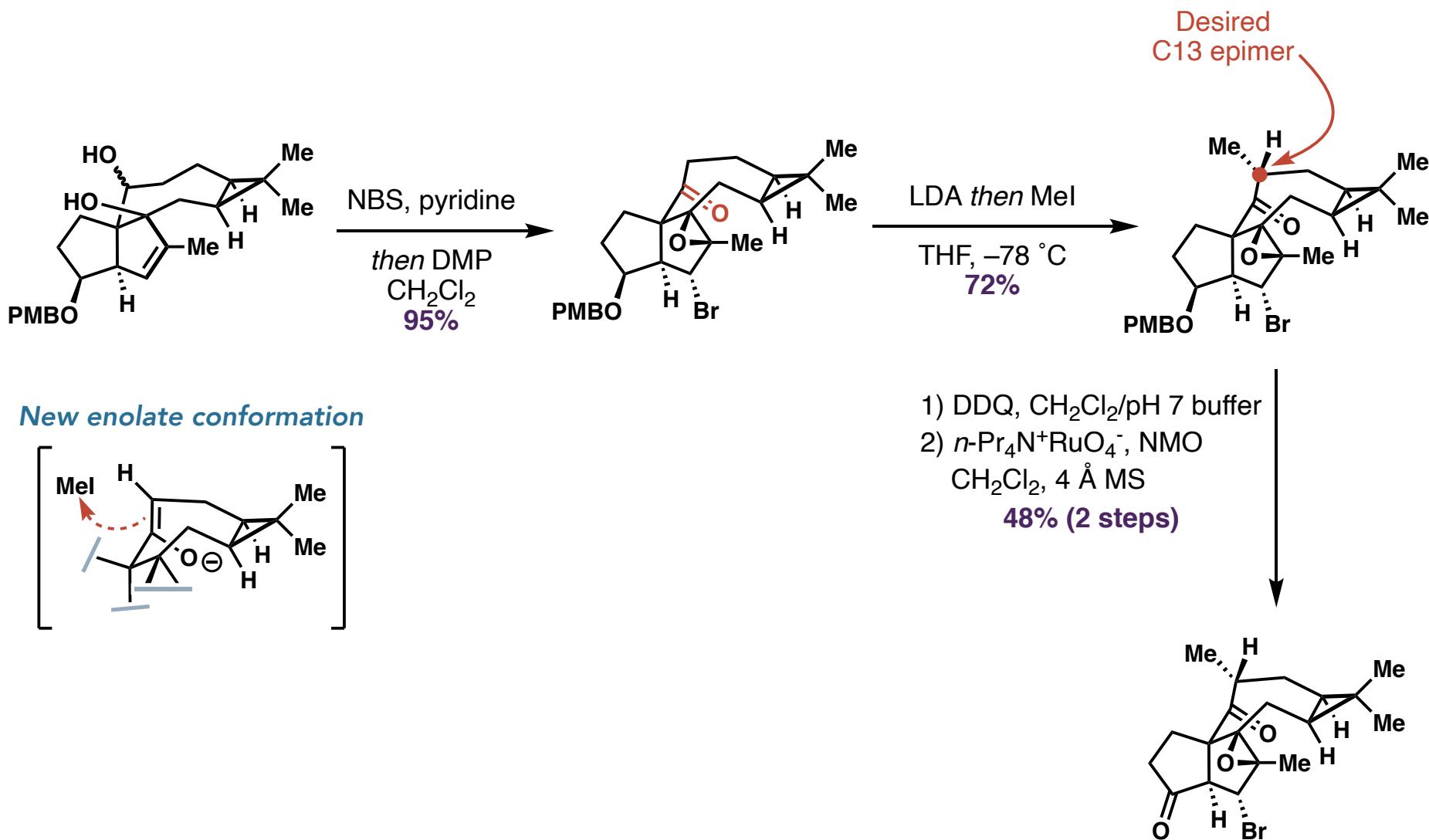
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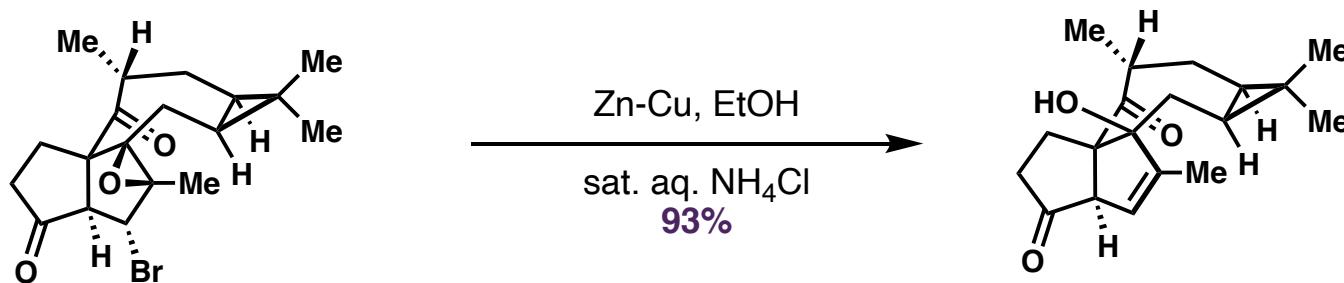
New enolate conformation



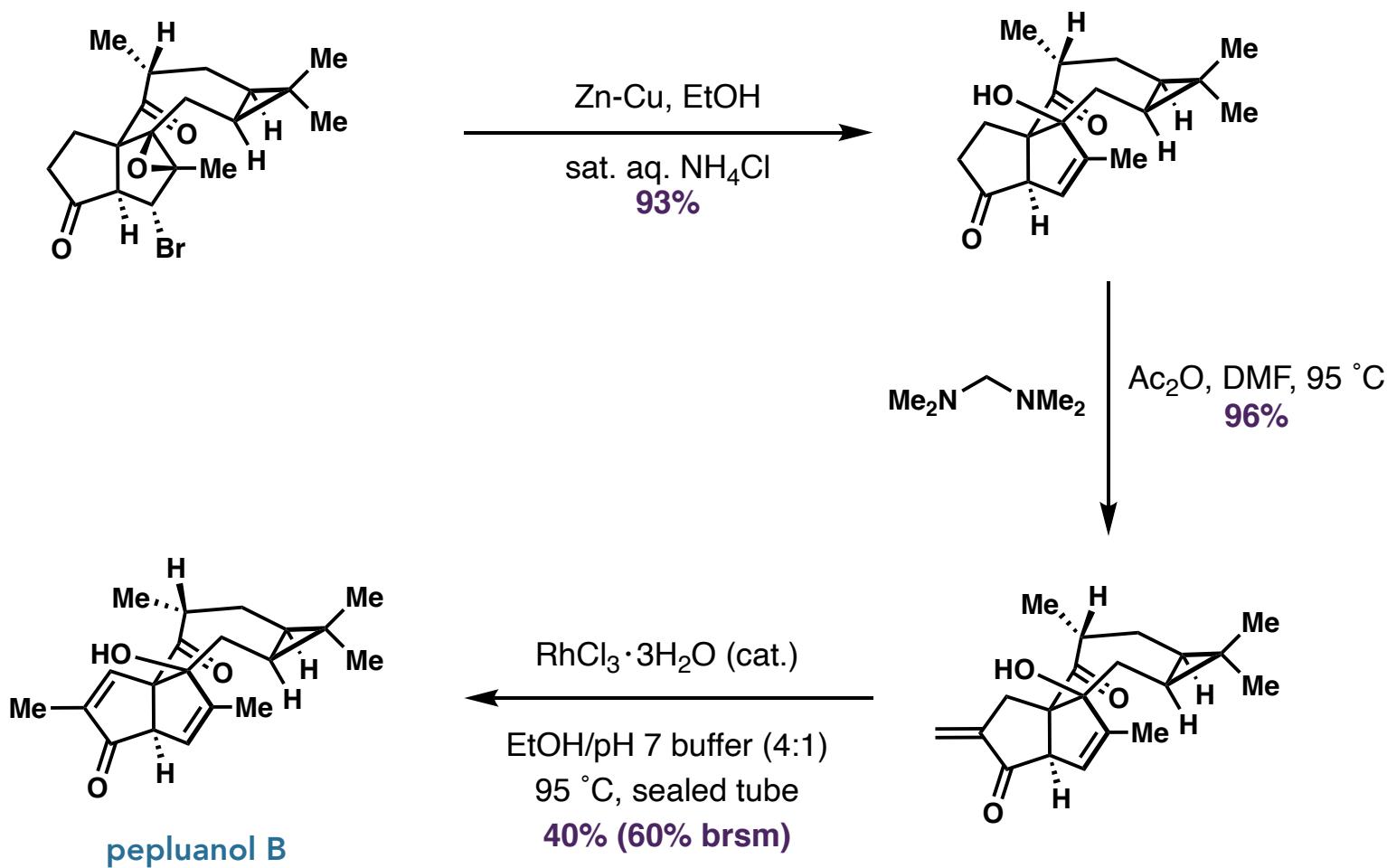
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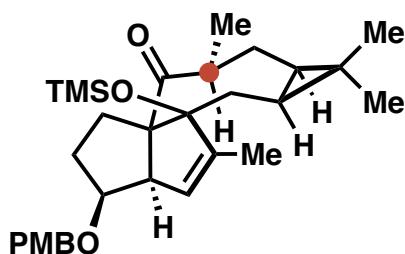
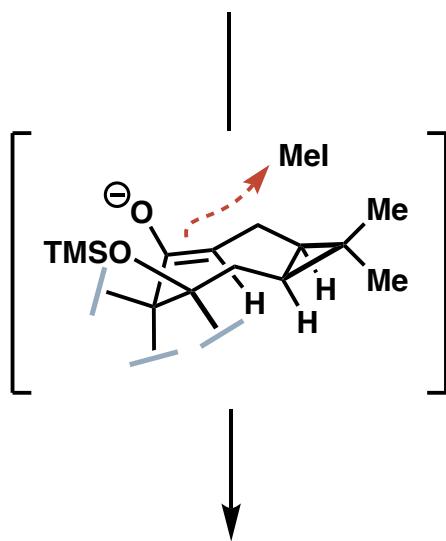
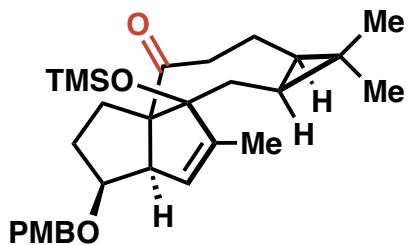
# Completing Pepluanol B



# Completing Pepluanol B

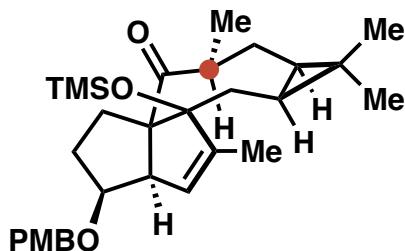
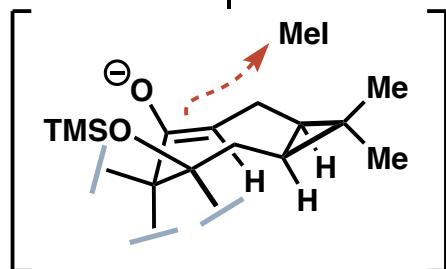
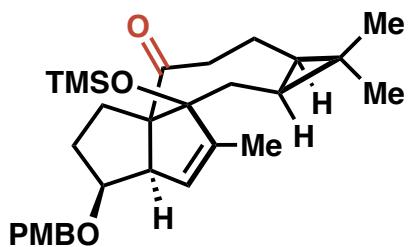


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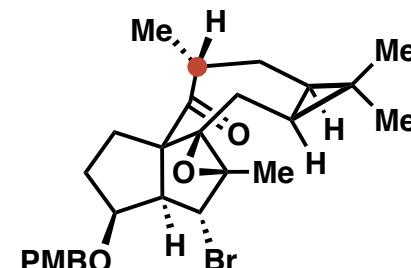
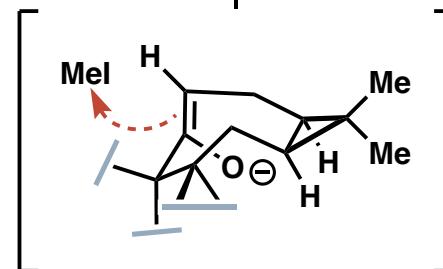
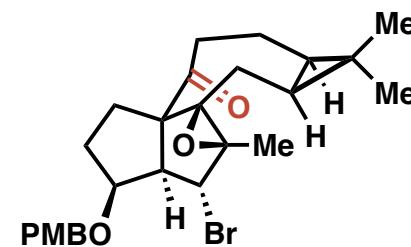


Undesired C13 epimer

# Completing Pepluanol B



Undesired C13 epimer



Desired C13 epimer