

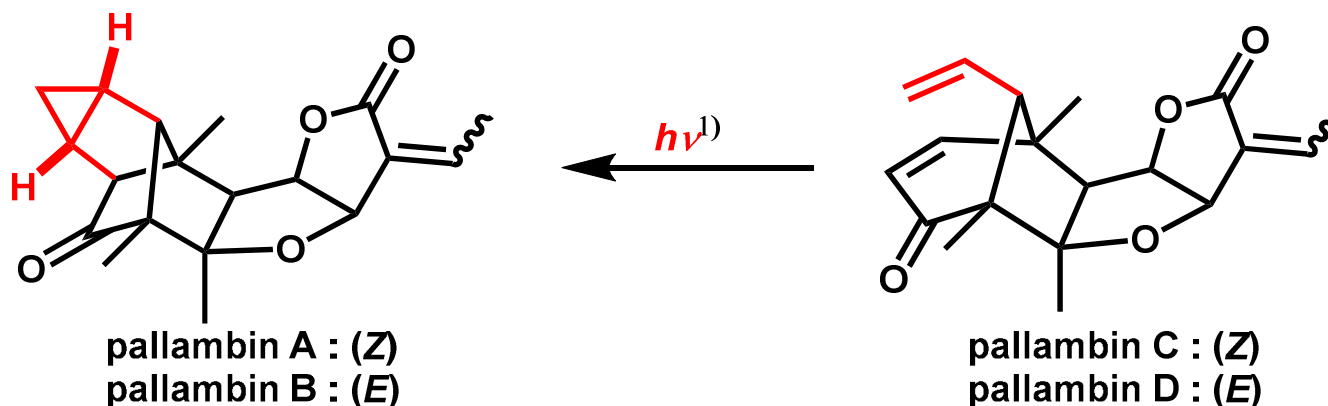
Total Syntheses of Pallambins A-D

**2020. 9. 5. Literature Seminar
M1 Risa Yoshinaga**

Contents

- 1. Introduction**
- 2. Total synthesis of Pallambins**
 - 2.1. Total synthesis of (\pm)-Pallambins A, B by Carreira's group (2015)**
 - 2.2. Total synthesis of (\pm)-Pallambins C, D by Baran's group (2016)**
 - 2.3. Total synthesis of (-)-Pallambins A-D by Jia's group (2019)**

Pallambins A-D



Isolation: pallambin D from *Pallavicinia subciliata* (1998)¹⁾
pallambin A-D from *Pallavicinia ambigua* (2012)²⁾

Structural features: 4-6 congested rings
7-10 contiguous stereocenters
1-2 all-carbon quaternary

Biological activity: limited biological evaluation

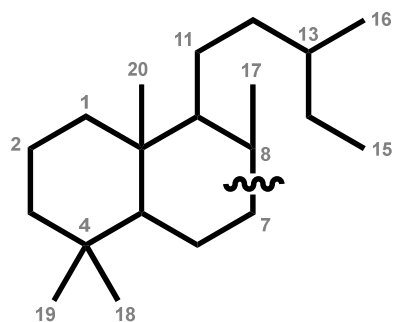
Total synthesis of (±)-Pallambins C, D : Wong (2012)³⁾, Baran (2016)⁴⁾

Total synthesis of (±)-Pallambins A, B : Carreira (2015)⁵⁾

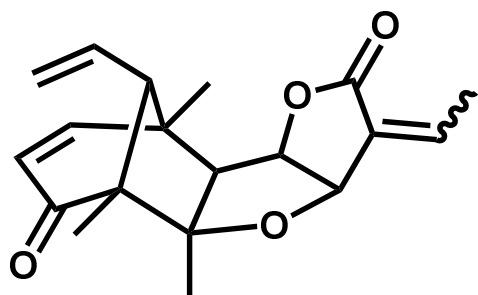
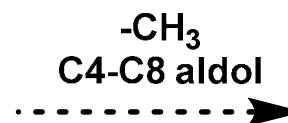
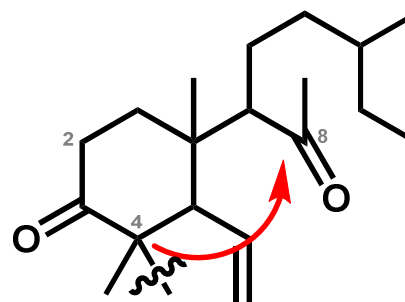
Total synthesis of (-)-Pallambins A-D : Jia (2019)⁶⁾

-
- 1) Toyota, M.; Saito, T.; Asakawa, Y. *Chem. Pharm. Bull.* **1998**, *46*, 178.
 - 2) Wang, L. N.; Zhang, J. Z.; Li, X.; Wang, X. N.; Xie, C. F.; Zhou, J. C.; Lou, H. X. *Org. Lett.* **2012**, *14*, 1102.
 - 3) Xu, X. S.; Li, Z. Y.; Zhang, Y. J.; Peng, X. S.; Wong, H. N. C.; *Chem. Commun.* **2012**, *48*, 8517.
 - 4) Martinez, L. P.; Umemiya, S.; Wengryniuk, S. E.; Baran, P. S.; *J. Am. Chem. Soc.* **2016**, *138*, 7536.
 - 5) Ebner, C.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2015**, *54*, 11227–11230; *Angew. Chem.* **2015**, *127*, 11379.
 - 6) Zhang, X.; Cai, X.; Huang, B.; Guo, L.; Gao, Z.; Jia, Y. *Angew. Chem. Int. Ed.* **2019**, *58*, 13380.

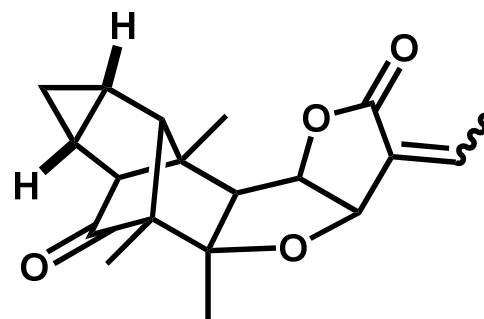
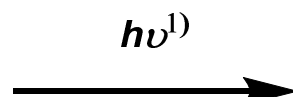
Possible Biosynthesis of Pallambins A-D



Labdane



pallambin C : (Z)
pallambin D : (E)

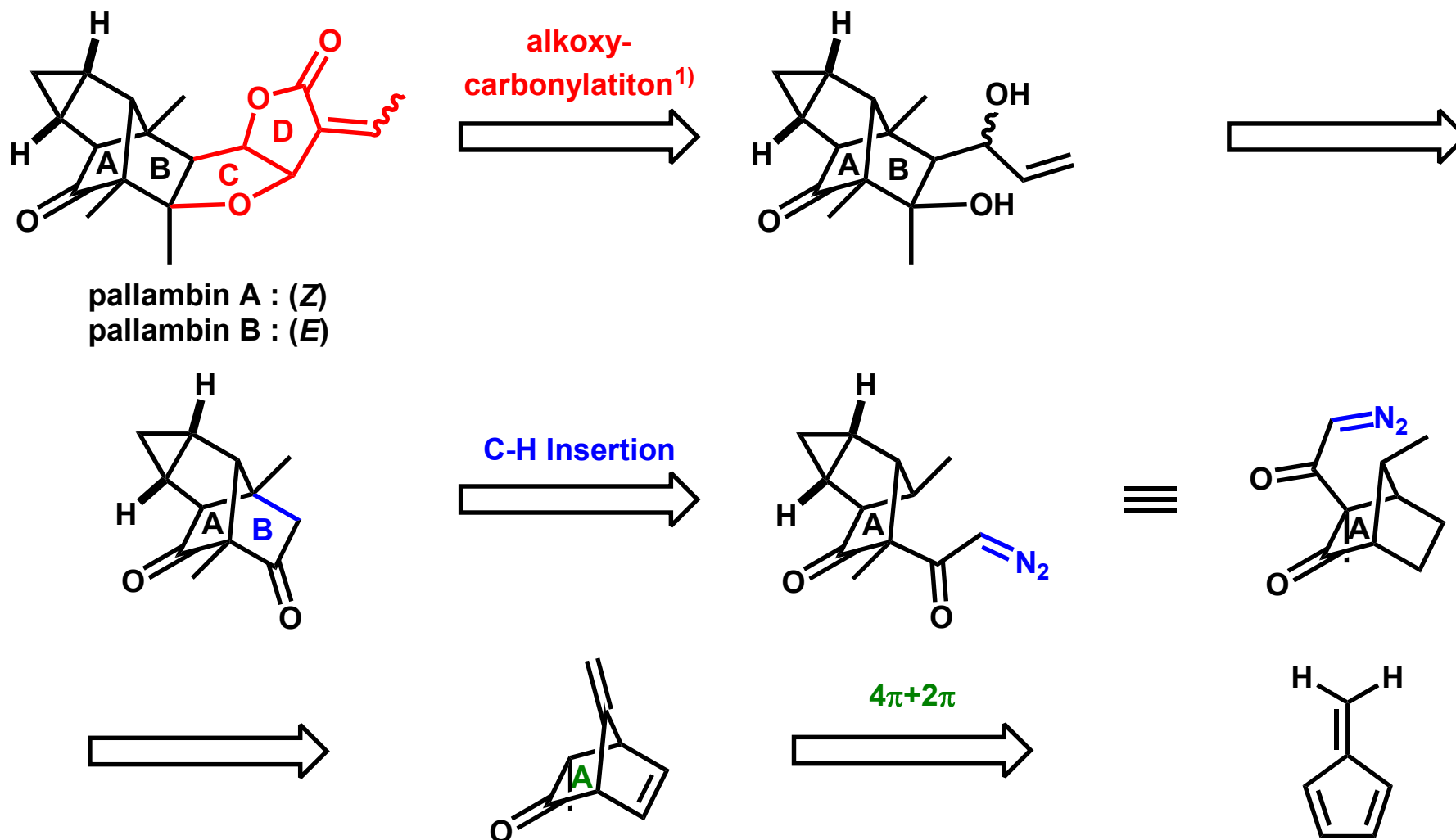


pallambin A : (Z)
pallambin B : (E)

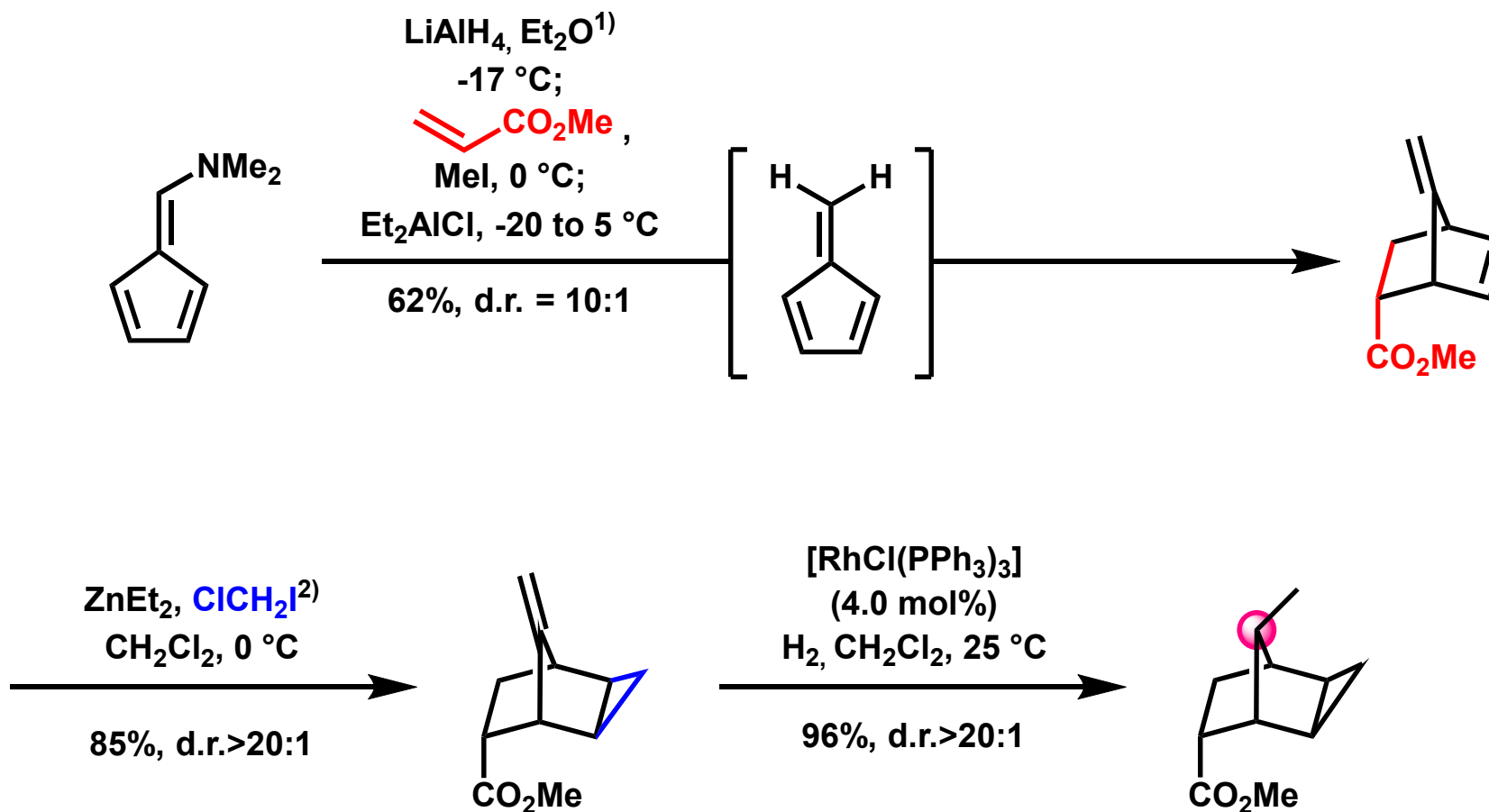
Contents

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Retrosynthetic Analysis of Pallambins A-B by Carreira



Synthesis of Tetracyclo [4.4.0.0] Decane Core (1)

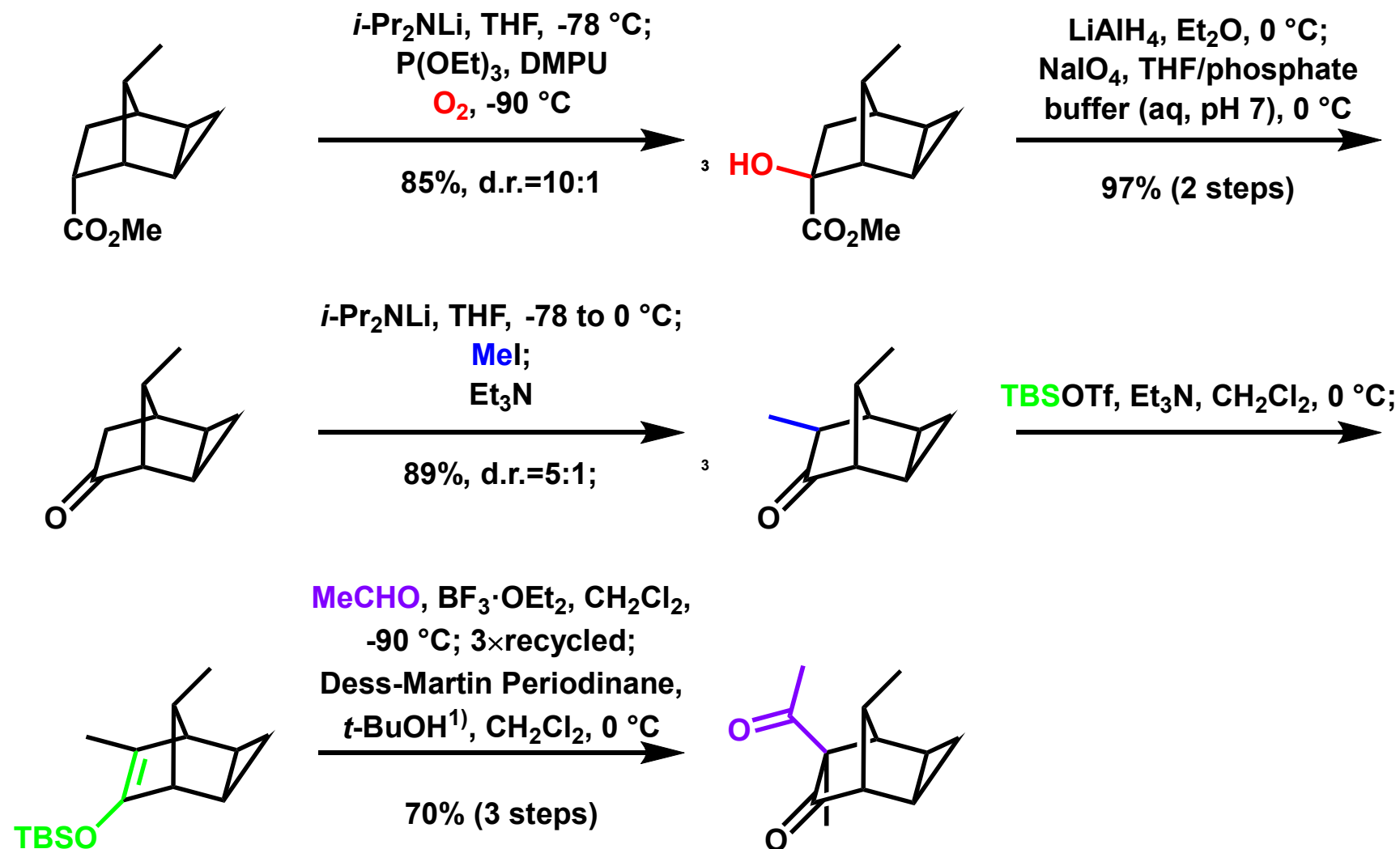


Ebner, C.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2015**, *54*, 11227; *Angew. Chem.* **2015**, *127*, 11379.

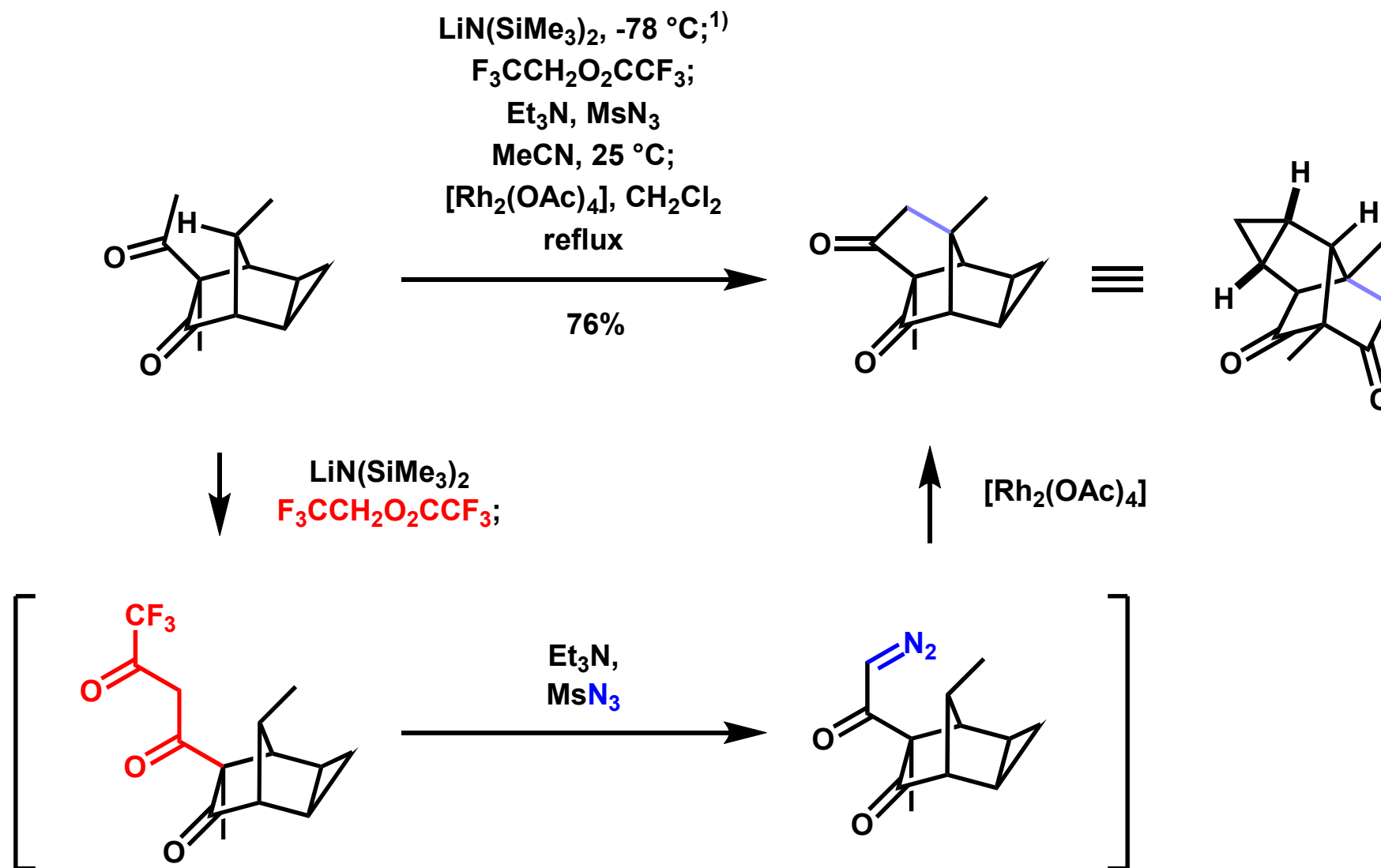
1) Trost, B. M.; Cory, R. M. *J. Org. Chem.* **1972**, *37*, 1106.

2) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974.

Synthesis of Tetracyclo [4.4.0.0] Decane Core (2)

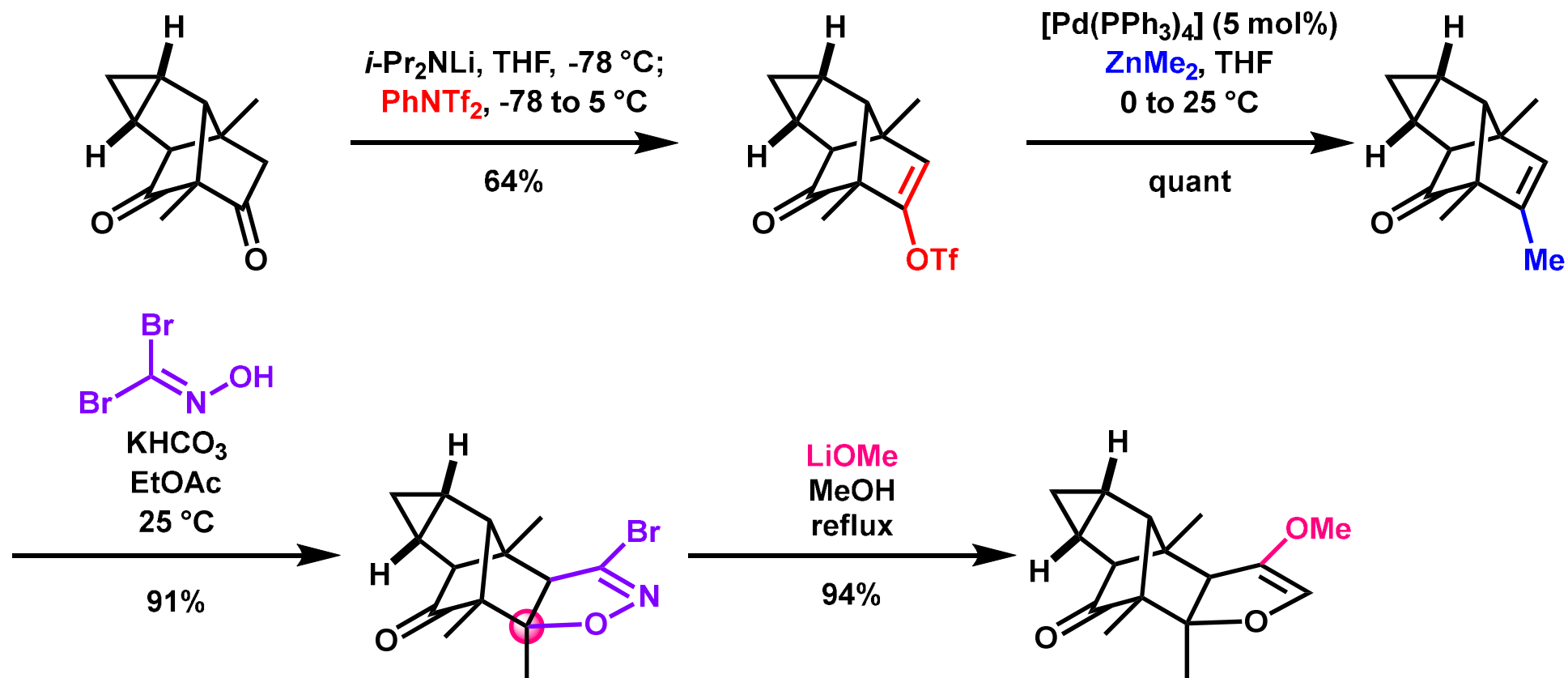


Synthesis of Tetracyclo [4.4.0.0] Decane Core (3)

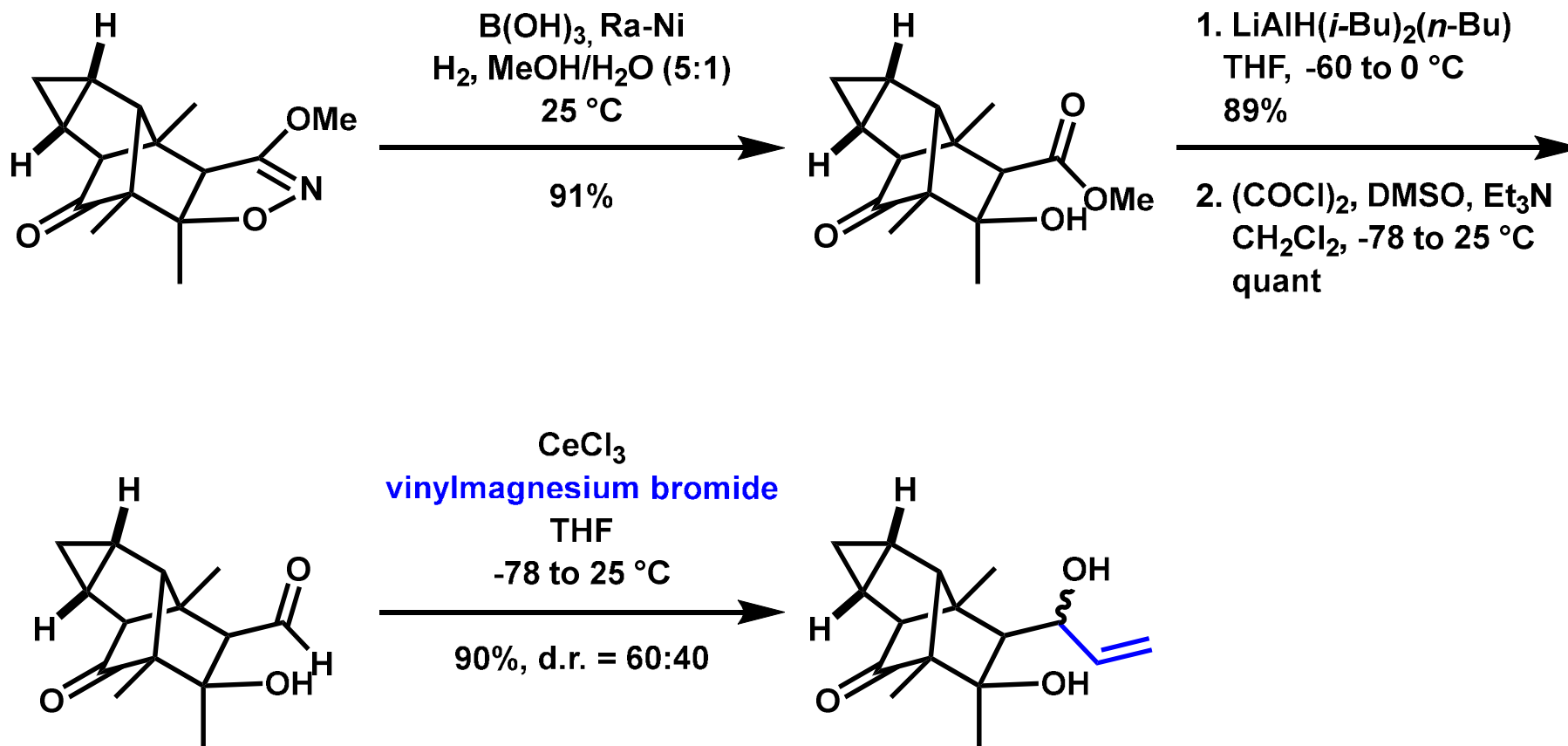


Ebner, C.; Carreira, E. M.; *Angew. Chem. Int. Ed.* **2015**, *54*, 11227–11230; *Angew. Chem.* **2015**, *127*, 11379.
 1) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.*, **1990**, *55*, 1959.

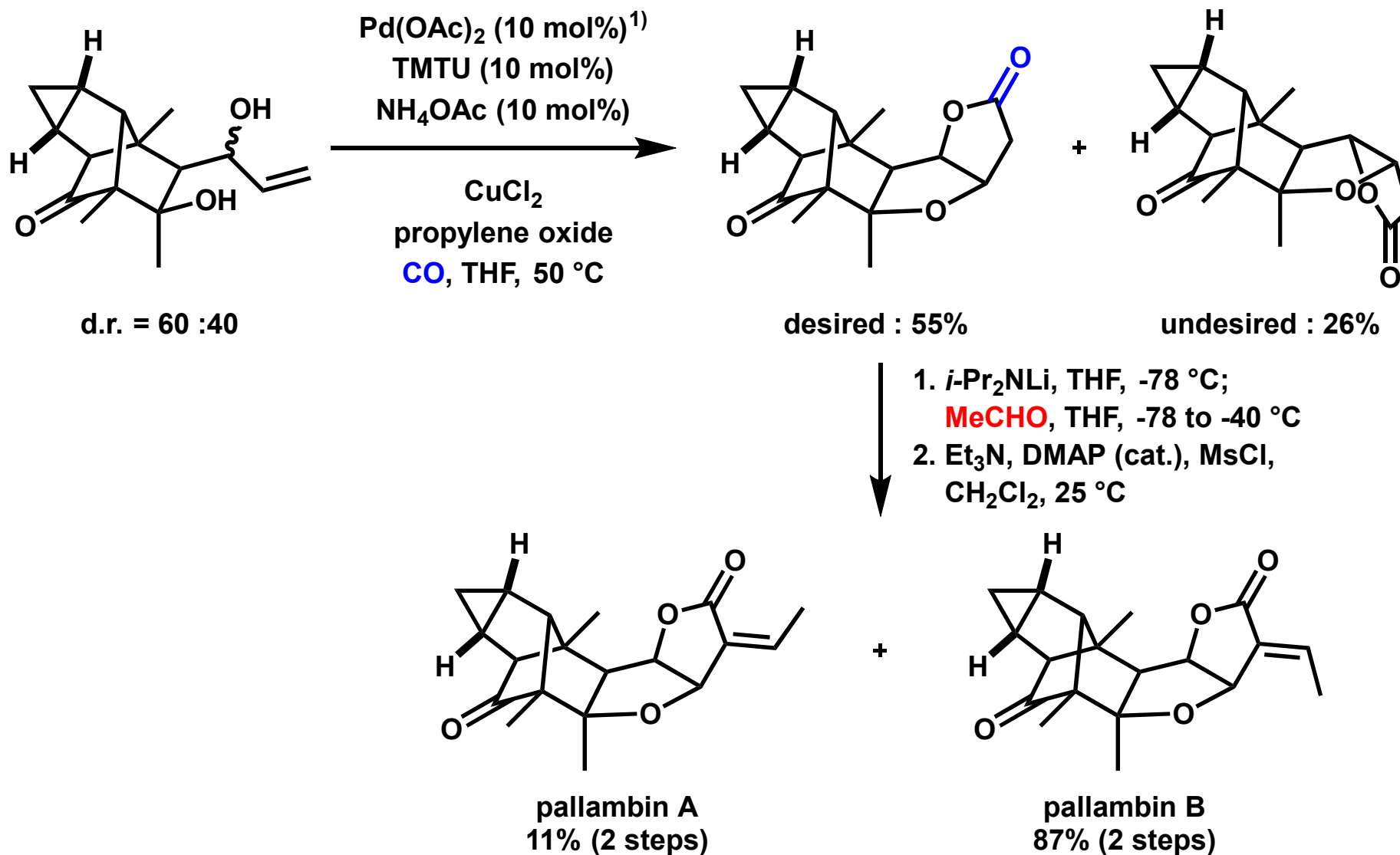
Synthesis of C-D Ring of Pallambins A-B (1)



Synthesis of C-D Ring of Pallambins A-B (1)



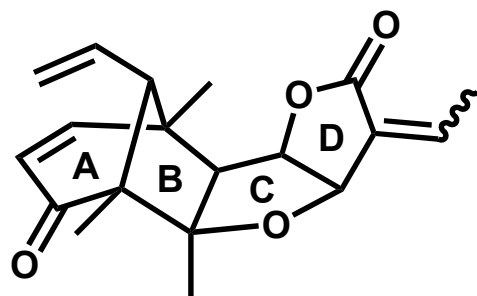
Synthesis of C-D Ring of Pallambins A-B (2)



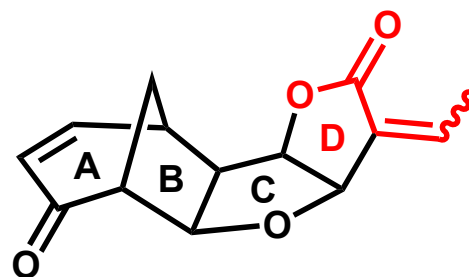
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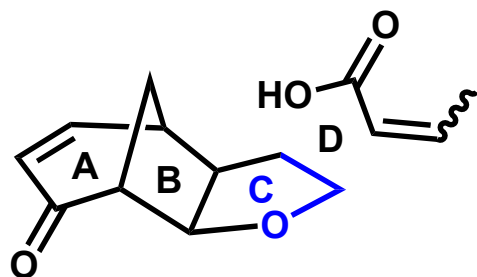
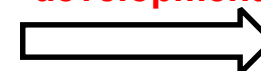
Retrosynthetic Analysis of Pallambins C, D by Baran's group



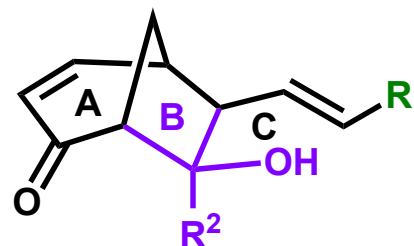
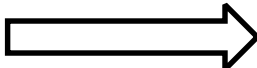
pallambin C : (Z)
pallambin D : (E)



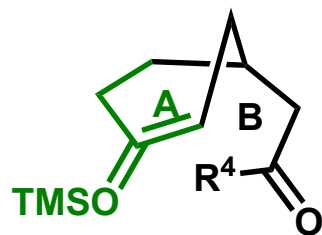
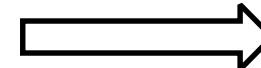
Cyclization 4:
requires
development



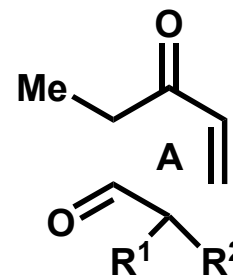
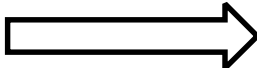
Cyclization 3:
reductive
etherification



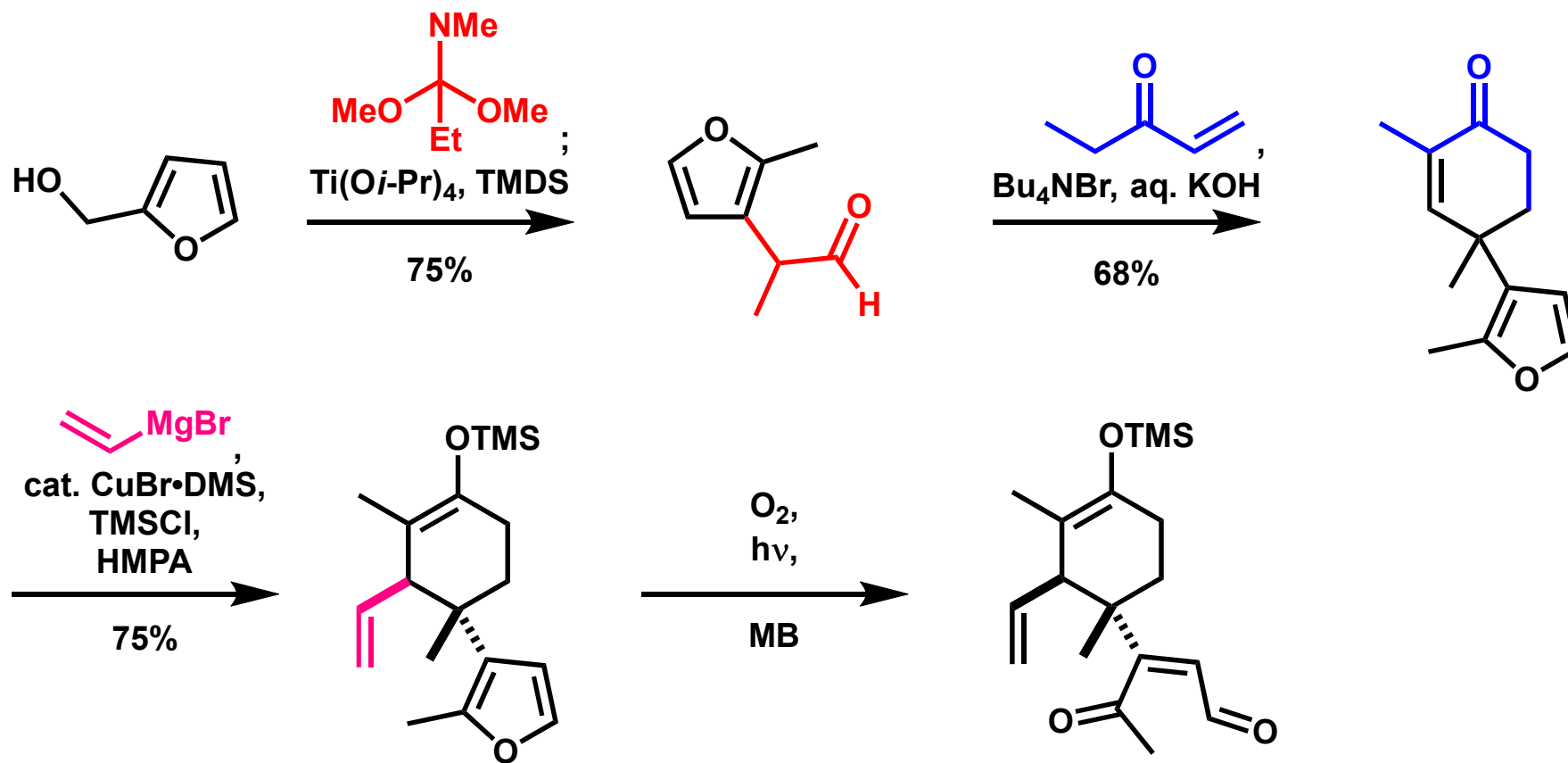
Cyclization 2:
Mukaiyama
aldol



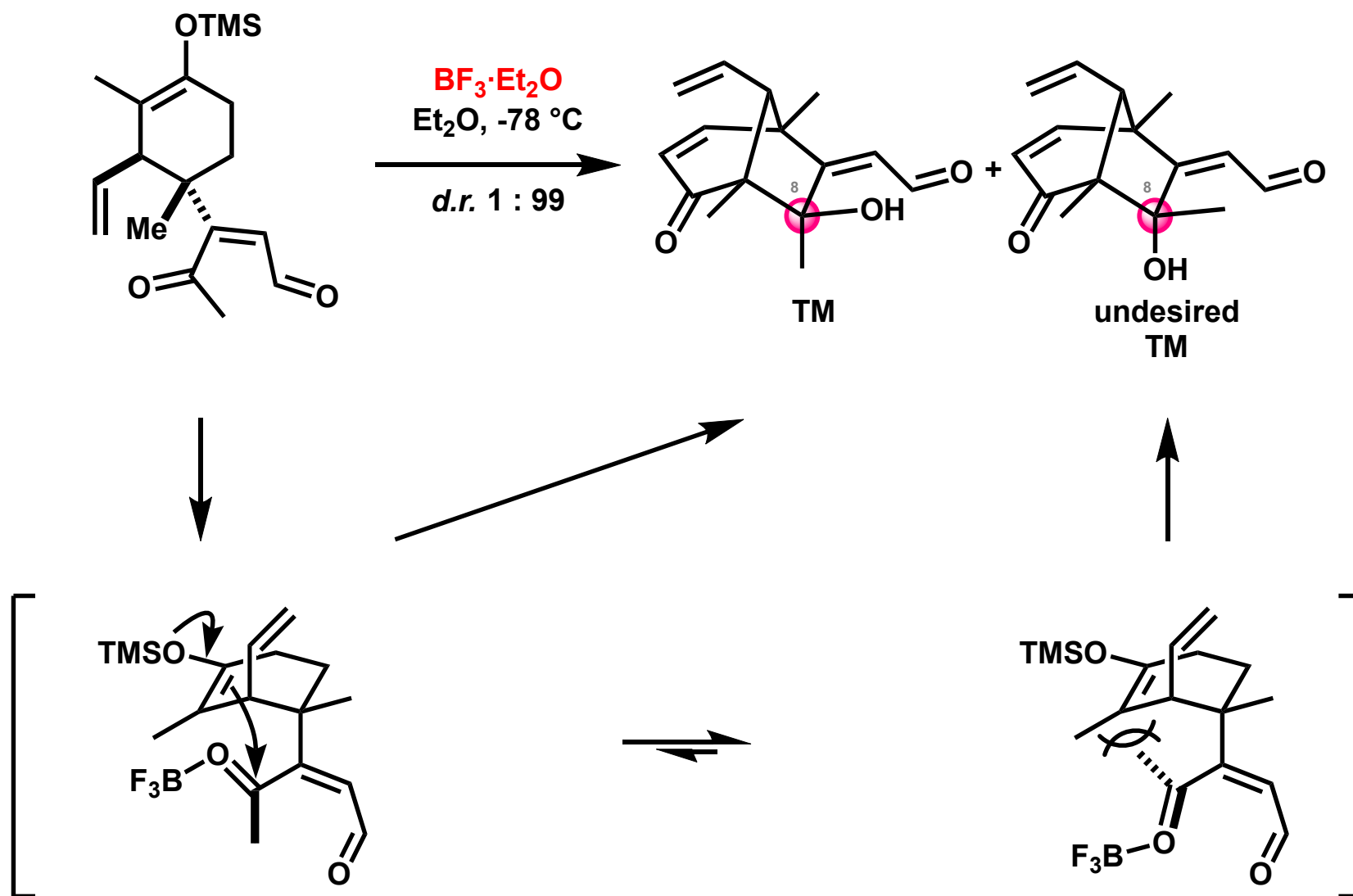
Cyclization 1:
Robinson
annulation



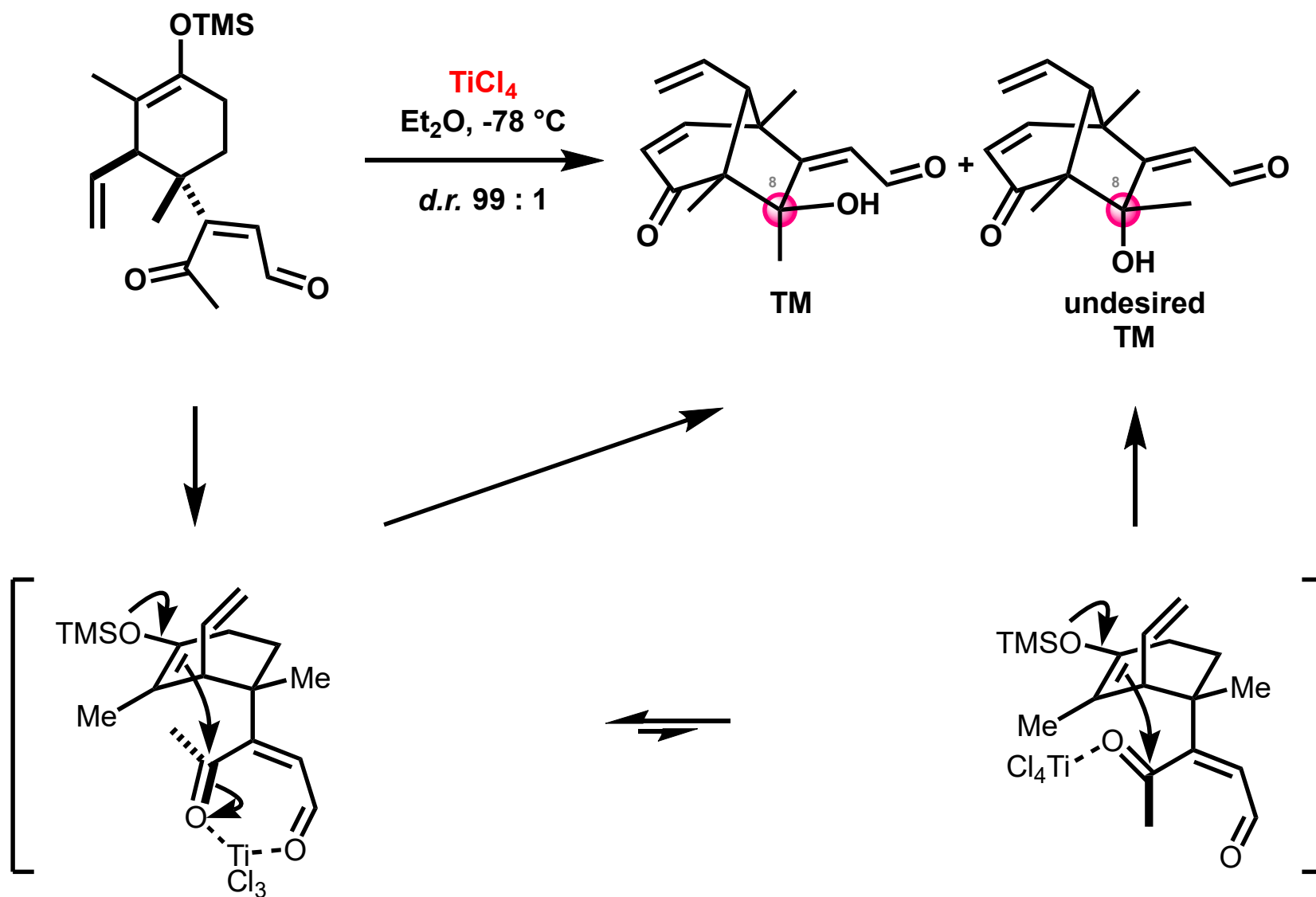
Installation of A-B Ring



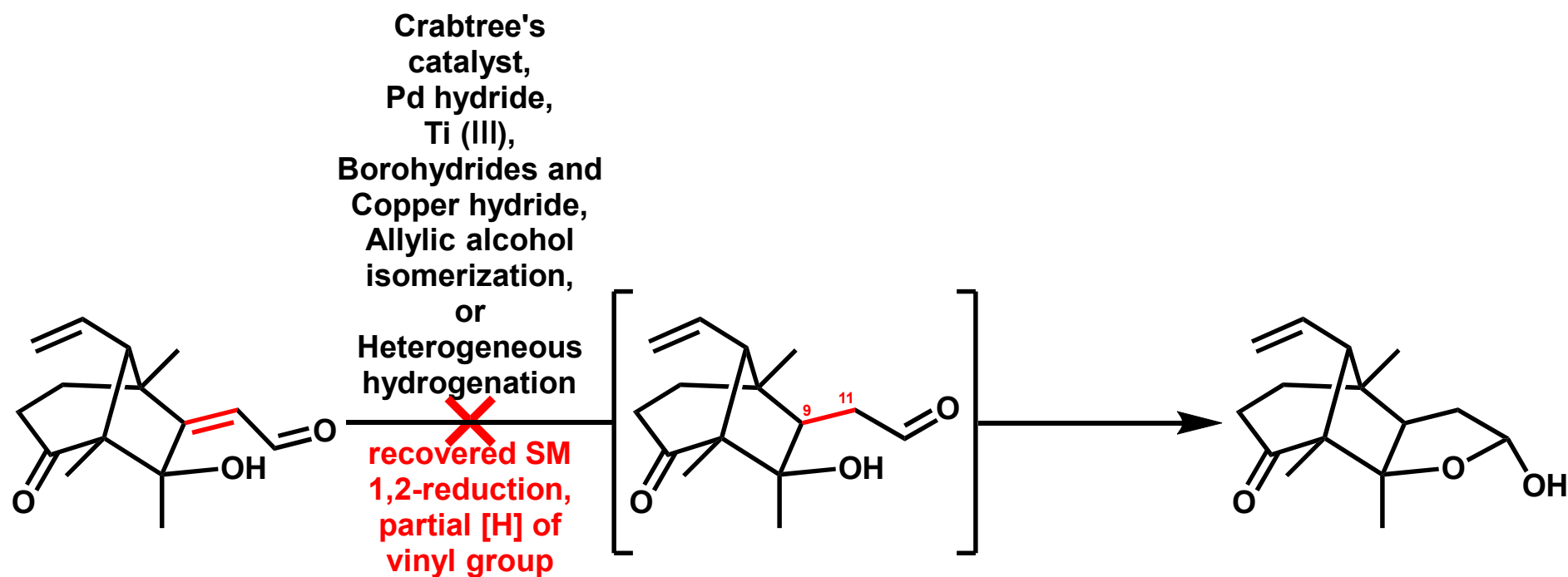
Installation of B Ring with $\text{BF}_3 \cdot \text{Et}_2\text{O}$



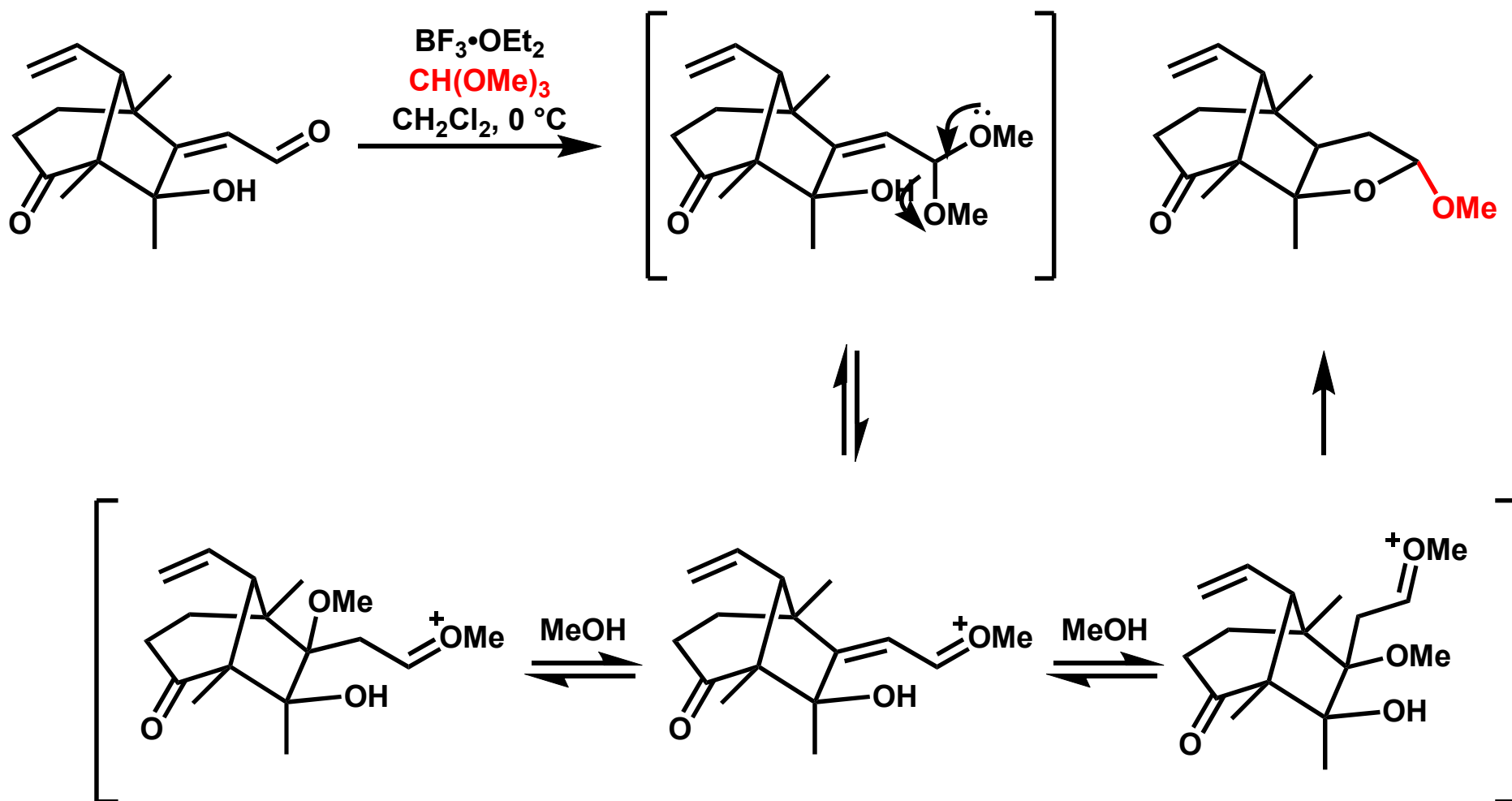
Installation of B Ring with TiCl_4



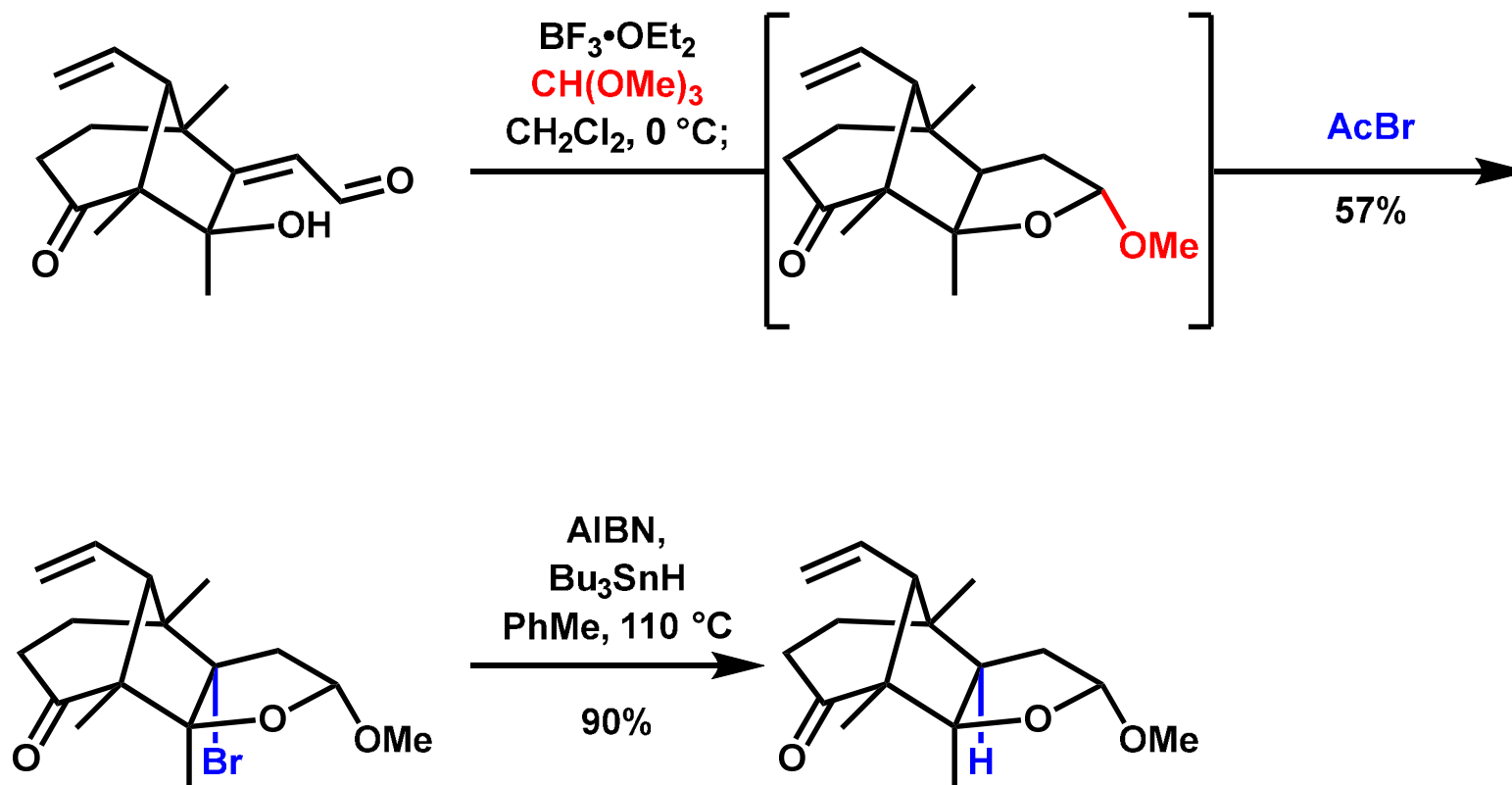
Failed Attempts at C9-C11 Reduction



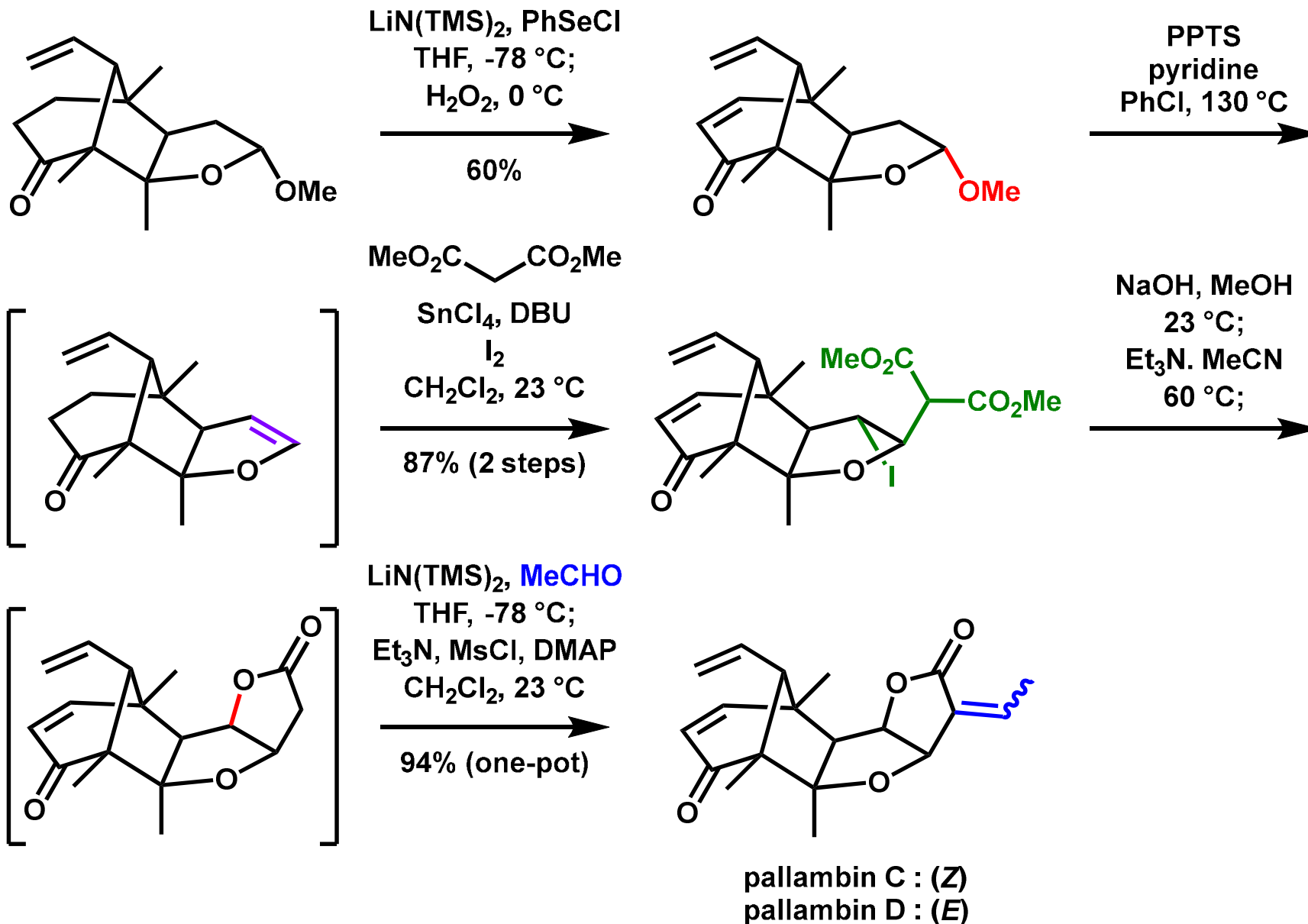
Saturation of C9-C11 olefin



Installation of C Ring through 2 Step-Reduction



Synthesis of D Ring and Total Synthesis of Pallambins C-D



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 - 2.3. Total synthesis of (-)-Pallambins A-D by Jia's group (2019)**

Introduction of Prof. Yanxing Jia



1993–1997 B. Sc., Chemistry, Lanzhou University Lanzhou, China

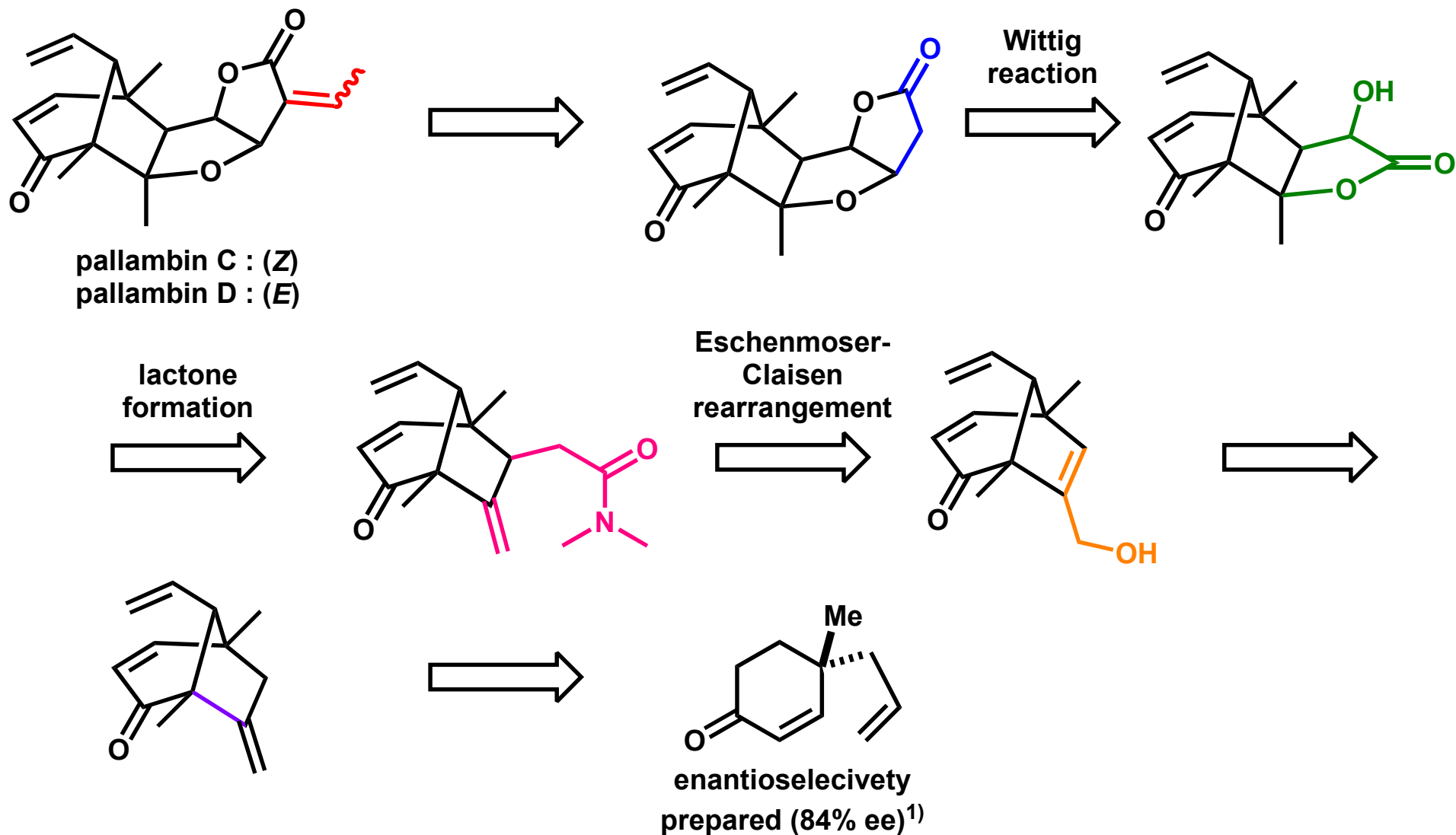
1997–2002 Ph.D., Organic Chemistry, Lanzhou University Lanzhou, China (Prof. Yongqiang Tu)

2002–2007 Postdoc, Institute of Chemistry of Natural Substances (ICSN), National Center for Scientific Research (CNRS), France (Prof. Jieping Zhu)

2007–2011 Associate Professor of Medicinal Chemistry (PI), Peking University

2011– Professor of Medicinal Chemistry (PI), Peking University

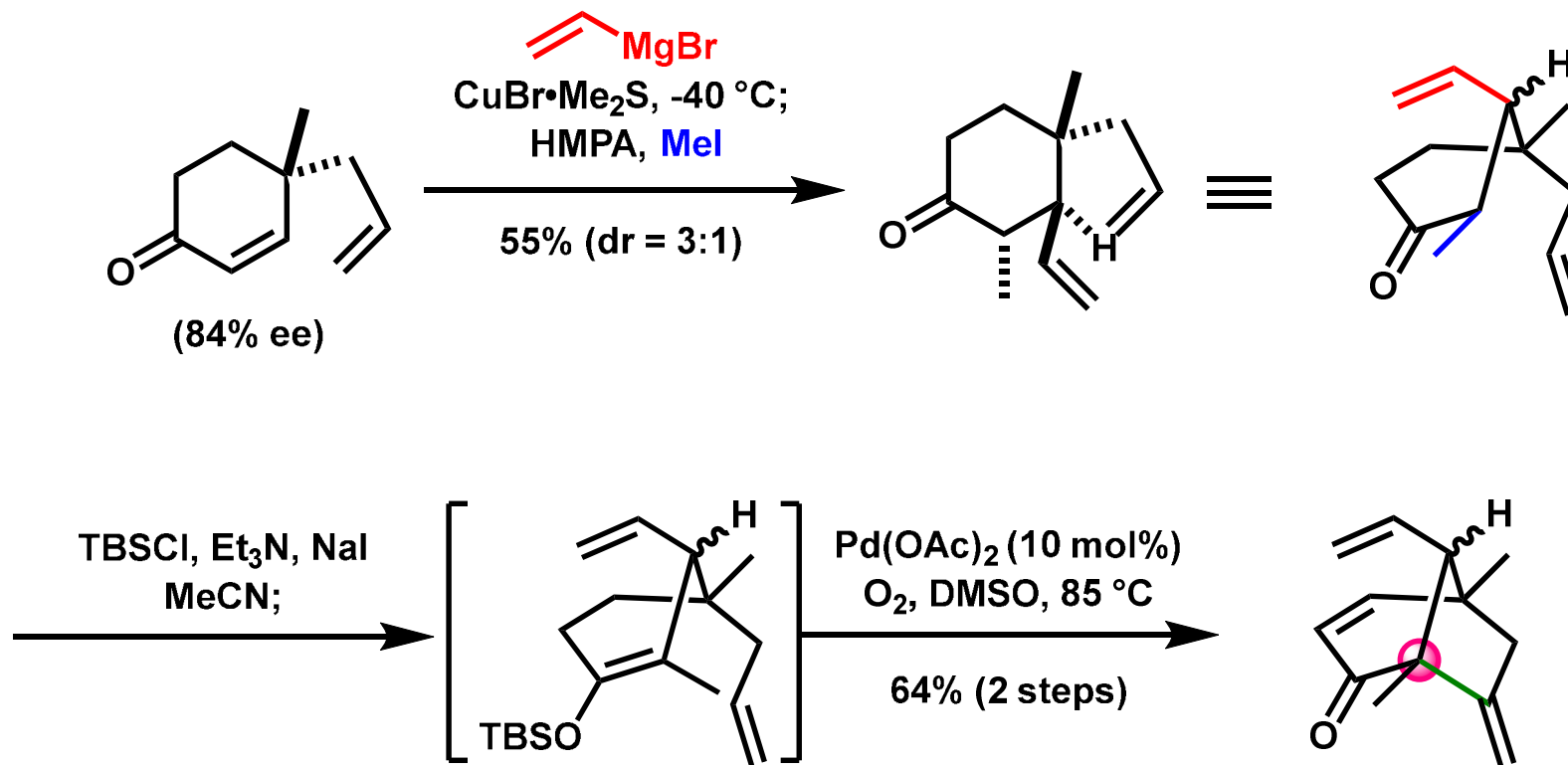
Retrosynthetic analysis of pallambins A-D by Jia's group



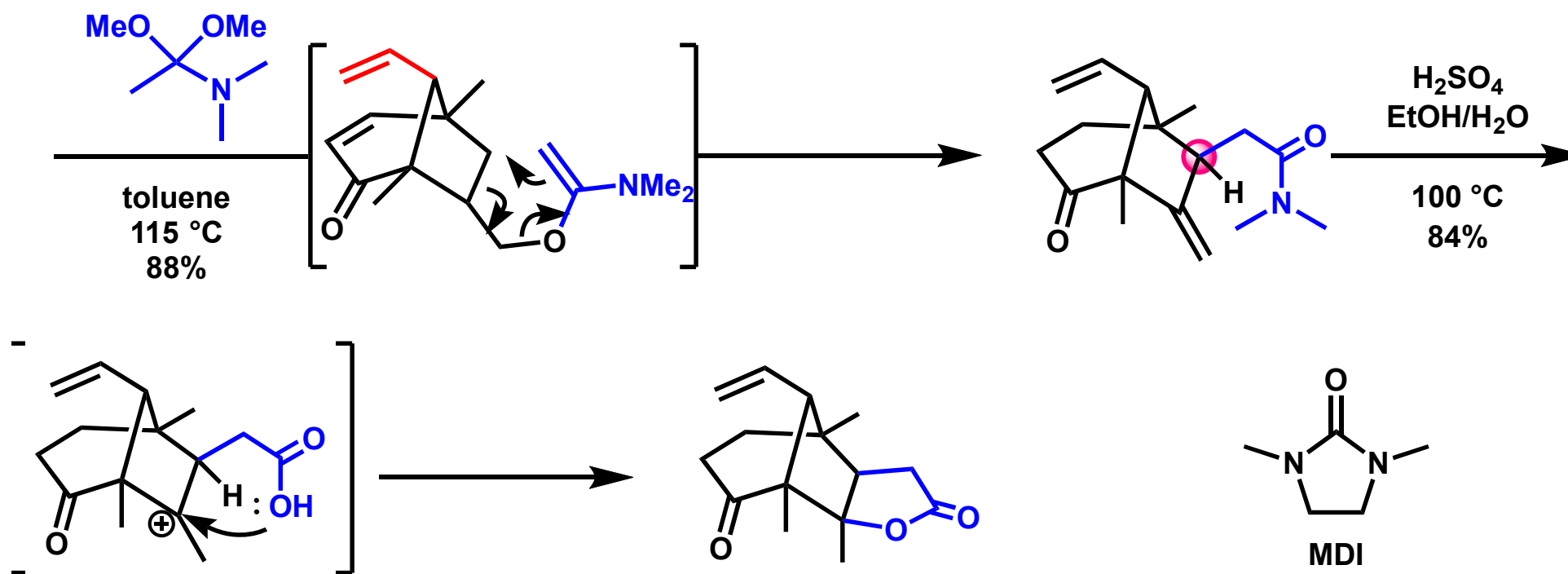
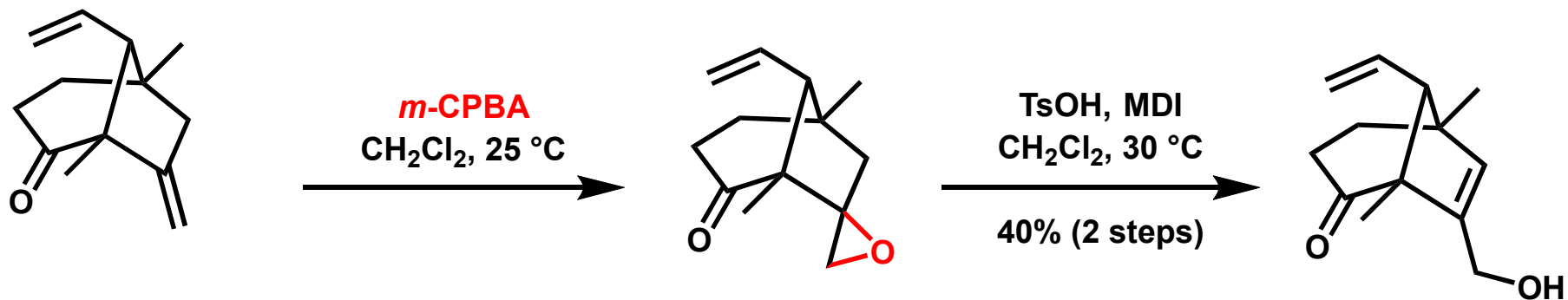
Zhang, X.; Cai, X.; Huang, B.; Guo, L.; Gao, Z.; Jia, Y. *Angew. Chem. Int. Ed.* **2019**, *58*, 13380.

1) Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 289.

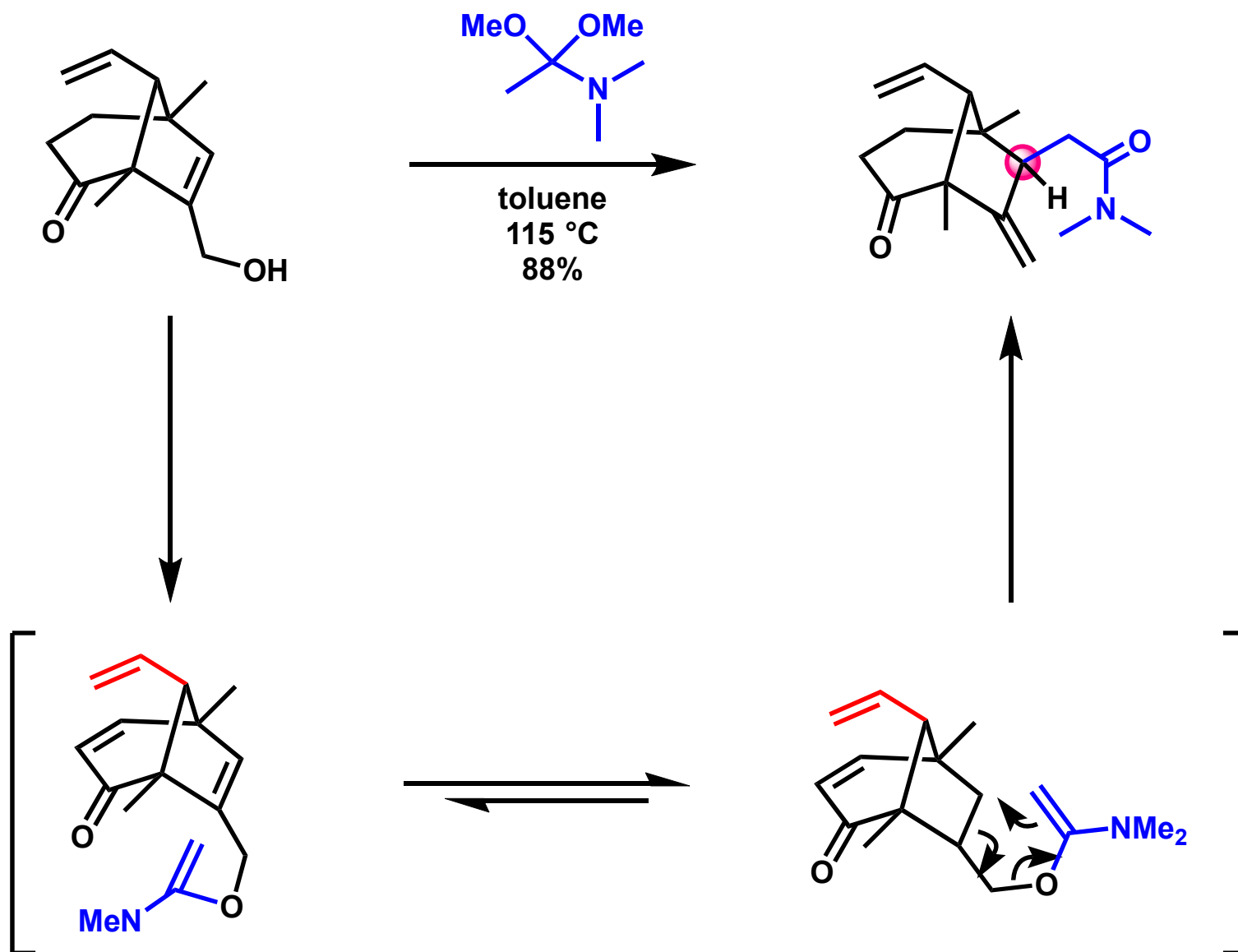
Installation of B Ring



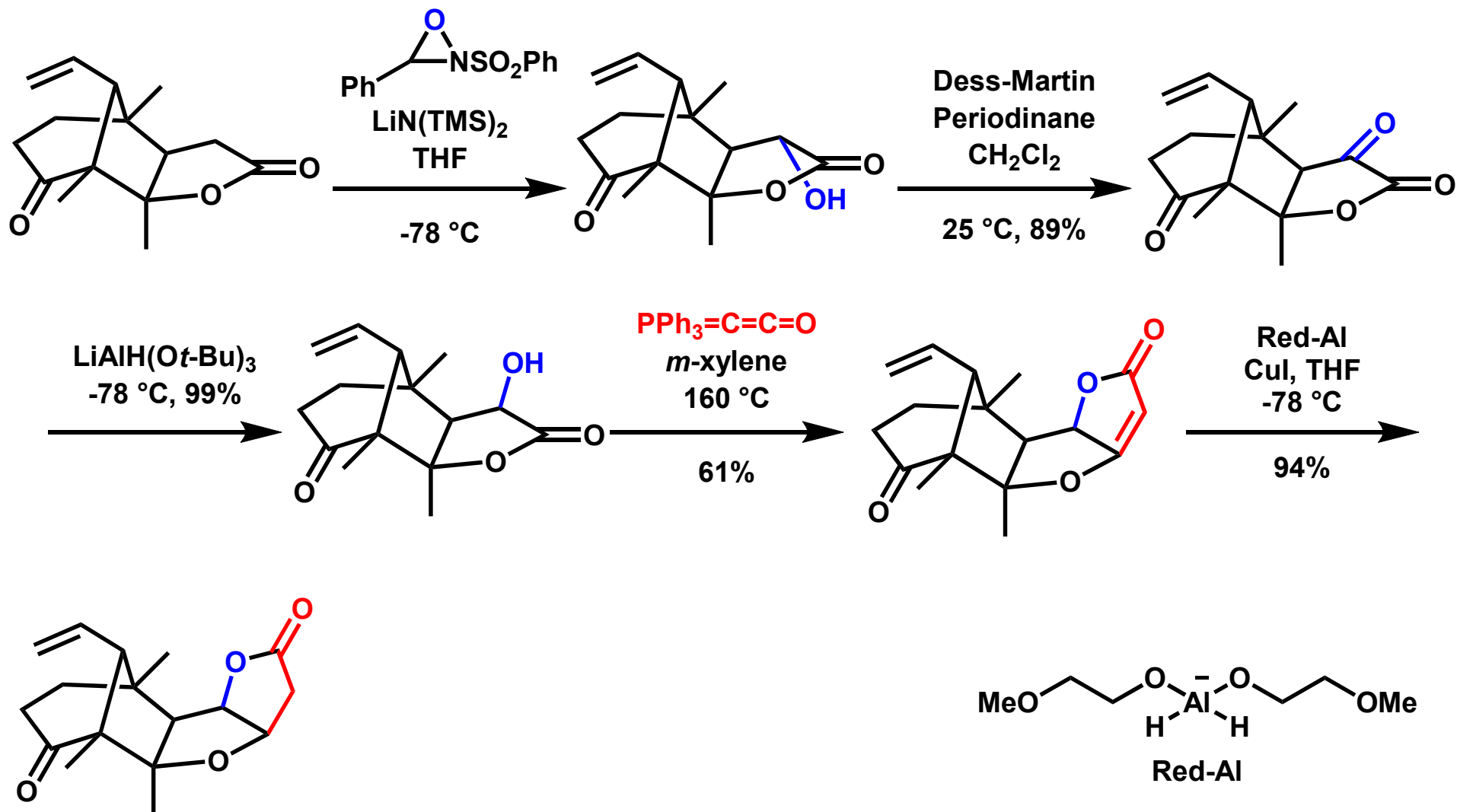
Installation of C Ring



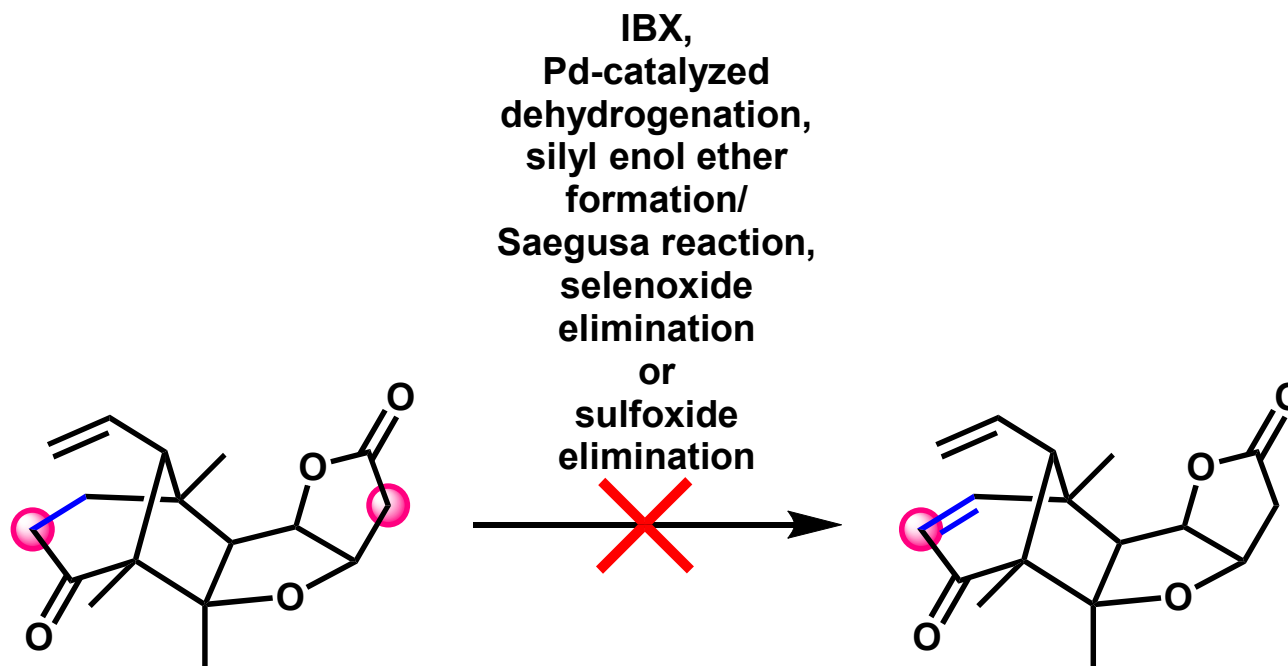
Installation of C Ring



Installation of D Ring



Installation of C1, C2 Double Bond

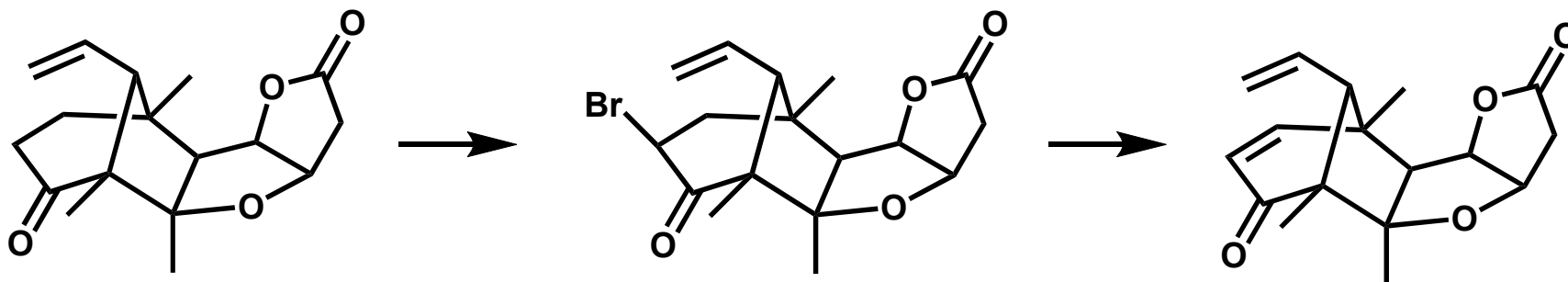


One-step methods and two-step methods for the direct dehydrogenation of ketones didn't give any desired product.

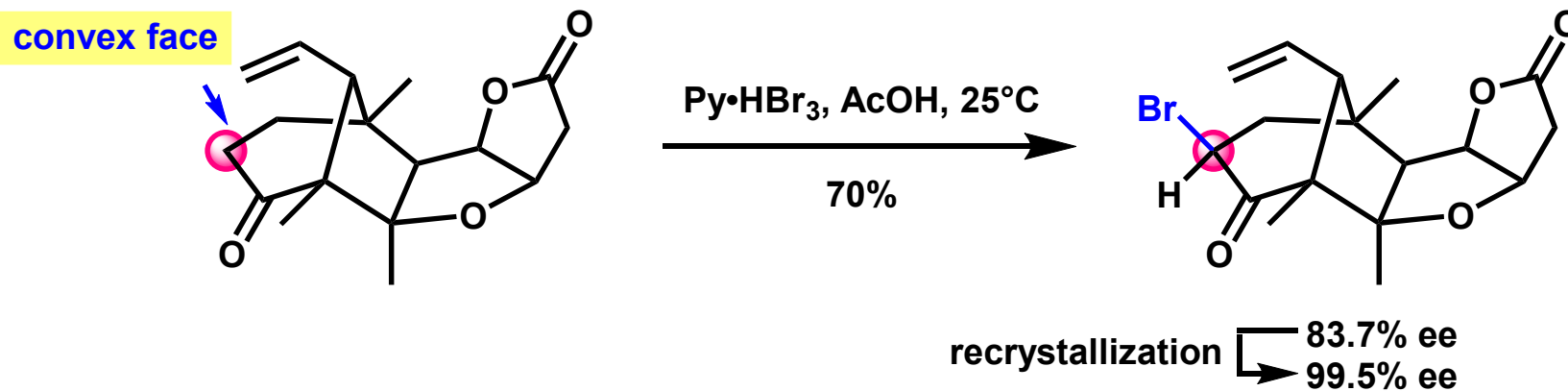
Zhang, X.; Cai, X.; Huang, B.; Guo, L.; Gao, Z.; Jia, Y. *Angew. Chem. Int. Ed.* **2019**, *58*, 13380.

Installation C1, C2 Double Bond

bromination/dehydrobromination

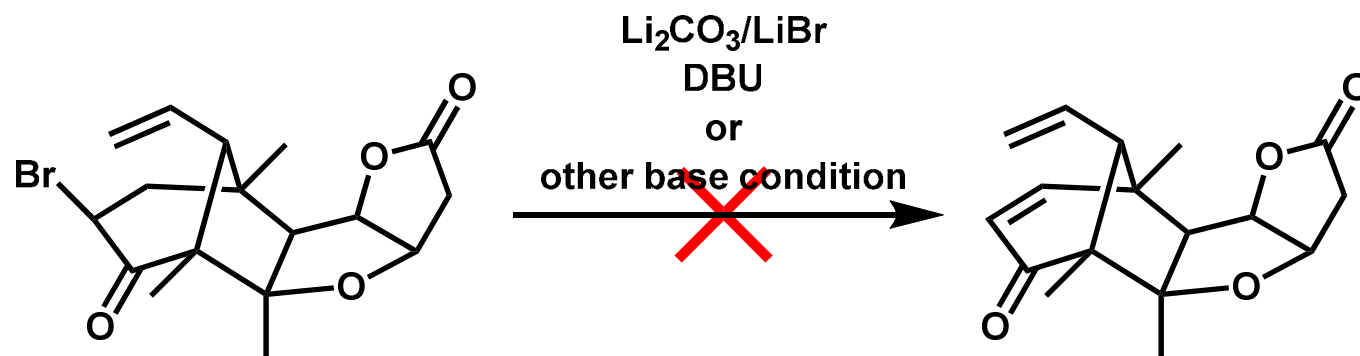


Synthesis of α -bromoketone



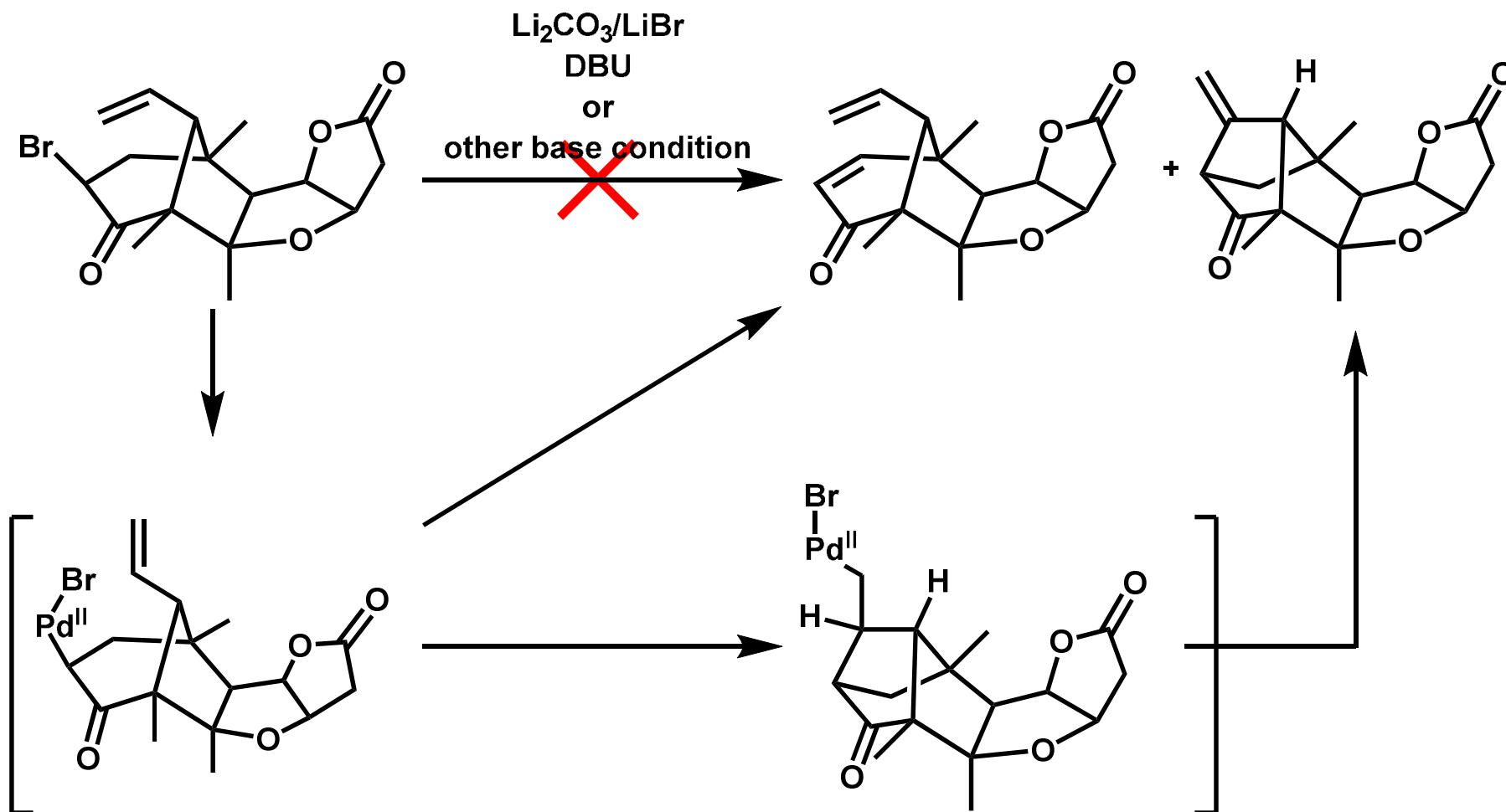
Debromination of α -Bromoketone

Failed attempts at debromination



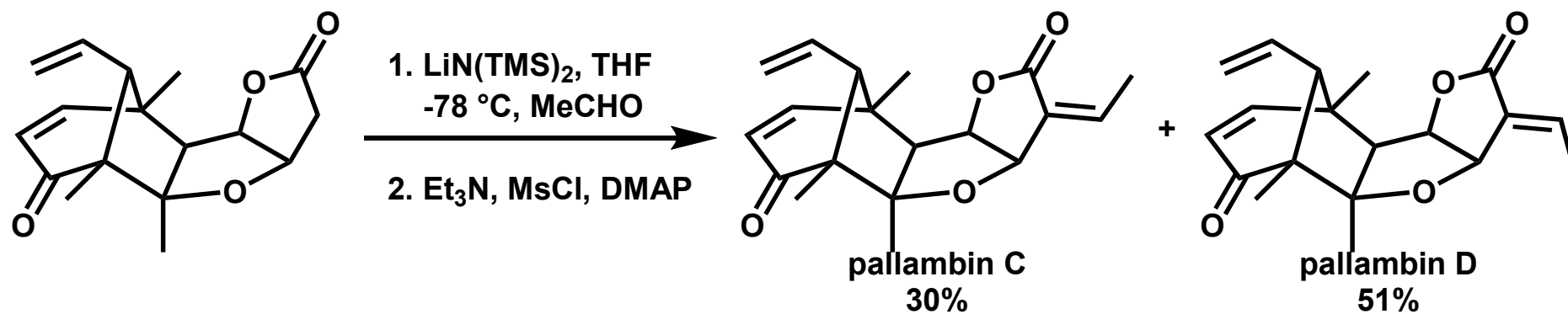
Debromination of α -Bromoketone

A mild dehydrobromination method

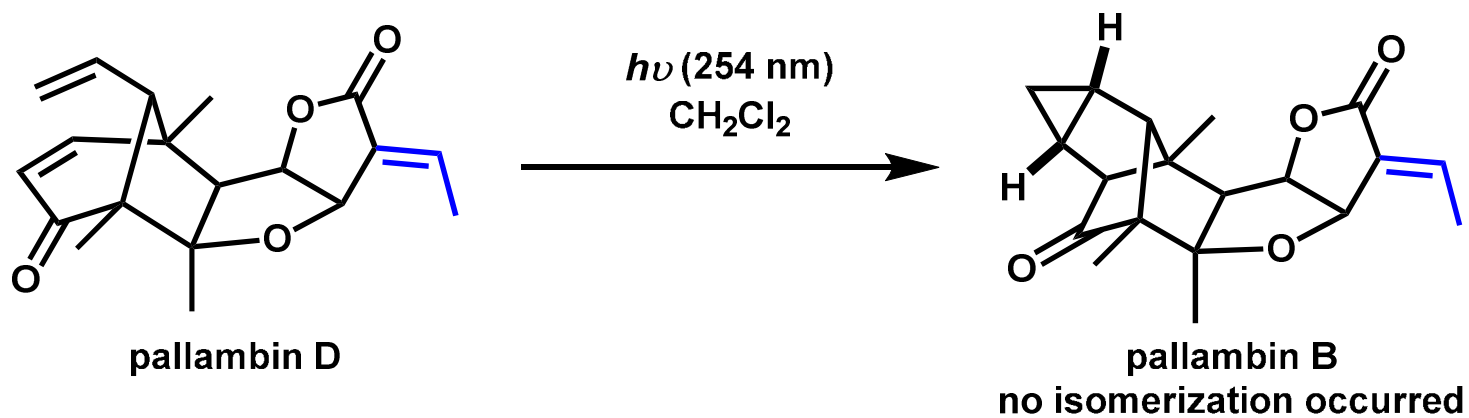
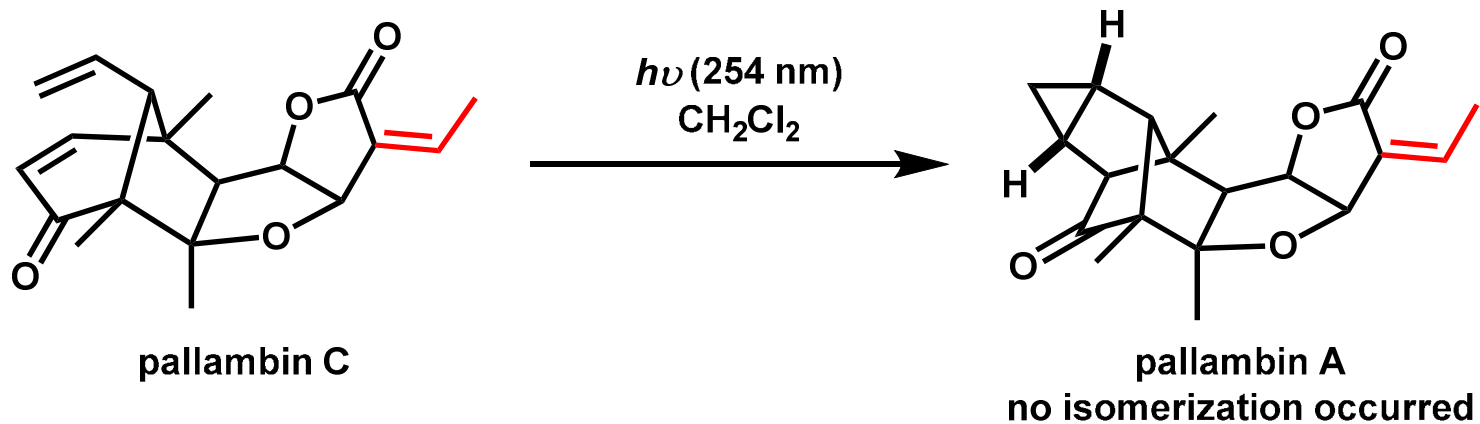


Zhang, X.; Cai, X.; Huang, B.; Guo, L.; Gao, Z.; Jia, Y. *Angew. Chem. Int. Ed.* **2019**, *58*, 13380.

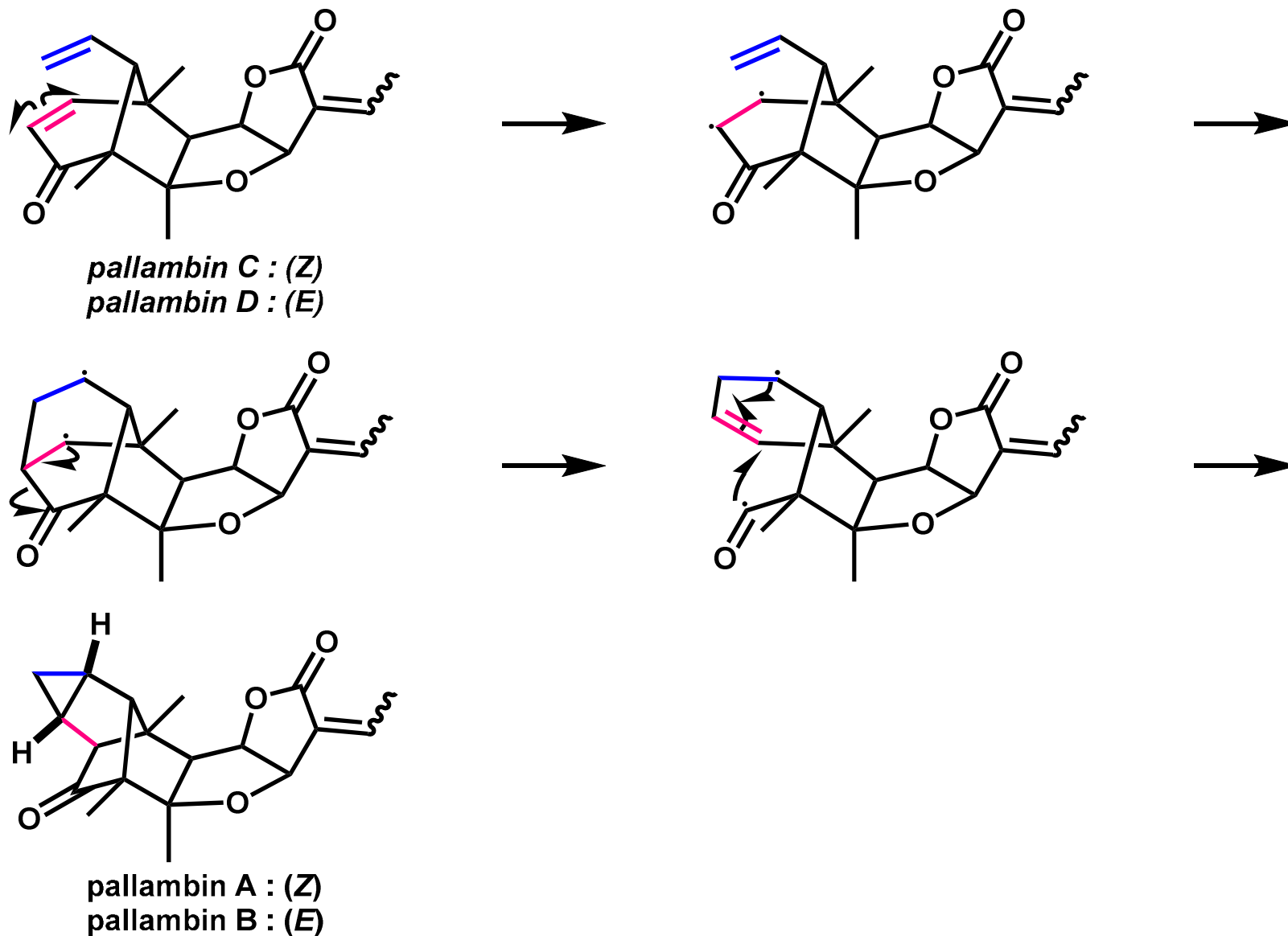
Total Synthesis of Pallambins C, D



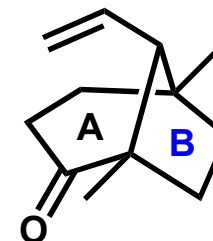
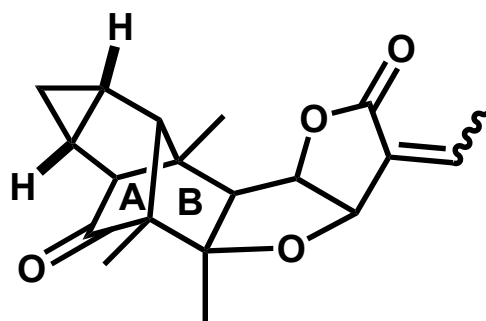
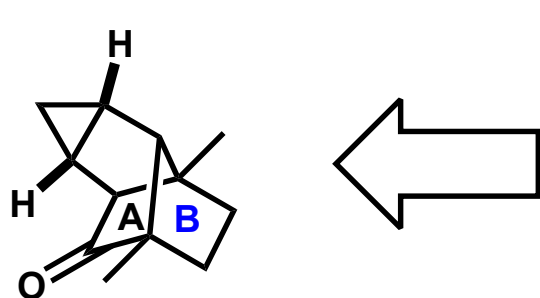
Total Synthesis of Pallambins A, B



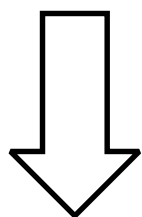
A Mechanism of Interconversion of Pallambins C·D into A·B



Conclusion



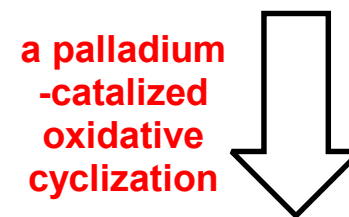
pallambin A : (*Z*)
pallambin B : (*E*)



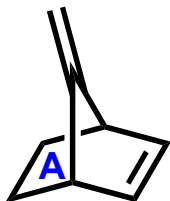
**C-H
insertion**



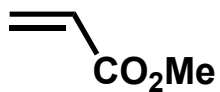
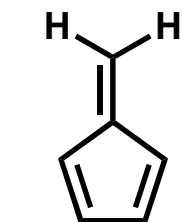
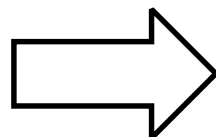
**Mukaiyama
aldol**



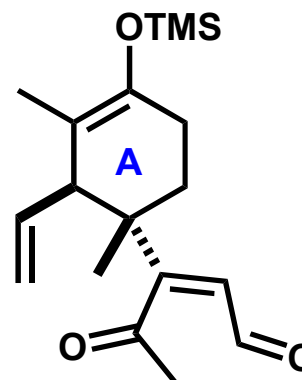
**a palladium
-catalyzed
oxidative
cyclization**



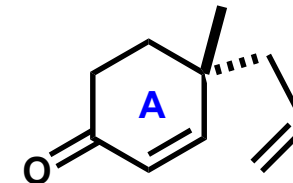
**Diels-Alder
reaction**



**Carreira's Group
(23 steps)**



**Baran's Group
(12 steps)**



**Jia's Group
(16 steps)**