Asymmetric total synthesis of Pedrolide

Chuang-Chuang Li

About the author

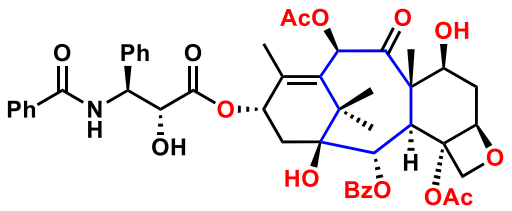
Chuang-Chuang Li

1997-2001: BS in Chemistry, China Agricultural University

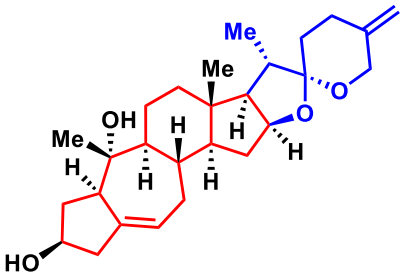
2001-2006: Ph.D. in Chemistry, Peking University. Research Advisor: Zhen Yang

2006-2008: Postdoc in Chemistry, The Scripps Research Institute. Research Advisor: Phil S. Baran

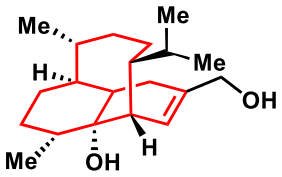
Present: Chair Professor in Department of Chemistry, Southern University of Science and Technology.



Taxol



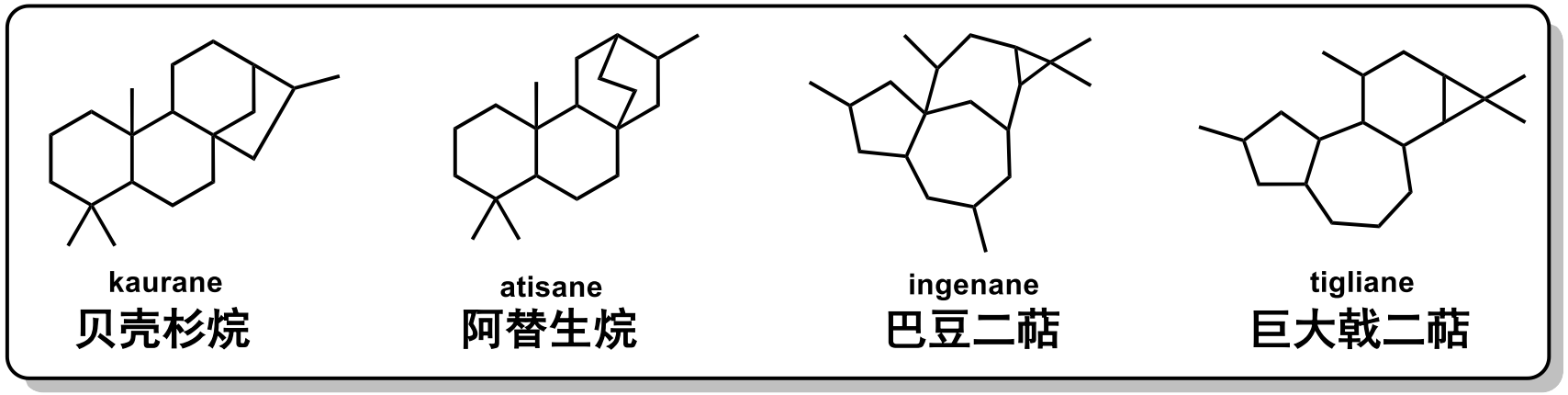
Bufospirostenin A



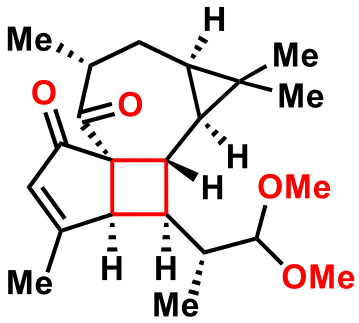
(-)-Vinigrol

Background

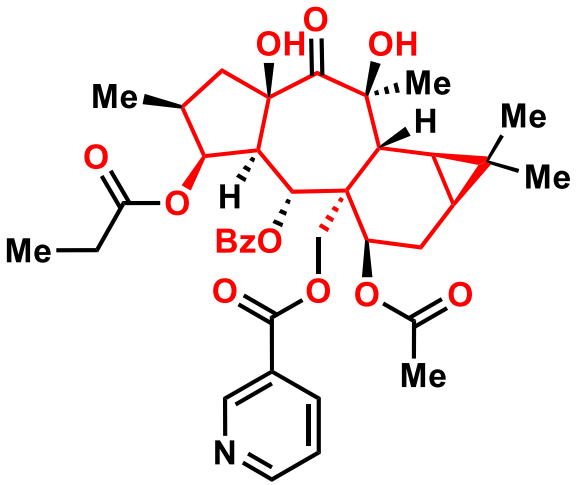
Represented skeleton of Euphorbia diterpenoids



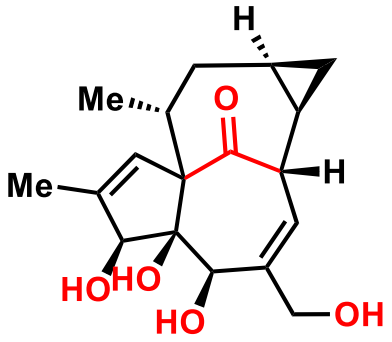
Sheng Yin. et. al. *Nat. Prod. Rep*. **2022**, *39*, 2132



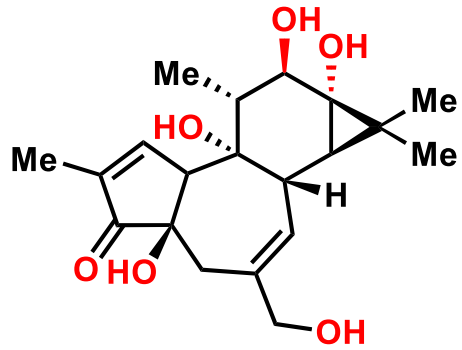
Pepluacetal
X.G. She, 2024



Euphorbialoid A
Masayuki Inoue, 2024



(+)-Ingenol
Phil S. Baran, 2016



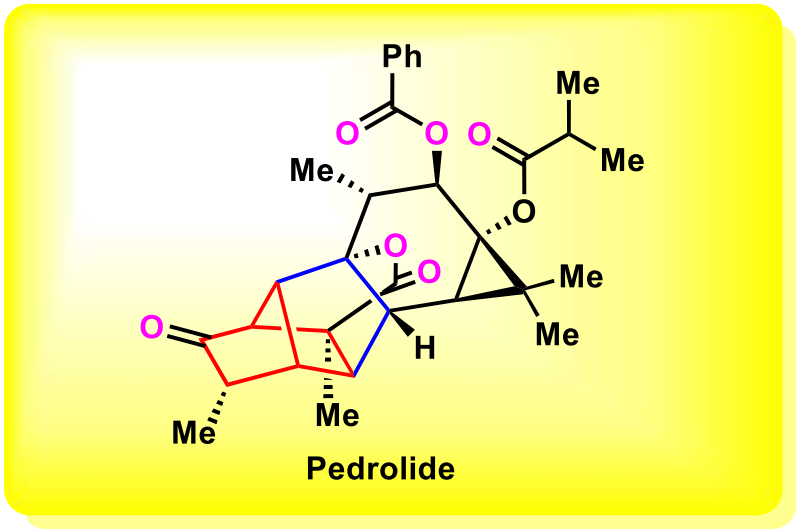
(+)-Phorbol
Phil S. Baran

Xuegong She. et. al. *Angew. Chem. Int. Ed*. **2024**, *63*, e202400943
Masayuki Inoue. et. al. *J. Am. Chem. Soc*. **2024**, *146*, 34221
Phil S. Baran. et. al. *Nature*. **2016**, *532*, 90; *Science*. **2013**, *341*, 878

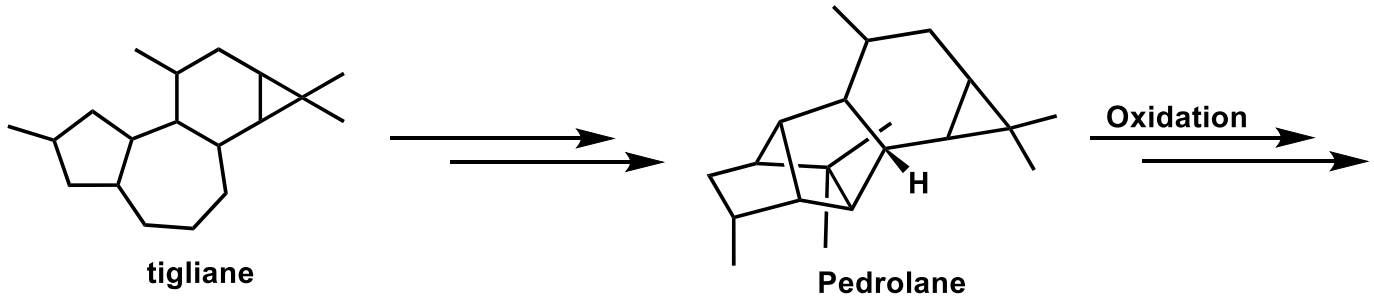
Background

Euphorbia pedroi

大戟科多肉植物



Proposed biosynthesis:



Pedrolane family was isolated in 2021.

Maria-José U. Ferreira. et. al. *Org. Lett*. **2021**, *23*, 274

Structural features:

Unprecedented skeleton: pedrolane

[5-5-5-6-6-3] hexacyclic core; bicyclo[2.2.1]heptane

12 contiguous stereocenters; 3 quaternary carbon

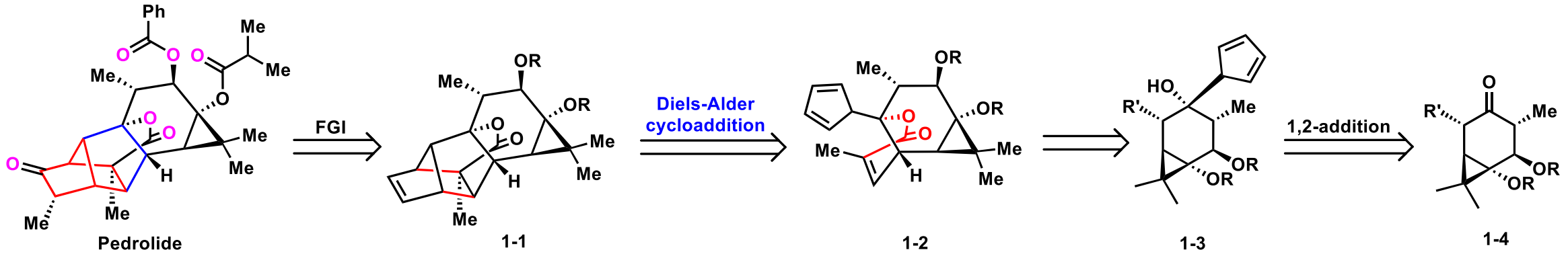
Highly oxygenated

Total synthesis: Erick M. Carriera (2023); Bo Liu (2024); Chuang-chuang Li (2024)

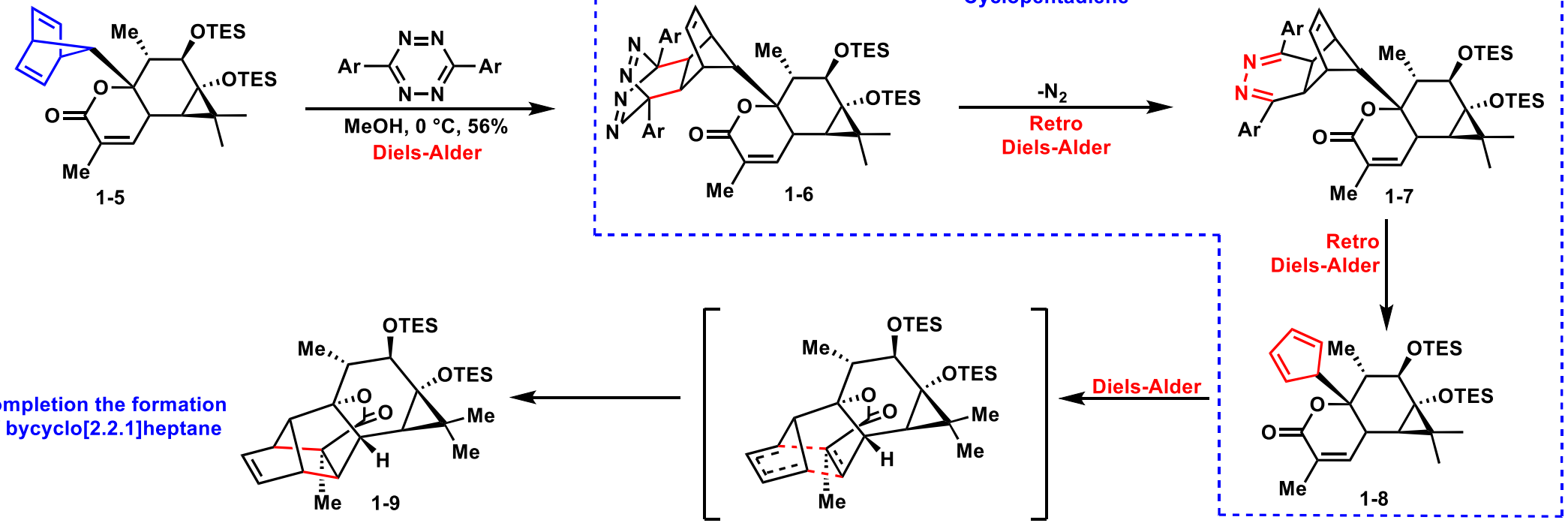
Chuang-Chuang Li. et. al. *J. Am. Chem. Soc*. **2024**, *146*, 2928

Background: Previous synthesis studies

Erick M. Carriera's synthesis towards Pedrolide:

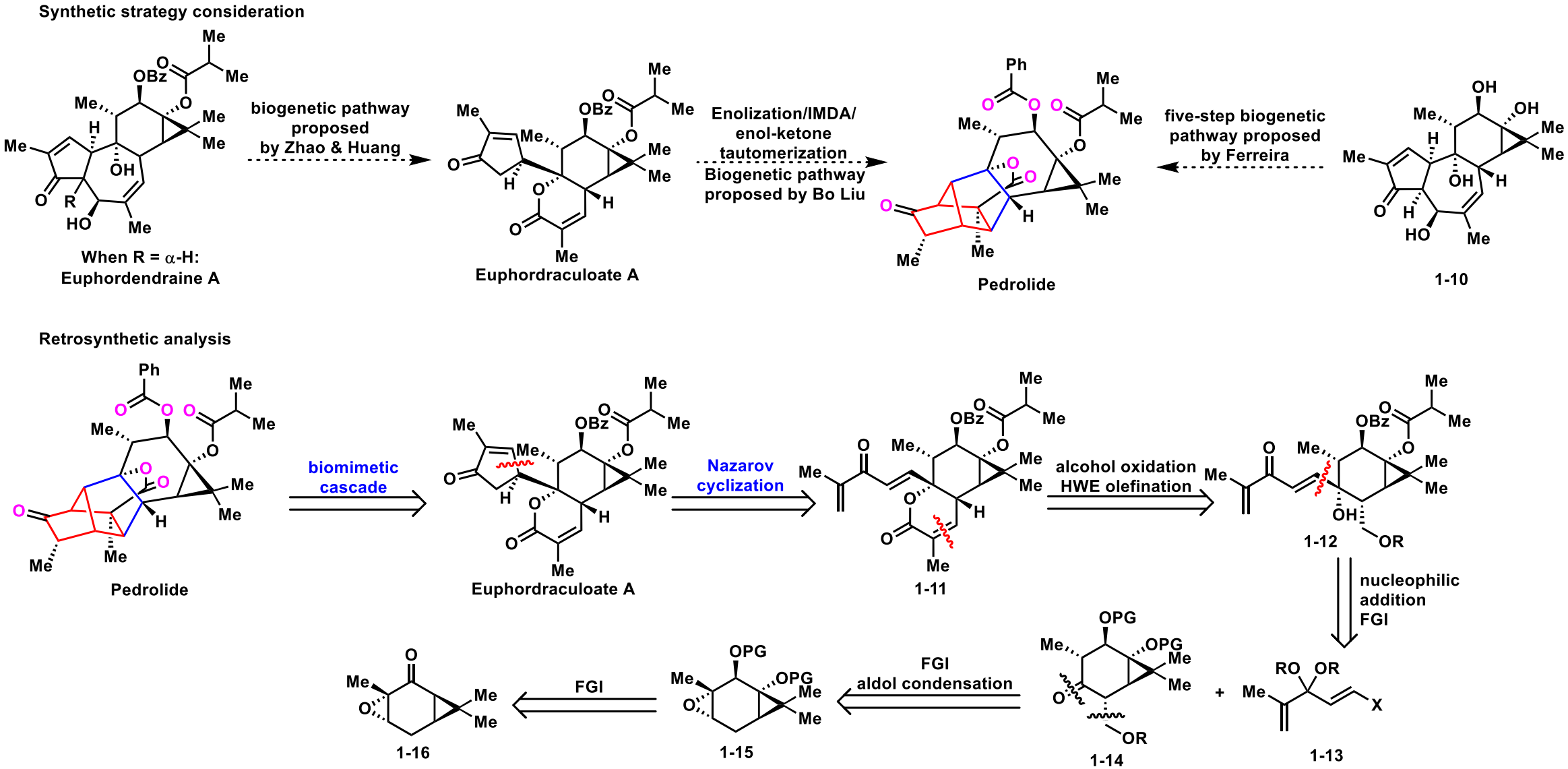


Key transformation:



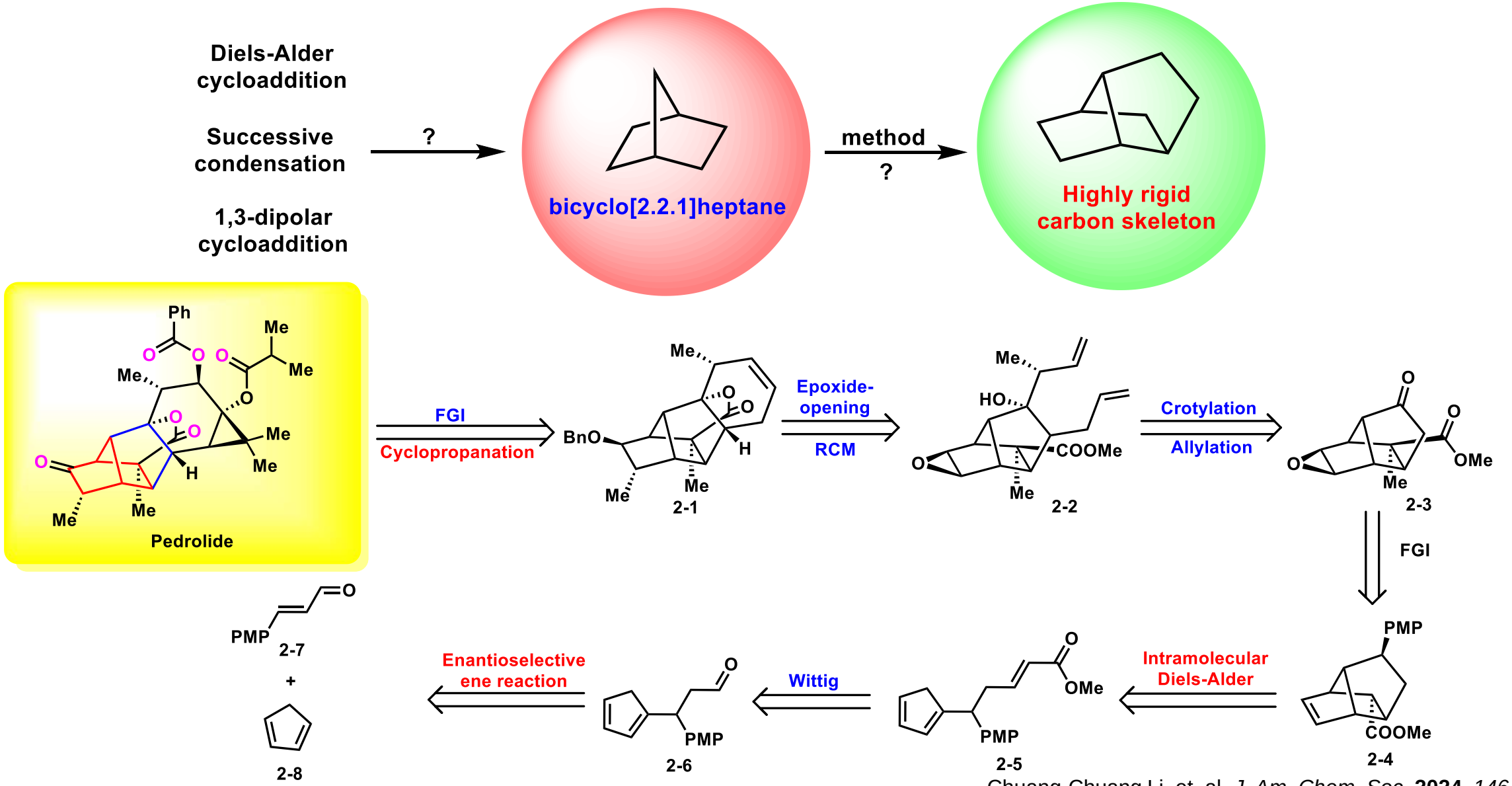
Background: Previous synthesis studies

Bo Liu's bio-inspired synthesis towards Pedrolide:

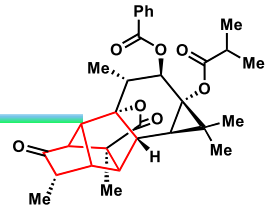


Total synthesis towards Pedrolide

Chuang-Chuang Li's work: Retrosynthetic analysis

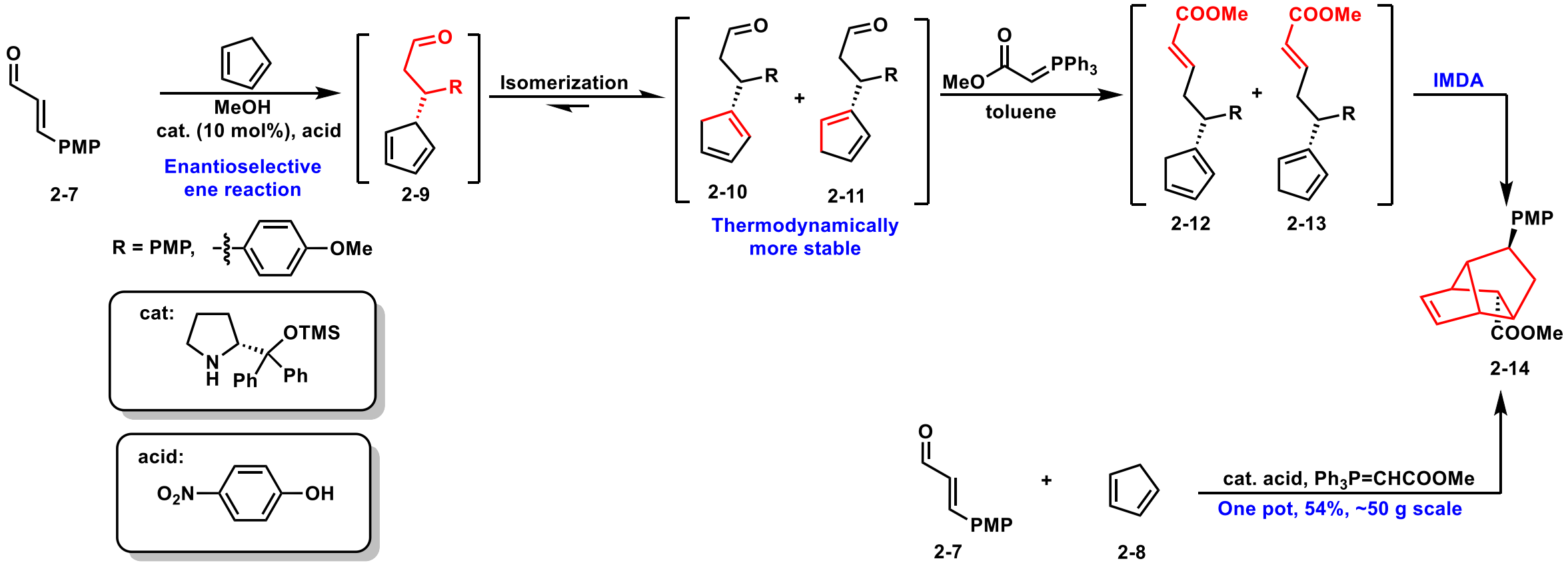


Total synthesis towards Pedrolide

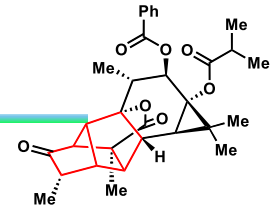


Chuang-Chuang Li's work: Construction the bicyclo[2.2.1]heptane

The enantioselective ene reaction & Intramolecular Diels-Alder cycloaddition sequence



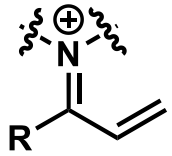
Total synthesis towards Pedrolide



About the enantioselective Ene reaction

We all know that:

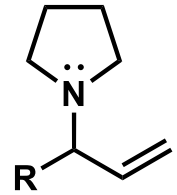
Iminium catalyst



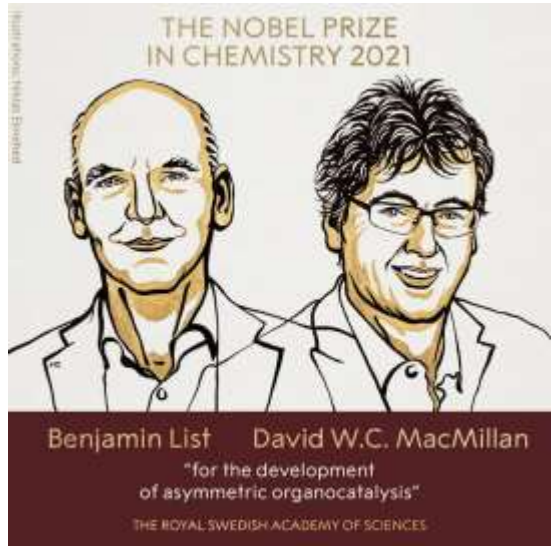
Additions of:
malonate ester / nitroalkanes /
aromatics / silyloxy furans
Diels-Alder / Dipolar cycloaddition

Chemistry of carbocation
David W. MacMillan

Enamine catalyst

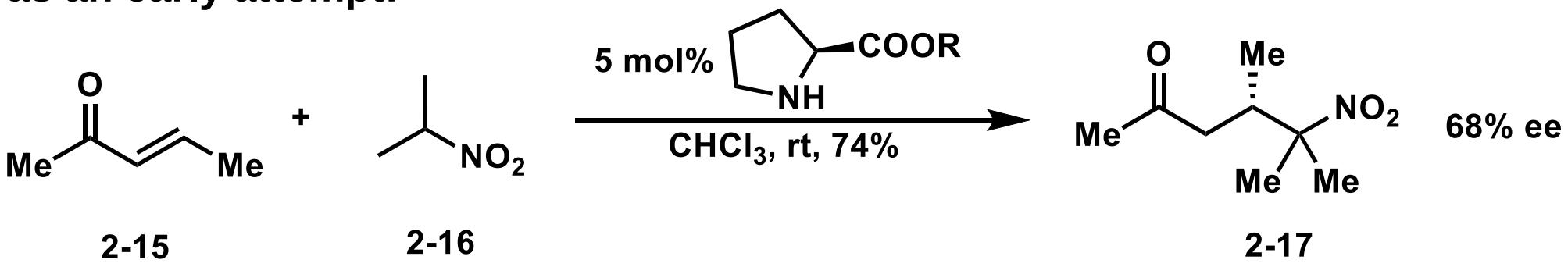


Chemistry of carbanion
Benjemin List



Mei-Xiang Wang, Shuo Tong. *Advanced Organic Chemistry Lecture.* Tsinghua. Univ. **2024**

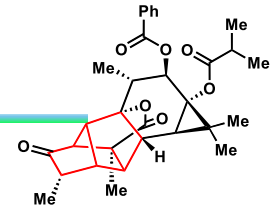
But as an early attempt:



2-15 **2-16** **2-17**

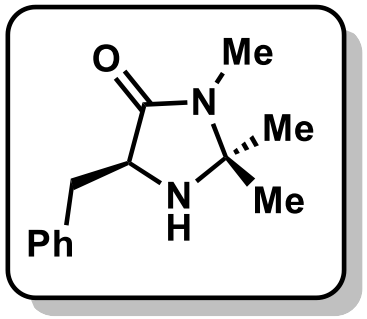
Masahiko Yamaguchi. et. al. *J. Org. Chem*. **1996**, *16*, 3520

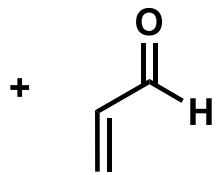
Total synthesis towards Pedrolide

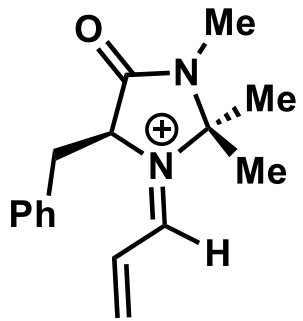


The enantioselective Ene reaction

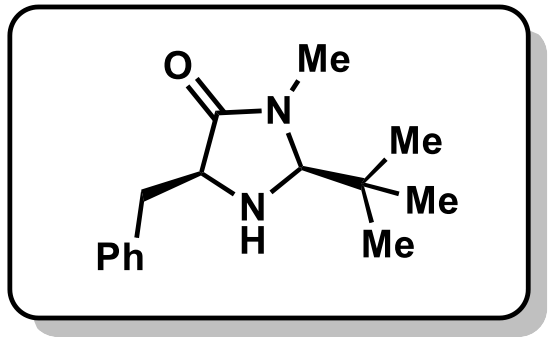
Macmillan catalyst:



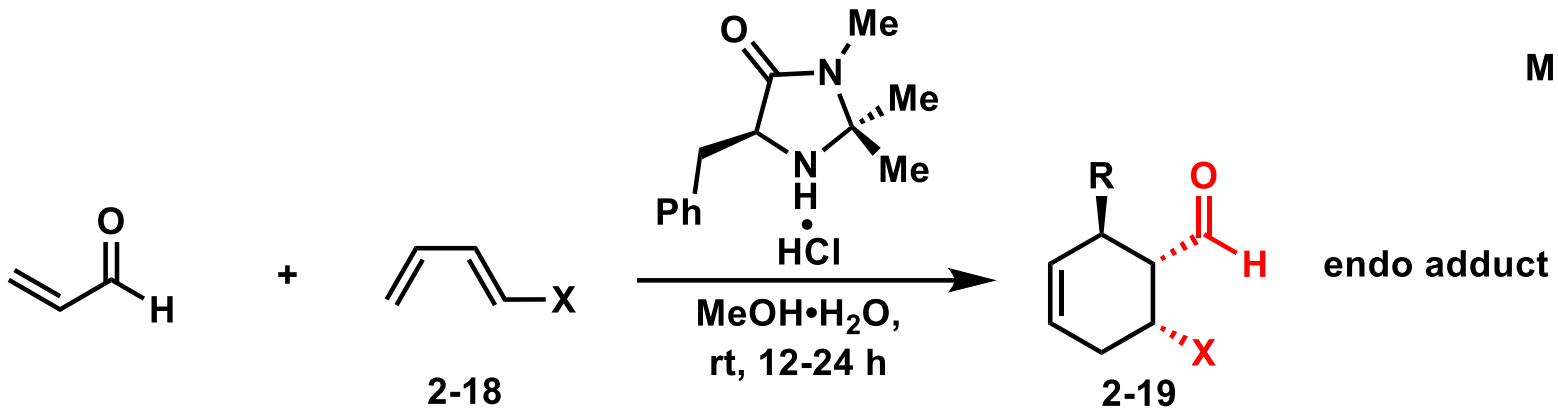




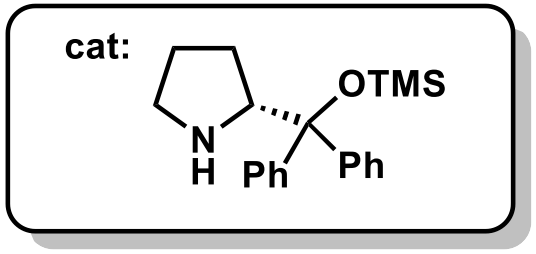
iminium salt



enhance the stereoselectivity



Modification of the traditional Macmillan catalyst:

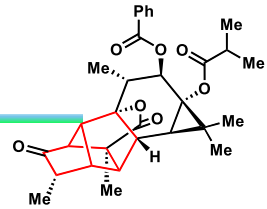


Make the Ene reaction stereocontrollable

David W. C. Macmillan. et. al. *J. Am. Chem. Soc.* **2002**, *124*, 1172

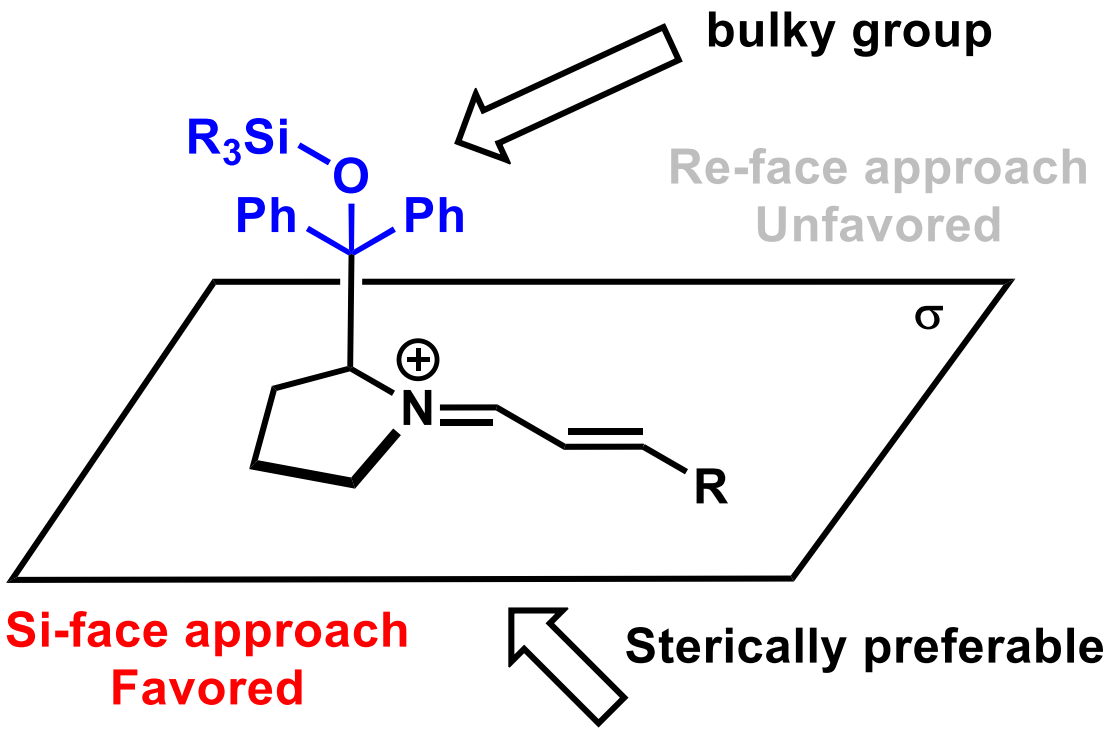
Yujiro Hayashi. et. al. *Chem. Eur. J.* **2015**, *21*, 12337

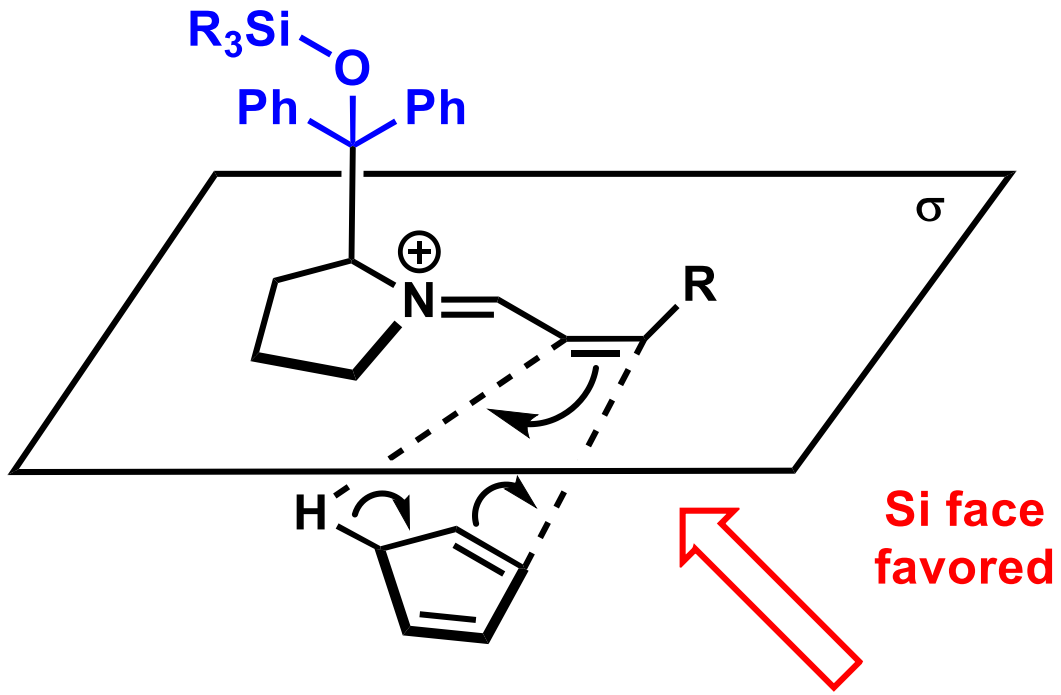
Total synthesis towards Pedrolide



The enantioselective ene reaction

Proposed reaction pathway & T.S.:



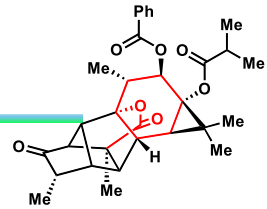


Isomerization:

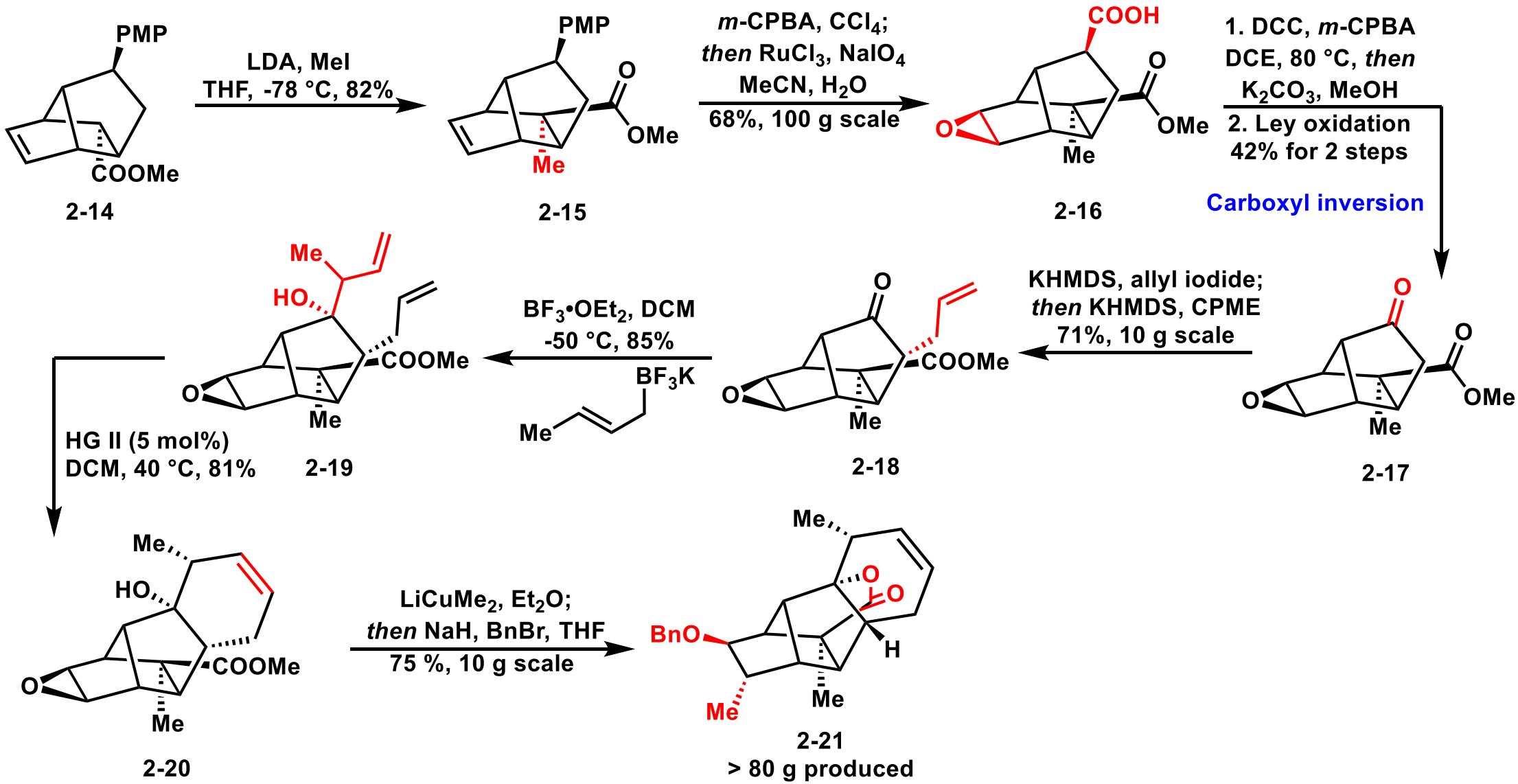
Calculation level: rev-DSDPBEP86-D3(BJ)/def2TZVPP//B3LYP-D3(BJ)-def2SVP

Yujiro Hayashi. et. al. *Chem. Eur. J.* **2015**, *21*, 12337

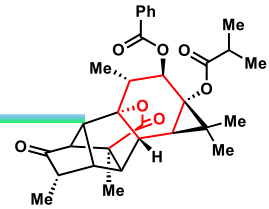
Total synthesis towards Pedrolide



Chuang-Chuang Li's work: Cyclization & lactonization

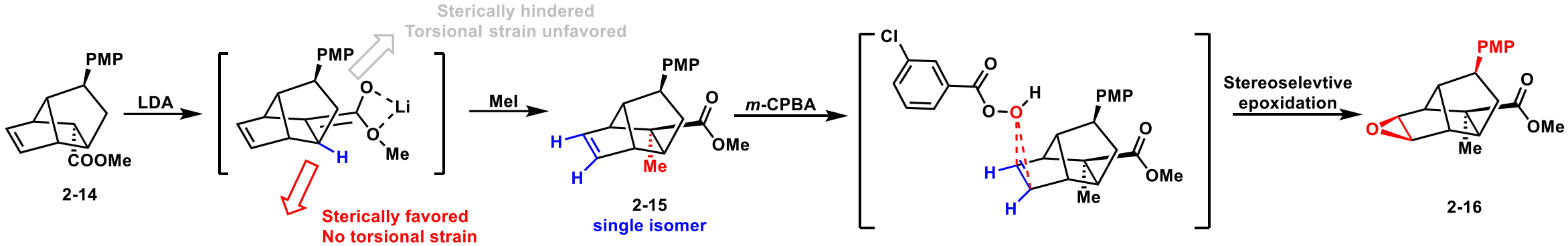


Total synthesis towards Pedrolide

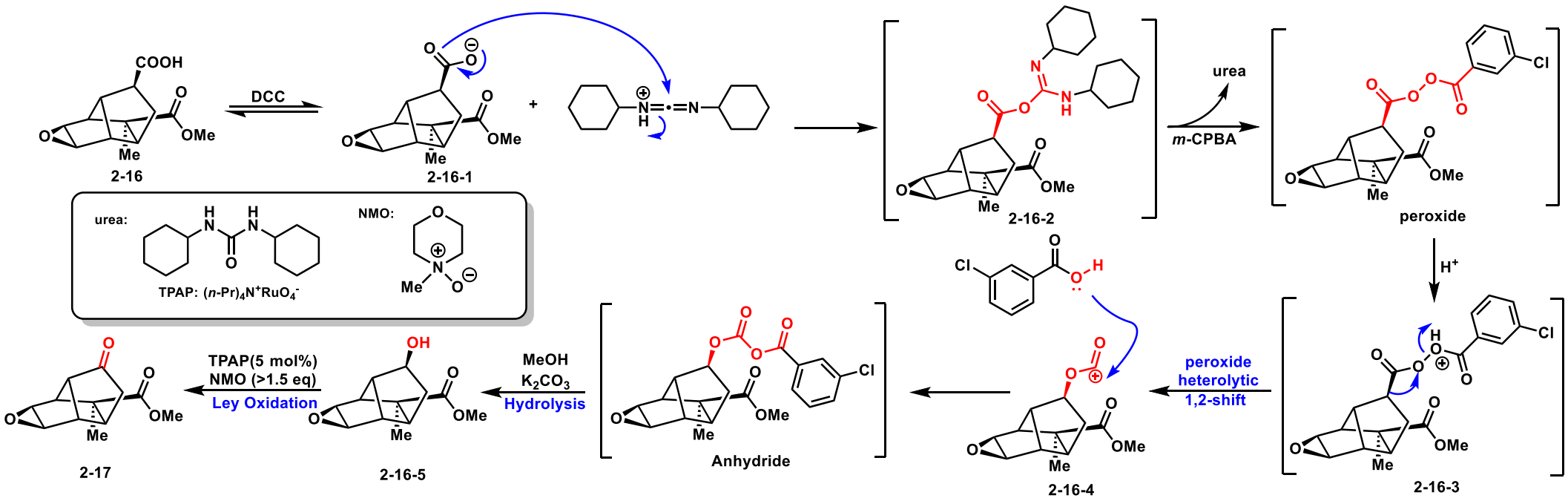


Chuang-Chuang Li's work: Mechanism & Selectivity

Enolate alkylation & Epoxidation:

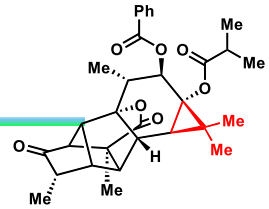


Carboxyl inversion reaction:



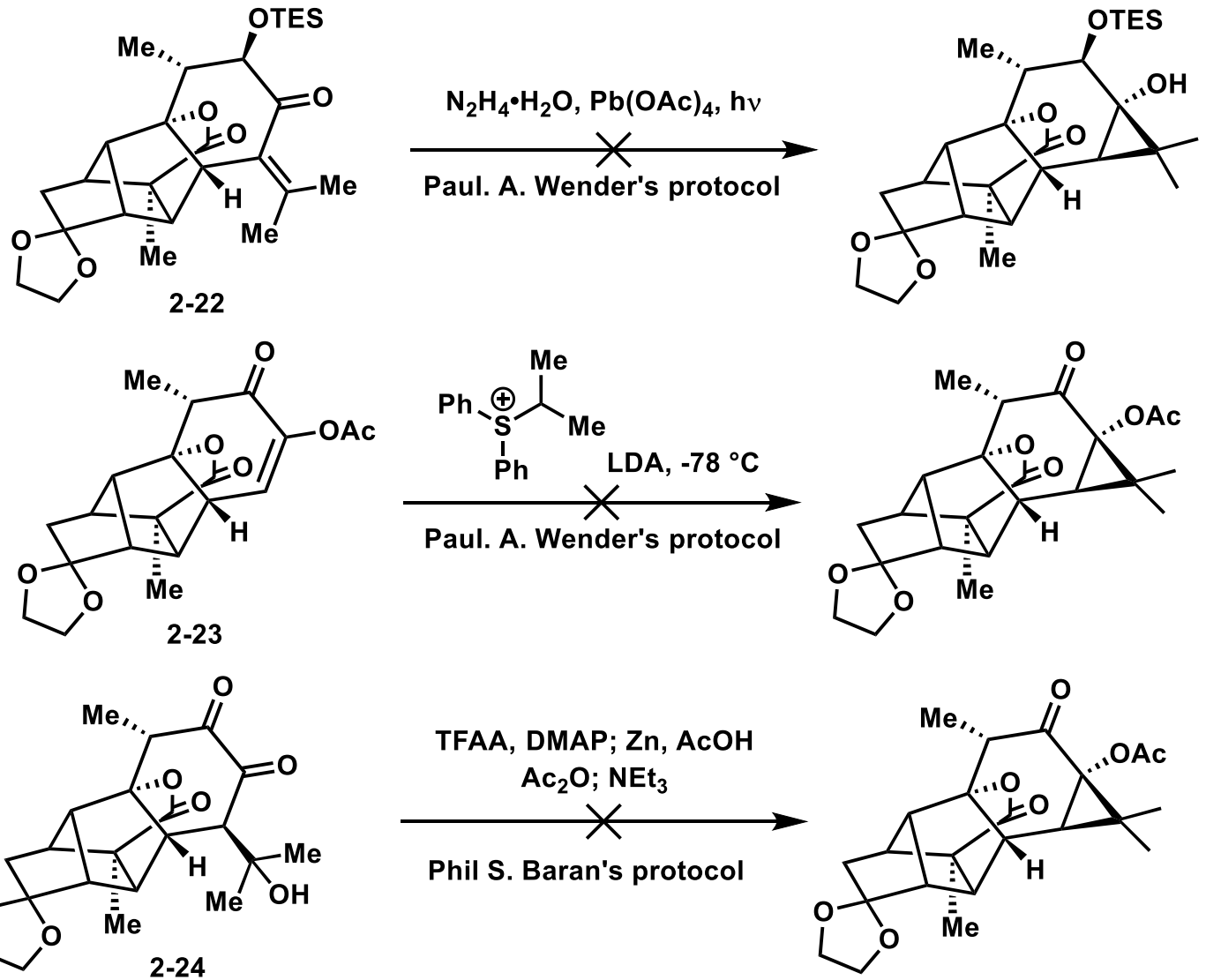
Norman Sherman. et. al. *J. Org. Chem.* **1965**, *30*, 3760

Total synthesis towards Pedrolide



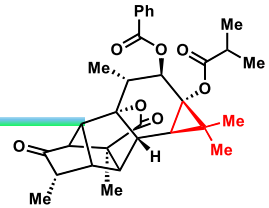
Chuang-Chuang Li's work: Cyclopropanation

Endeavor to the cyclopropane ring:

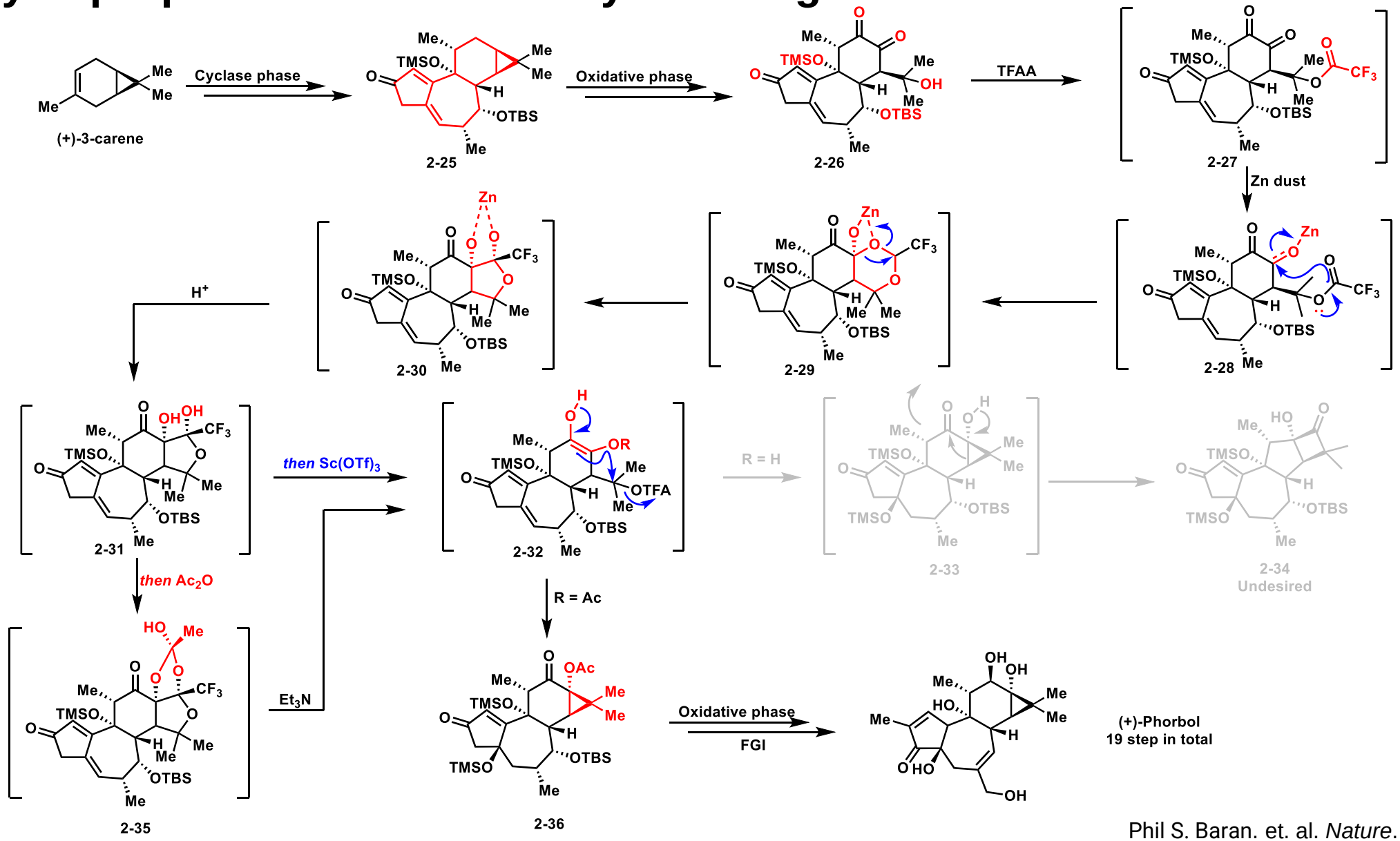


Chuang-Chuang Li. et. al. *J. Am. Chem. Soc*. **2024**, *146*, 2928

Total synthesis towards Pedrolide

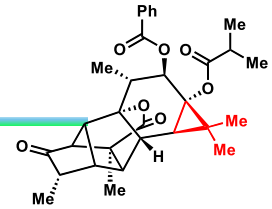


Cyclopropanation studies: Maybe a tough road !



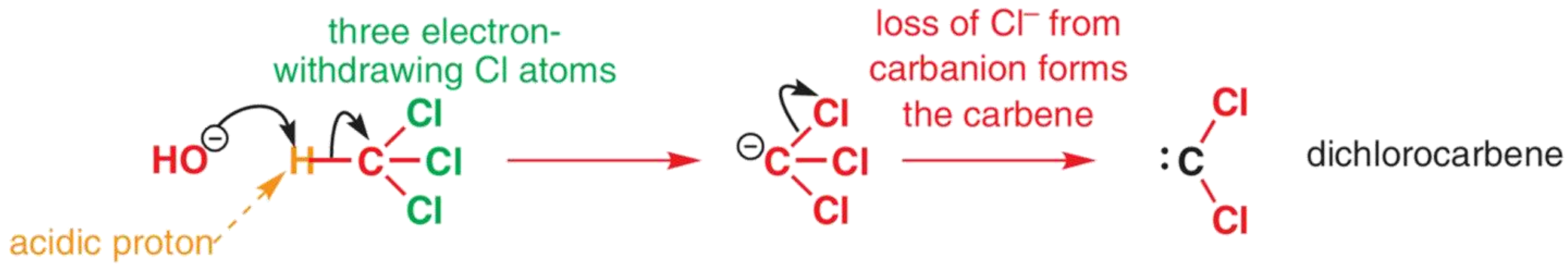
Phil S. Baran. et. al. *Nature*. **2016**, *532*, 90

Total synthesis towards Pedrolide



Cyclopropanation studies: Maybe “less is more” !

base-catalysed α elimination of HCl from chloroform



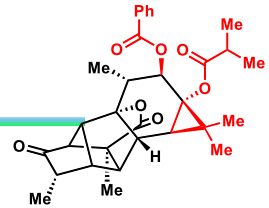
Nucleophilic	Ambiphilic	Electrophilic
$:C(OCH_3)_2$	$:C(OCH_3)Cl$	$:CCl_2$
$:C(OCH_3)NMe_2$	$:C(OCH_3)F$	$:CCH_3Cl$
$:C(SR)_2$		$:CPhCl$
$:C(SPr\text{-}n)_2$		$:C(Br)CO_2Et$

Heteroatoms, such as halogen, oxygen, nitrogen, act as *pi*-electron donor, which elevate the *p*-orbital energy in carbene, making these carbene prefer singlet.

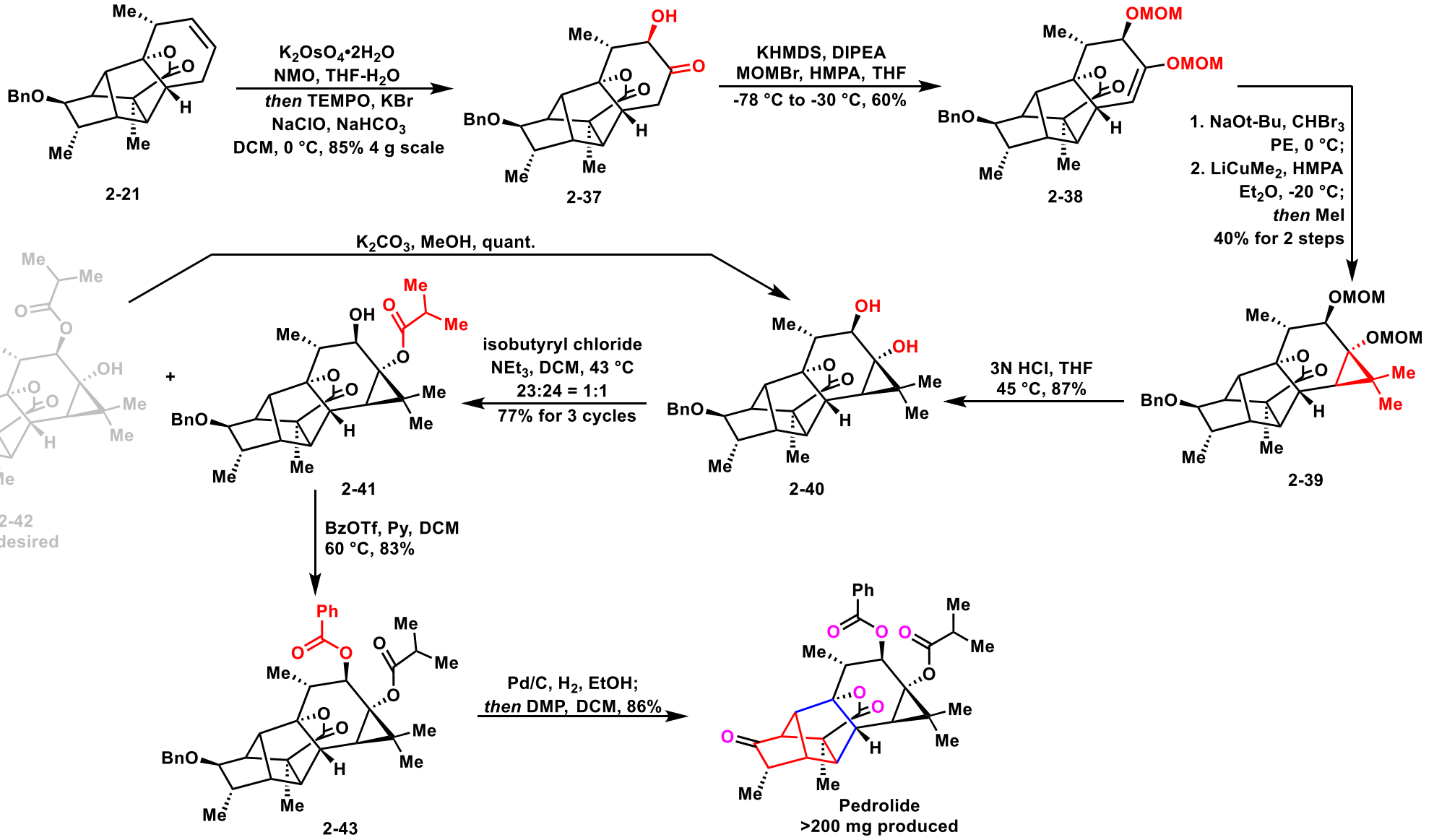
Bo Wang. *Organic Chemistry(T) Lecture.* Jilin. Univ. **2021**

Mei-Xiang Wang, Shuo Tong. *Advanced Organic Chemistry Lecture.* Tsinghua. Univ. **2024**

Total synthesis towards Pedrolide



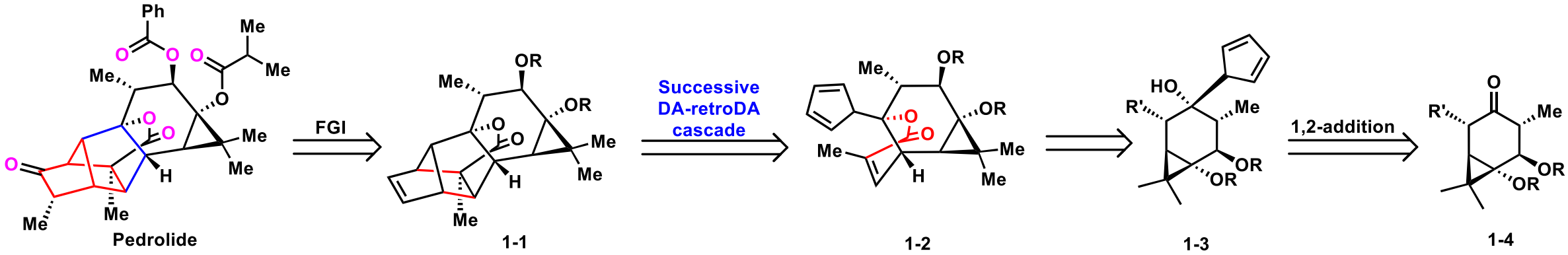
Chuang-Chuang Li's work: Achieve the synthesis



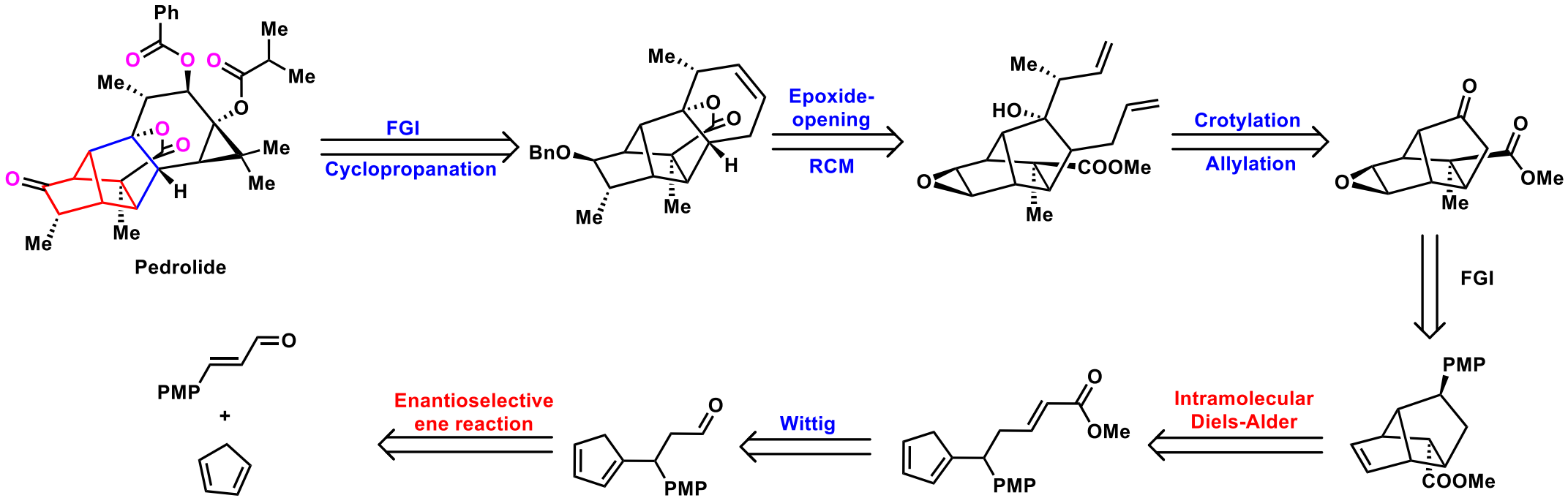
Chuang-Chuang Li. et. al. *J. Am. Chem. Soc*. **2024**, *146*, 2928

Summary

Erick M. Carriera's work: Late-stage IMDA reaction



Chuang-Chuang Li's work: Early-stage IMDA reaction

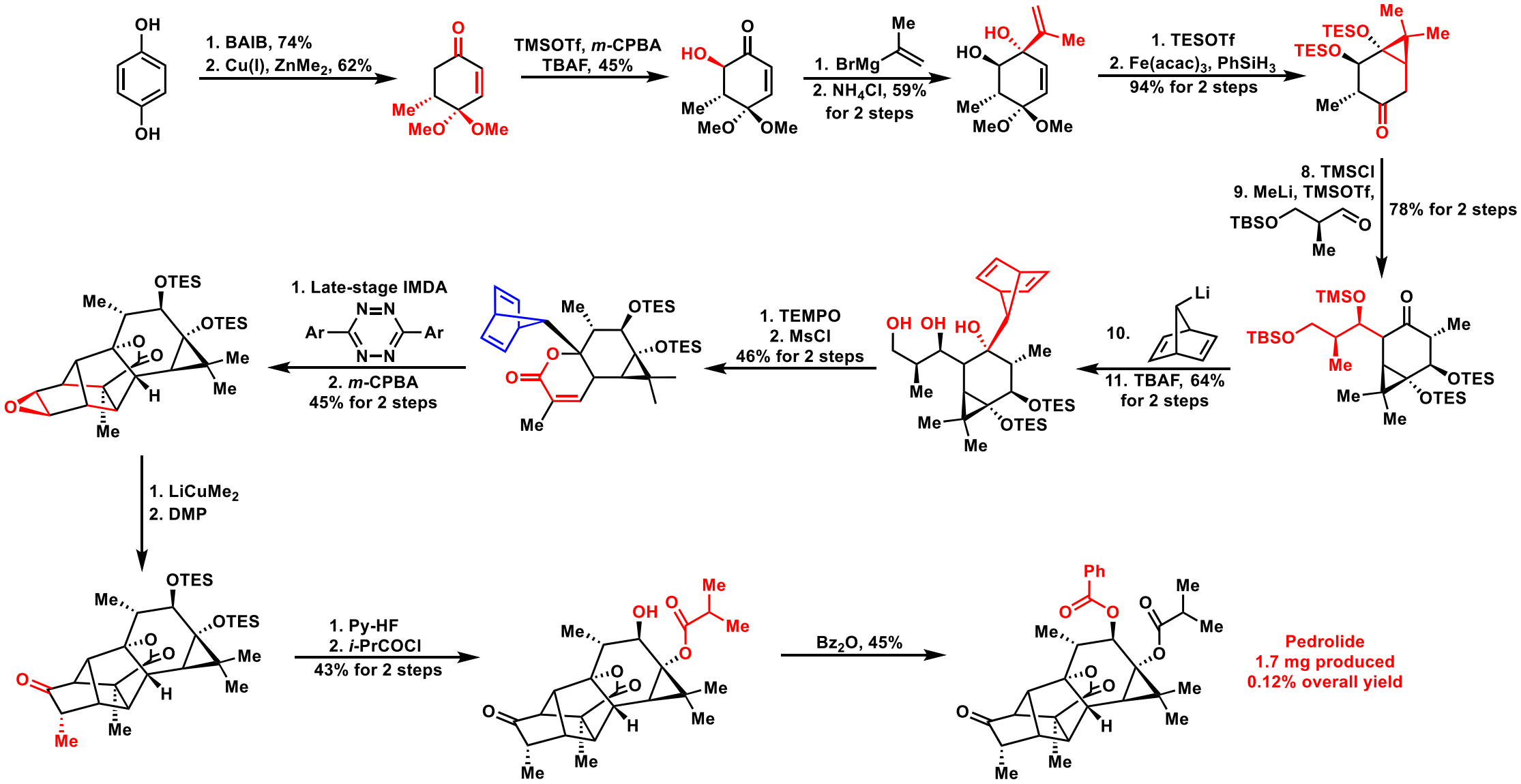


Acknowledgement

Thanks for your attention!

Complement

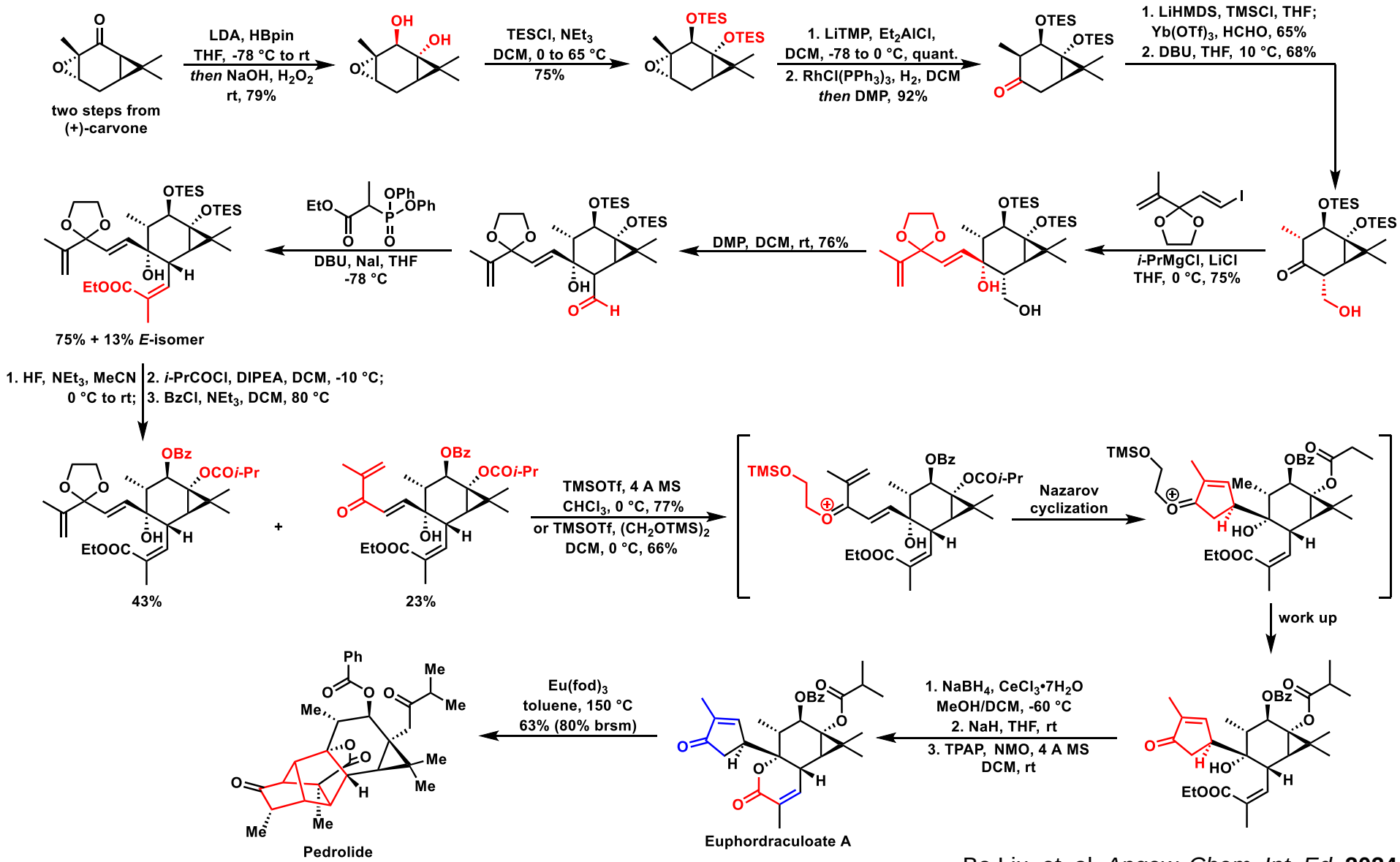
Erick M. Carriera's work: First total synthesis of Pedrolide



Erick M. Carriera. et. al. *J. Am. Chem. Soc*. **2023**, *145*, 8332

Complement

Bo Liu's work: Bioinspired synthesis of Pedrolide & Euphordraculoate A



Bo Liu. et. al. *Angew. Chem. Int. Ed*. **2024**, *63*, e202409997