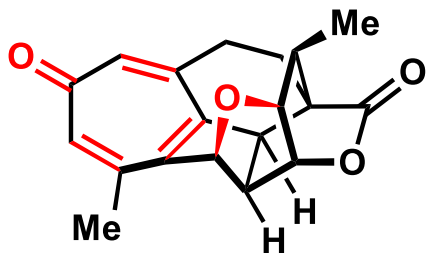
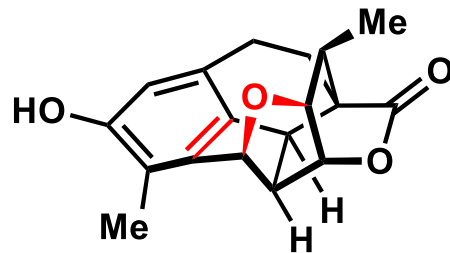


Total synthesis of (+)-mannolide B

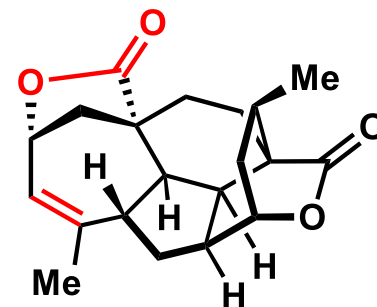
Yan-Xing Jia



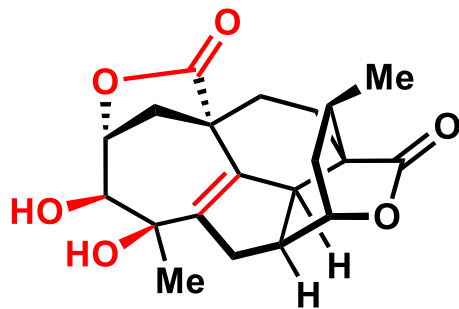
harringtonolide



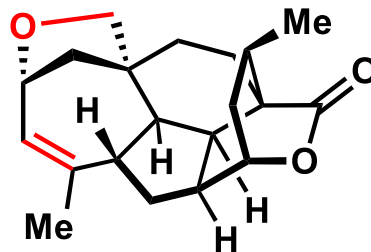
cephanolide B



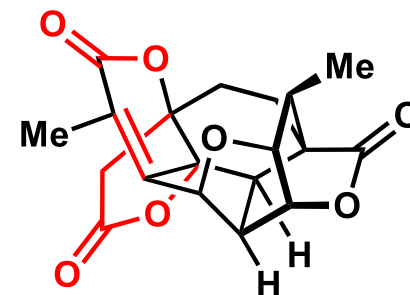
manolide C



cephanolide E



cephanolide F



(-)-Cephalotantin B

● About the author

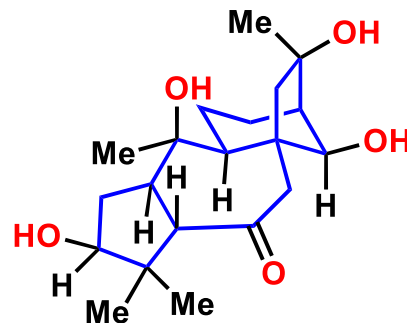
Yanxing Jia:

1993-1997: B.S. in Lanzhou University

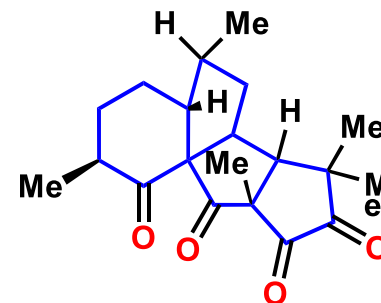
1997-2002: Ph. D. in Lanzhou University
Director: Yongqiang Tu

**2002-2007: Postdoctoral Fellow, Institut
de Chimie des Substances Naturelles
(ICSN), France**
Director: Jieping Zhu

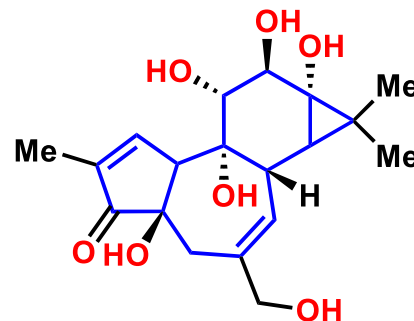
**Present: Peking University Boya
Distinguished Professor**



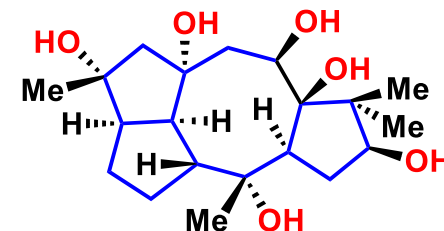
(-)-Principinol C



(+)-Aberrarone

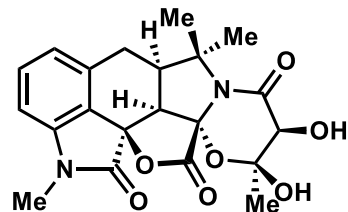


(+)-Phorbol

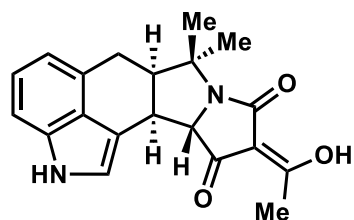


Kalmanol

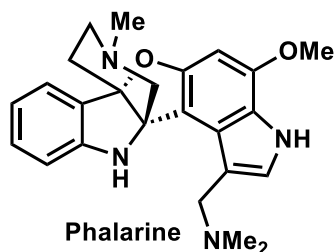
About Dr. Prof. Jia



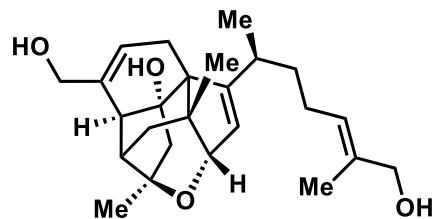
Speradine C



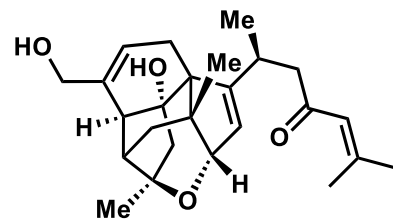
α -cyclopiazonic acid



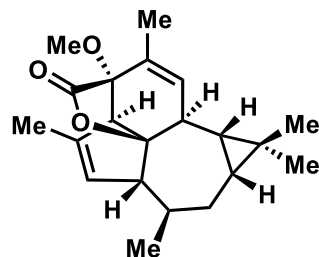
Phalarine



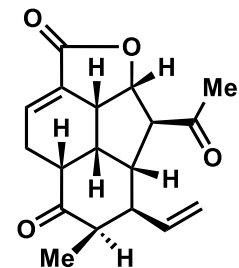
Bipolarolide B



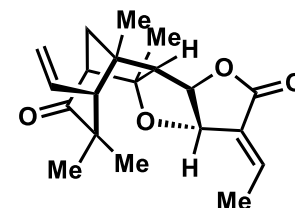
Bipolarolide A



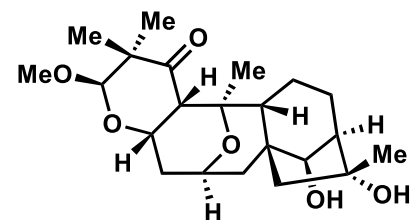
Euphorikanin A



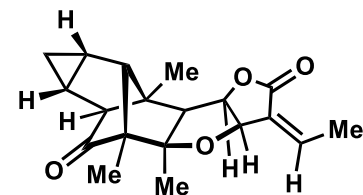
Pallavicinolide B



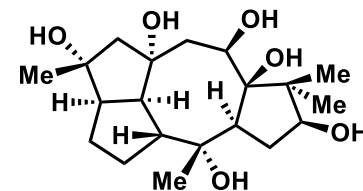
Pallavicinin



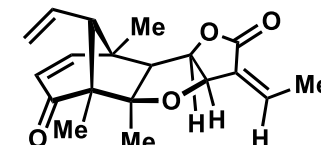
Rhodomollacetal A



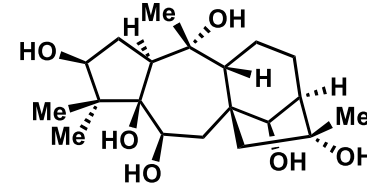
Pallambin A



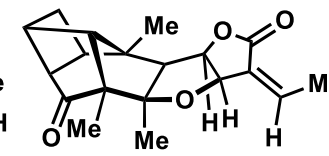
Kalmanol



Pallambin C



Grayanotoxin III



Pallaviambin A

Skeletal diversification
Since 2024

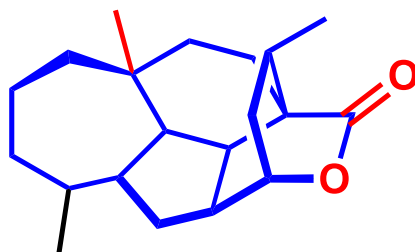
New biosynthetic pathway
Since 2022

Key cyclization steps
Since 2011

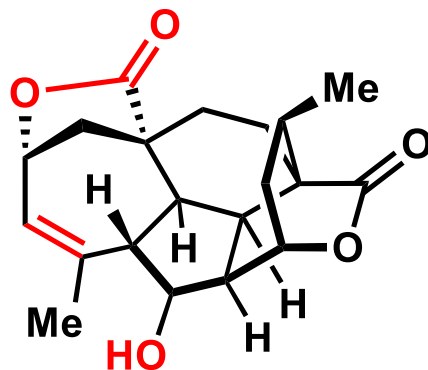
Yanxing Jia. et, al. *Acc. Chem. Res.* **2024**, 57, 3524–3540.
Yanxing Jia. et, al. *Chem.* **2024**, 10, 2473–2483.

● Background

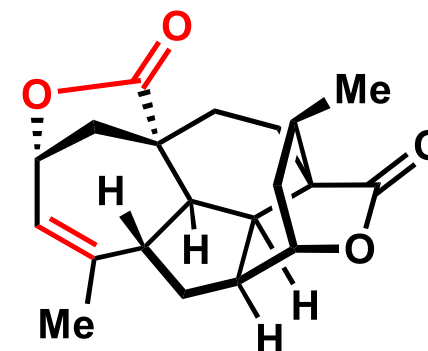
Cephalotaxus diterpenoids



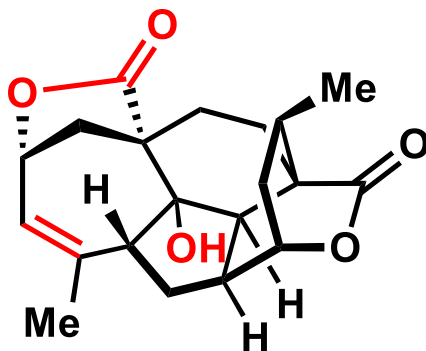
prototype diterpenoids
 C_{20}



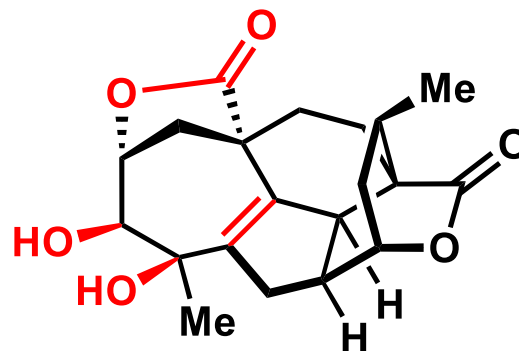
mannolide B



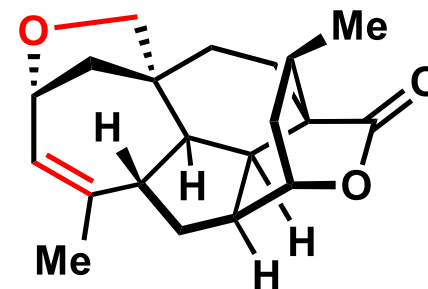
mannolide C



mannolide A



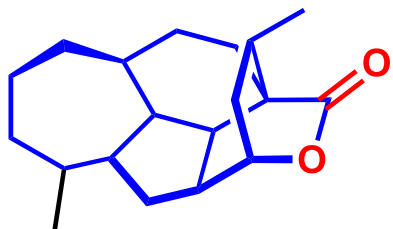
cephanolide E



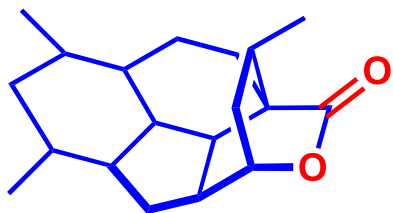
cephanolide F

● Background

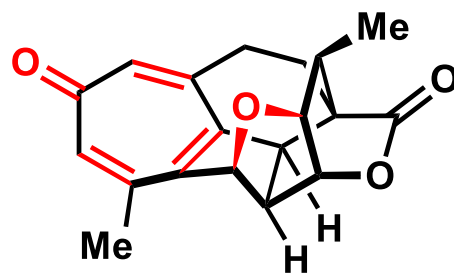
Cephalotaxus diterpenoids



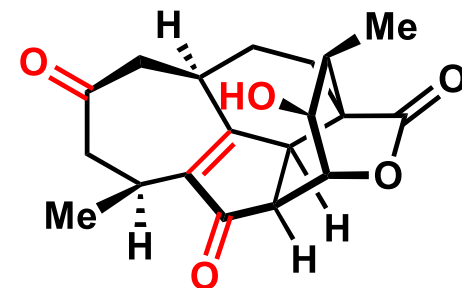
17-*nor* diterpenoids
 C_{19}



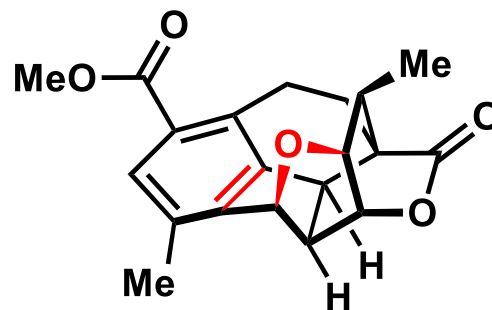
17-*nor* or 14/17-*dinor*
diterpenoids
 C_{18} or C_{19}



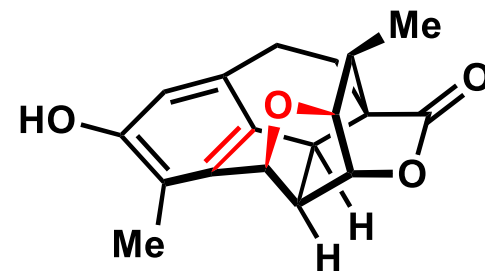
harringtonolide



cephinoid P



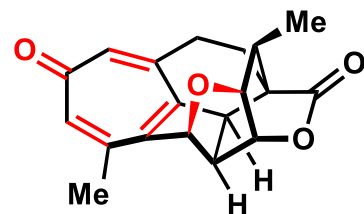
cephanolide D



cephanolide B

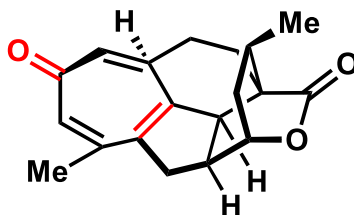
Background

Cephalotaxus diterpenoids



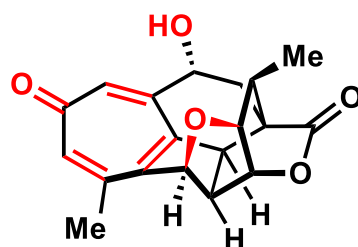
harringtonolide

IC₅₀ = 43 nM against KB cells
Anticancer activity



(+)-cephinoid H

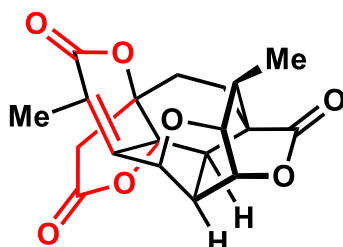
GI₅₀ = 1.9 μM against HL-60 cells
Cytotoxicity



Cephinoid F

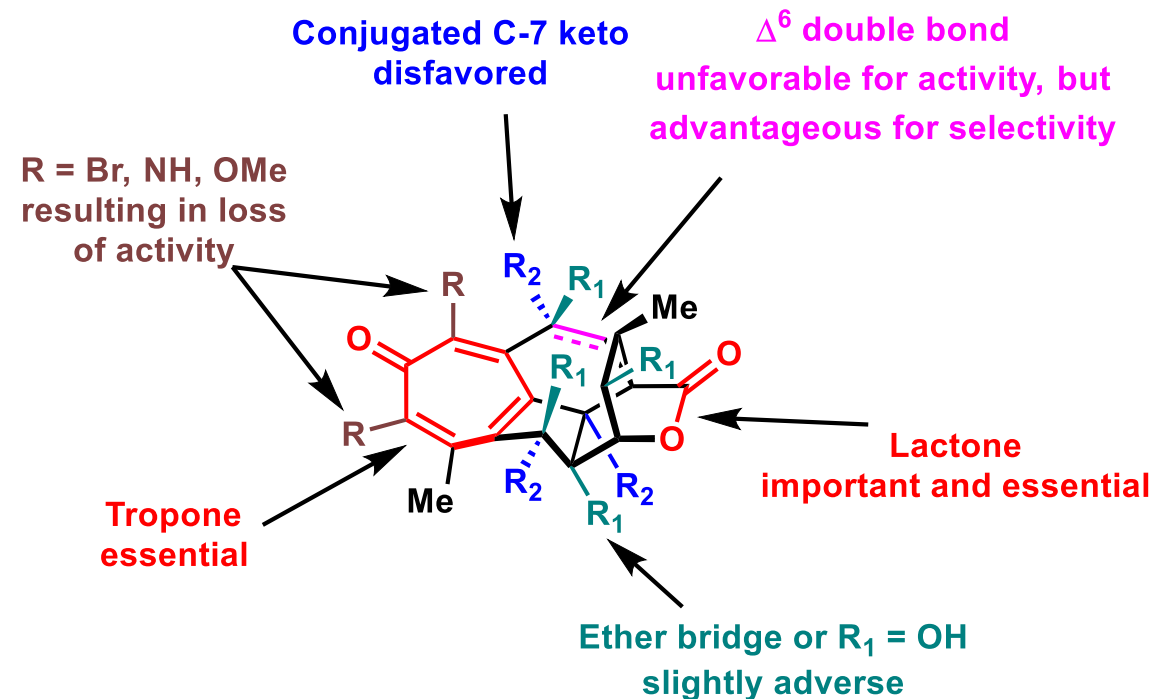
IC₅₀ = 12 μM against A549 cells
Cytotoxicity

Inhibition of NF-κB pathway and NO production



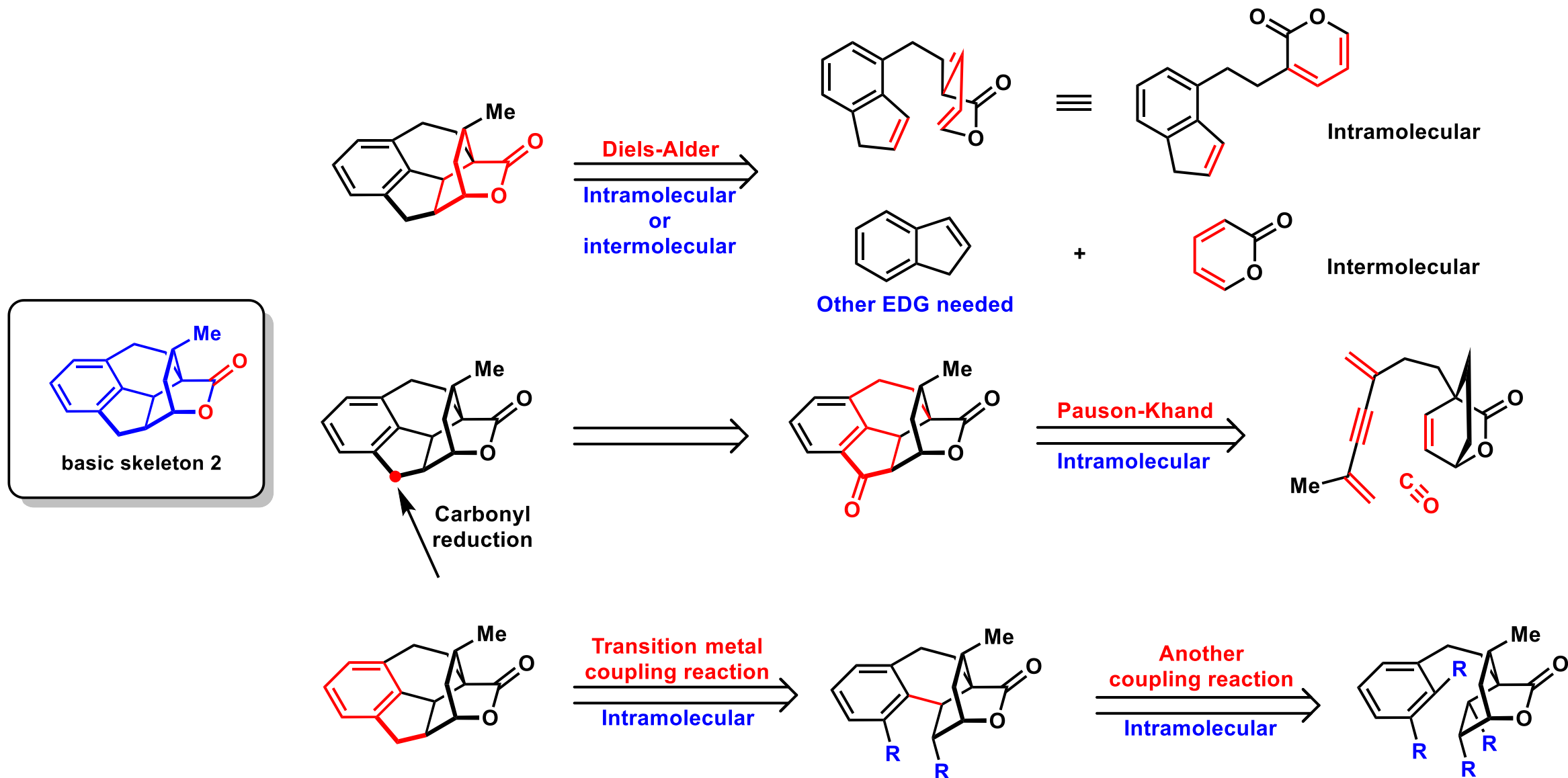
(-)-Cephalotanin B

Inhibitory effect on Th17 cell differentiation



● Preface: Synthetic strategies

Retrosynthetic analysis towards *Cephalotaxus* diterpenoids



● Preface: Parts of synthesis work

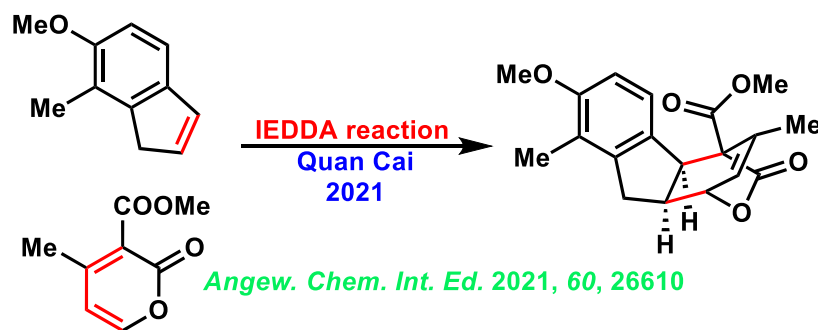
Total synthesis towards *Cephalotaxus* diterpenoids



J. Am. Chem. Soc. 2018, 140, 5653



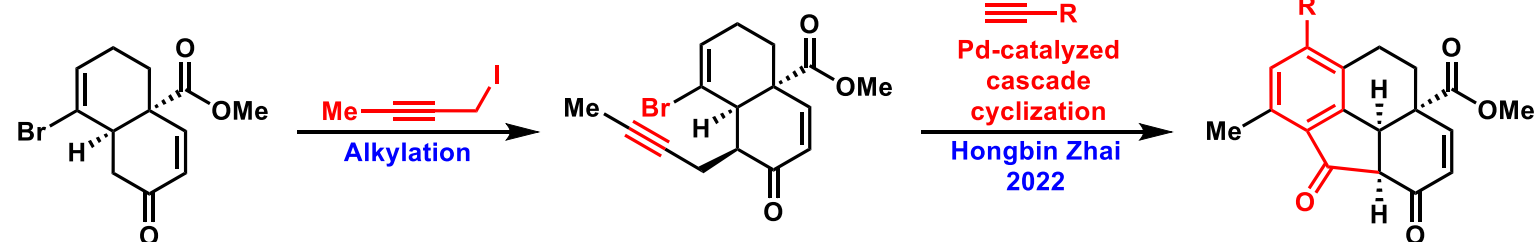
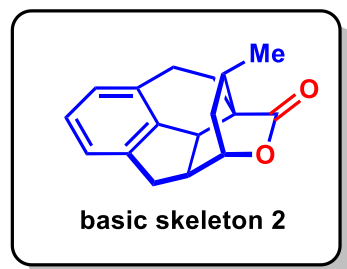
Angew. Chem. Int. Ed. 2020, 59, 20417
Org. Chem. Front. 2021, 8, 555



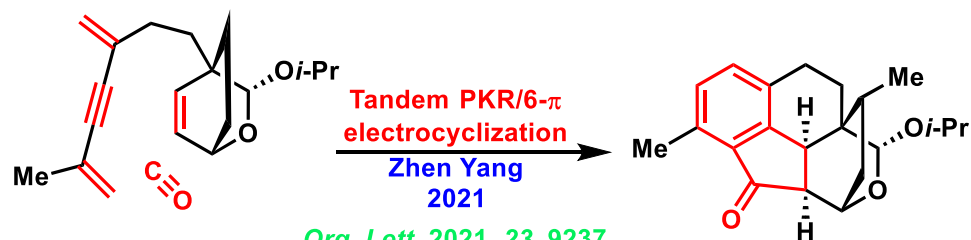
Angew. Chem. Int. Ed. 2021, 60, 26610



J. Am. Chem. Soc. 2021, 143, 2710



J. Am. Chem. Soc. 2022, 144, 10640



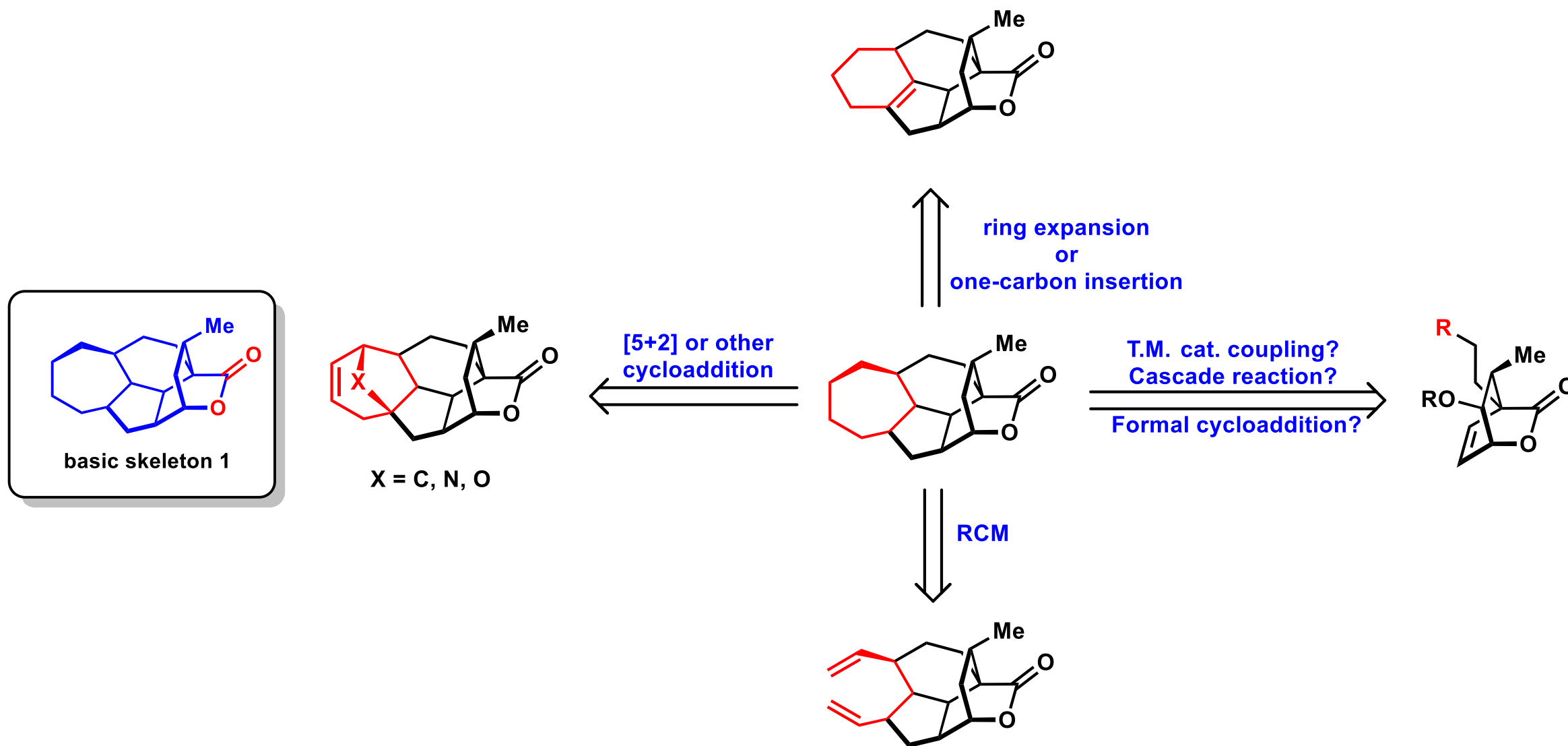
Org. Lett. 2021, 23, 9237



Angew. Chem. Int. Ed. 2023, 62, e202312599

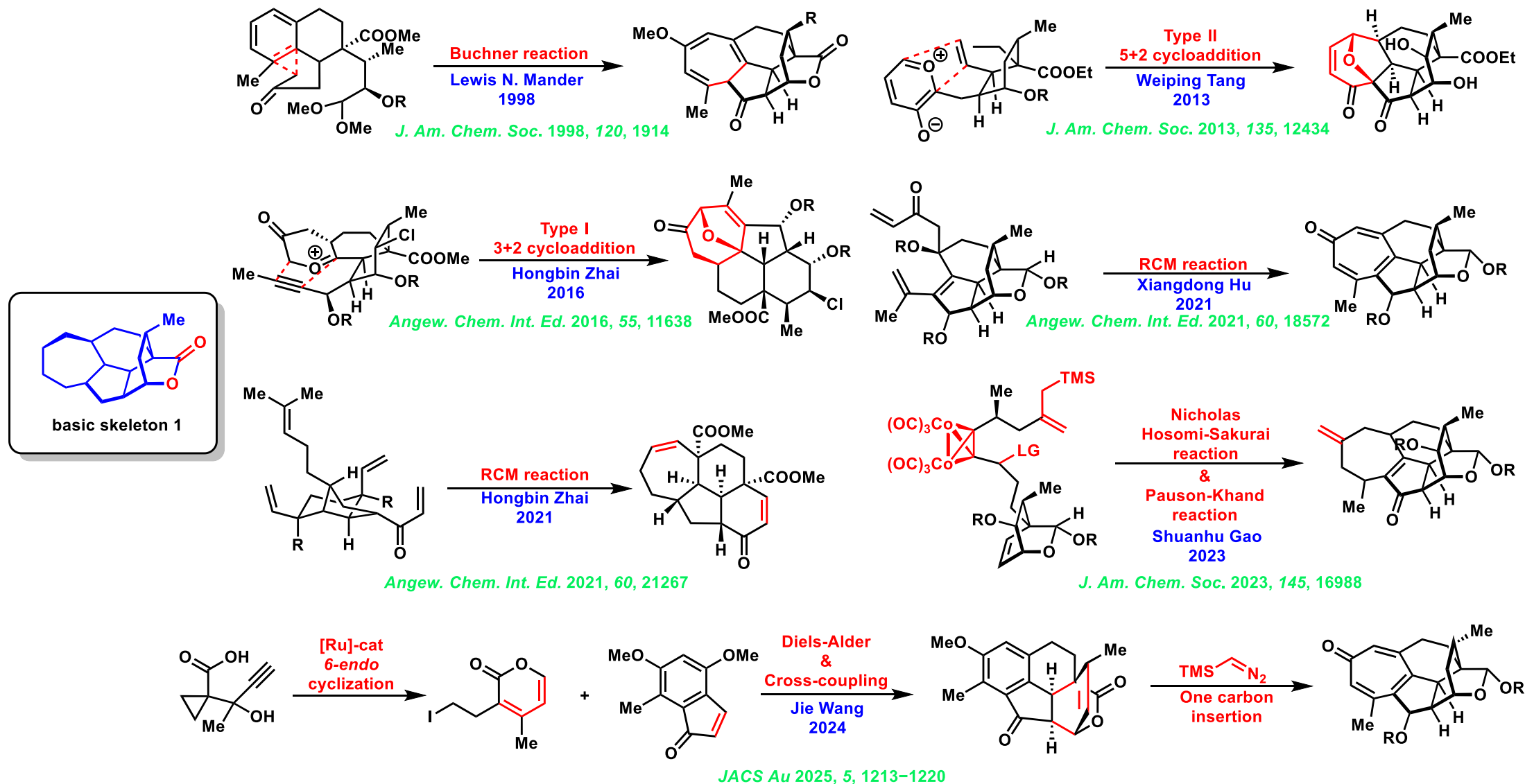
● Preface: Synthetic strategies

Retrosynthetic analysis towards *Cephalotaxus* diterpenoids

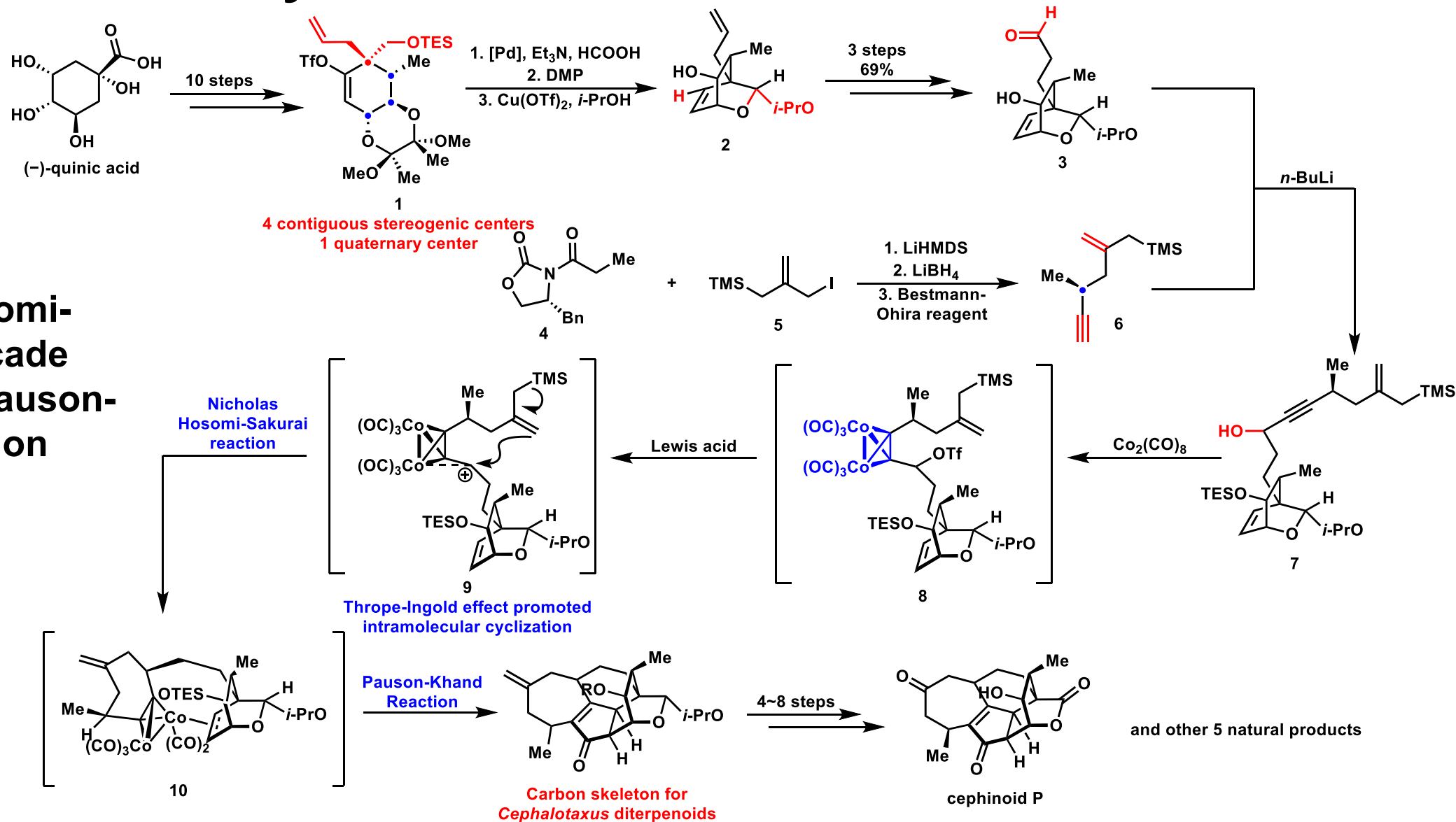


● Preface: Parts of synthesis work

Total synthesis towards *Cephalotaxus* diterpenoids

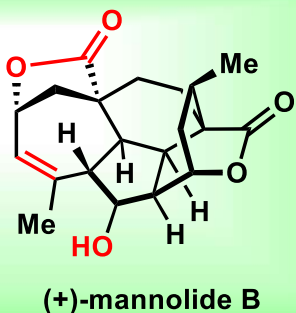


● Preface: Parts of synthesis work Gao's brilliant synthesis work in 2023

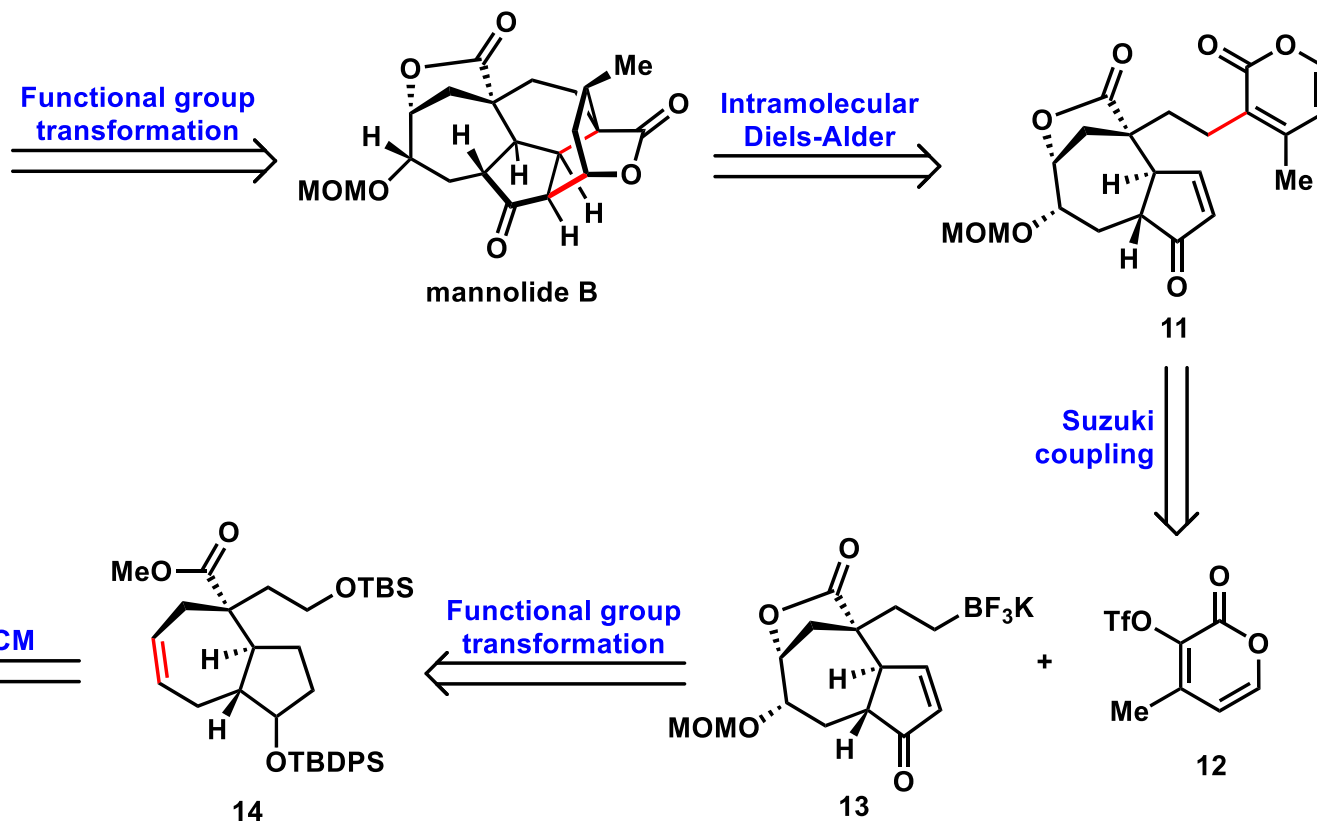


● Total synthesis towards (+)-mannolide B

1st retrosynthetic analysis & synthetic route:

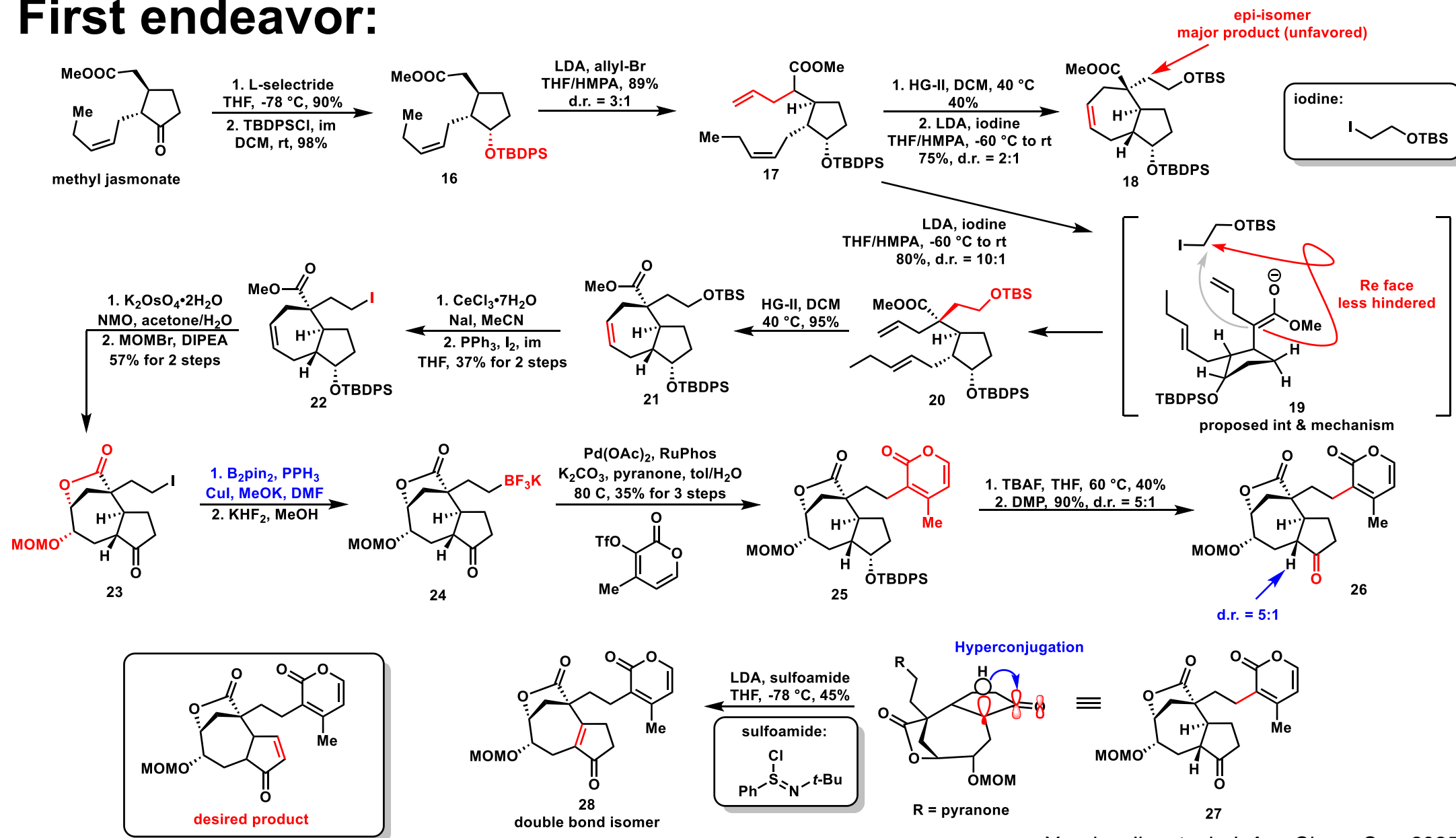


- 5/7/5/6/6/6-Fused hexacyclic scaffold
- 2 Bridged-lactone moieties
- 10 Stereocenters; 9 contiguous
- 2 Quaternary carbon centers
- First total synthesis by Jia's group



Total synthesis towards (+)-mannolide B

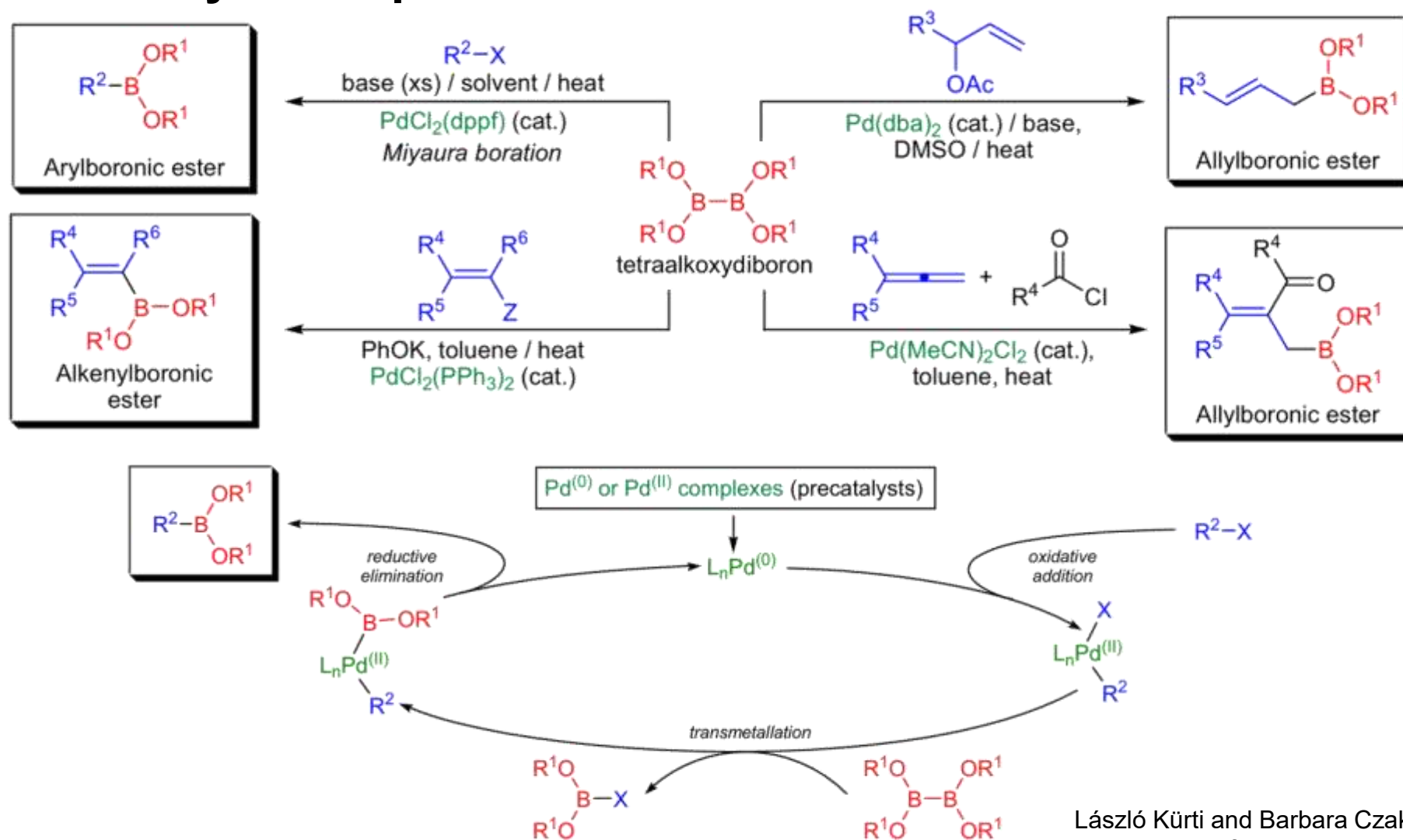
First endeavor:



● Total synthesis towards (+)-mannolide B

Complement 1: Cu(I)-catalyzed borylation

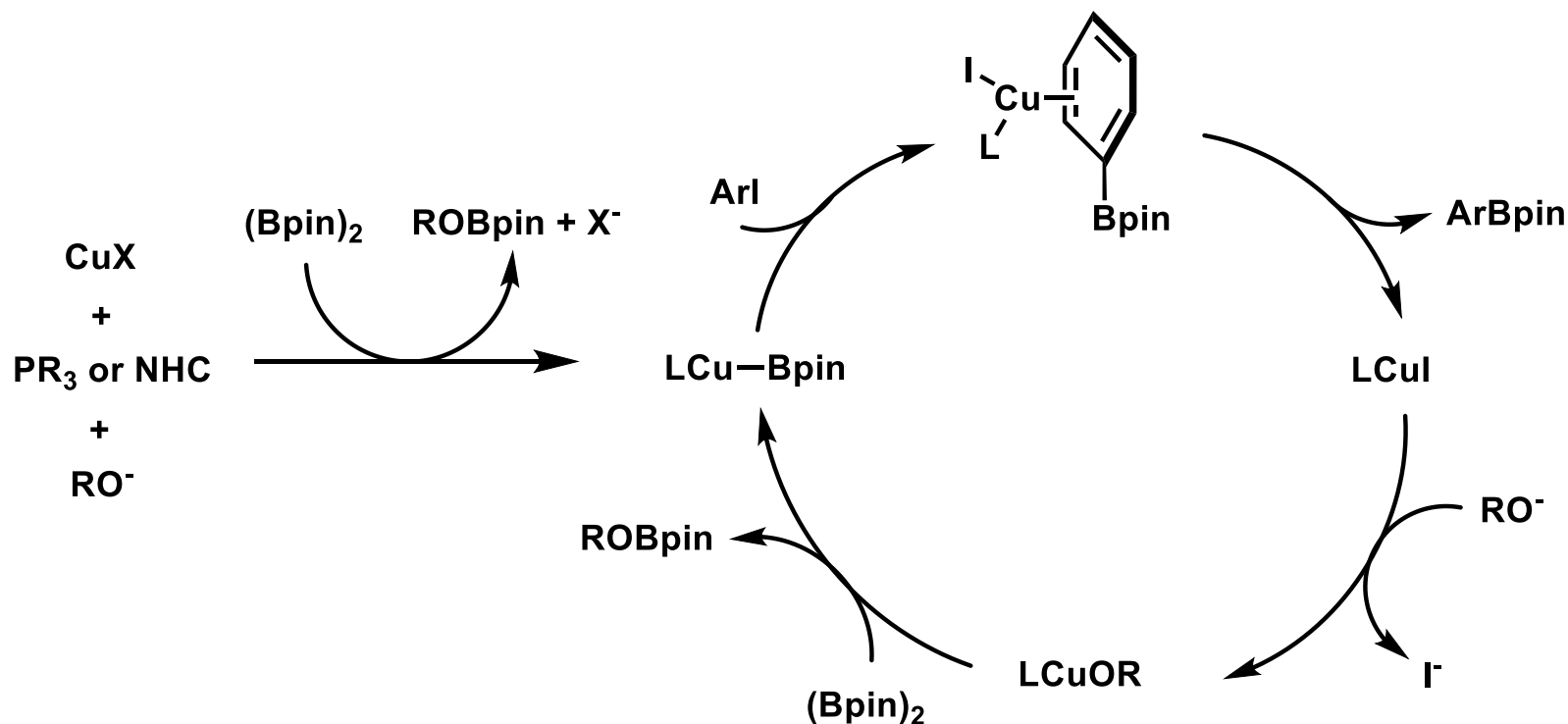
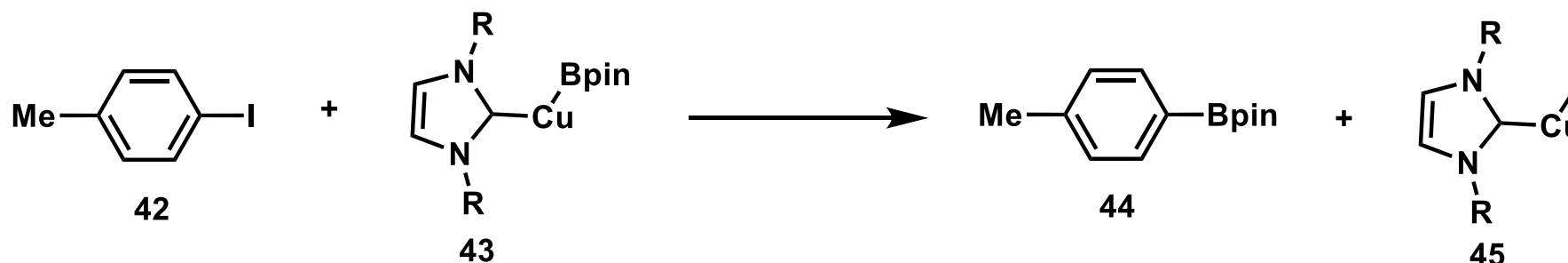
Traditional Miyaura's protocol:



● Total synthesis towards (+)-mannolide B

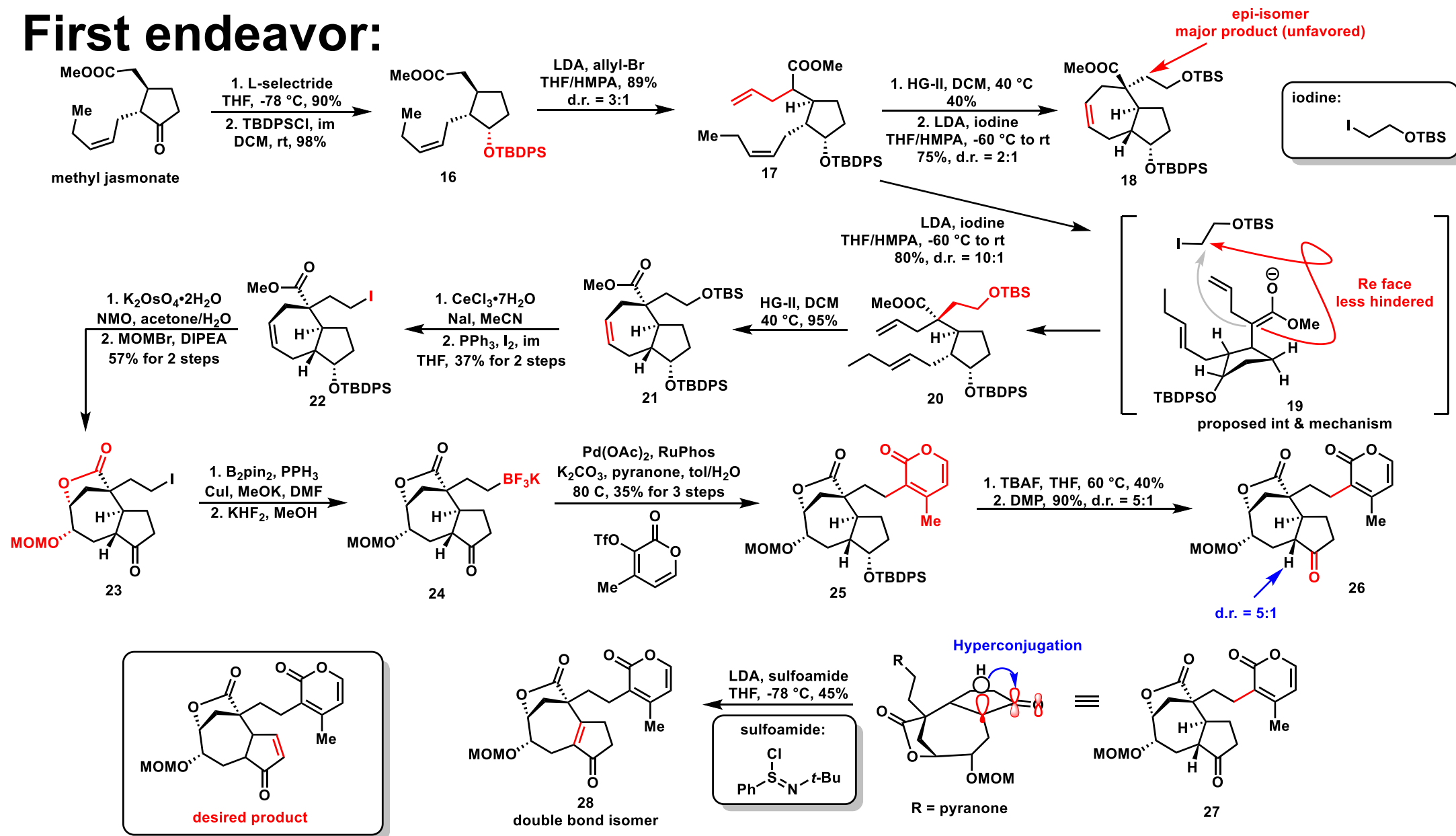
Complement 1: Cu(I)-catalyzed borylation

Todd. Marder & Lei Liu's protocol:



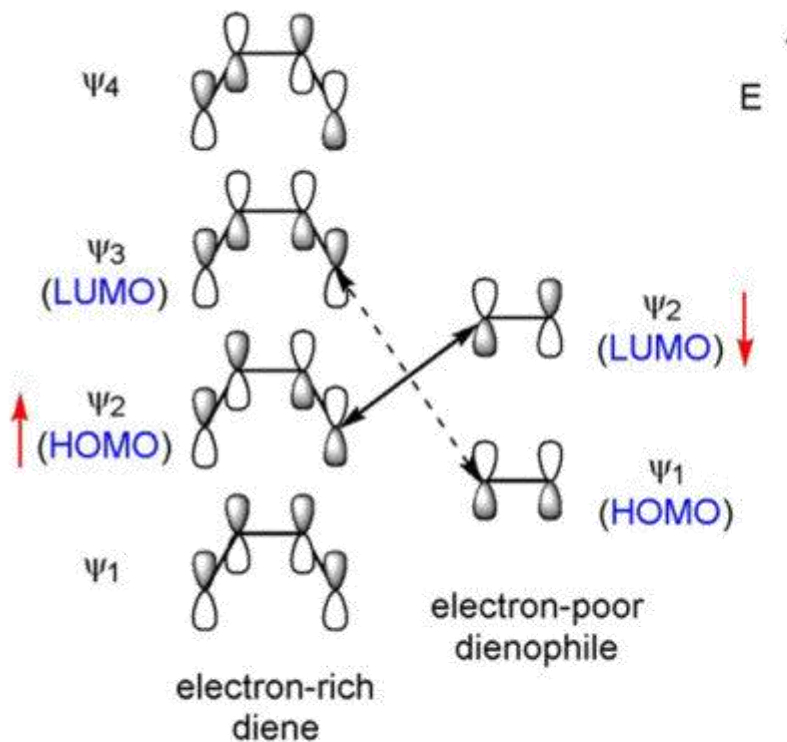
Total synthesis towards (+)-mannolide B

First endeavor:

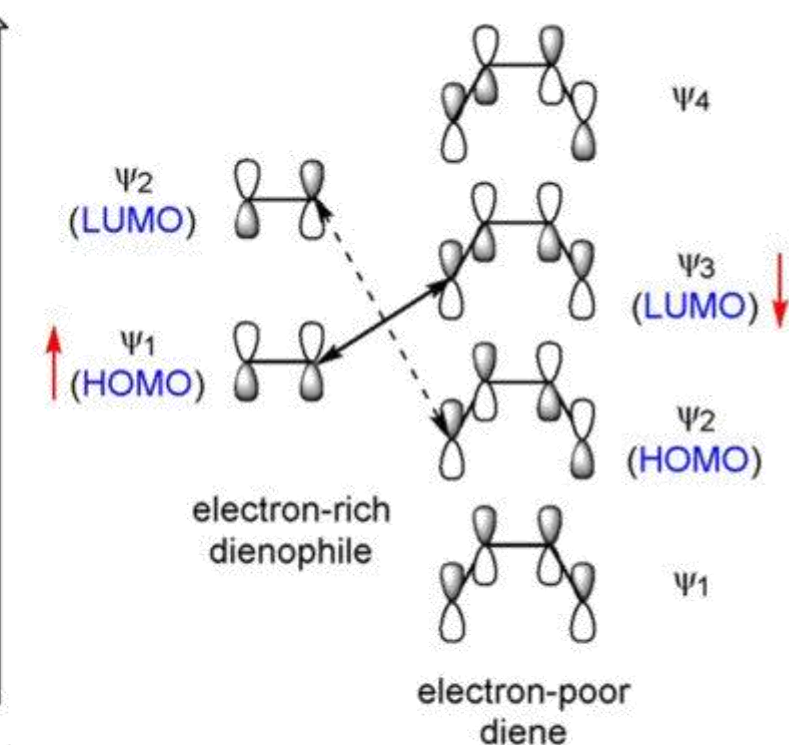


● Total synthesis towards (+)-mannolide B

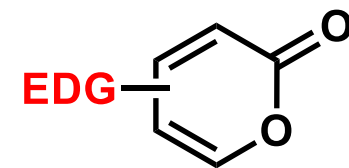
Complement 2: IEDDA reaction



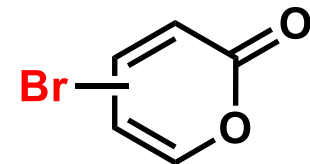
Normal-Electron-Demand Diels-Alder (NEDDA)



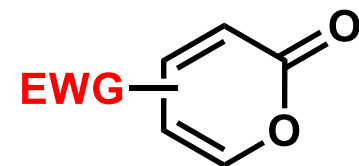
Inverse-Electron-Demand Diels-Alder (IEDDA)



Diene for NEDDA



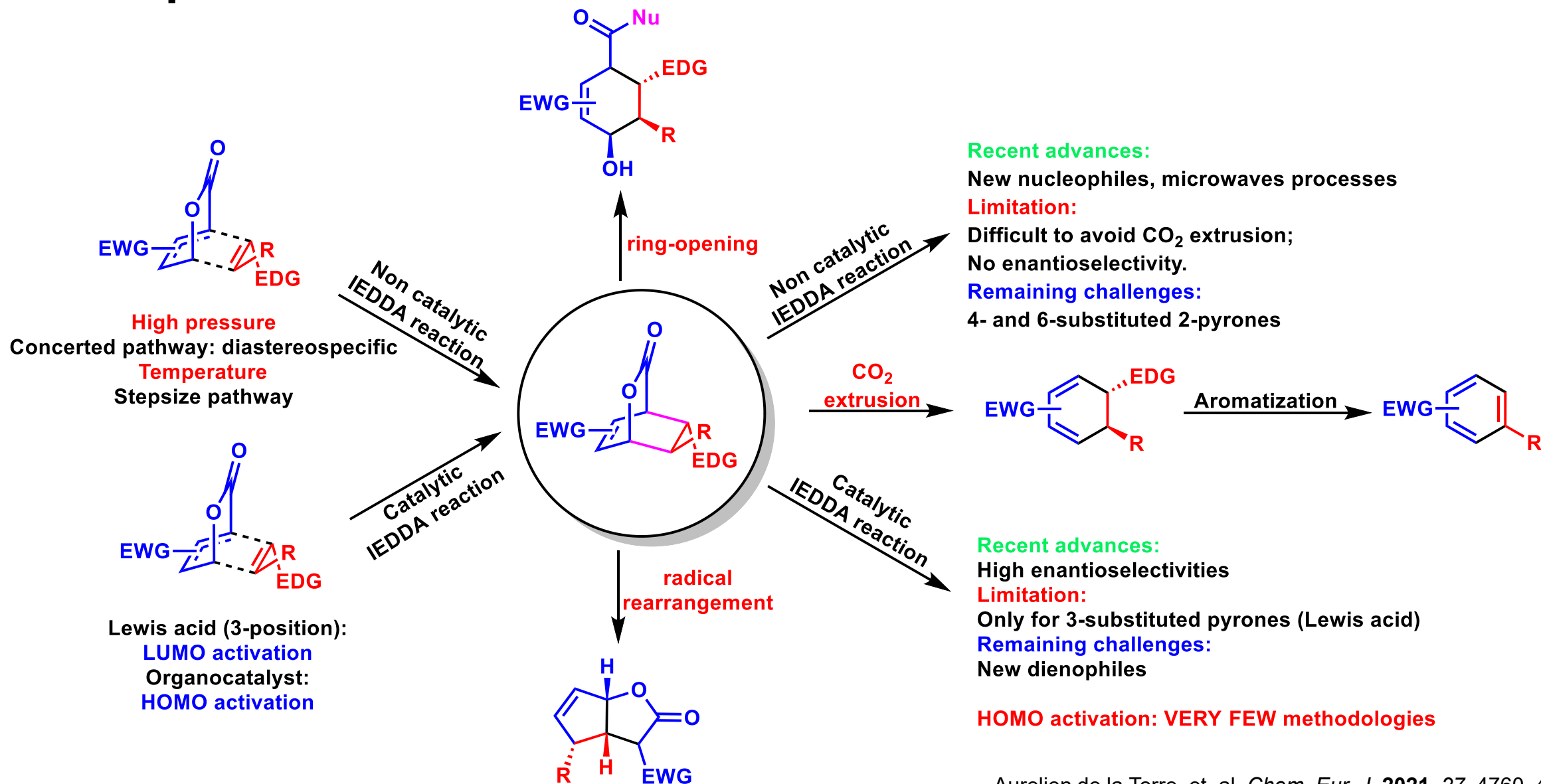
Both



Diene for IEDDA

● Total synthesis towards (+)-mannolide B

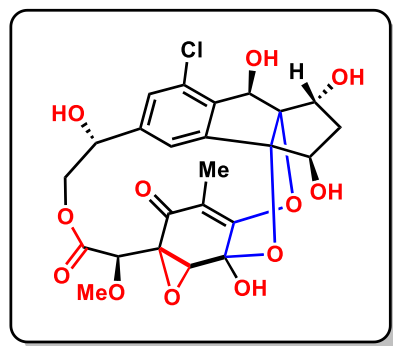
Complement 2: IEDDA reaction



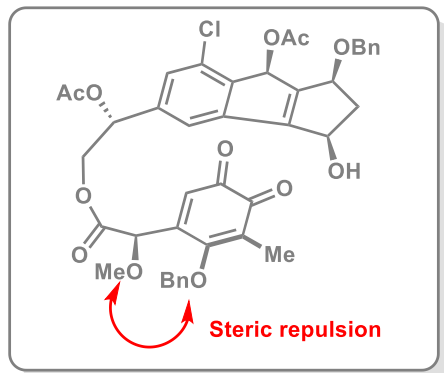
● Total synthesis towards (+)-mannolide B

Complement 2: IEDDA reaction: another example

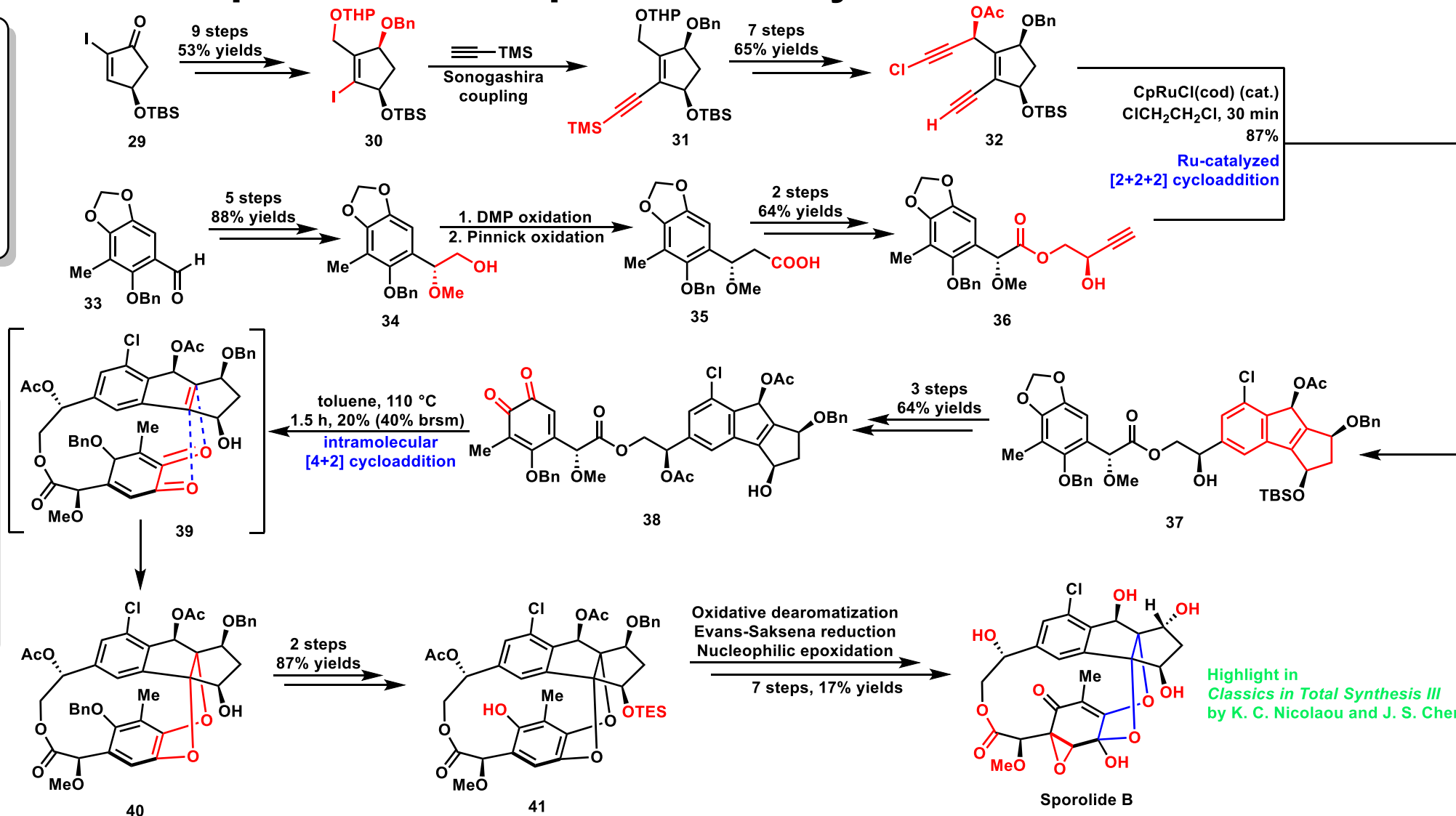
Total synthesis of Sporolide B: o-quinone DA cycloaddition



Sporolide B
Highly oxydized
Striking molecular architectures



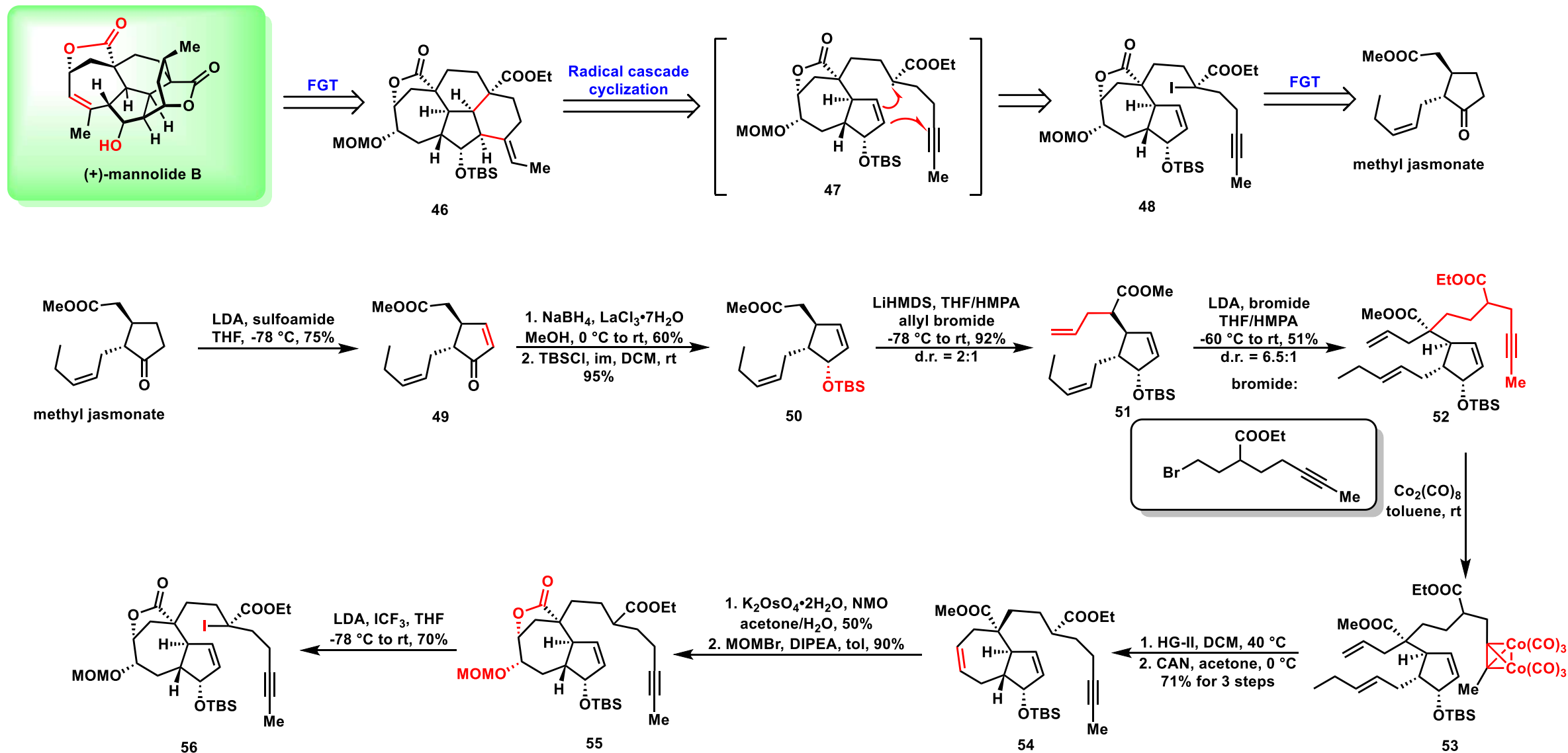
Steric repulsion



Highlight in
Classics in Total Synthesis III
by K. C. Nicolaou and J. S. Chen

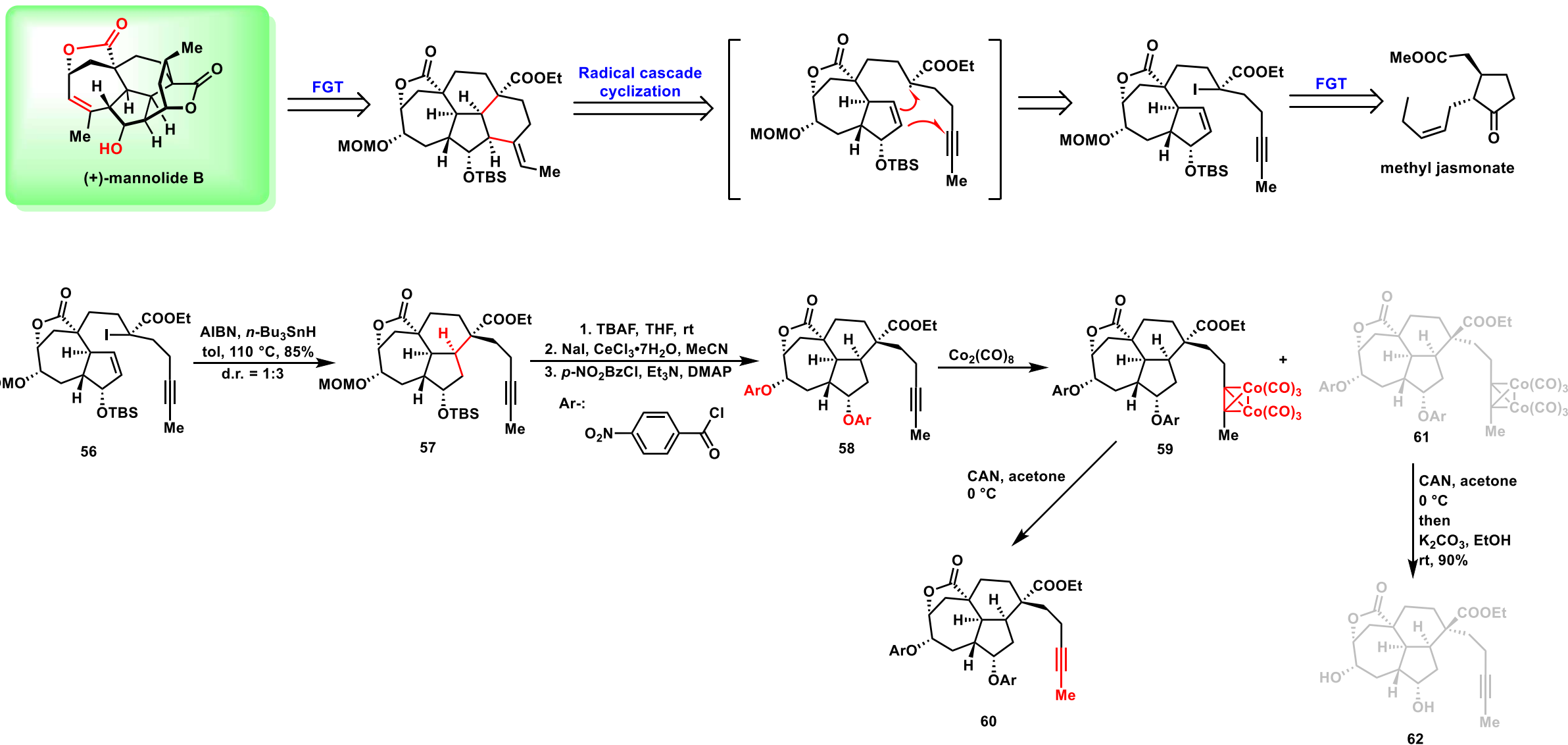
● Total synthesis towards (+)-mannolide B

Second endeavor:



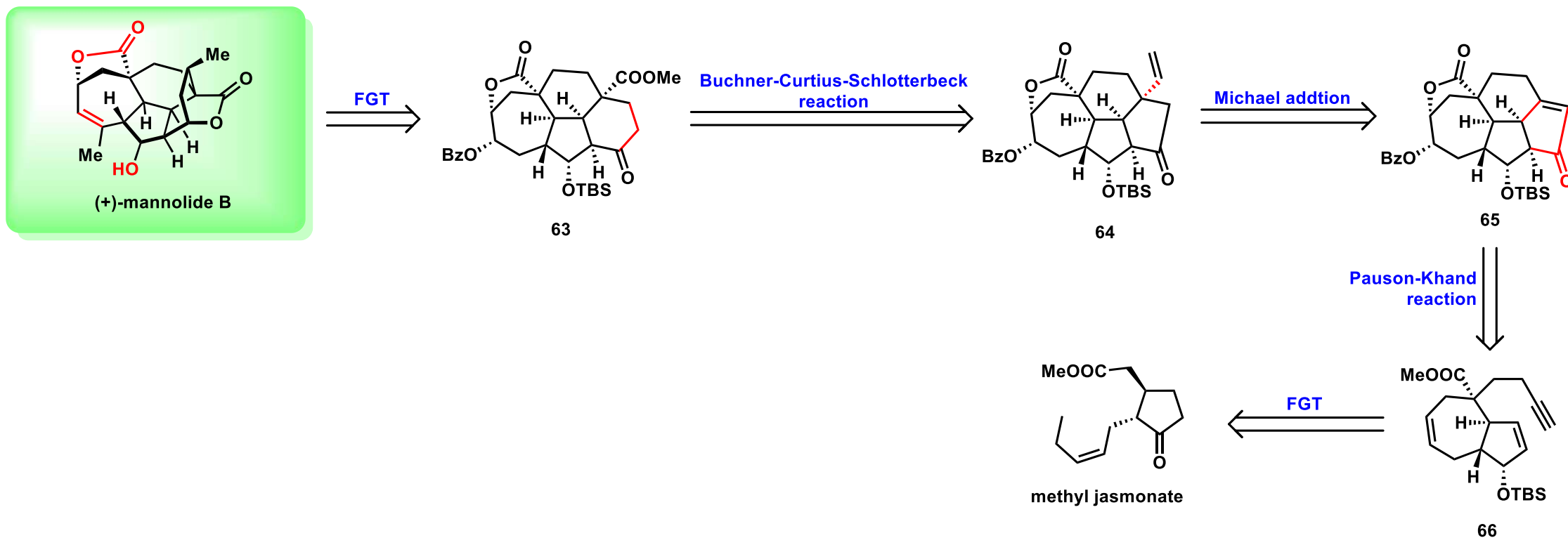
● Total synthesis towards (+)-mannolide B

Second endeavor:



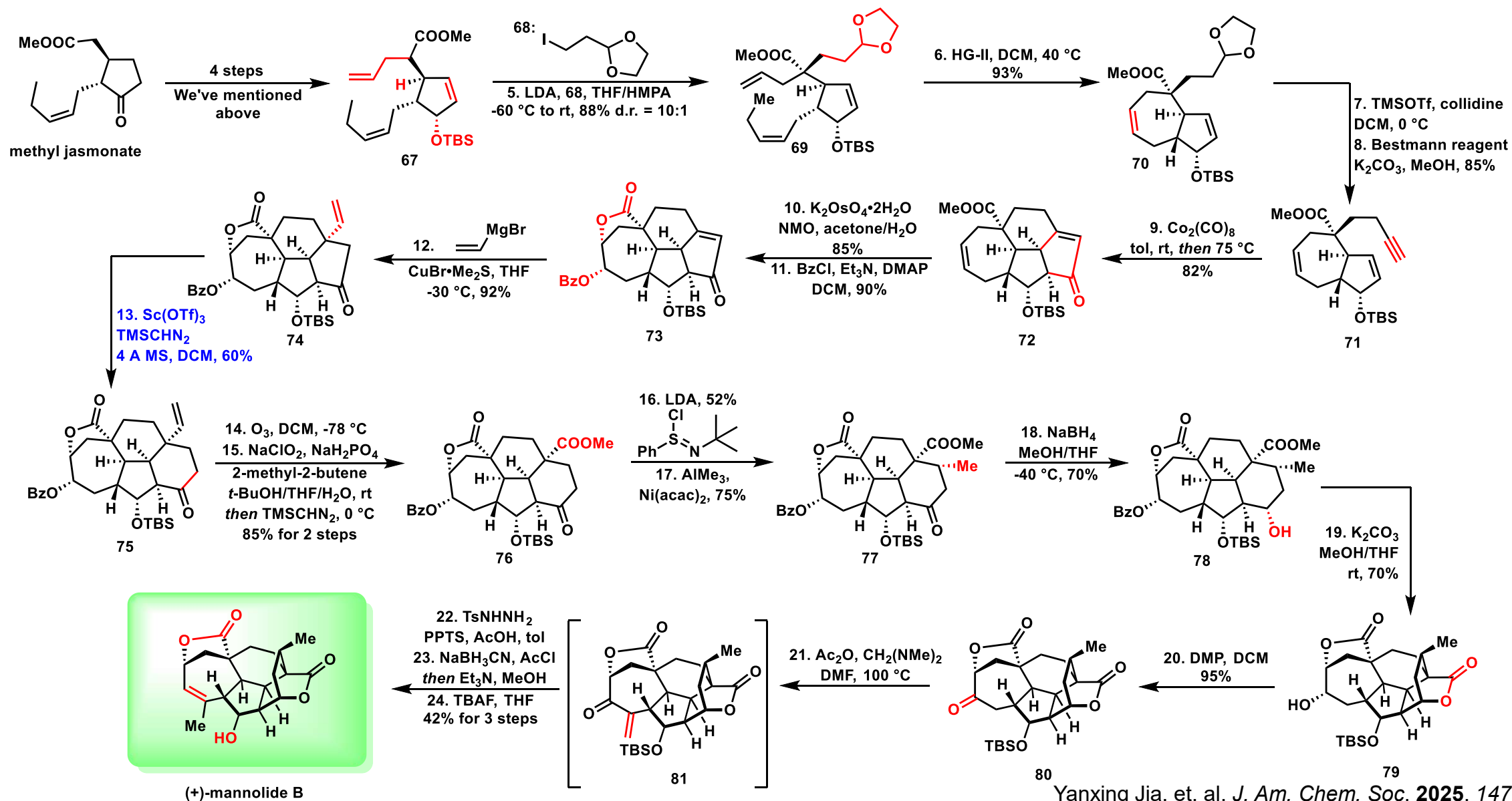
● Total synthesis towards (+)-mannolide B

Third endeavor:



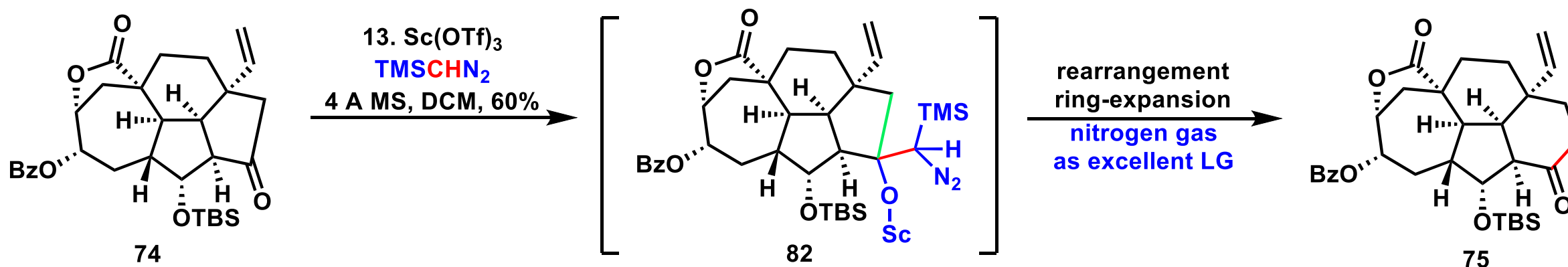
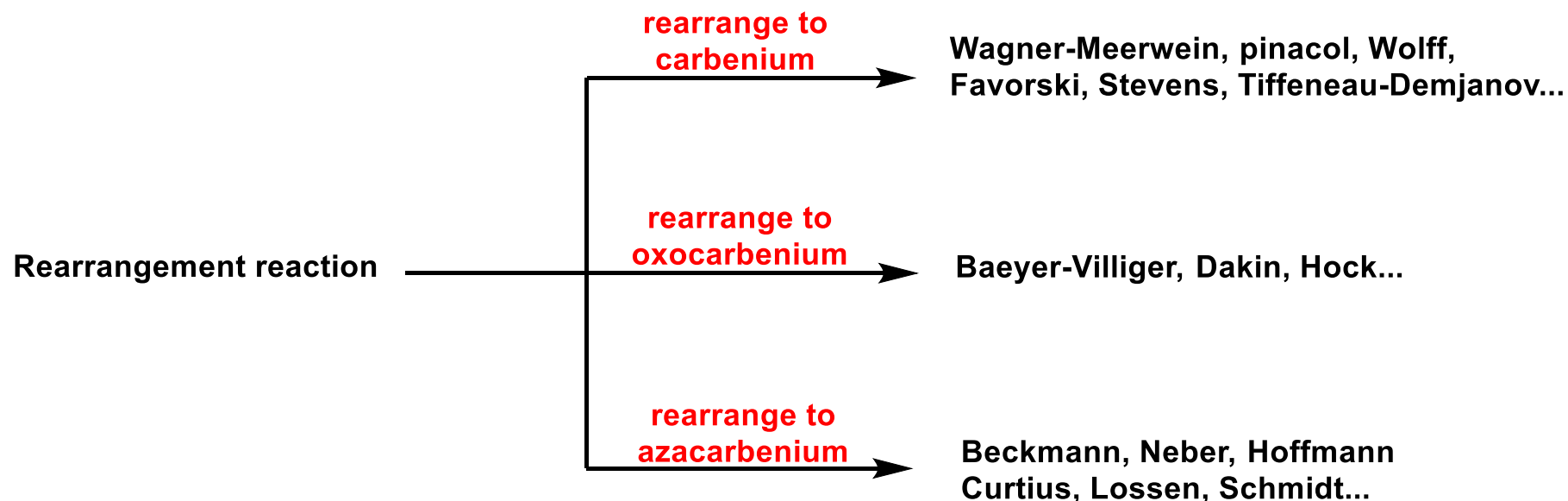
Total synthesis towards (+)-mannolide B

Third endeavor:



● Total synthesis towards (+)-mannolide B

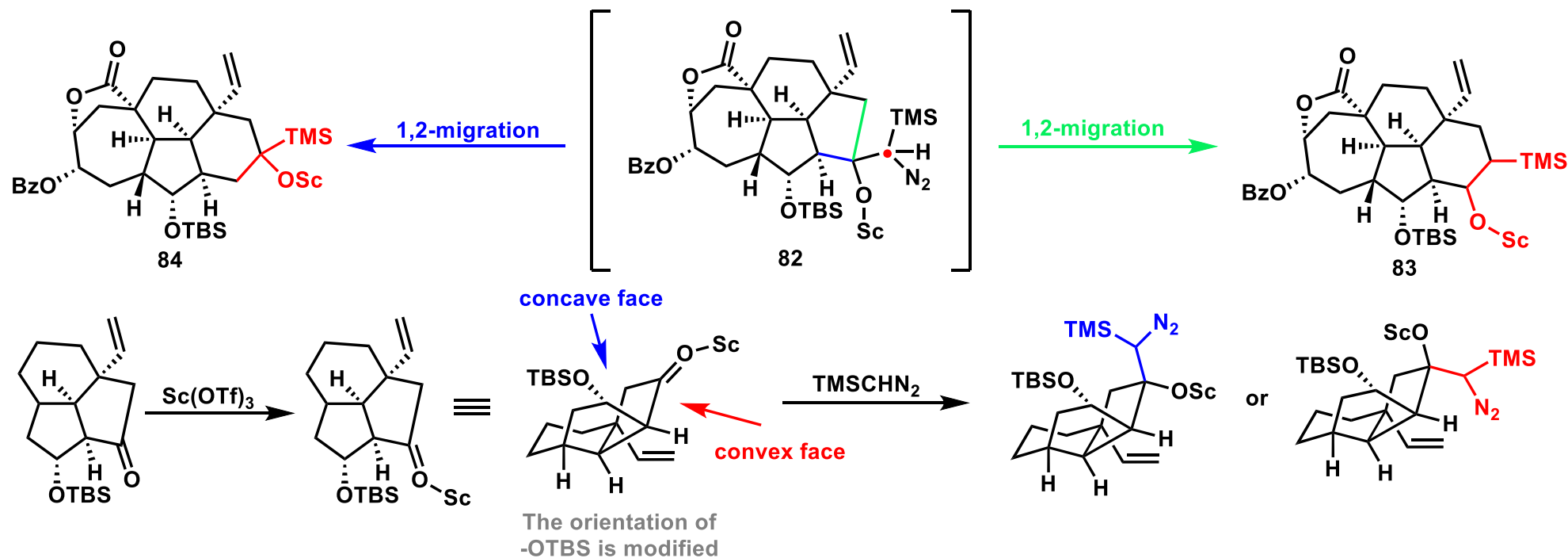
Complement 3: Selectivities in BCS reaction



Buchner-Curtius-Slotterbeck reaction

● Total synthesis towards (+)-mannolide B

Complement 3: Selectivities in BCS reaction

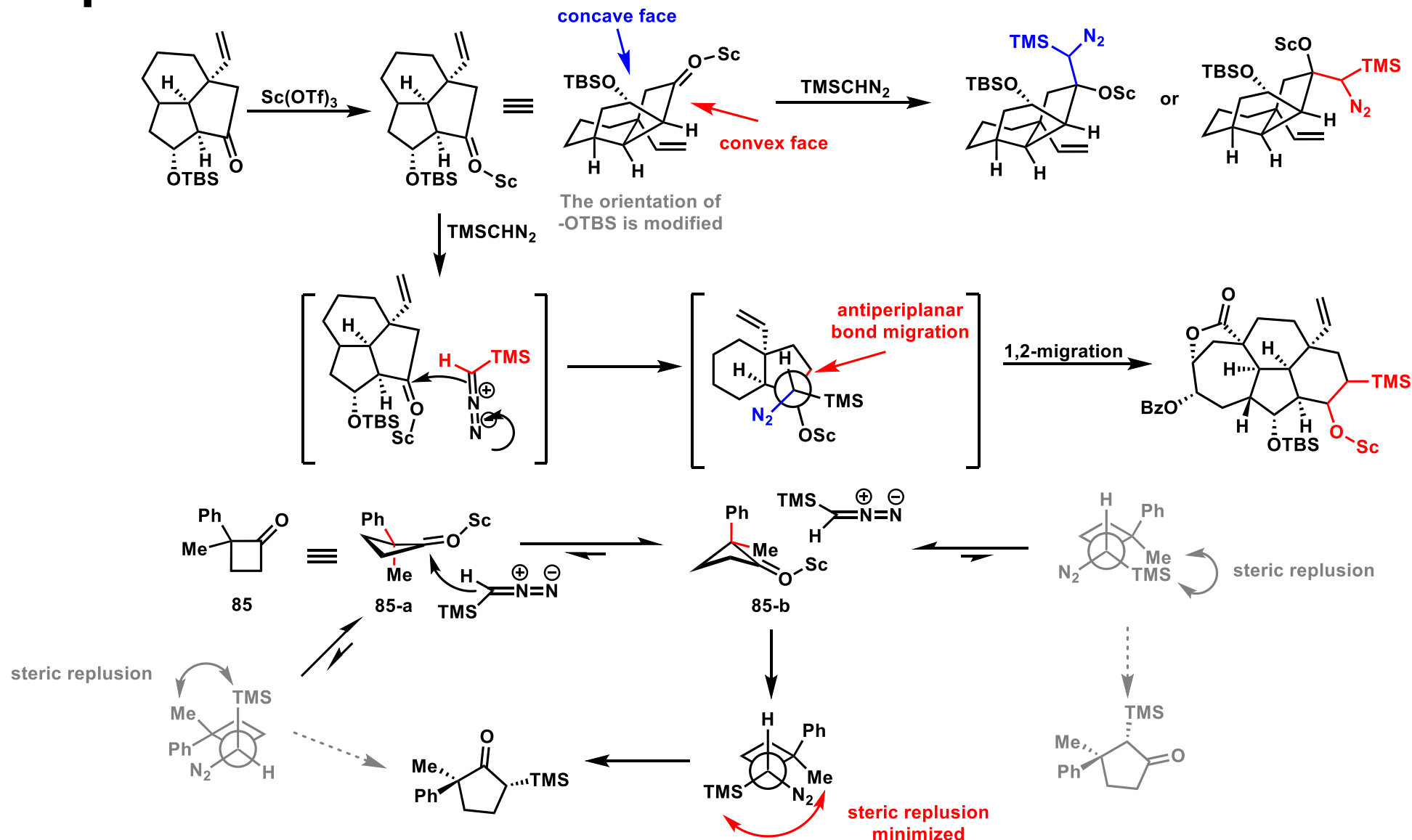


Complement 3: Selectivities in BCS reaction



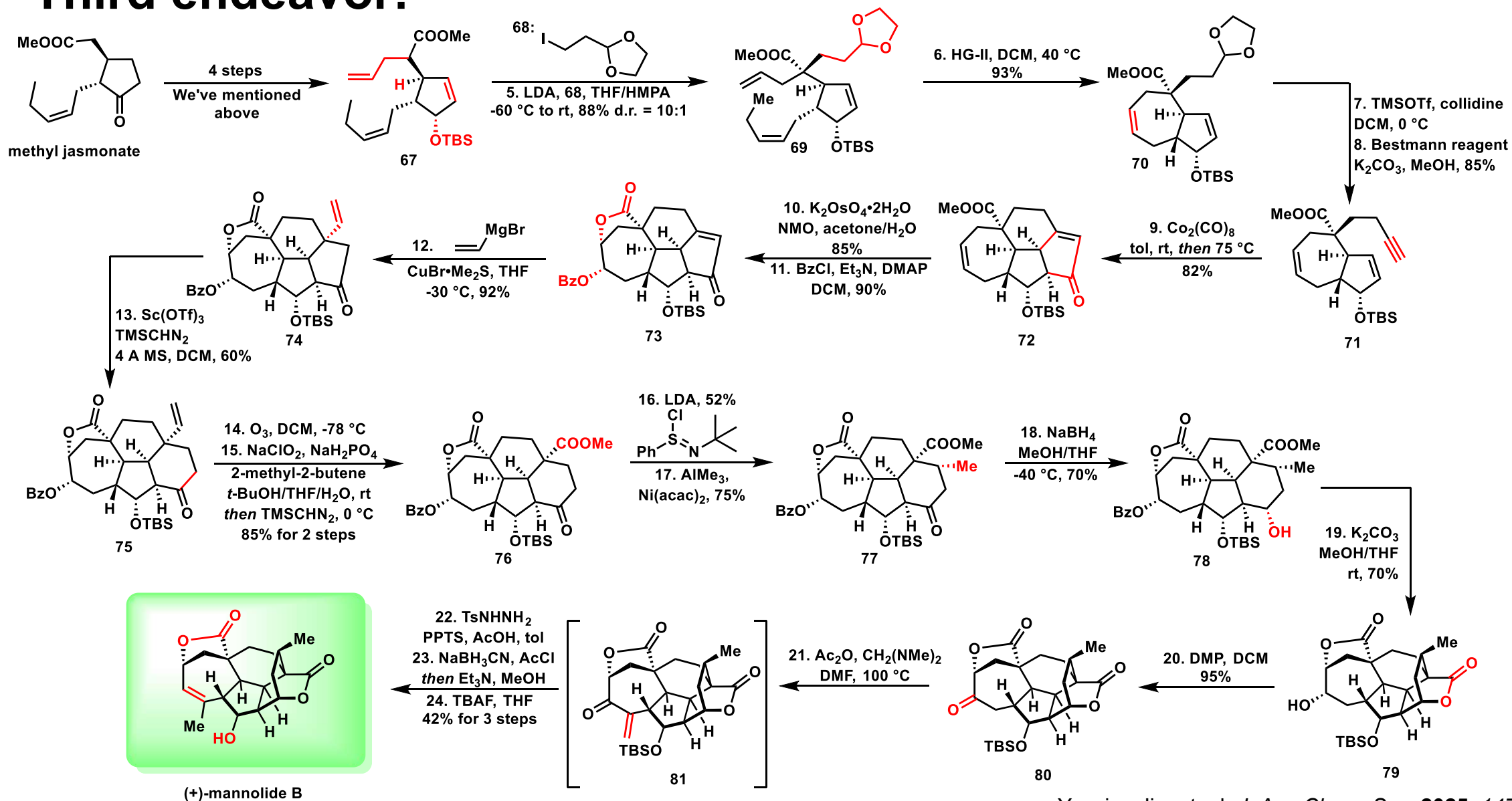
● Total synthesis towards (+)-mannolide B

Complement 3: Selectivities in BCS reaction

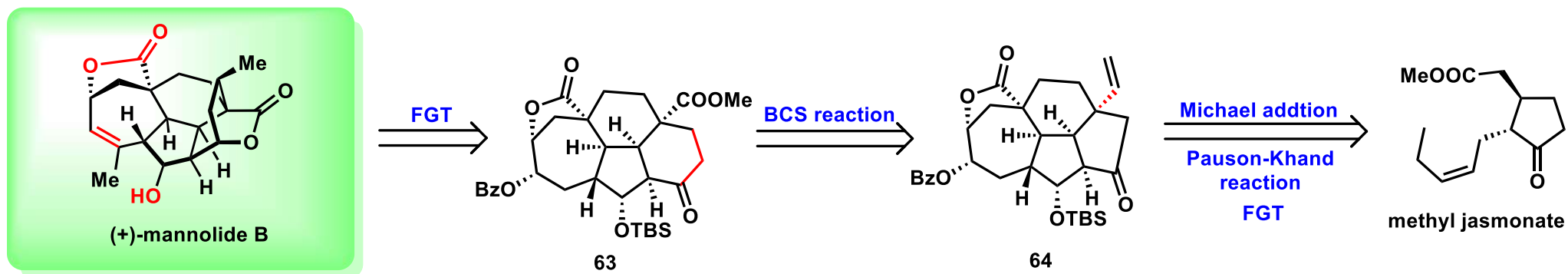
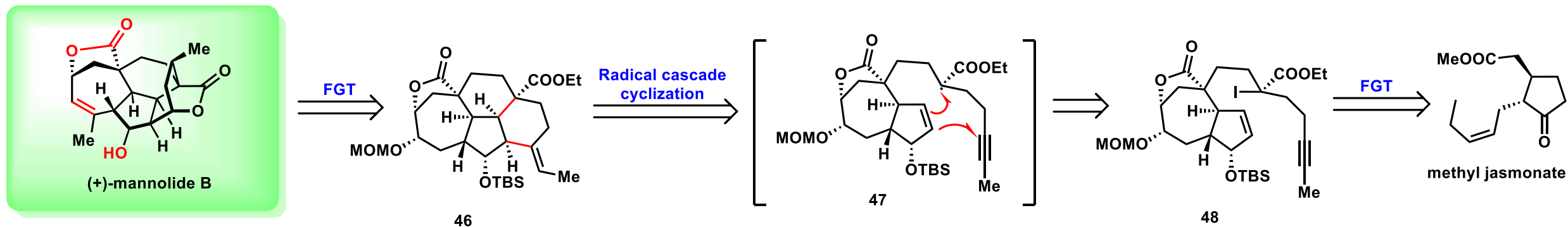
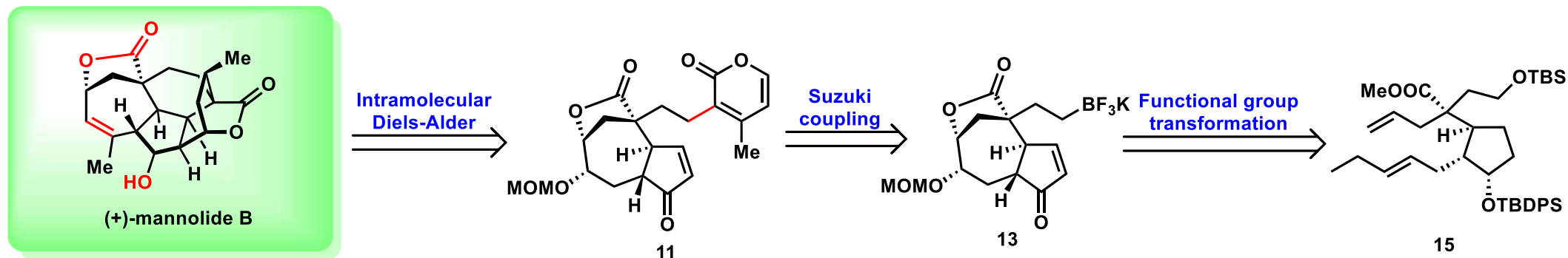


● Total synthesis towards (+)-mannolide B

Third endeavor:



● A brief conclusion



Acknowledgement

Thanks for listening and attention!

● C:
