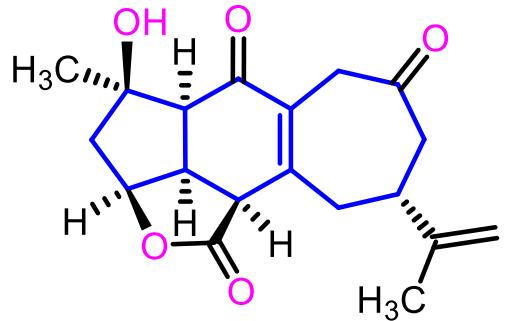
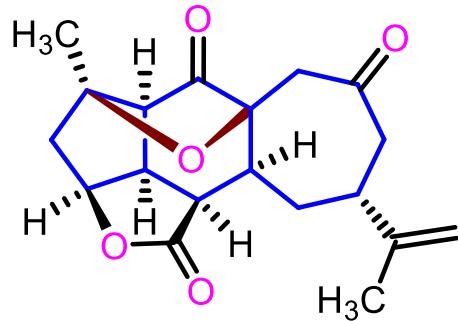


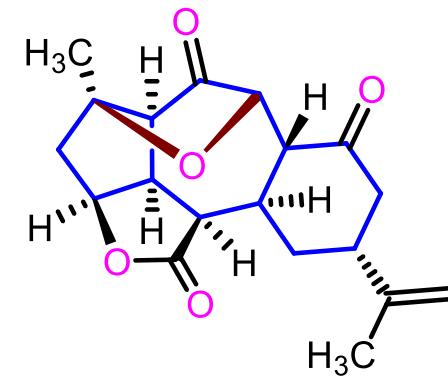
# Total Syntheses of Scabrolide A, Sinulochmodin C and Ineleganolide



**Scabrolide A**



**Sinulochmodin C**



**Ineleganolide**

**Reporter: Shixiong Feng**

**Supervisor: Prof. Quan Cai**

**2023.12.22**

# Content

---

## 1. Introduction

## 2. Total Synthesis of Scabrolide A

- ✓ Brian M. Stoltz (2020)
- ✓ Alois Fürtner (2022)
- ✓ David Sarlah (2023)

## 3. Total Syntheses of Sinulochmodin C and Ineleganolide

- ✓ John L. Wood (2022)
- ✓ Brian M. Stoltz (2023)
- ✓ Zhang Hongbin (2023)

## 4. Summary

# Content

---

## 1. Introduction

## 2. Total Synthesis of Scabrolide A

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## 3. Total Synthesis of Sinulochmodin C and Ineleganolide

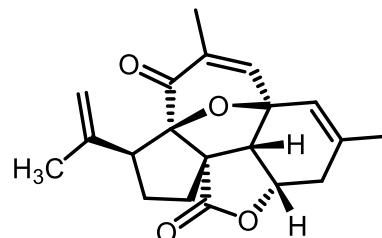
- ✓ John L. Wood (2022)
- ✓ Brian M. Stoltz (2023)
- ✓ Zhang Hongbin (2023)

## 4. Summary

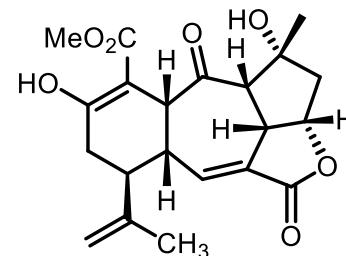
# Introduction——Isolation



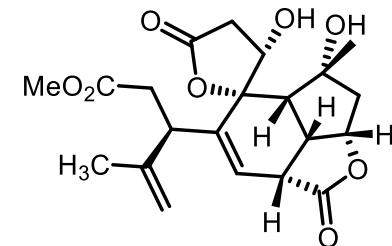
*Representative cembranoid diterpenoids* (西松烷二萜)



Intricarene

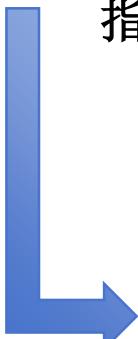


Rameswaralide

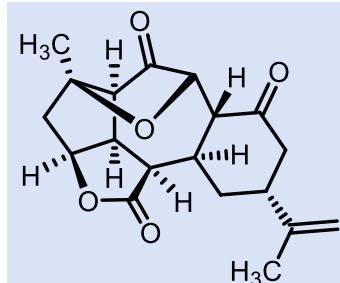


Havellockate

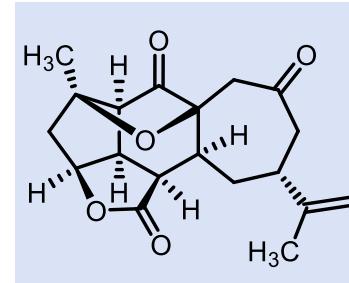
指形软珊瑚



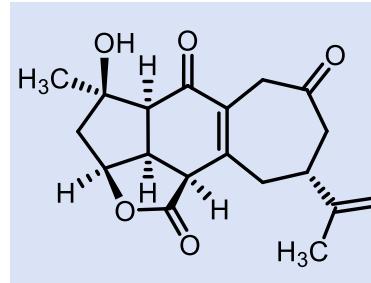
*Representative norcembranoid diterpenoids* (降西松烷二萜)



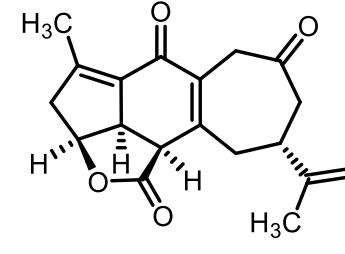
Ineleganolide



Sinulochmodin C



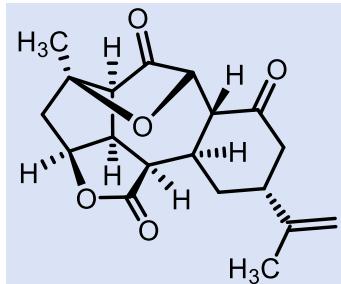
Scabrolide A



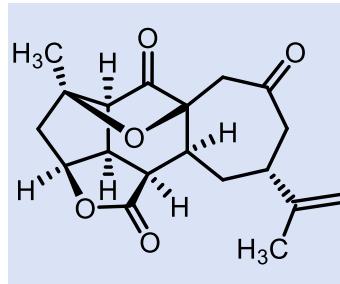
Yonaolide

# Introduction—Biosynthesis

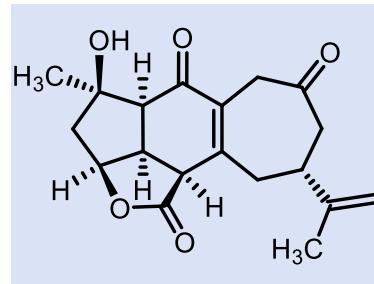
## Representative furanobutenolide-derived norcembranoid



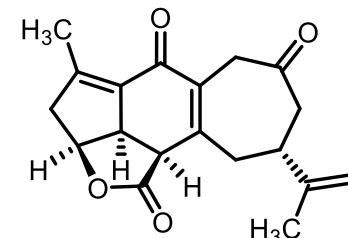
Ineleganolide



Sinulochmodin C

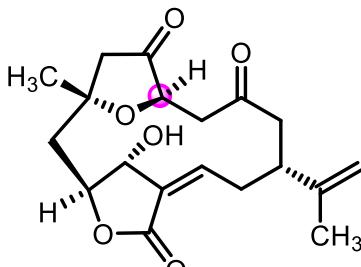


Scabrolide A

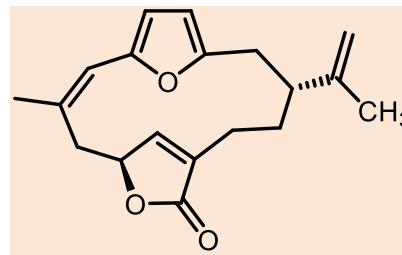


Yonaolide

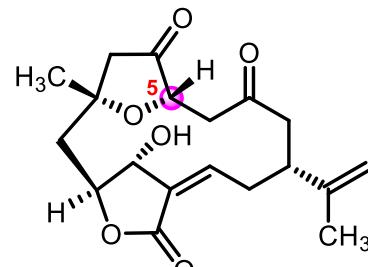
Origins



Sinuleptolide



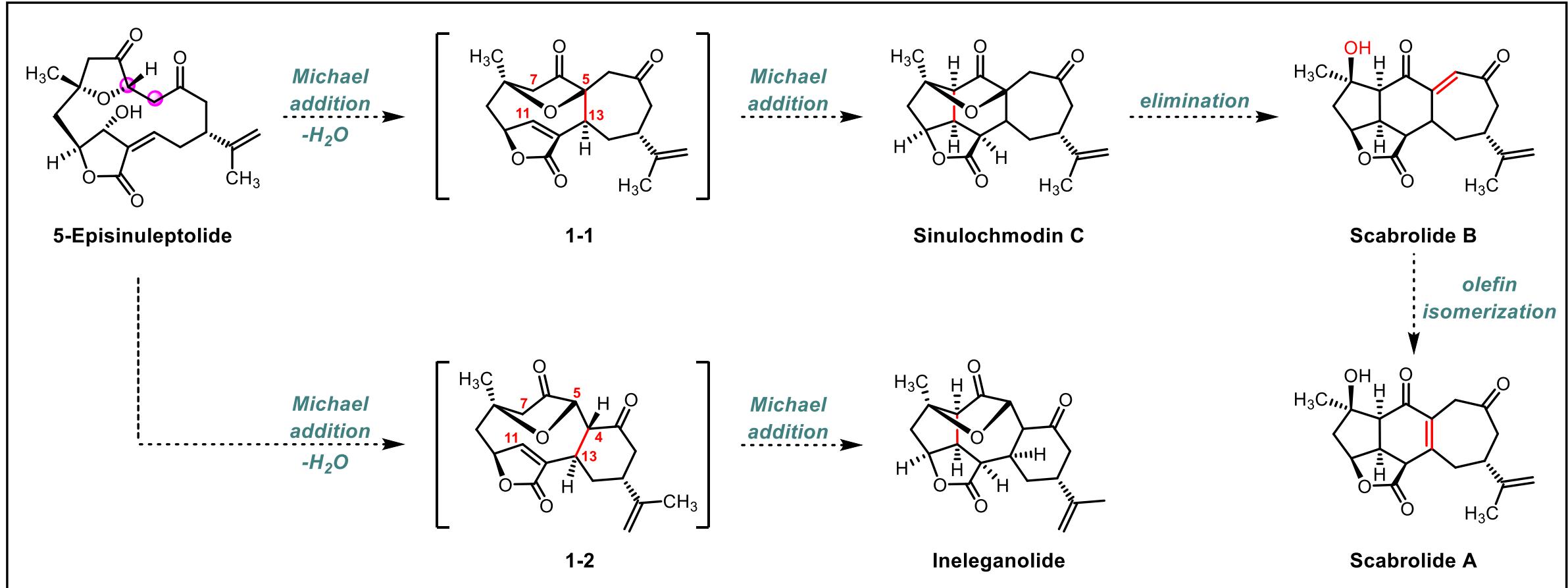
Norcembranoid Scaffold



5-Episinuleptolide

# Introduction——Biosynthesis

## *Proposed biosynthesis of norcembranoid*



# Content

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## 1. Introduction

## 2. Total Synthesis of Scabrolide A

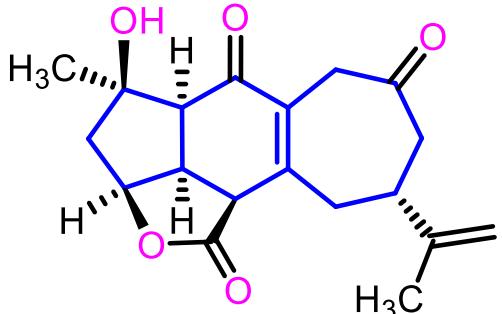
- ✓ Brian M. Stoltz (2020)
- ✓ Alois Fürtner (2022)
- ✓ David Sarlah (2023)

## 3. Total Syntheses of Sinulochmodin C and Ineleganolide

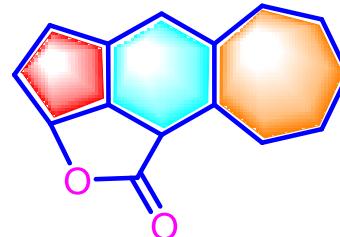
- ✓ John L. Wood (2022)
- ✓ Brian M. Stoltz (2023)
- ✓ Zhang Hongbin (2023)

## 4. Summary

# Introduction of Scabrolide A



Scabrolide A



[7,6,5,5]-tetracyclic core

## 结构挑战:

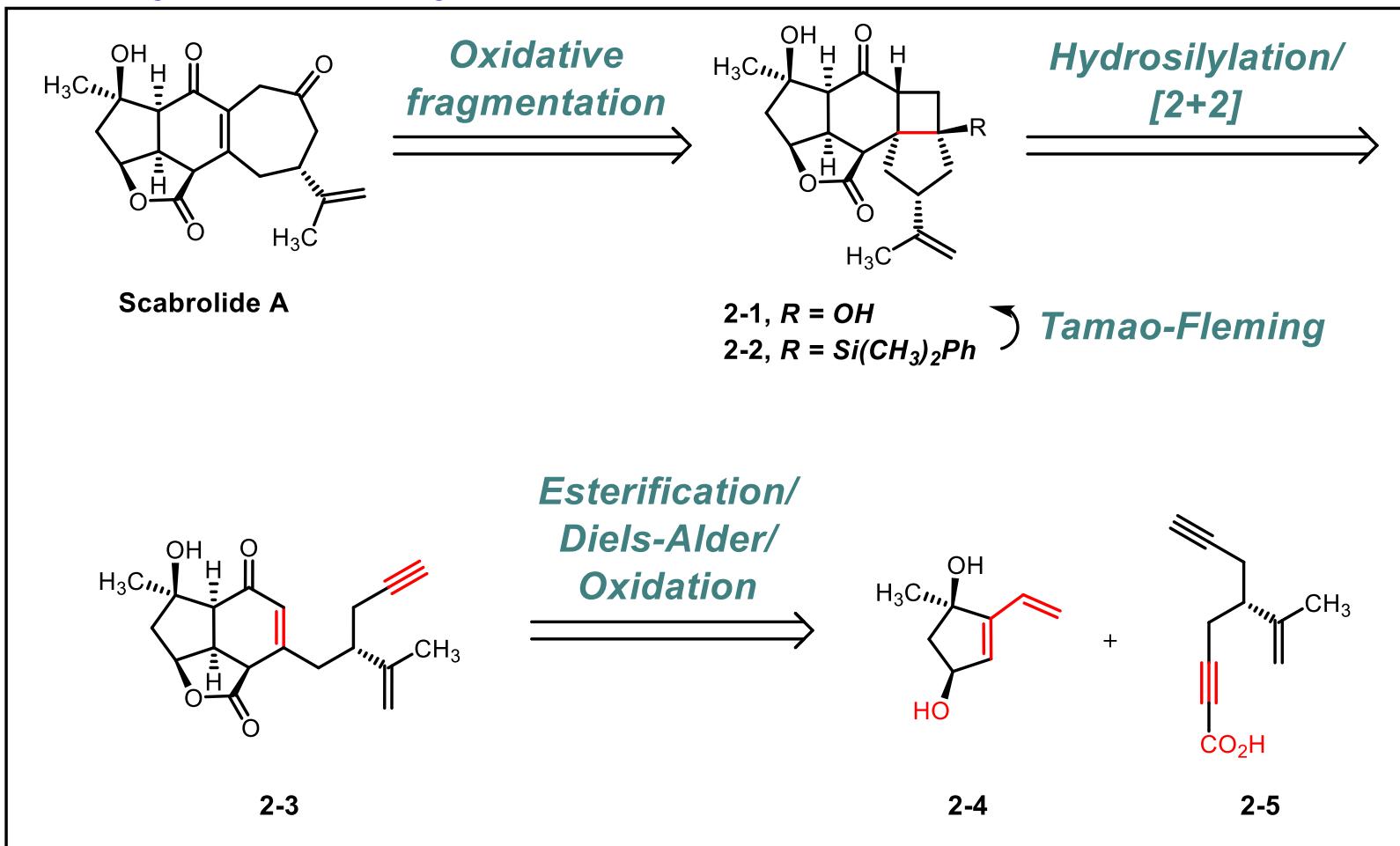
- 稠合的[5-6-7]全碳三环
- 五元内酯环
- 6个手性中心
- 远端异丙烯基取代手性中心
- 较高的氧化态

## 生物活性:

- 体外生物活性测试显示，对IL-6 ( $IC_{50}=69.85 \pm 4.11 \mu M$ )和IL-12 ( $IC_{50}=23.52 \pm 1.37 \mu M$ )有抑制作用，具有潜在的消炎作用。

# First Total Synthesis of Scabrolide A——Stoltz (2020)

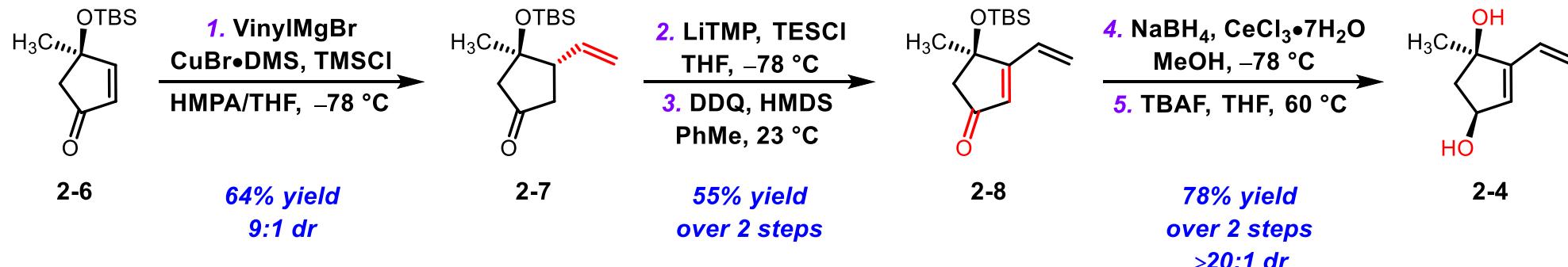
## Retrosynthetic Analysis



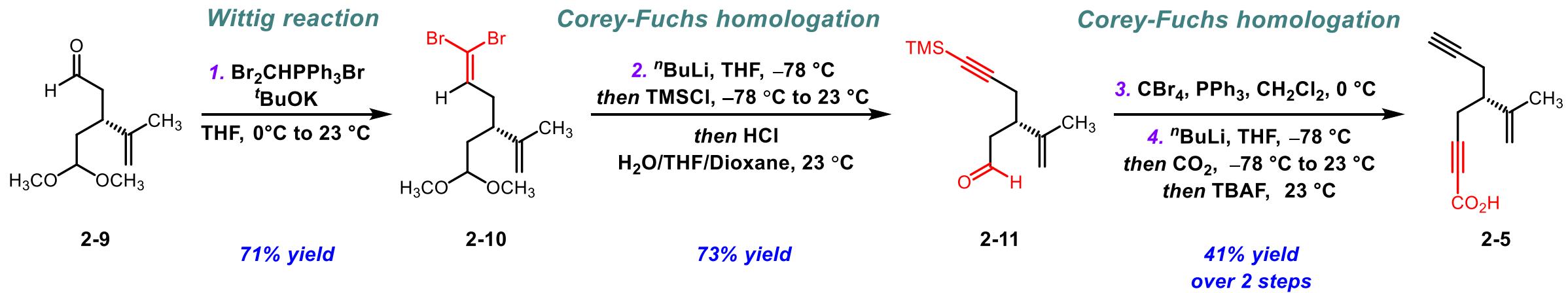
Brian M. Stoltz

# First Total Synthesis of Scabrolide A——Stoltz (2020)

## Preparation of dihydroxyvinylcyclopentene 2-4

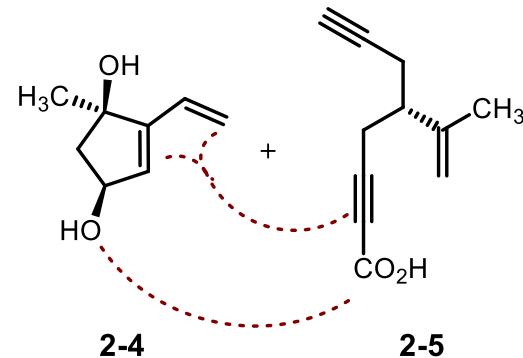


## Preparation of ynoic acid 2-5



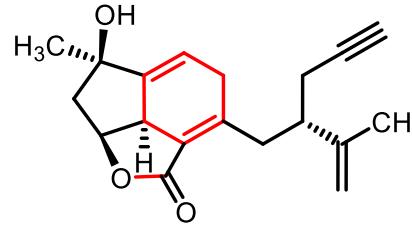
# First Total Synthesis of Scabrolide A——Stoltz (2020)

## Failed photocycloaddition



## Esterification/ D-A reaction

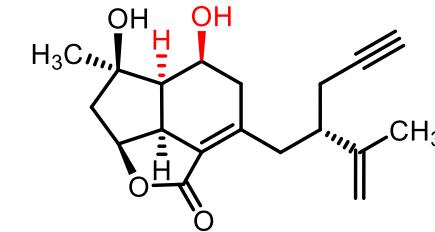
6. DIC, DMAP  
 $\text{CH}_2\text{Cl}_2$ , 0 °C  
 7. 140 °C  
 xylenes



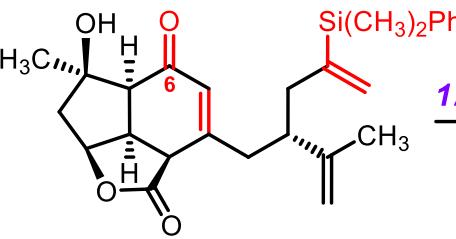
59% yield  
 over 2 steps  
 >20:1 dr

8.  $\text{VO}(\text{acac})_2$ , TBHP  
 $\text{CH}_2\text{Cl}_2/\text{PhH}$ , 23 °C  
 9.  $\text{Cp}_2\text{TiCl}_2$ ,  $\text{Mn}^0$   
 collidine•HCl  
 1,4-CHD  
 THF, 23 °C

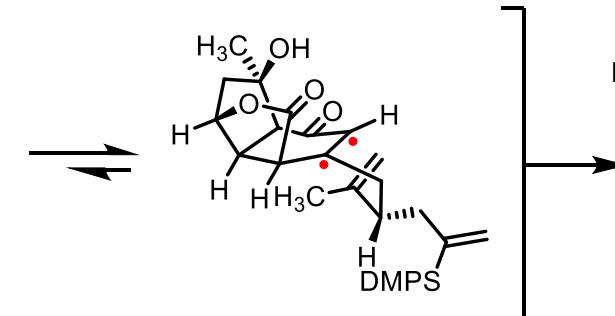
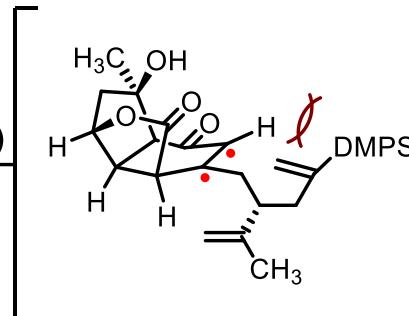
81% yield  
 over 2 steps  
 >20:1 dr



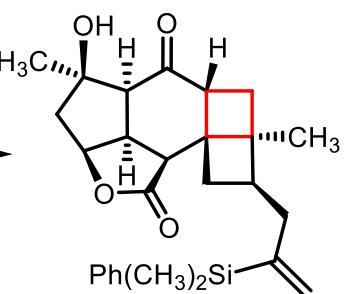
10. IBX  
 $\text{MeCN}$ , 50 °C  
 11.  $\text{Ph}(\text{CH}_3)_2\text{SiH}$   
 $[\text{RuCp}^*(\text{MeCN})_3]\text{PF}_6$   
 $\text{CH}_2\text{Cl}_2$ , 0 °C



12'.  $h\nu$  (350 nm)  
 PhH, 23 °C

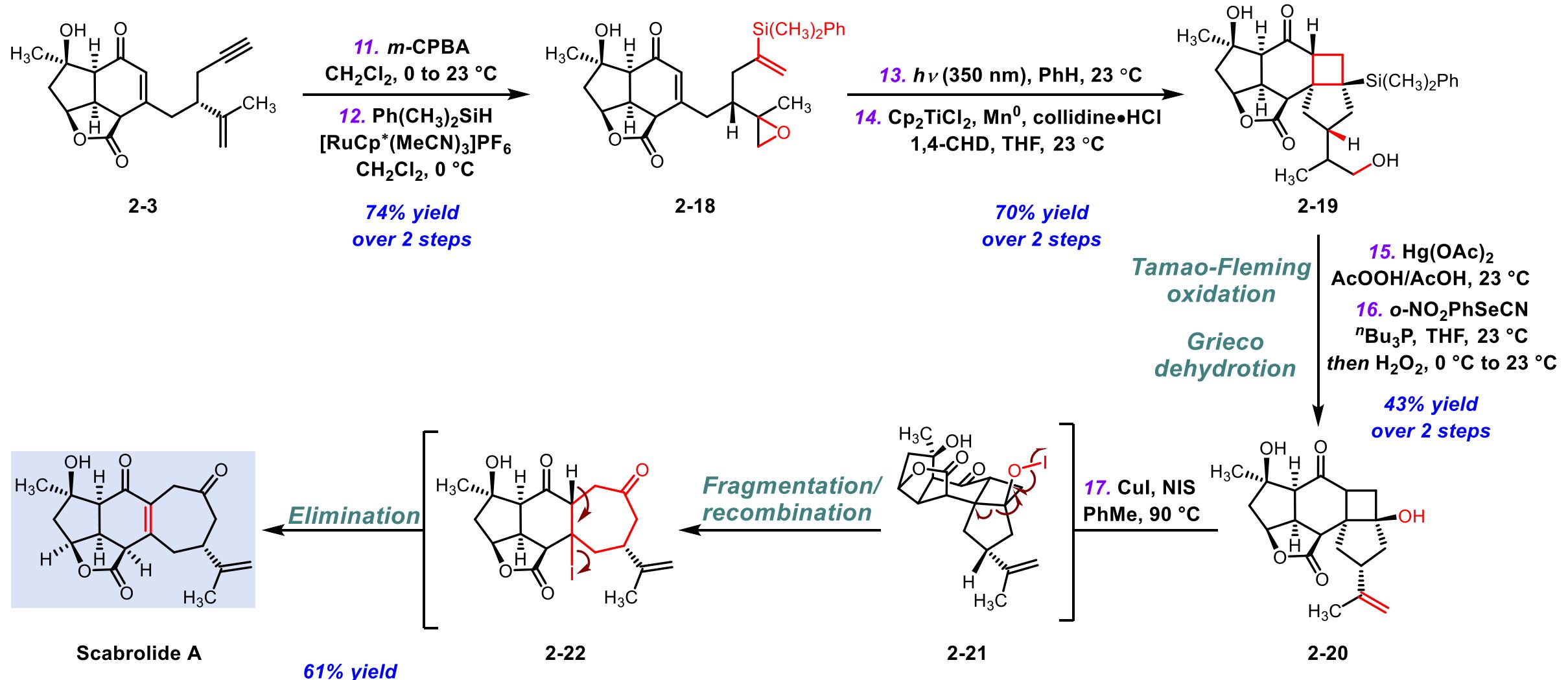


65% yield  
 over 2 steps



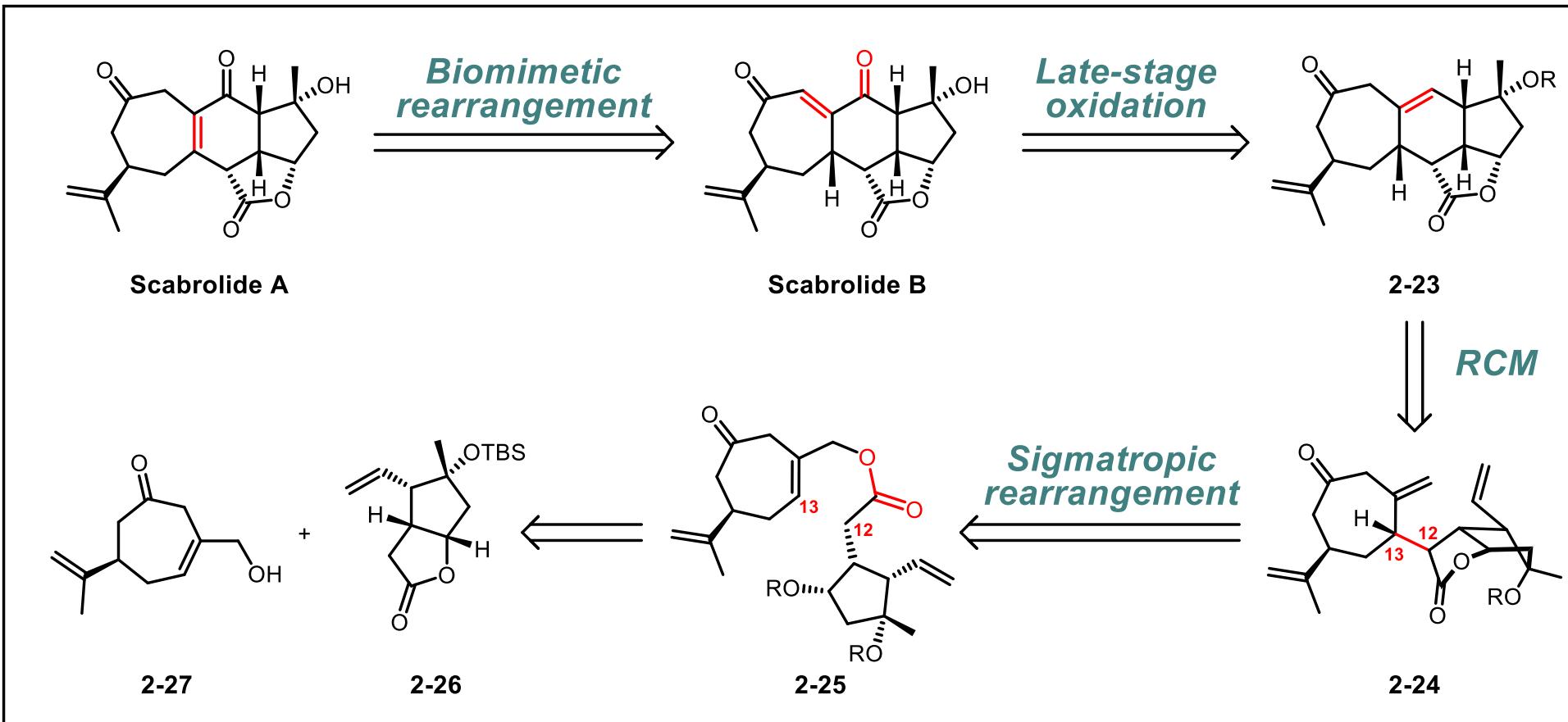
Undesired

# First Total Synthesis of Scabrolide A——Stoltz (2020)



# Total Synthesis of Scabrolide A——Fürstner (2022)

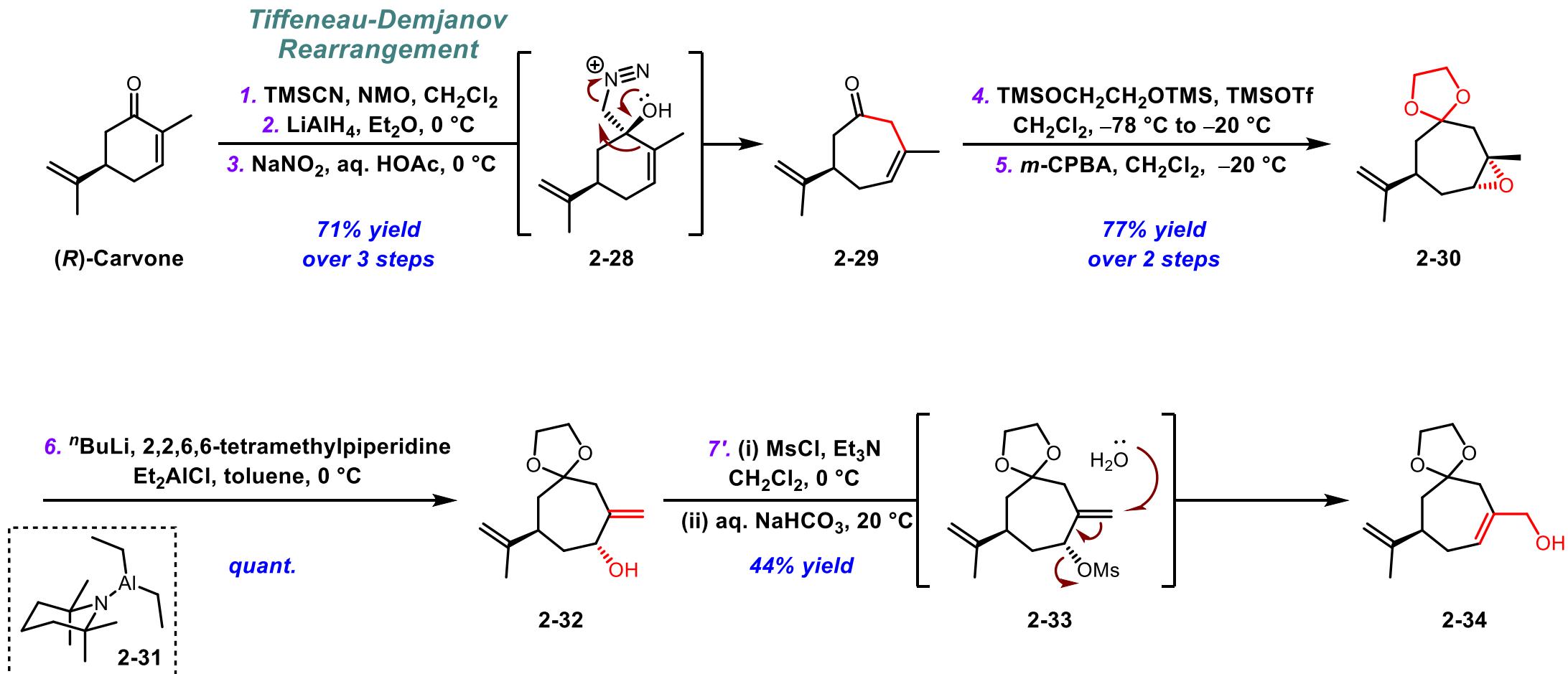
## Retrosynthetic Analysis



Alois Fürstner

# Total Synthesis of Scabrolide A——Fürstner (2022)

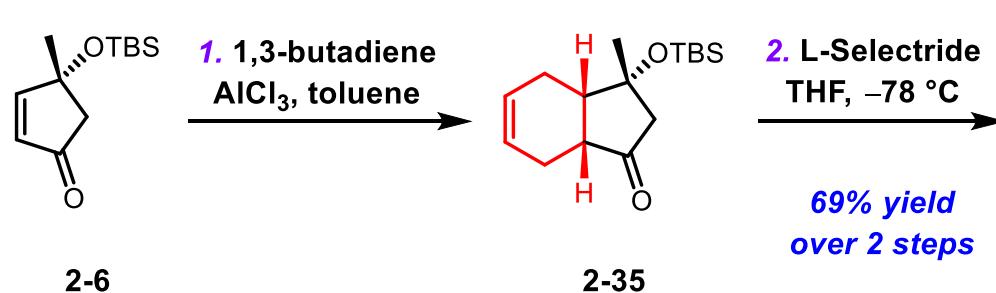
## Preparation of cycloheptene 2-34



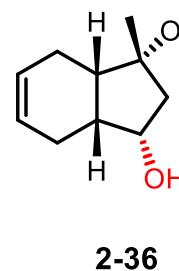
# Total Synthesis of Scabrolide A——Fürstner (2022)

## Preparation of bicyclic lactone 2-26

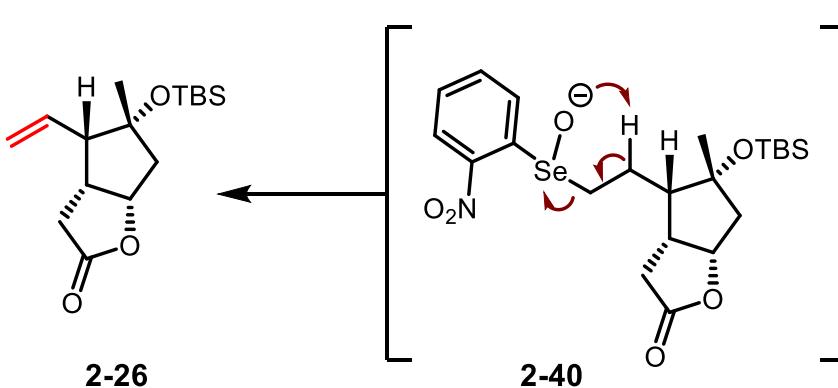
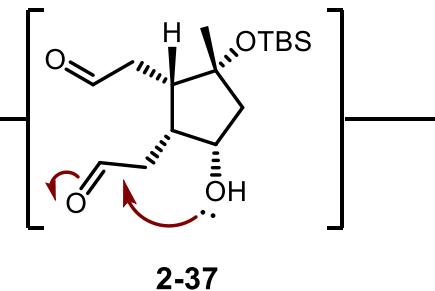
### Diels-Alder reaction



2. L-Selectride  
THF,  $-78^\circ\text{C}$   
*69% yield over 2 steps*



3. (i)  $\text{O}_3$ ,  $\text{CH}_2\text{Cl}_2$   
(ii)  $\text{PPh}_3$



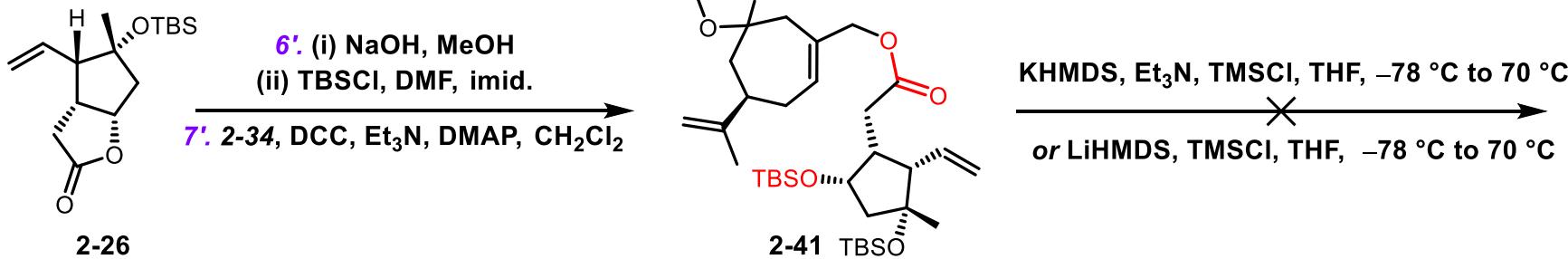
2-39

4. (i) PCC,  $\text{CH}_2\text{Cl}_2$   
 $4\text{\AA MS}$ ,  $0^\circ\text{C}$   
(ii)  $\text{NaBH}_4$ ,  $0^\circ\text{C}$   
*44% yield over 3 steps*

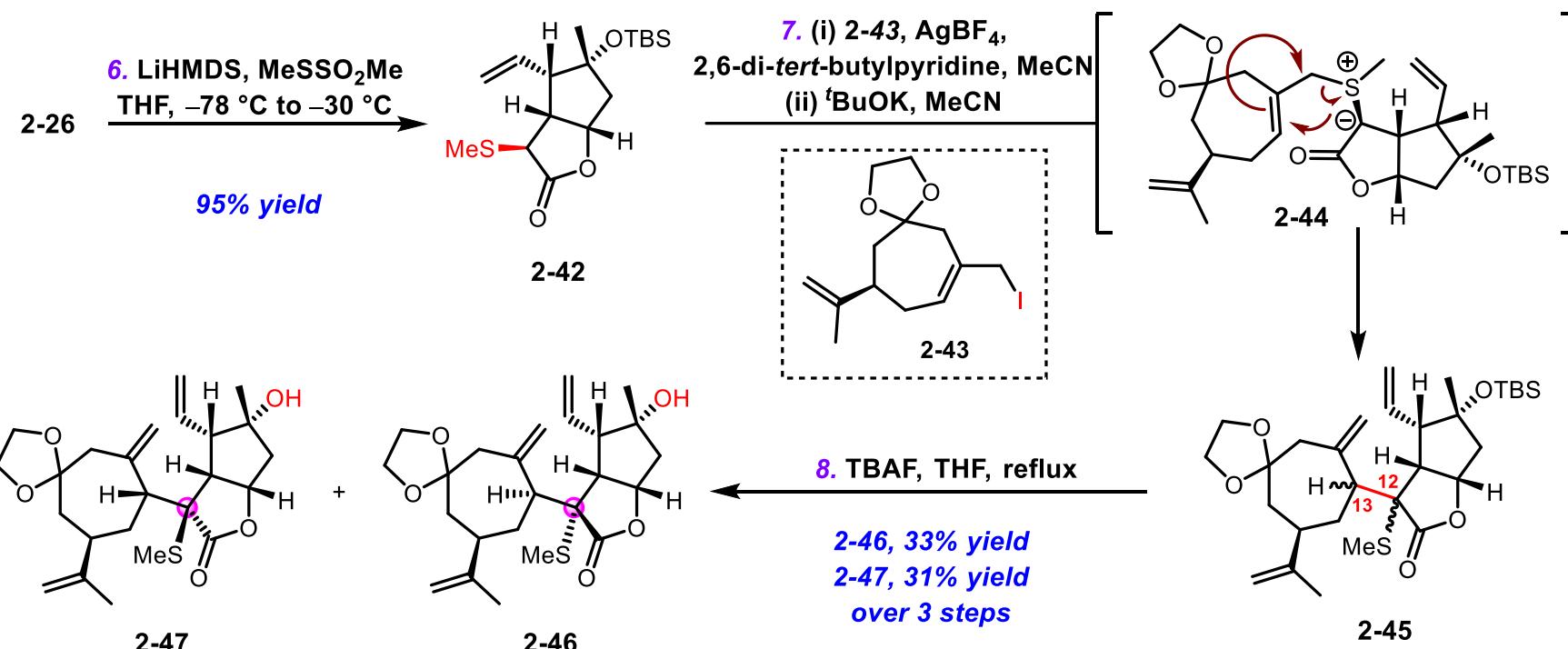
2-38

# Total Synthesis of Scabrolide A——Fürstner (2022)

## Failed Ireland-Claisen rearrangement

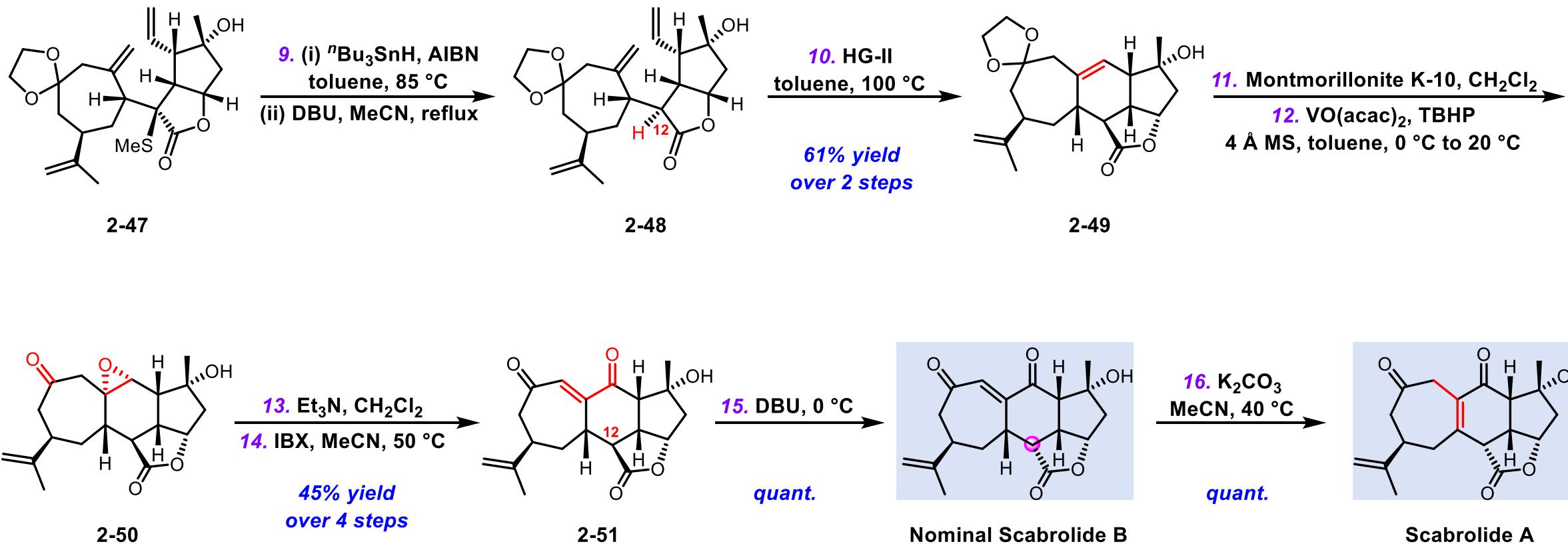


## [2,3]-Sigmatropic rearrangement



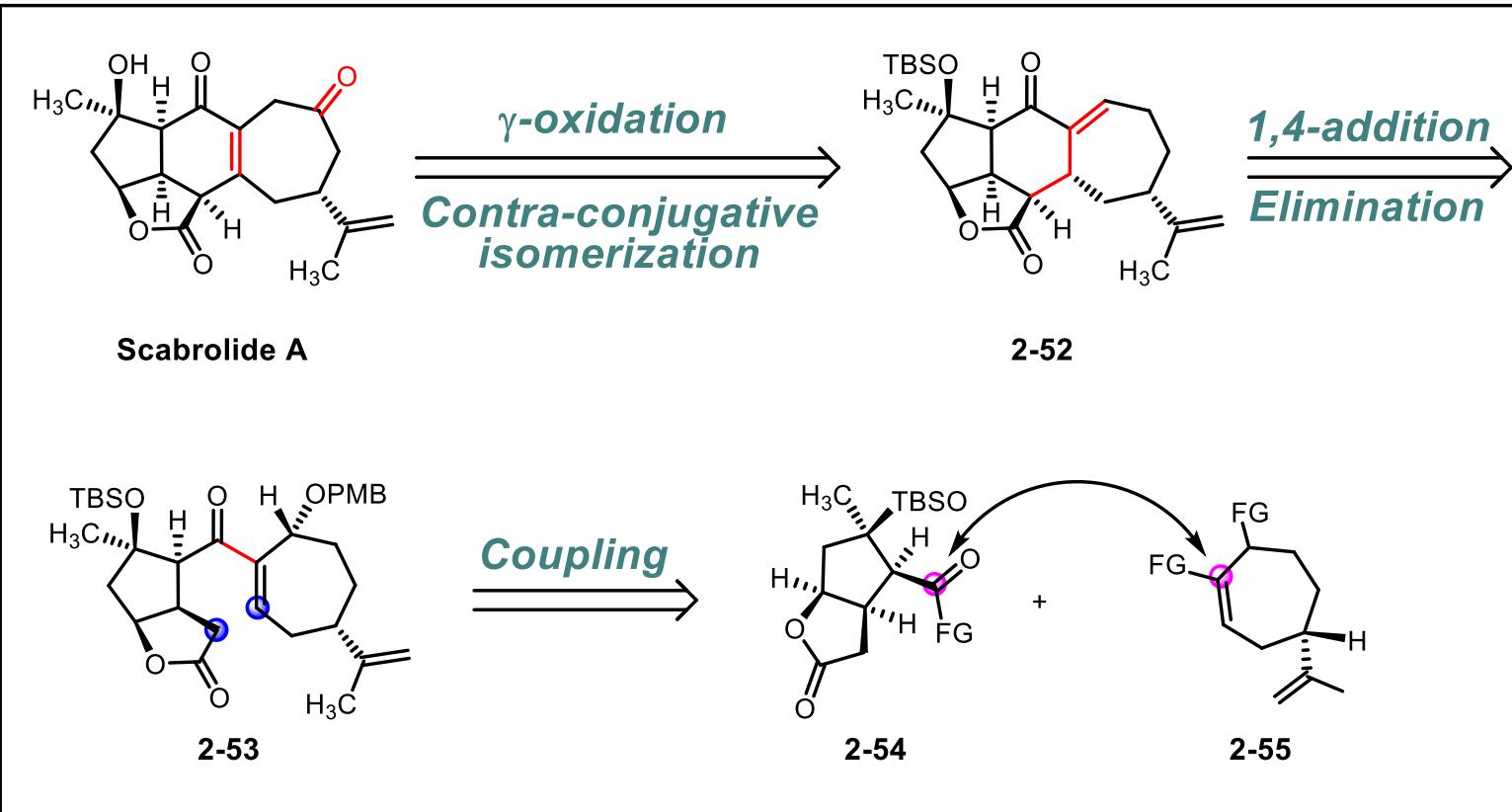
# Total Synthesis of Scabrolide A——Fürstner (2022)

## End game



# Total Synthesis of Scabrolide A——Sarlah (2023)

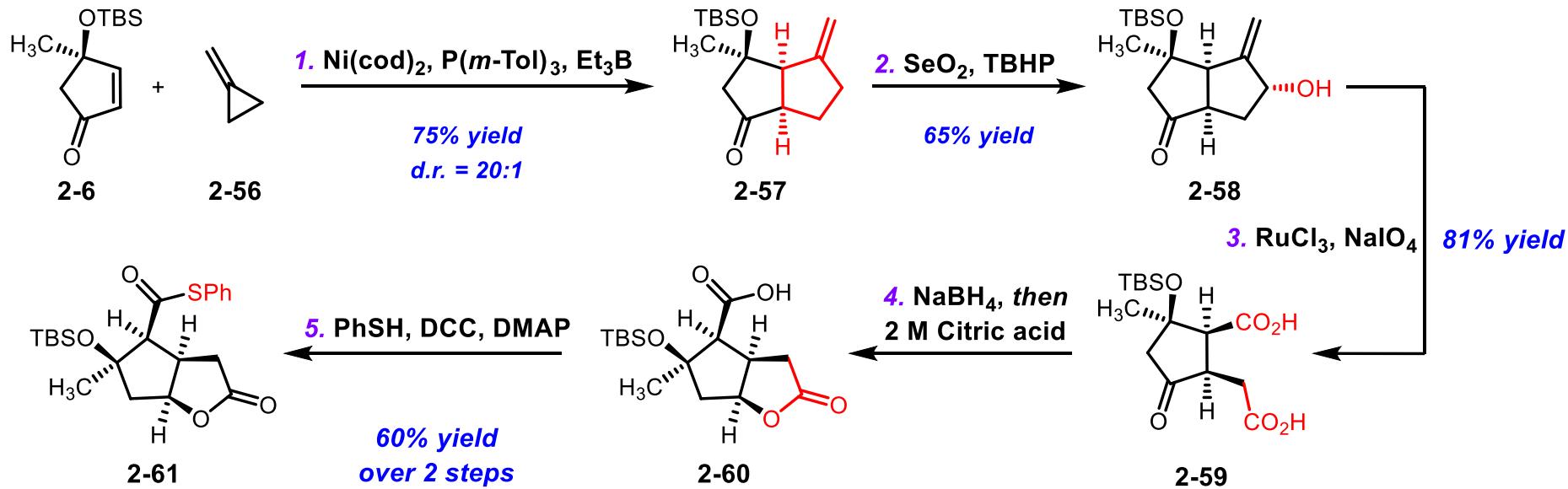
## Retrosynthetic Analysis



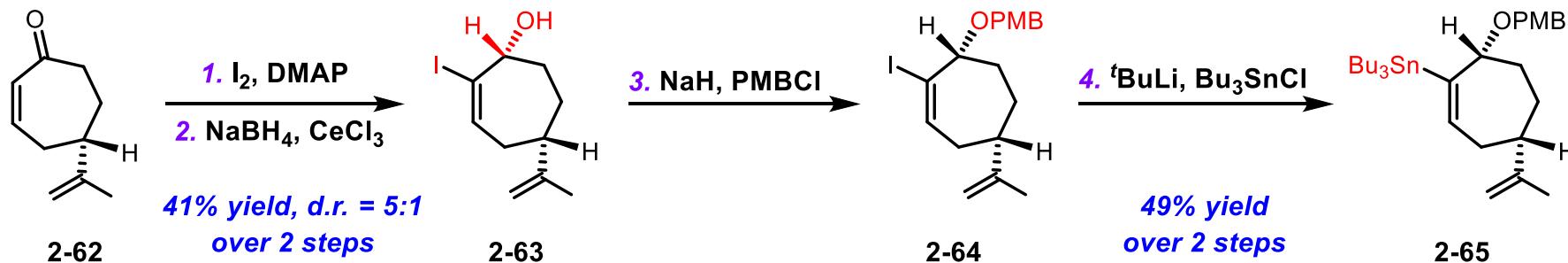
David Sarlah

# Total Synthesis of Scabrolide A——Sarlah (2023)

## *Preparation of Bicyclic lactone 2-61*

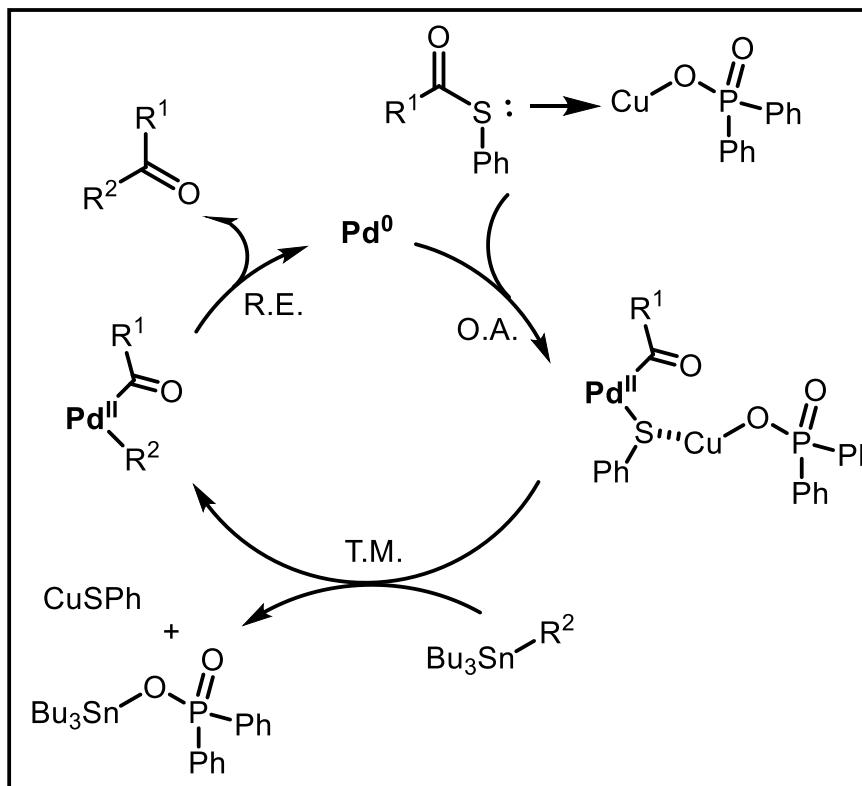
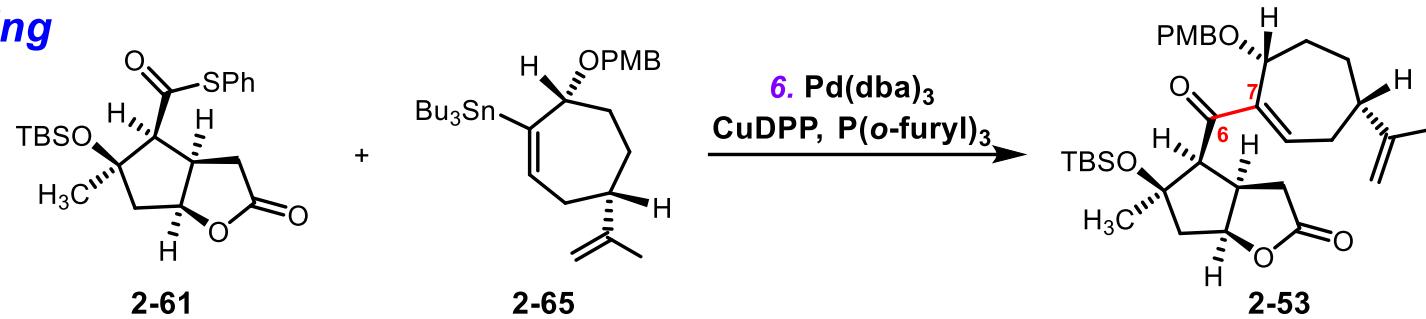


## *Preparation of cycloheptenyl 2-65*



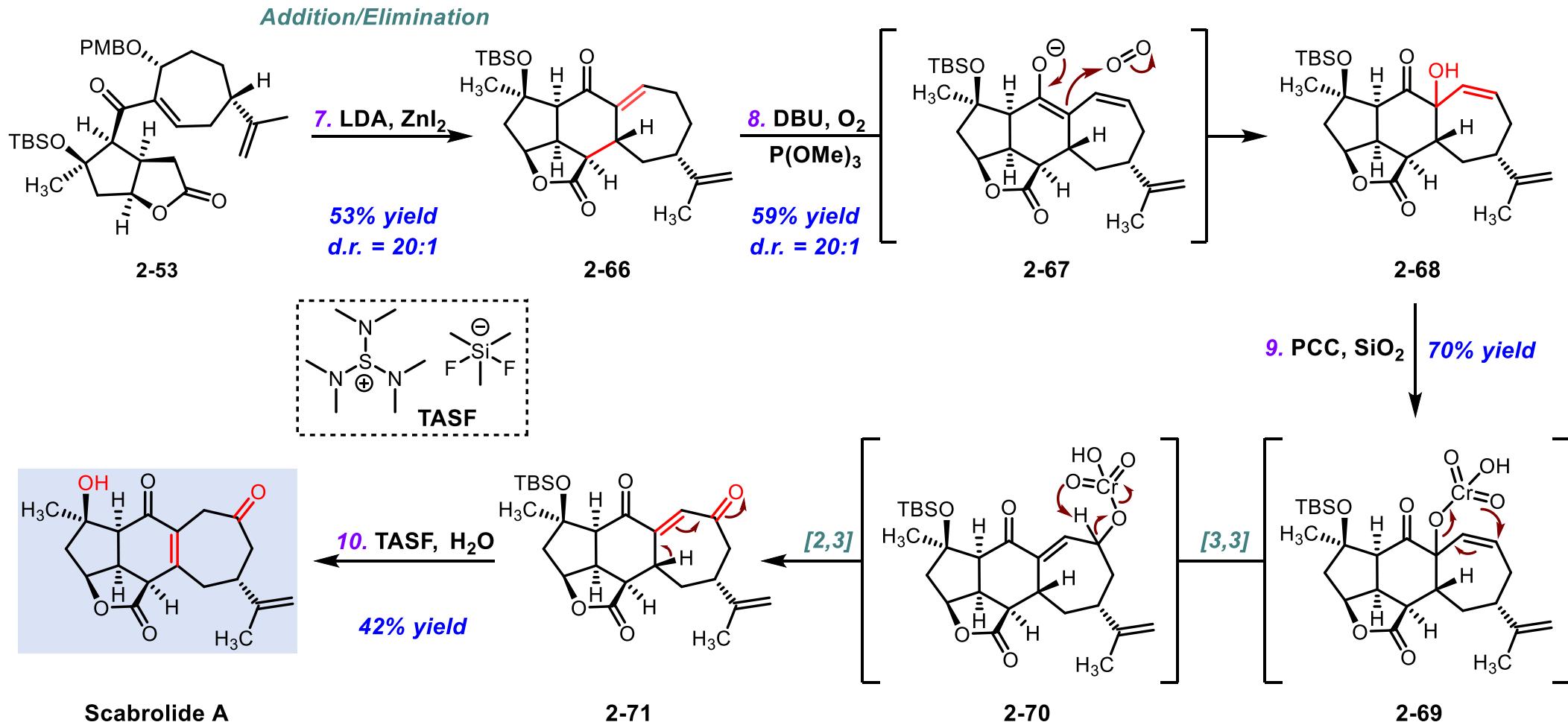
# Total Synthesis of Scabrolide A——Sarlah (2023)

## Liebeskind-Srogl coupling



# Total Synthesis of Scabrolide A——Sarlah (2023)

## Formation of C<sub>12</sub>/C<sub>13</sub> and Oxidative decoration



# Content

---

## 1. Introduction

## 2. Total Synthesis of Scabrolide A

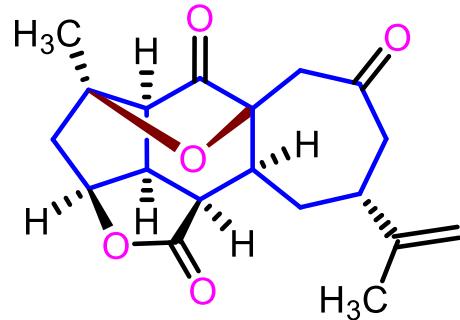
- ✓ Brian M. Stoltz (2020)
- ✓ Alois Fürstner (2022)
- ✓ David Sarlah (2023)

## 3. Total Syntheses of Sinulochmodin C and Ineleganolide

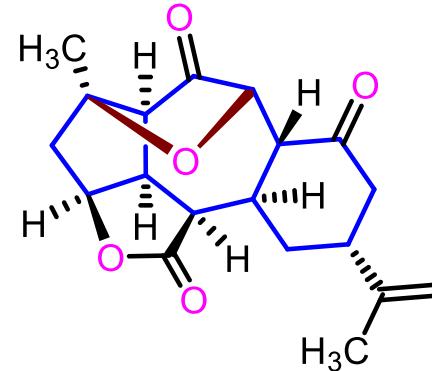
- ✓ John L. Wood (2022)
- ✓ Brian M. Stoltz (2023)
- ✓ Zhang Hongbin (2023)

## 4. Summary

# Introduction of Sinulochmodin C and Ineleganolide



Sinulochmodin C



Ineleganolide

## 结构挑战:

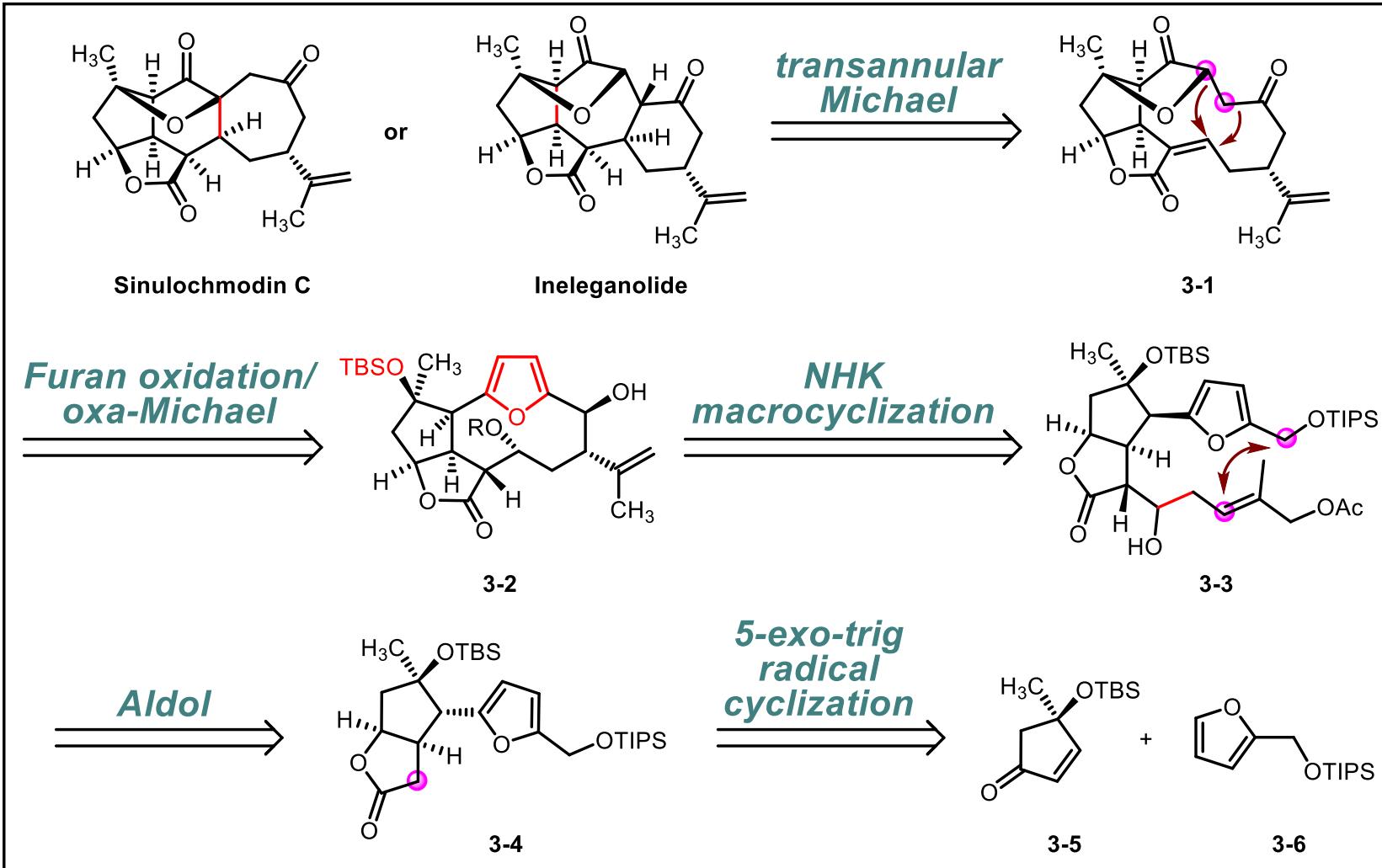
- 稠合的[5-6-7]、[5-7-6]三环结构及五元内酯环
- β-酮基四氢呋喃环
- 多个连续的手性中心
- 大量的氧化修饰

## 生物活性:

- 对杜氏利什曼原虫具有较好的抑制作用( $IC_{50}=4.4 \mu M$ )，对 P-388 细胞培养体系表现出细胞毒性  $ED_{50}=3.82 \mu g/ml$  )。

# First Total Synthesis of Ineleganolide and Sinulochmodin C——Wood (2022)

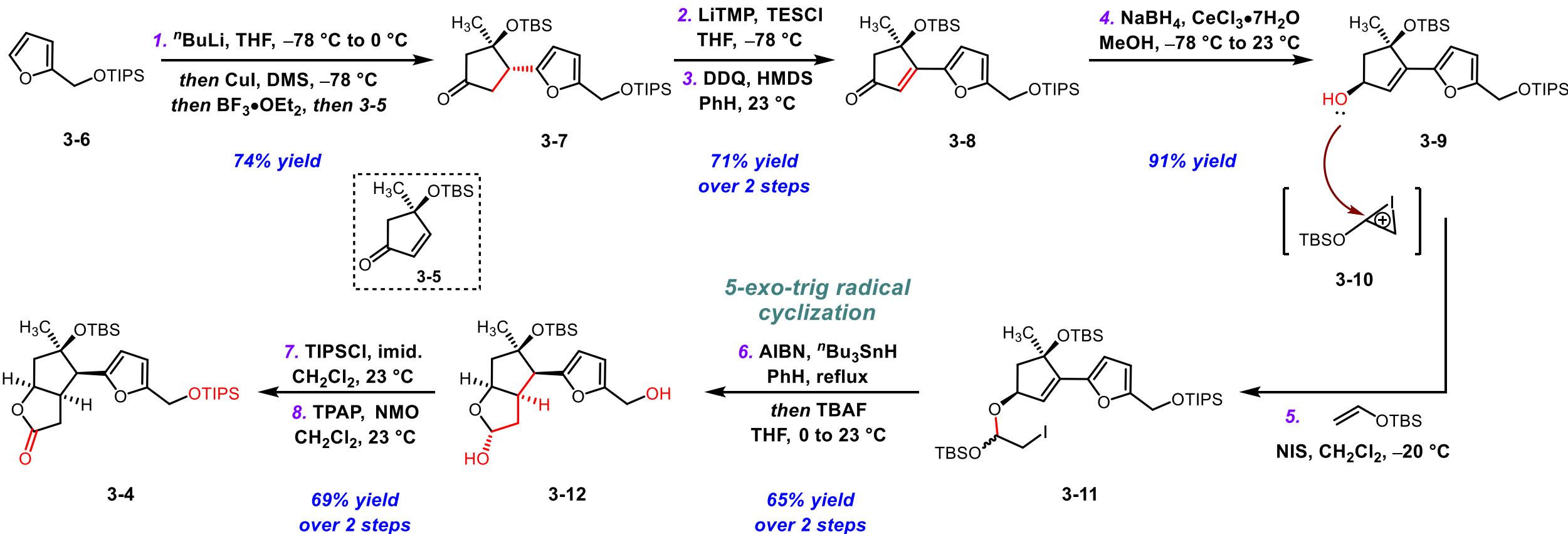
## Retrosynthetic Analysis



John L. Wood

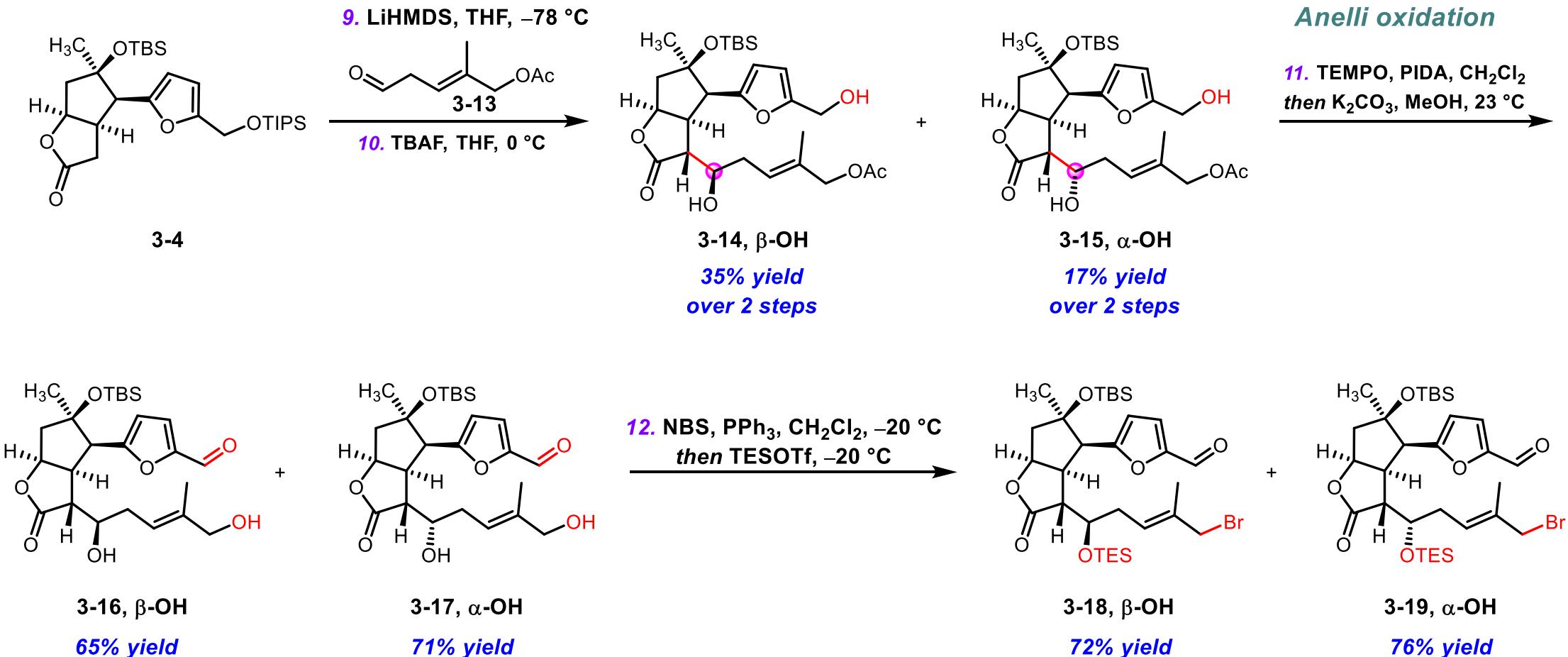
# First Total Synthesis of Ineleganolide and Sinulochmodin C——Wood (2022)

## Preparation of bicyclic lactone 3-4



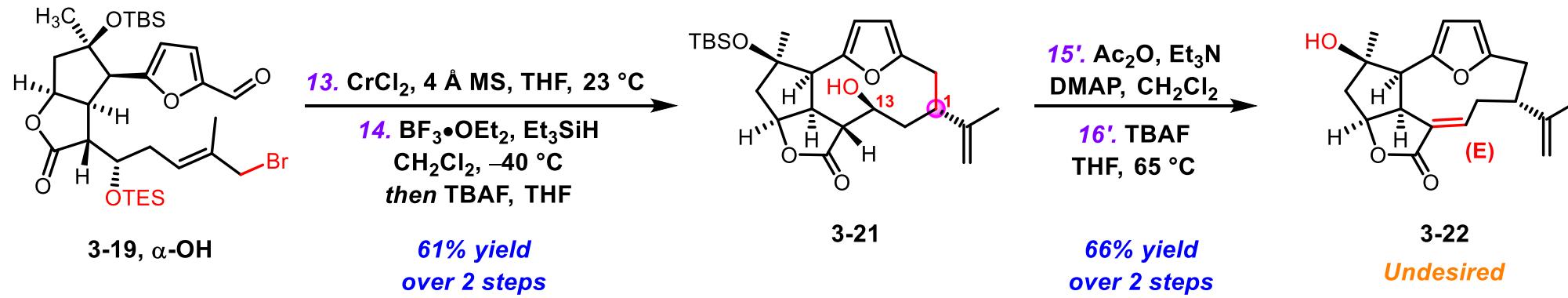
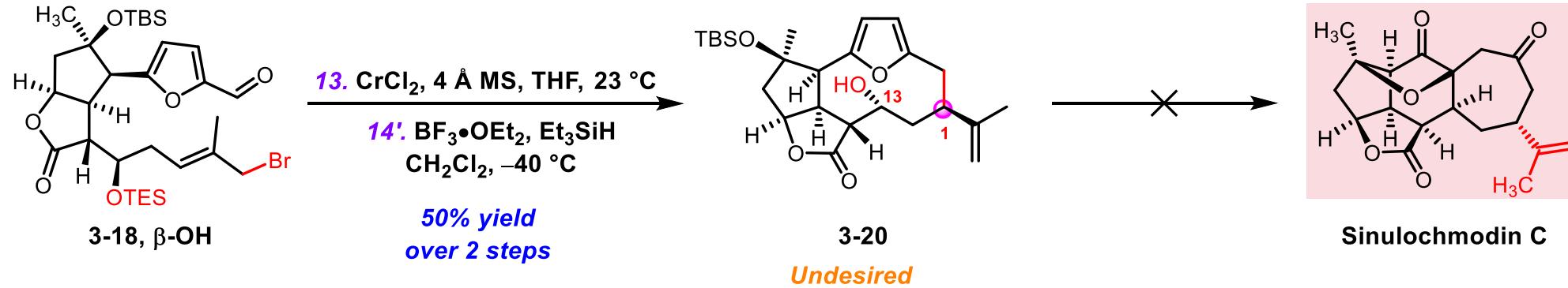
# First Total Synthesis of Ineleganolide and Sinulochmodin C——Wood (2022)

## Preparation of NHK macrocyclization precursors



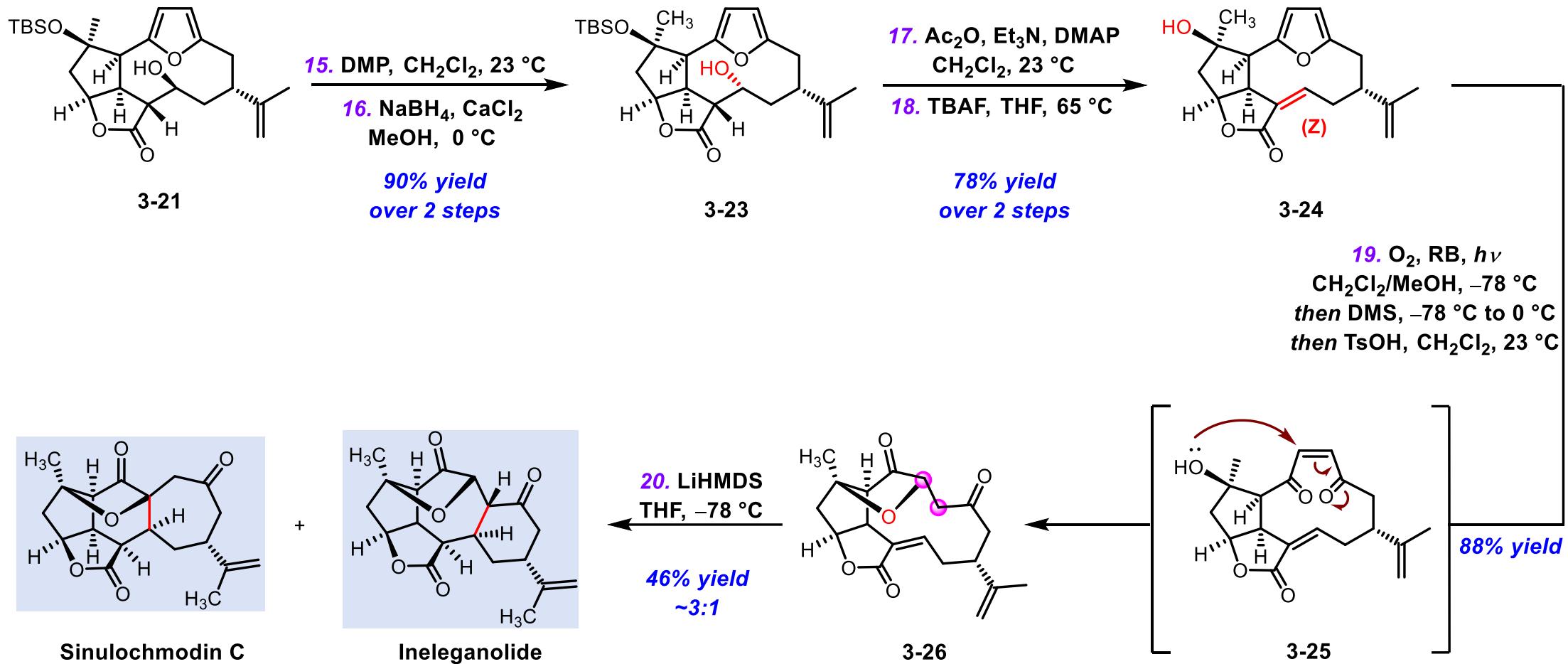
# First Total Synthesis of Ineleganolide and Sinulochmodin C——Wood (2022)

## NHK macrocyclization



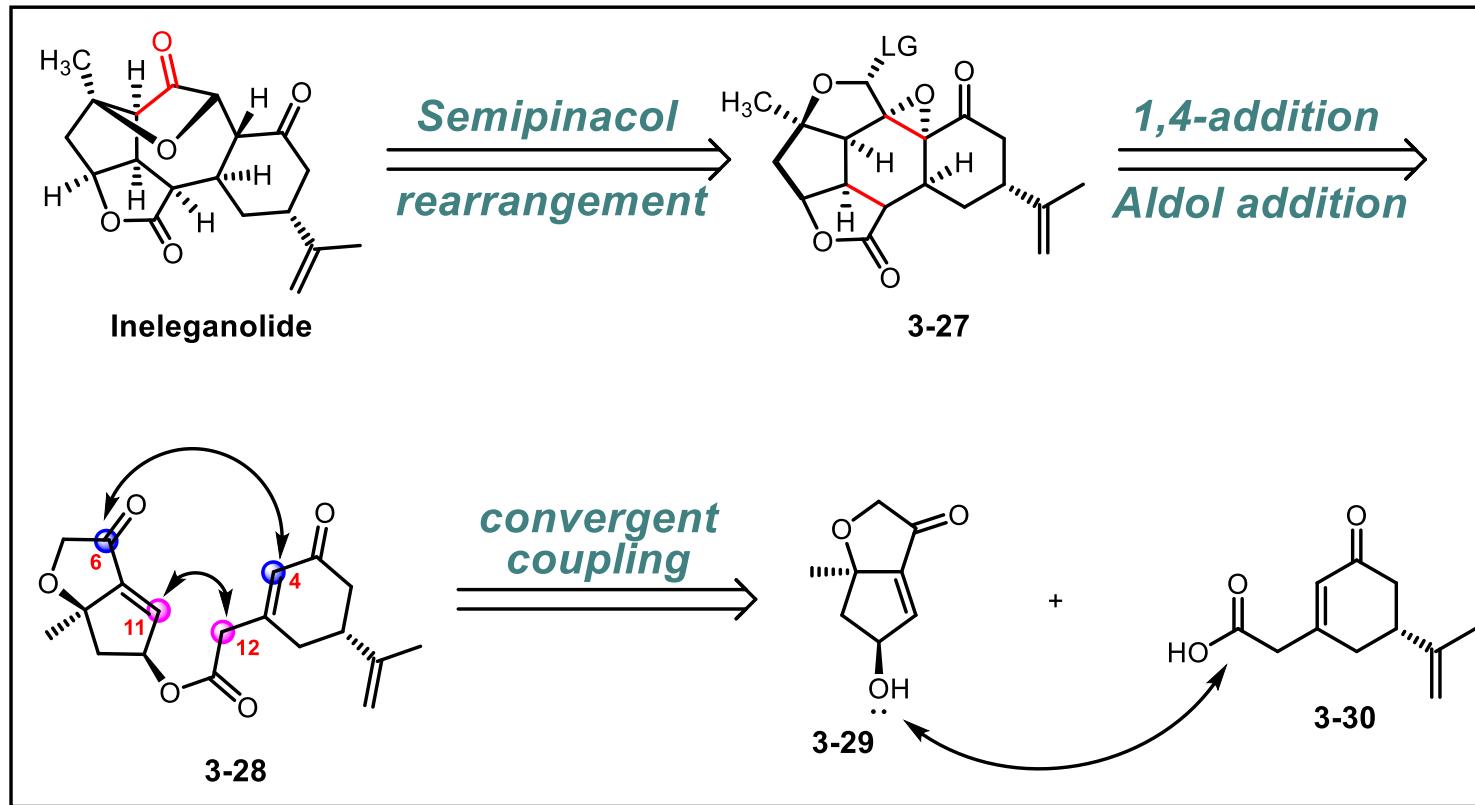
# First Total Synthesis of Ineleganolide and Sinulochmodin C——Wood (2022)

## End game



# Total Synthesis of Ineleganolide——Stoltz (2023)

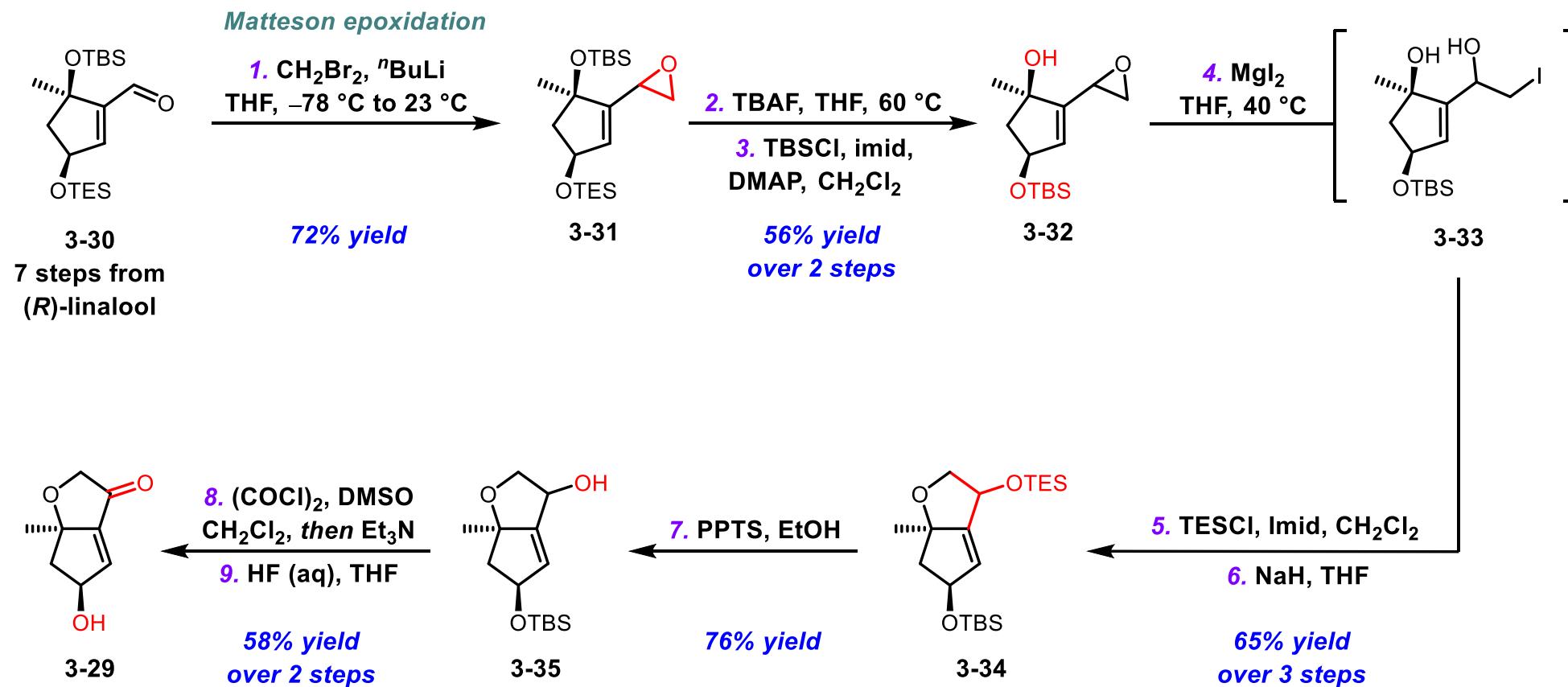
## Retrosynthetic Analysis



Brian M. Stoltz

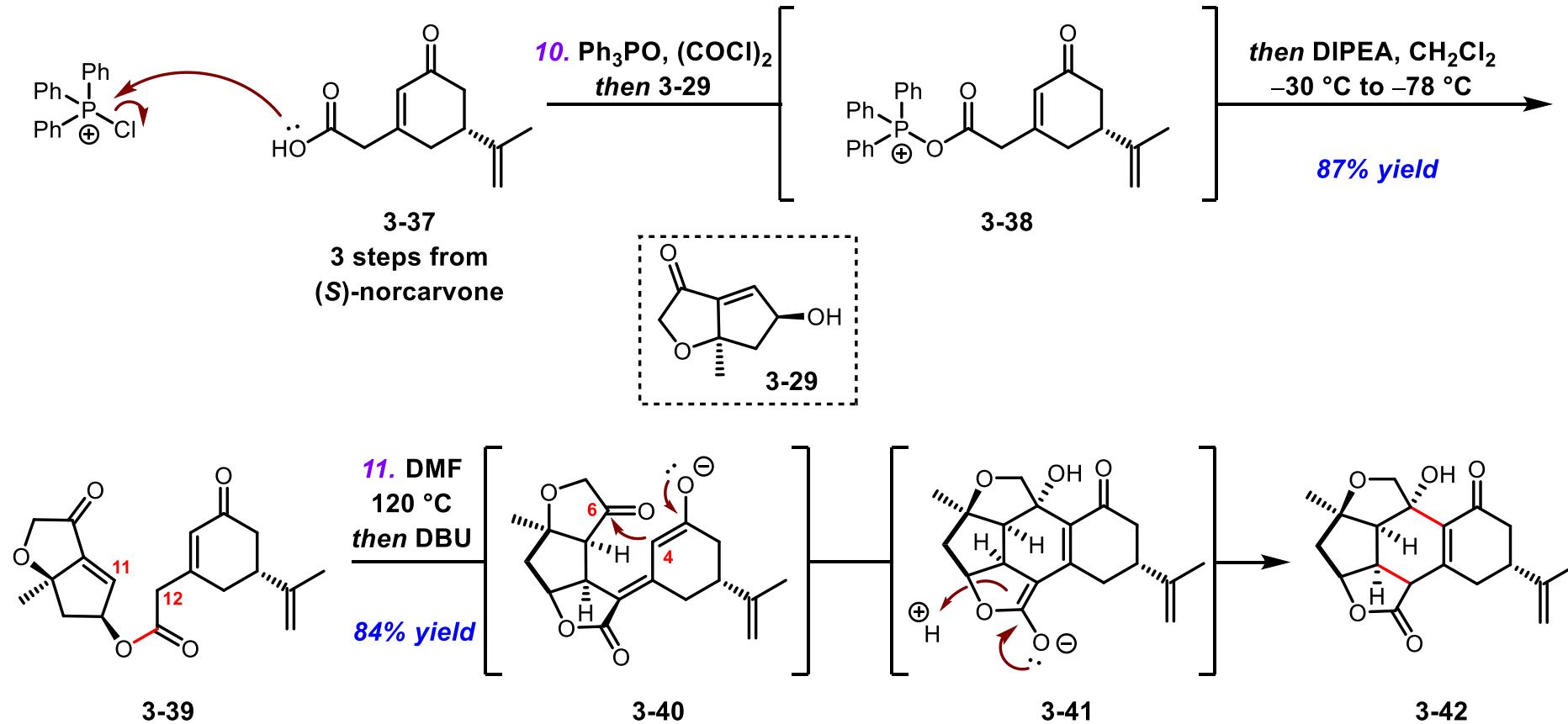
# Total Synthesis of Ineleganolide——Stoltz (2023)

## Preparation of bicyclic enone 3-29

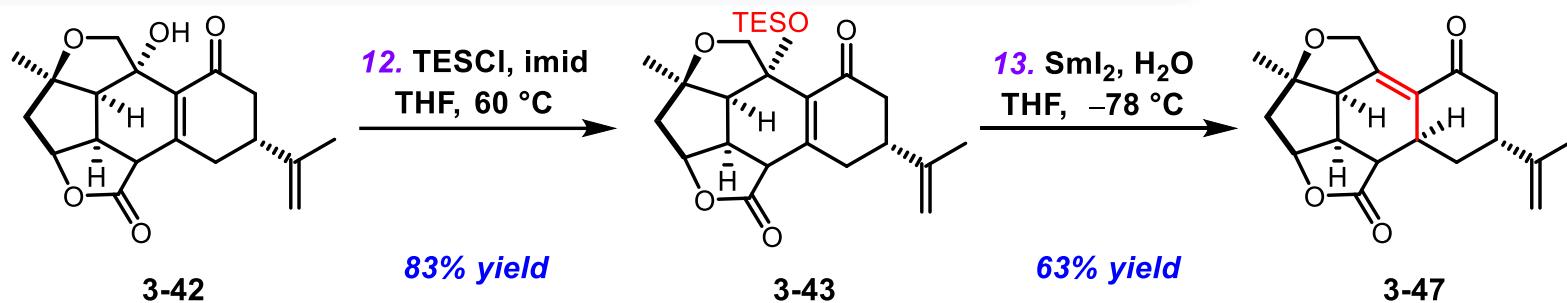


# Total Synthesis of Ineleganolide——Stoltz (2023)

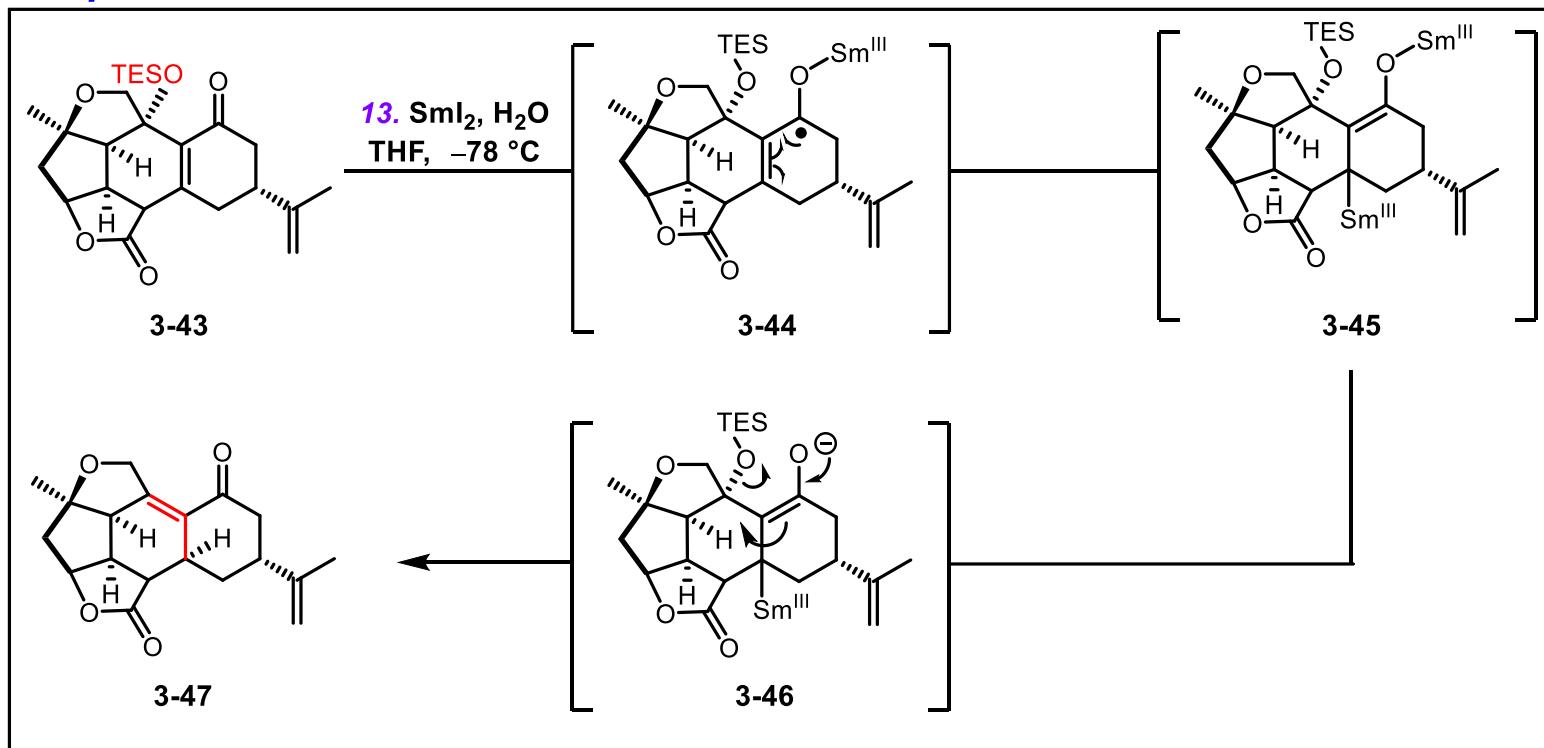
## Convergent coupling and formation of C<sub>11</sub>/C<sub>12</sub> & C<sub>4</sub>/C<sub>6</sub>



# Total Synthesis of Ineleganolide——Stoltz (2023)

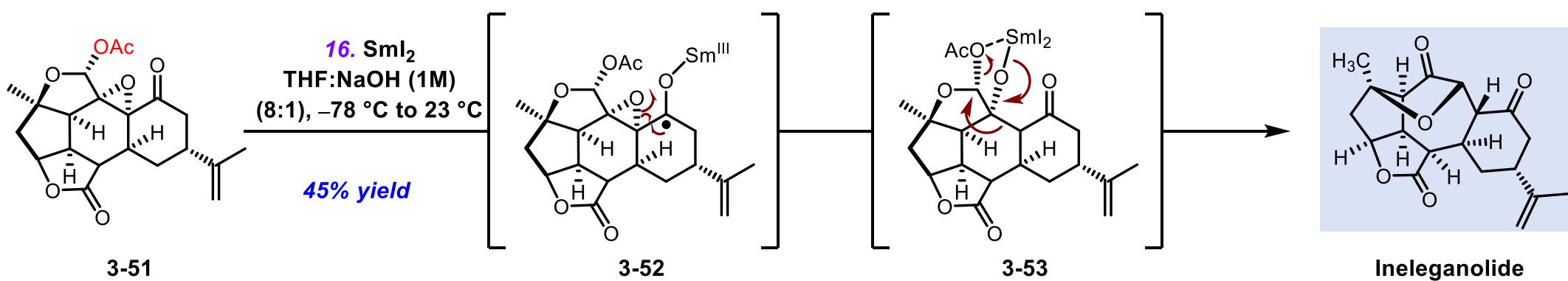
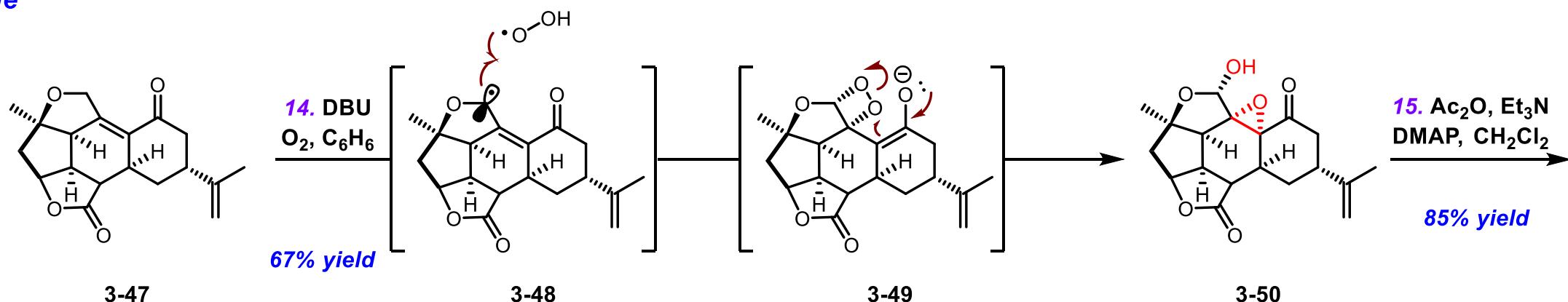


## Proposed mechanisms



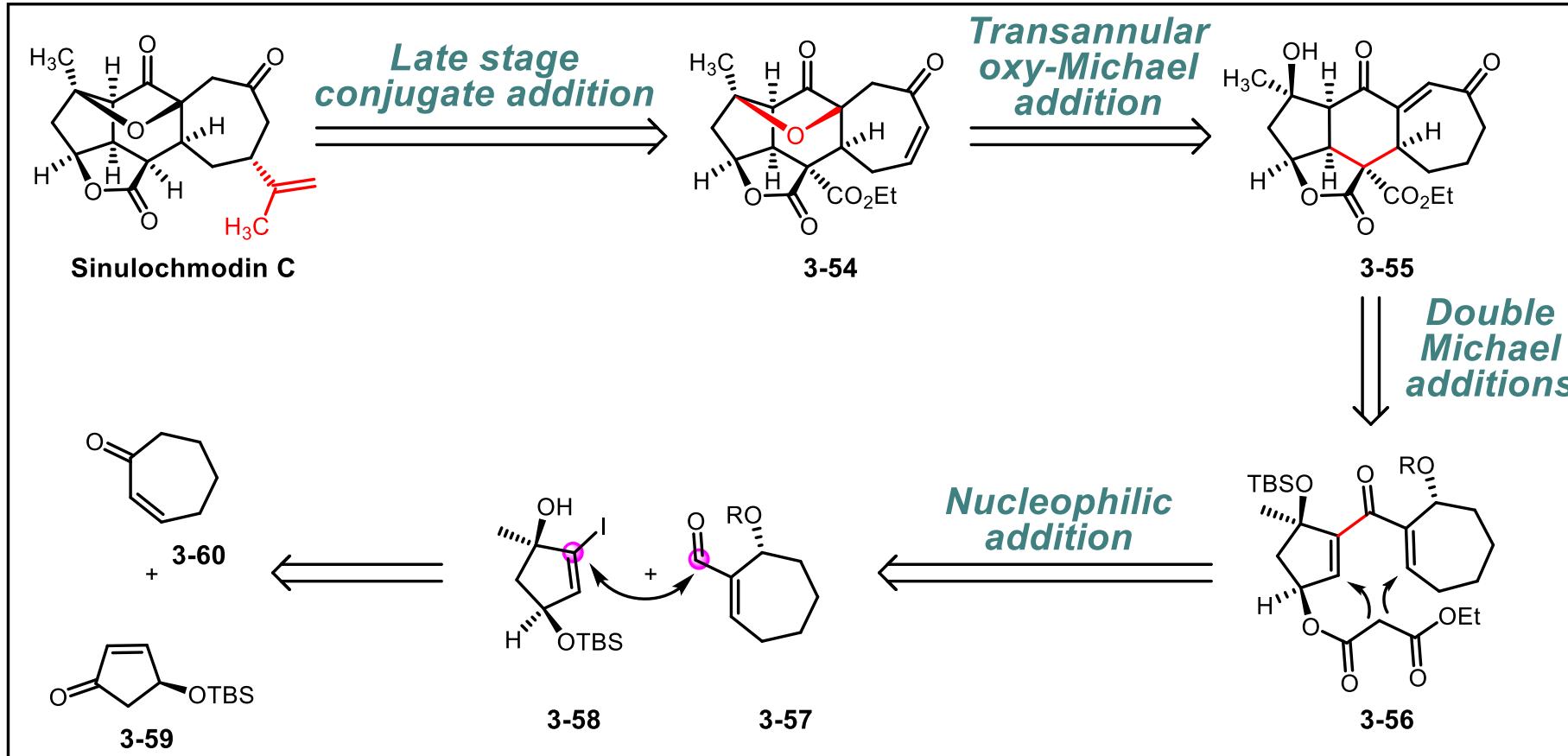
# Total Synthesis of Ineleganolide——Stoltz (2023)

*End game*



# Total Synthesis of Sinulochmodin C——Zhang (2023)

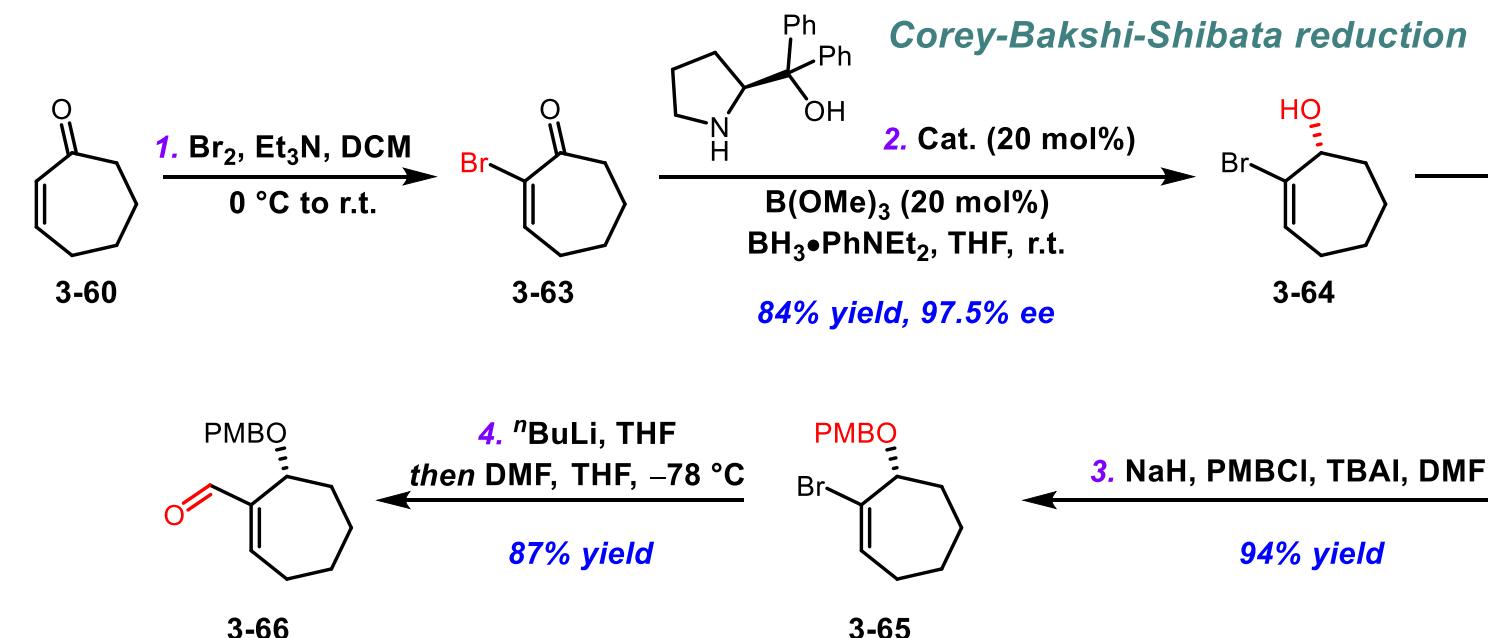
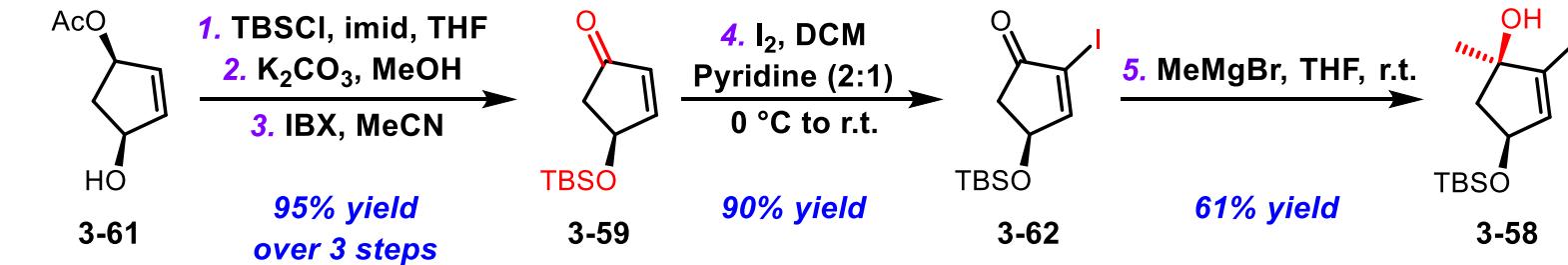
## Retrosynthetic Analysis



Zhang Hongbin

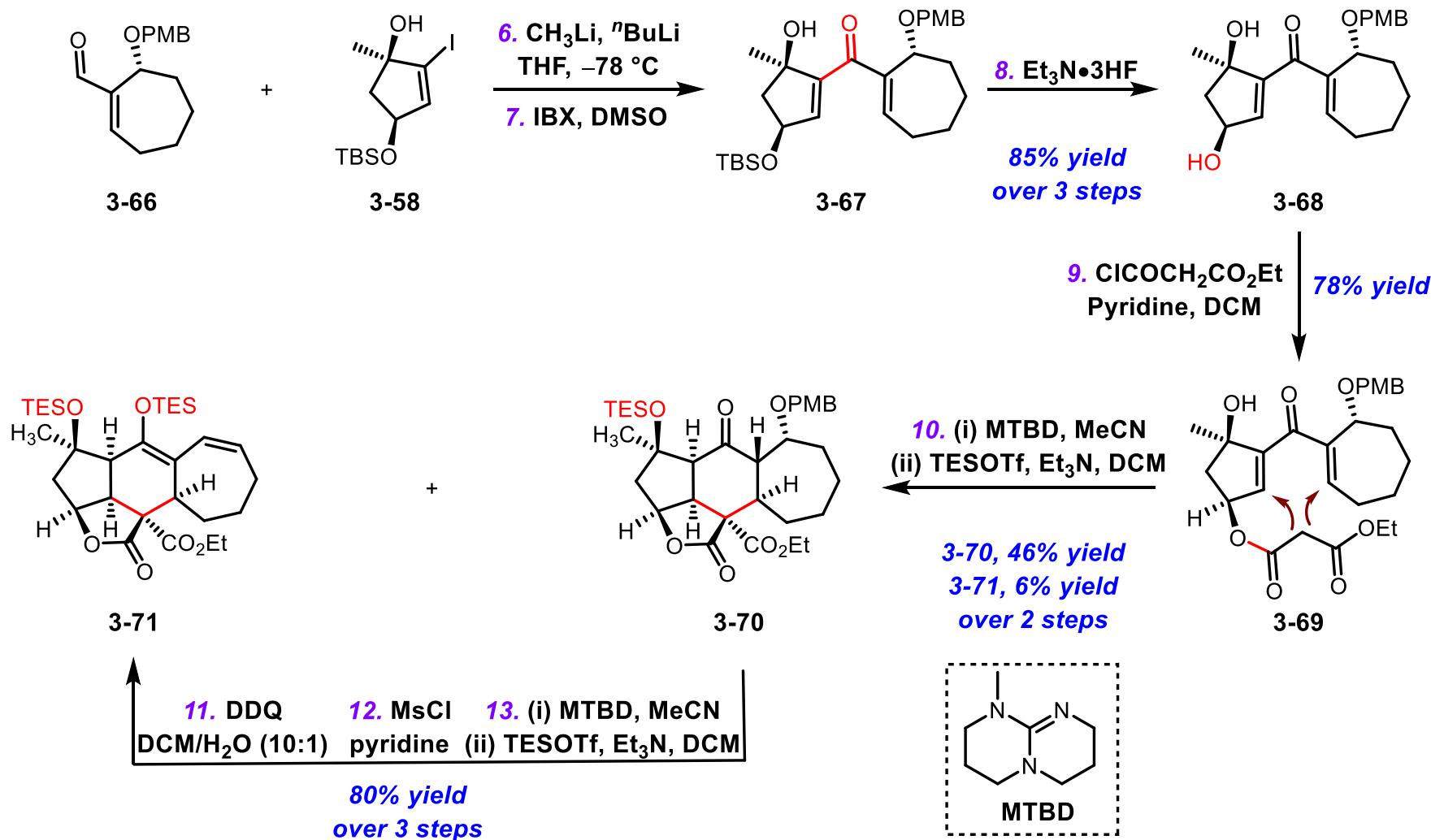
# Total Synthesis of Sinulochmodin C——Zhang (2023)

## Preparation of cyclopentene 3-58 and cycloheptene 3-66



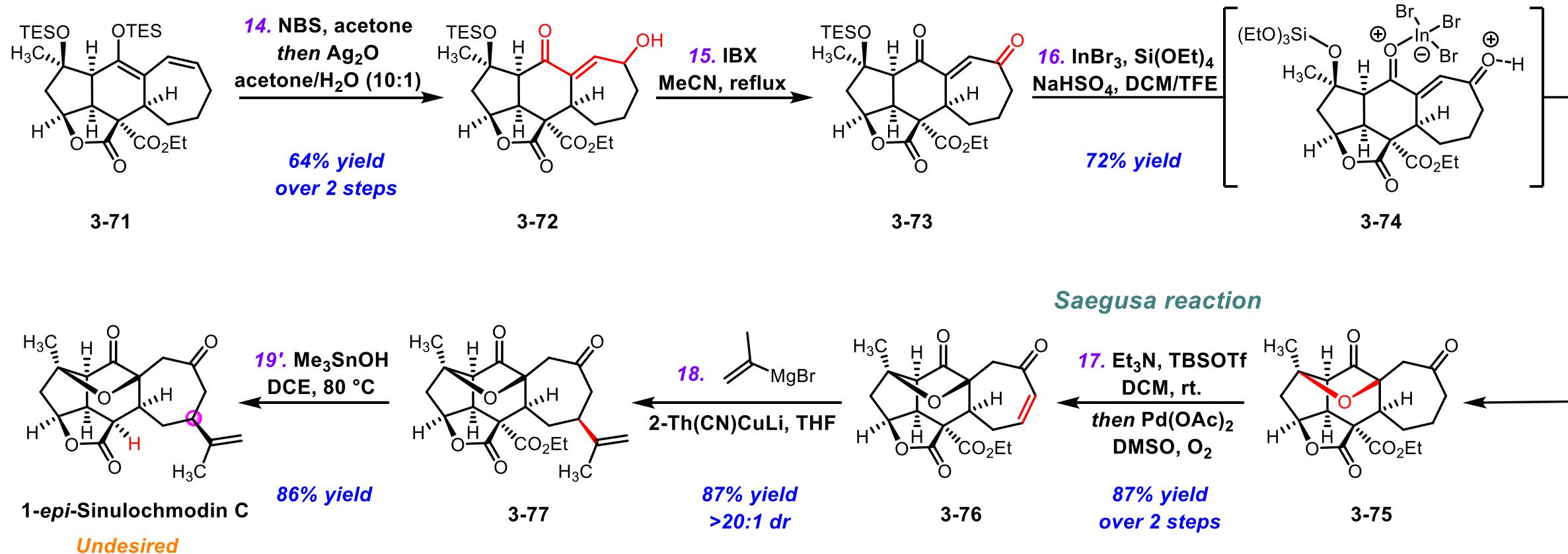
# Total Synthesis of Sinulochmodin C——Zhang (2023)

## Preparation of the [7,6,5,5] tetracyclic ring skeleton



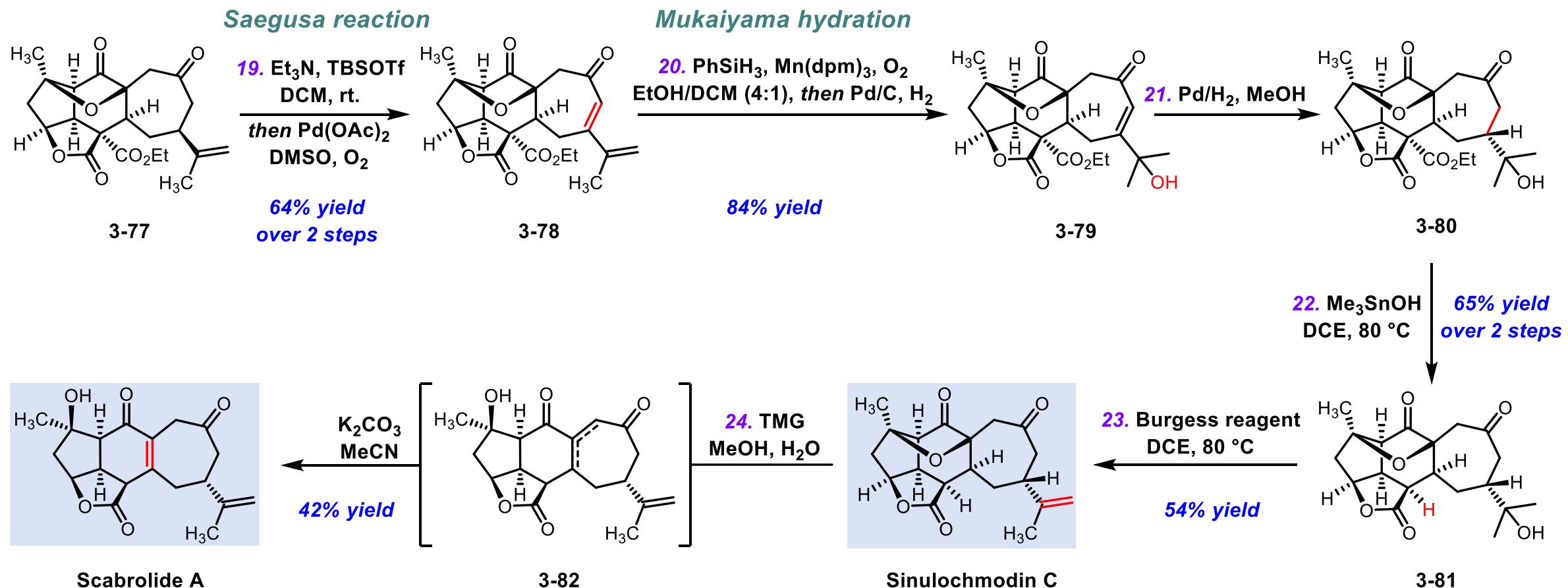
# Total Synthesis of Sinulochmodin C——Zhang (2023)

## The wrong C<sub>1</sub> configuration



# Total Synthesis of Sinulochmodin C——Zhang (2023)

*Reverse the C<sub>1</sub> configuration*



# Content

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## 1. Introduction

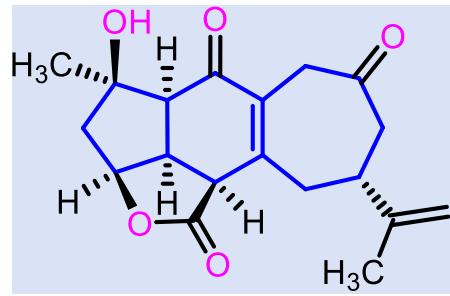
## 2. Total Synthesis of Scabrolide A

- ✓ Brian M. Stoltz (2020)
- ✓ Alois Fürstner (2022)
- ✓ David Sarlah (2023)

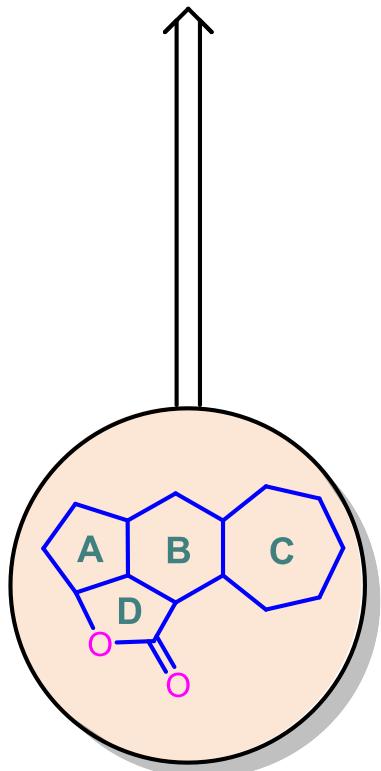
## 3. Total Syntheses of Sinulochmodin C

- ✓ John L. Wood (2022)
- ✓ Zhang Hongbin (2023)

## 4. Summary

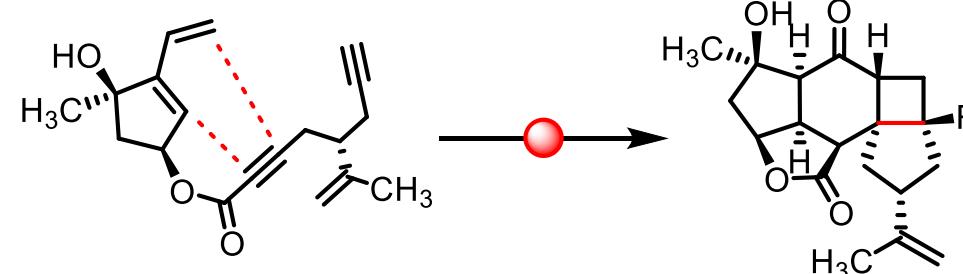


Scabrolide A

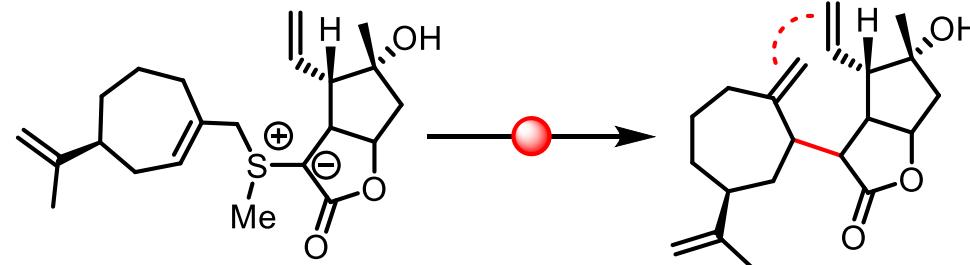


Stoltz, B. M. : 17 steps

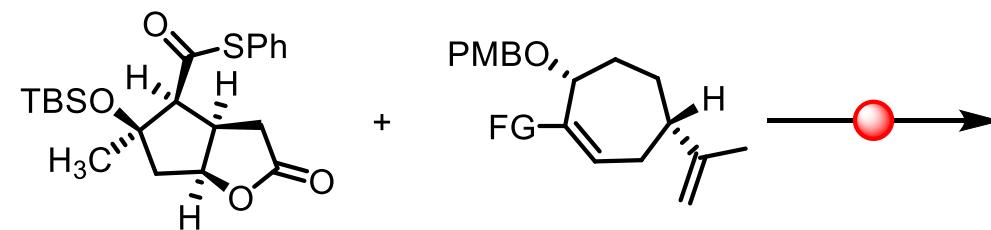
*First total synthesis*

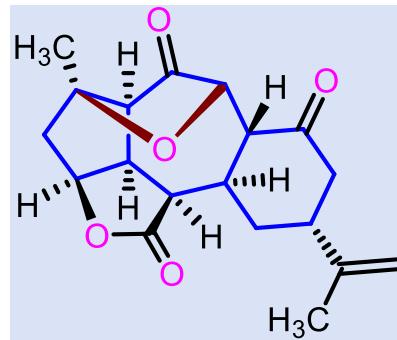


Fürstner, A. : 16 steps



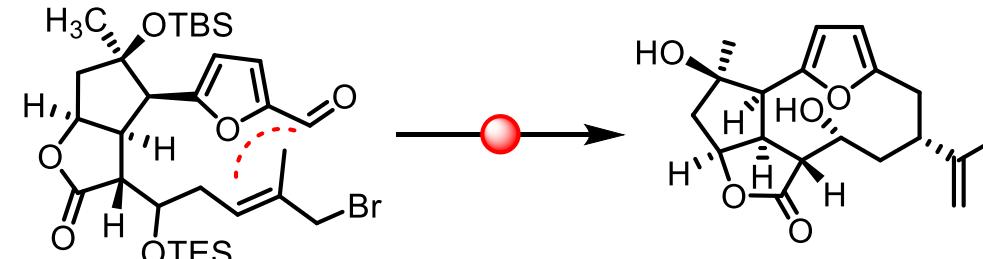
Sarlah, D. : 10 steps



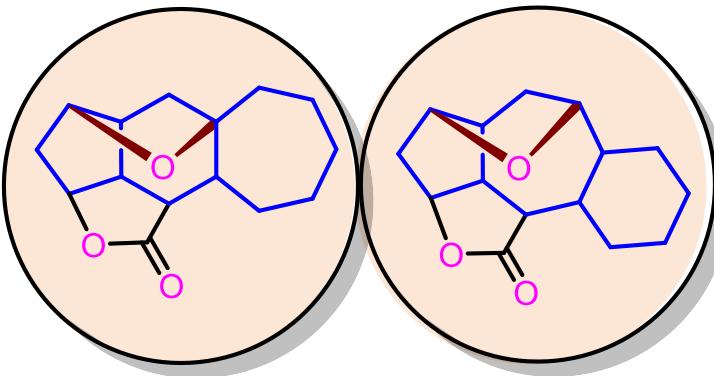


Wood, J. L. : 20 steps

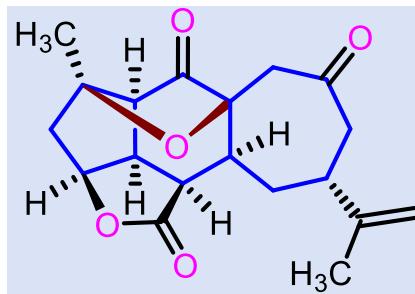
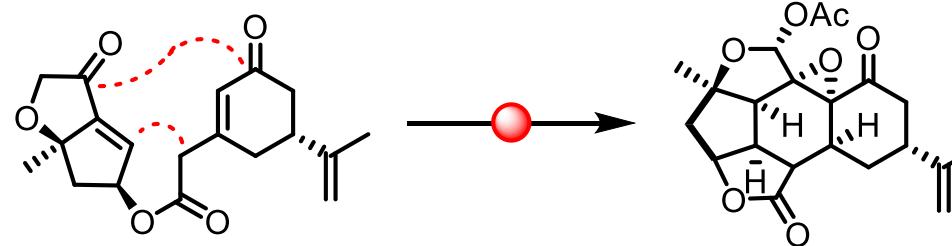
*First total synthesis*



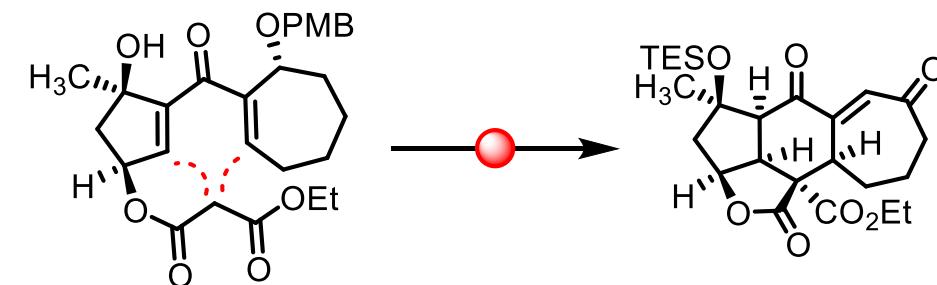
Ineleganolide



Stoltz, B. M. : 23 steps



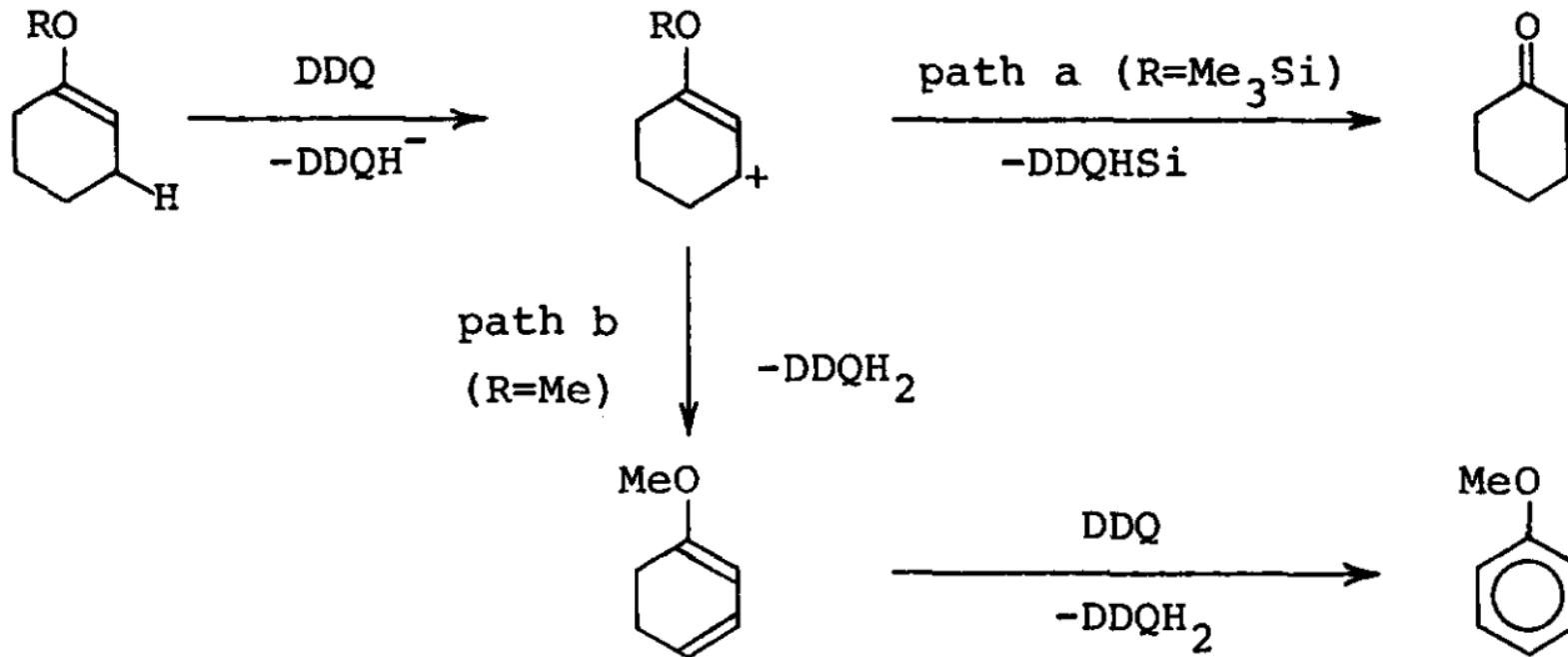
Zhang, H. : 23 steps



Sinulochmodin C

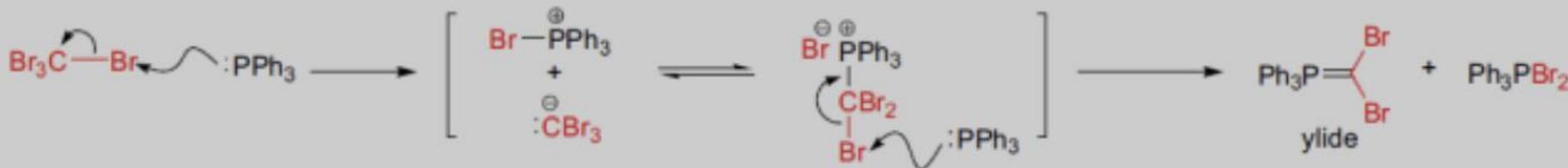
**Thanks for your kind attention!**

# 烯醇硅醚氧化脱氢

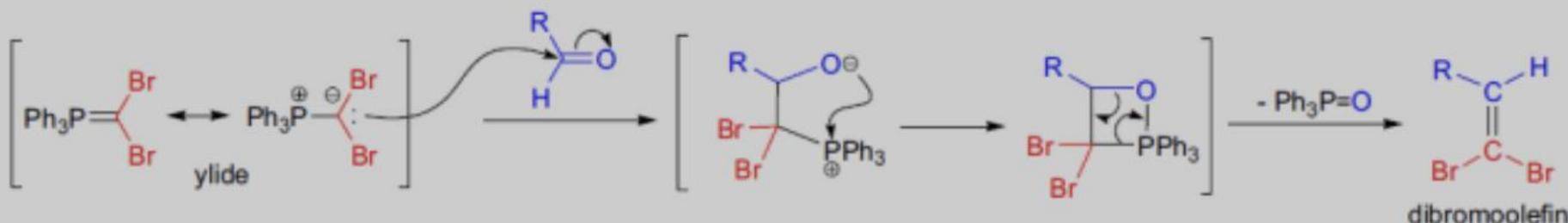


# Corey-Fuchs reaction

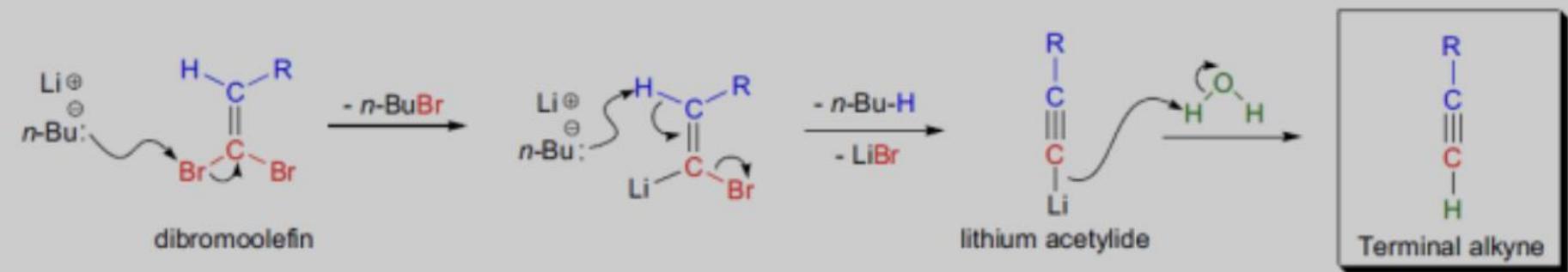
Generation of the phosphorous ylide:



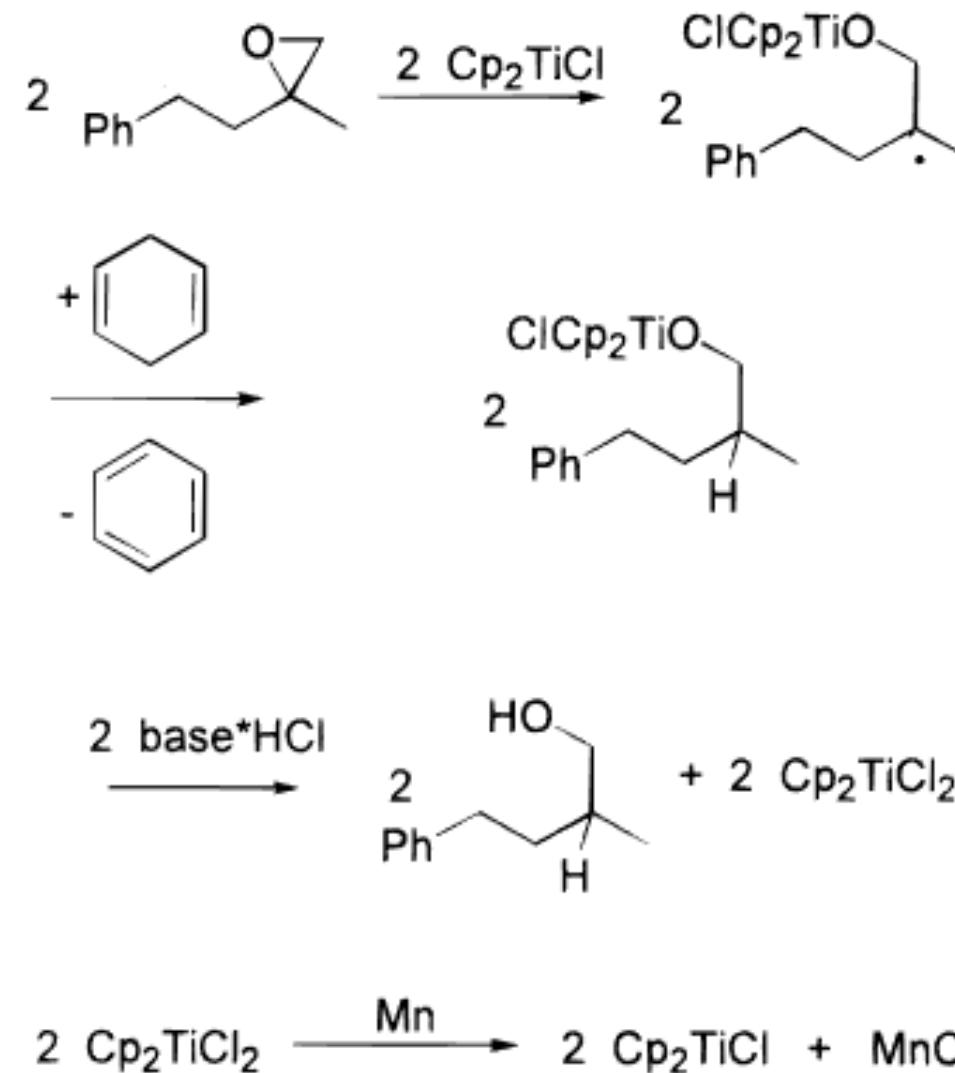
Reaction of the phosphorous ylide with the aldehyde:



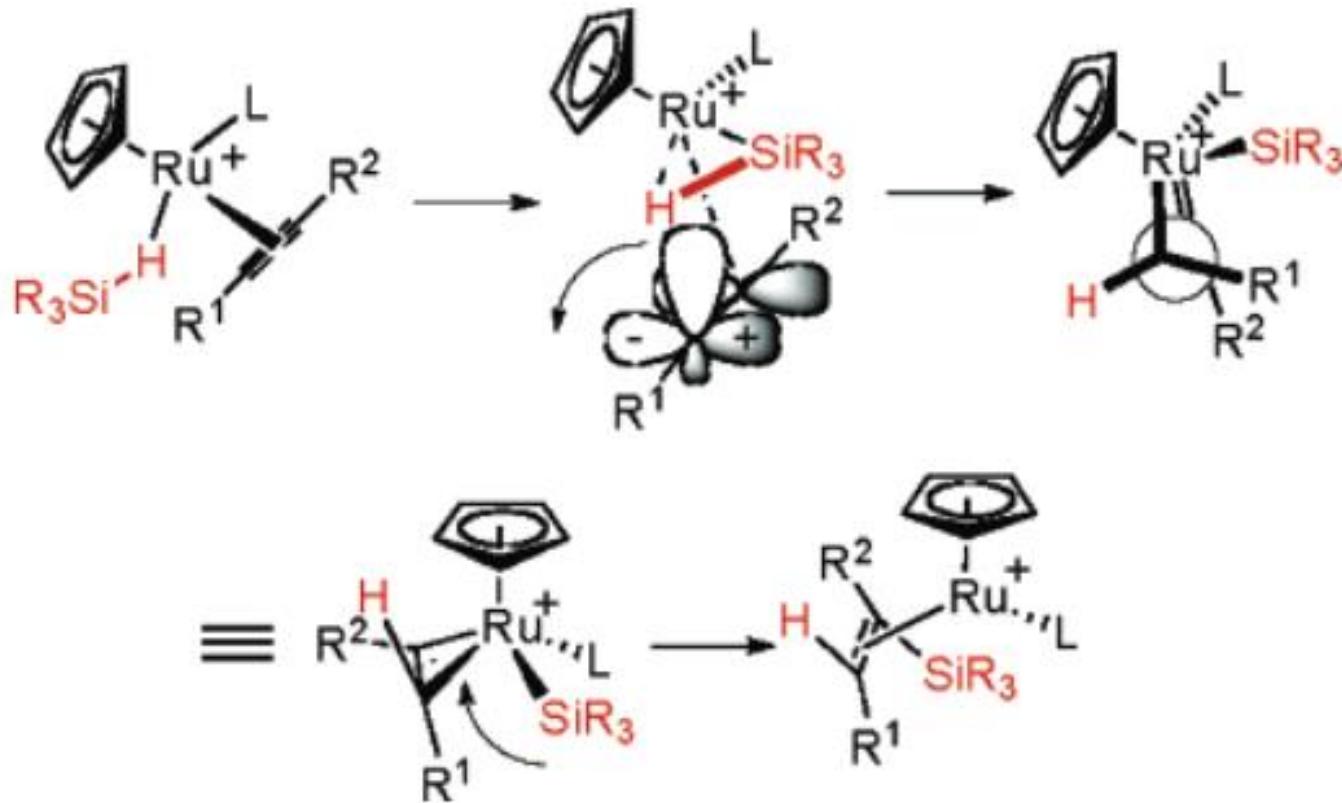
Conversion of dibromoolefin to terminal alkyne:



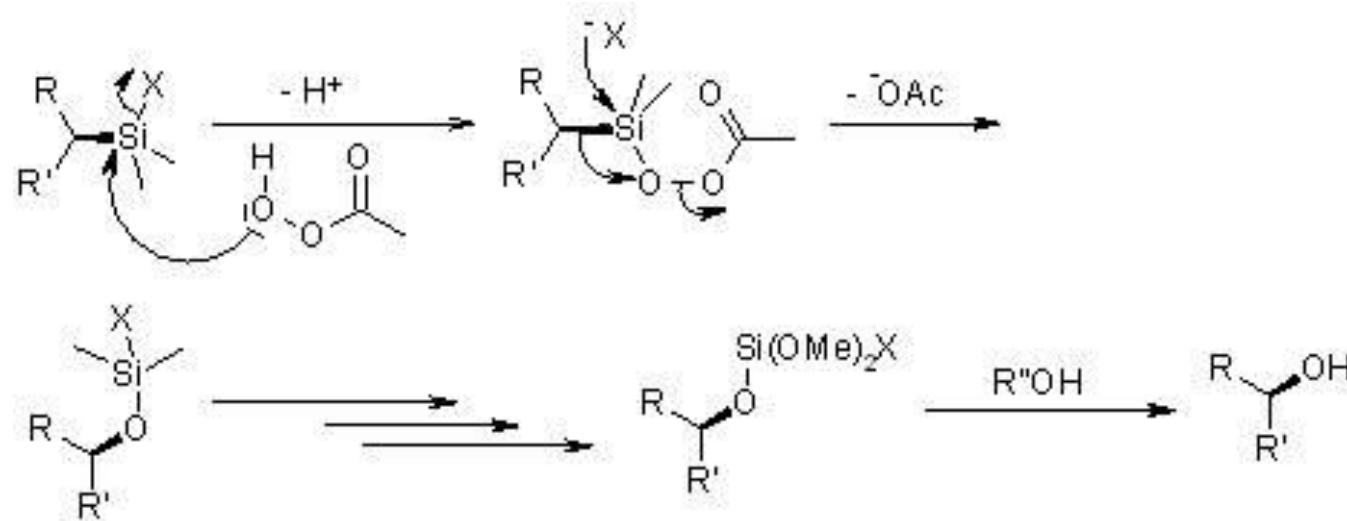
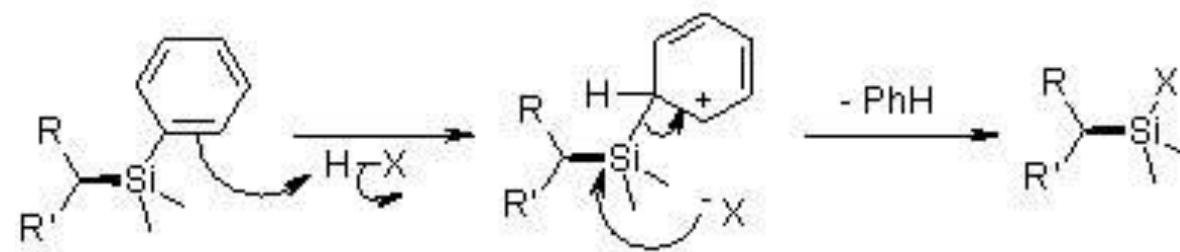
## Ti-催化环氧开环



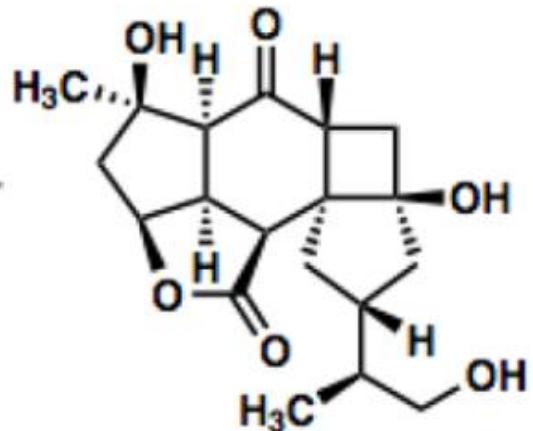
# Alkyne Hydrosilylation Catalyzed by [Cp\*Ru(MeCN)<sub>3</sub>]PF<sub>6</sub>



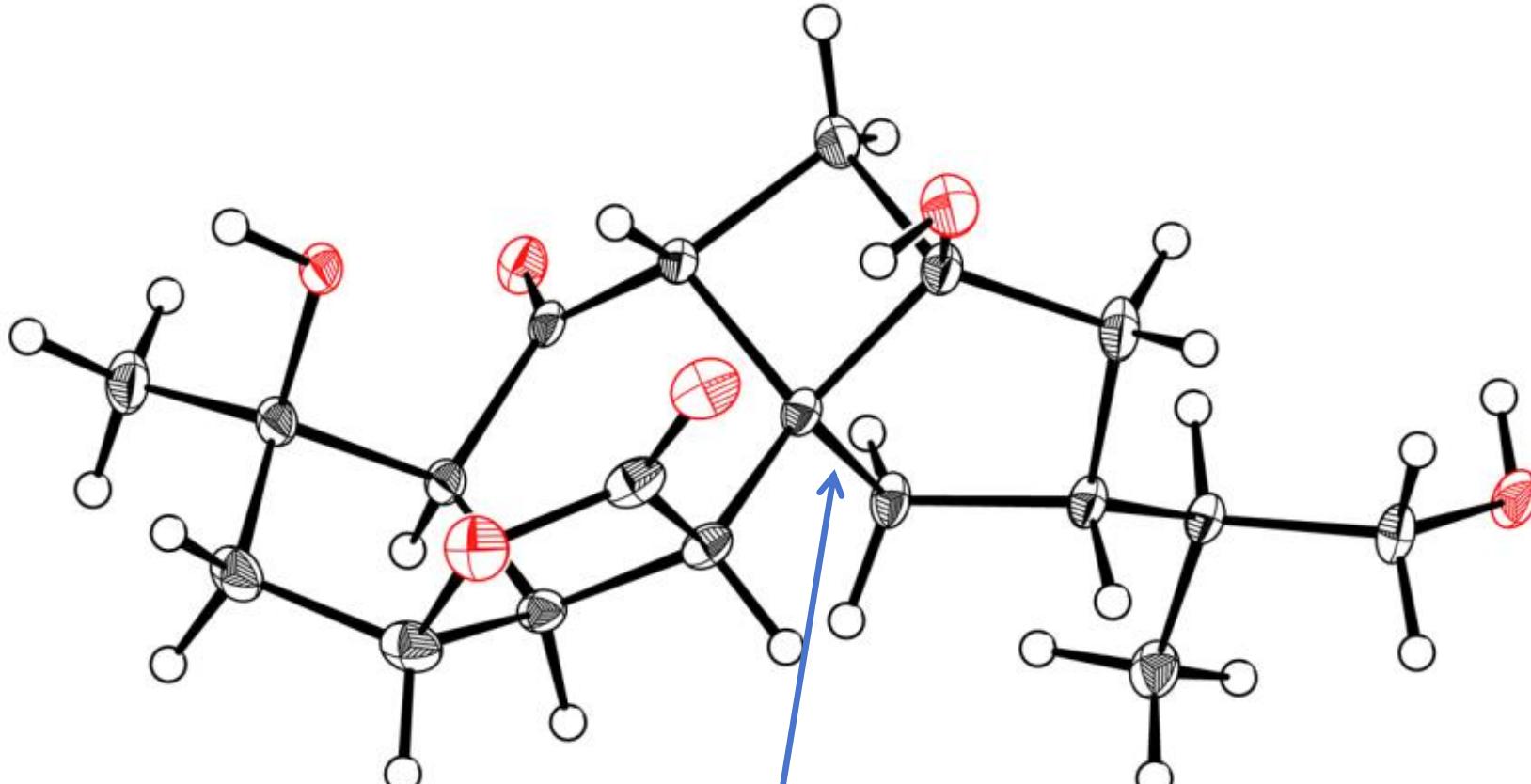
## Tamao-Fleming oxidation



# 单晶：解释[6-4]反式结构

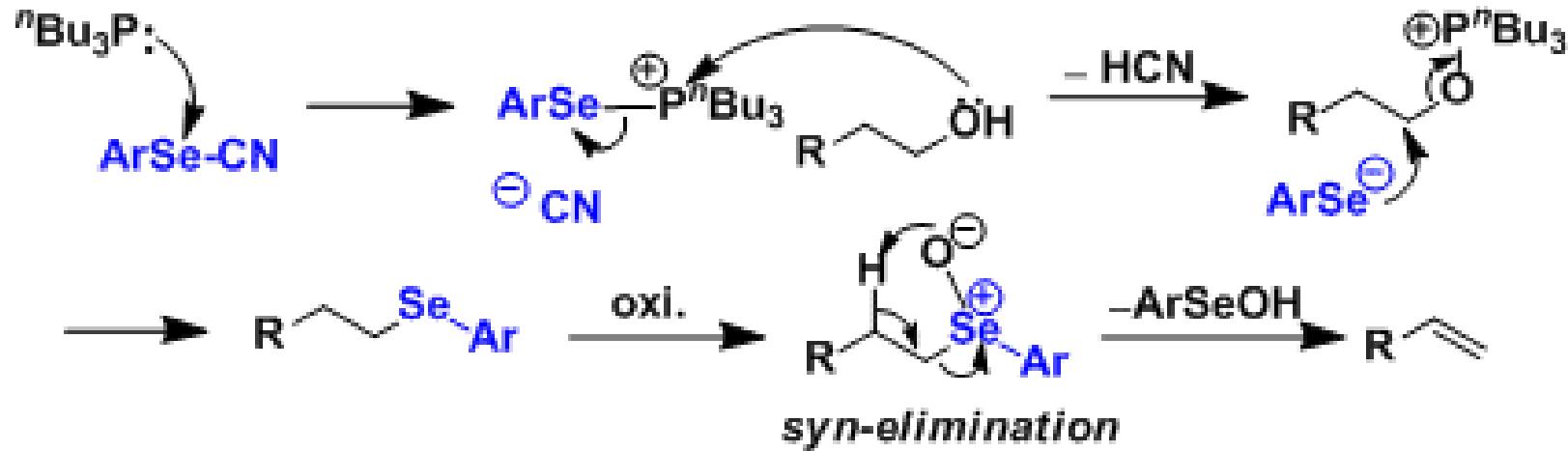


25

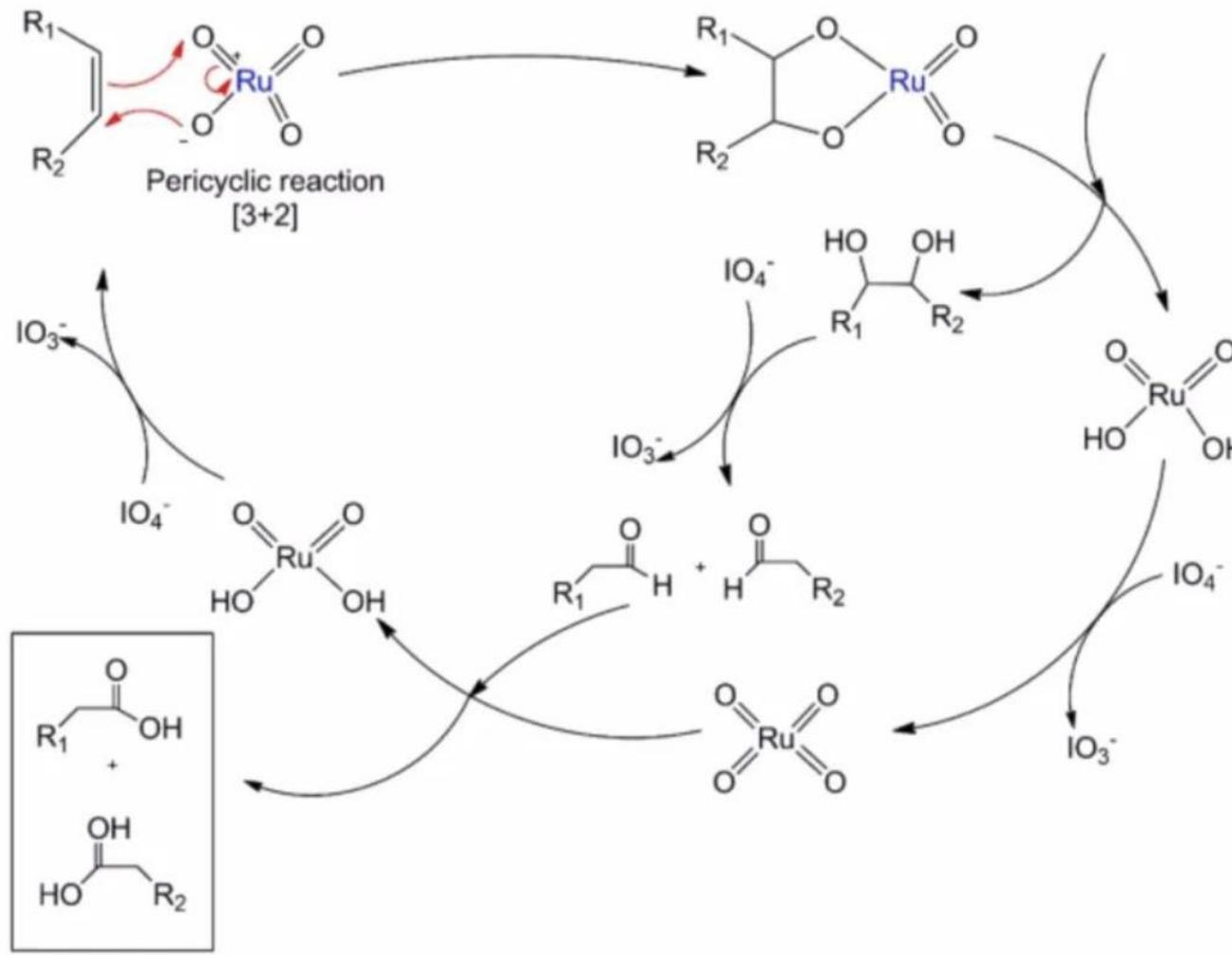


直立键

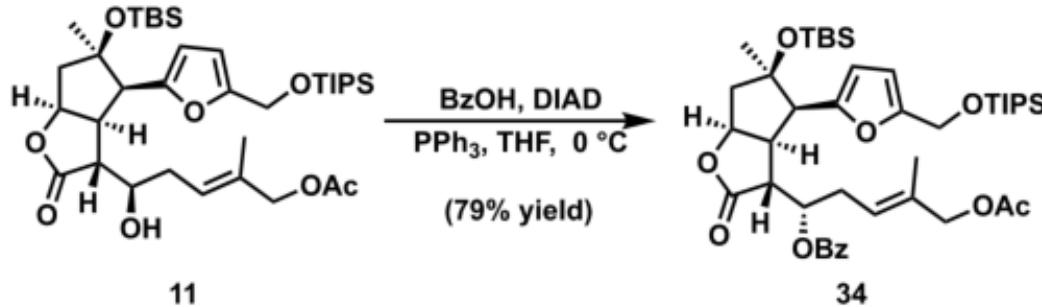
# Grieco dehydration



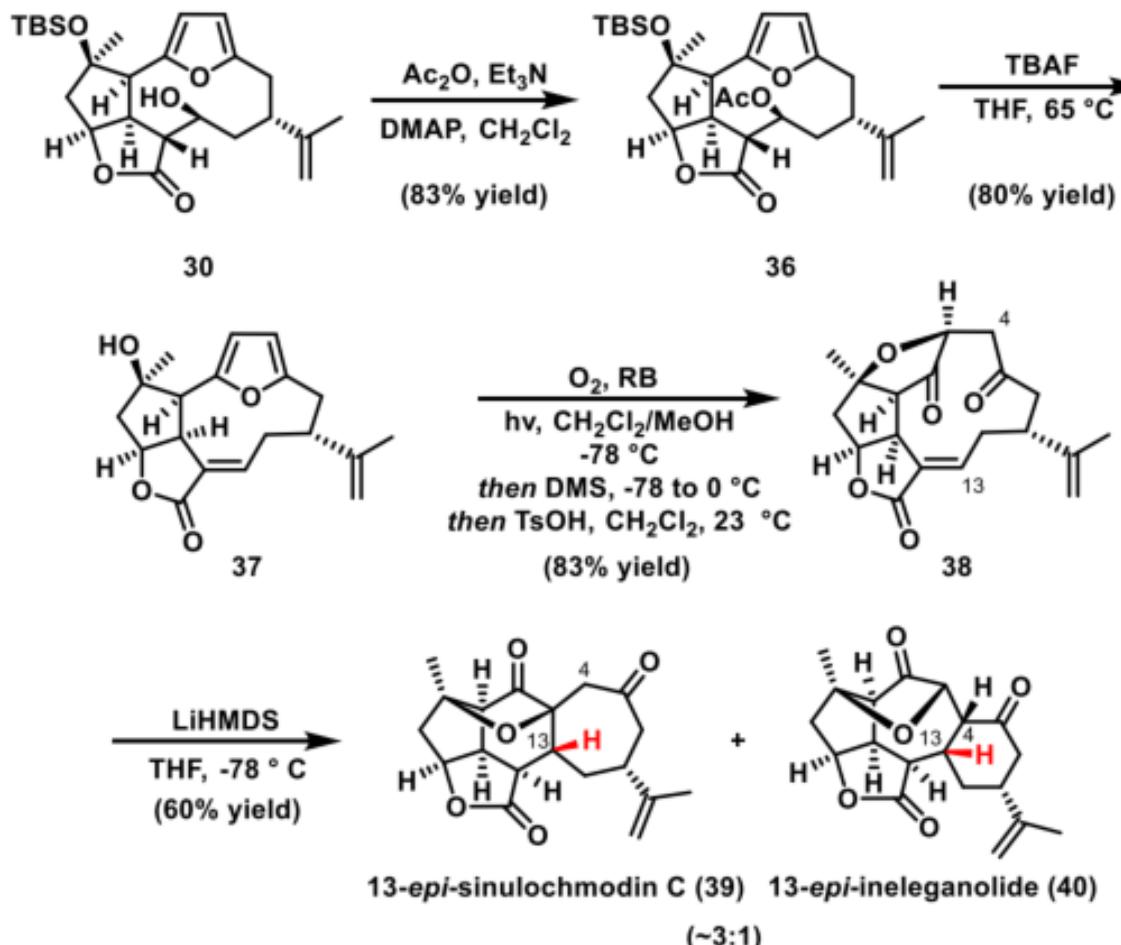
# RuCl<sub>3</sub>/NaIO<sub>4</sub> oxidation



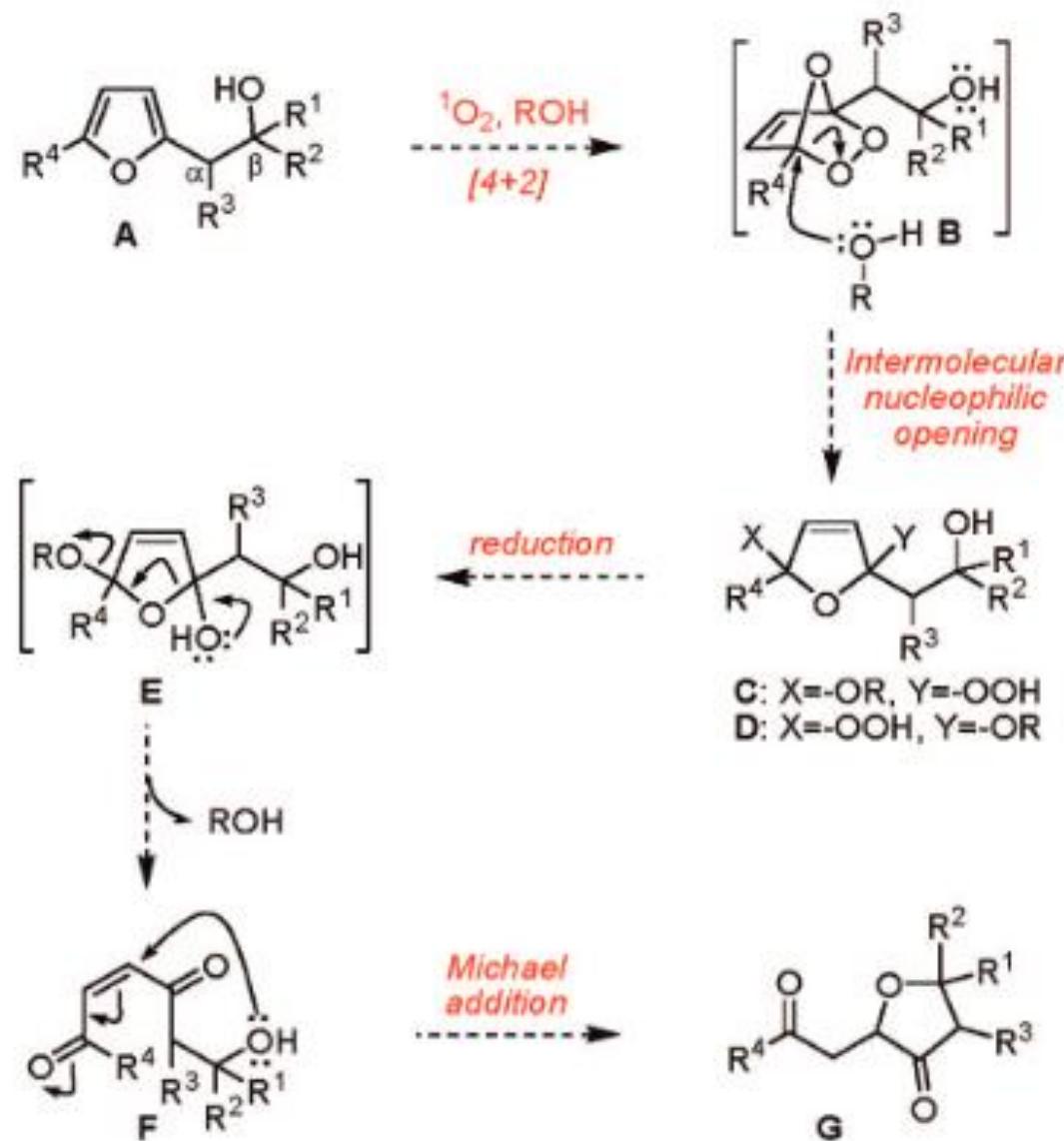
# 构型翻转



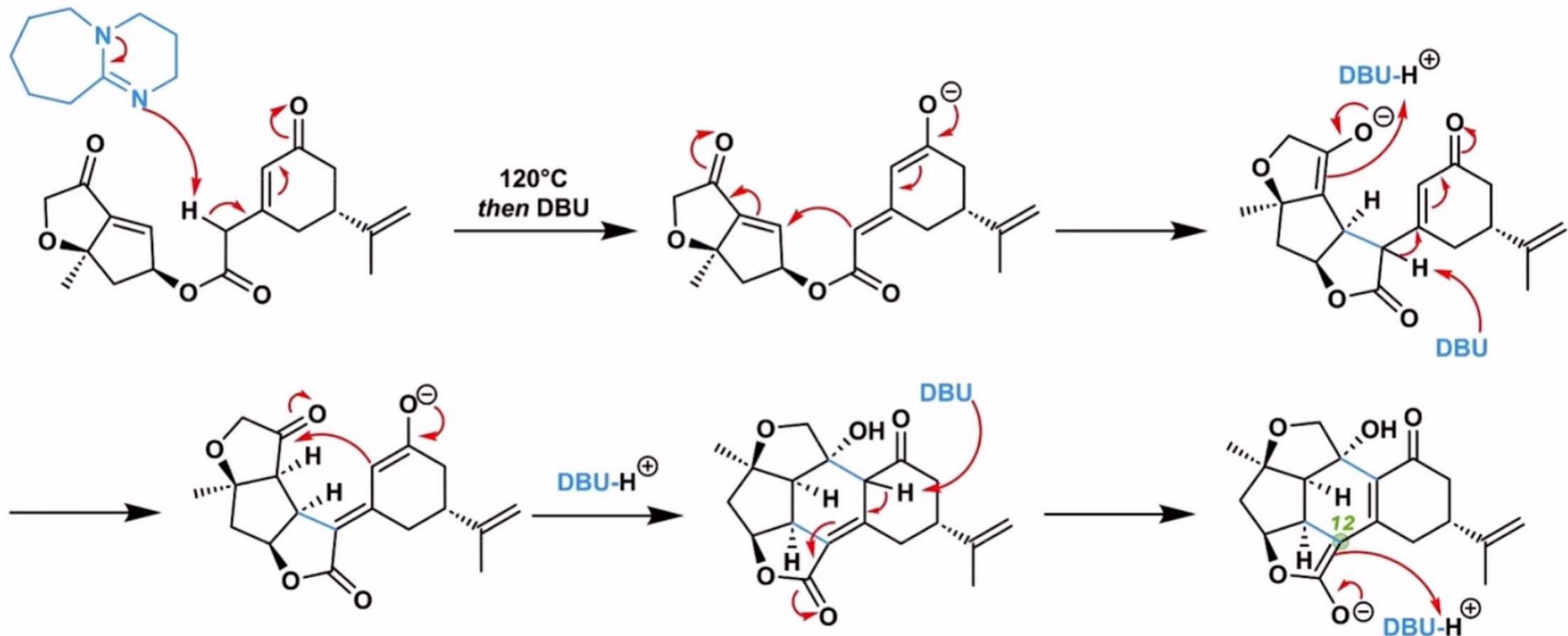
(E)-的结果



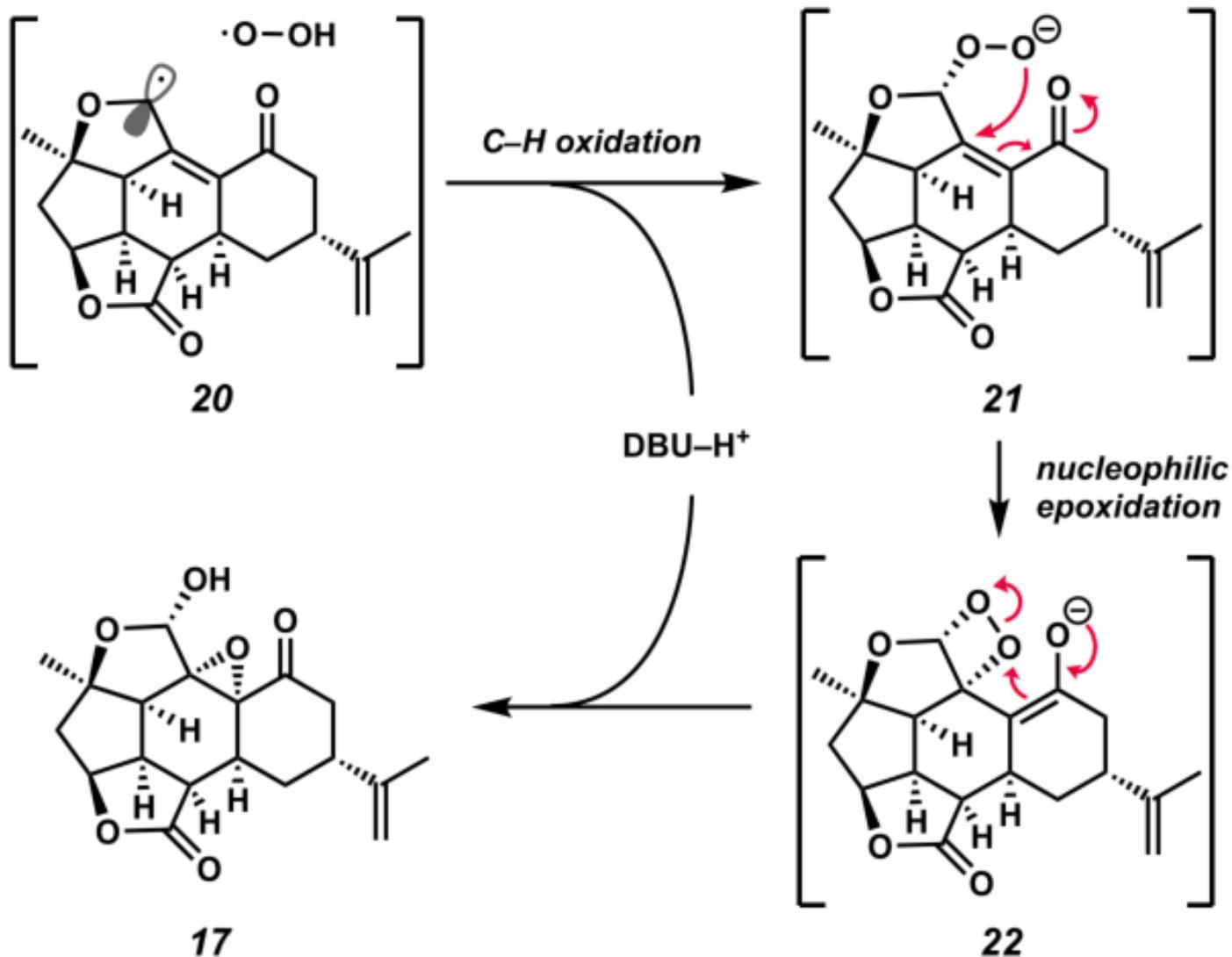
# Furan oxidation



# Michael addition and aldol cascade

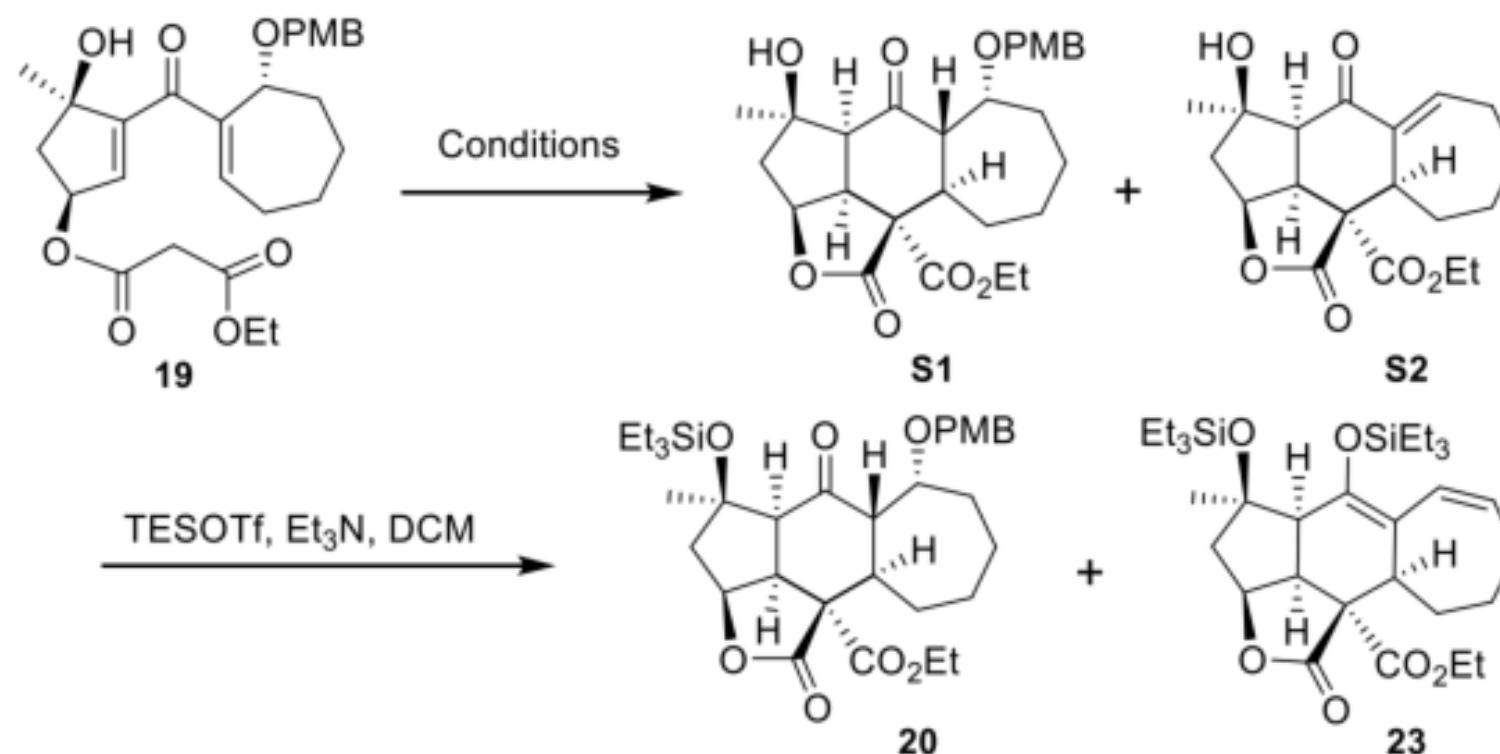


# Air oxidation



## Double Michael reaction

Table 1 Studies on the double Michael additions of compound 19



# 异丙烯基加成构型

