Literature Report

Total Synthesis of Maoecrystal V:
Early-Stage of C-H Functionalization and Lactone Assembly by Radical Cyclization

Reporter: Ji Yue
Checker: Chen Muwang
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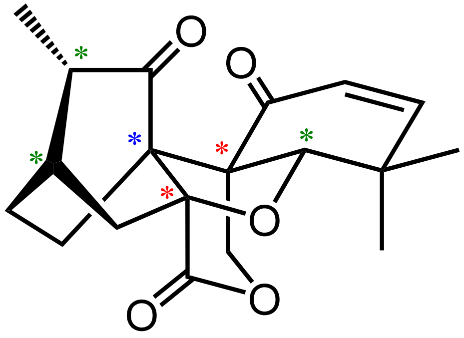
University of California at Santa Barbara

Zakarian, A. *et al.*
J. Am. Chem. Soc. **2013**, *135*, 14552.

Content

Introduction



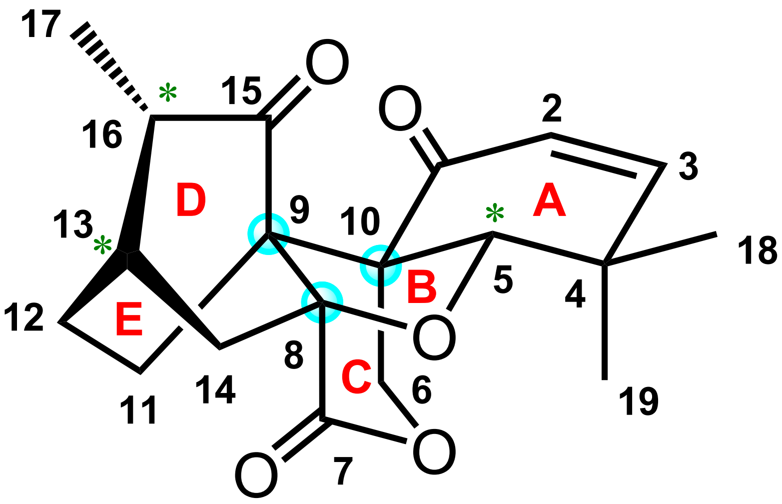
Maoecrystal V

Isodon species
毛萼香茶菜

- ➢ Isolated and characterized by Sun and coworkers in 2004
- ➢ Remarkably selective cytotoxicity against HeLa cells (IC_{50} = 20 ng/mL); Cisplatin (IC_{50} = 990 ng/mL).

Sun, H.-D. *et al*. *Org. Lett*. **2004**, *6*, 4327.

Introduction



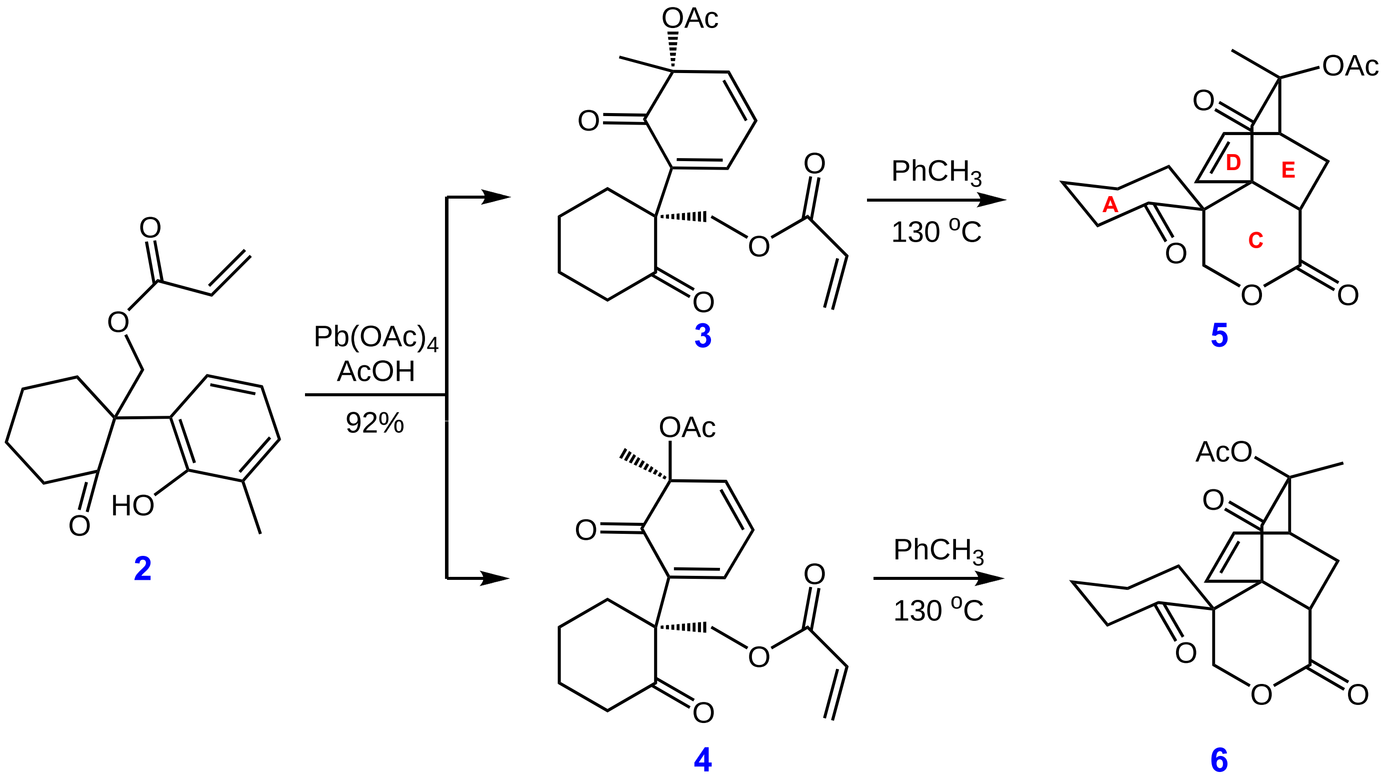
Maoecrystal V

- C_{19} Diterpenoid
- Compact pentacyclic system
- Six stereocenters (two all-carbon)
- Three contiguous quaternary stereocenters

Introduction

Yang's Synthesis

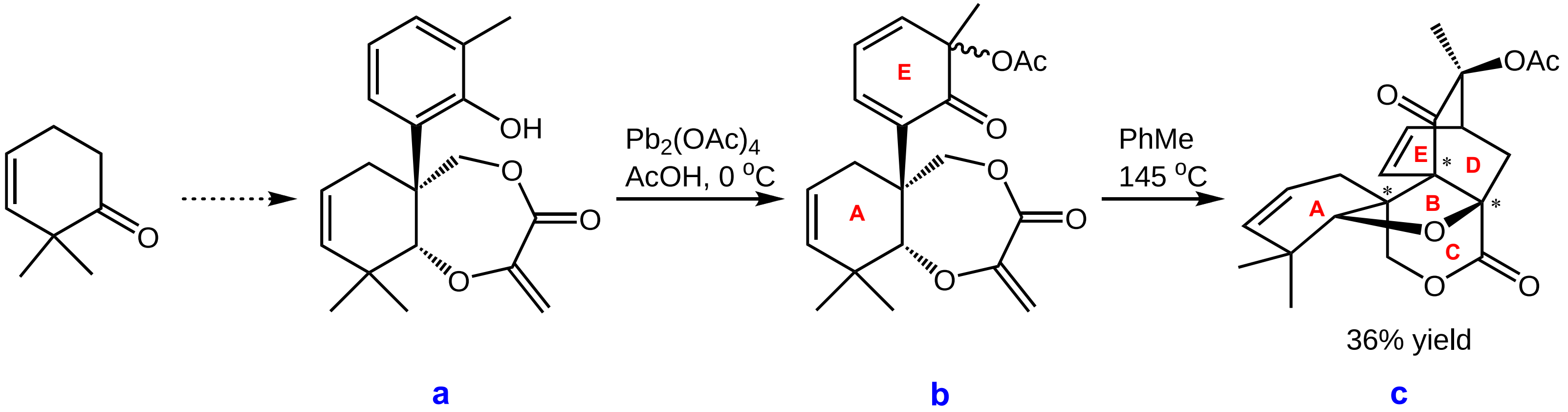
The model reaction of dearomatic-Diels-Alder reaction



Yang, Z. *et al. Org. Lett.* **2009**, *11*, 4770.

Introduction

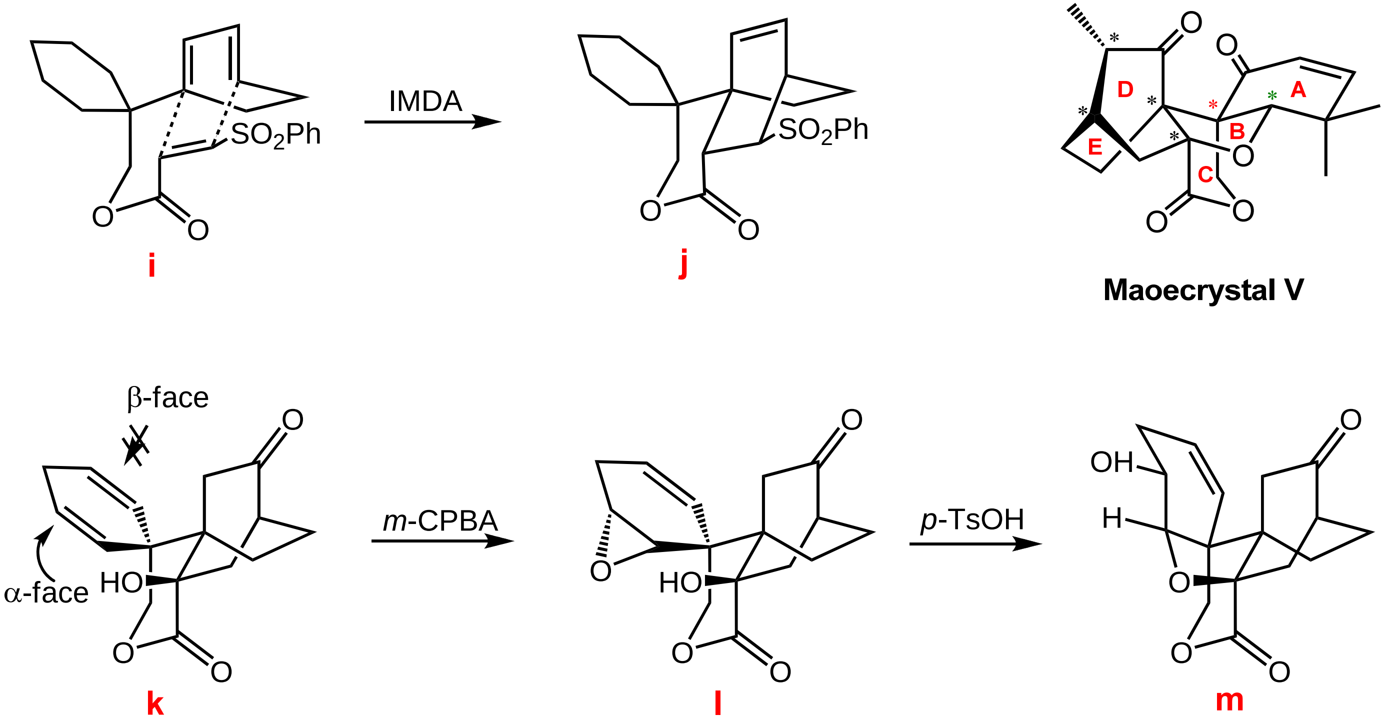
Yang’s Synthesis：The first total synthesis of (±)-maoecrystal V



Yang, Z. *et al*. *J. Am. Chem. Soc.* **2010**, *132*, 16745.

Introduction

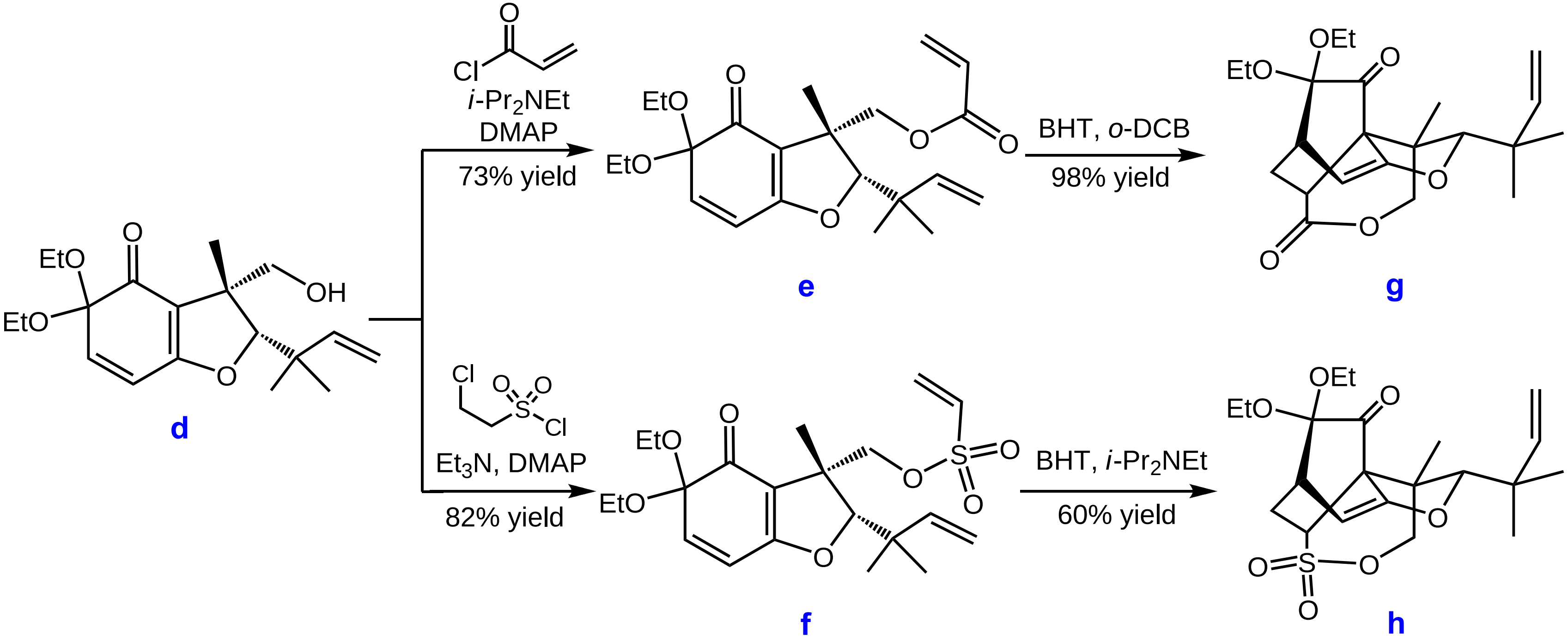
Danishefsky's Synthesis



Danishefsky, S.-J. *et al. J. Am. Chem. Soc.* **2012**, *134*, 18860.

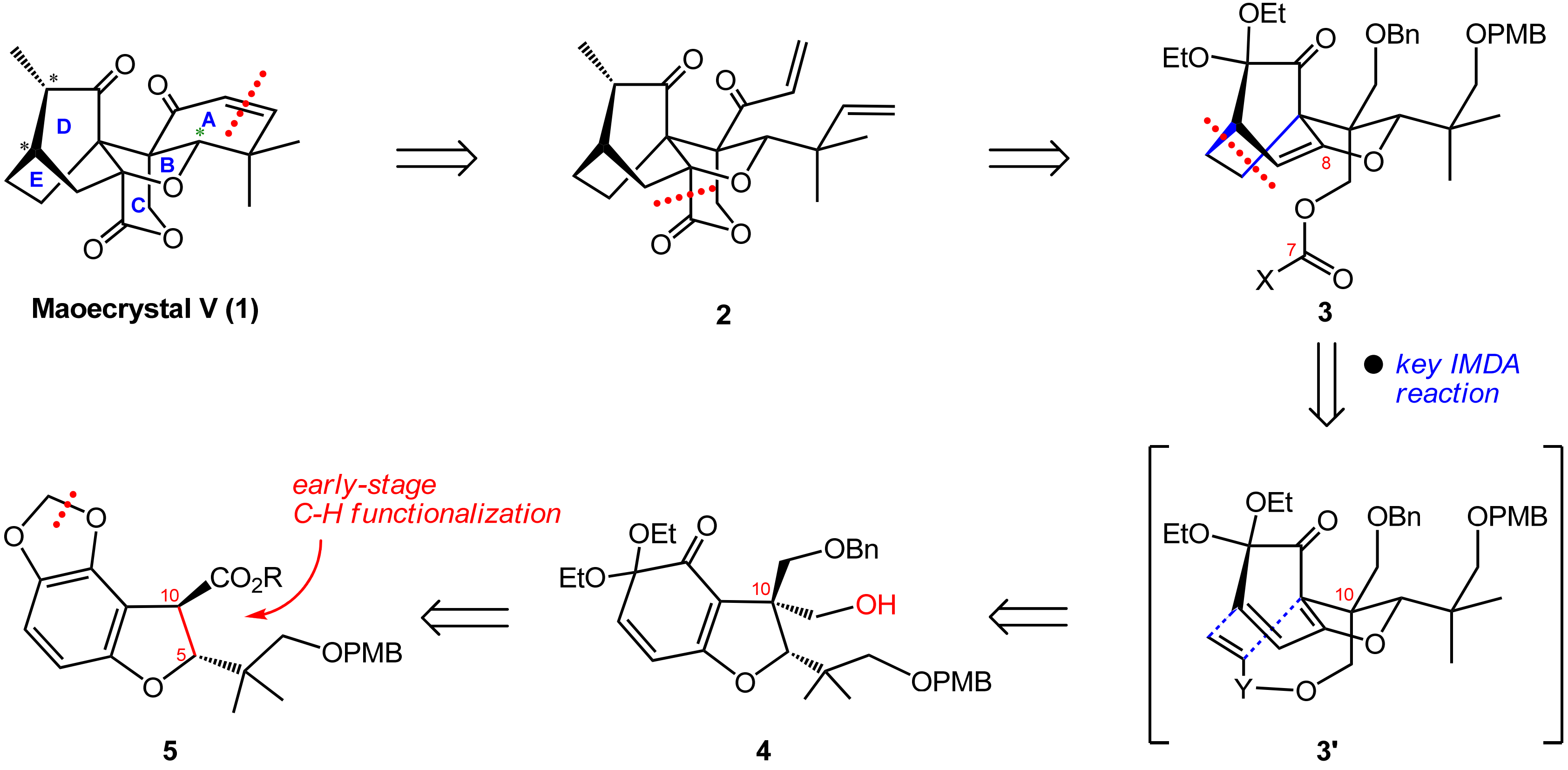
Constuction of Bicyclic [2.2.2] octane *via* an IMDA Reaction

IMDA: Intramolecular Diels-Alder reaction



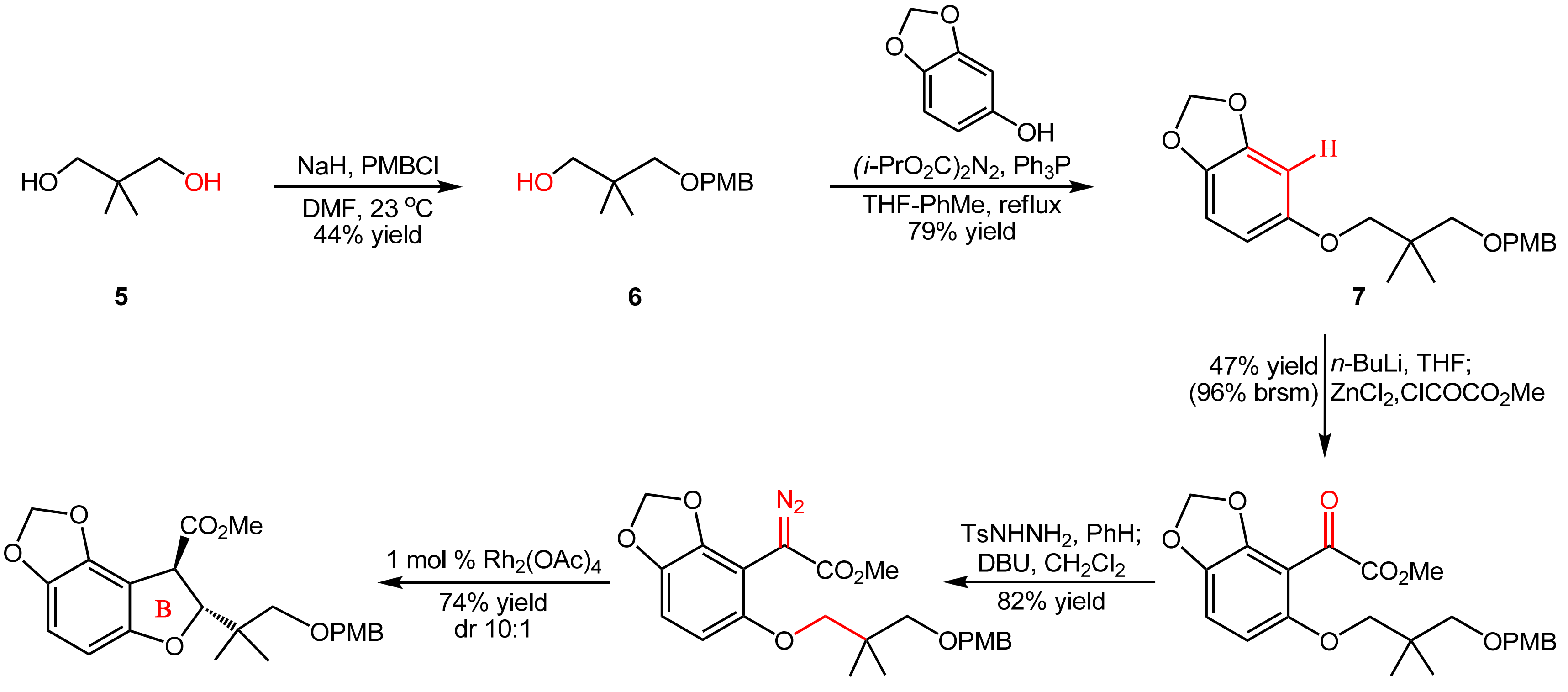
Zakarian, A. *et al. Org. Lett.* **2011**, *13,* 1080.

Retrosynthesis of Maoecrystal V



Zakarian, A. *et al. J. Am. Chem. Soc.* **2013**, *135*, 14552.

An Early Installation of Dihydrobenzofuran Intermediate

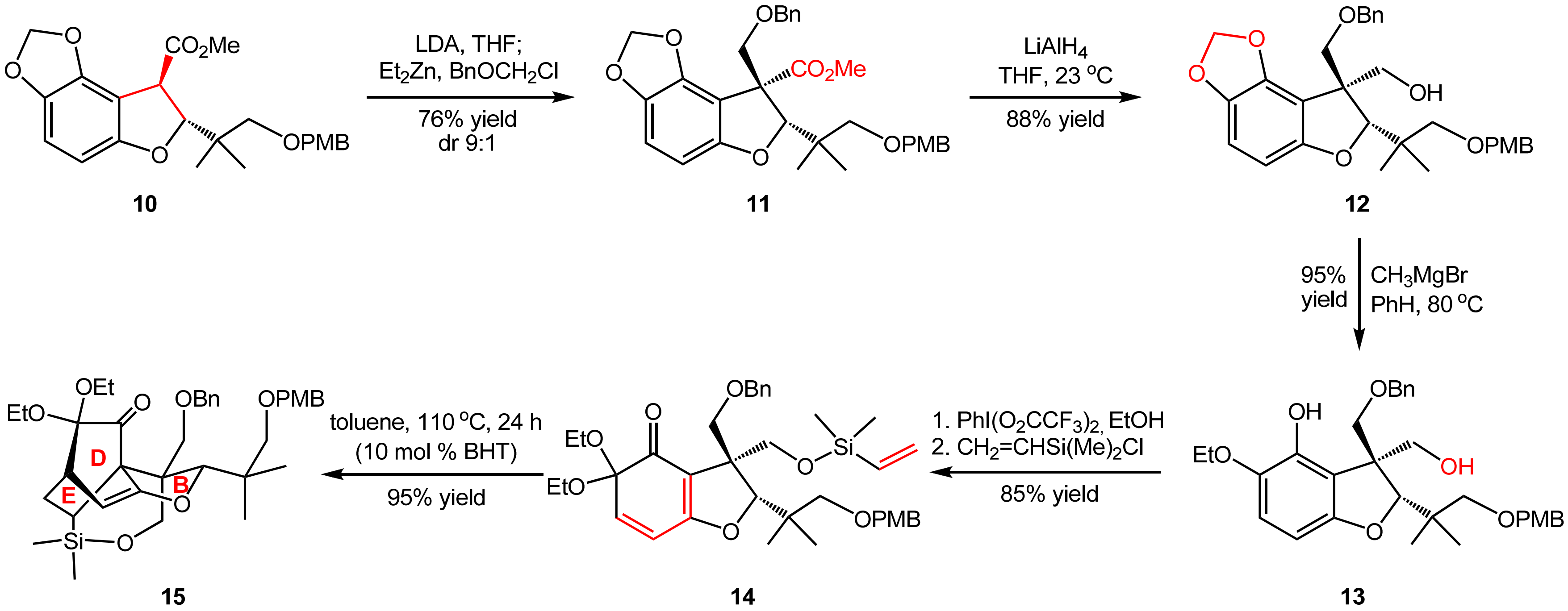


5 **6** **7**

10 **9** **8**

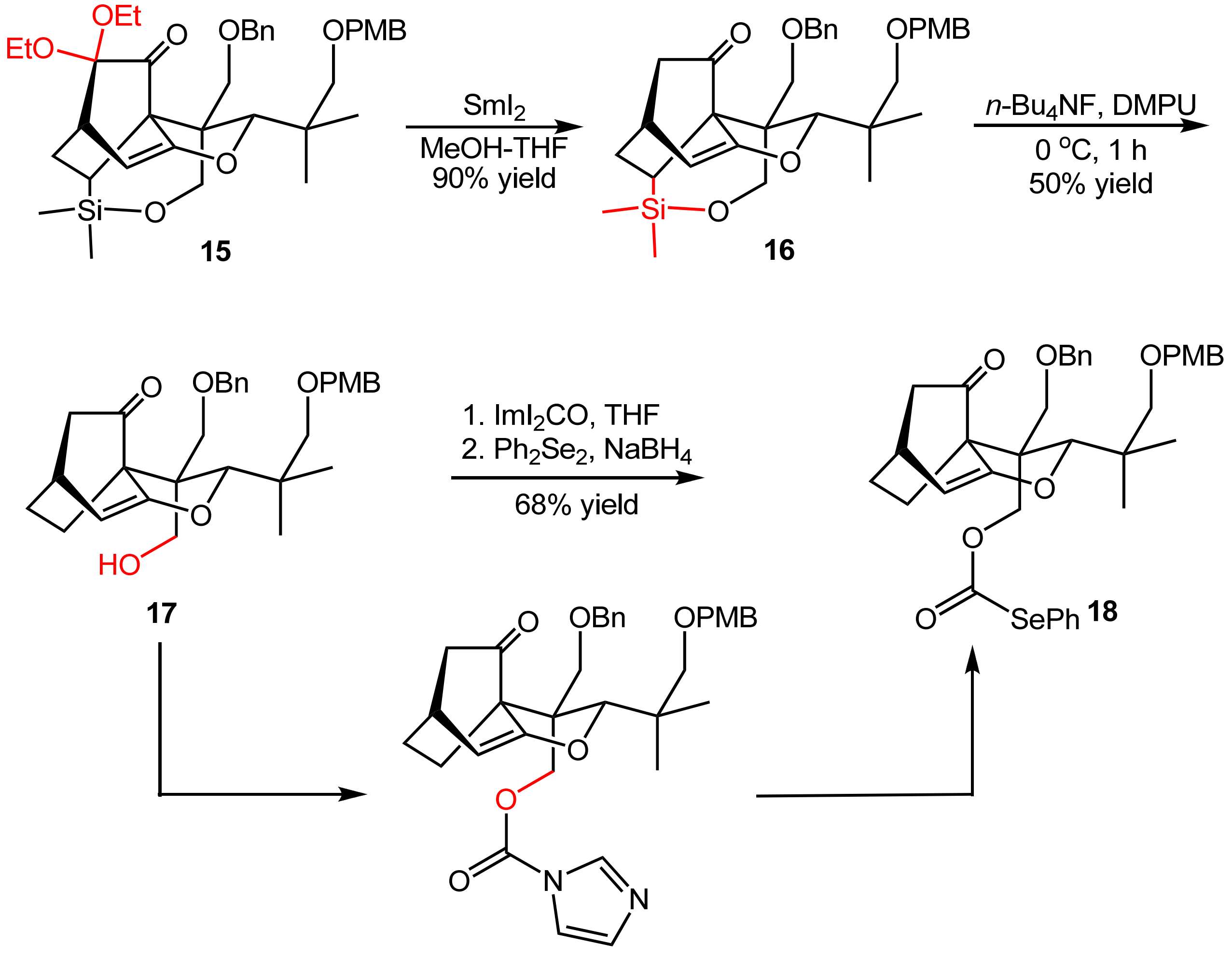
mechanism

An IMDA Reaction



Mechanism

Lactone Assembly by Radical Cyclization



15

SmI$_2$
MeOH-THF
90% yield

16

n-Bu$_4$NF, DMPU
0 °C, 1 h
50% yield

17

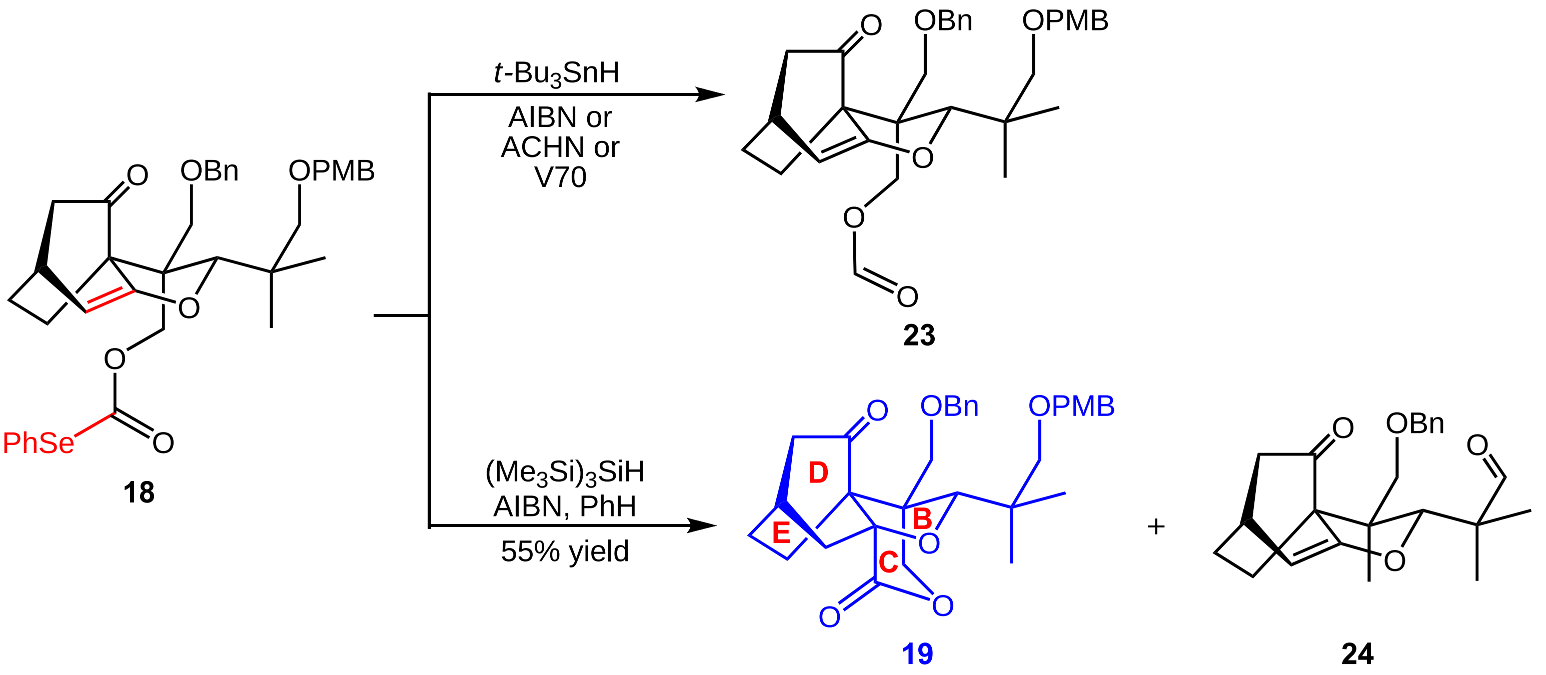
1. ImI$_2$CO, THF
2. Ph$_2$Se$_2$, NaBH$_4$

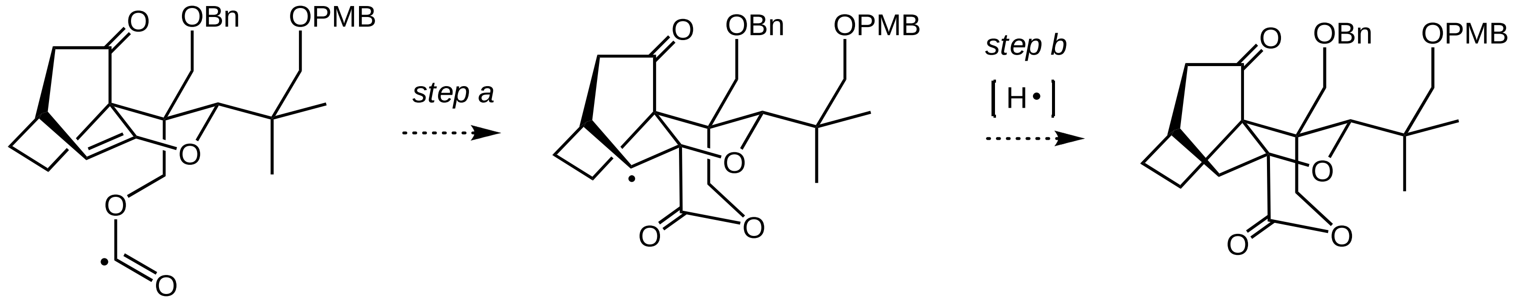
68% yield

18

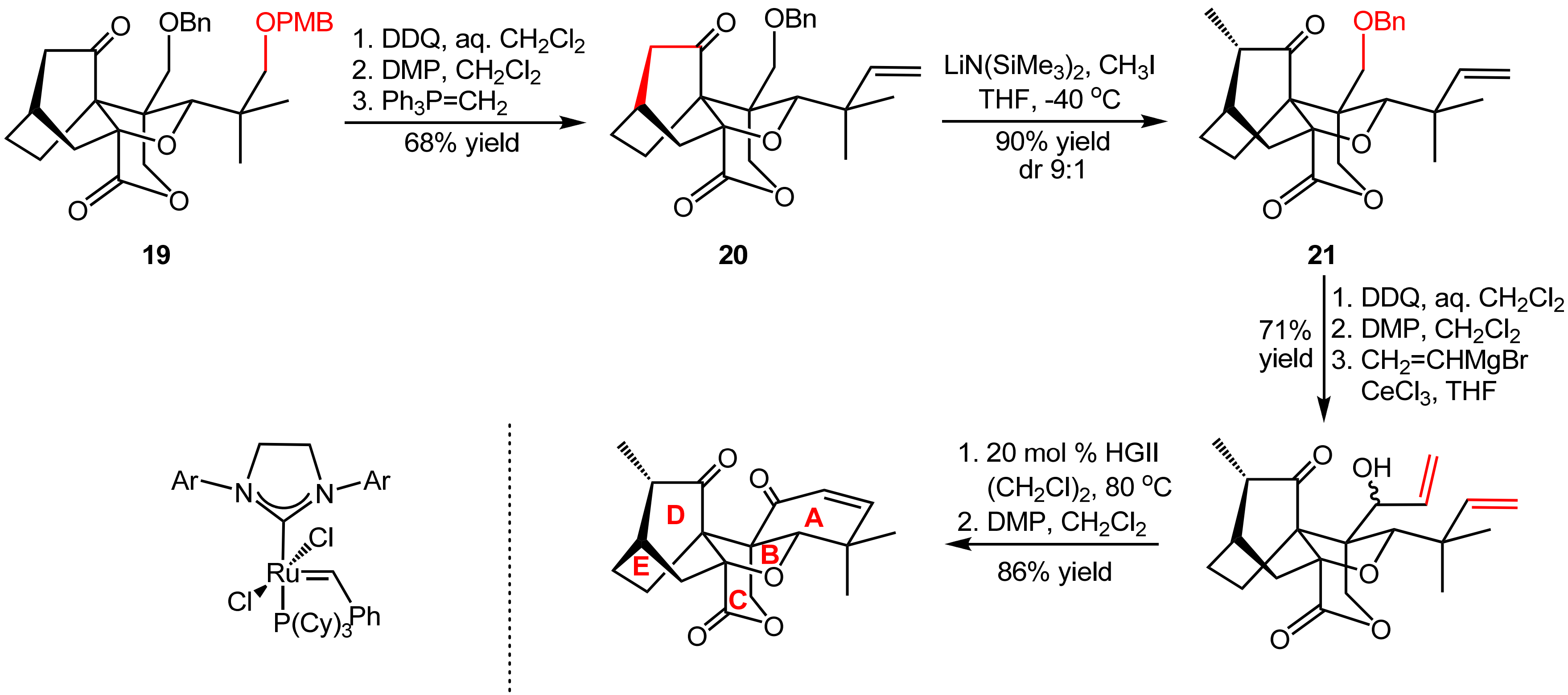
17'

Lactone Assembly by Radical Cyclization





Synthesis of Maoecrystal V



19

1. DDQ, aq. CH_2Cl_2
2. DMP, CH_2Cl_2
3. $Ph_3P{=}CH_2$

68% yield

20

$LiN(SiMe_3)_2$, CH_3I
THF, -40 °C

90% yield
dr 9:1

21

1. DDQ, aq. CH_2Cl_2
2. DMP, CH_2Cl_2
3. $CH_2{=}CHMgBr$
   $CeCl_3$, THF

71% yield

22

1. 20 mol % HGII
   $(CH_2Cl)_2$, 80 °C
2. DMP, CH_2Cl_2

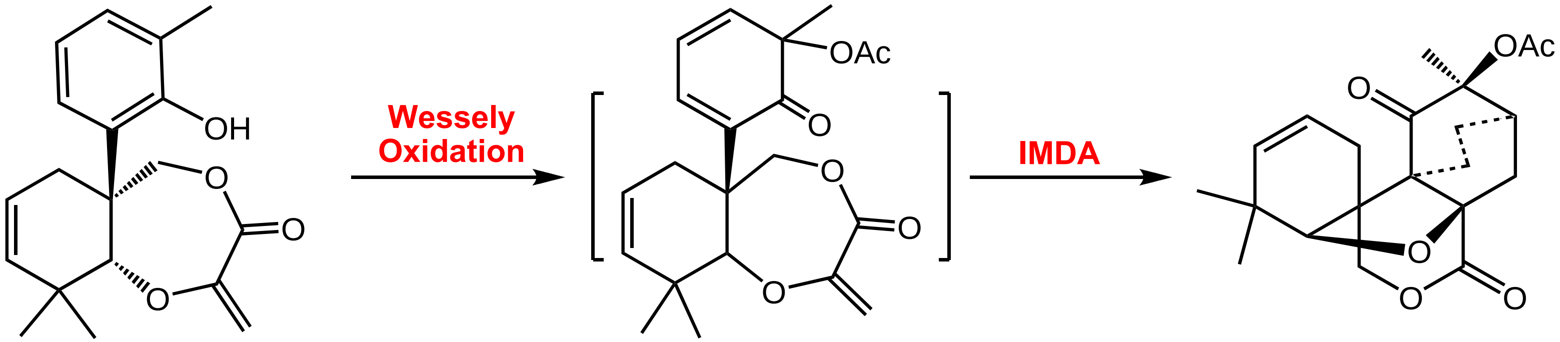
86% yield

Maoecrystal V (1)

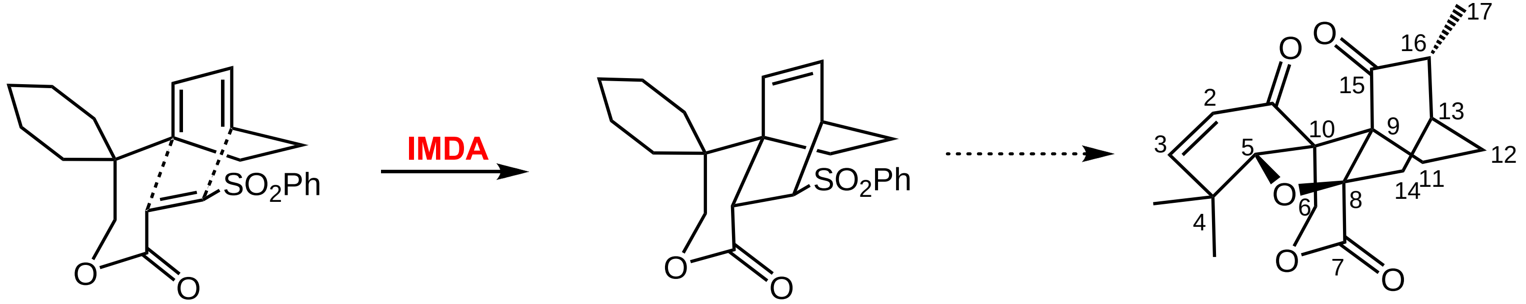
Hoveyda-Grubbs Catalyst

Summary

Yang's Method



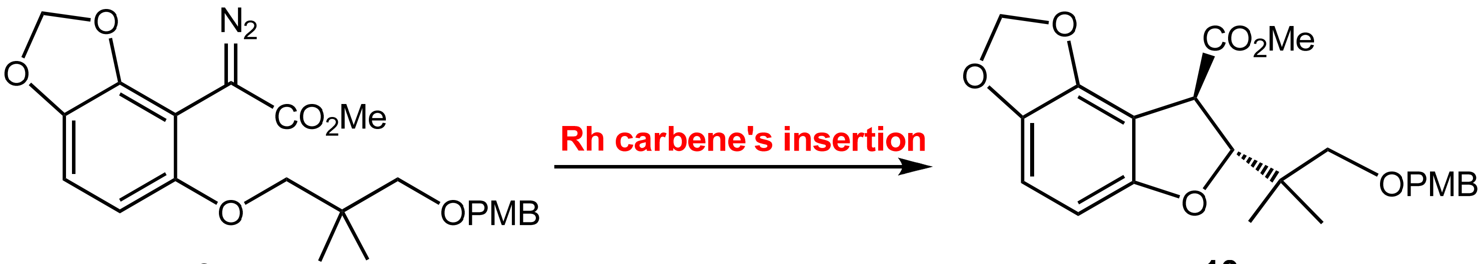
Danishefsky's Method



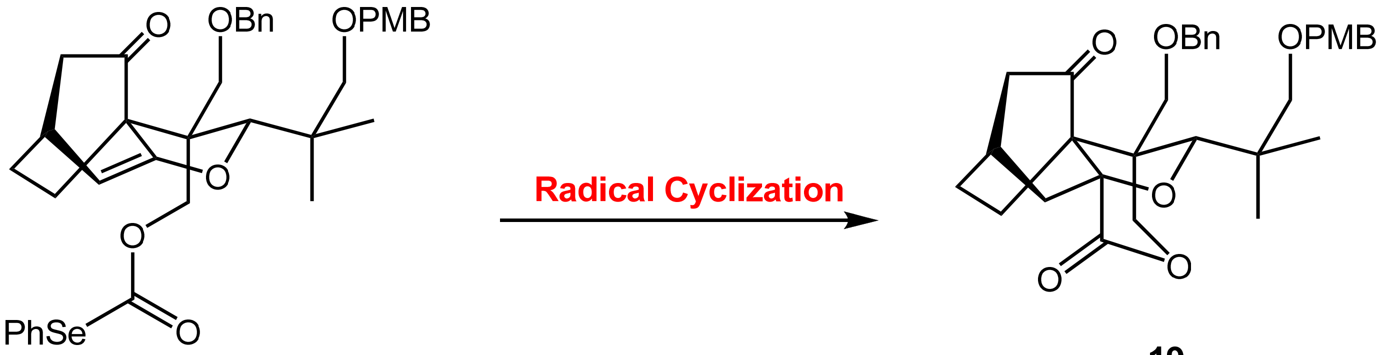
(±)-Maoecrystal V (1)

Summary

Zakarian's Method



9 **10**



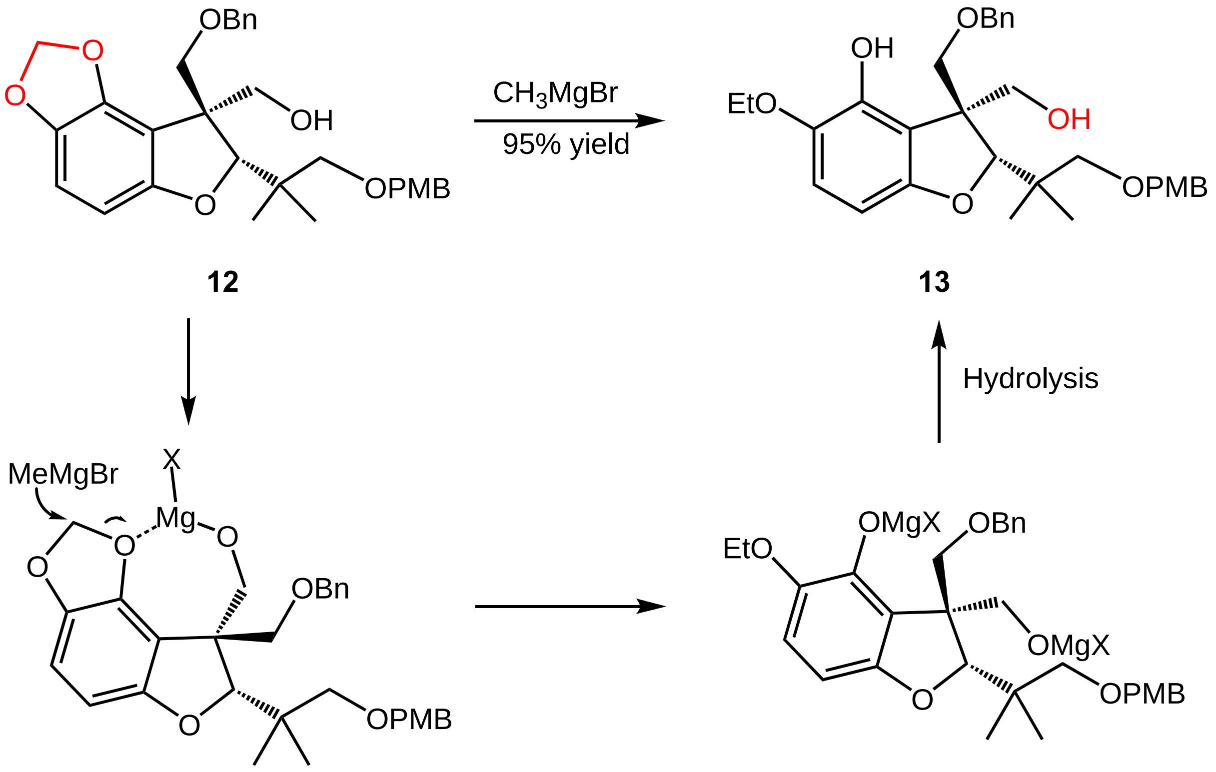
18 **19**

Among many known *ent*-kauranoids, maoecrystal V stands out for its atypical molecular architecture in this class of natural products. Isolated and characterized by Sun and co-workers in 2004, this unique C_{19} diterpenoid displayed potent (IC_{50} = 20 ng/mL) and remarkably selective cytotoxicity against HeLa cells. The pentacyclic framework of maoecrystal V integrates three contiguous quaternary stereocenters (two all-carbon), a bicyclo[2.2.2]octan-2-one subunit, and a strained central tetrahydrofuran flanked by *trans*-fused six-membered rings. Collectively, these structural characteristics amount to an exquisite challenge for chemical synthesis. Numerous research groups initiated programs directed at the synthesis of maoecrystal V, identifying the construction of the quaternary stereogenic centers as one of the main strategic goals and developing many effective solutions.

The successful completion of the first total synthesis of maoecrystal V in racemic form, reported by Yang and co-workers in 2010, relied on a concise strategy centered on an intramolecular Diels−Alder reaction (IMDA). The reaction enables a rapid assembly of the bicyclooctanone and tetrahydrofuran ring systems in one event, albeit with low facial selectivity for the diene counterpart. The second of the two completed total syntheses of (±)-maoecrystal V reported to date was described by Peng and Danishefsky in 2012. Other research groups have also developed creative and efficient approaches based on IMDA chemistry that is envisioned to precede tetrahydrofuran formation.

In closing, a concise total synthesis of maoecrystal V has been accomplished (24 steps, ~1.5% overall yield from sesamol). The strategic focus on the central strained tetrahydrofuran ring resulted in an initial disassembly of the lactone ring to a polycyclic enol ether. The enol ether was constructed by an IMDA reaction of a tethered $CH_2=CH_2$ equivalent with a 2,4-cyclohexadienone fragment obtained by oxidative dearomatization of a dihydrobenzofuran intermediate. This intermediate, in turn, was prepared by an effective Rhodium-catalyzed C−H functionalization reaction which can potentially be modified to access enantioenriched products using chiral Rhodium catalysts.

An IMDA Reaction



CH_3MgBr

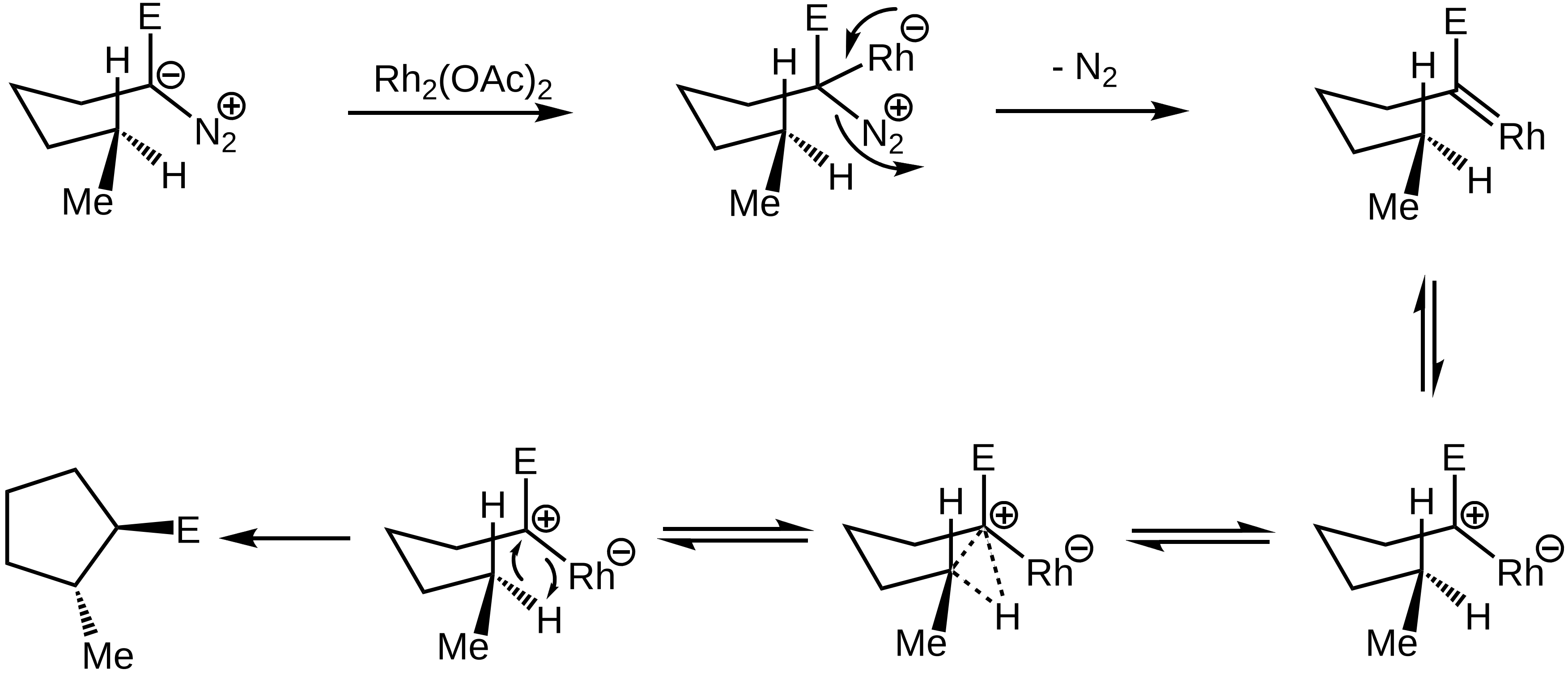
95% yield

12

13

Hydrolysis

Back



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