A Concise Total Synthesis of (-)-Maoecrystal Z

Reisman, S. E. et al. *J. Am. Chem. Soc.* **2011**, *133*, 14964.

报告： 时磊　　检查：叶智识

手性合成研究组

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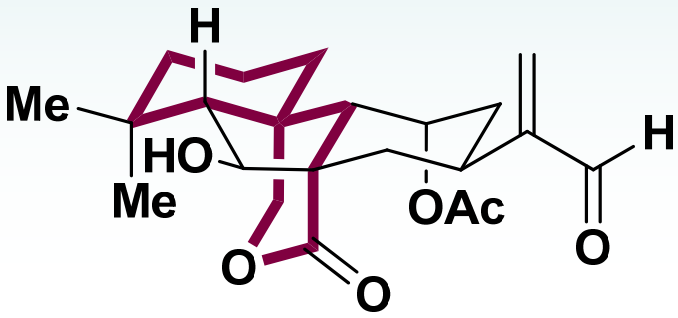


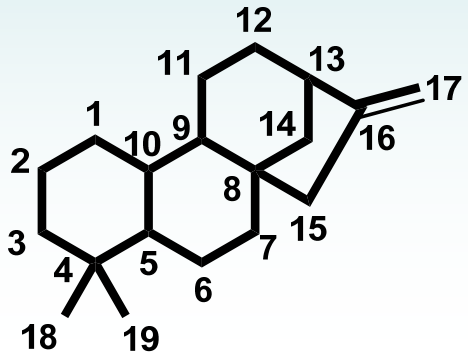
***maoecrystal Z* (1)**

毛萼香茶菜

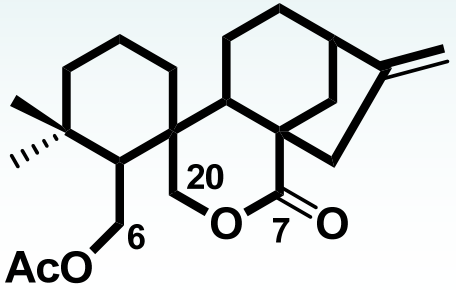
Isodon eriocalyx

- Isolation from Chinese medicinal herb *isodon eriocalyx* in 2006.
- In vitro cytotoxicity toward A2780 ovarian cancer cell lines (IC_{50} = 1.45μg/mL).

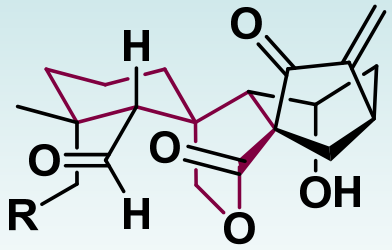
Xu, H-X et al. *Org. Lett.* **2006**, *8*, 4727



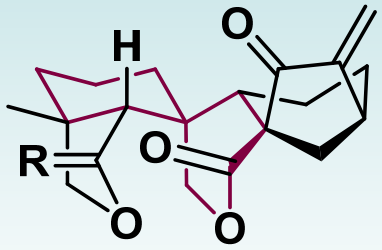
ent-kaurane(ene)



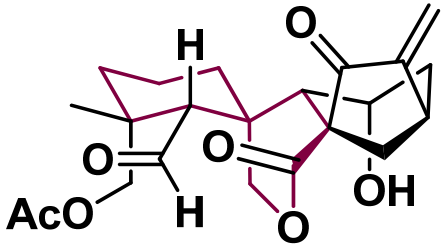
6,7-seco-ent-kaurane(ene)



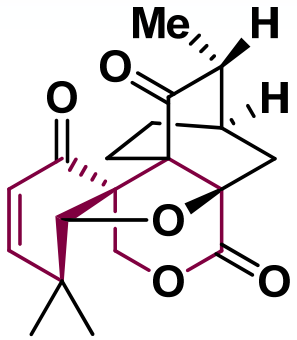
Trichorabdal A **(2, R = H)**
Trichorabdal B **(3, R = OAc)**



Shikodonin **(4, R = OH, H)**
Longirabdolactone **(5, R = O)**



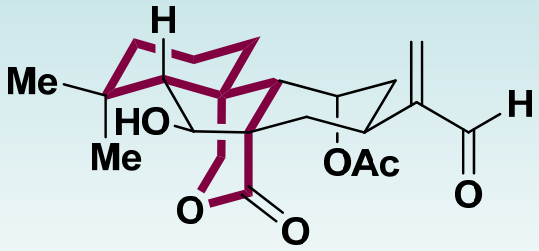
Effusin **(6)**



Maoecrystal V **(7)**

The first total synthesis in 2010 by Yang

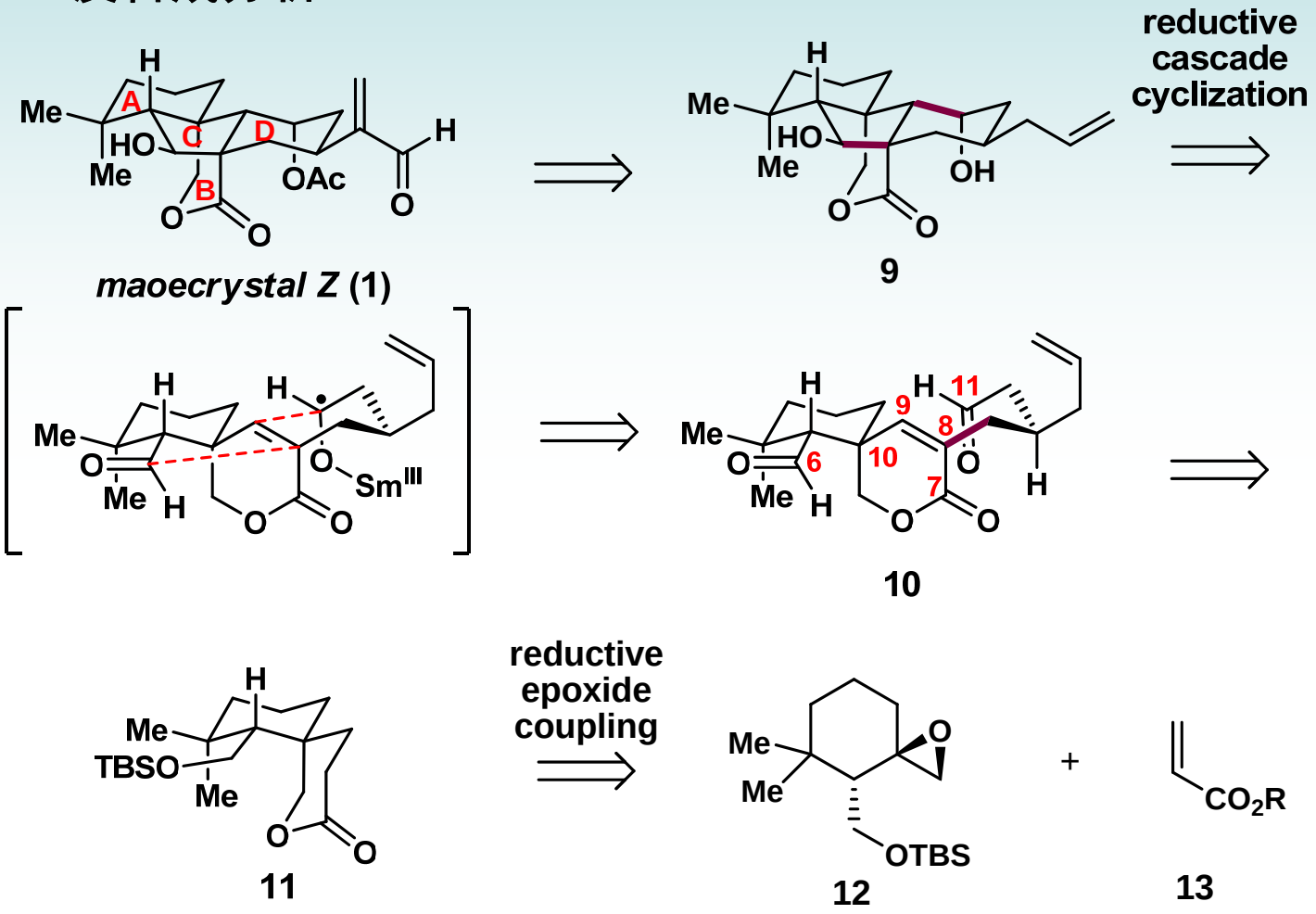
Synthetic Challenges



***maoecrystal Z* (1)**

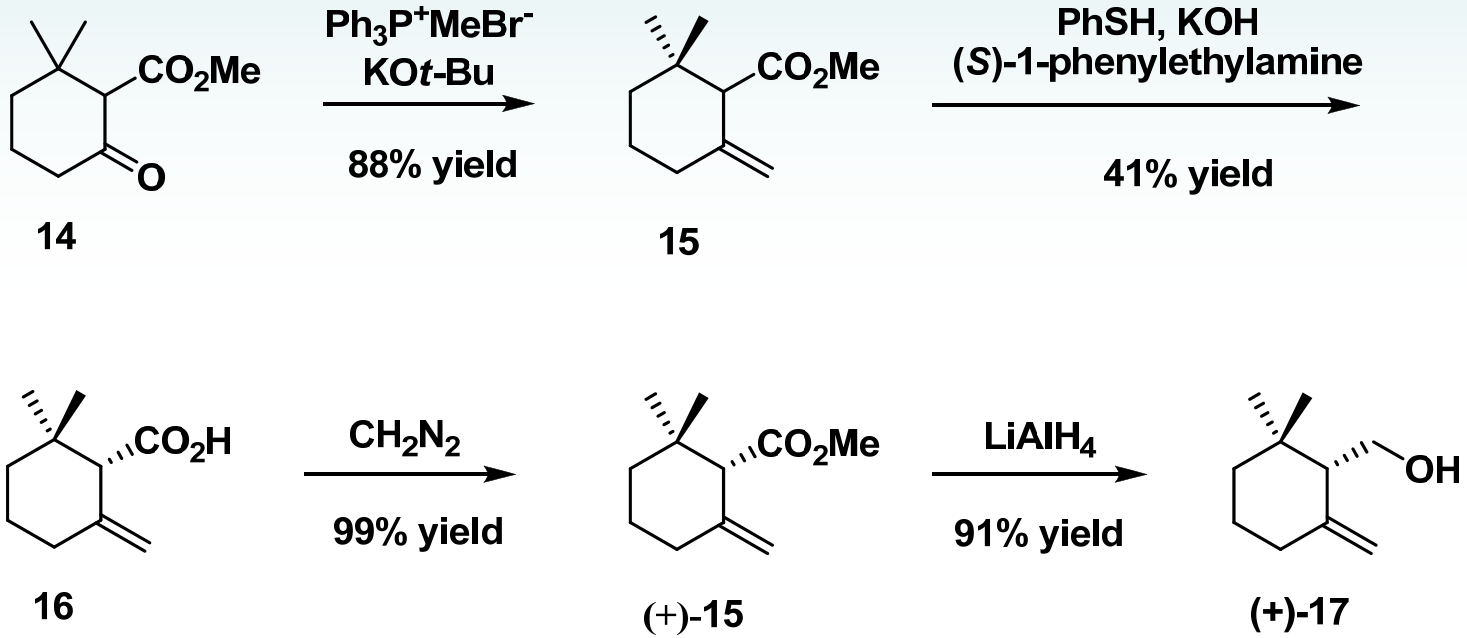
- Compact tetracyclic system
- Six vicinal stereogenic centers
- Two all-carbon quaternary centers

2. 反合成分析


reductive
cascade
cyclization
reductive
epoxide
coupling
maoecrystal Z (1)
9
10
11
12
13
+

3. *(-)-Maoecrystal Z* 的合成

3.1 (+)–γ–cyclogeraniol 环香叶醇的合成

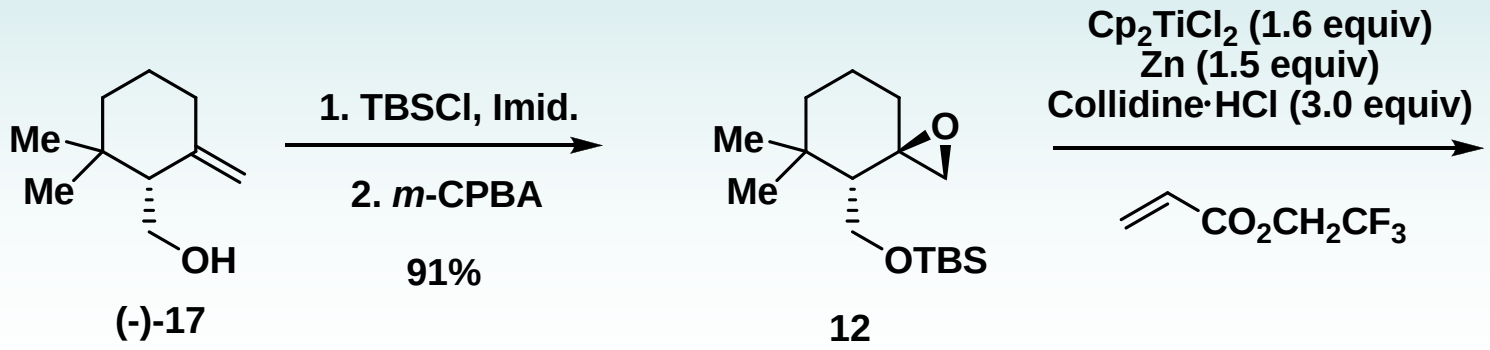


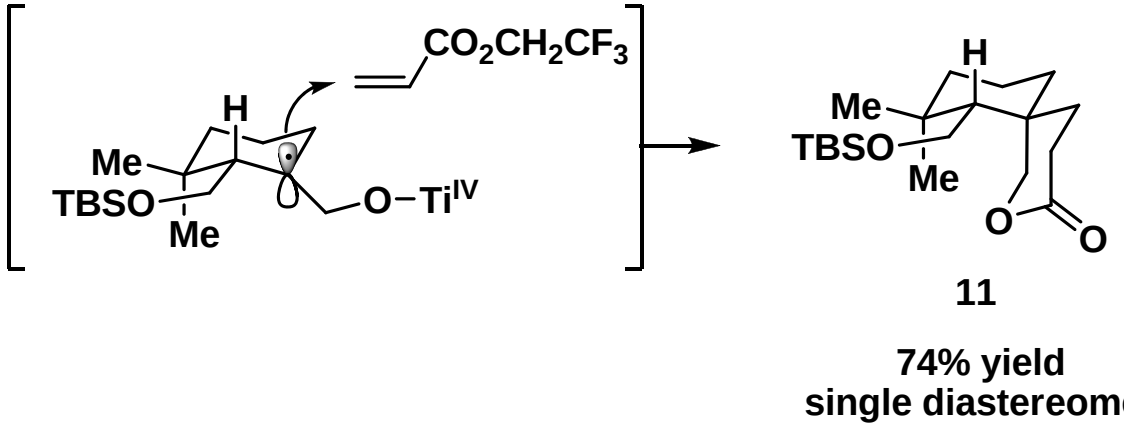
14　　15

16　　(+)-15　　(+)-17

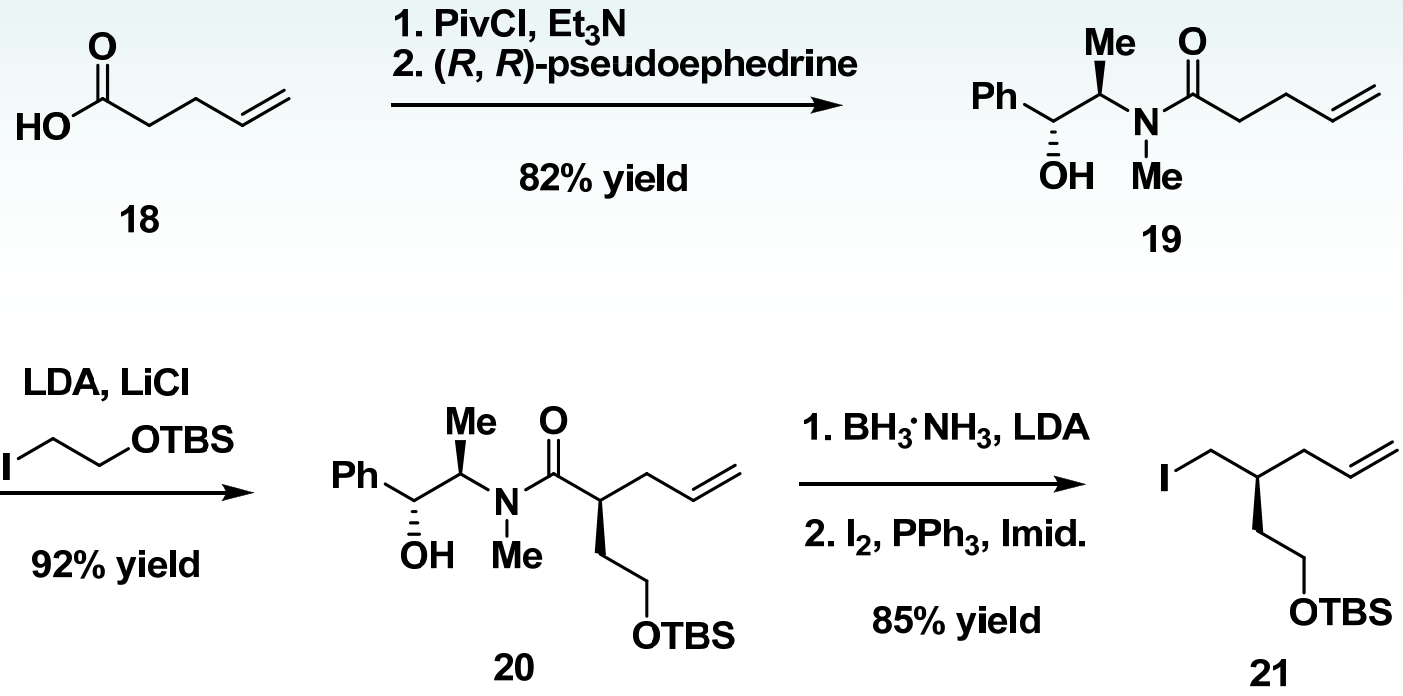
Tanimoto, H. et al. *Tetrahedron* **1997**, *53*, 3527.

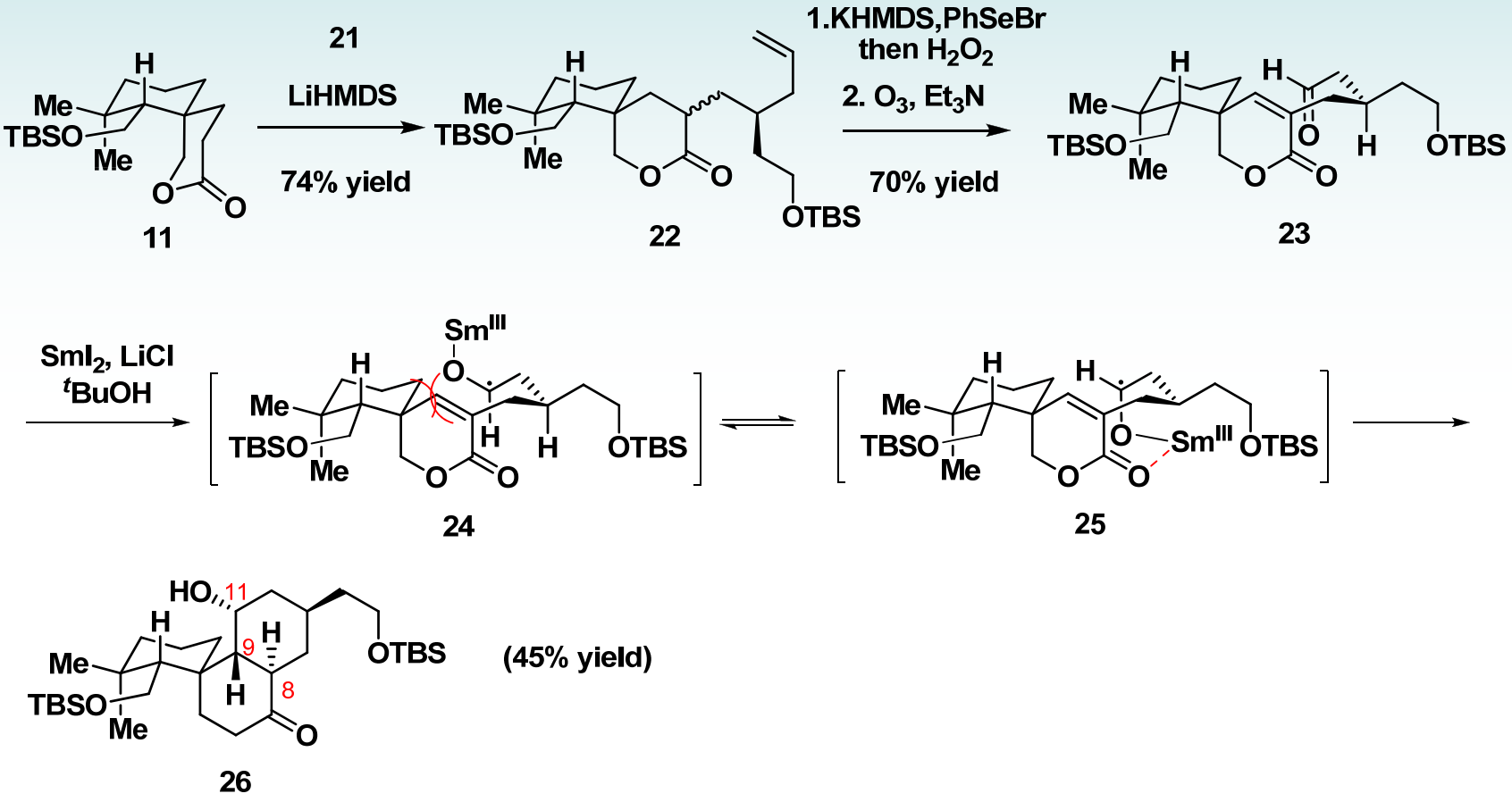
3.2 Spirolactone **11的合成**

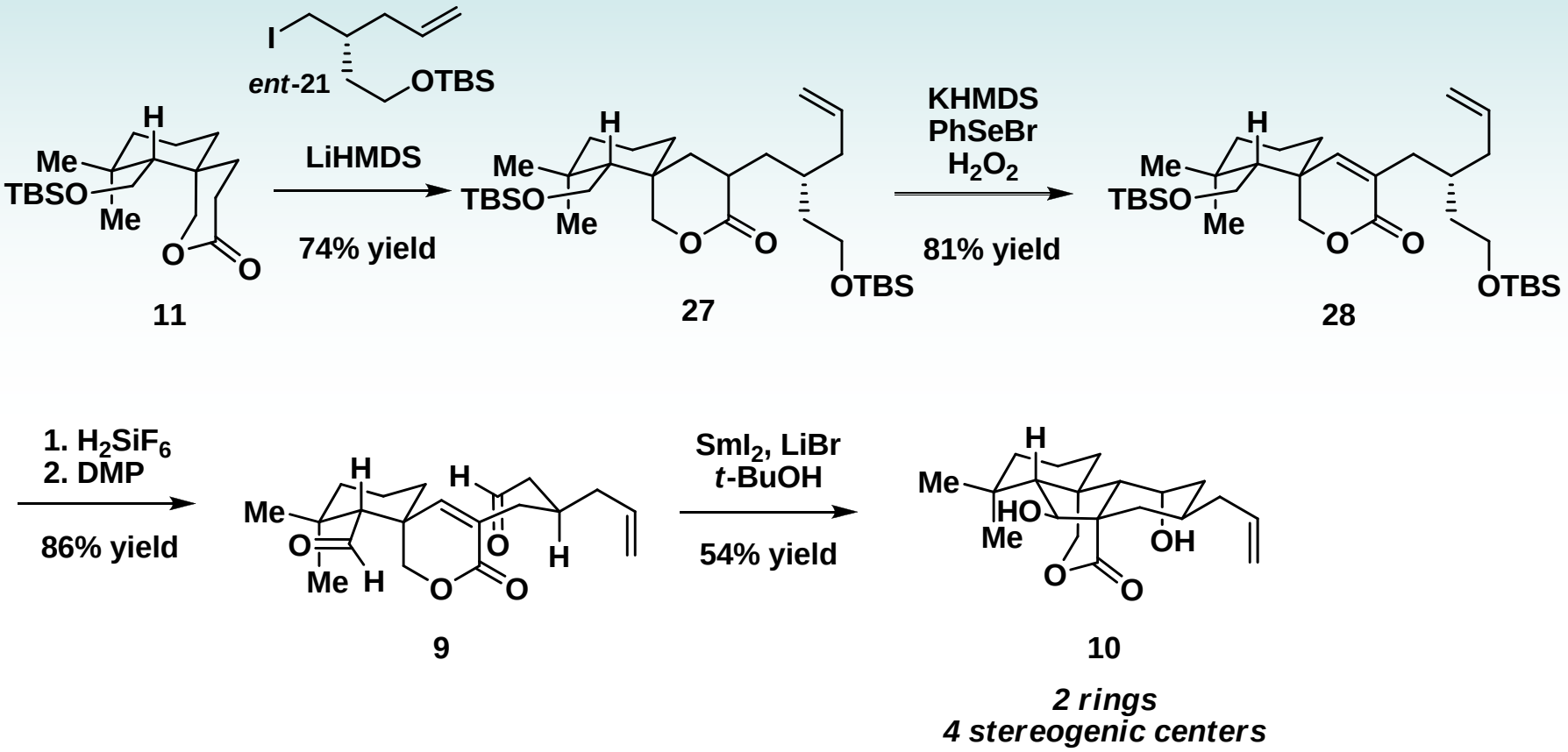


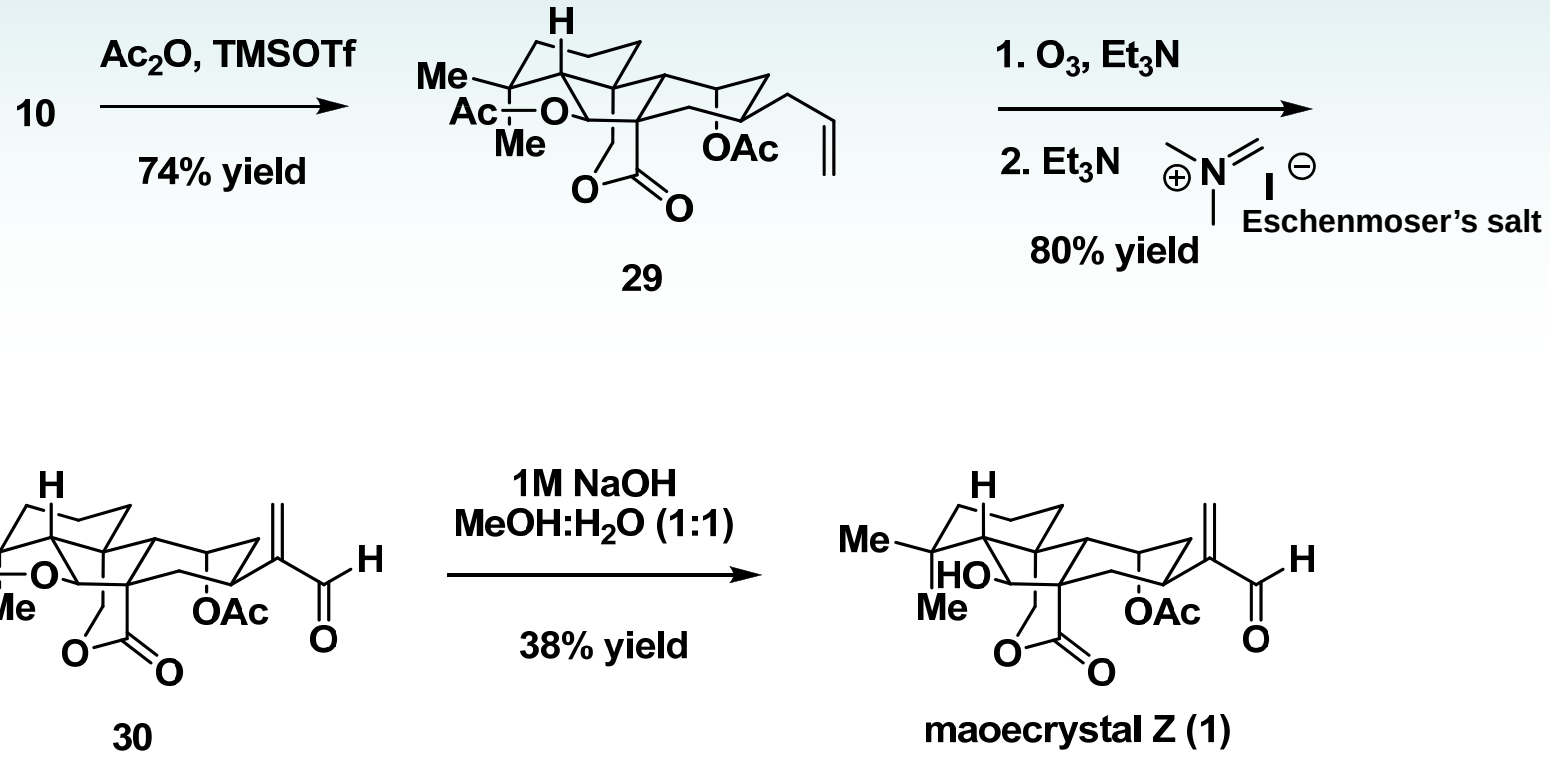


3.3 串联环化反应

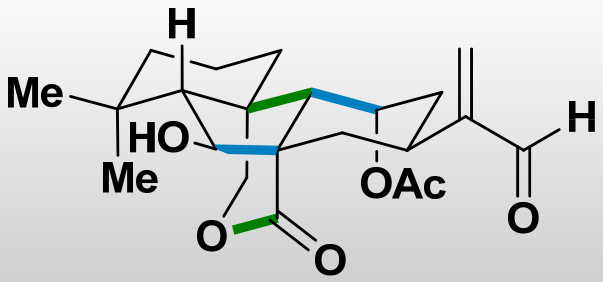

1. PivCl, Et3N
2. (R, R)-pseudoephedrine
82% yield
18
19
LDA, LiCl
92% yield
20
1. BH3·NH3, LDA
2. I2, PPh3, Imid.
85% yield
21


21
LiHMDS
74% yield
1.KHMDS,PhSeBr
then H_2O_2
2. O_3, Et_3N
70% yield
SmI_2, LiCl
^tBuOH
Sm^{III}
(45% yield)
11
22
23
24
25
26


I
ent-21
OTBS
H
Me
TBSO
Me
O
O
11
LiHMDS
74% yield
H
Me
TBSO
Me
O
O
OTBS
27
KHMDS
PhSeBr
H2O2
81% yield
H
Me
TBSO
Me
O
O
OTBS
28
1. H2SiF6
2. DMP
86% yield
H
H
Me
O
O
Me H
O
O
H
9
SmI2, LiBr
t-BuOH
54% yield
H
Me
HO
Me
OH
O
O
10
2 rings
4 stereogenic centers


10
Ac2O, TMSOTf
74% yield
29
1. O3, Et3N
2. Et3N
80% yield
Eschenmoser's salt
30
1M NaOH
MeOH:H2O (1:1)
38% yield
maoecrystal Z (1)

3. 总结与讨论



■ Ti^{III} –mediated reductive epoxide coupling

■ Sm^{II}-mediated reductive cascade cyclization

12 steps, 4.2% overall yield

自由基反应的优点：

中性条件，避免酸碱条件。

高反应活性，适合构建拥挤的季碳。

有效的串联反应可一步形成多个碳碳键。

常见单电子转移试剂：

Cp_2TiCl, SmI_2, $Mn(OAc)_3$

Maoecrystal Z (**6**) is an unusual rearranged 6,7-*seco*-*ent*-kauranoid natural product that was isolated in 2006 as a minor constituent from the Chinese medicinal herb Isodon eriocalyx. Its compact tetracyclic ring system comprises six vicinal stereogenic centers, two of which are all-carbon quaternary centers. Maoecrystal Z is closely related to several additional 6,7-*seco*-*ent*-kauranoid natural products, including trichorabdals A (**1**) and B (**2**), shikodonin (**3**), longirabdolactone (**4**), and effusin (**5**), as well as the rearranged *ent*-kauranoid maoecrystal V (**7**). Collectively, these compounds share a common central spiro-fused lactone. Compounds **1-3** exhibit in vivo antitumor activity against Ehrlich ascites carcinoma in mice, while **6** and **7** display in vitro cytotoxicity toward A2780 ovarian and HeLa cancer cell lines, respectively.

In summary, the first total synthesis of (-)-maoecrystal Z has been described. The key steps include a highly diastereoselective Ti^{III}-mediated reductive epoxide coupling and a Sm^{II}-mediated reductive cascade cyclization. Collectively, these transformations illustrate the utility of single-electron chemistry for the preparation of congested polycyclic systems bearing vicinal stereogenic centers. Efforts to employ readily accessible spirolactone **12** in the syntheses of additional *seco-ent*-kauranoid natural products, such as trichorabdals A and B, are the subject of ongoing research in our laboratory.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