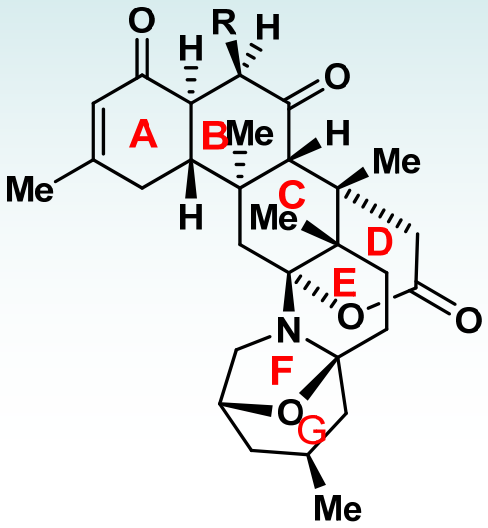
Total Synthesis of Norzoanthamine

Miyashita, M. et al. *Science* **2004**, *305*, 495.

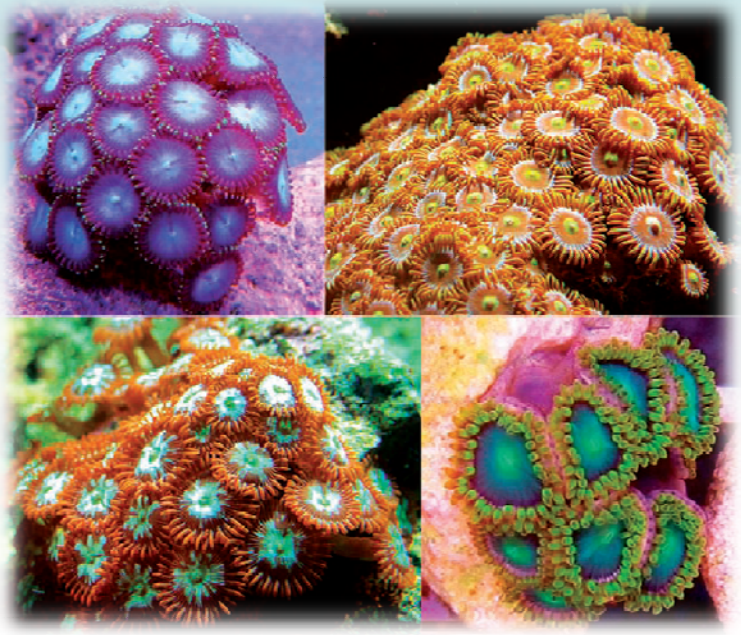
报告： 时磊　　检查：高凯

目　录

1. 简介



Norzoanthamine (1): R=H
Zoathamine (2): R=Me



纽扣珊瑚 Zoanthids

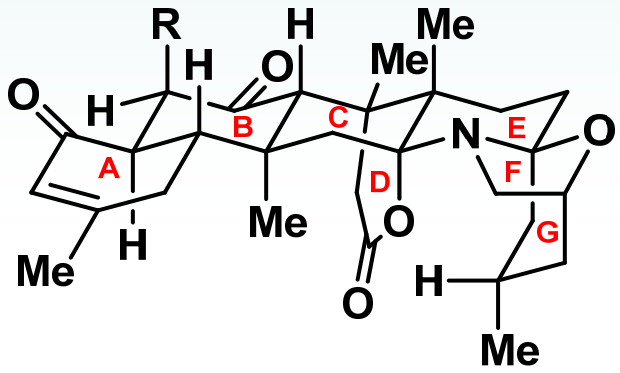
- ***Isolation***

  Norzoanthamine: Rao and Faulker, the coast of India in 1984.
  Zoanthamine: Uemura, the coast of islands of south of Japan in 1995.

- ***Biological activity***

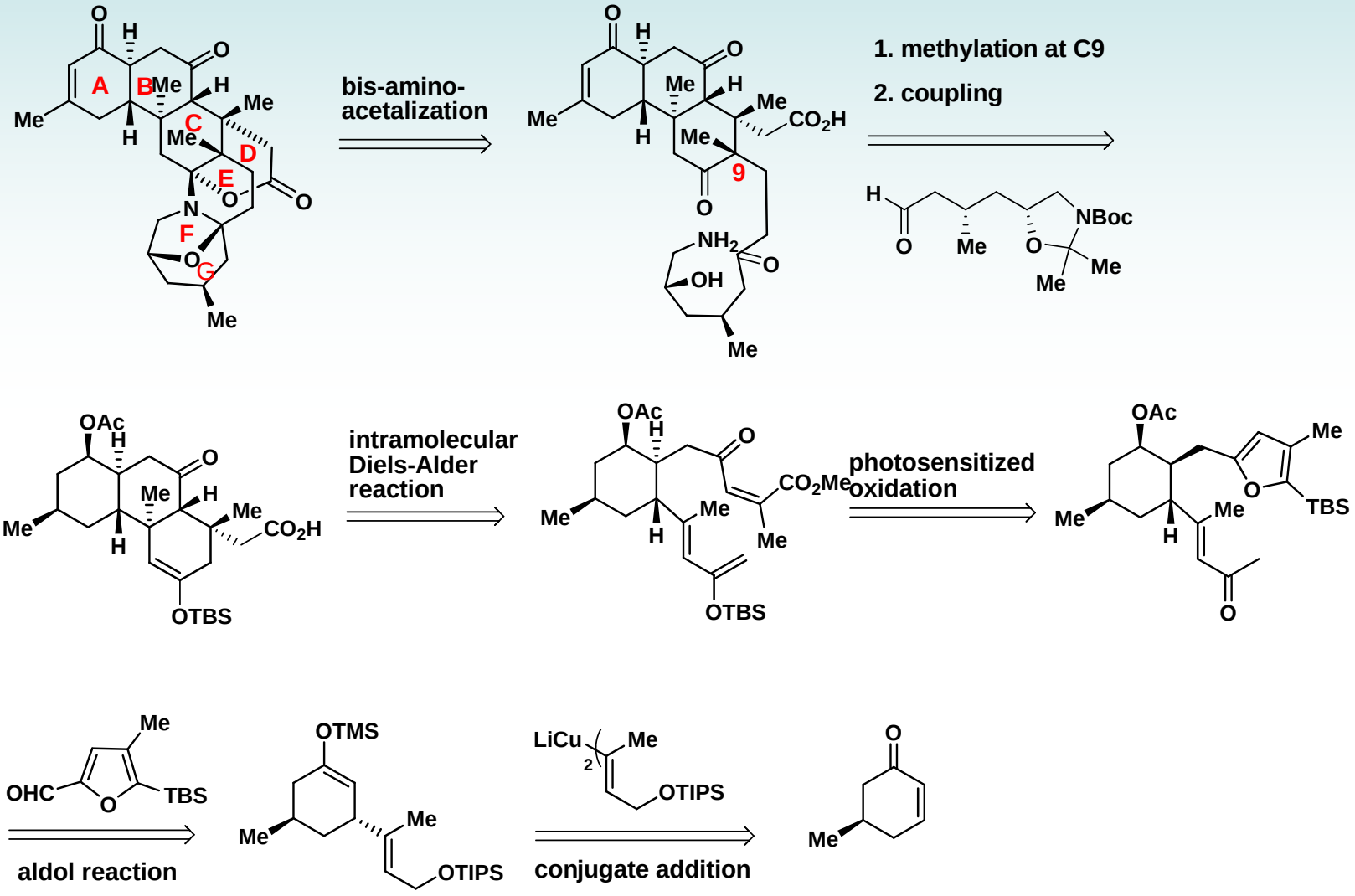
  Norzoanthamine: Inhibits human platelet aggregation and antisteoporotic drug.
  Zoanthamine: Analgesic and inhibitor of phorbol myristate-induced inflammation.

Synthetic Challenges

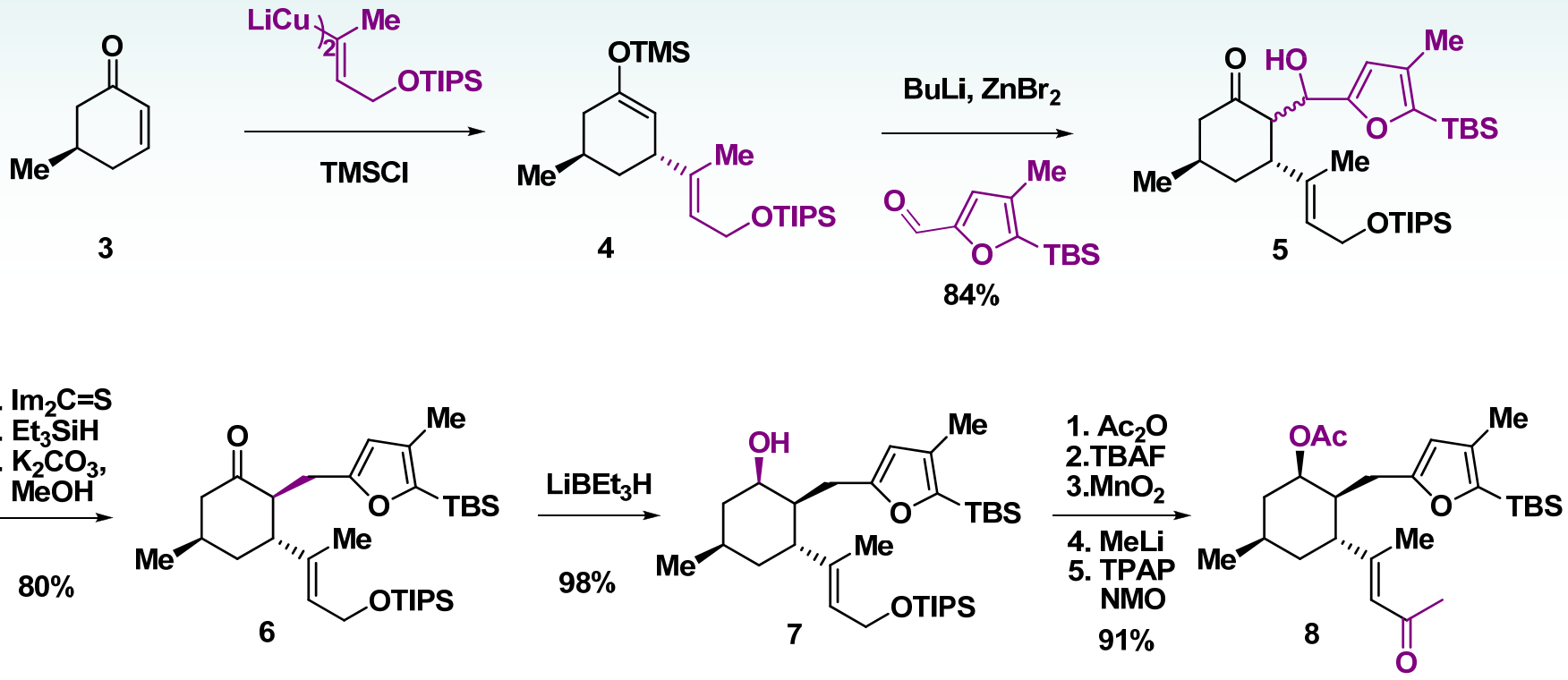


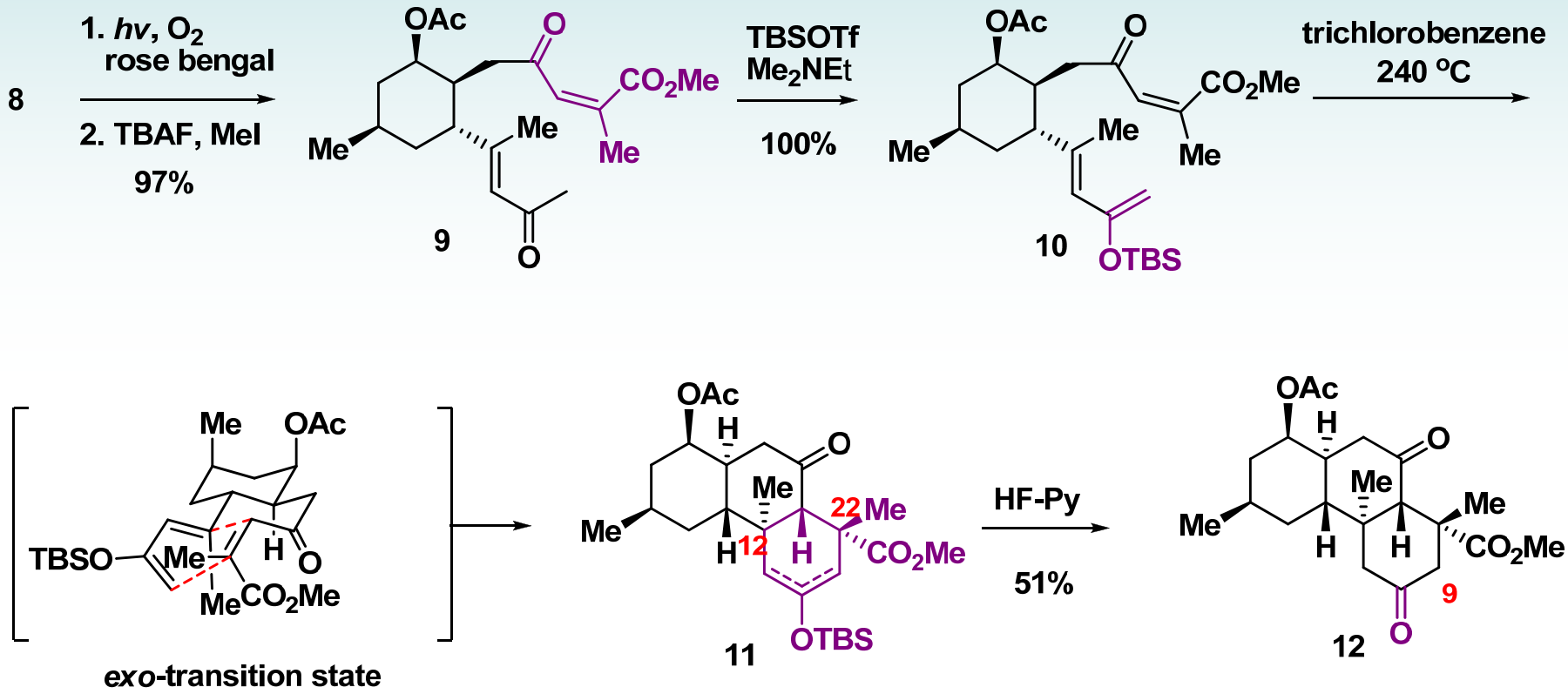
- trans-anti-trans-fused perhydro-phenanthrene
- three all-carbon quarterary centers in C ring (C9, 12, 22)
- two novel aminoacetal structure (D, G ring)

2. 反合成分析

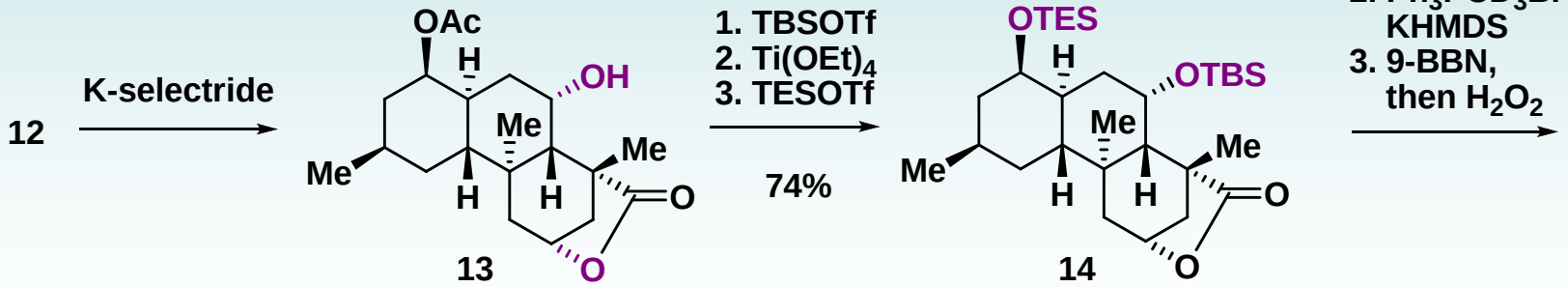

bis-amino-acetalization
1. methylation at C9
2. coupling
intramolecular Diels-Alder reaction
photosensitized oxidation
aldol reaction
conjugate addition

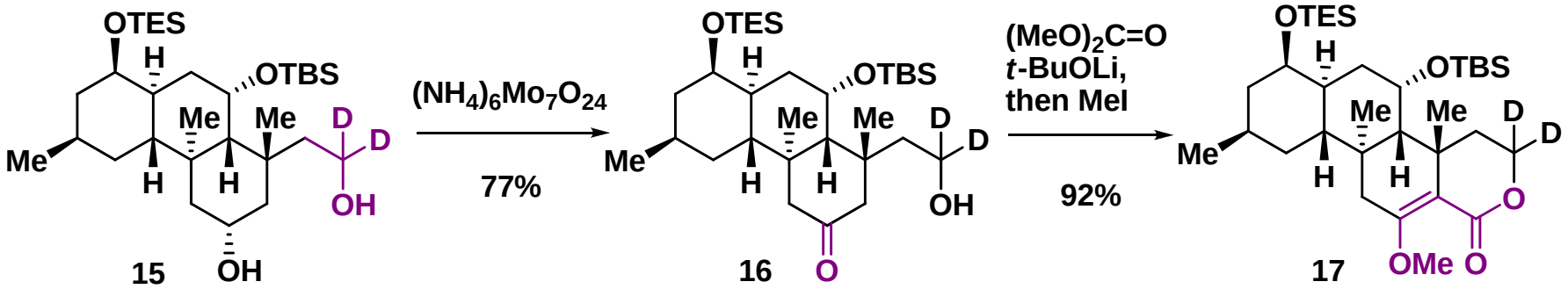
2. Norzoanthamine的合成



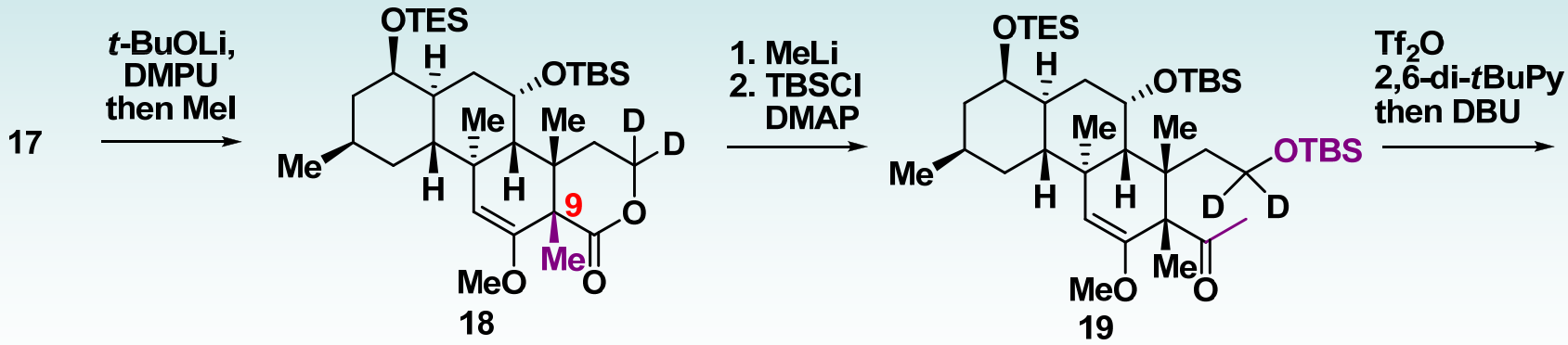


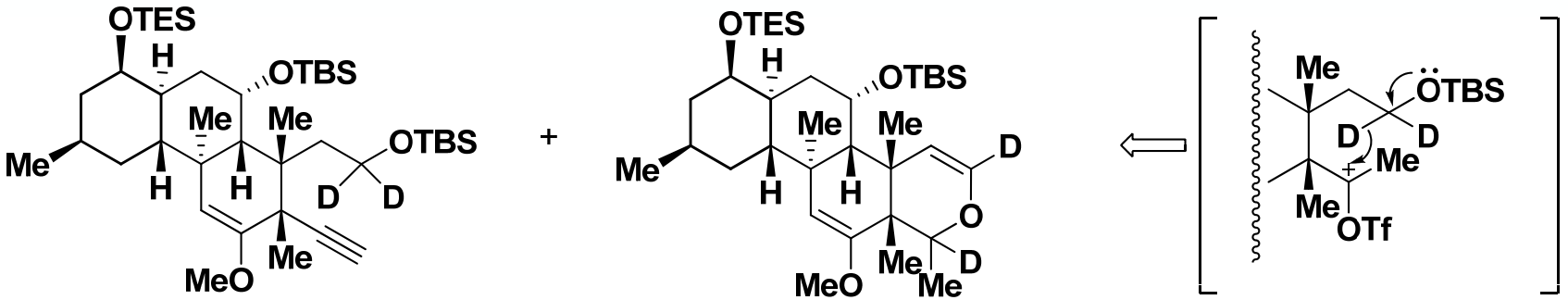
exo: *endo*=72:28

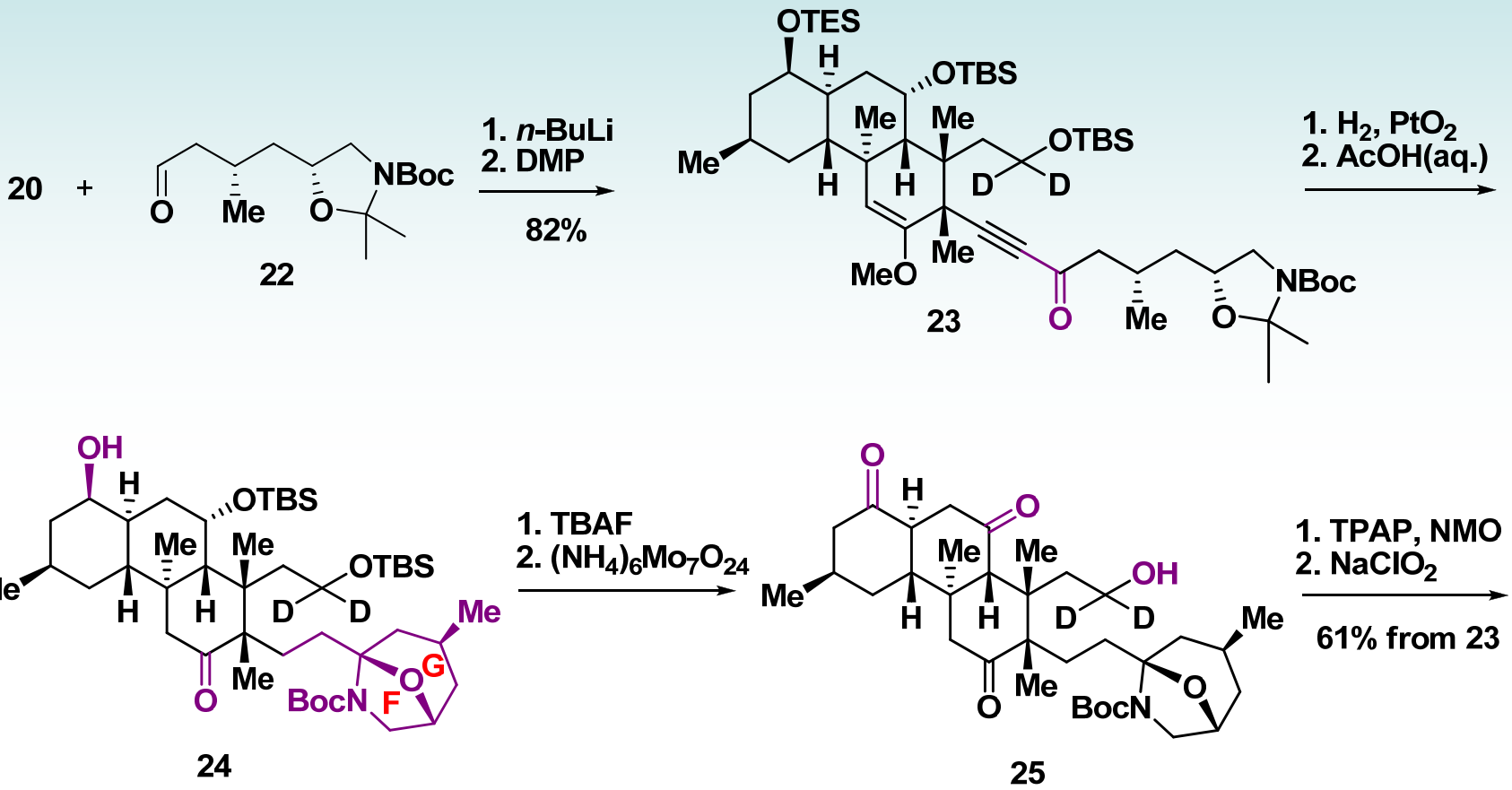

12
K-selectride
OAc
H
OH
Me
Me
Me
H
H
O
13
1. TBSOTf
2. Ti(OEt)4
3. TESOTf
74%
OTES
H
OTBS
Me
Me
Me
H
H
O
14
1. Dibal
2. Ph3PCD3Br
KHMDS
3. 9-BBN,
then H2O2

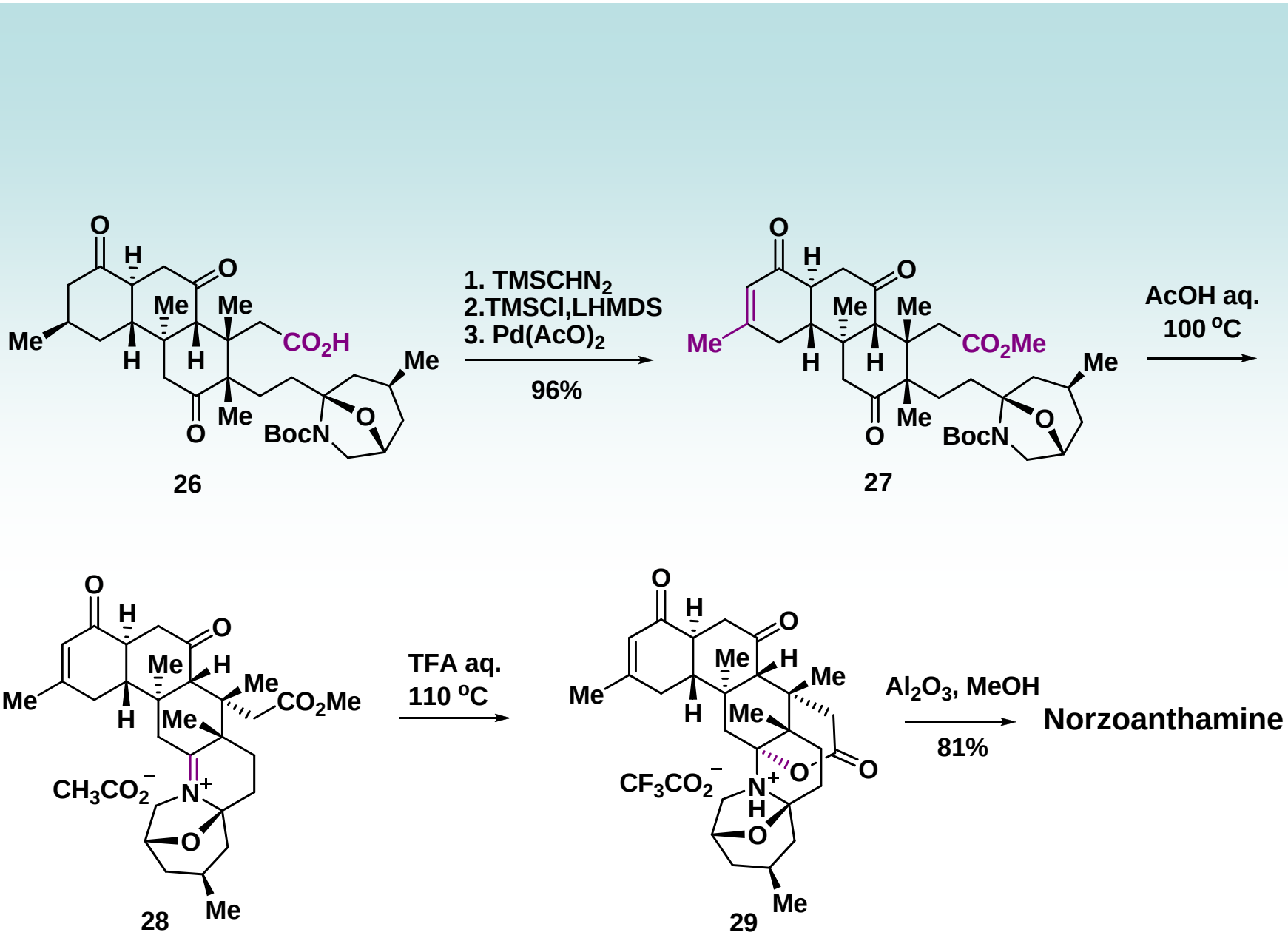

OTES
H
OTBS
Me
Me
D
D
Me
H
H
OH
OH
15
(NH4)6Mo7O24
77%
16
(MeO)2C=O
t-BuOLi,
then MeI
92%
17
OMe
O

手性合成研究组


17
t-BuOLi,
DMPU
then MeI
OTES
H
OTBS
Me
Me
D
D
Me
H
H
9
O
Me
MeO
O
18
1. MeLi
2. TBSCl
DMAP
OTES
H
OTBS
Me
Me
OTBS
Me
H
H
D
D
Me
MeO
O
19
Tf2O
2,6-di-tBuPy
then DBU


OTES
H
OTBS
Me
Me
OTBS
Me
H
H
D
D
Me
MeO
20 81%
nondeuterated 20 66%
+
OTES
H
OTBS
Me
Me
D
Me
H
H
O
Me
D
MeO
Me
21 9%
Me
ÖTBS
D
D
Me
Me
OTf


20
+
NBoc
O
Me
O
22
1. n-BuLi
2. DMP
82%
OTES
H
OTBS
Me
Me
Me
H
H
D
D
OTBS
MeO
Me
23
O
Me
O
NBoc
1. H2, PtO2
2. AcOH(aq.)
OH
H
OTBS
Me
Me
Me
H
H
D
D
OTBS
Me
O
Me
BocN
F
O
G
Me
24
1. TBAF
2. (NH4)6Mo7O24
O
H
O
Me
Me
Me
H
H
D
D
OH
Me
O
Me
BocN
O
25
1. TPAP, NMO
2. NaClO2
61% from 23


1. TMSCHN2
2.TMSCl,LHMDS
3. Pd(AcO)2
96%
AcOH aq.
100 °C
TFA aq.
110 °C
Al2O3, MeOH
81%
Norzoanthamine
26
27
28
29

3. 总结与讨论

41 steps, 3.5% overall yield (average of 92% per step)

- Intramolecular Diels-Alder reaction (ABC ring, C12, C22)
- Kinetic isotope effect for synthesis of alkyne (not only for mechanism)
- Bis-aminoacetalization (DEFG ring, C12, C22)

These distinctive biological properties, combined with novel chemical structures, make this family of alkaloids extremely attractive targets for chemical synthesis. However, the chemical synthesis of the zoanthamine alkaloids has remained as an unexplored summit, despite great synthetic efforts, owing to their densely functionalized complex stereostructures. Synthetic challenges posed by norzoanthamine (**1**) and zoanthamine **(2)** include construction of the stereochemically dense C ring that has three adjacent quaternary asymmetric carbon atoms at the C-9, C-12, and C-22 positions; stereoselective synthesis of the ABC carbon framework consisting of the *trans-anti-trans-fused perhydrophenanthren* skeleton; and stereoselective construction of two novel aminoacetal structures, including a bridged -lactone. We set about synthetic studies of norzoanthamine (**1)** that aimed at developing a**n** efficient synthetic route flexible enough to provide access to several members of the zoanthamine alkaloids while allowing the synthesis of various analogs for biological testing. We report herein the stereoselective total synthesis of **1.**

The total yield of synthetic norzoanthamine was 3.5% (an average of 92% yield each step) in 41 steps, starting from **3.** The synthetic compound was identical in all respects with naturally occurring norzoanthamine, including spectroscopic characteristics [^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra, infrared spectroscopy, and mass spectra], circular dichroism (CD), and optical rotation $[\alpha]^{24}_{D}$ = –6.0 (*c* 0.23, $CHCl_3$); natural norzoanthamine $[\alpha]^{24}_{D}$ = –6.2 (*c* 0.23, $CHCl_3$)]. The absolute structure of norzoanthamine (**1)** was rigorously verified by the present total synthesis. The chemistry described here not only offers a solution to a formidable synthetic challenge but also opens a completely chemical avenue to norzoanthamine, other naturally occurring zoanthamine alkaloids, and synthetic, designed norzoanthamine derivatives.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