Literature Report

Changbin Yu 2012-05-08 检查: Kai Gao

Total Synthesis of (−)-Fusarisetin A and Reassignment of the Absolute Configuration of Its Natural Counterpart

Ang Li* *et al*. *J. Am. Chem. Soc*. **2012**, *134*, 920−923.

Research Interests

Divergent total synthesis of biologically active natural products based on biosynthetic hypothesis or privileged core structures
Desymmetrization strategy in natural product total synthesis
Ring strain-promoted reactions in natural product synthesis

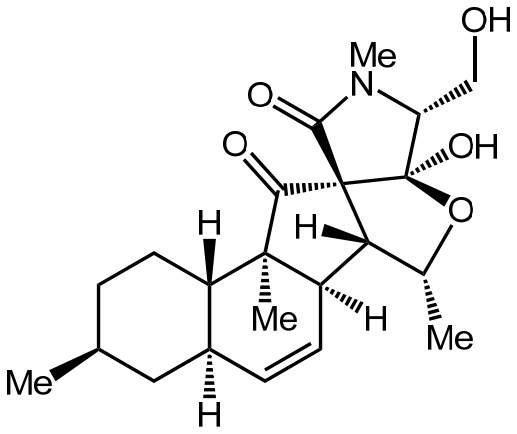
Professional Experience

2010–present "Bairen Jihua" Professor, Shanghai Institute of Organic Chemistry,
2010 Research fellow, Institute of Chemical and Engineering Sciences, Singapore
Advisor: Prof. K. C. Nicolaou

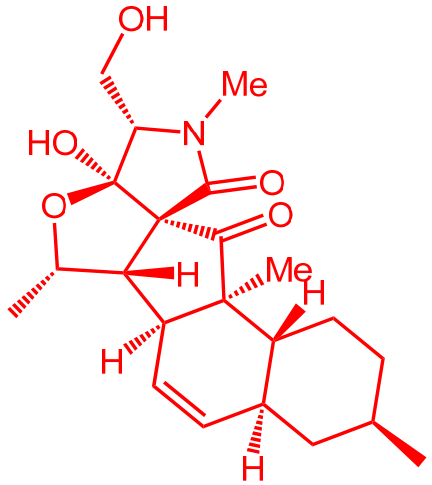
Education

2004–2009 Ph.D., The Scripps Research Institute
Advisor: Prof. K. C. Nicolaou
2000–2004 B.Sc., Peking University
Advisor: Prof. Zhen Yang

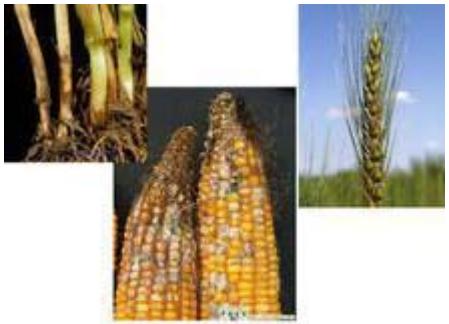
Structures of (-)-Fusarisetin A

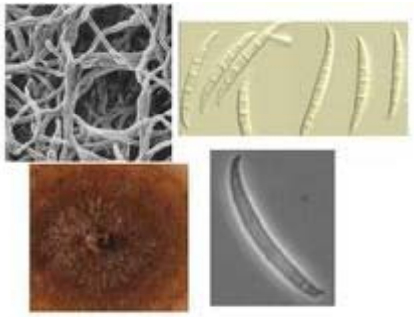


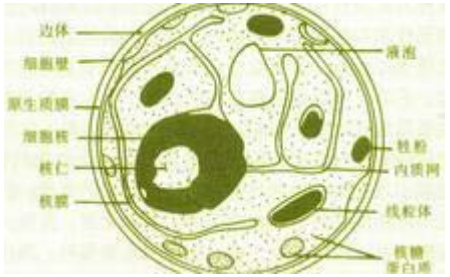
proposed structure of fusarisetin A



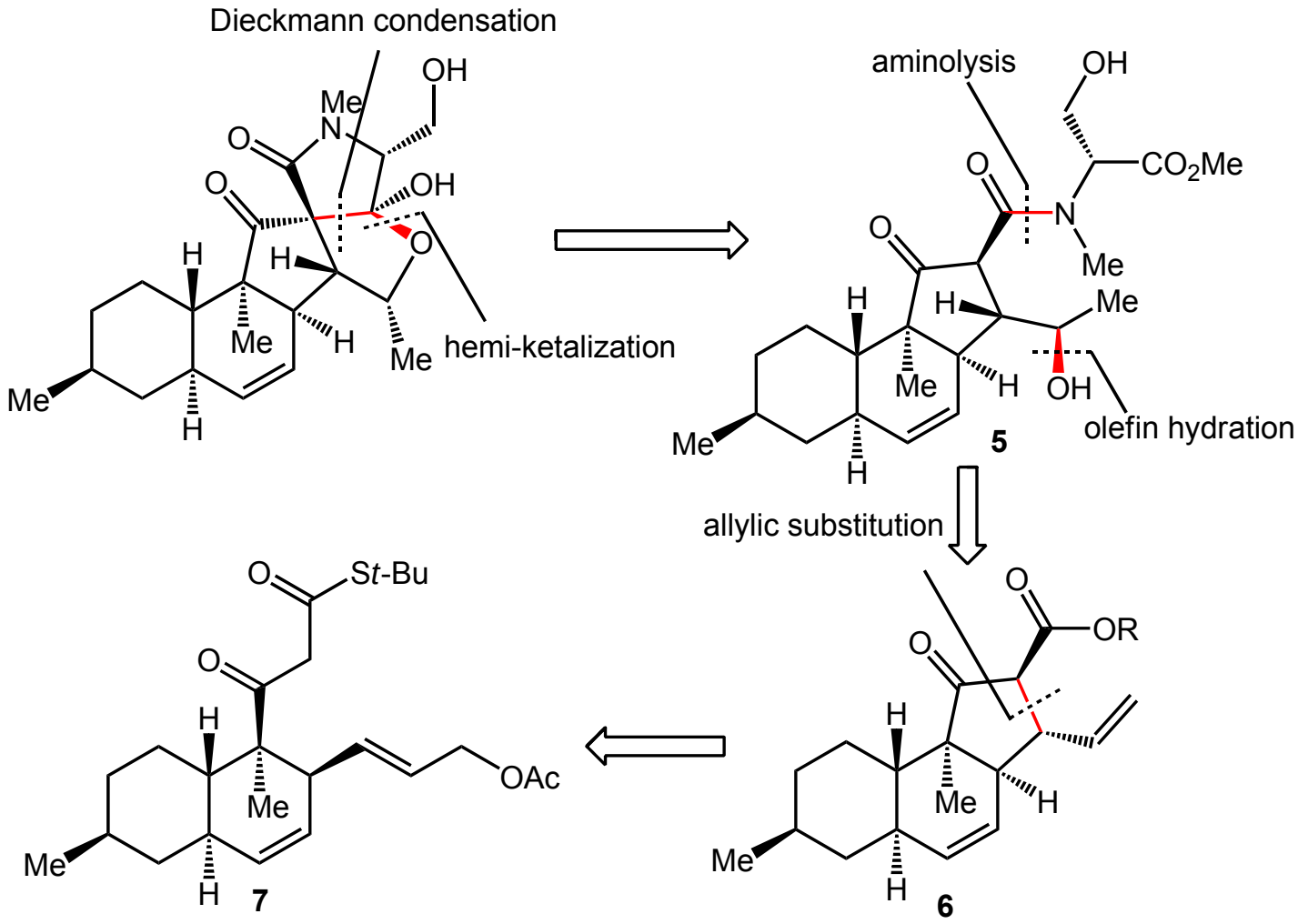
revised structure of fusarisetin A

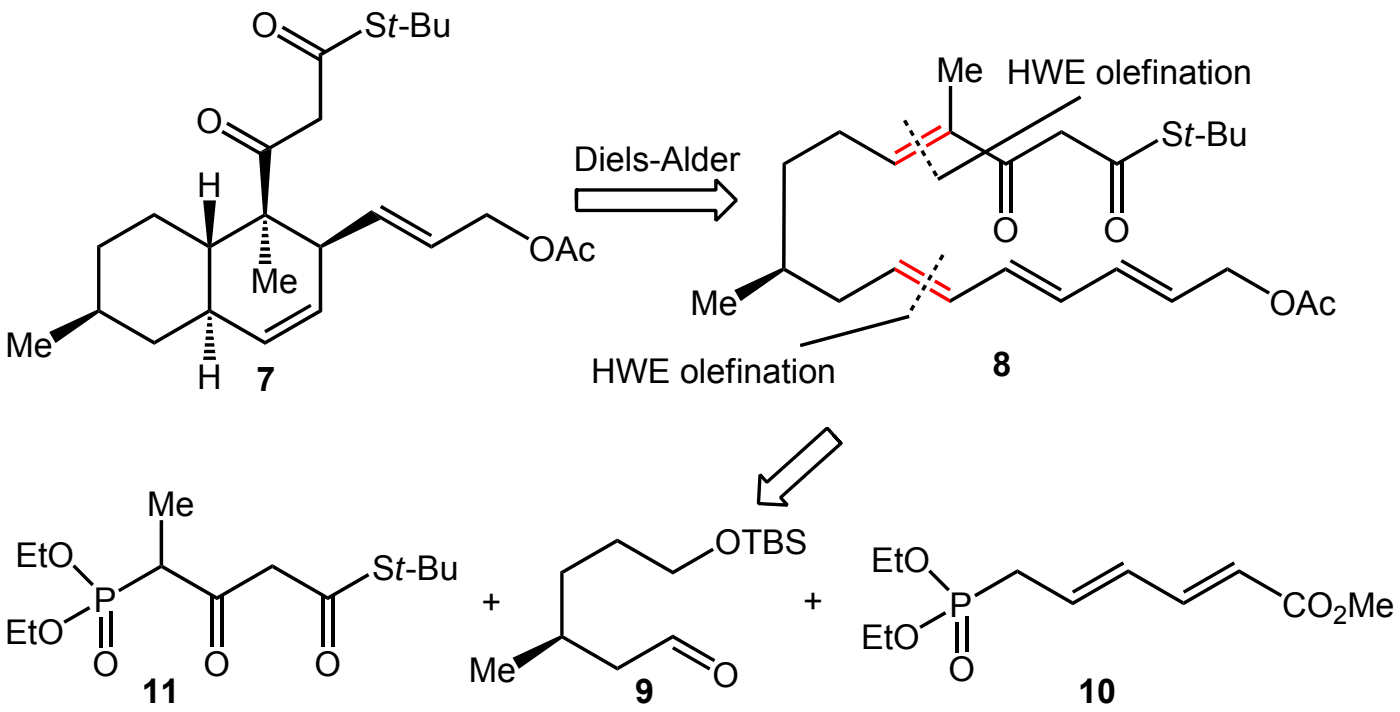


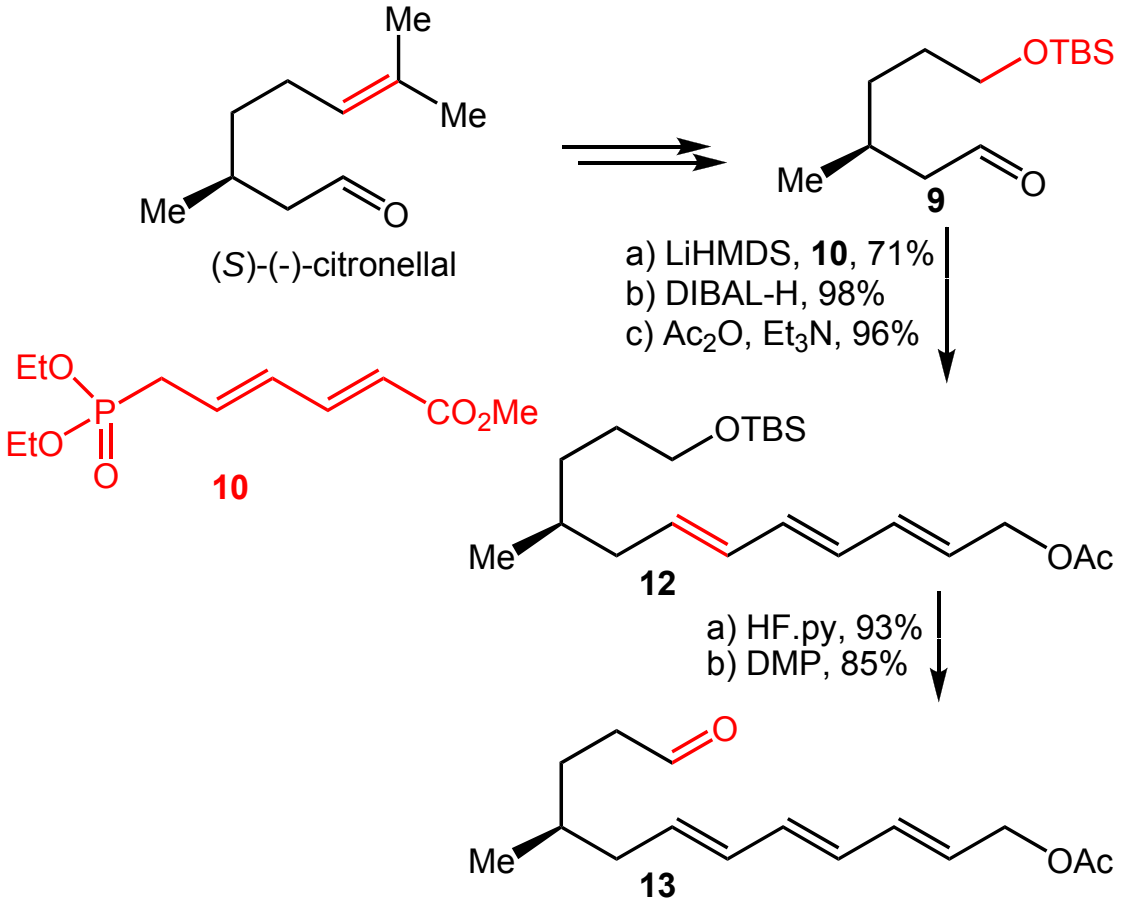


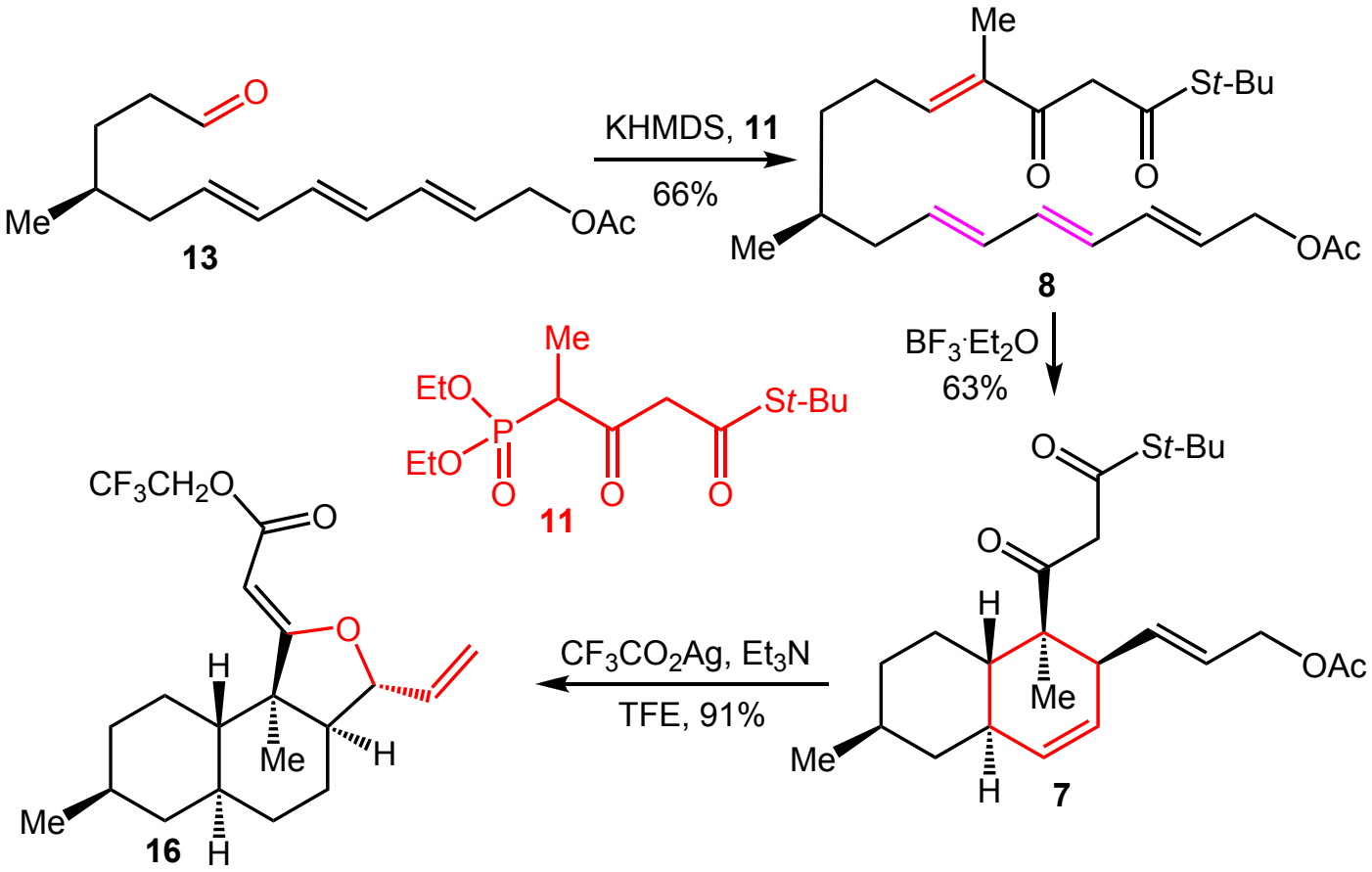


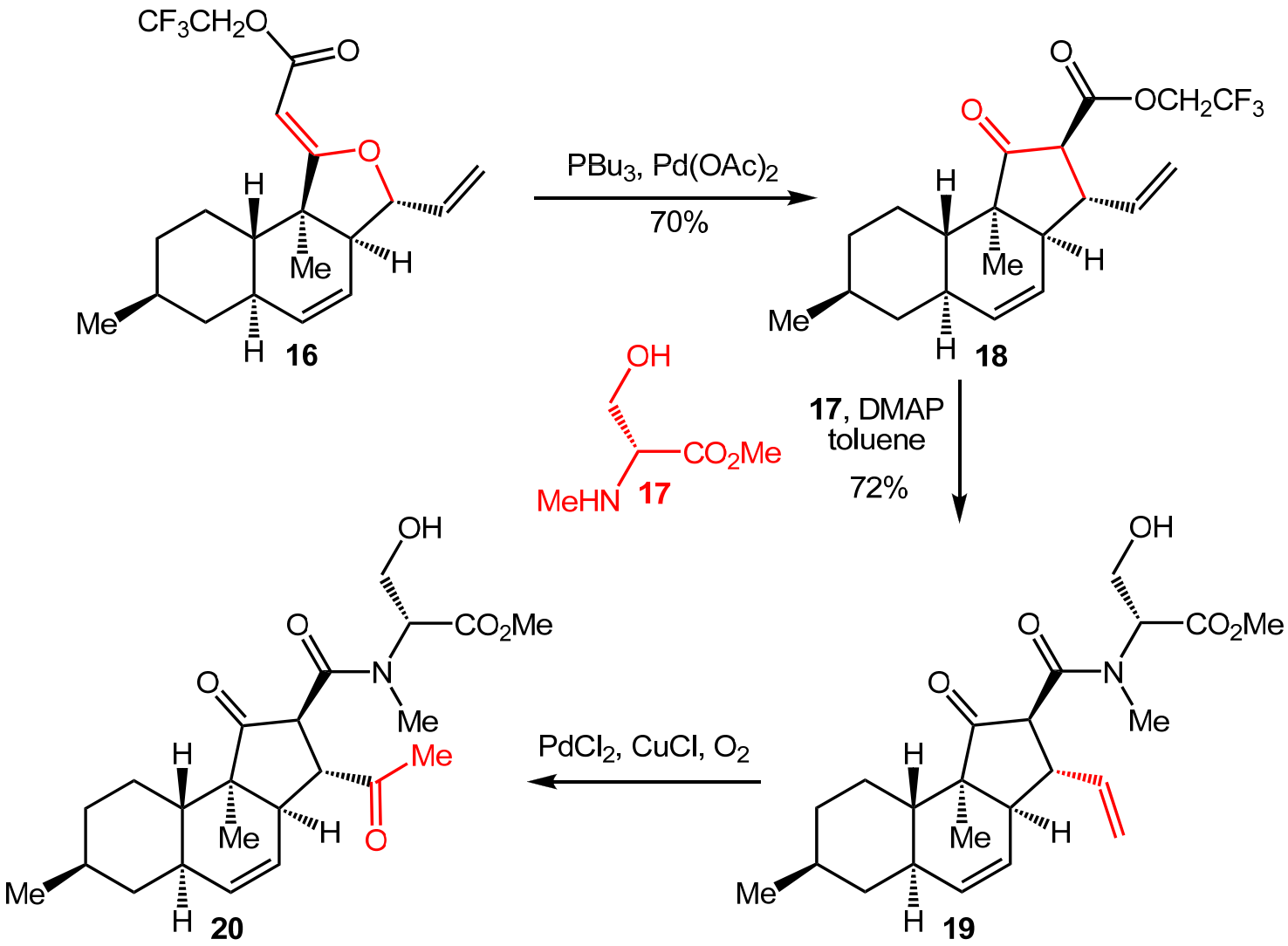
Retrosynthetic analysis of fusarisetin (**1**)

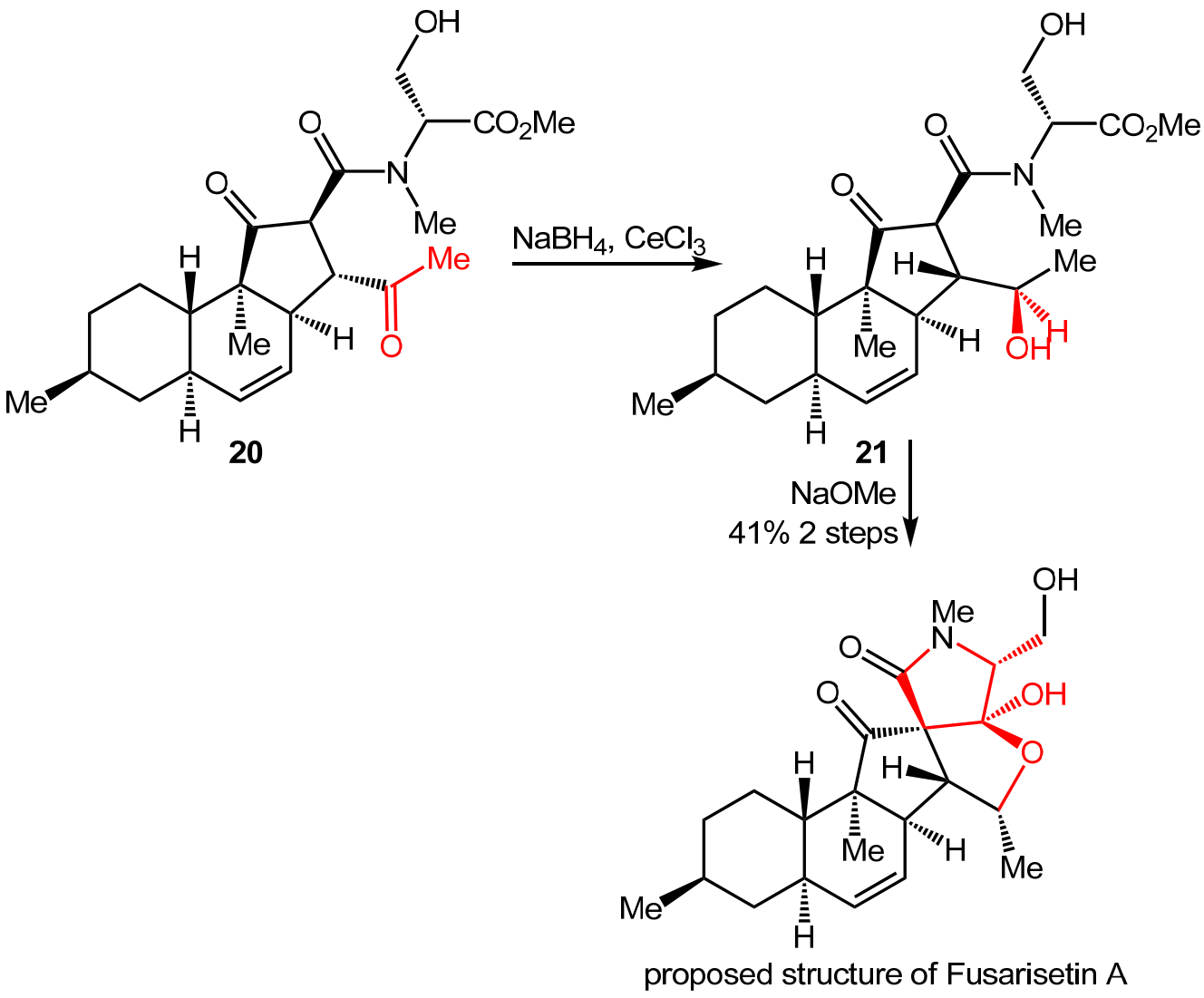


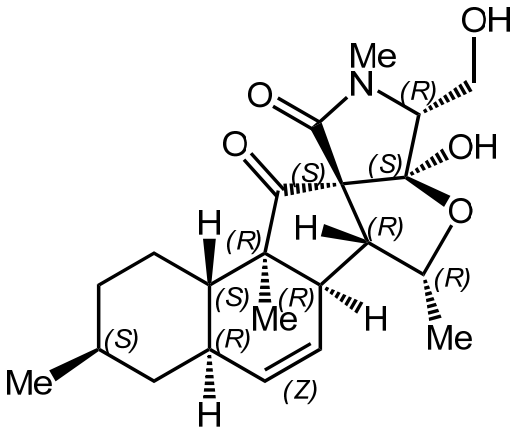

O
St-Bu
O
H
Me
OAc
Me
H
7
Diels-Alder
Me
HWE olefination
St-Bu
O
O
Me
OAc
HWE olefination
8
Me
EtO
P
EtO
O
St-Bu
O
O
11
+
OTBS
Me
O
9
+
EtO
P
EtO
O
CO2Me
10

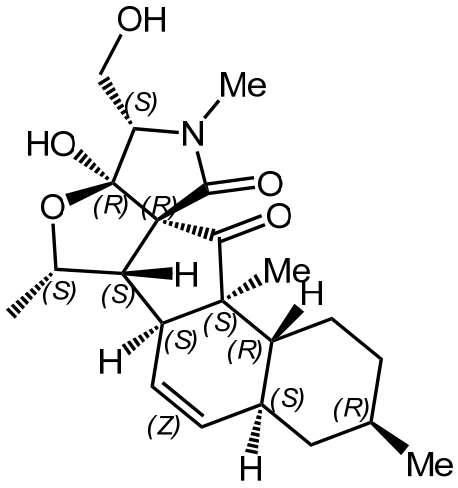

Me
Me
Me
O
(S)-(-)-citronellal
OTBS
Me
O
9
a) LiHMDS, 10, 71%
b) DIBAL-H, 98%
c) Ac2O, Et3N, 96%
EtO
P
EtO
O
CO2Me
10
OTBS
Me
OAc
12
a) HF.py, 93%
b) DMP, 85%
O
Me
OAc
13


Me
O
OAc
13
KHMDS, 11
66%
Me
St-Bu
O
O
Me
OAc
8
BF3·Et2O
63%
Me
EtO
EtO
P
O
St-Bu
O
O
11
O
St-Bu
O
H
Me
Me
H
OAc
7
CF3CO2Ag, Et3N
TFE, 91%
CF3CH2O
O
O
H
Me
H
Me
H
16


CF3CH2O
O
O
H
Me
H
Me
H
16
PBu3, Pd(OAc)2
70%
O
OCH2CF3
O
H
Me
H
Me
H
18
OH
CO2Me
MeHN
17
17, DMAP
toluene
72%
OH
CO2Me
O
N
Me
O
H
Me
H
Me
19
PdCl2, CuCl, O2
OH
CO2Me
O
N
Me
O
Me
H
Me
H
Me
H
20


OH
CO2Me
O
N
Me
O
O
Me
H
Me
H
H
Me
20
NaBH4, CeCl3
OH
CO2Me
O
N
Me
O
H
H
Me
Me
H
OH
H
Me
H
21
NaOMe
41% 2 steps
OH
Me
N
O
O
OH
O
H
H
Me
H
Me
Me
H
proposed structure of Fusarisetin A



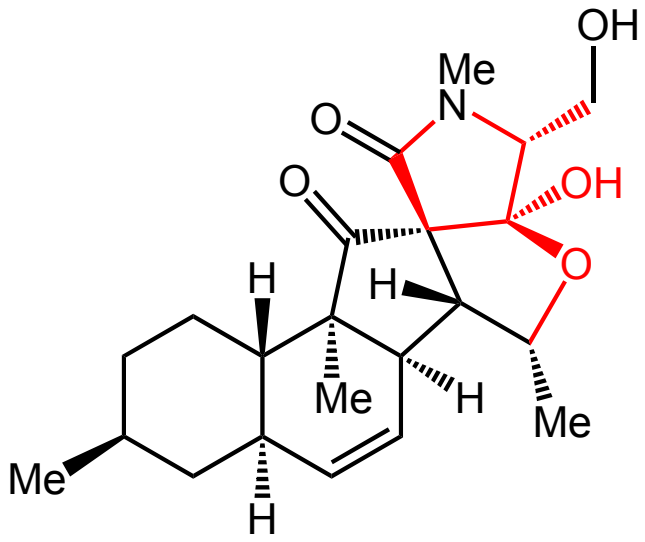


revised structure
of **fusarisetin A**

$[\alpha]^{25}_{D}$ = -88.0 (*c* = 0.15 in MeOH)

$[\alpha]^{25}_{D}$ = +84.6 (*c* = 0.2 in MeOH)

总结:



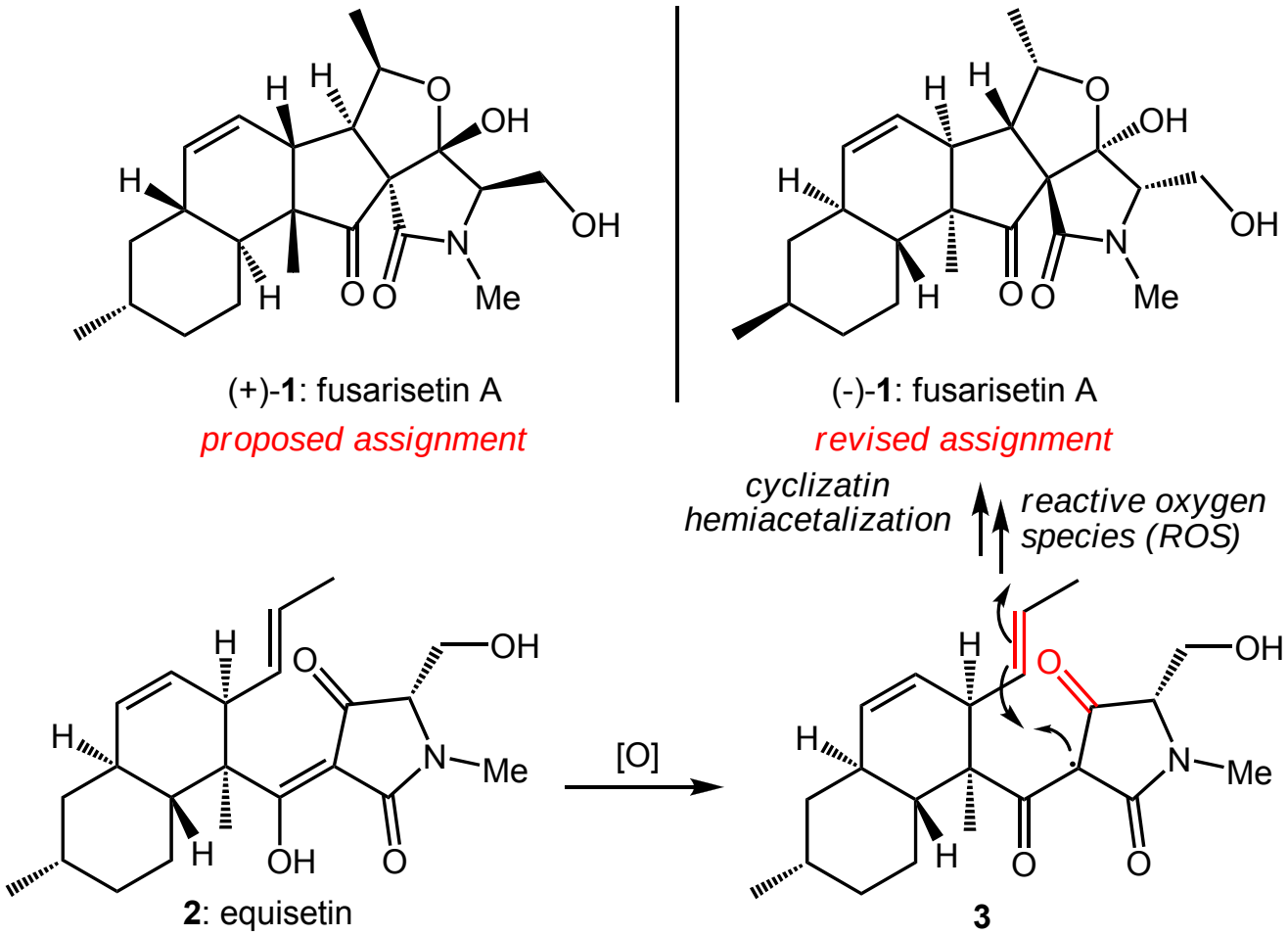
1, **13 steps.**

2, **Lewis Acid-promoted intramolecular Diels-Alder reaction.**

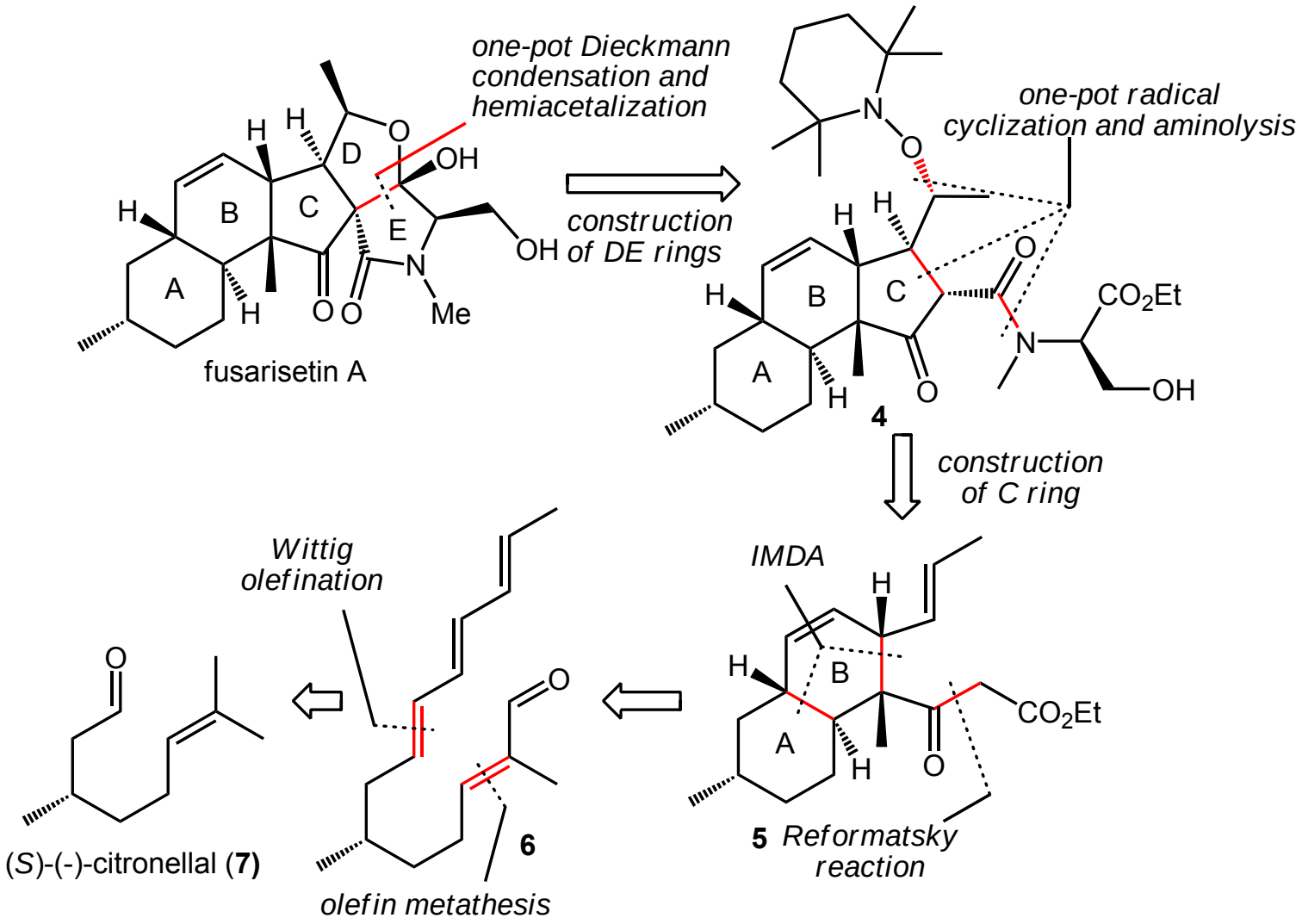
3, **Pd-catalyzed O to C allylic rearrangement.**

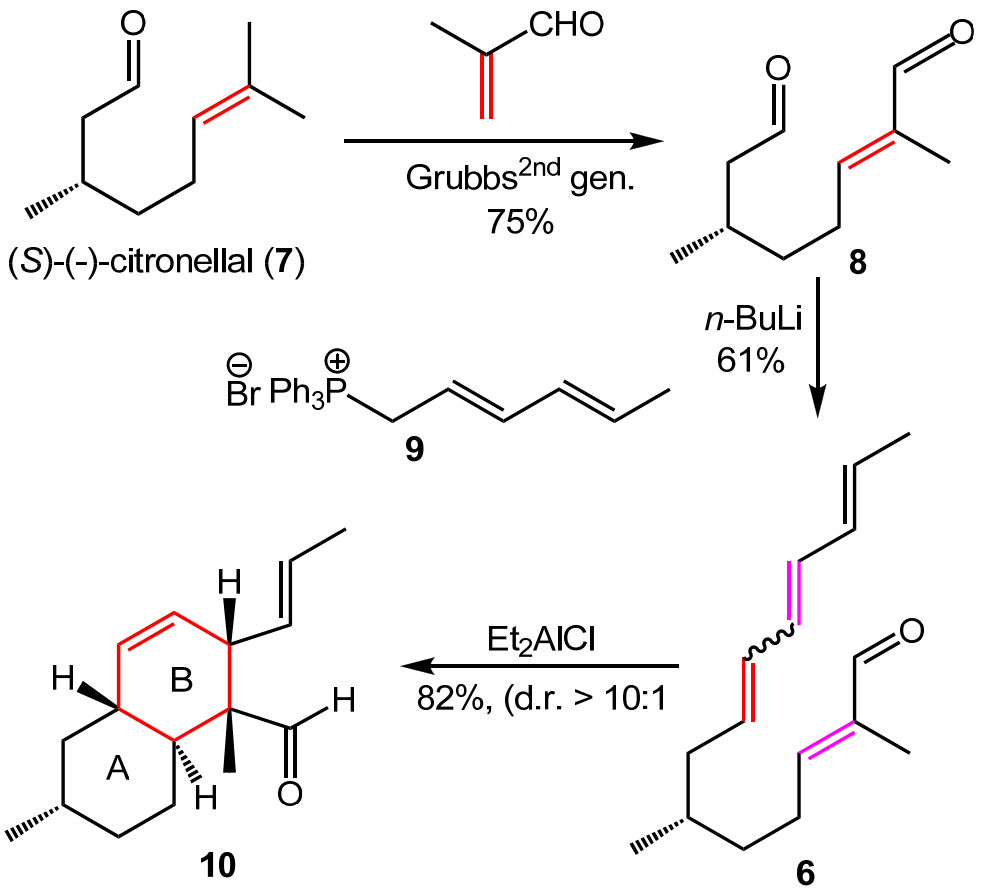
4, **Wacker oxidation.**

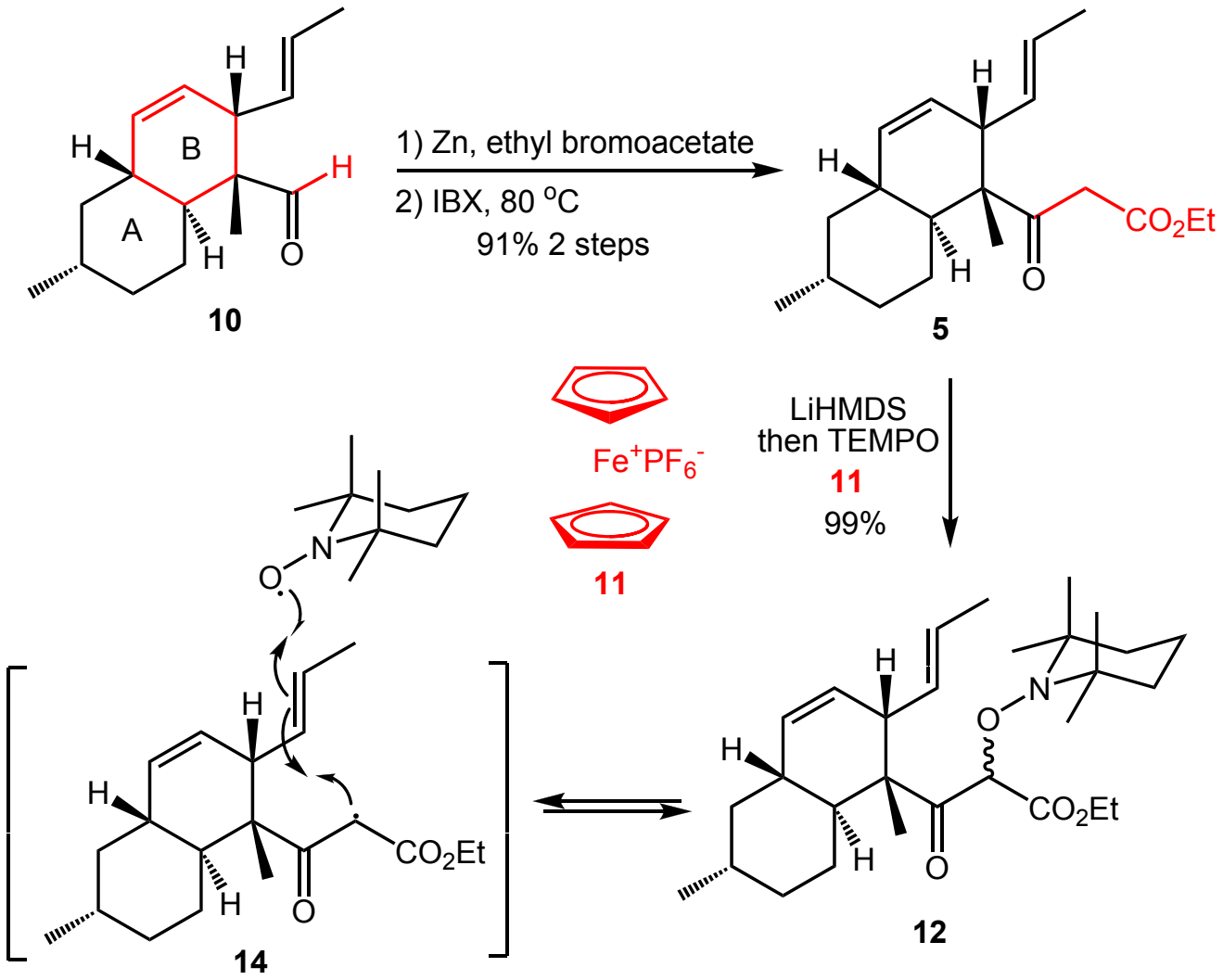
5, **Dieckmann condensation/hemiketalization cascade.**

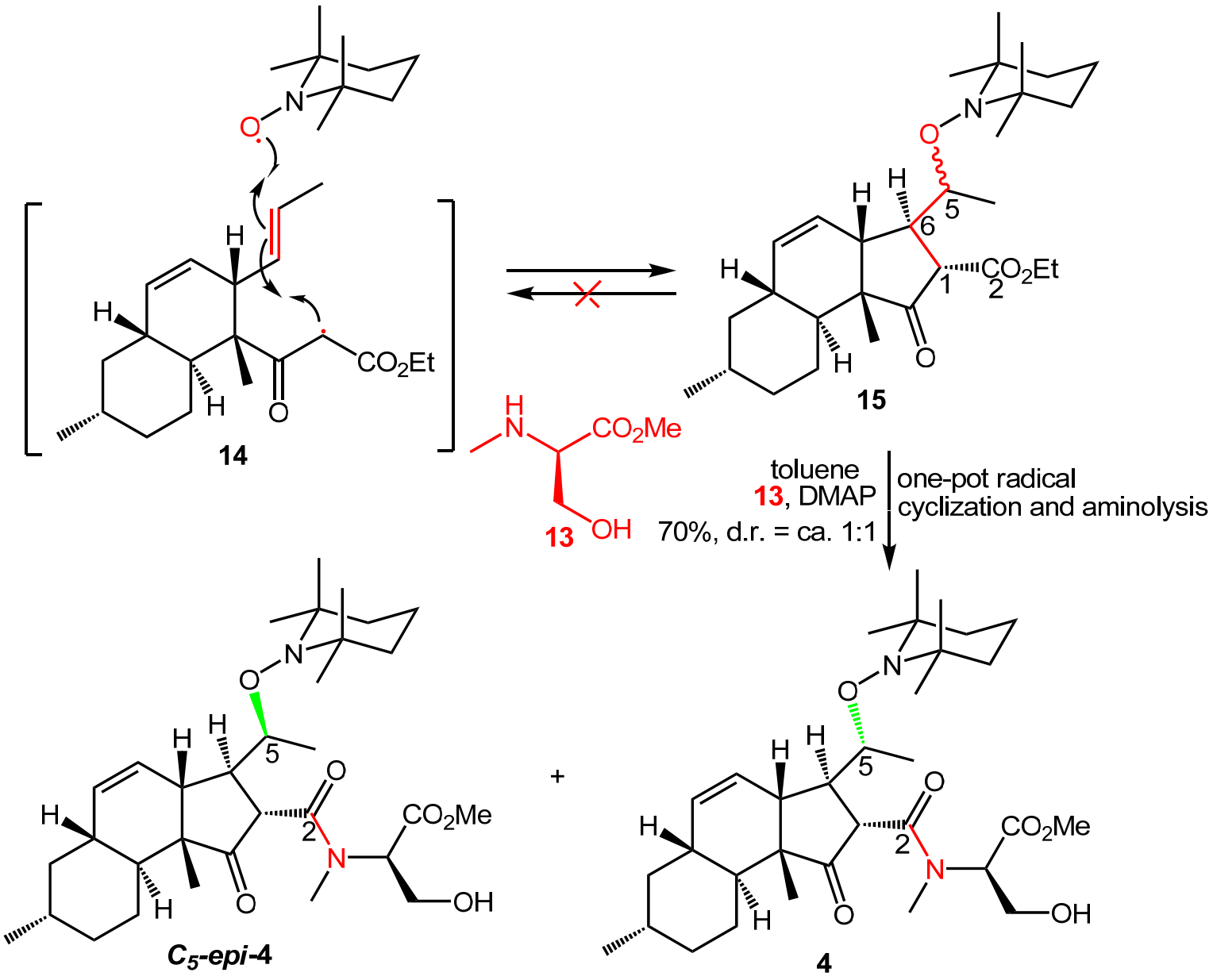


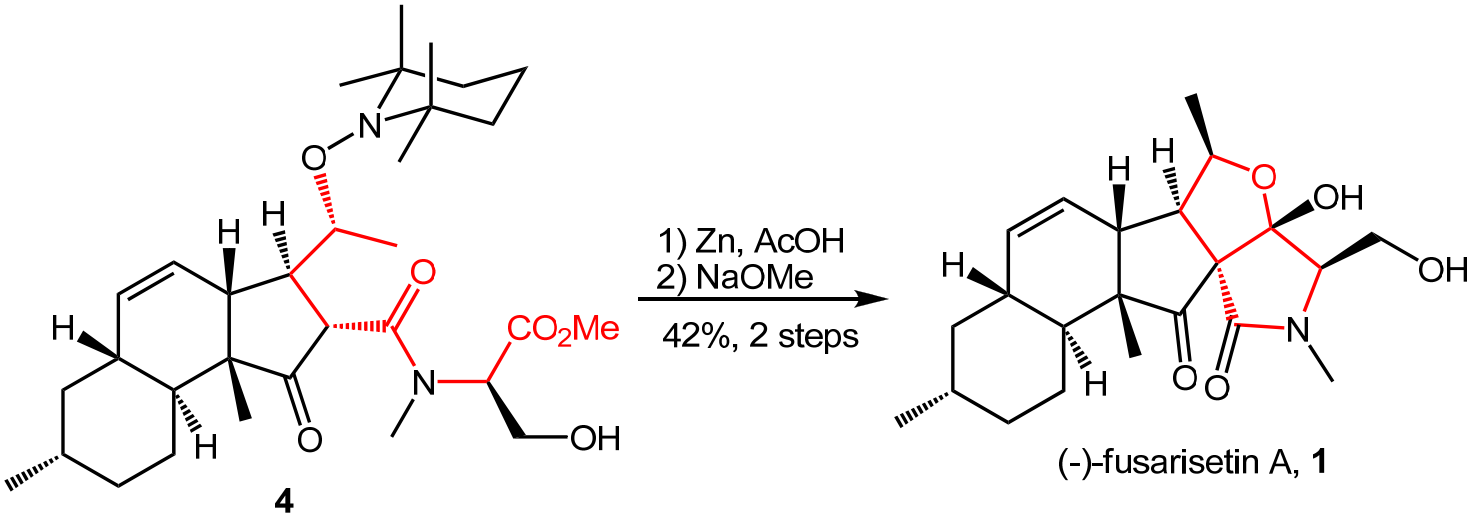
Emmanuel A. Theodorakis* *et al*. *J. Am. Chem. Soc*. **2012**, *134*, 5075−5075.


one-pot Dieckmann condensation and hemiacetalization
fusarisetin A
construction of DE rings
one-pot radical cyclization and aminolysis
4
construction of C ring
IMDA
5 Reformatsky reaction
Wittig olefination
6
olefin metathesis
(S)-(-)-citronellal (7)

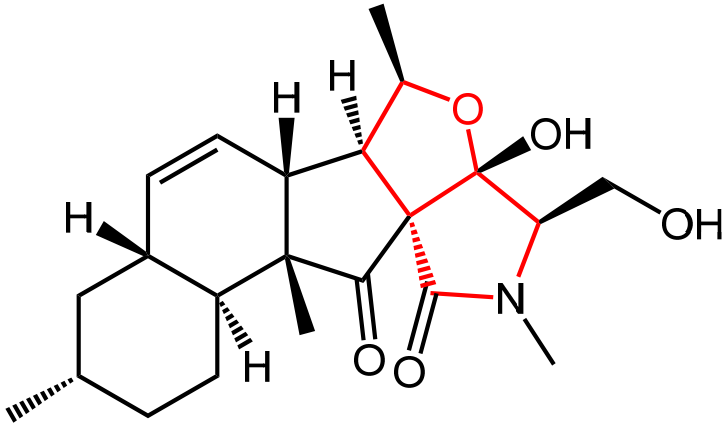

O
CHO
Grubbs2nd gen.
75%
(S)-(-)-citronellal (7)
O
O
8
n-BuLi
61%
Br Ph3P
9
Et2AlCl
82%, (d.r. > 10:1
H
B
A
H
H
O
10
O
6


H
B
H
A
H
O
10
1) Zn, ethyl bromoacetate
2) IBX, 80 °C
91% 2 steps
H
H
CO2Et
O
H
5
Fe+PF6-
11
LiHMDS
then TEMPO
11
99%
N
O
H
H
CO2Et
O
14
H
N
O
H
CO2Et
O
H
12


14
15
13
toluene
13, DMAP
70%, d.r. = ca. 1:1
one-pot radical
cyclization and aminolysis
C5-epi-4
4


1) Zn, AcOH
2) NaOMe
42%, 2 steps
(-)-fusarisetin A, 1
4

总结:



(-)-fusarisetin A, **1**

1, **9 steps, 10% (overall yield).**

2, **Protecting group-free.**

3, **Lewis Acid-promoted intramolecular Diels-Alder reaction.**

4, **One-pot TEMPO-induced radical cyclization/aminolysis.**

Natural products serve as an abundant source in the search for anticancer agents due to unparalleled structural diversity and accompanying molecular modes of action. Recently, small molecules that inhibit cancer cell metastasis have received increasing interest in related drug discovery process, because such action may complement that of existing anticancer drugs such as the tubulin stabilizers/destabilizers and topoisomerase inhibitors. In May 2011, Ahn et al. reported the isolation of a biologically intriguing natural product, fusarisetin from a soil fungus, **Fusarium sp. FN080326**, which displays significant inhibition of acinar morphogenesis as well as cell migration and invasion without apparent cytotoxicity. The mechanism of action remains to be elucidated. The molecular structure of **1** was determined by employing X-ray crystallographic analysis (relative stereochemistry) and the exciton chirality circular dichroism method (absolute configuration). From a structural perspective, **1** exhibits a 6,6,5,5,5-fused pentacyclic ring system bearing 10 stereogenic centers. The interesting chemical structure as well as biological activity of **fusarisetin A** made it an attractive target for total synthesis. Herein, we report the first total synthesis of the proposed structure of this molecule.

In conclusion, we developed an efficient synthetic strategy for the total synthesis of the enantiomer of fusarisetin A, a newly discovered acinar morphogenesis inhibitor possessing an intricate structure, and reassigned the absolute configuration of the natural product through our synthesis. The synthesis featured an intramolecular Diels−Alder reaction, a Pd-mediated O→C allylic rearrangement, a chemoselective Wacker oxidation, and a Dieckmann condensation/hemiketalization cascade. The reported synthetic strategy and methods are expected to be applicable to the construction of other structurally or biosynthetically related natural products, as well as designed analogues of fusarisetin A, and thus to facilitate the exploration of its mechanism of action on a molecular level.