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Communication

Enantioselective Total Synthesis of Cotylenin A

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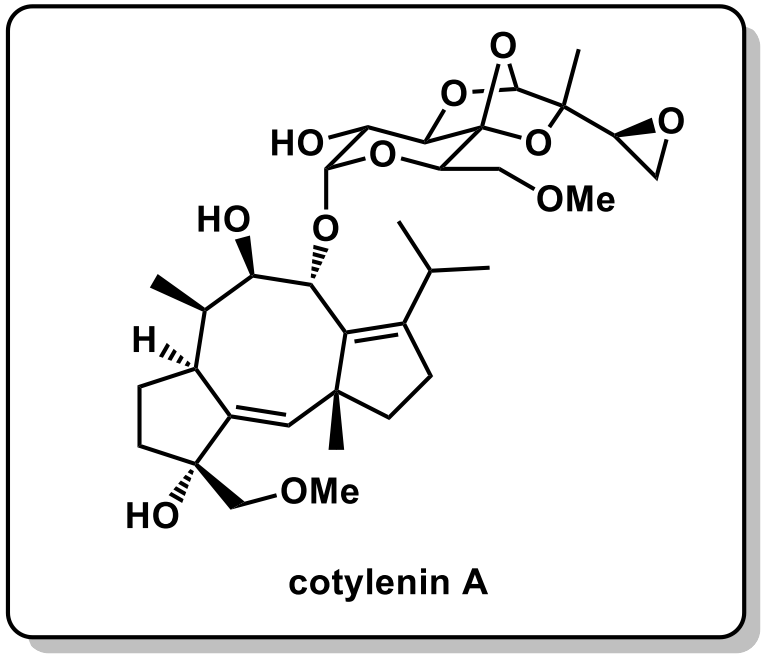
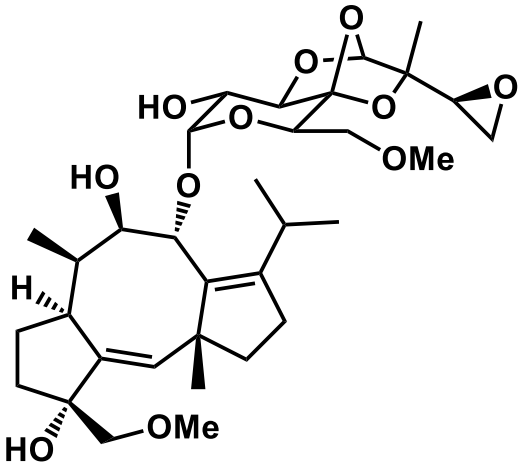


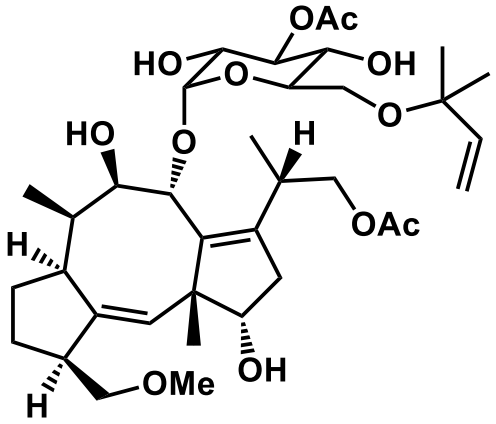
cotylenin A

J. Am. Chem. Soc. **2020**, *142*, 5556-5561.

- *Isolated as a plant growth regulator in 1970*
- *Induce the differentiation of murine and human myeloid leukemia cells*
- *Induce the apoptosis of a wide range of human cancer cell lines*

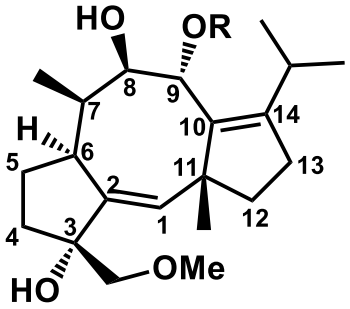


cotylenin A



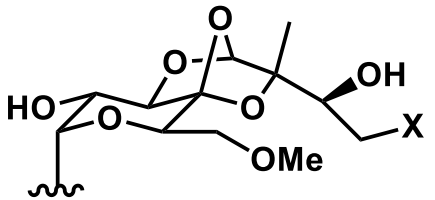
fusicoccin A

- *Fused 5-8-5 ring system*
- *All-carbon quaternary stereogenic center*
- *Acid-sensitive chiral allylic tertiary alcohol*
- *Trans-1,2-diol*
- *Structurally unique glucose-fused trioxabicyclo[2.2.1]hep tane*



cotylenol (R = H)

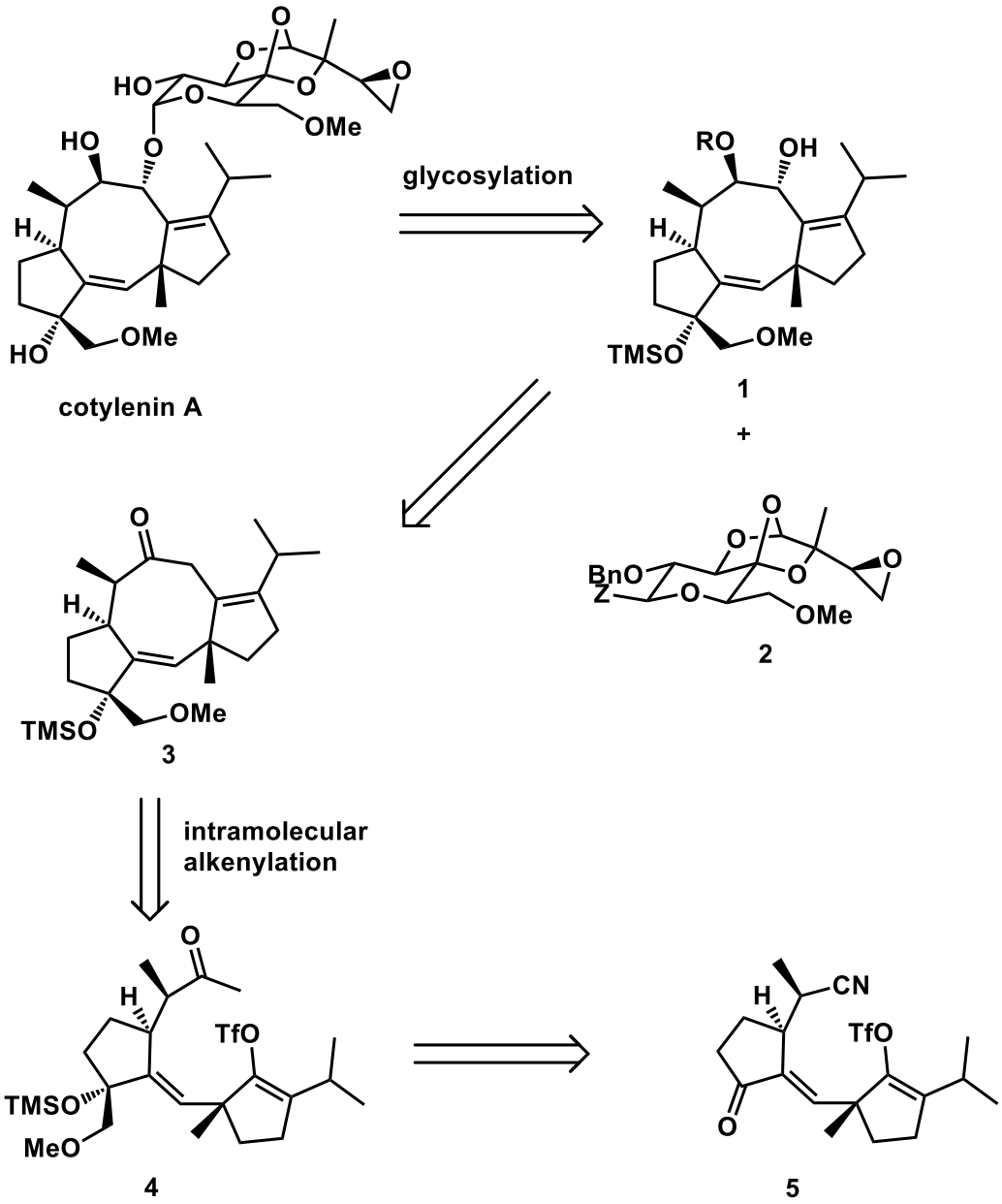
R =

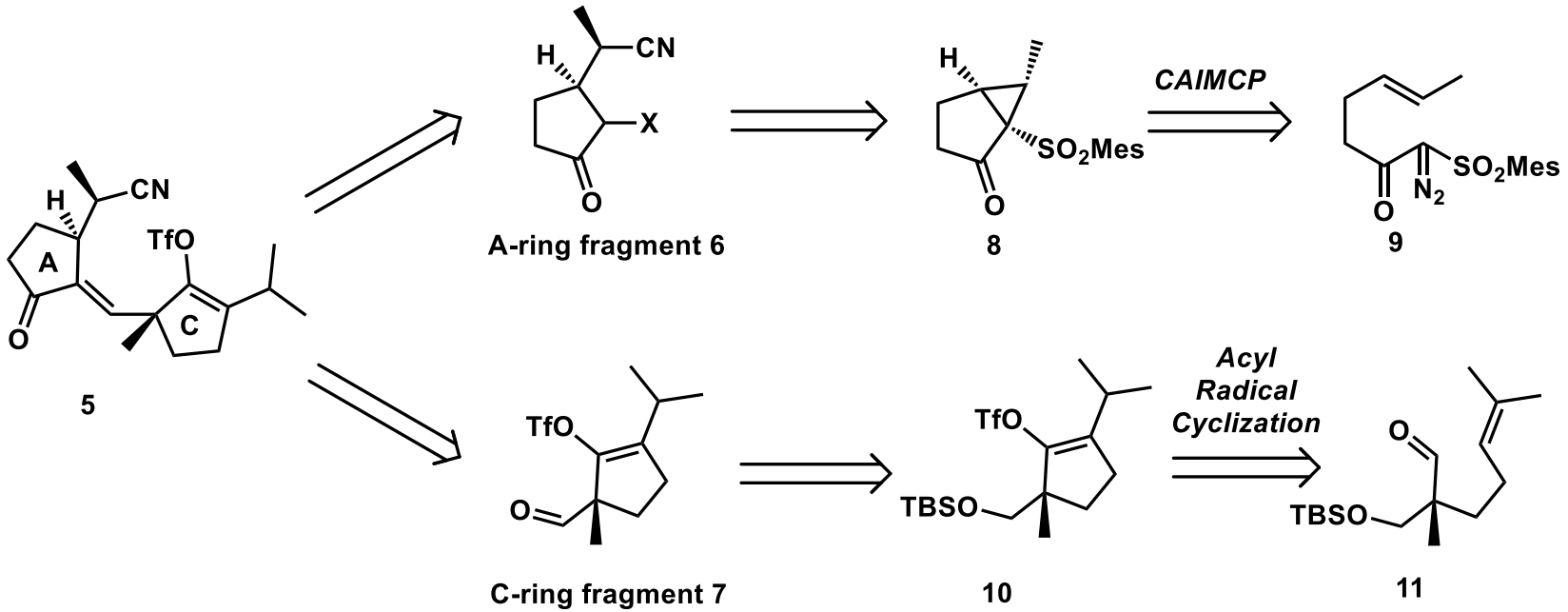


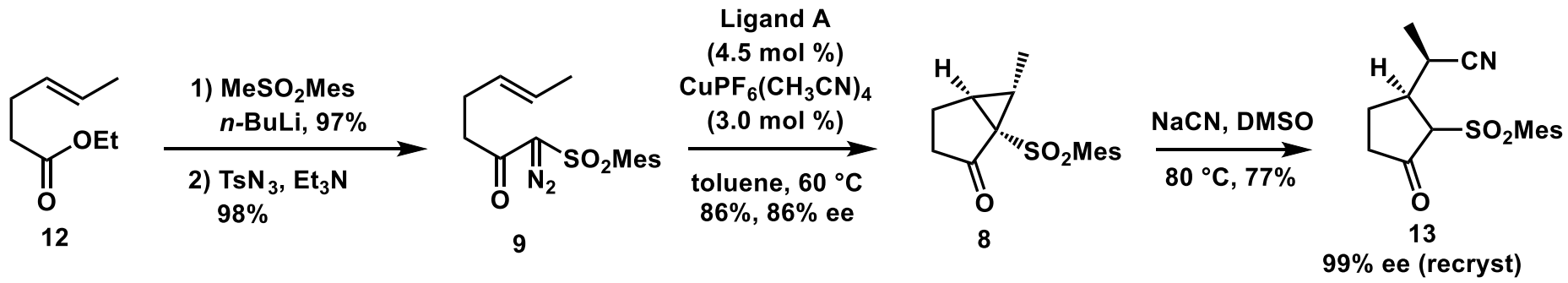
cotylenin B (X = Cl)
cotylenin D (X = OH)

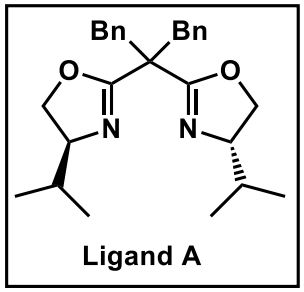
Figure 1. Structures of cotylenin A, B, and D, cotylenol, and fusicoccin A

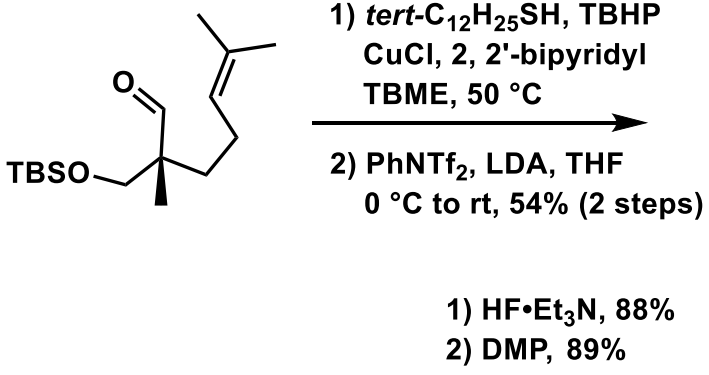
Retrosynthetic Analysis of Cotylenin A

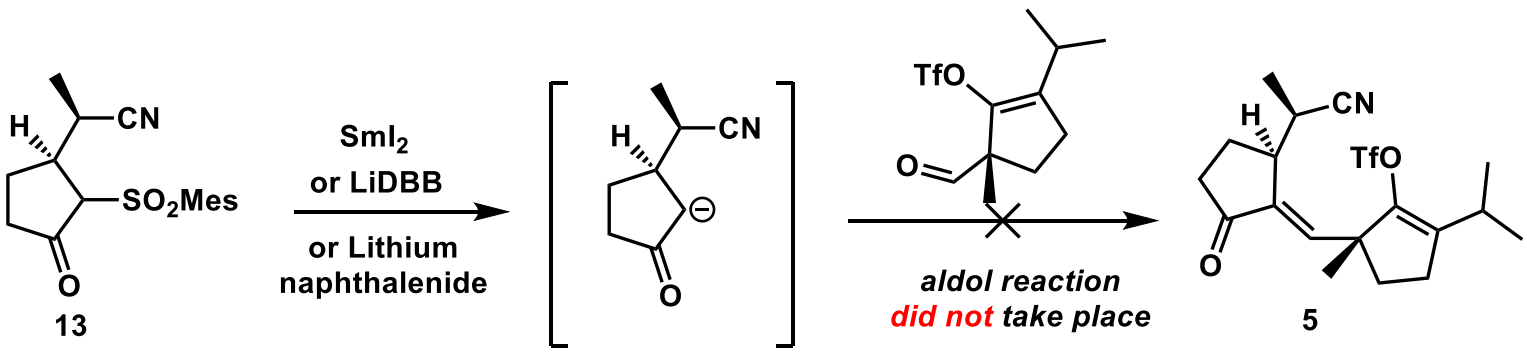


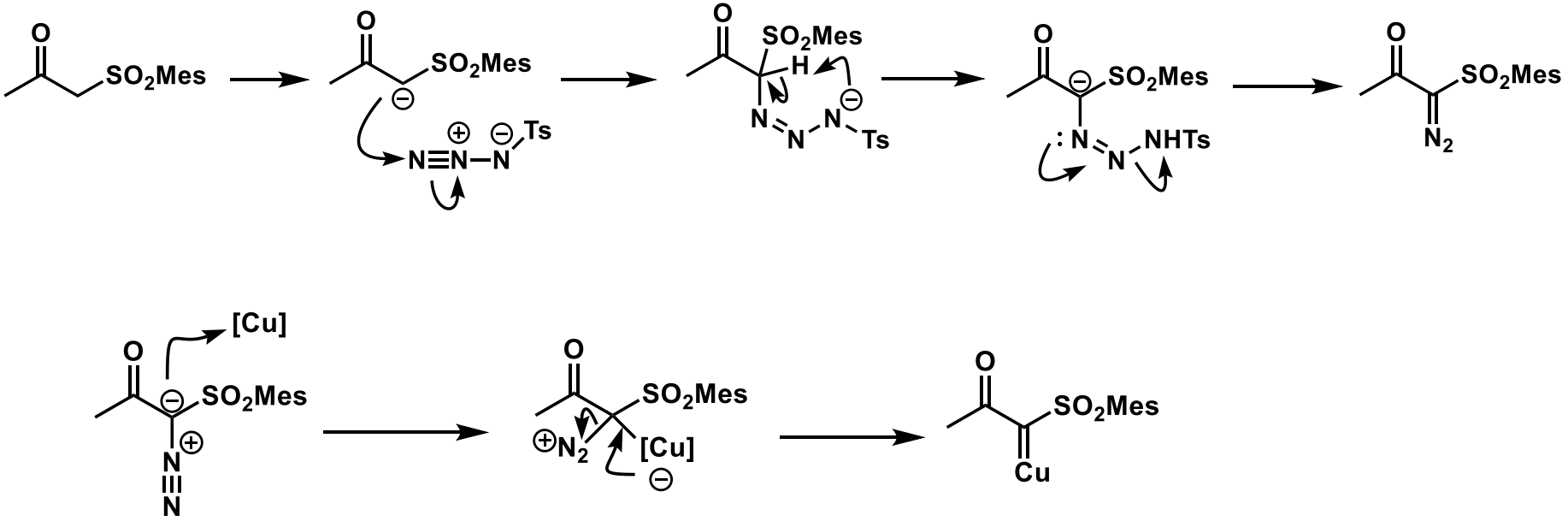

H
CN
TfO
A
C
O
5
H
CN
X
O
A-ring fragment 6
H
SO2Mes
O
8
CAIMCP
SO2Mes
N2
O
9
TfO
O
C-ring fragment 7
TfO
TBSO
10
Acyl
Radical
Cyclization
O
TBSO
11

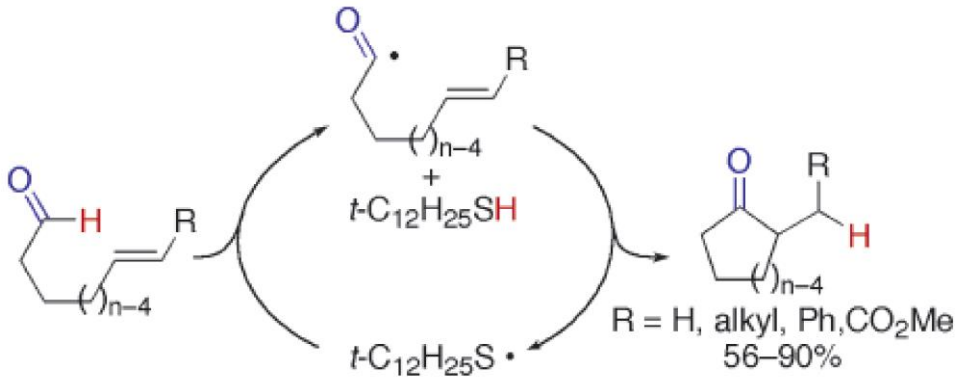

OEt
O
12
1) MeSO2Mes
n-BuLi, 97%
2) TsN3, Et3N
98%
SO2Mes
N2
9
Ligand A
(4.5 mol %)
CuPF6(CH3CN)4
(3.0 mol %)
toluene, 60 °C
86%, 86% ee
H
SO2Mes
8
NaCN, DMSO
80 °C, 77%
CN
13
99% ee (recryst)


Bn
Bn
O
N
Ligand A

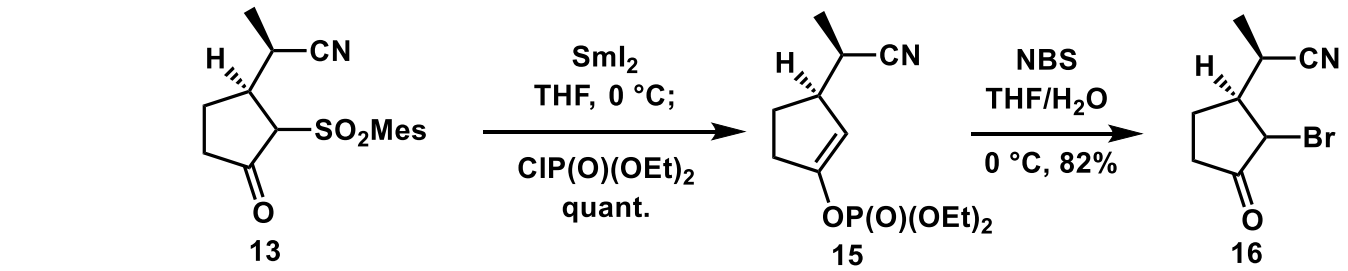

TBSO
1) tert-C12H25SH, TBHP
CuCl, 2, 2'-bipyridyl
TBME, 50 °C
2) PhNTf2, LDA, THF
0 °C to rt, 54% (2 steps)
TfO
R
1) HF•Et3N, 88%
2) DMP, 89%
14 (R = CH2OTBS)
7 (R = CHO)

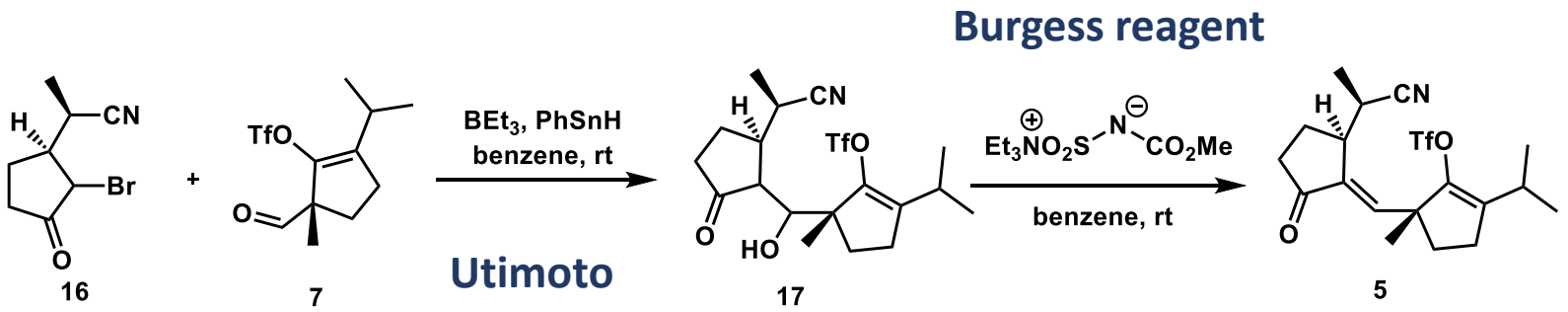

13
SmI2
or LiDBB
or Lithium
naphthalenide
TfO
aldol reaction
did not take place
5

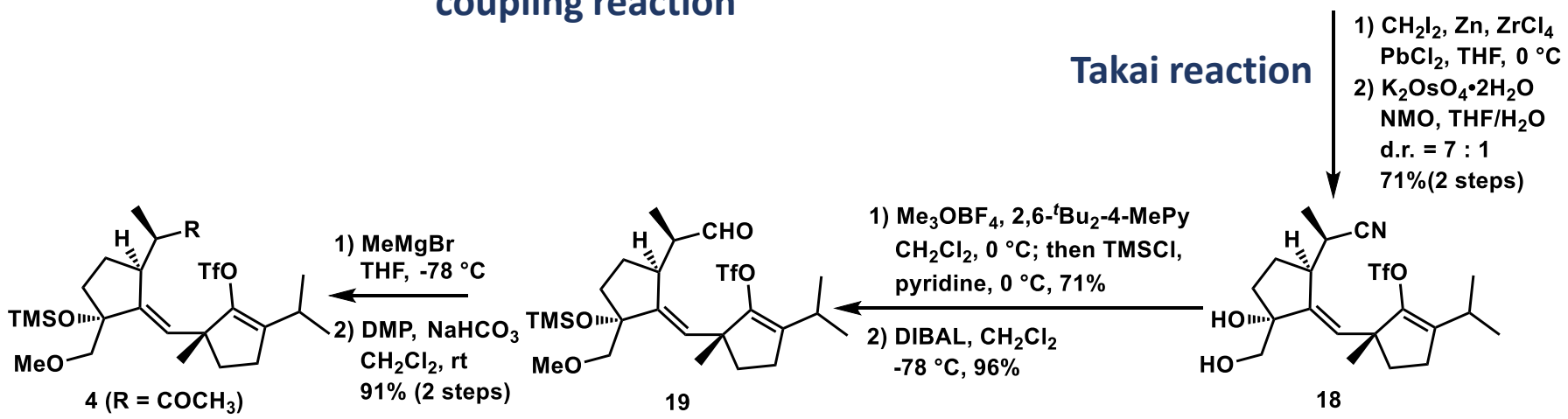




J. Org. Chem. **2005**, *70*, 681.

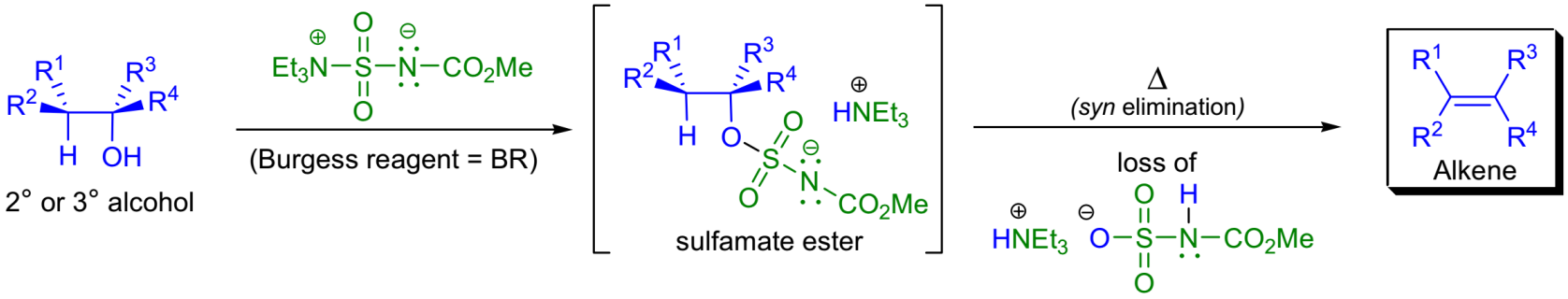

SmI2
THF, 0 °C;
ClP(O)(OEt)2
quant.
NBS
THF/H2O
0 °C, 82%
13
15
16


Burgess reagent
BEt3, PhSnH
benzene, rt
benzene, rt
16
7
17
5
Utimoto
coupling reaction

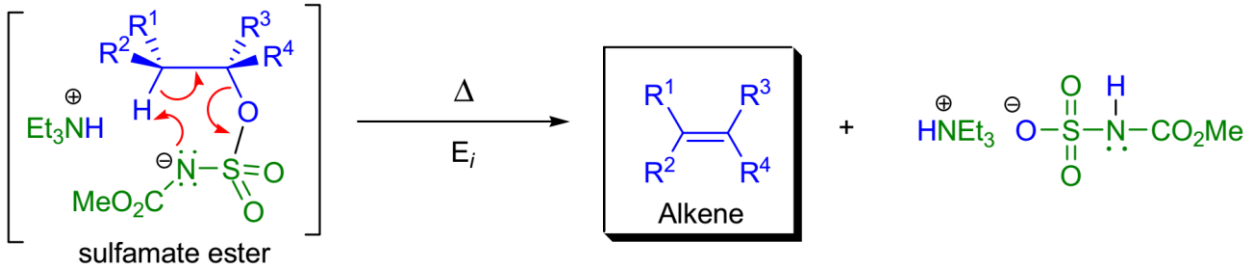

Takai reaction
1) CH2I2, Zn, ZrCl4
PbCl2, THF, 0 °C
2) K2OsO4•2H2O
NMO, THF/H2O
d.r. = 7 : 1
71%(2 steps)
1) Me3OBF4, 2,6-tBu2-4-MePy
CH2Cl2, 0 °C; then TMSCl,
pyridine, 0 °C, 71%
2) DIBAL, CH2Cl2
-78 °C, 96%
1) MeMgBr
THF, -78 °C
2) DMP, NaHCO3
CH2Cl2, rt
91% (2 steps)
4 (R = COCH3)
19
18

BURGESS DEHYDRATION REACTION

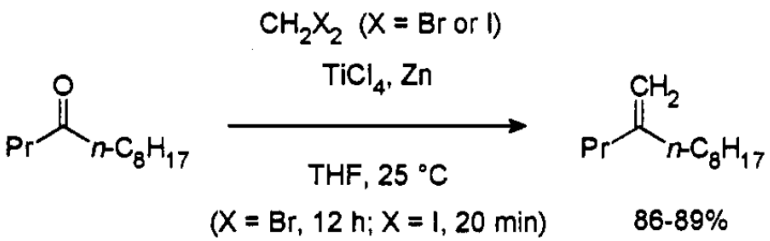
(References are on page 556)



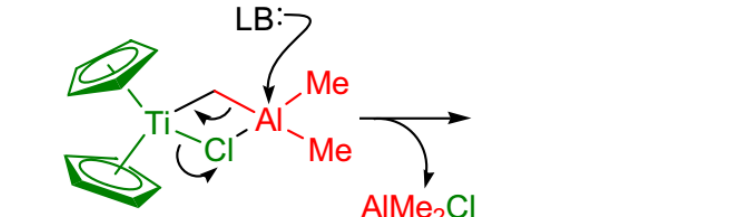
Mechanism:

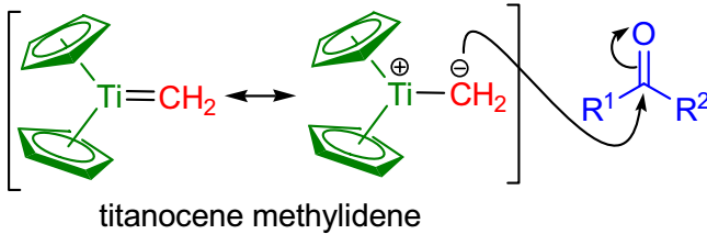


Takai Reaction

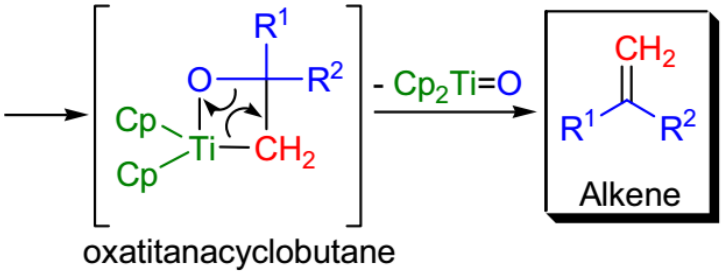


Tebbe Olefination

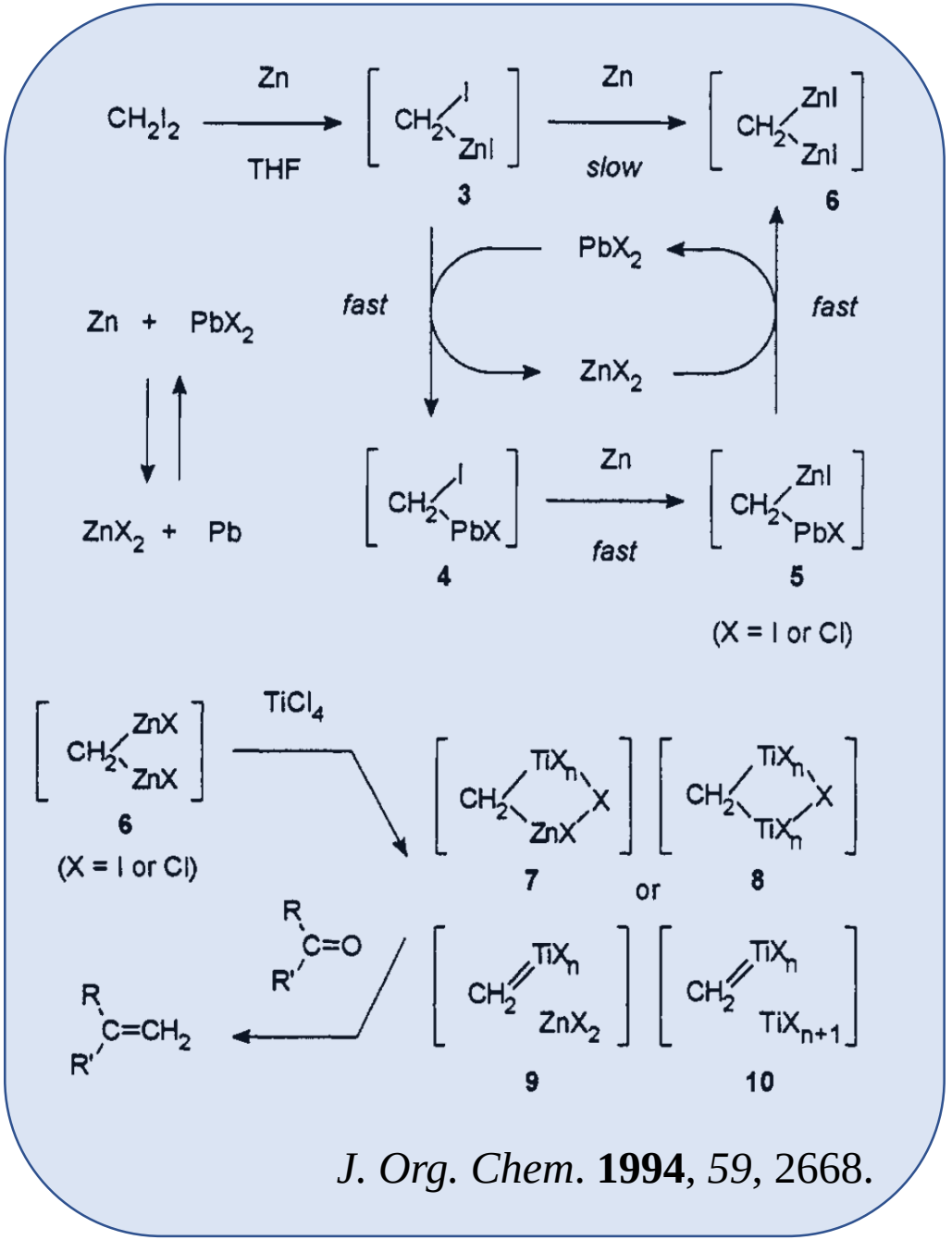




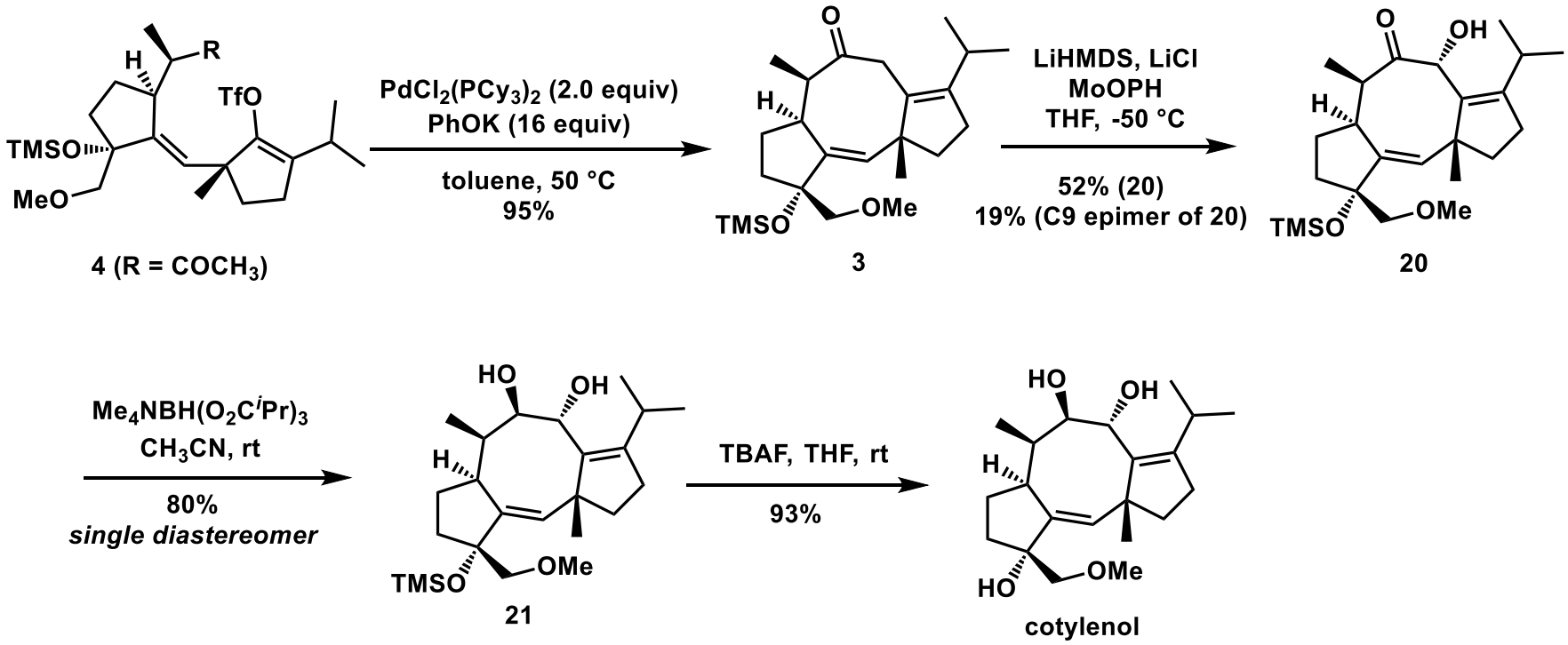
titanocene methylidene

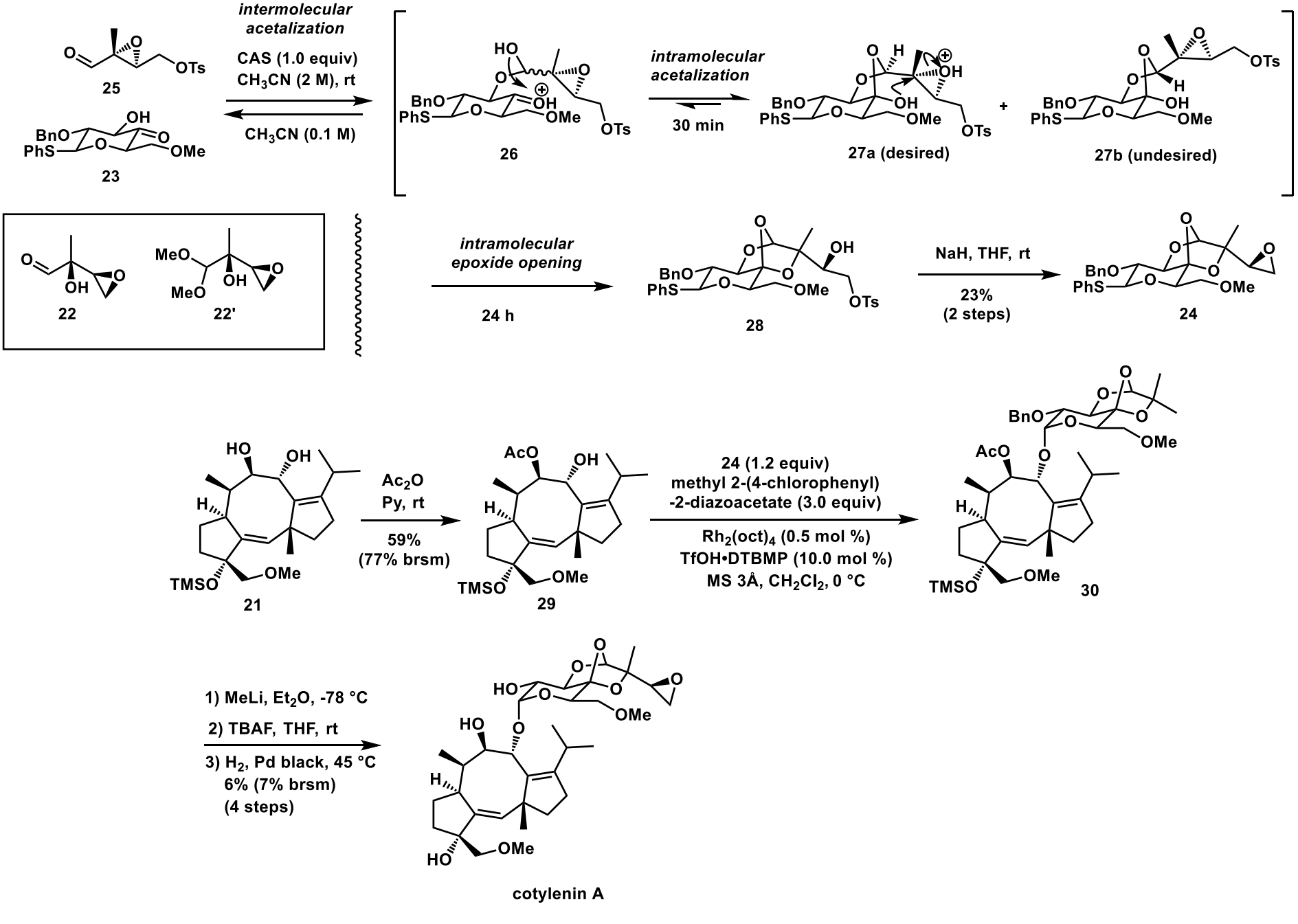


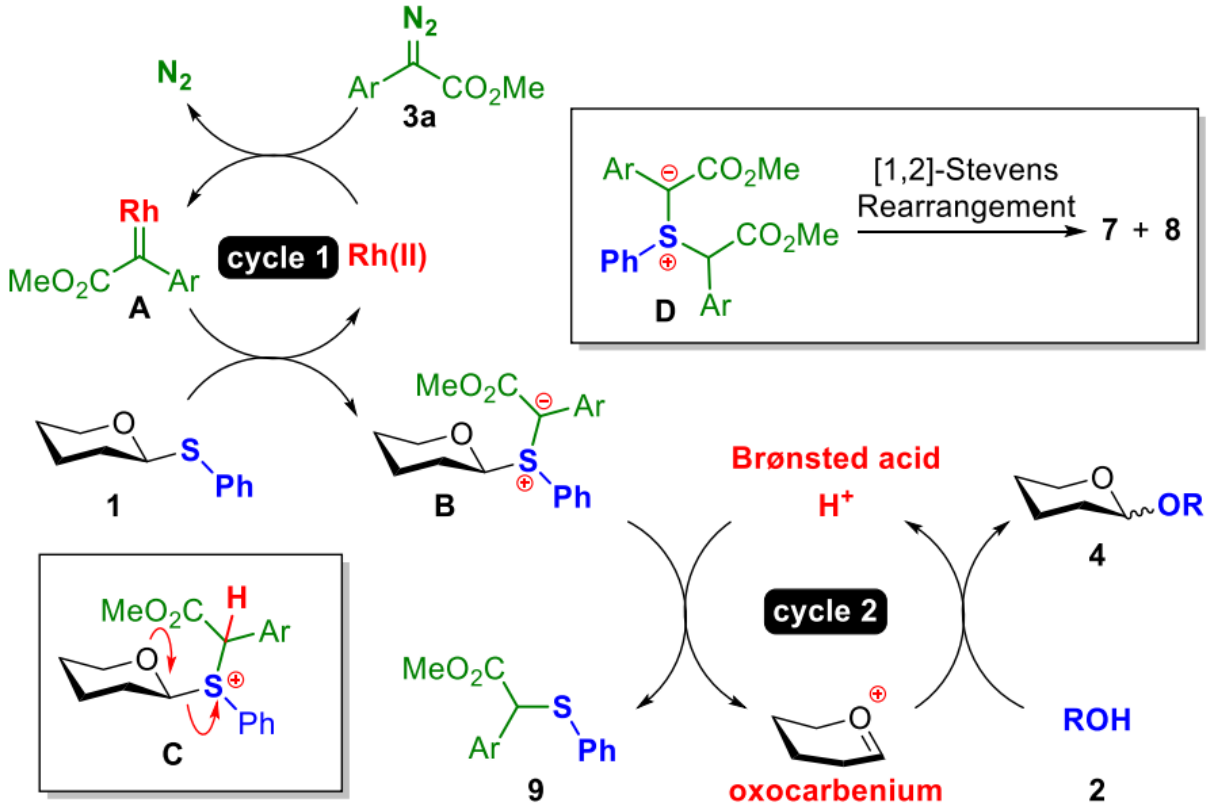
oxatitanacyclobutane



J. Org. Chem. **1994**, *59*, 2668.


H
R
TfO
TMSO
MeO
4 (R = COCH3)
PdCl2(PCy3)2 (2.0 equiv)
PhOK (16 equiv)
toluene, 50 °C
95%
O
H
TMSO
OMe
3
LiHMDS, LiCl
MoOPH
THF, -50 °C
52% (20)
19% (C9 epimer of 20)
O
OH
H
TMSO
OMe
20
Me4NBH(O2CiPr)3
CH3CN, rt
80%
single diastereomer
HO
OH
H
TMSO
OMe
21
TBAF, THF, rt
93%
HO
OH
H
HO
OMe
cotylenol


intermolecular acetalization
CAS (1.0 equiv)
CH3CN (2 M), rt
CH3CN (0.1 M)
25
23
26
intramolecular acetalization
30 min
27a (desired)
27b (undesired)
22
22'
intramolecular epoxide opening
24 h
28
NaH, THF, rt
23%
(2 steps)
24
21
Ac2O
Py, rt
59%
(77% brsm)
29
24 (1.2 equiv)
methyl 2-(4-chlorophenyl)
-2-diazoacetate (3.0 equiv)
Rh2(oct)4 (0.5 mol %)
TfOH•DTBMP (10.0 mol %)
MS 3Å, CH2Cl2, 0 °C
30
1) MeLi, Et2O, -78 °C
2) TBAF, THF, rt
3) H2, Pd black, 45 °C
6% (7% brsm)
(4 steps)
cotylenin A



J. Am. Chem. Soc. **2019**, *141*, 11775.