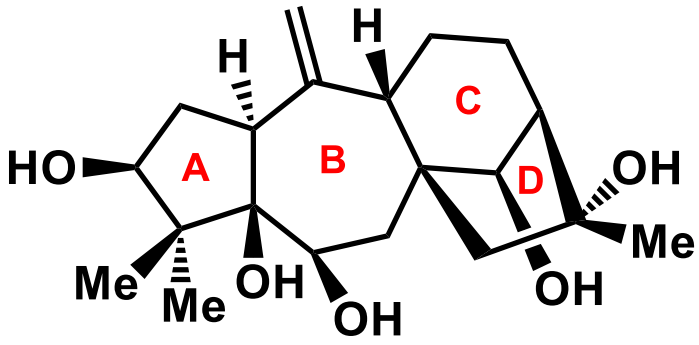
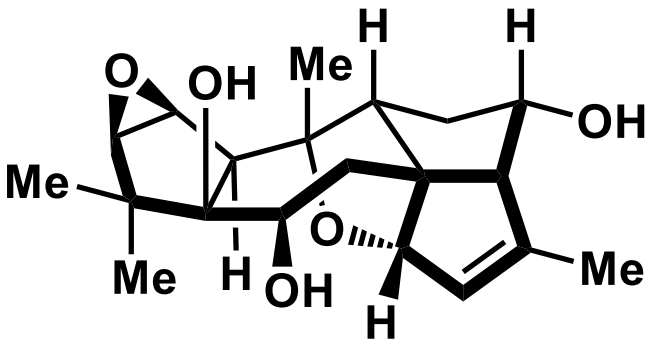
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

Total Synthesis of (−)-Rhodomollanol A

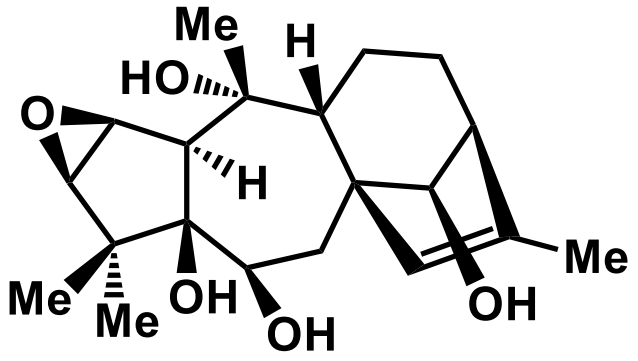
Jianhong Gao,[§] Peirong Rao,[§] Kaixiang Xu, Shuaifeng Wang, Yufei Wu, Chi He, and Hanfeng Ding*



grayanotoxin II (1)



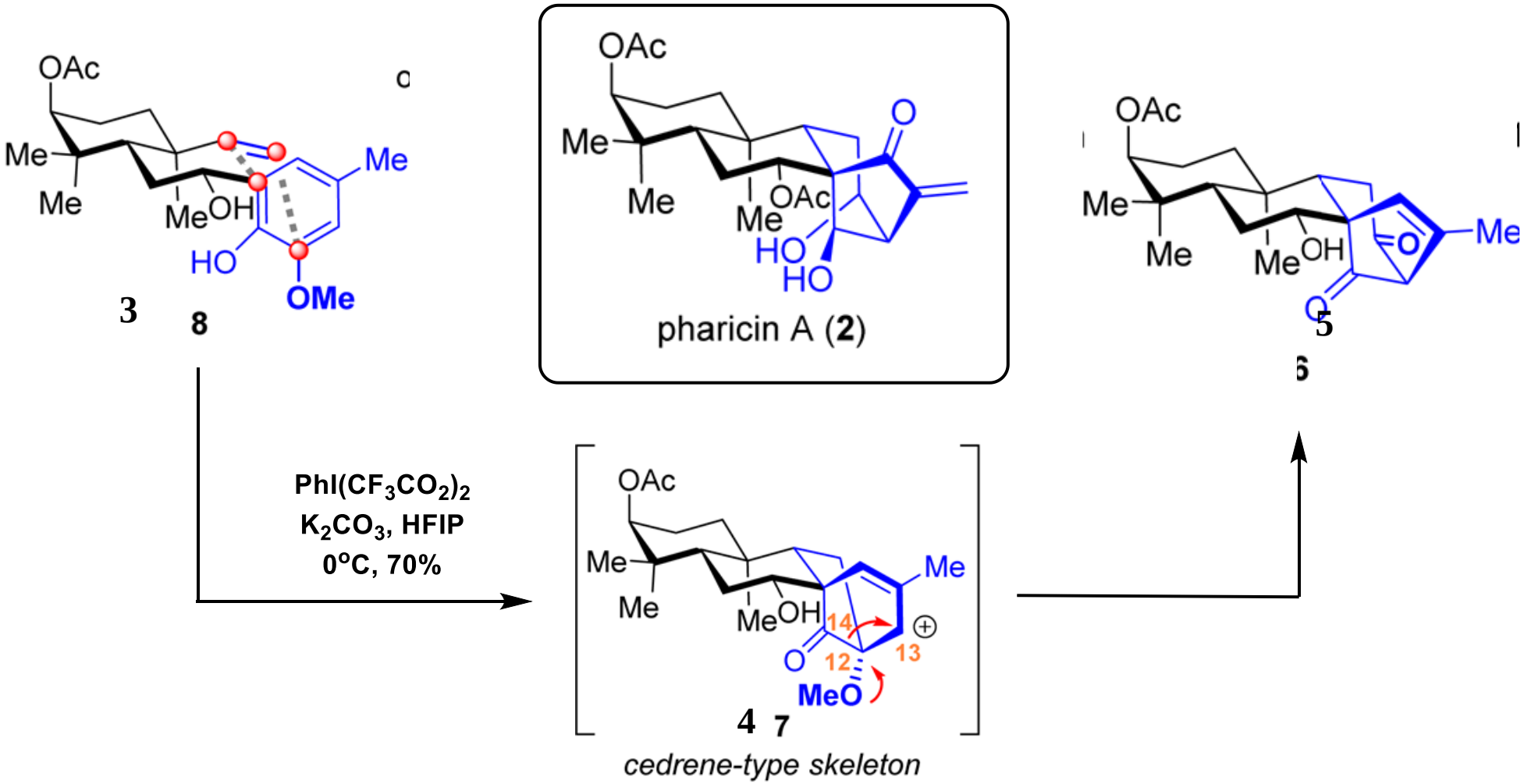
(-)-rhodomollanol A (7)



rhodomollein XXXI (6)

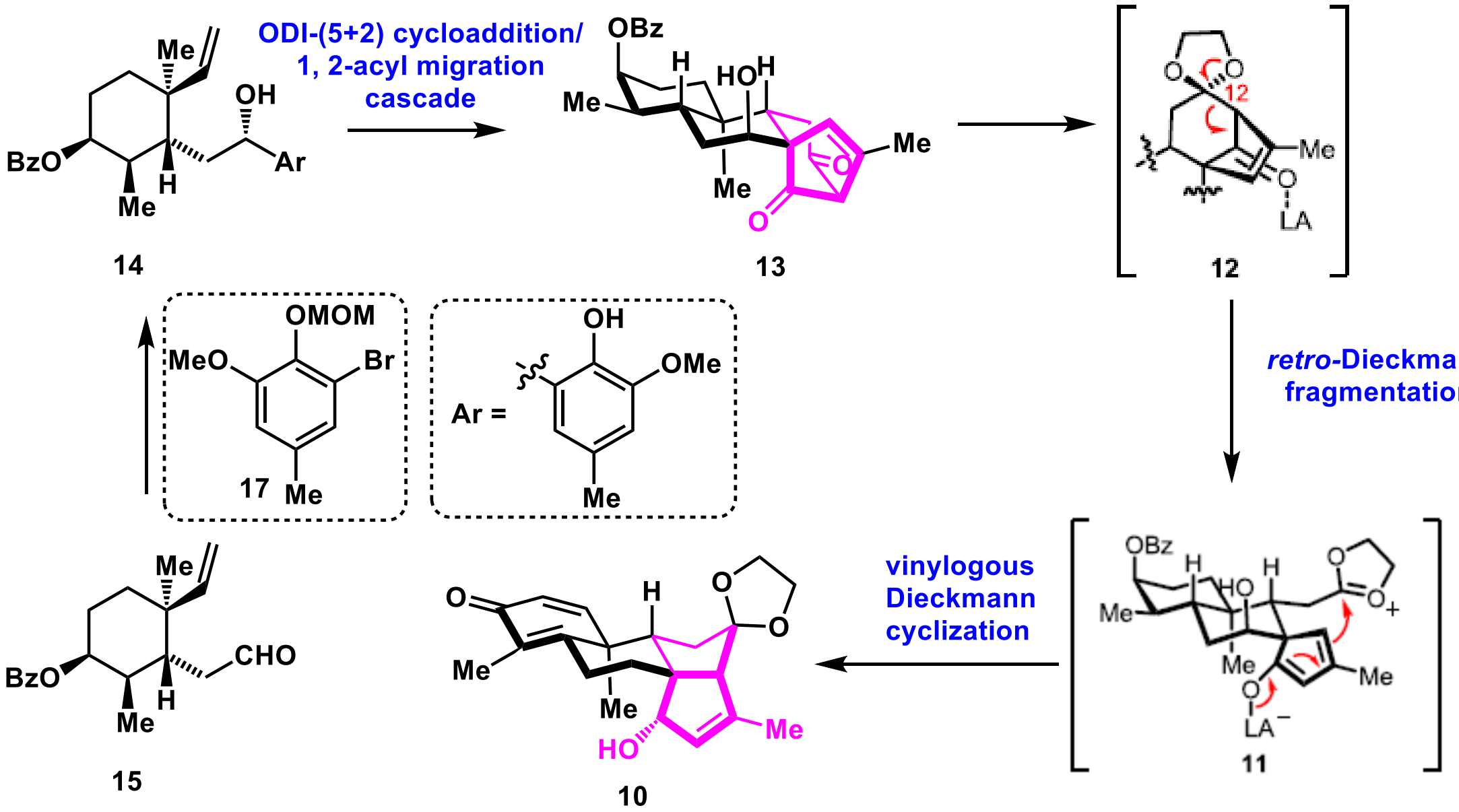
J. Am. Chem. Soc. **2020**, *142*, 4592-4597.

The ODI-[5+2] Cycloaddition/Pinacol-Type 1, 2-Acyl Migration Cascade reaction by Ding, s group

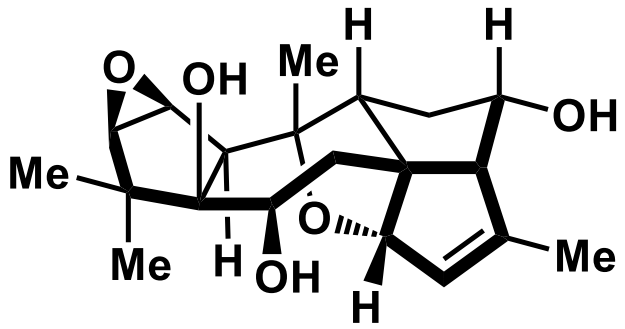


J. Am. Chem. Soc. **2017**, *139*, 6098-6101.

The Synthetic Strategy for intermediate **10**

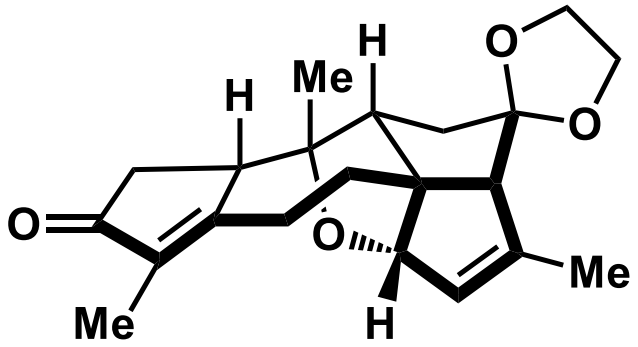


The retrosynthetic analysis of (-)-rhodomollanol A **(7)**



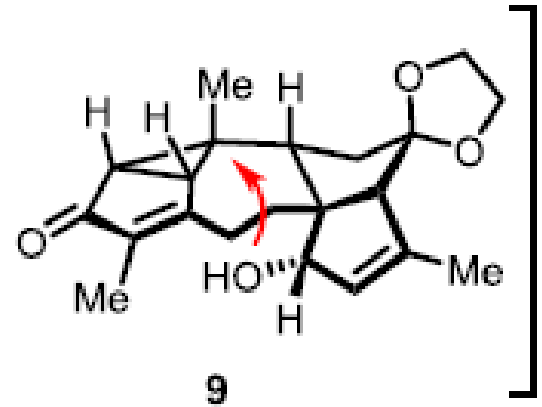
(-)-rhodomollanol A (7)

late-stage functionalization



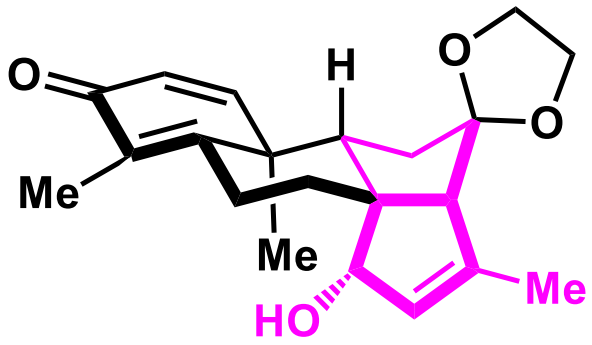
8

intramolecular cycloetherification



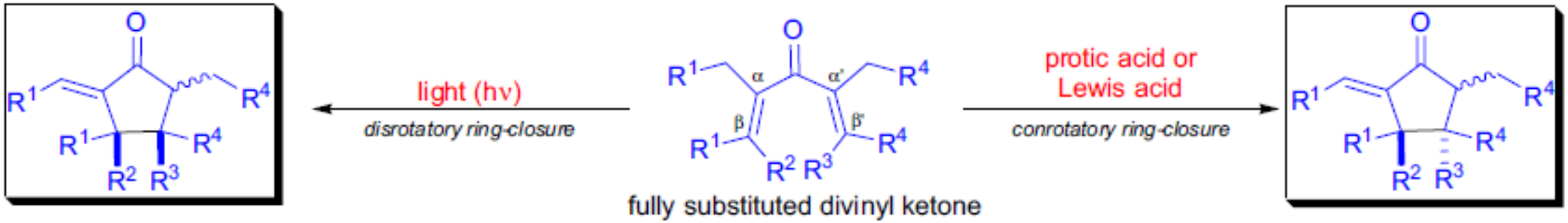
9

photo-Nazarov cyclization



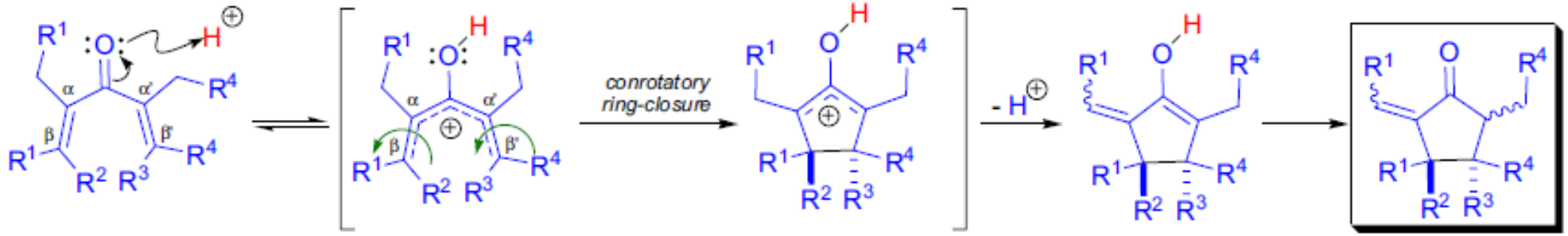
10

The Nazarov cyclization Reaction



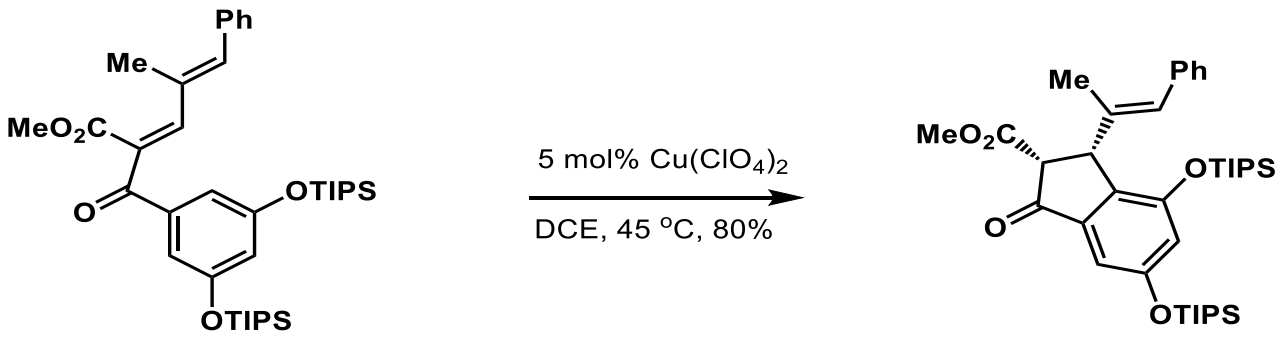
Mechanism: [32-37,15,10]

The mechanism of the *Nazarov cyclization* was not clarified until 1952, when it was realized that the cyclization proceeded *via* carbocation intermediates.[32] The *Nazarov cyclization* is a pericyclic reaction that belongs to the class of 4π electrocyclizations. The first step is the coordination of the Lewis acid to the carbonyl group of the substrate and the formation of the pentadienylic cation, which undergoes a conrotatory ring closure to give a cyclic carbocation that may be captured by a nucleophile, may undergo deprotonation, or further rearrangement may take place. The electrocyclization step may proceed in a clockwise or counterclockwise fashion (torquoselectivity) generating two diastereomers when the divinyl ketone substrate is chiral. The sense of torquoselection is primarily controlled by steric factors such as the torsional and nonbonding interactions between the substituents in the vicinity of the newly forming bond. Under photochemical conditions the cyclization proceeds in a disrotatory fashion.



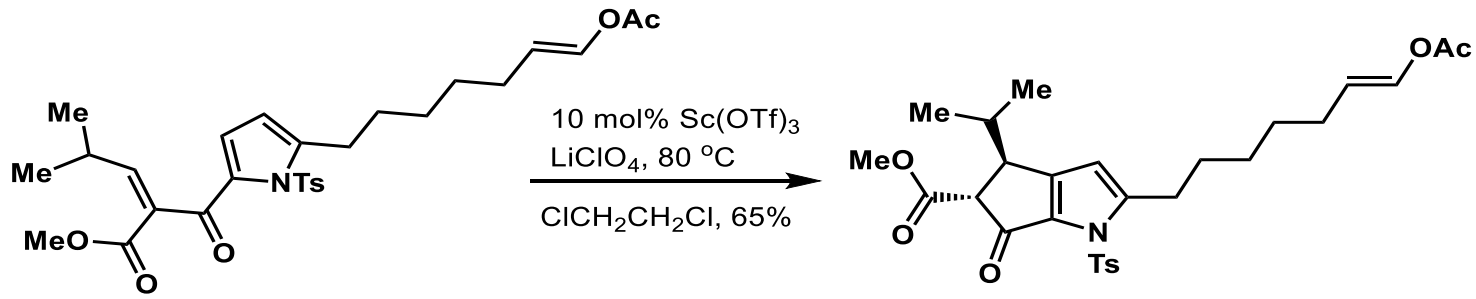
Several examples for Nazarov cyclization

1.



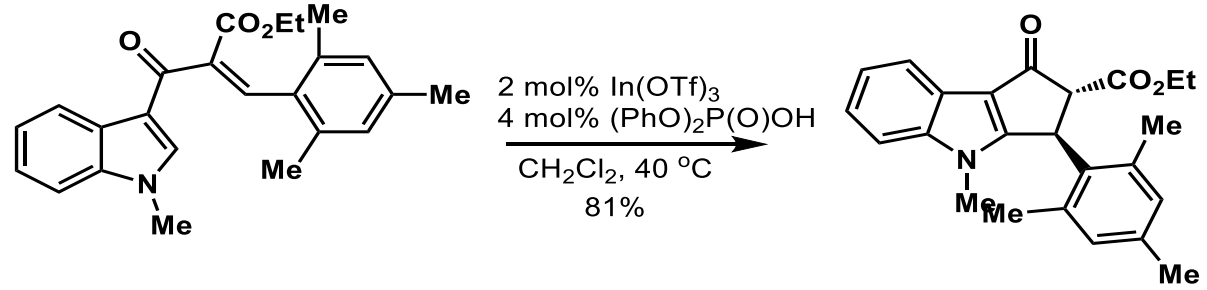
Angew. Chem. Int. Ed. **2008**, *47*, 6379-6383.

2.



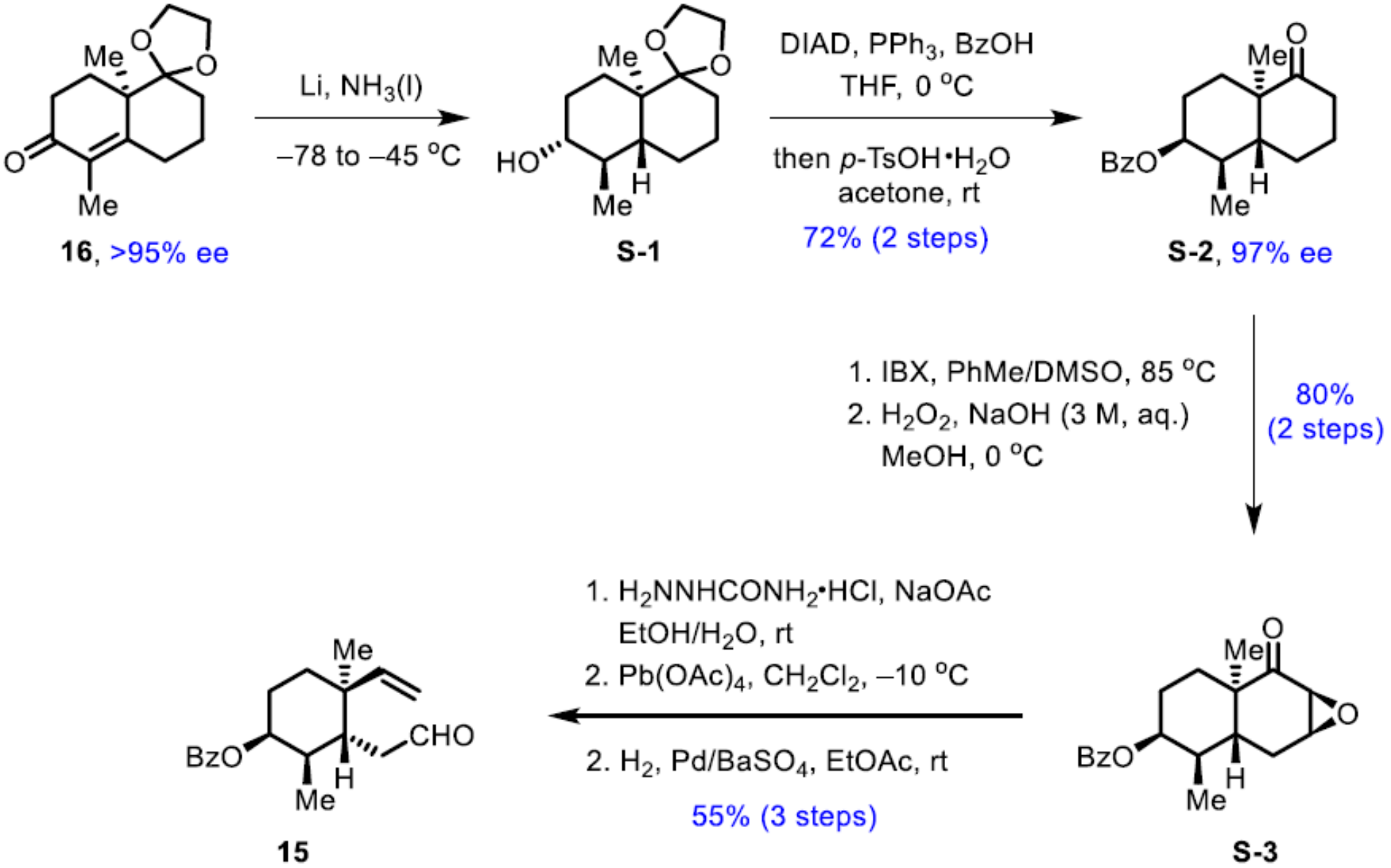
Org. Lett. **2009**, *11*, 49-52.

3.

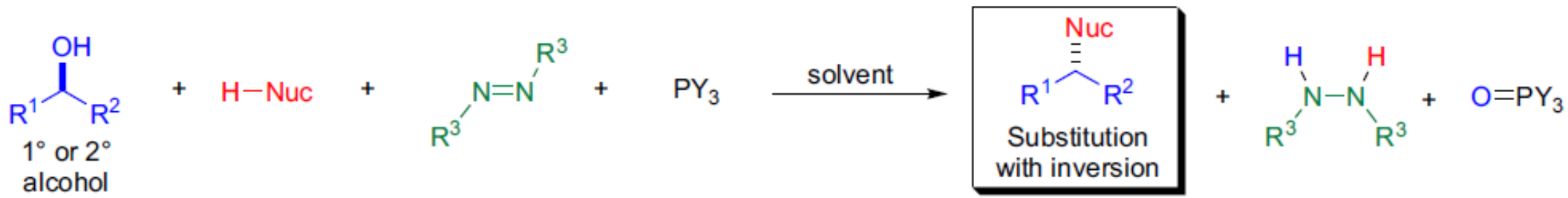


J. Org. Chem. **2013**, *78*, 606-613.

Procedures for the Preparation of Aldehyde **15**

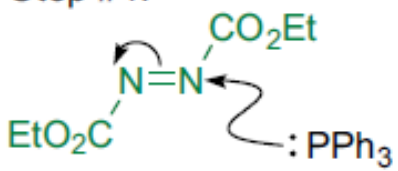


MITSUNOBU REACTION

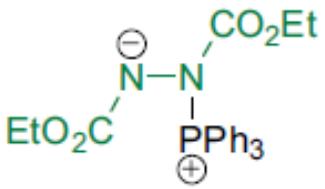


Mechanism: [25-45]

Step #1:



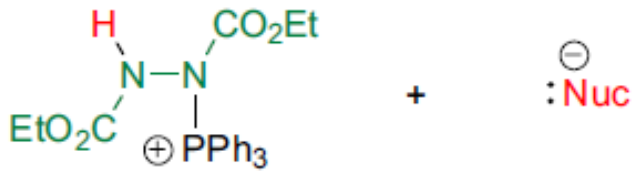
irreversible addition



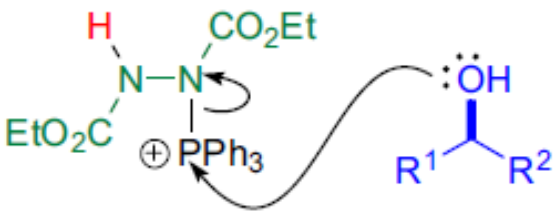
zwitterionic adduct

Step #2:

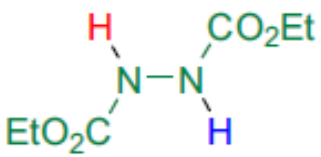
H—Nuc



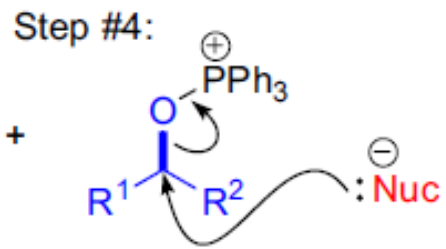
Step #3:



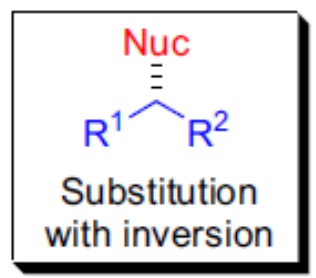
P.T.



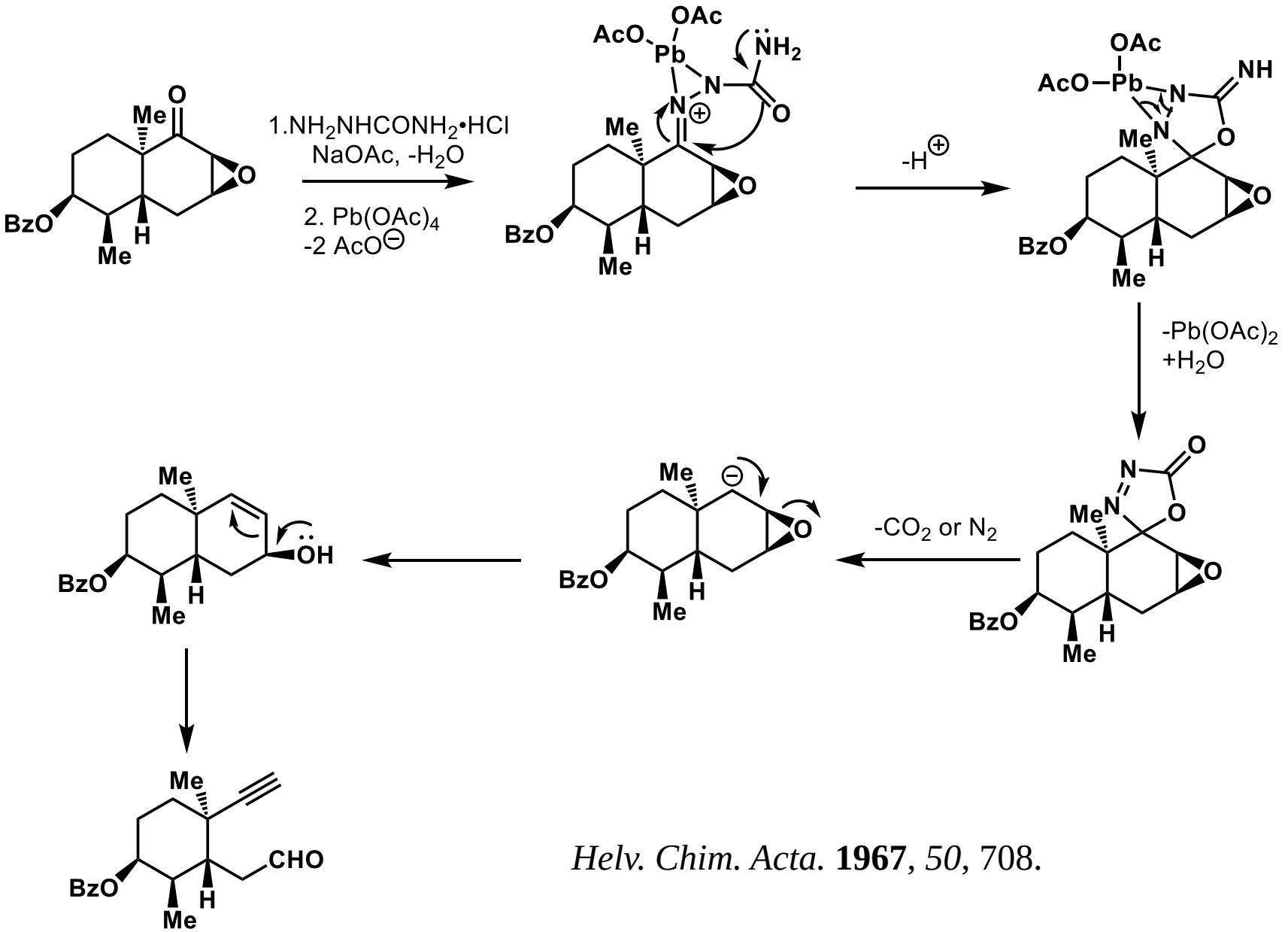
Step #4:



S_N2

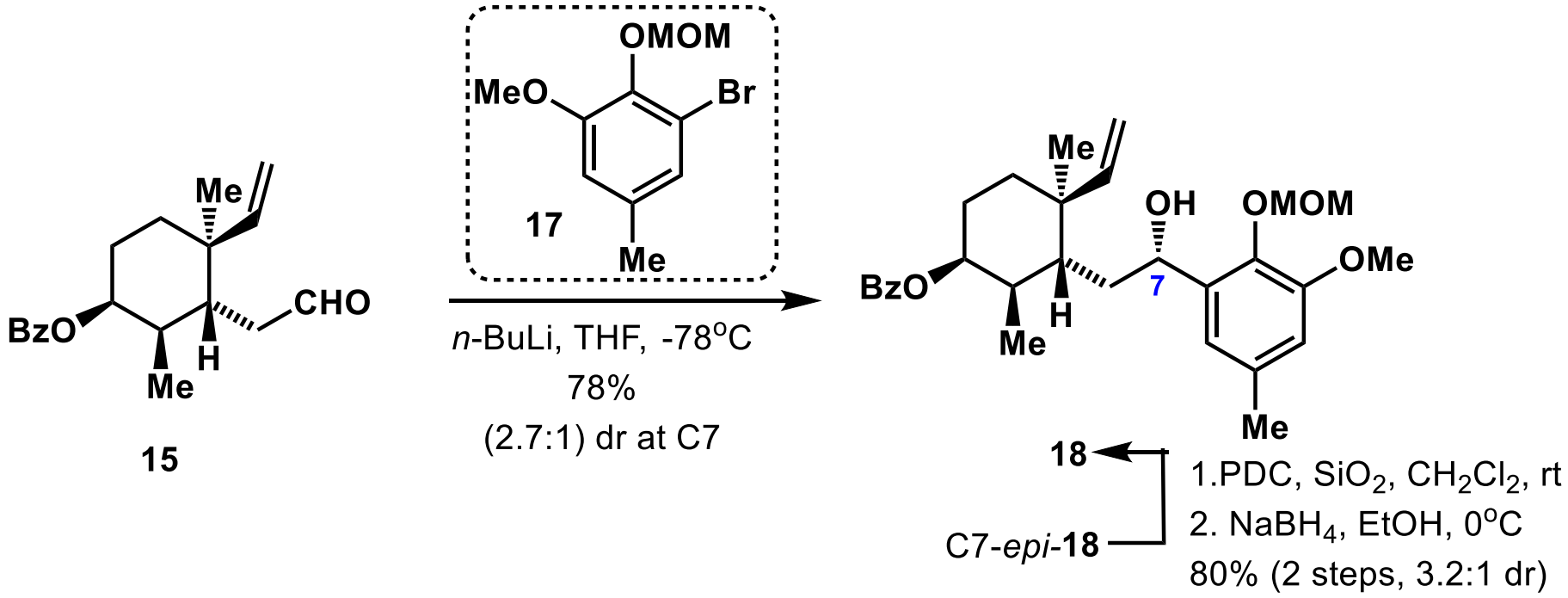


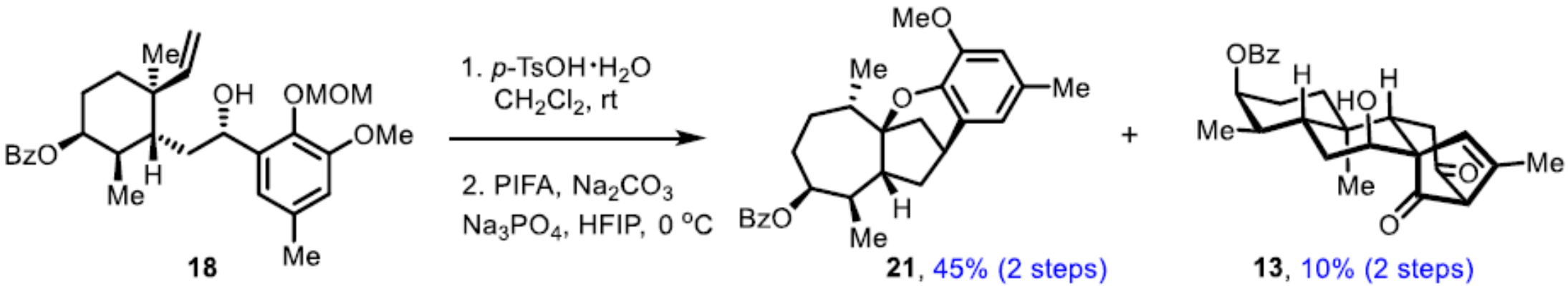
Eschenmoser–Tanabe fragmentation

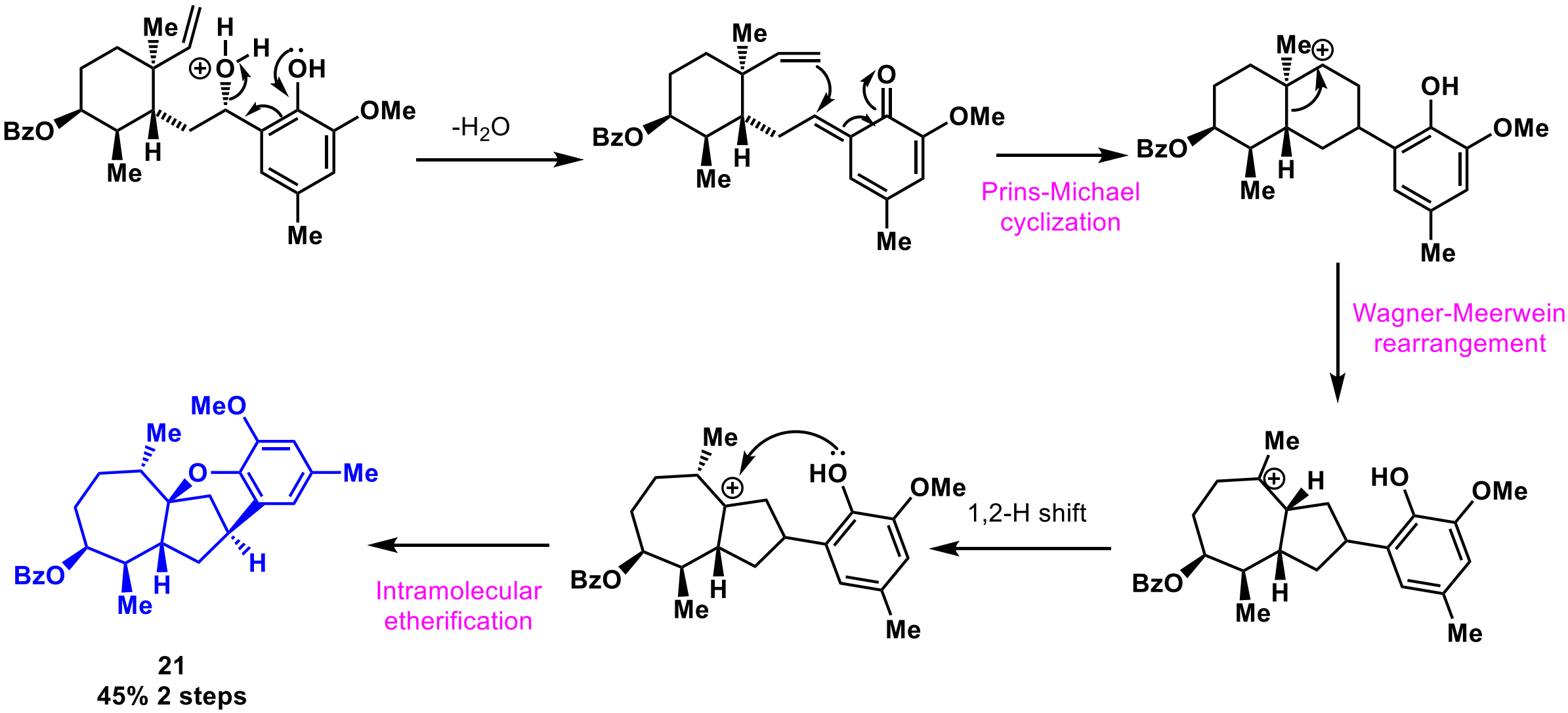


Helv. Chim. Acta. **1967**, *50*, 708.

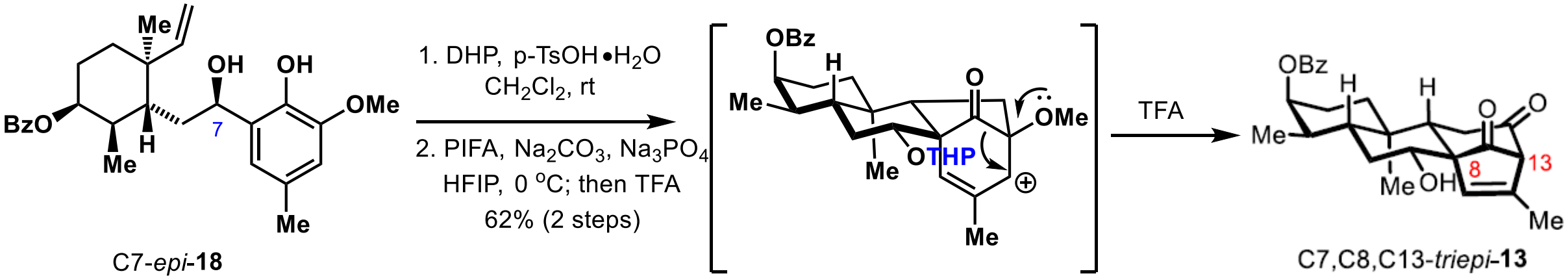
The ODI-(5+2)-cycloaddition/migration reaction for constructing intermediate **13**






-H2O
Prins-Michael cyclization
Wagner-Meerwein rearrangement
1,2-H shift
Intramolecular etherification
21
45% 2 steps

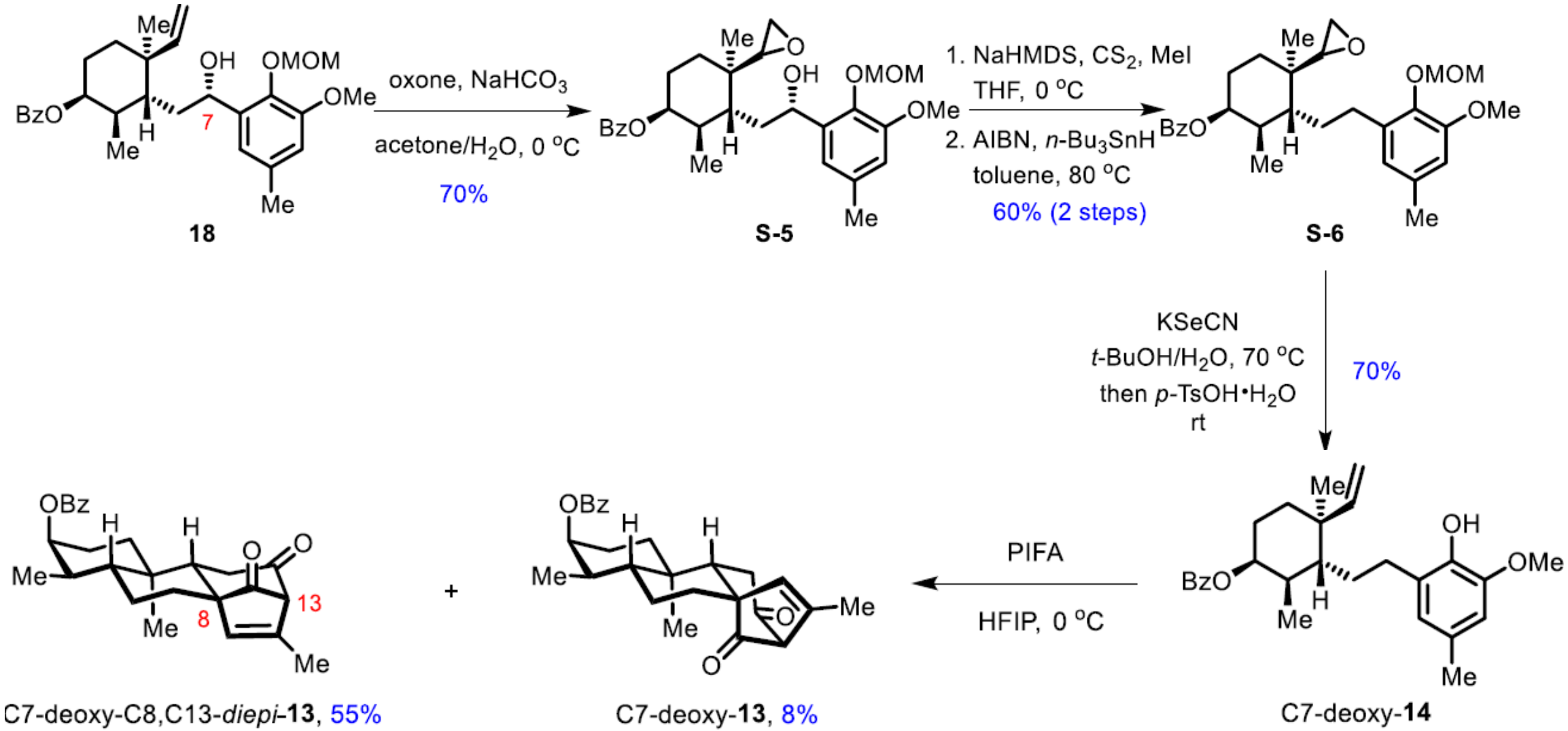
The ODI-(5+2)-cycloaddition/migration reaction for constructing intermediate **13**

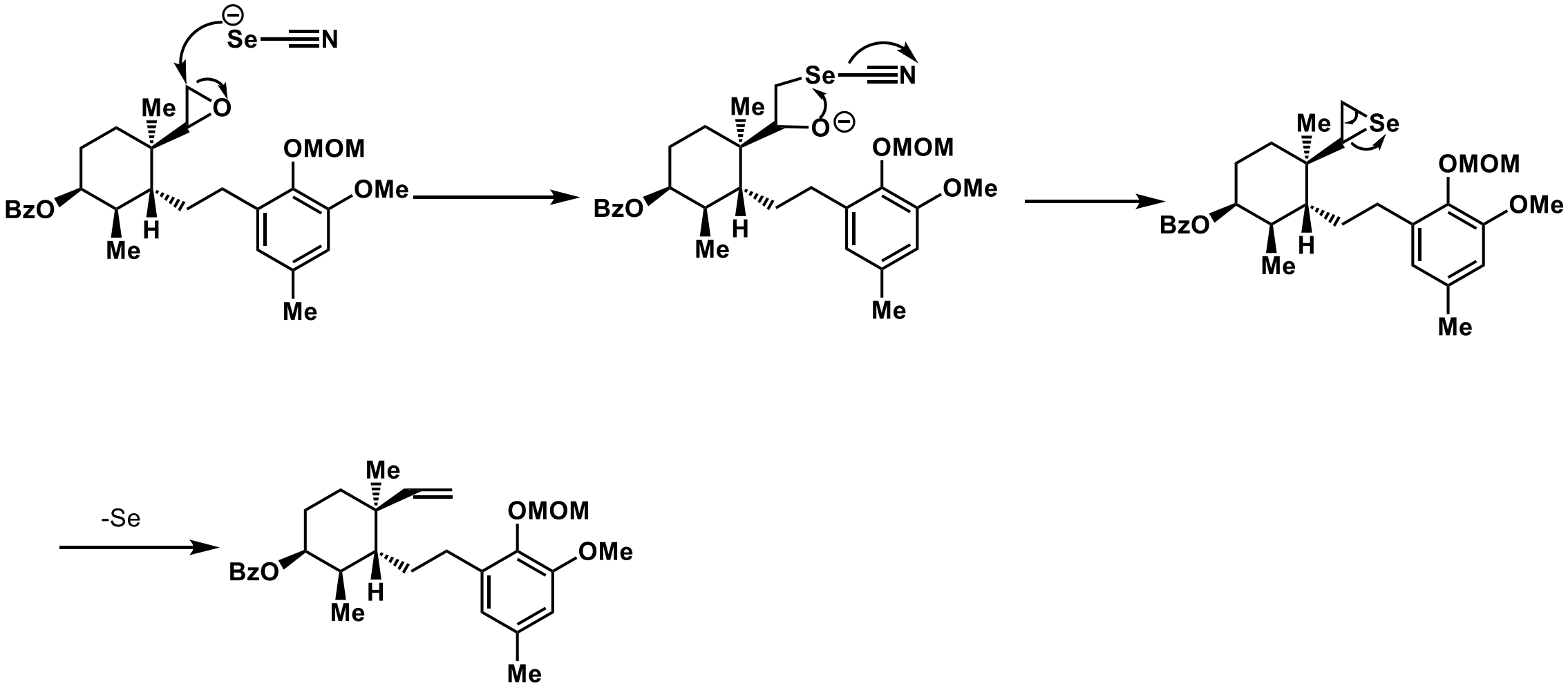


C7-*epi*-**18**

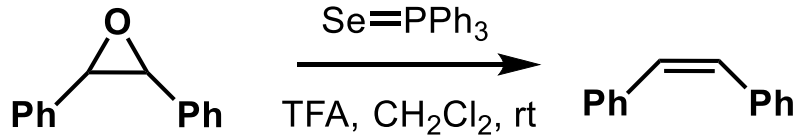
C7,C8,C13-*triepi*-**13**

The ODI-(5+2)-cycloaddition/migration reaction for constructing intermediate **13**

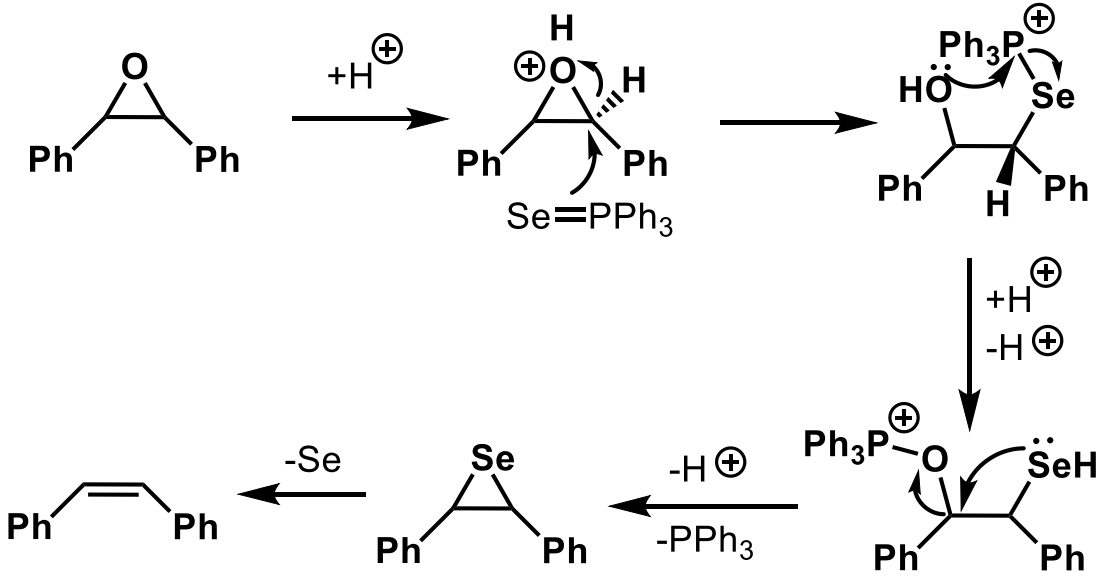



Se
N
Me
O
OMOM
OMe
BzO
H
Me
Me
Se
N
Me
O
OMOM
OMe
BzO
H
Me
Me
Me
Se
OMOM
OMe
BzO
H
Me
Me
-Se
Me
OMOM
OMe
BzO
H
Me
Me

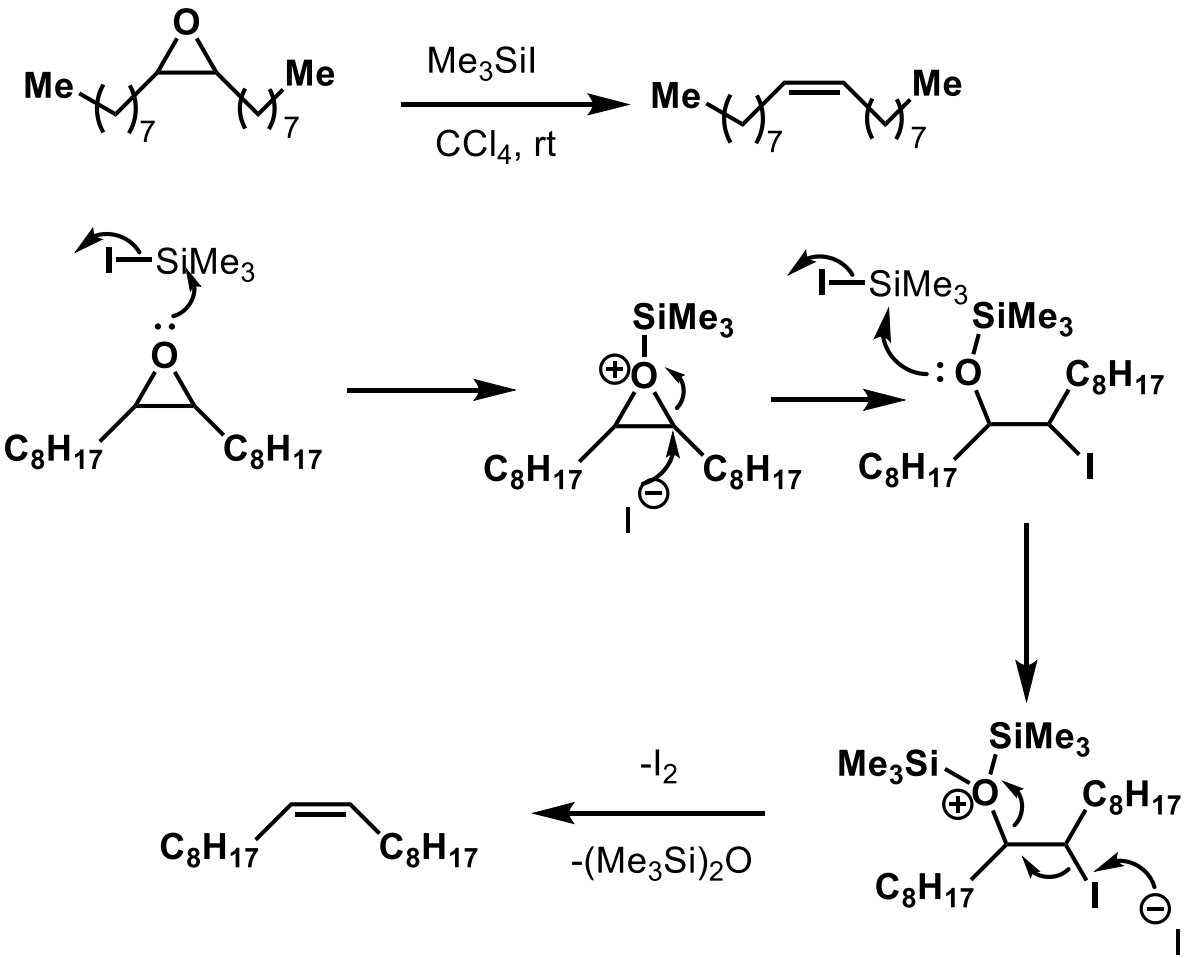
1.



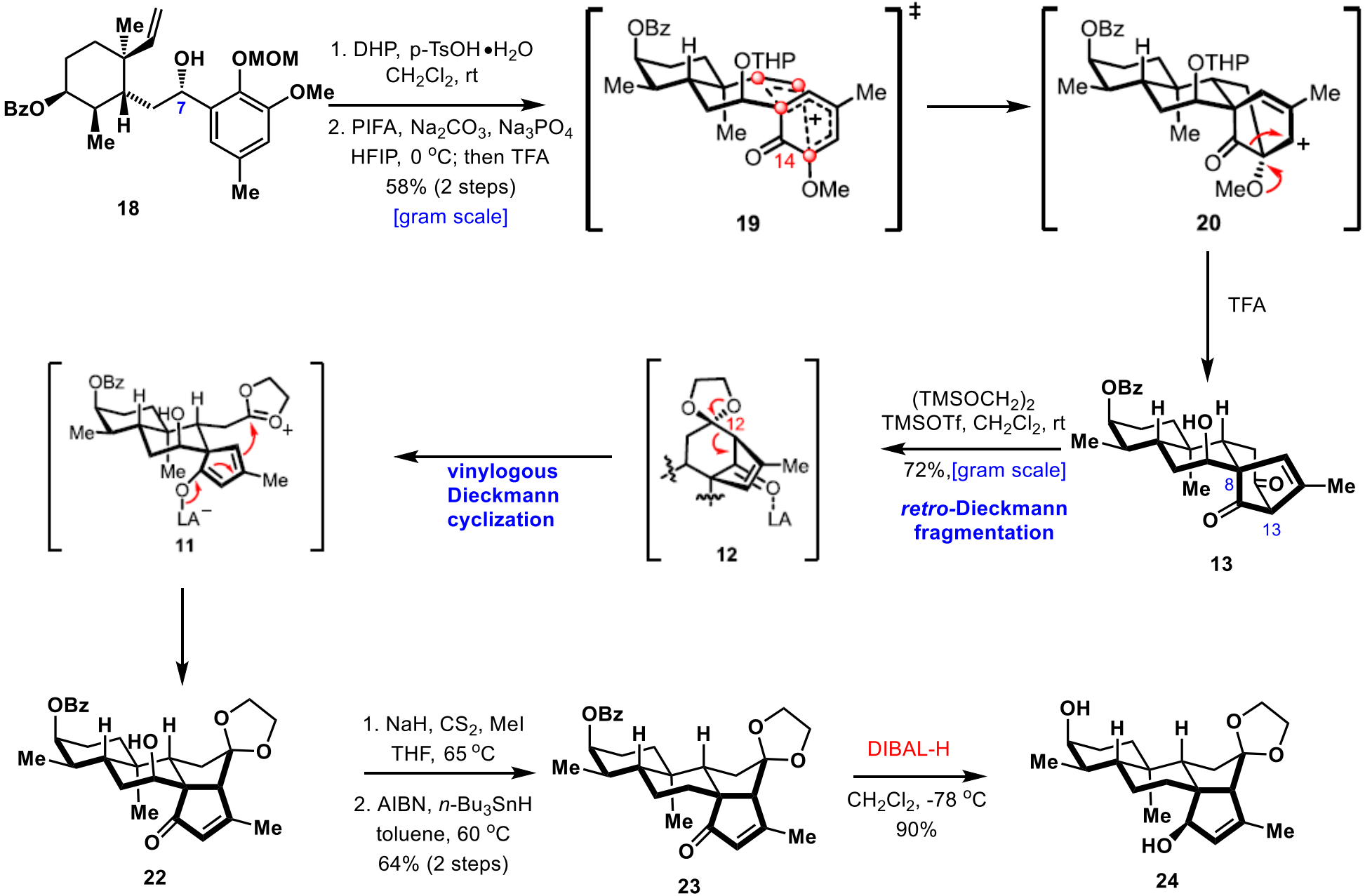
J. Chem. Soc., Chem. Commun. **1973**, 253.



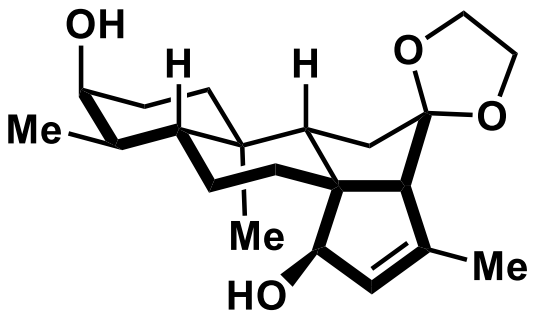
2.



Construction of Cyclohexadienone **27**



Construction of Cyclohexadienone **27**

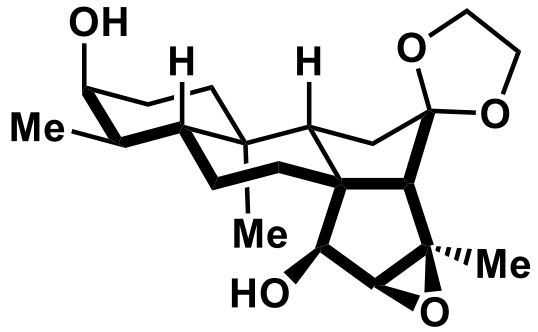


24

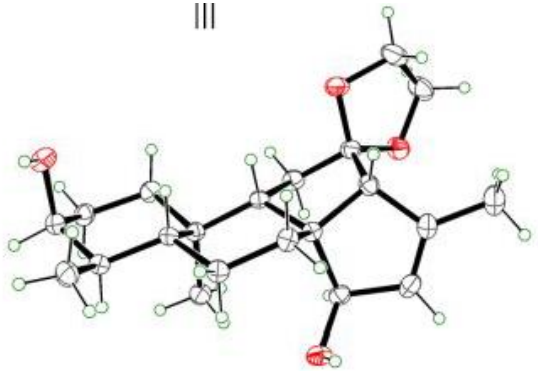
$VO(acac)_2$, TBHP

CH_2Cl_2, 0 °C

87%



25

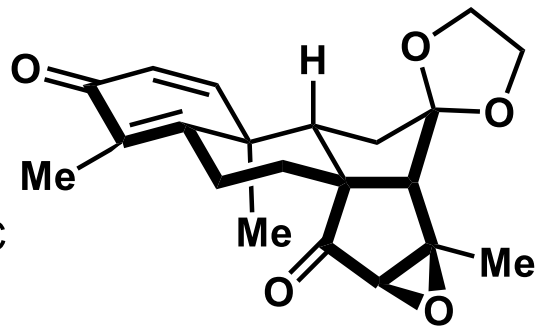


X-ray of **24**

$(PhSeO)_2O$, py

toluene, 90 °C

43%



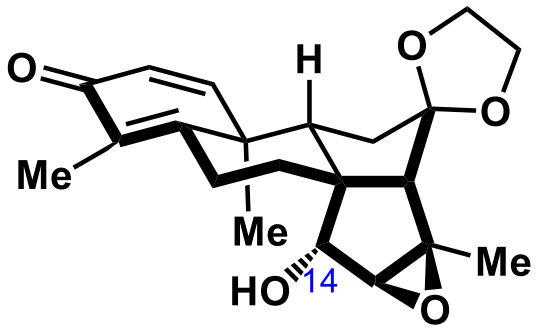
26

$NaBH_4$, $CeCl_3 \cdot 7H_2O$

$MeOH/CH_2Cl_2$, -20 °C

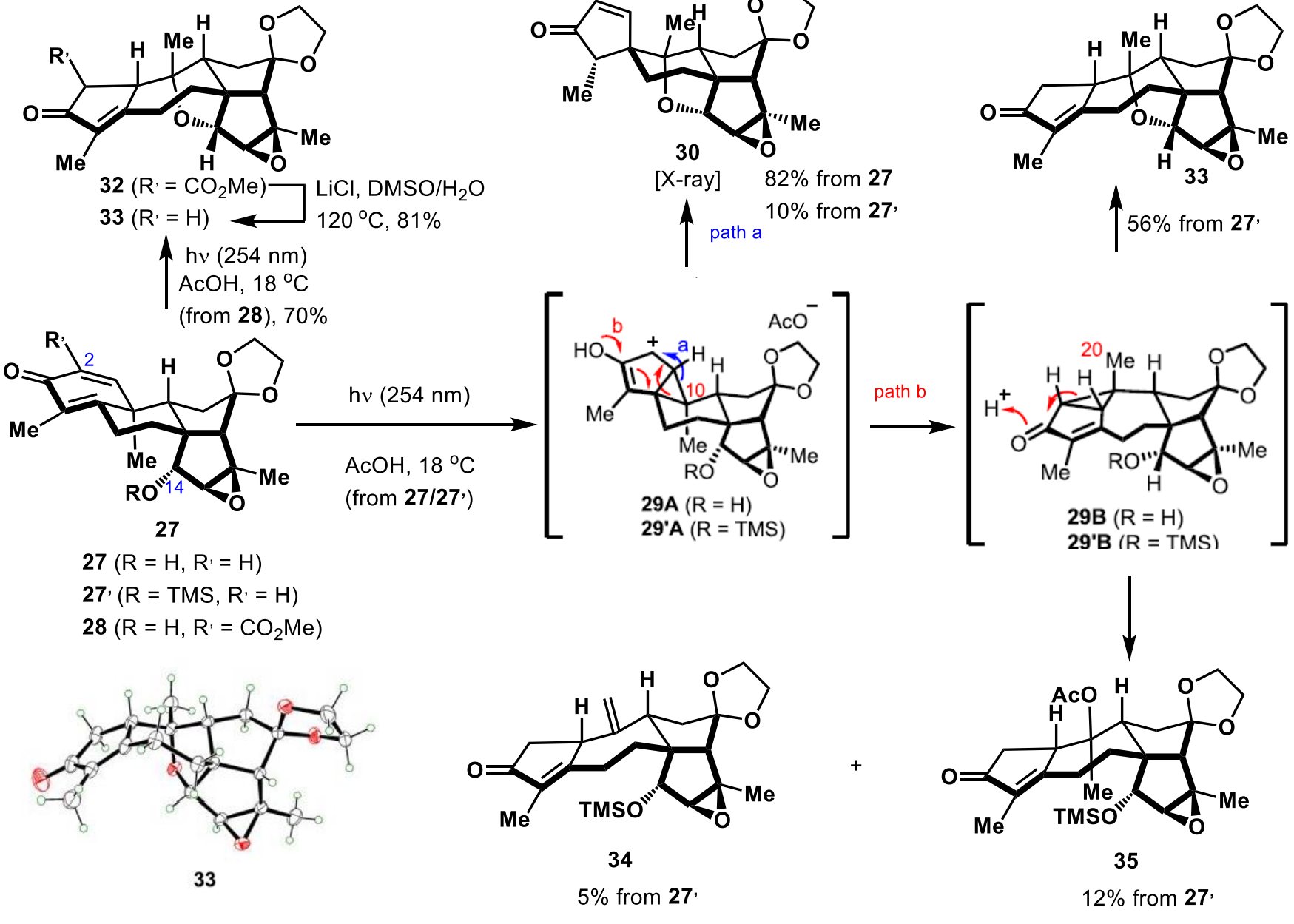
85%

(6:1 dr at C14)

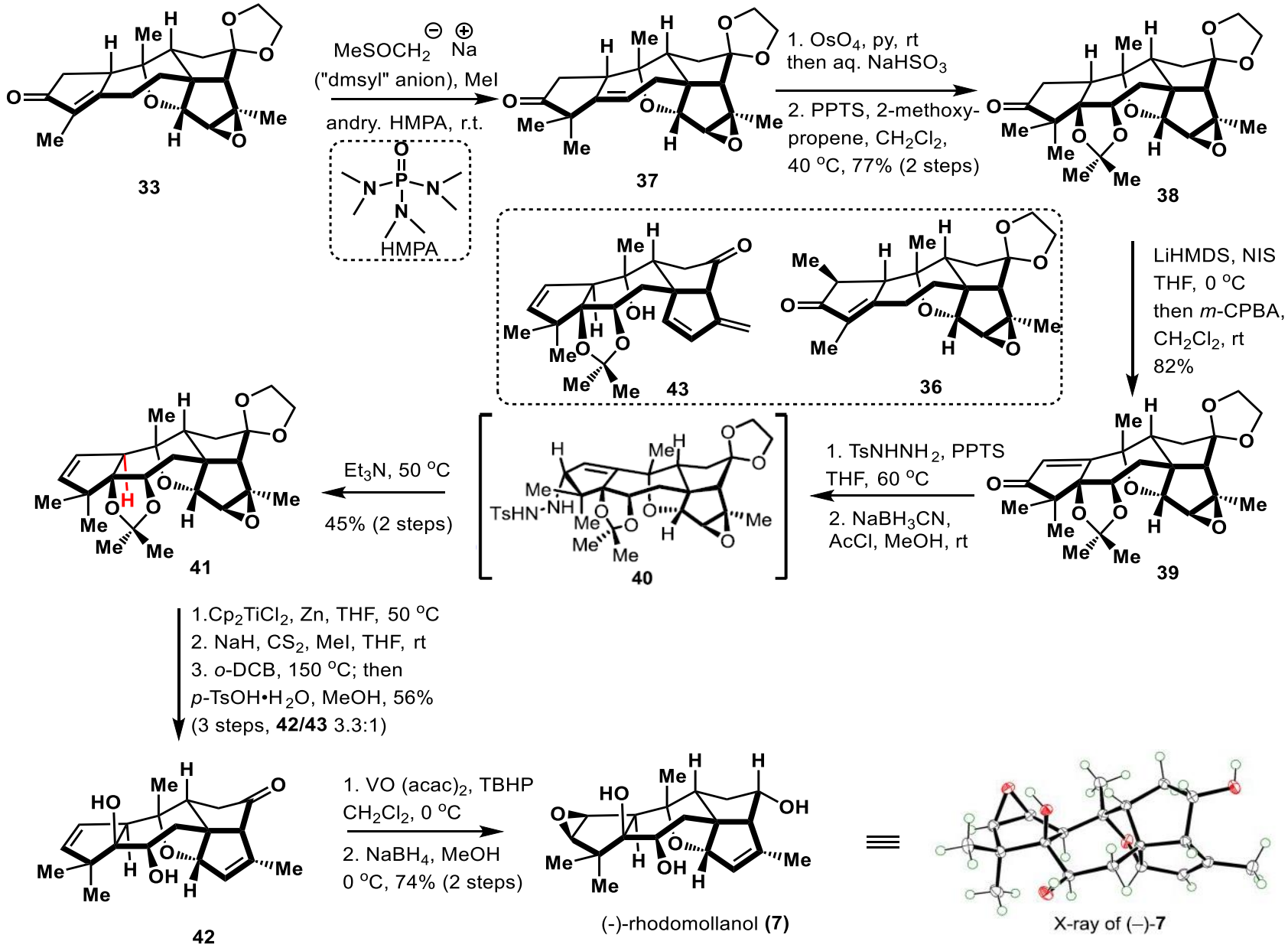


27

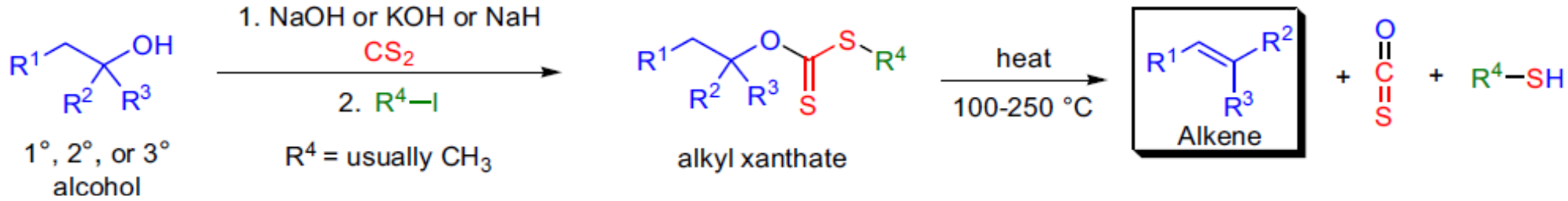
Photo-Nazarov Cyclizations of Cyclohexadienones **27**, **27'**, and **28**



Late-Stage Synthesis of (-)-Rhodomollanol A (7)

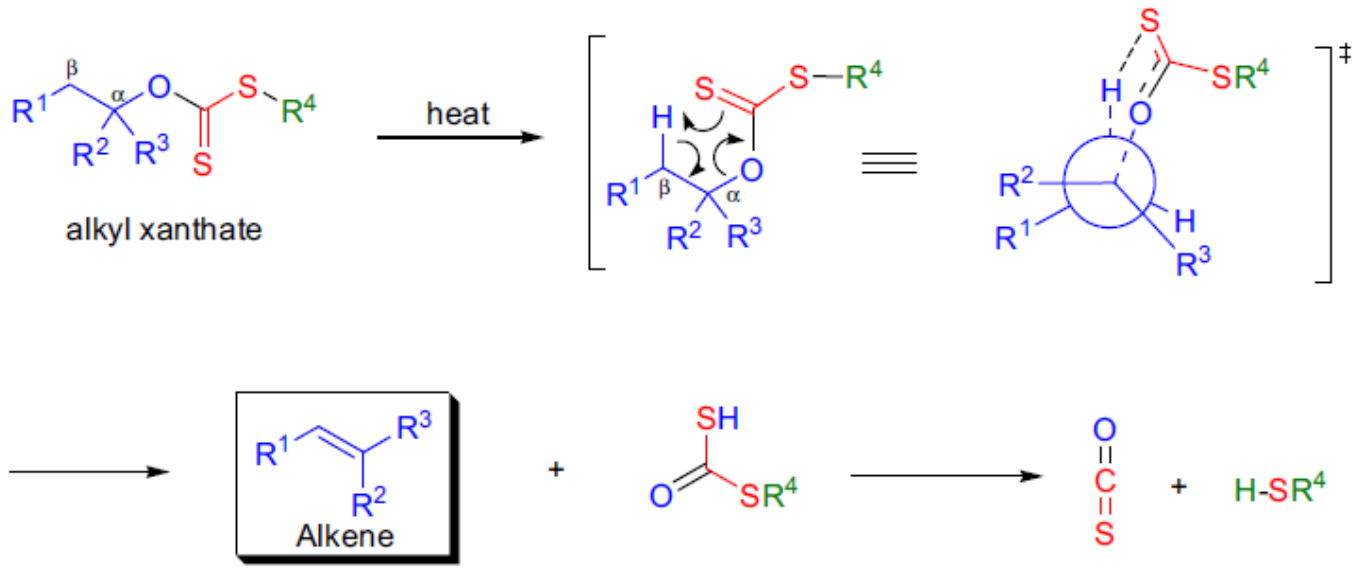


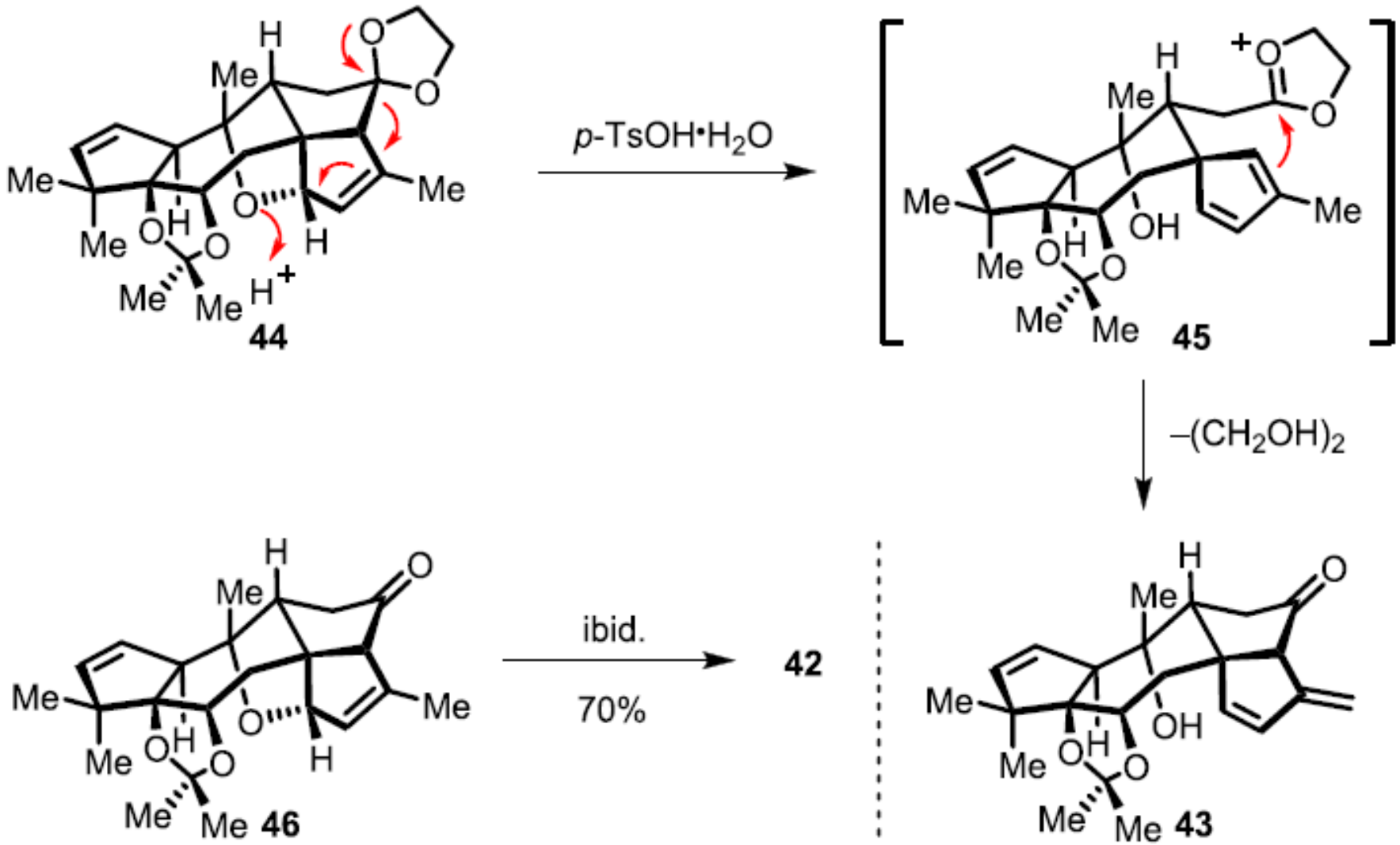
CHUGAEV ELIMINATION REACTION
(XANTHATE ESTER PYROLYSIS)



Mechanism: [8-12]

The *Chugaev reaction* is an intramolecular *syn* elimination (E_i), and it proceeds through a six-membered transition state involving a *cis*-β-hydrogen atom of the alcohol moiety and the thione sulfur atom of the xanthate. Isotopic studies involving ^{34}S and ^{13}C showed that the C=S, and not the thiol sulfur atom, closes the ring in the transition state.[12] The β-hydrogen and the xanthate group must be coplanar in the cyclic transition state.




H
Me
O
O
Me
Me
OH
O
O
H
Me
Me
H+
44
p-TsOH•H2O
+O
45
–(CH2OH)2
ibid.
70%
42
46
43