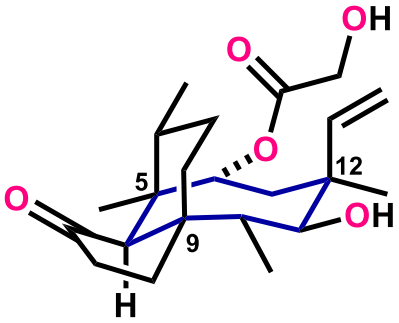
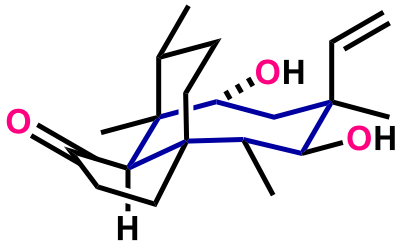
Total Synthesis of Pleuromutilin

2017/06/17 Hiroaki Matoba

Pleuromutilin



(+)-pleuromutilin



(+)-mutilin

Isolation
from edible mushroom *Pleurotus mutilus* (*Clitopilus scyphoides*)
Kavanagh, F. et al. *PNAS*, **1951**, *37*, 570.

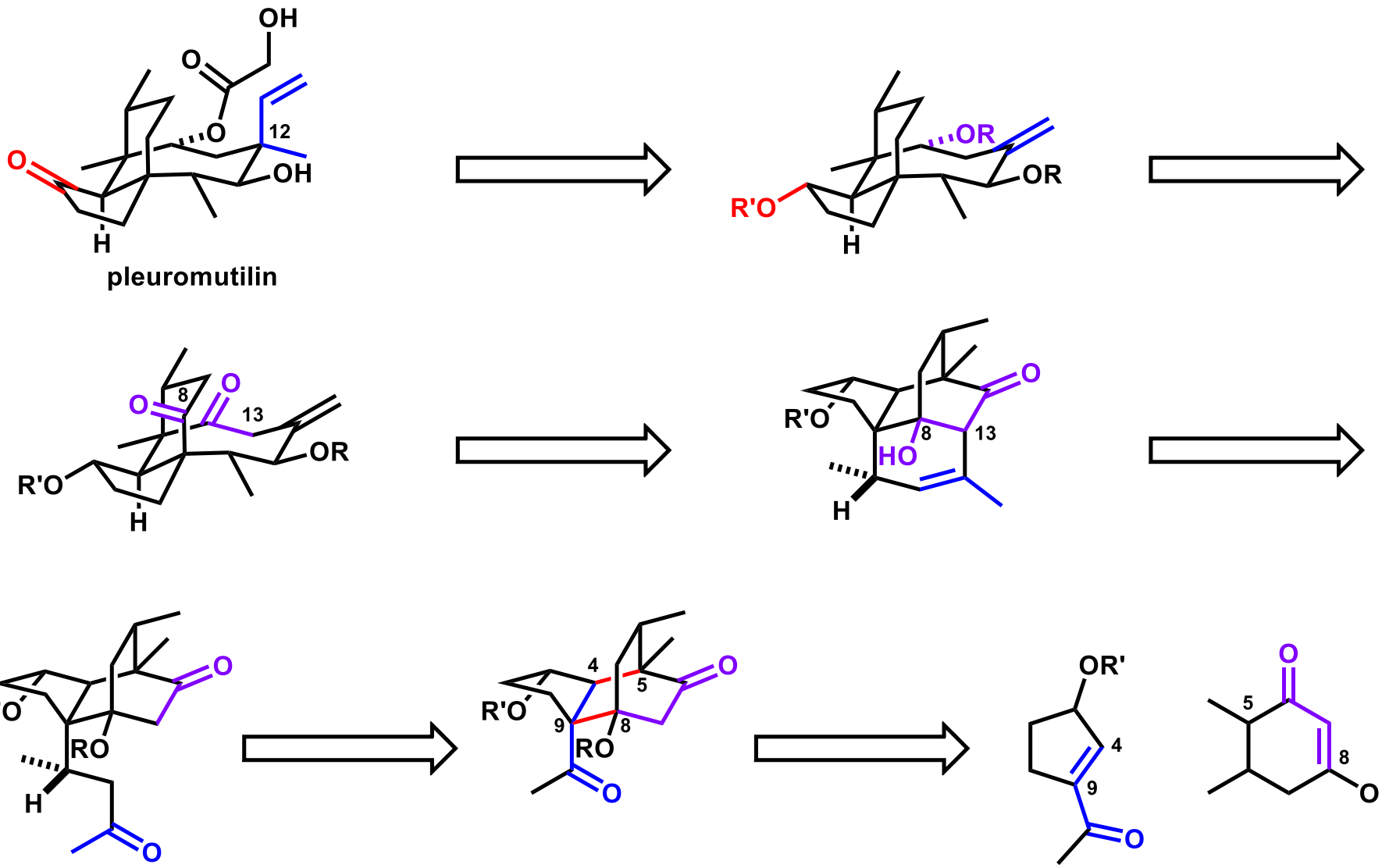
Biological activity
Antibacterial (Gram-positive bacteria)

Structural features
8-membered ring
three quaternary carbons (C5, 9, 12)

Synthesis
Gibbons, E. G. *JACS*, **1982,** *104*, 1767. (racemic)
Boeckman, R. K. Jr. et al. *JACS*, **1989**, *111* , 8284. (racemic)
Procter, D. J. et al. *Chem. Eur. J.*, **2013**, *19*, 6718. (+)-pleuromutilin
Herzon, S. B. et al. *Science,* **2017**, *356*, 956. (+)-pleuromutilin

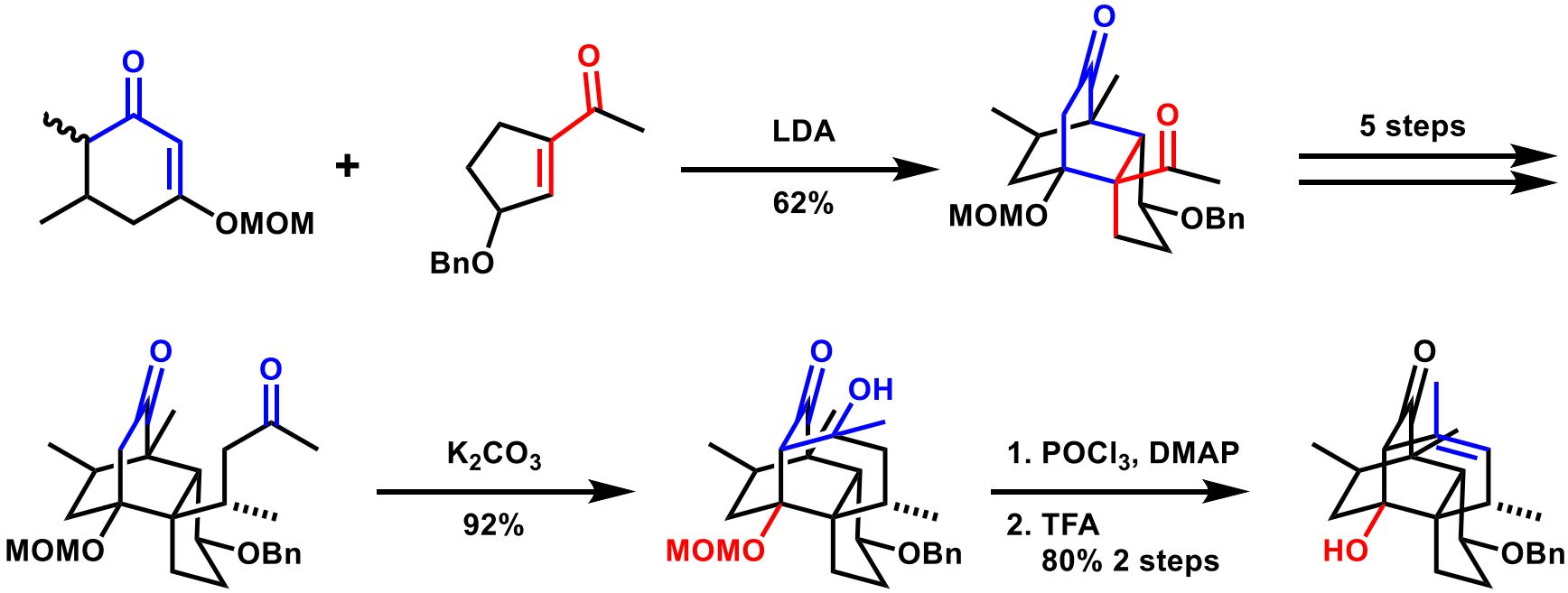
Clitopilus scyphoides

Retrosynthesis

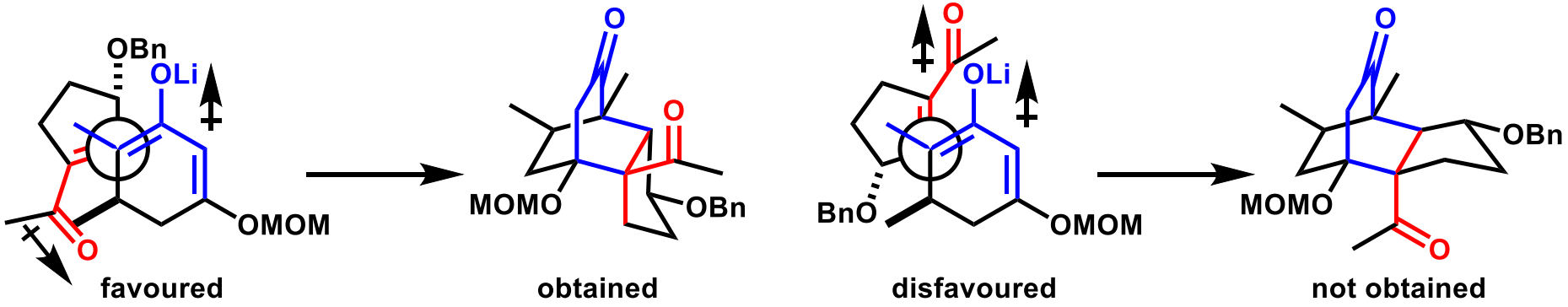


Gibbons, E. G. *JACS*, **1982**, *104*, 1767.

Gibbons' synthesis (1)

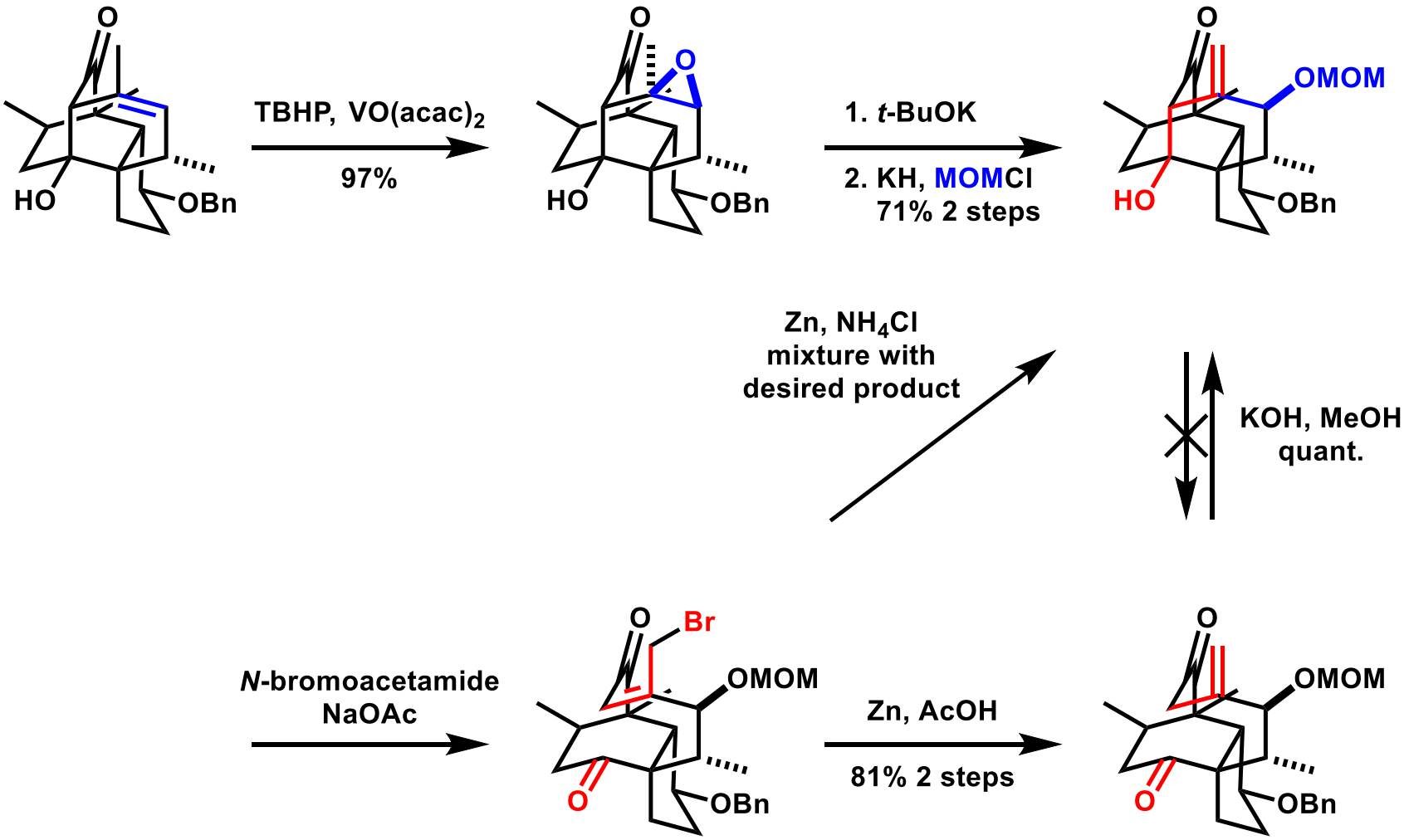


diastereo selectivity



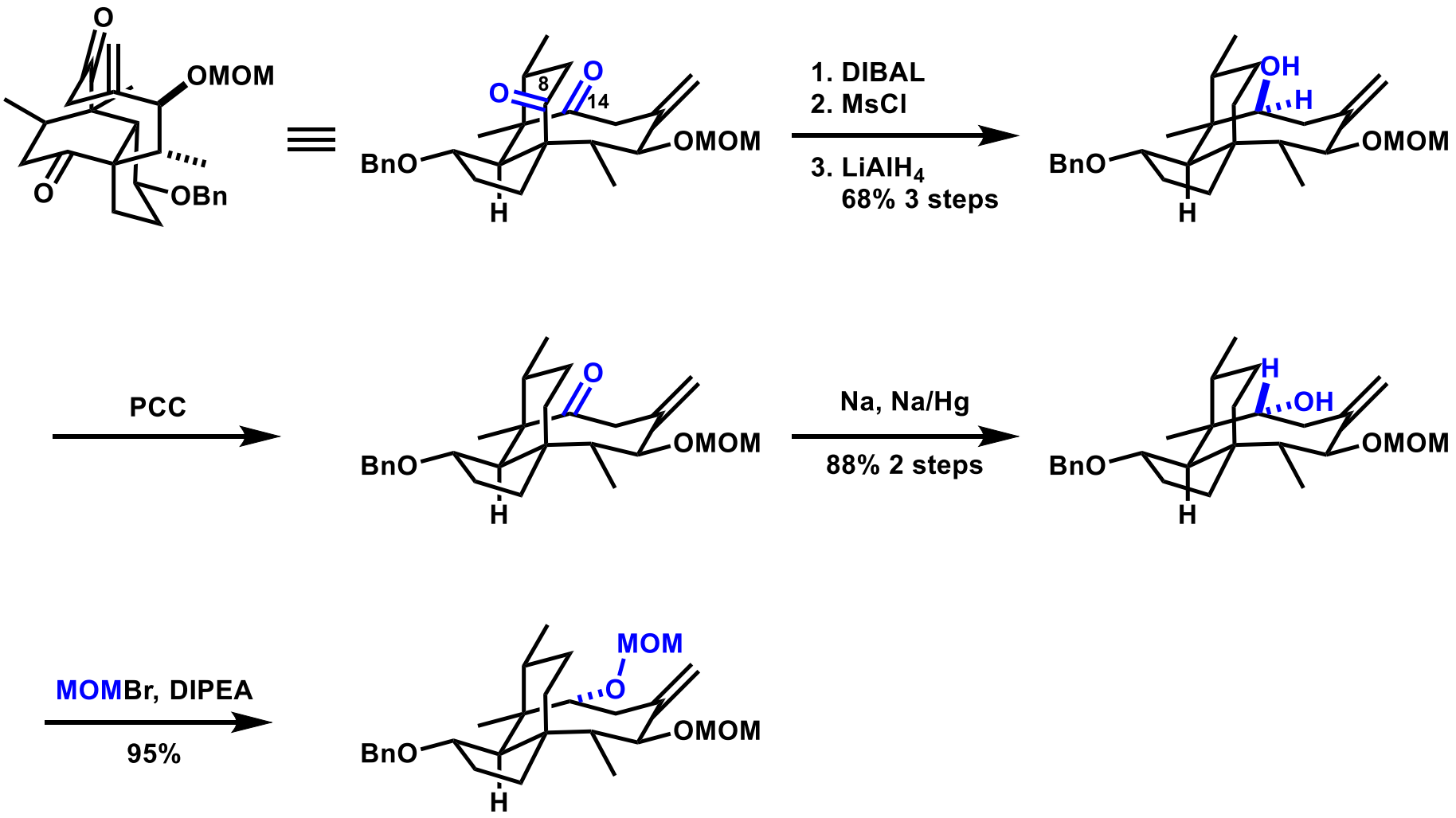
Gibbons, E. G. *JACS,* **1982**, *104*, 1767.

Gibbons' synthesis (2)



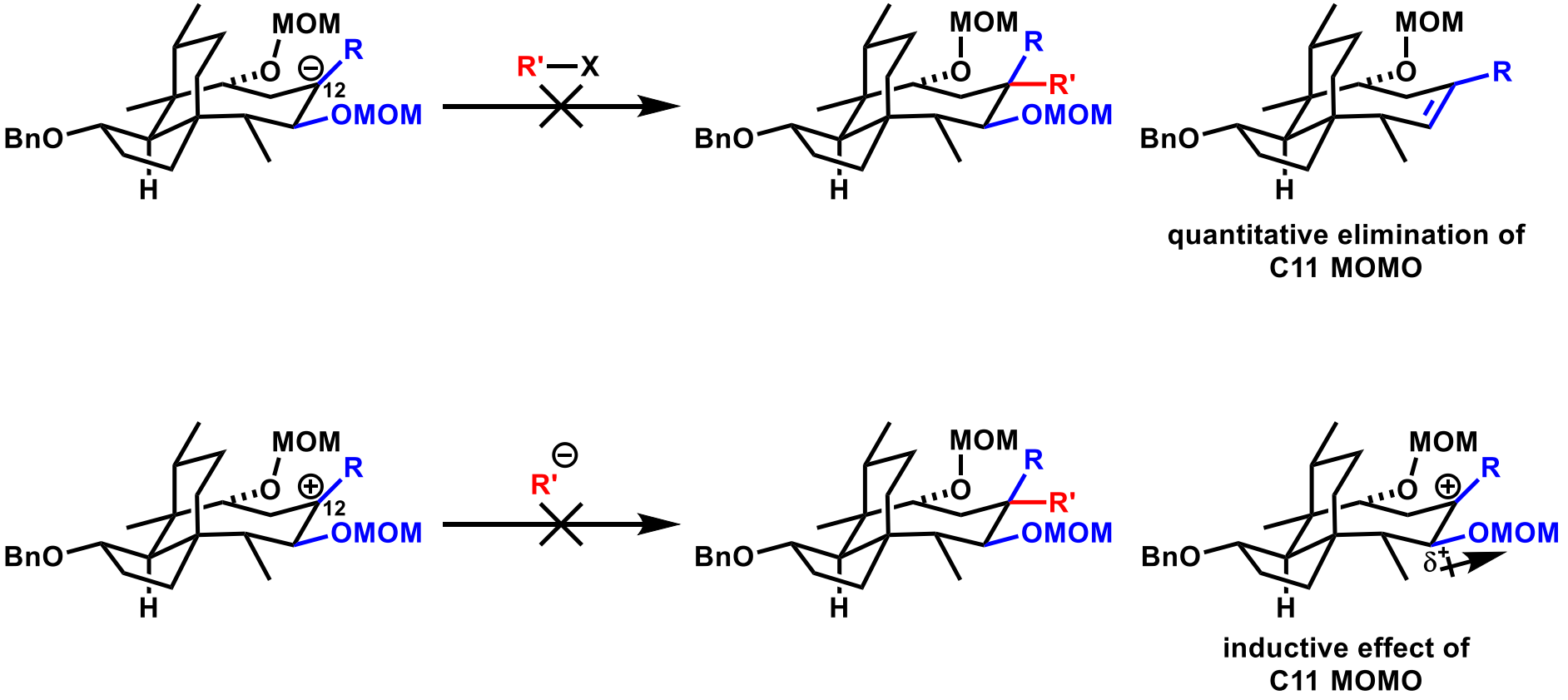
Gibbons, E. G. *JACS,* **1982**, *104*, 1767.

Gibbons' synthesis (3)



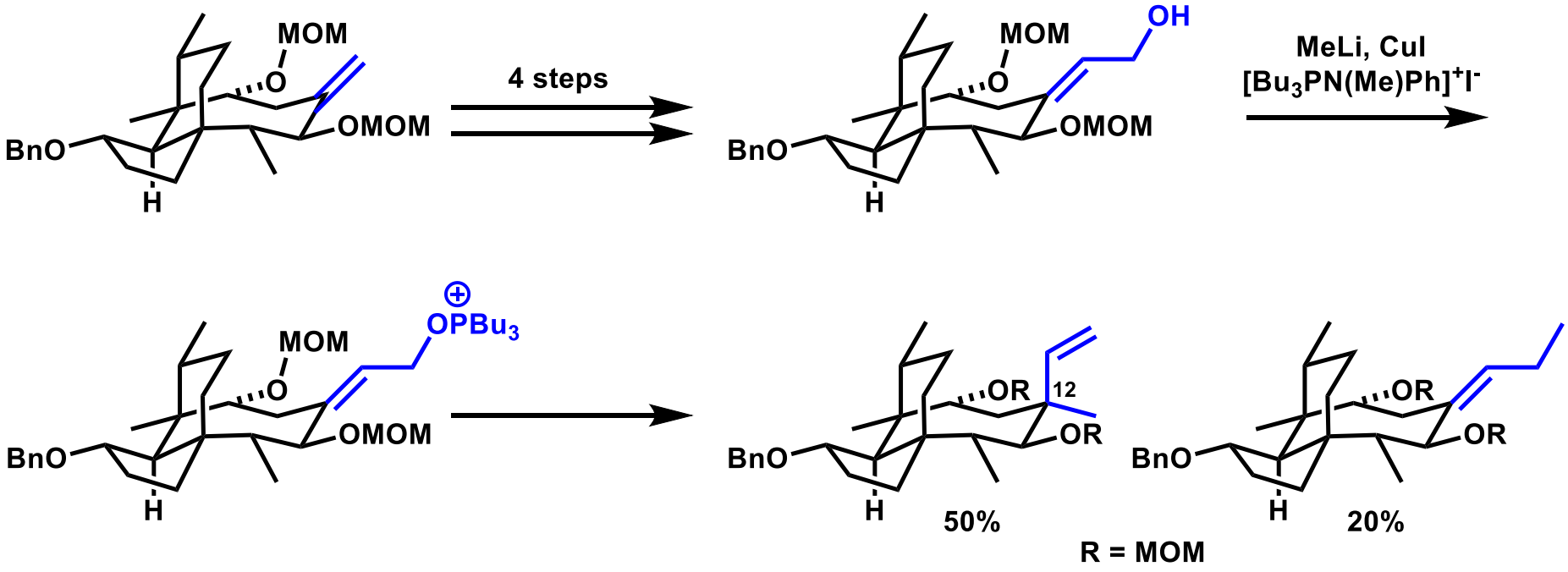
Gibbons, E. G. *JACS,* **1982**, *104*, 1767.

Problem for construction of C12 quaternary center

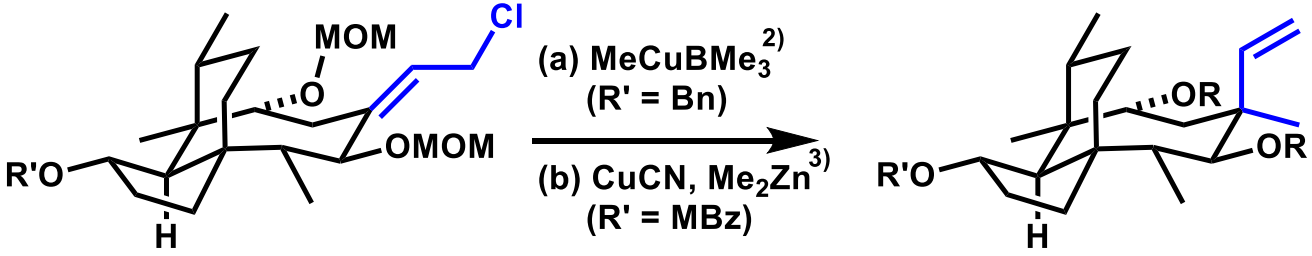


Gibbons, E. G. *JACS,* **1982**, *104*, 1767.

Gibbons' synthesis (4)

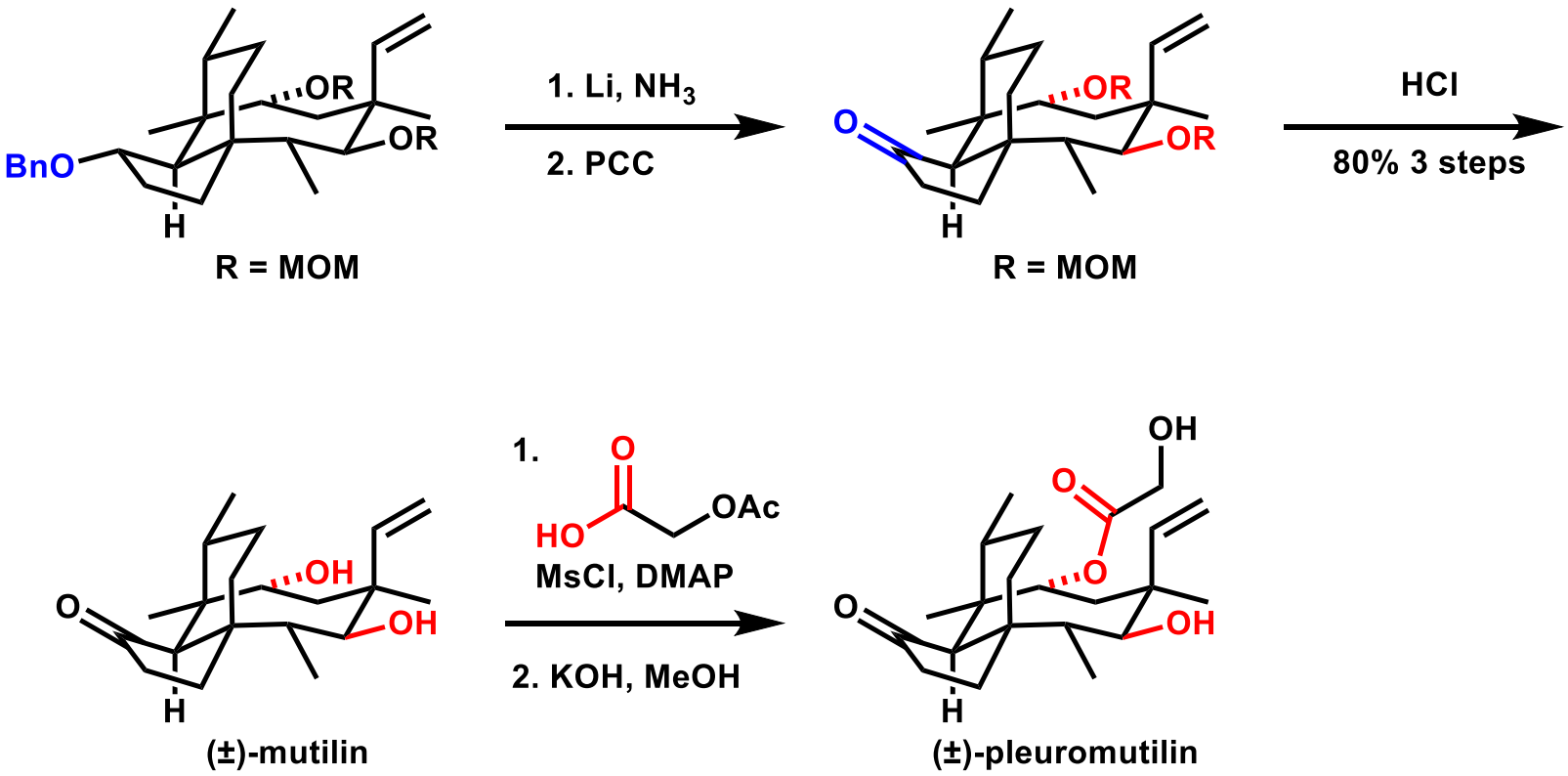


Other total syntheses



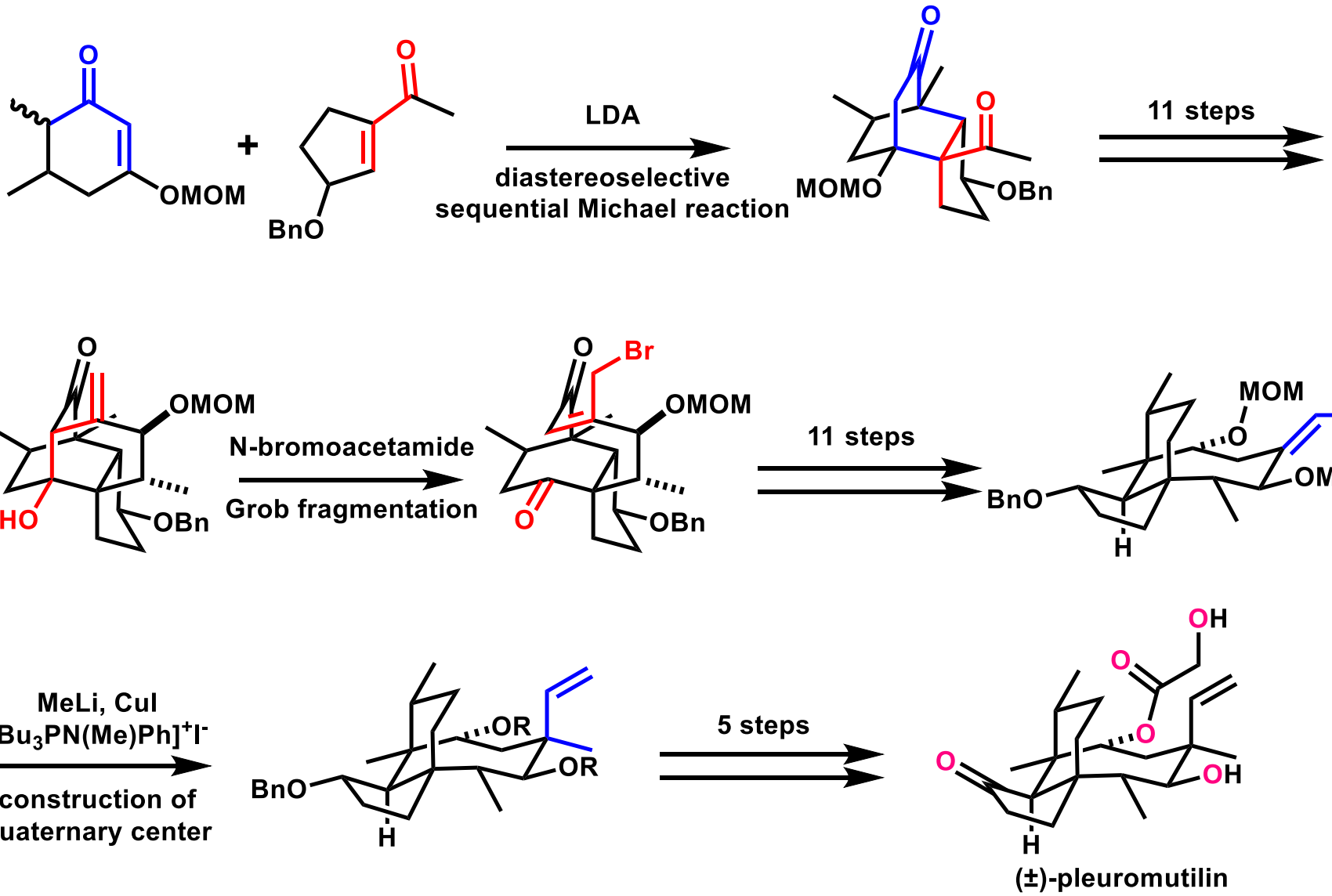
1) Gibbons, E. G. *JACS,* **1982**, *104*, 1767. 2) Boekman, R. K. Jr. et al. *JACS*, **1989**, *111* , 8284. 3) Procter, D. J. et al. *Chem. Eur. J.* **2013**, *19*, 6718.

Gibbons' synthesis (5)



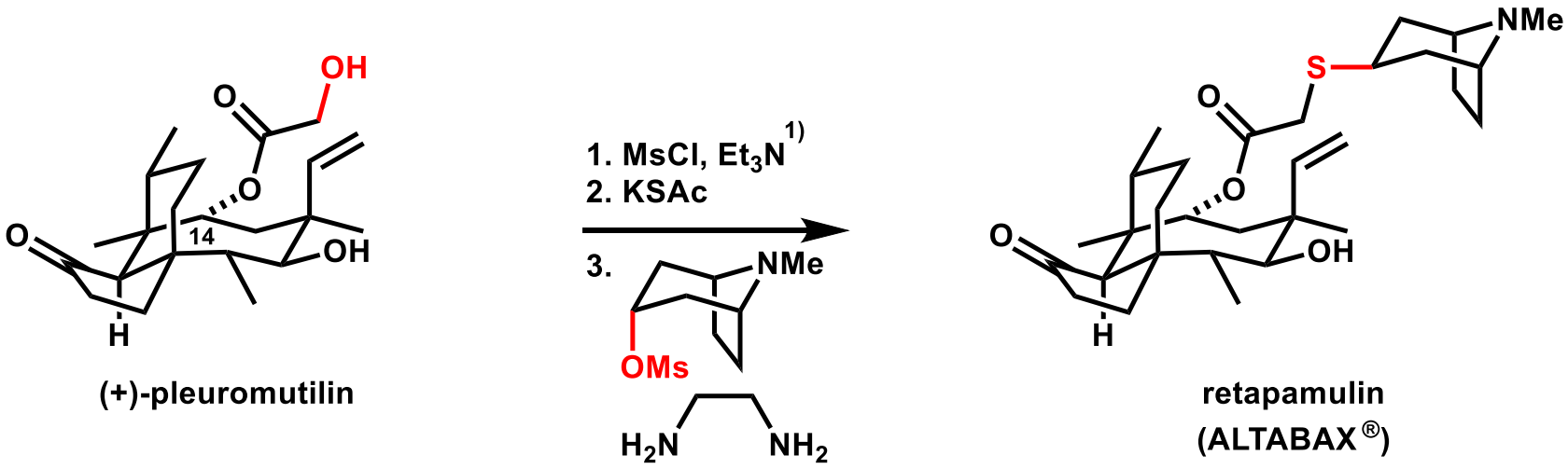
Gibbons, E. G. *JACS,* **1982**, *104*, 1767.

Short summary



Gibbons, E. G. *JACS*, **1982**, *104*, 1767.

Derivatization of preulomutilin

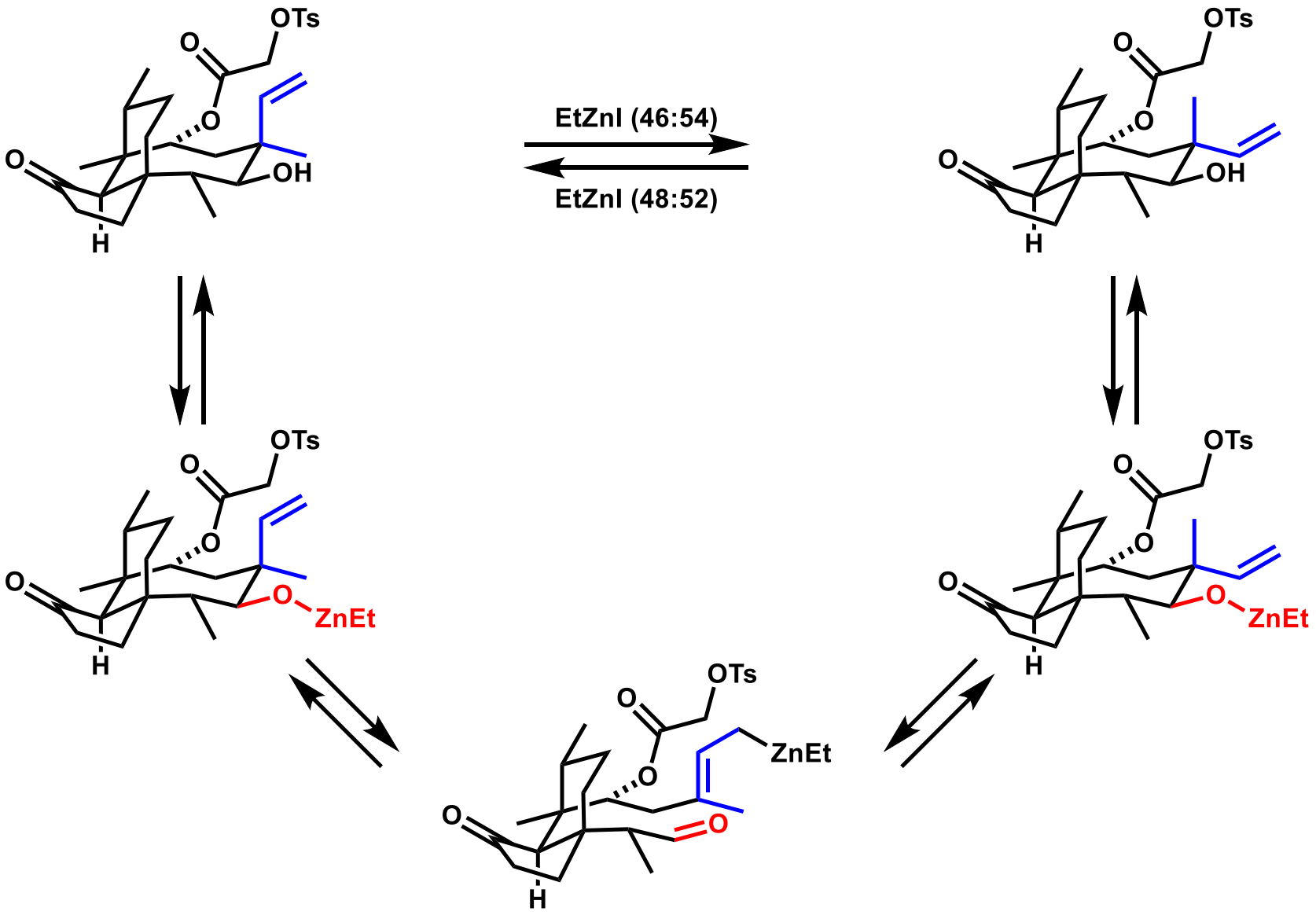


Antimacrobial activity[2)]

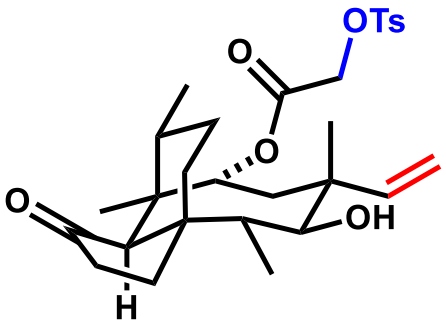
Species	ATCC number	MIC [μg/mL]
Staphylococcus aureus (Gram-positive bacteria)	ATCC 49951	< 0.03
Escherichia coli (Gram-negative bacteria)	ATCC 25922	32

1) WO 2010/056855 A1 2) WO 2015/110481 A1

Epimerization at C12 position

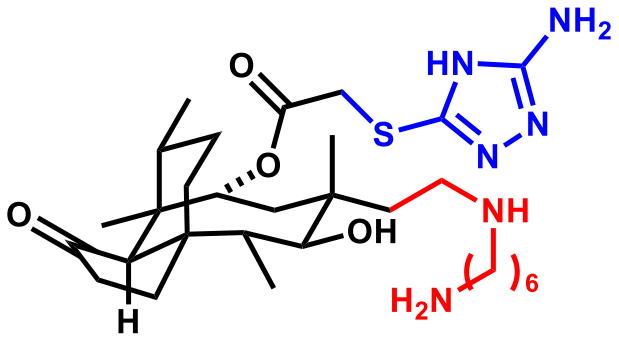


12-*epi*-preulomutilin derivative



12-*epi*-pleuromutilintosylate

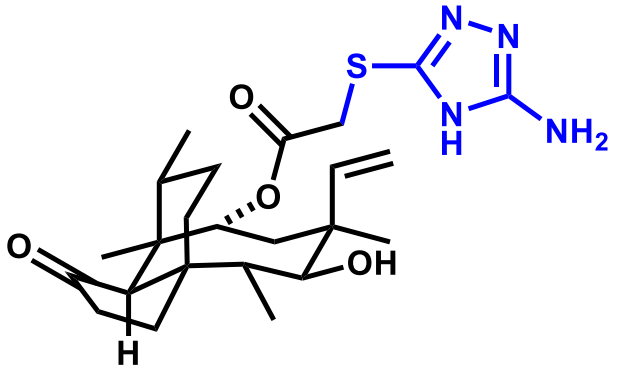
1. $(MeO)_3CH$, H_2SO_4
2. 9-BBN, H_2O_2
3. BocNHArSAc
   K_2CO_3
4. Dess-Martin ox.
5. $BocNH(CH_2)_6NH_2$
   $NaBH(OAc)_3$
6. HCl



A (12-*epi* derivative)

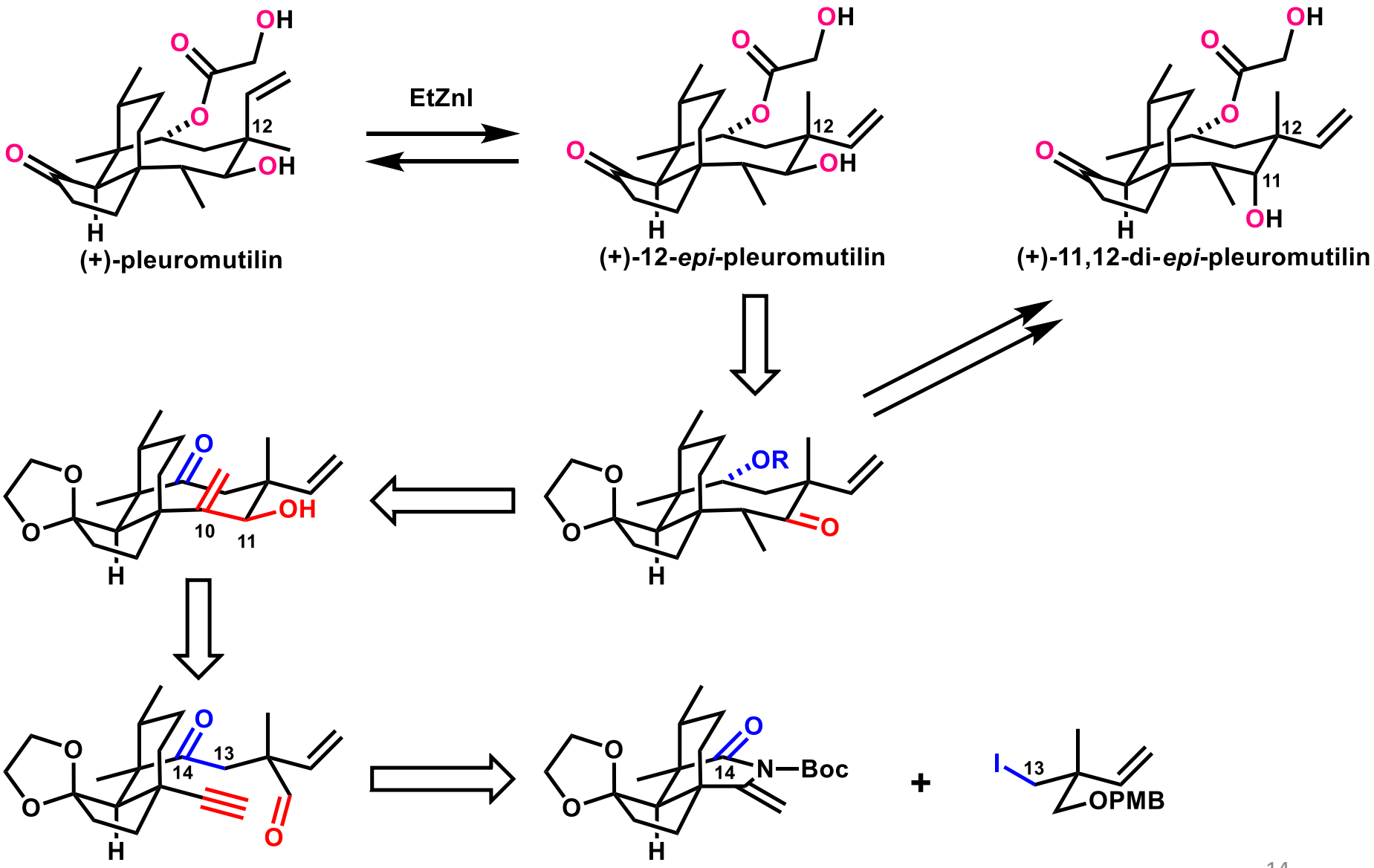
Antimacrobial activity

Species	ATCC number	MIC [μg/mL] A	MIC [μg/mL] B
Staphylococcus aureus (Gram-positive bacteria)	ATCC 49951	0.5	0.5
Escherichia coli (Gram-negative bacteria)	ATCC 25922	4	128

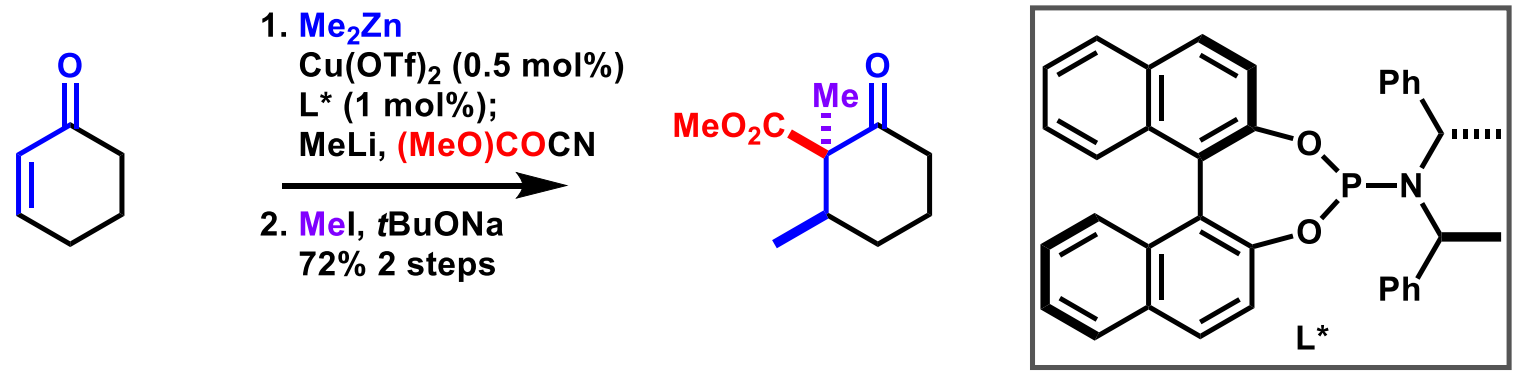


B (pleuromutilin derivative)

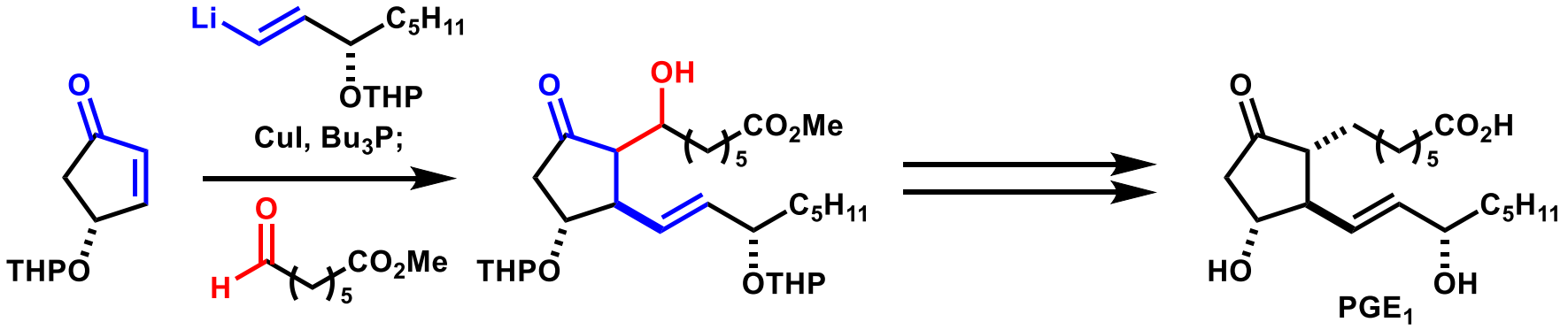
Retrosynthesis



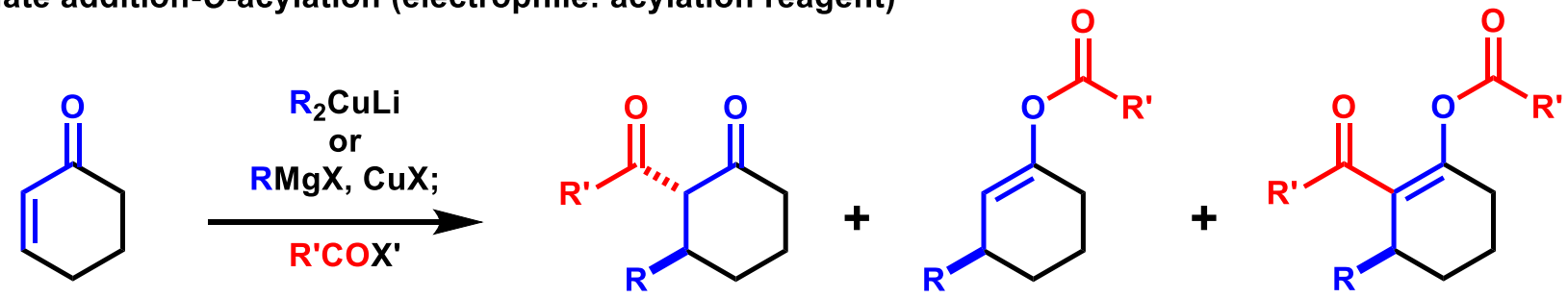
Herzon's synthesis (1)



Noyori's 3 component coupling (electrophile: aldehyde)

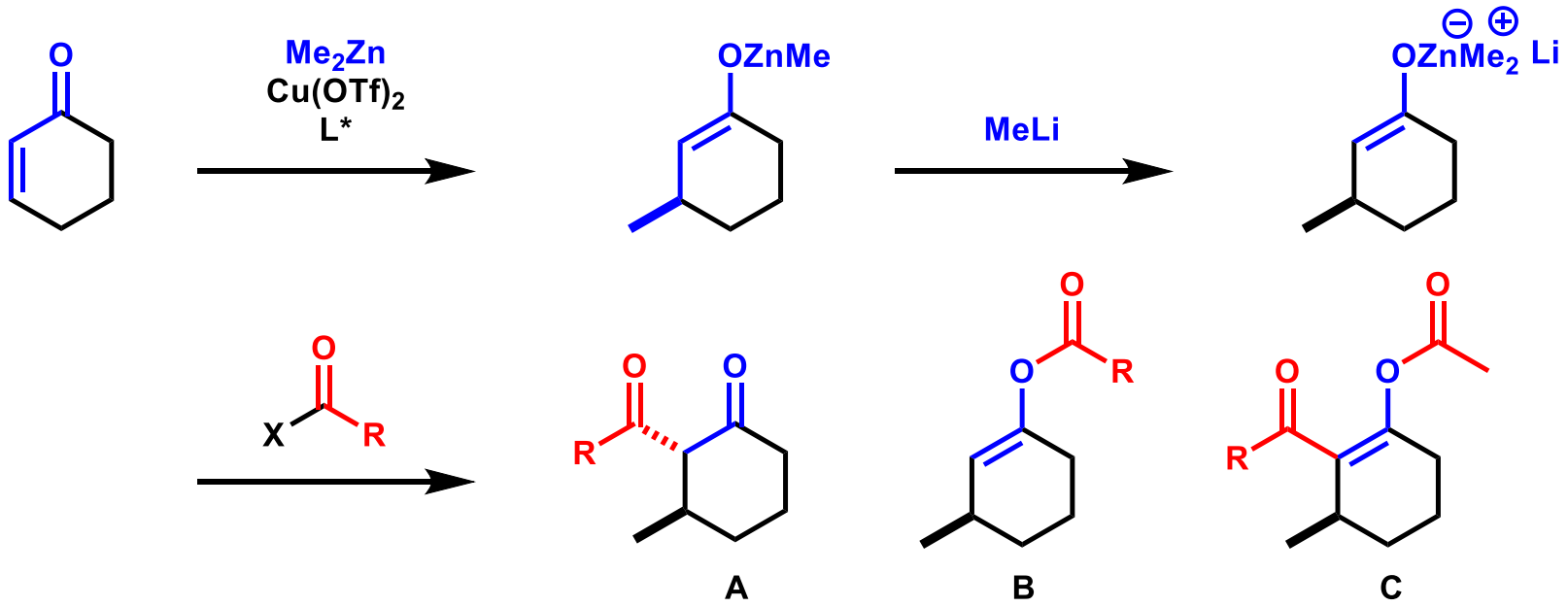


Conjugate addition-*C*-acylation (electrophile: acylation reagent)

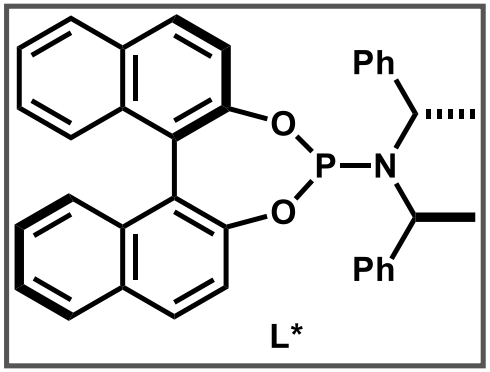


Noyori, R. et al. *TL*, **1982**, *23*, 4057.

Zincate mediated 3 component coupling reaction

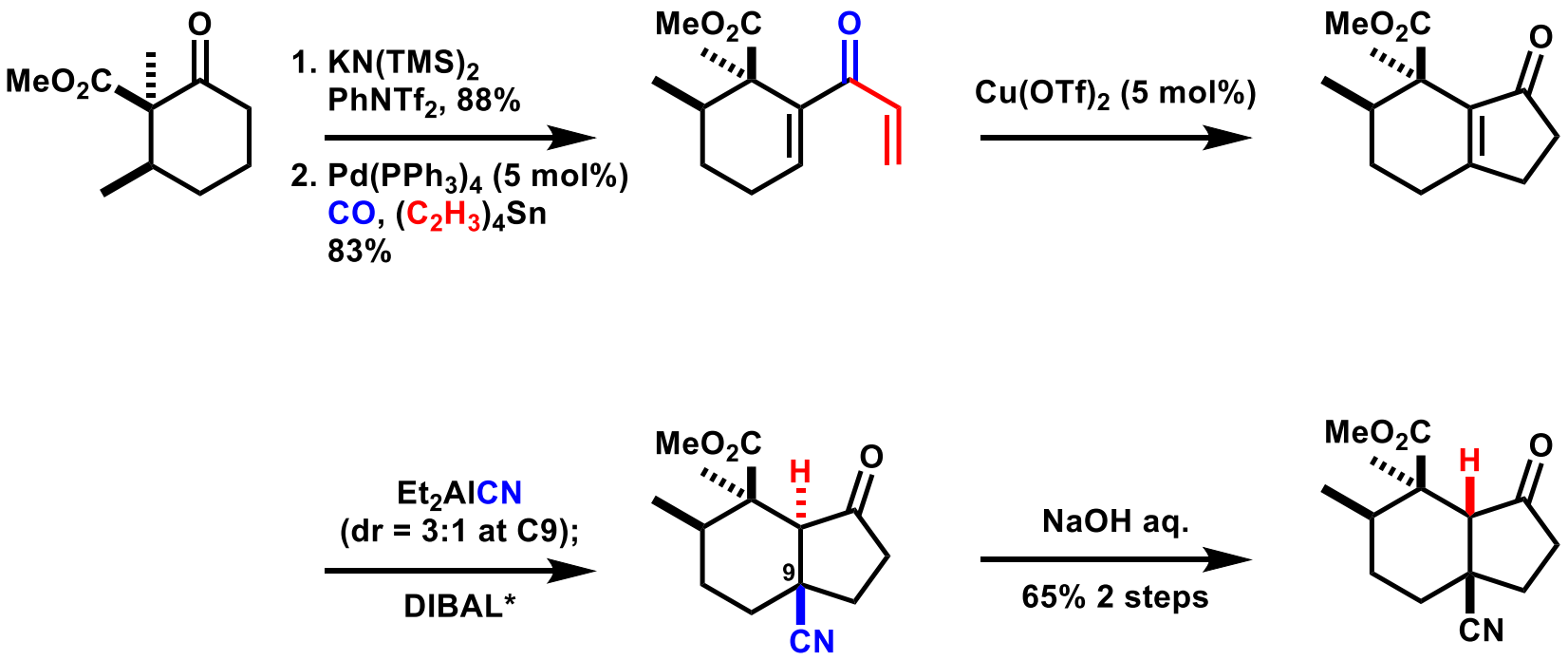


R	X	yield (%) A	B	C	
Me	Cl	80	<1	<1	
Me	Cl	11	36	12	w/o MeLi
Ph	Cl	81	-	-	
OMe	CN	72	-	-	
OMe	CN	<1	-	-	w/o MeLi



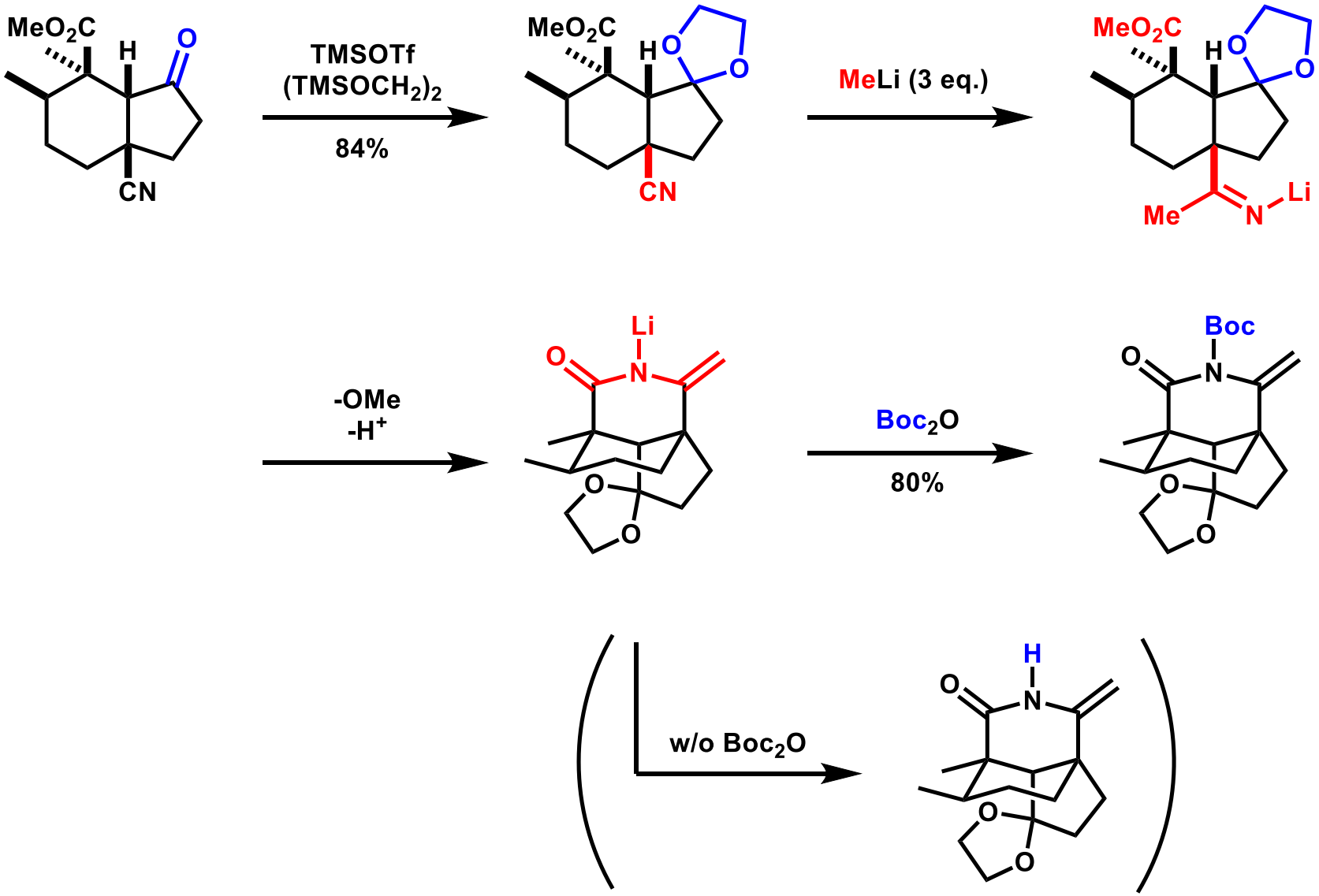
Herzon, S. B. et al. *OL*, **2016**, *18*, 4880.

Herzon's synthesis (2)

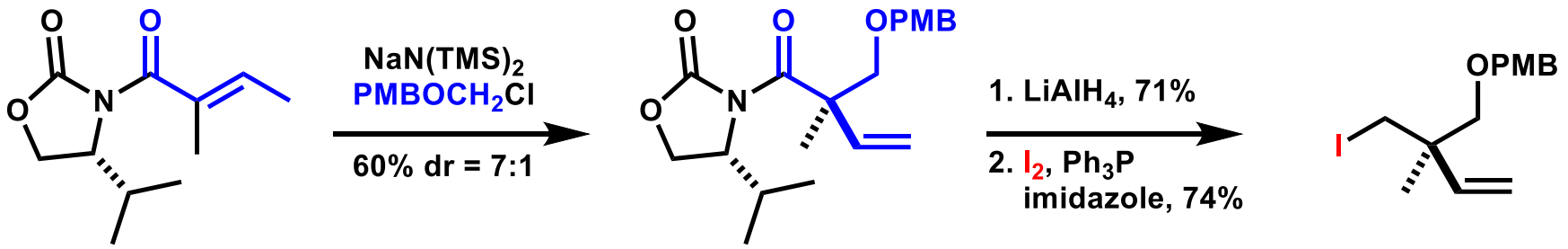


*: selective reduction of undesired epimer

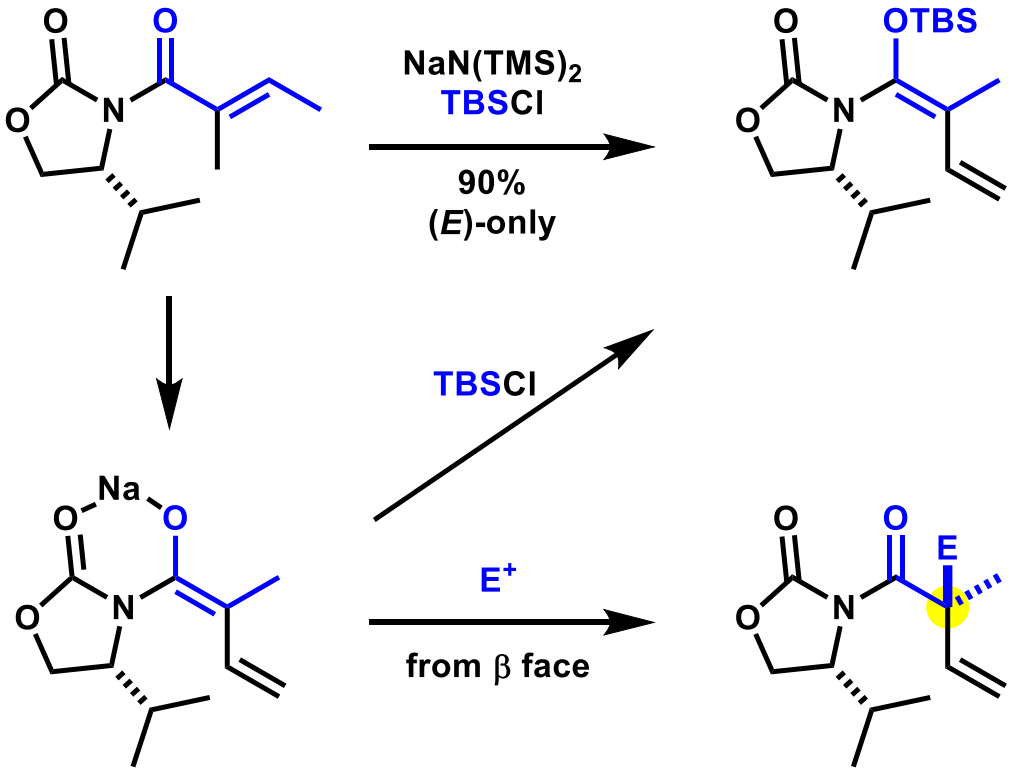
Herzon's synthesis (3)



Herzon's synthesis (4)

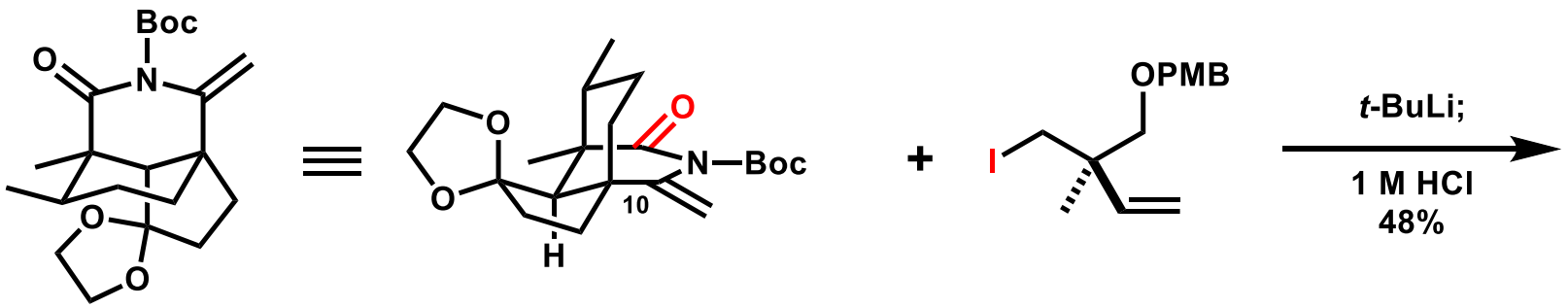


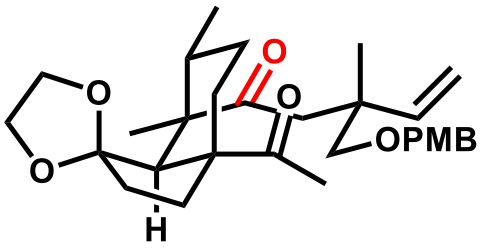
Stereoselectivity



Kobayashi, S. et al. *TL,* **2000**, *41*, 6429.

Herzon's synthesis (5)



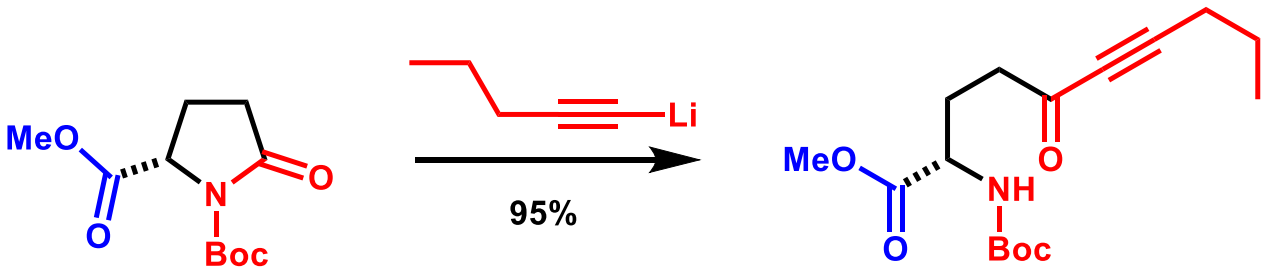


rigid cyclic structure of electrophile fixed the C=O bond
-> nucleophile approached from the lower face of the lactam

minimized nonbonded interaction around carbonyl group
-> C10 position is sp2 carbon

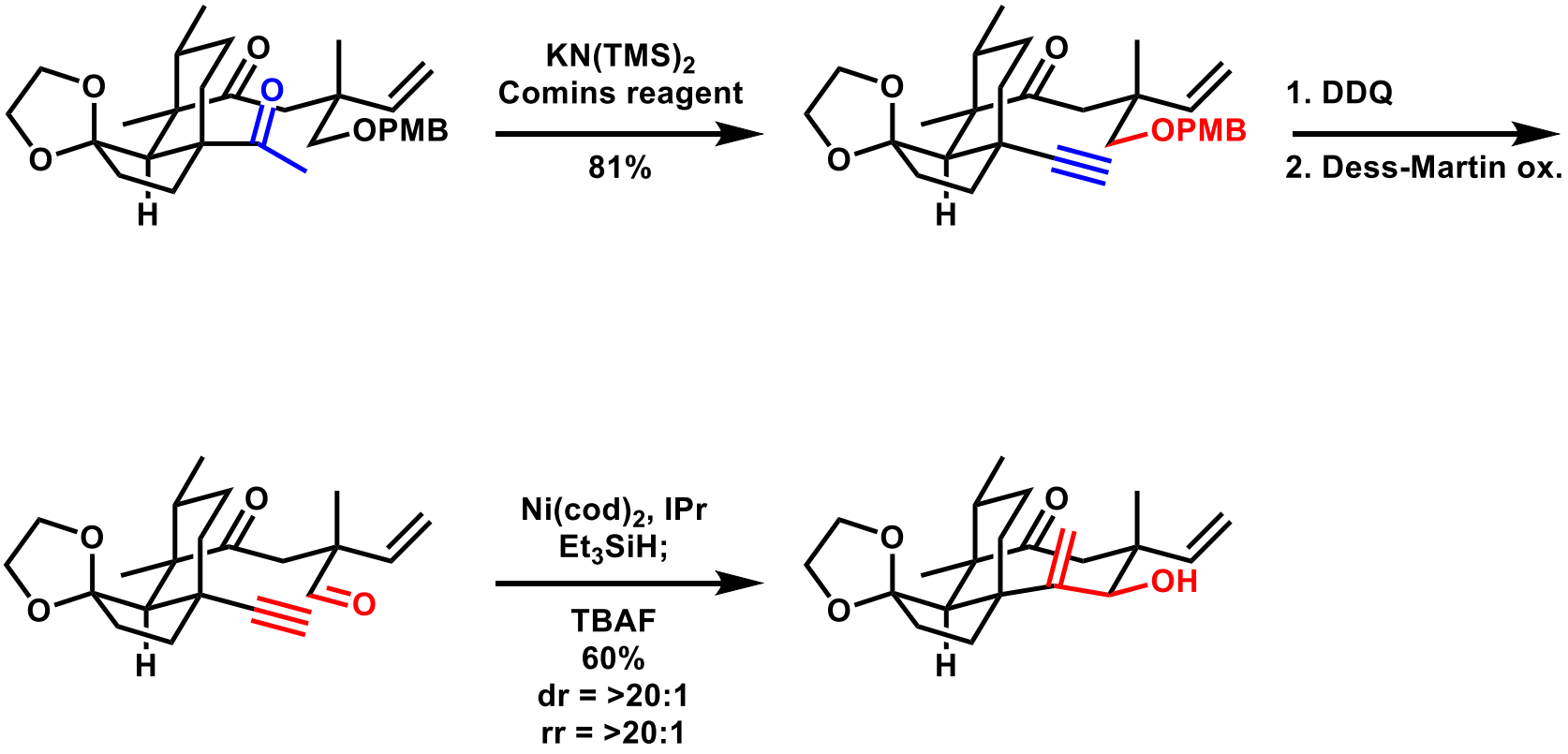
activation of carbonyl group
-> Boc protected amide shows higher reactivity than Me ester

relative reactivity (Boc protected amide vs Me ester)

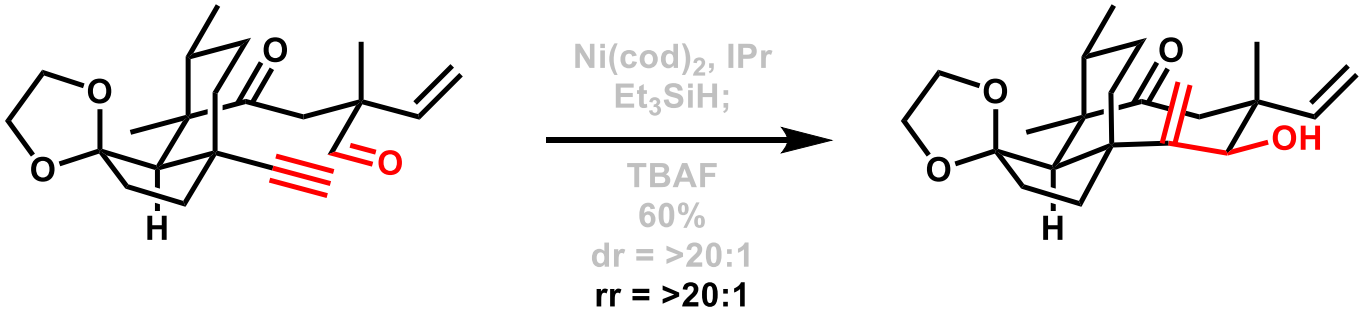


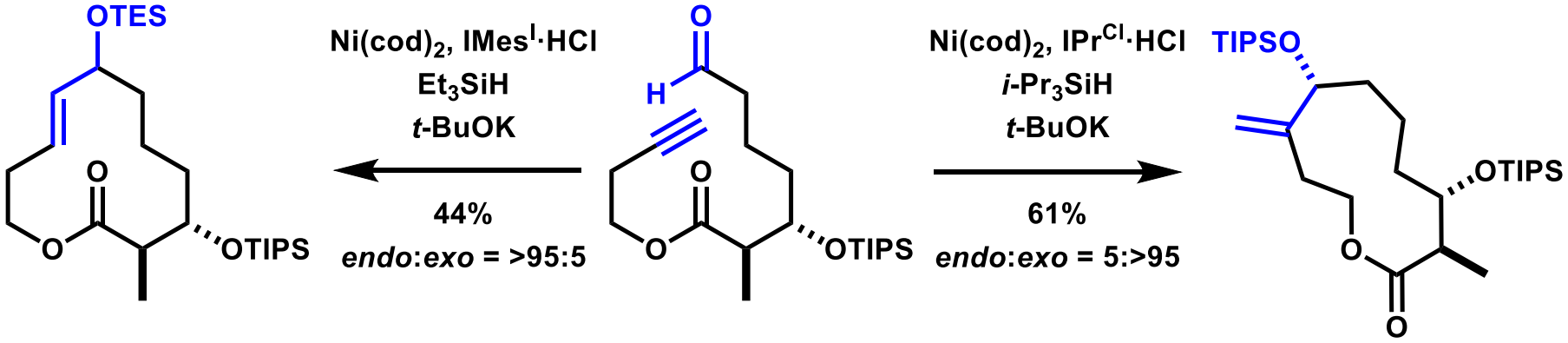
Renault, J. et al. *EurJOC.* **2014**, 4506.

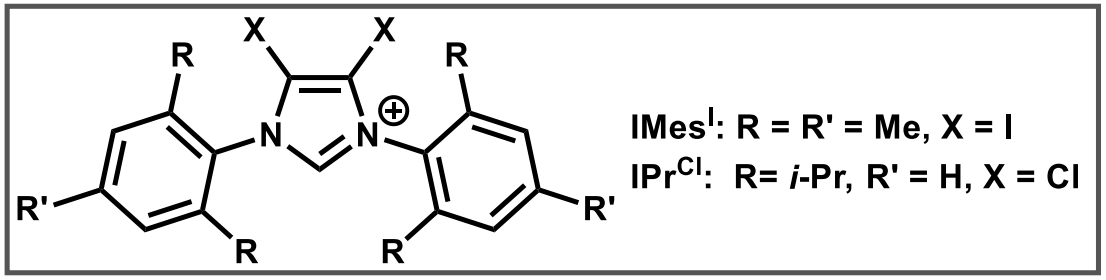
Herzon's synthesis (6)



Regioselective reductive cyclization (1)

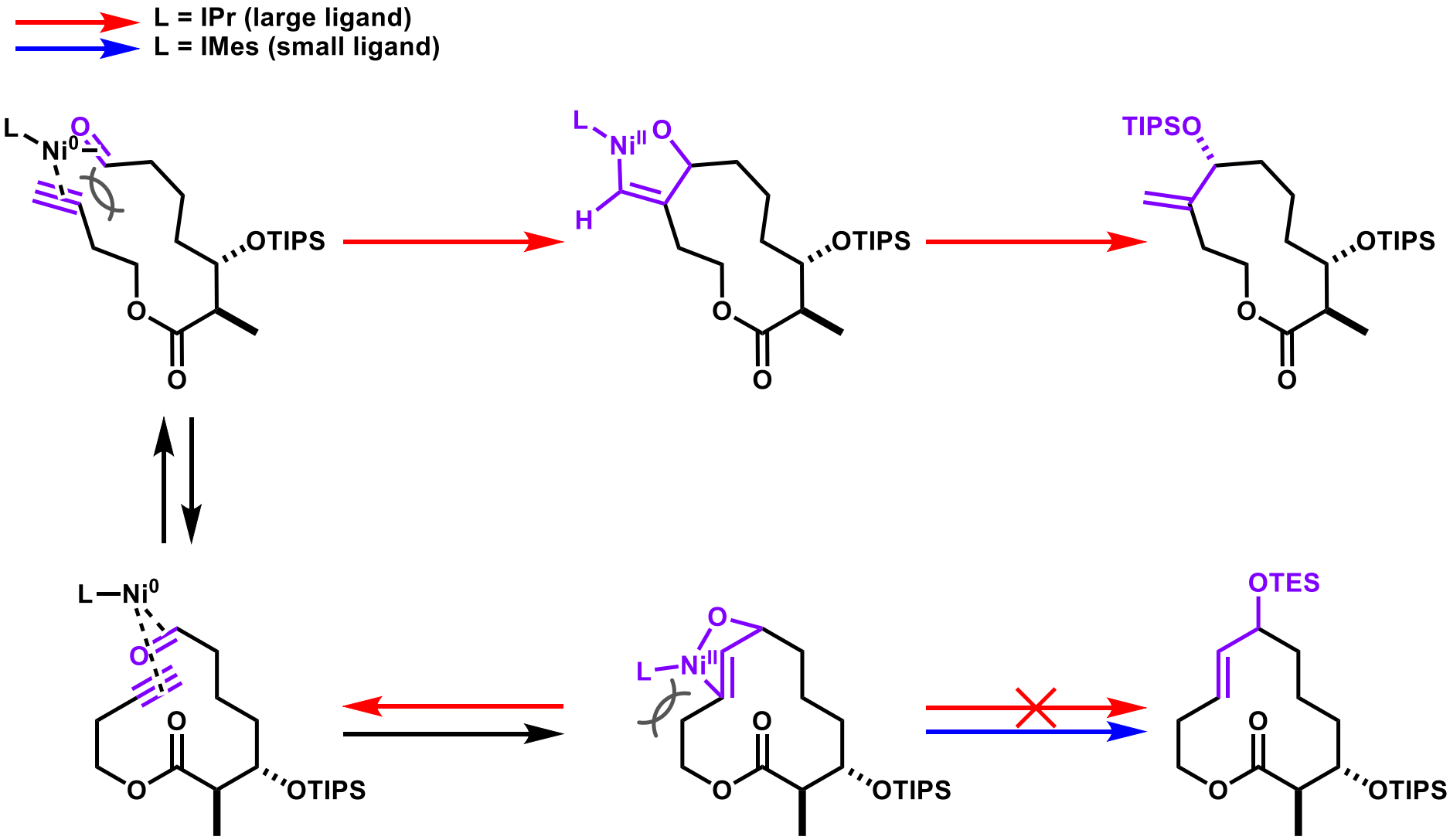






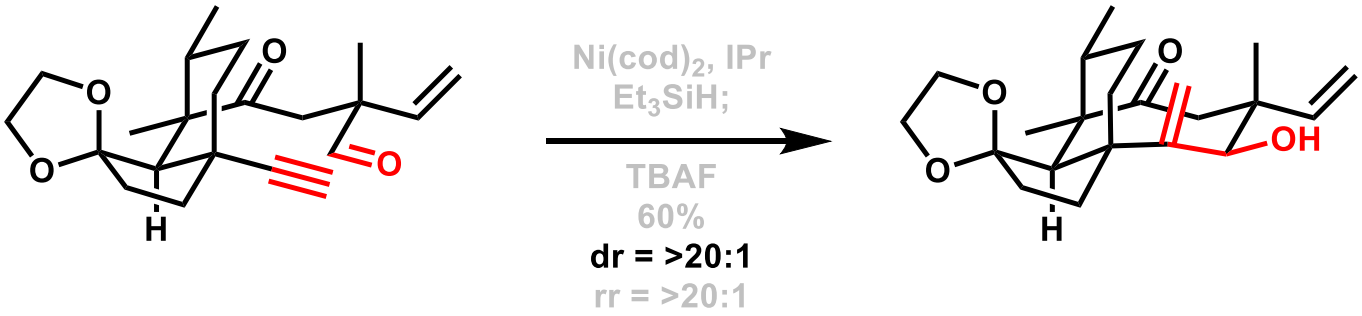
Montgomery, J. et al. *OL.* **2015**, *17*, 1493.

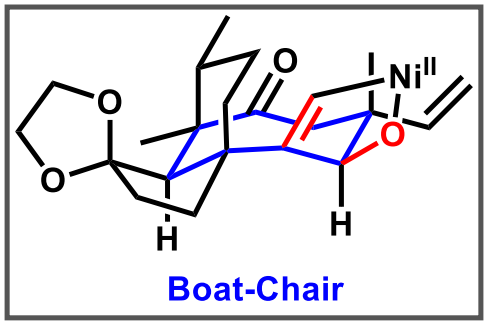
Regioselective reductive cyclization (2)



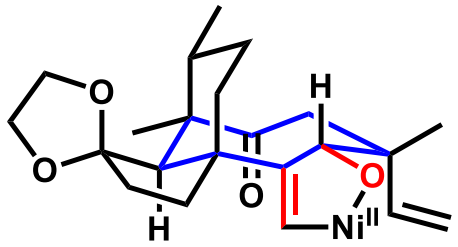
Montgomery, J. et al. *OL.* **2015**, *17*, 1493.

Stereoselectivity

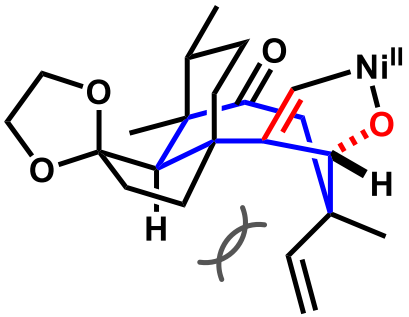




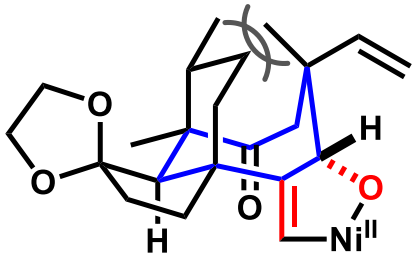
Boat-Chair



Chair-Chair

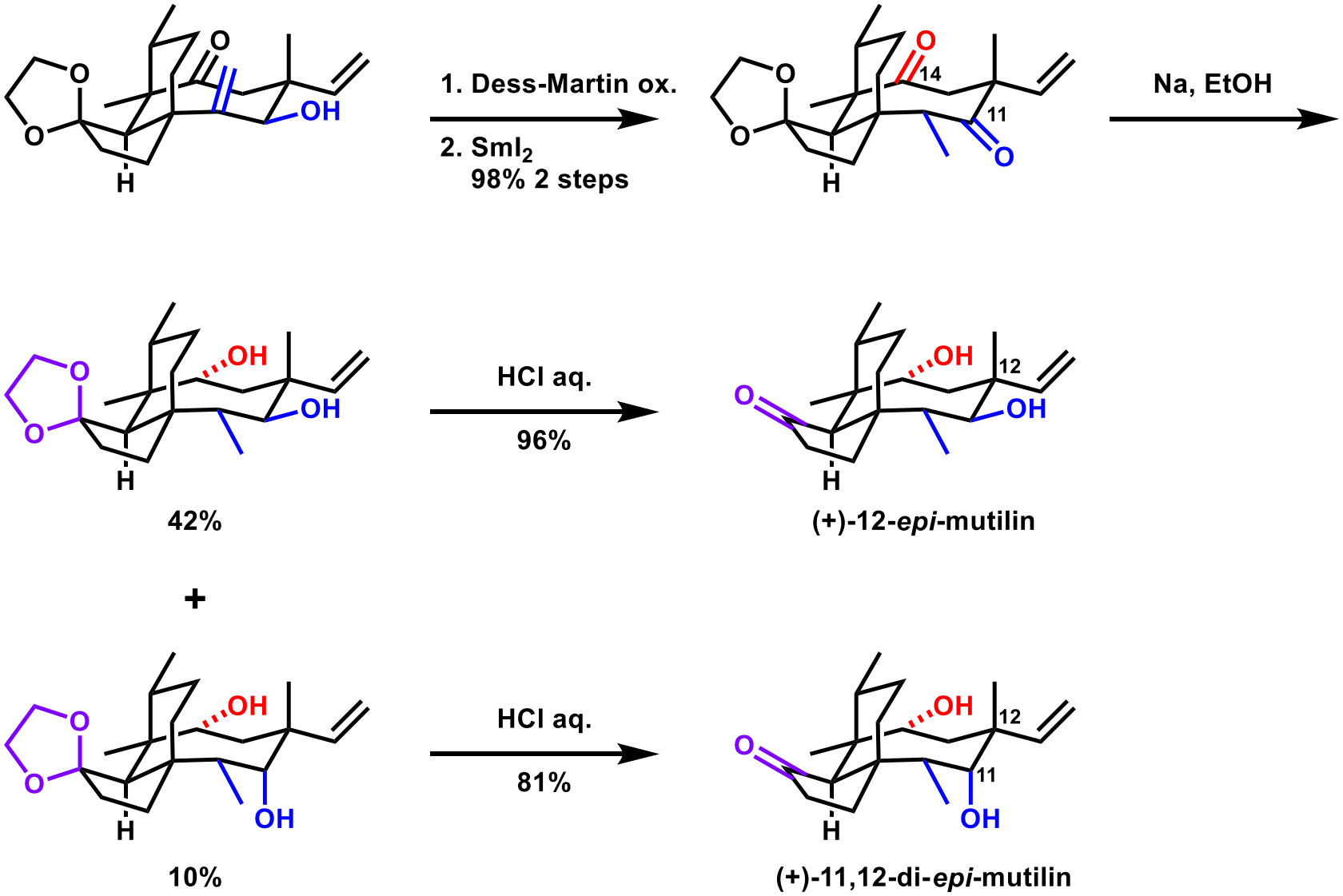


Boat-Boat

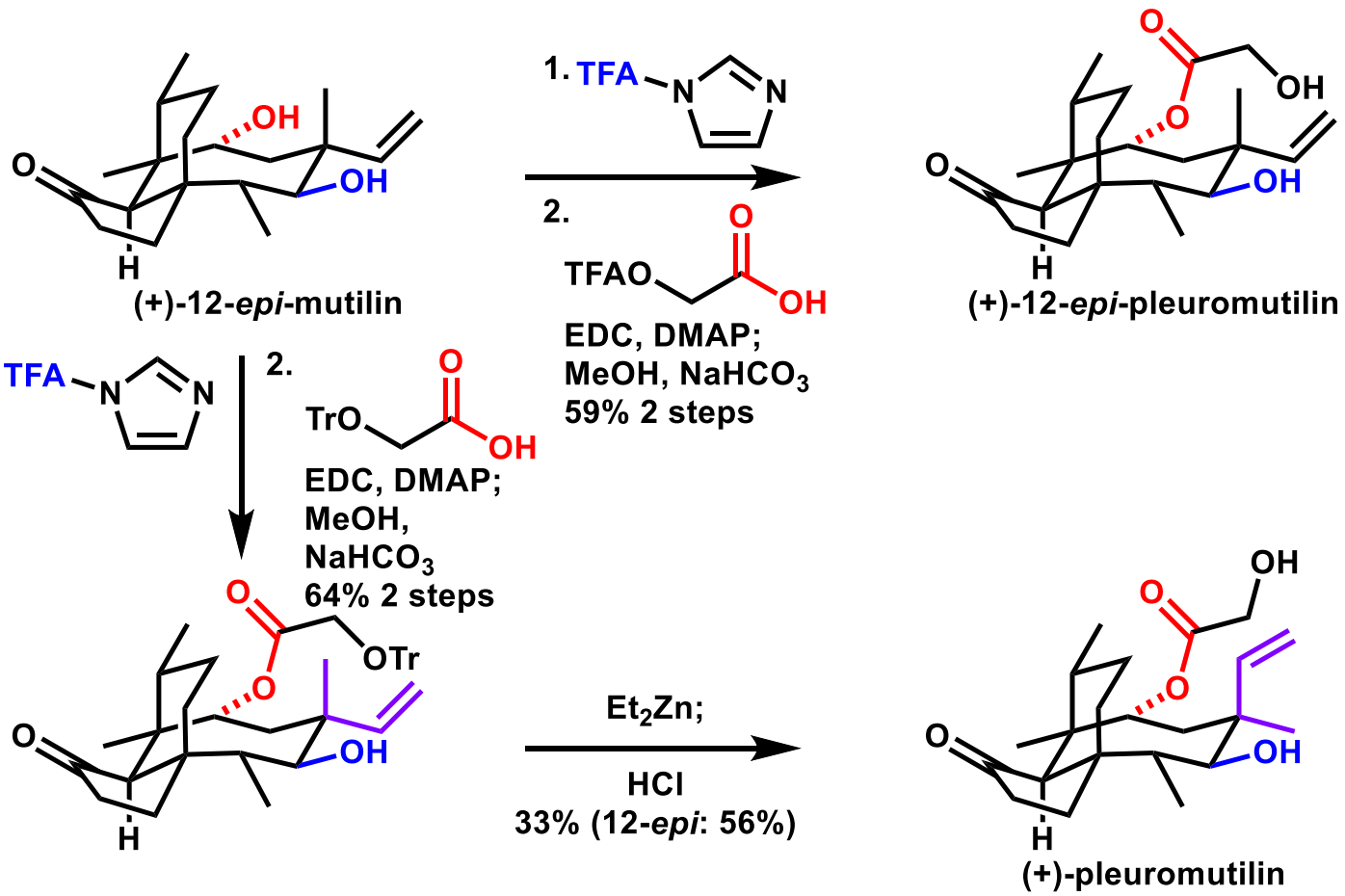


Chair-Boat

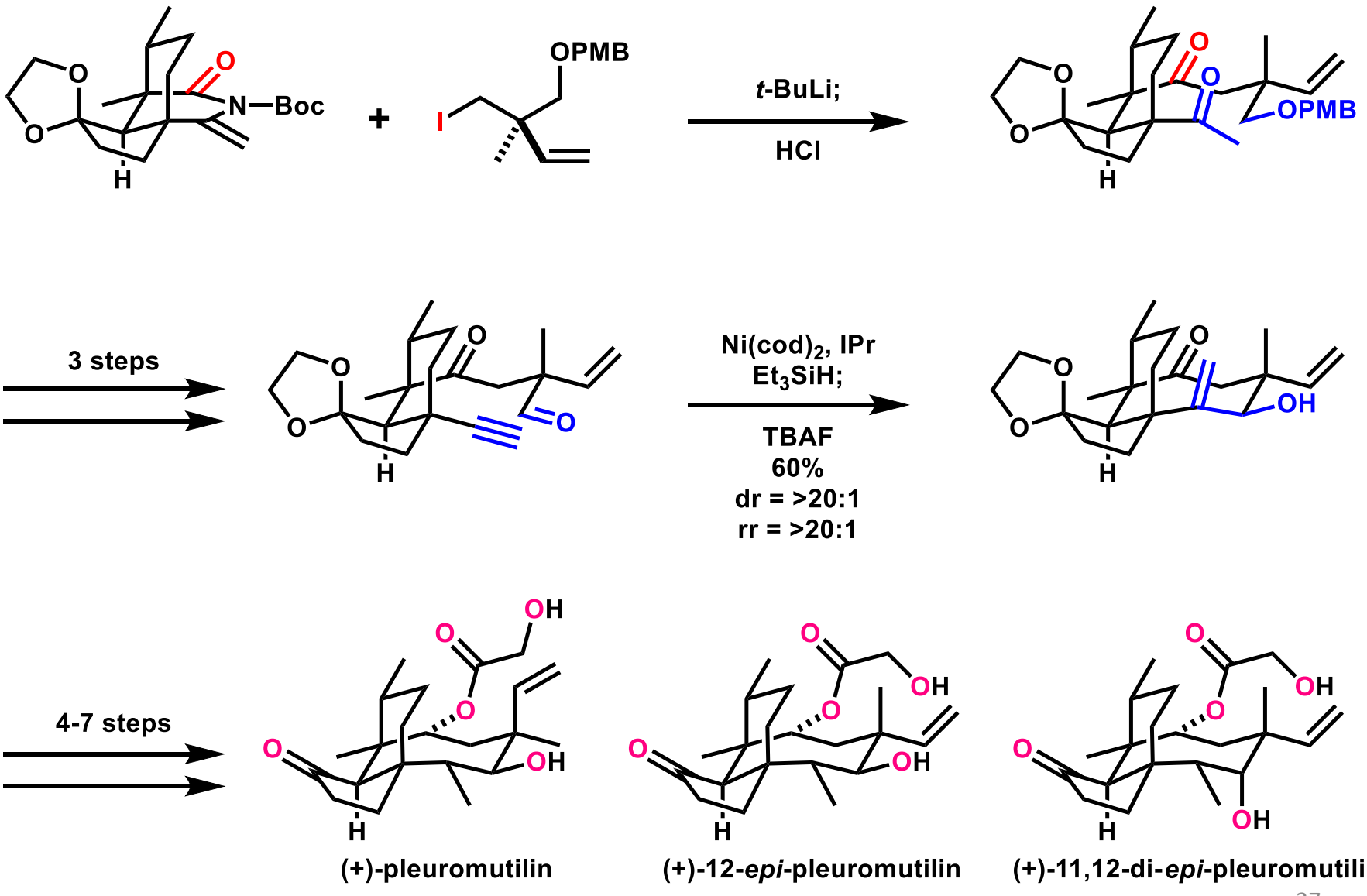
Herzon's synthesis (7)



Herzon's synthesis (8)



Summary


O
N—Boc
H
+
I
OPMB
t-BuLi;
HCl
O
OPMB
3 steps
Ni(cod)2, IPr
Et3SiH;
TBAF
60%
dr = >20:1
rr = >20:1
OH
4-7 steps
(+)-pleuromutilin
(+)-12-epi-pleuromutilin
(+)-11,12-di-epi-pleuromutilin