Current Literature July 22 2017

Keita Takubo -Wipf group-

A modular and enantioselective synthesis of the pleuromutilin antibiotics

Stephen K.Murphy, Mingshuo Zeng, Seth B. Herzon*

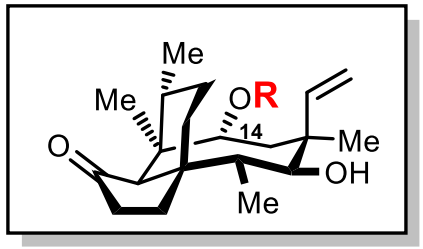
Science **2017**, *356*, 956-959.

Key Facts on Antimicrobial Resistance

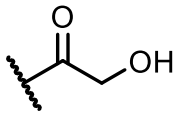
- Antimicrobial resistance (AMR) threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi.

WHO Website (http://www.who.int/mediacentre/factsheets/fs194/en/)

Pleuromutilin and C14-Modified Derivatives



Natural products



(+)-pleuromutilin (**1**)

H

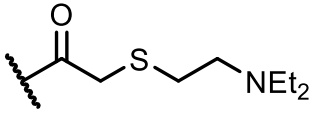
(+)-mutilin (**2**)

Isolation: Pleurotus mutilus (Clitopilus scyphoides)

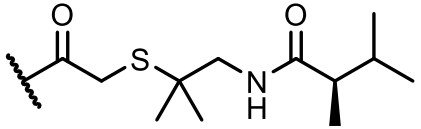
Activity: Inhibition of protein synthesis in bacteria by binding to the peptidyl transferase component of the 50S subunit of ribosomes.

R =

Veterinary antibiotics

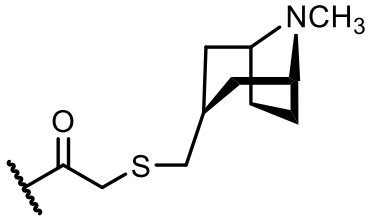


tiamulin (DENEGARD®)



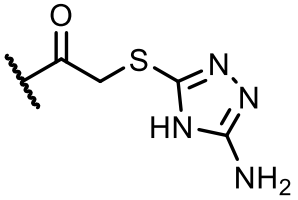
valnemulin (ECONOR®)

Human topical antibiotic

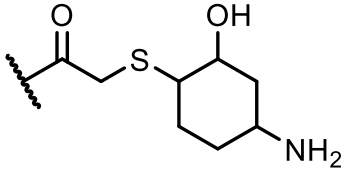


retapamulin (ALTABAX®, **3**)
anti-MRSA infections

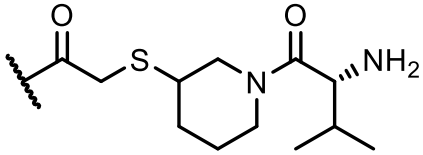
Unlisenced



azamulin



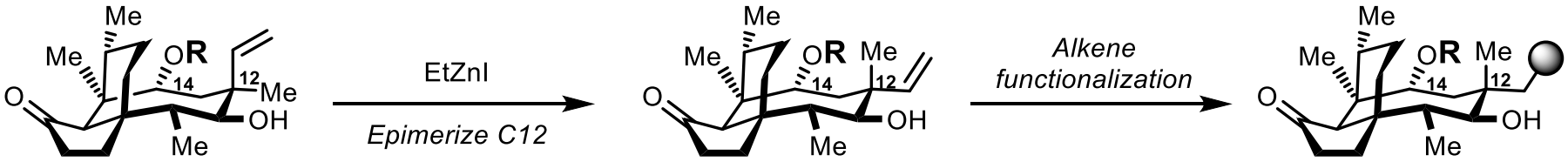
BC-3781



BC-3205

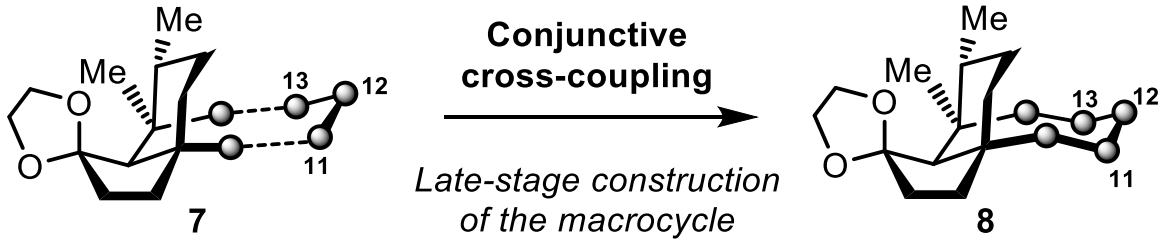
D. J. Procter *et al. Tetrahedron* **2014**, *70*, 6911-6930

Retrosynthetic anlysis of the mutilin scaffold



(+)-Pleuromutilins **(+)-12-*epi*-pleuromutilins**

- Epimerization at C12 caused expression of activity against various Gram-negative pathogens (GNPs)
- Functionalization of the alkene at C12 extends the activity against GNPs

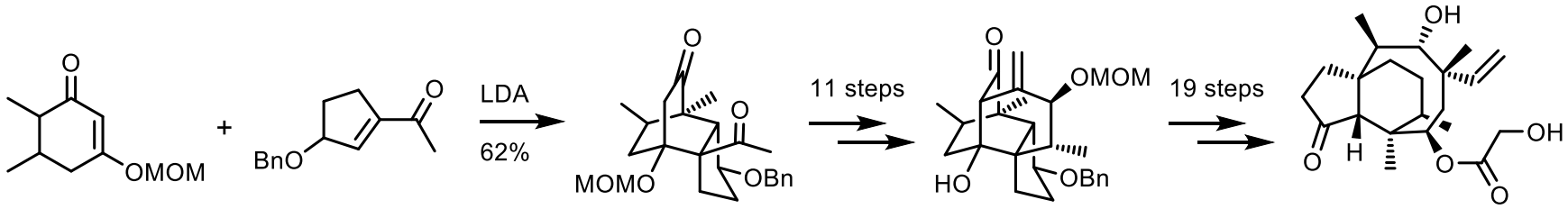


This approach maximizes the scope of accessible derivatives at positions 11 to 13

H. Berner et al. *Monatsh. Chem*. **1986**, *117*, 1073−1080
K. Thirring et al., U.S. Patent WO2015110481A1, **2015**

Total Synthesis of Pleuromutilin

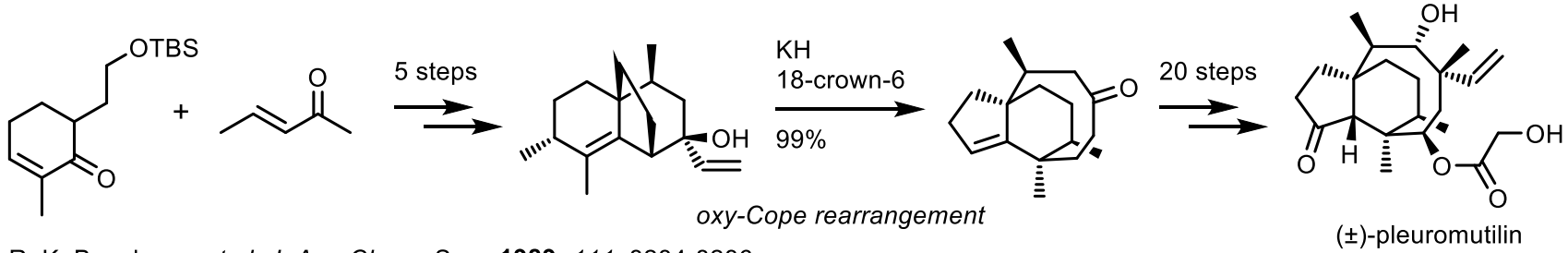
Gibbons' synthesis (1982): • Racemic • 31 linear steps • Overall <0.6% yield



(±)-pleuromutilin

E. G. Gibbons *J. Am. Chem. Soc.*, **1982**, *104*, 1767-1769

Boeckman's synthesis (1989): • Racemic • 27 linear steps • Overall 0.4% yield

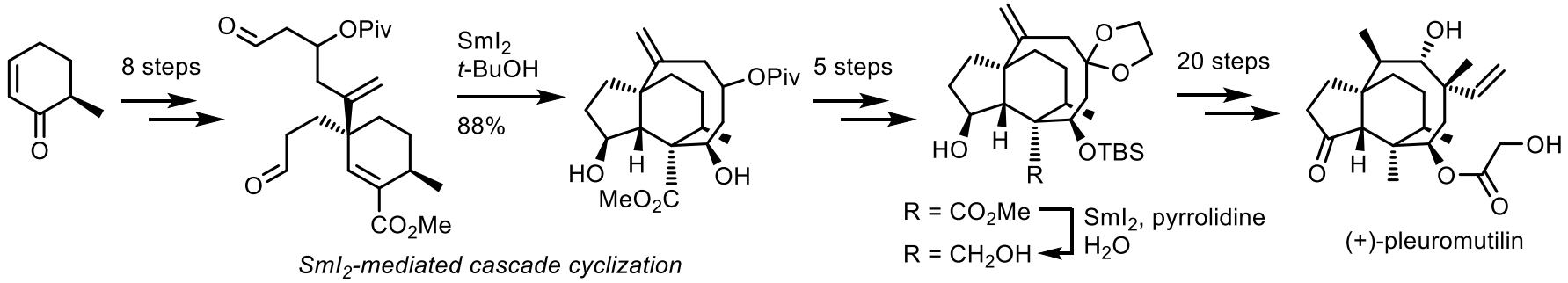


oxy-Cope rearrangement

(±)-pleuromutilin

R. K. Boeckman *et al*. *J. Am. Chem. Soc.*, **1989**, *111*, 8284-8286

Procter's synthesis (2013): • Non-racemic • 34 linear steps • Overall 0.7% yield



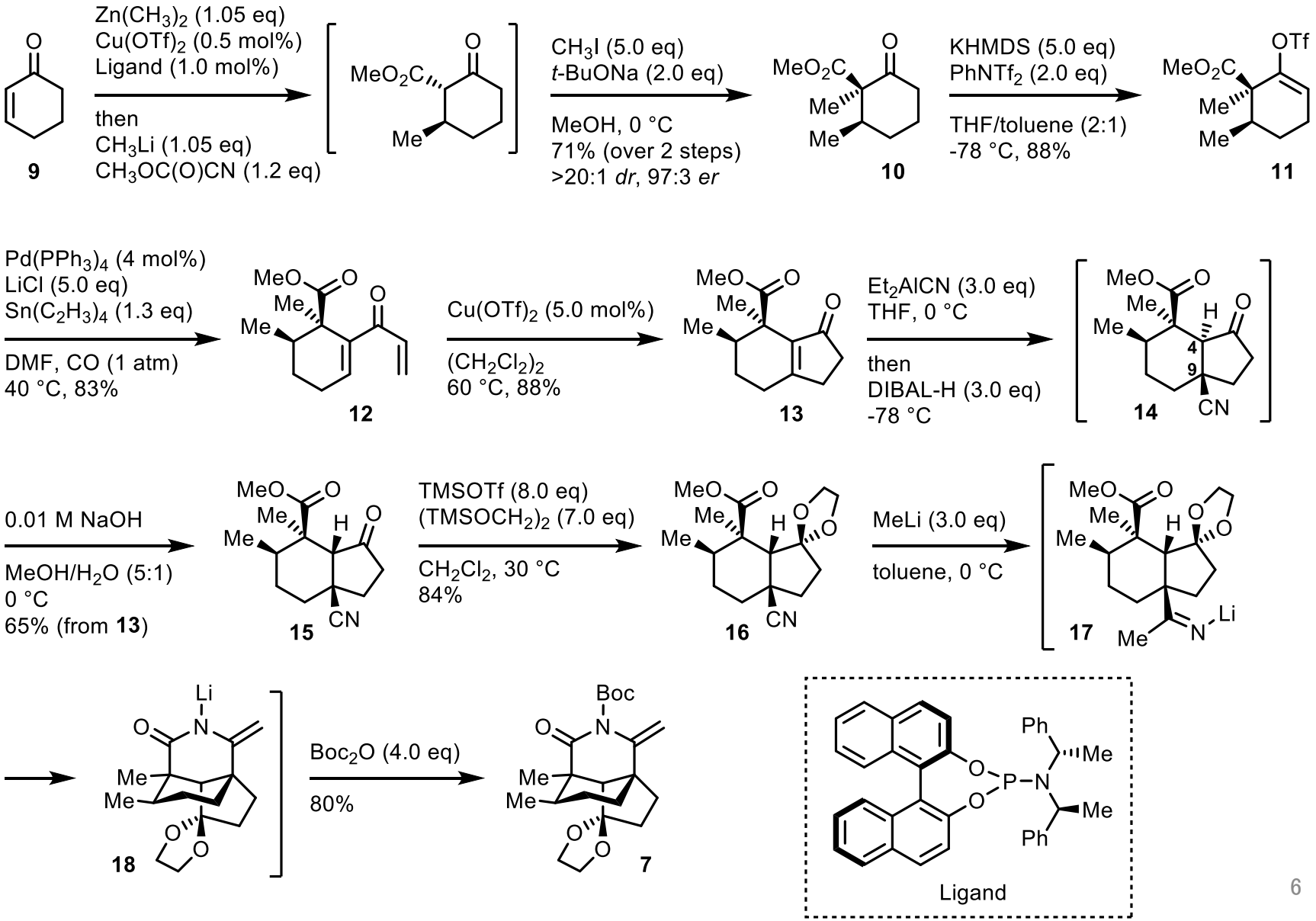
SmI_2-mediated cascade cyclization

SmI_2-amine-H_2O mediated reduction

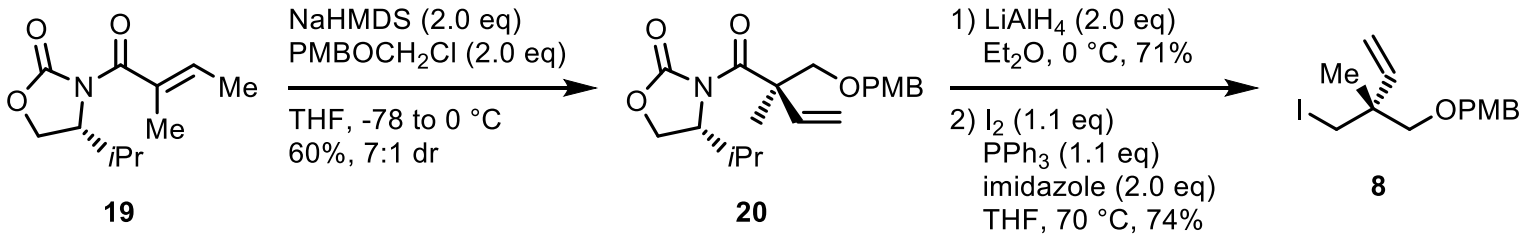
(+)-pleuromutilin

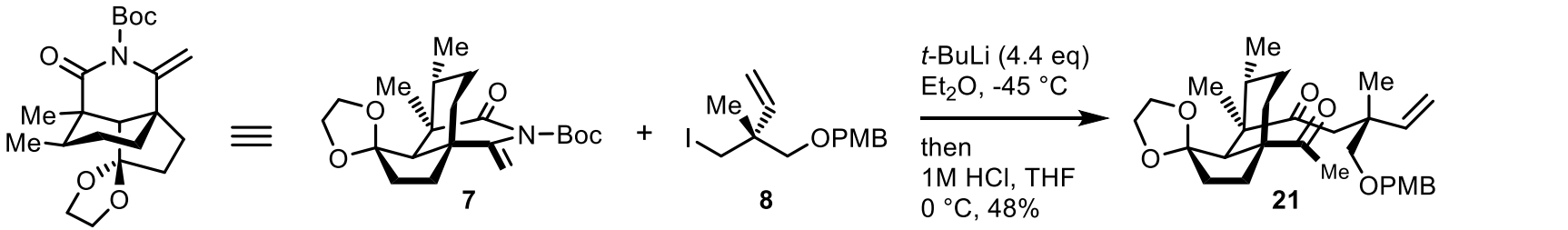
D. J. Procter *et al*. *Chemistry*, **2013**, *19*, 6718-6723

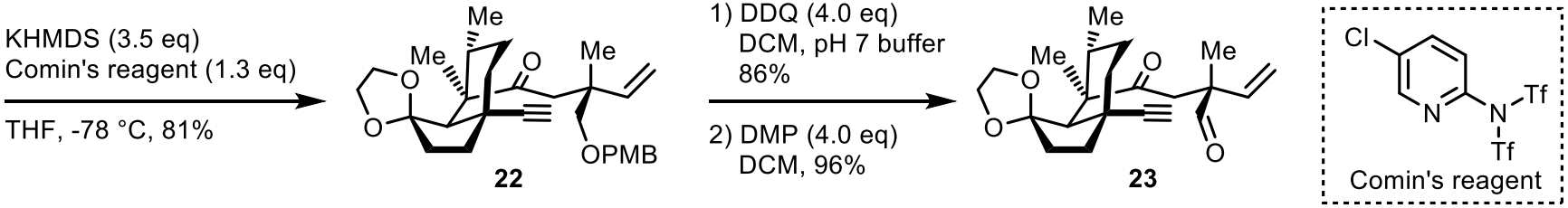
Synthesis of Coupling Fragment 7

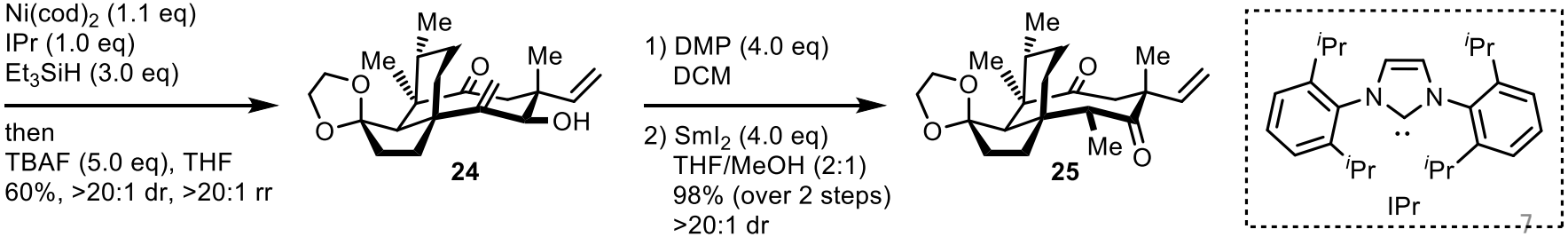


Synthesis of Diketone 25

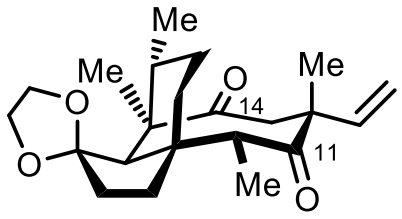








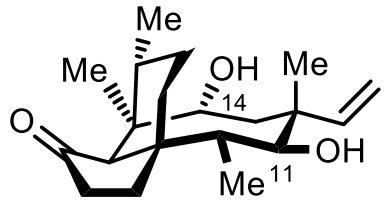
Synthesis of (+)-12-*epi*-mutilin and (+)-11,12-di-*epi*-mutilin



25

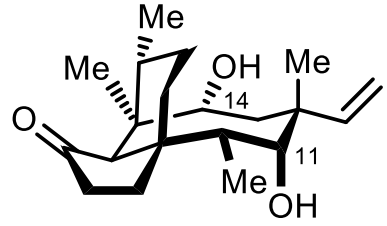
Na (excess)
EtOH, >20 °C, 52%
C14: >20:1 dr
C11: equatorial/axial, 3:1 dr

then
conc. HCl (excess)
THF/MeOH (1:1)
96% (for **4**), 81% (for **26**)



(+)-12-*epi*-mutilin (**4**)

+

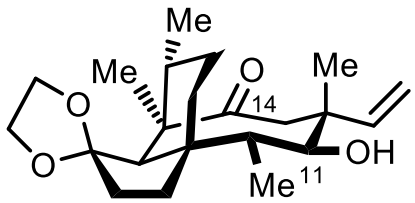


(+)-11,12-di-*epi*-mutilin (**26**)

conditions	**28** : **27**	yield
1. SmI_2, H_2O	1.3 : 1	80%
2. $LiEt_3BH$	1 : >20	81%

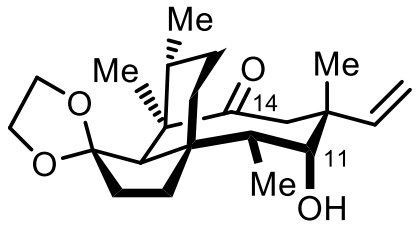
Na (excess)
EtOH, >20:1 dr
then
conc. HCl (excess)

92% (for **28** to **4**)
81% (for **27** to **26**)



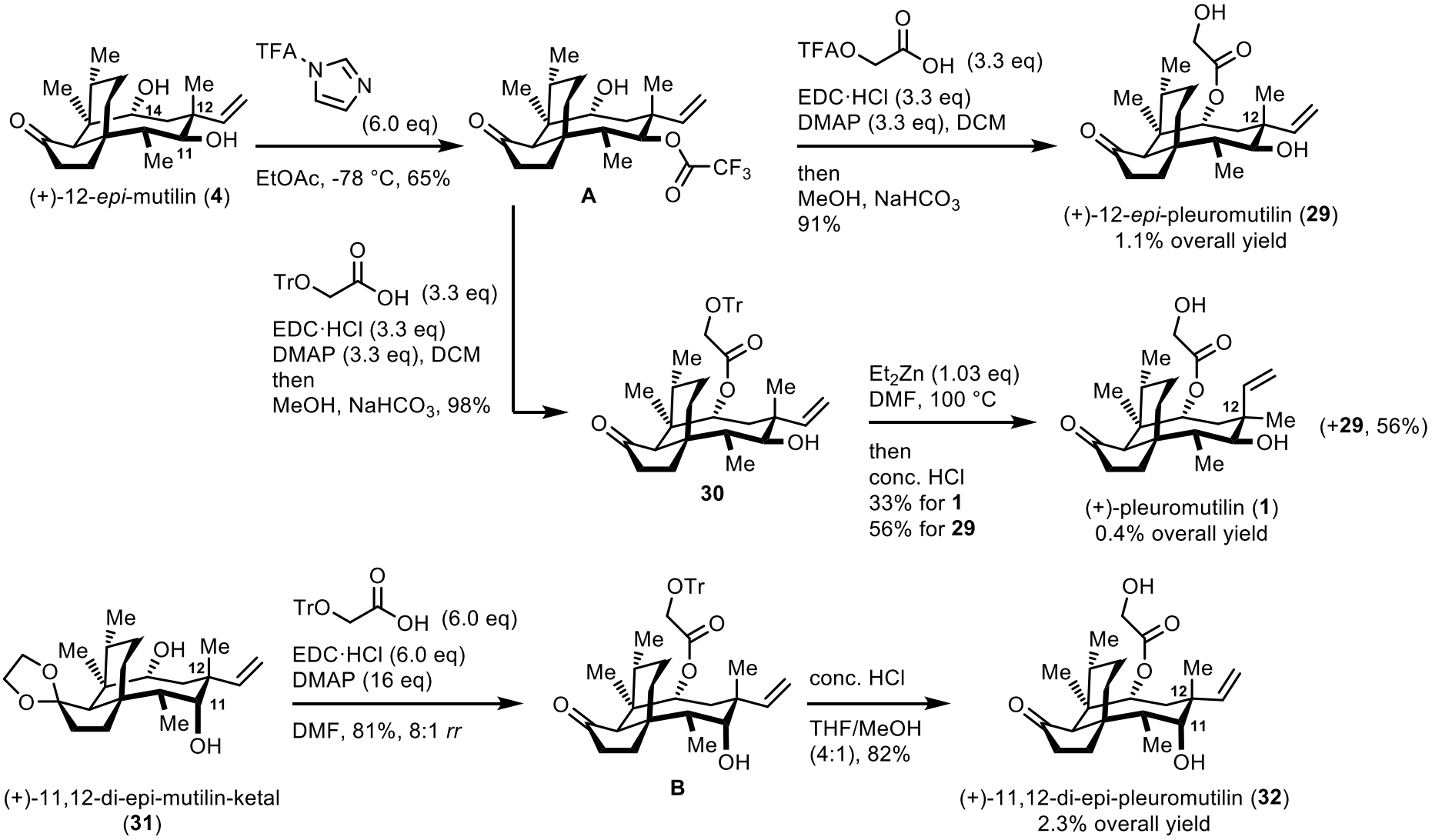
28

+

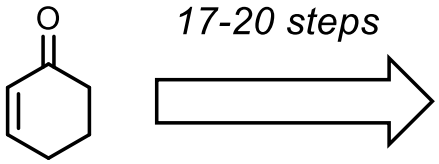


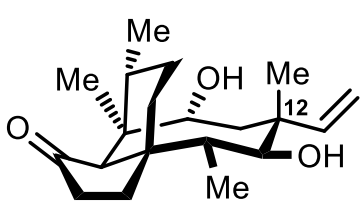
27

Synthesis of (+)-12-*epi*-pleuromutilin, (+)-pleuromutilin and (+)-11,12-di-*epi*-pleuromutilin



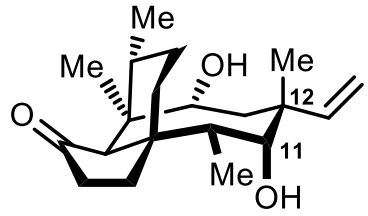
Conclusion



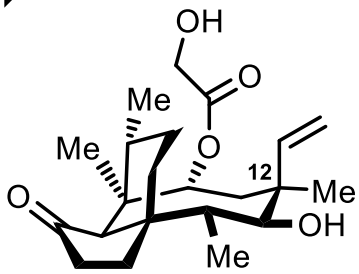


(+)-12-*epi*-mutilin (**4**)
3.6% overall yield

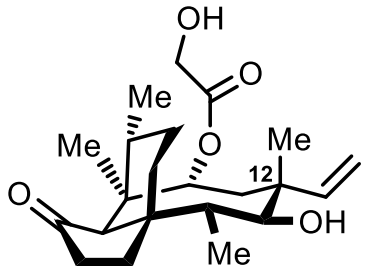
+



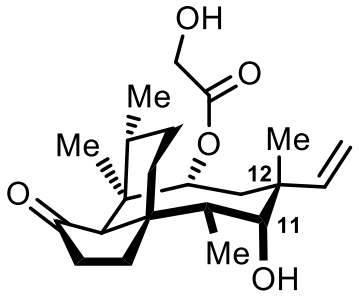
(+)-11,12-di-*epi*-mutilin (**26**)
3.0% overall yield



(+)-pleuromutilin (**1**)
0.4% overall yield



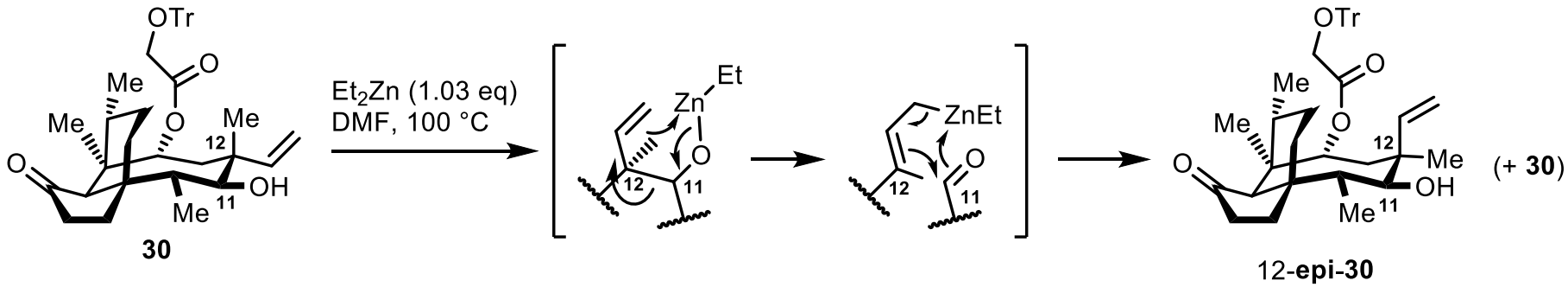
(+)-12-*epi*-pleuromutilin (**29**)
1.1% overall yield



(+)-11,12-di-*epi*-pleuromutilin (**32**)
2.3% overall yield

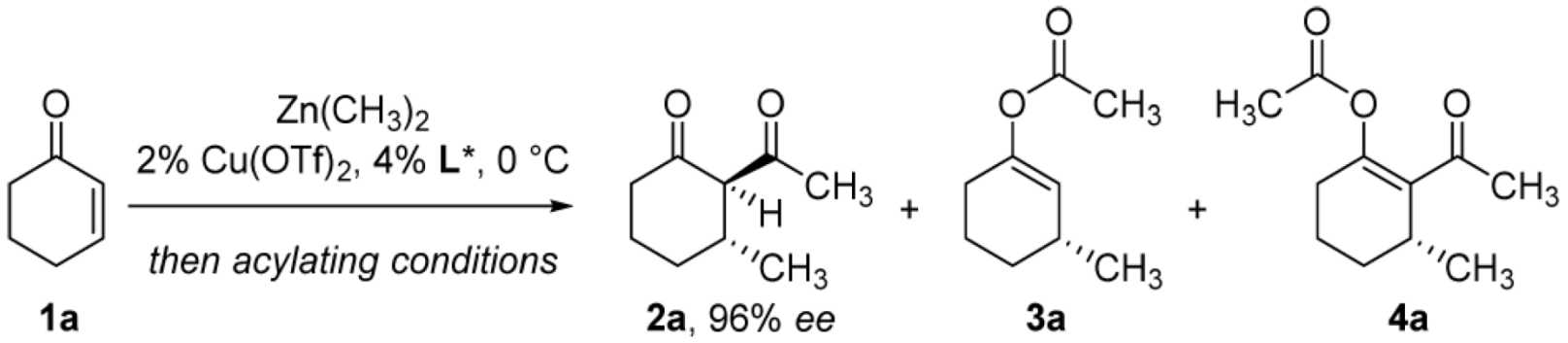
Questions?

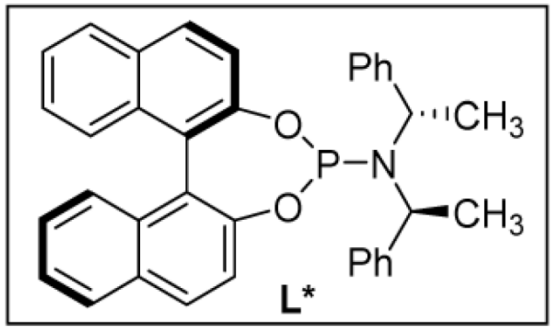
Epiperization at C12 quaternary stereocenter



H. Berner, H. Vyplel, G. Schulz, H. Schneider, *Monatsh. Chem.* **1986**, *117*, 1073–1080.

Tandem conjugate addition–acylation

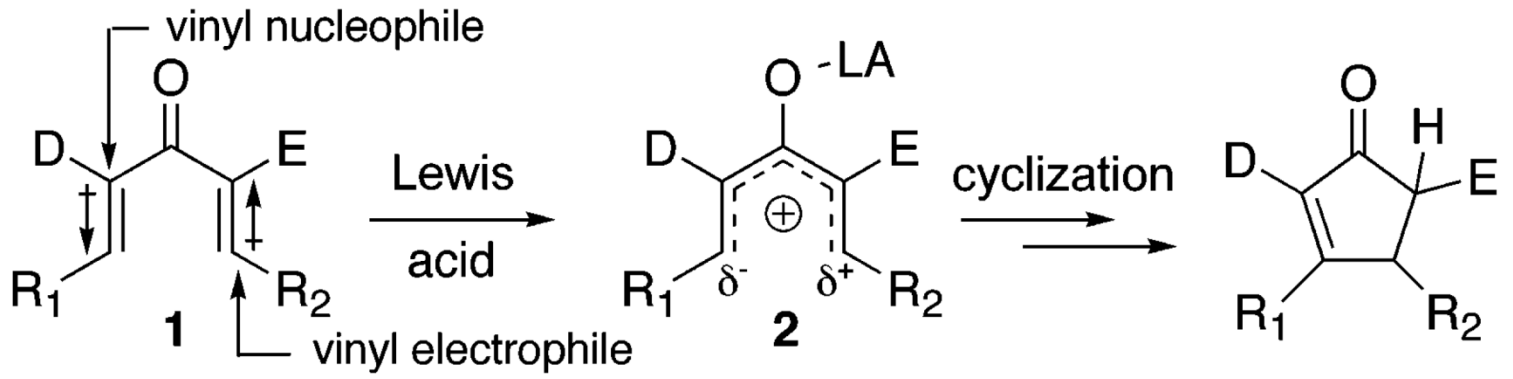




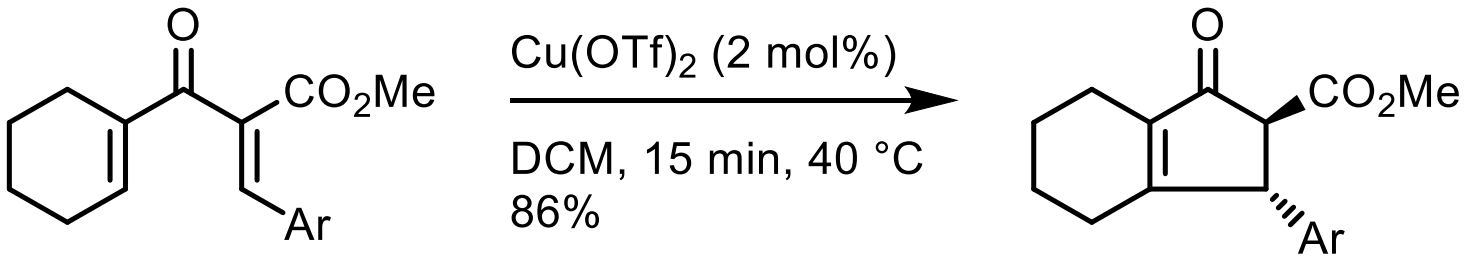
acylating conditions	**2a (%)**	**3a (%)**	**4a (%)**
CH_3COCl, 0 °C to 22 °C, 4 h	11	36	12
CH_3Li, –78 °C, 1 min then CH_3COCl, –78 °C, 15 min	80	<1	<1

S. B. Herzon et al. *Org. Lett*. **2016**, *18*, 4880–4883

Polarized Nazarov Cyclization



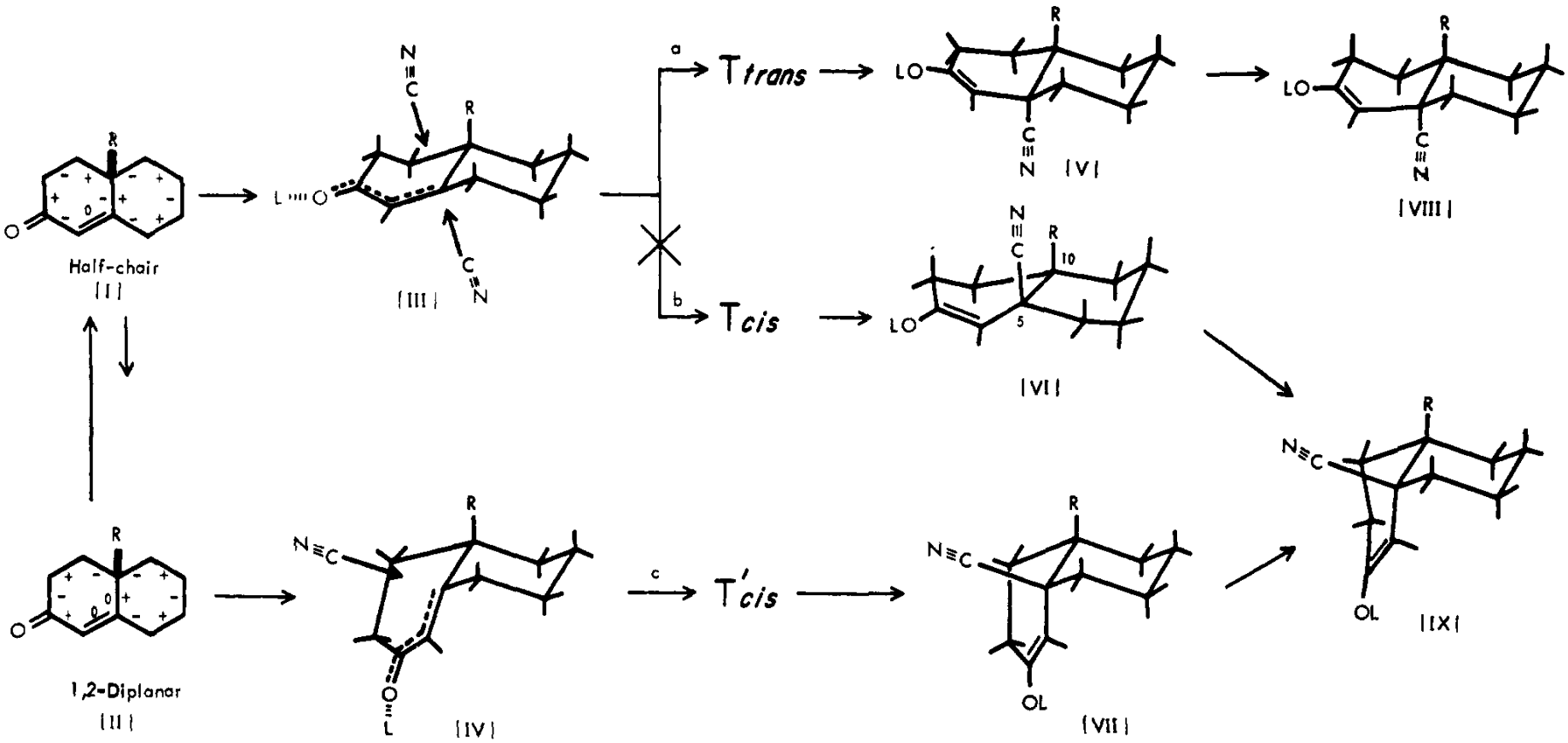
(D=electron-donating group; E=electron-withdrawing group)



Ar = 2,4,6-trimethoxyphenyl

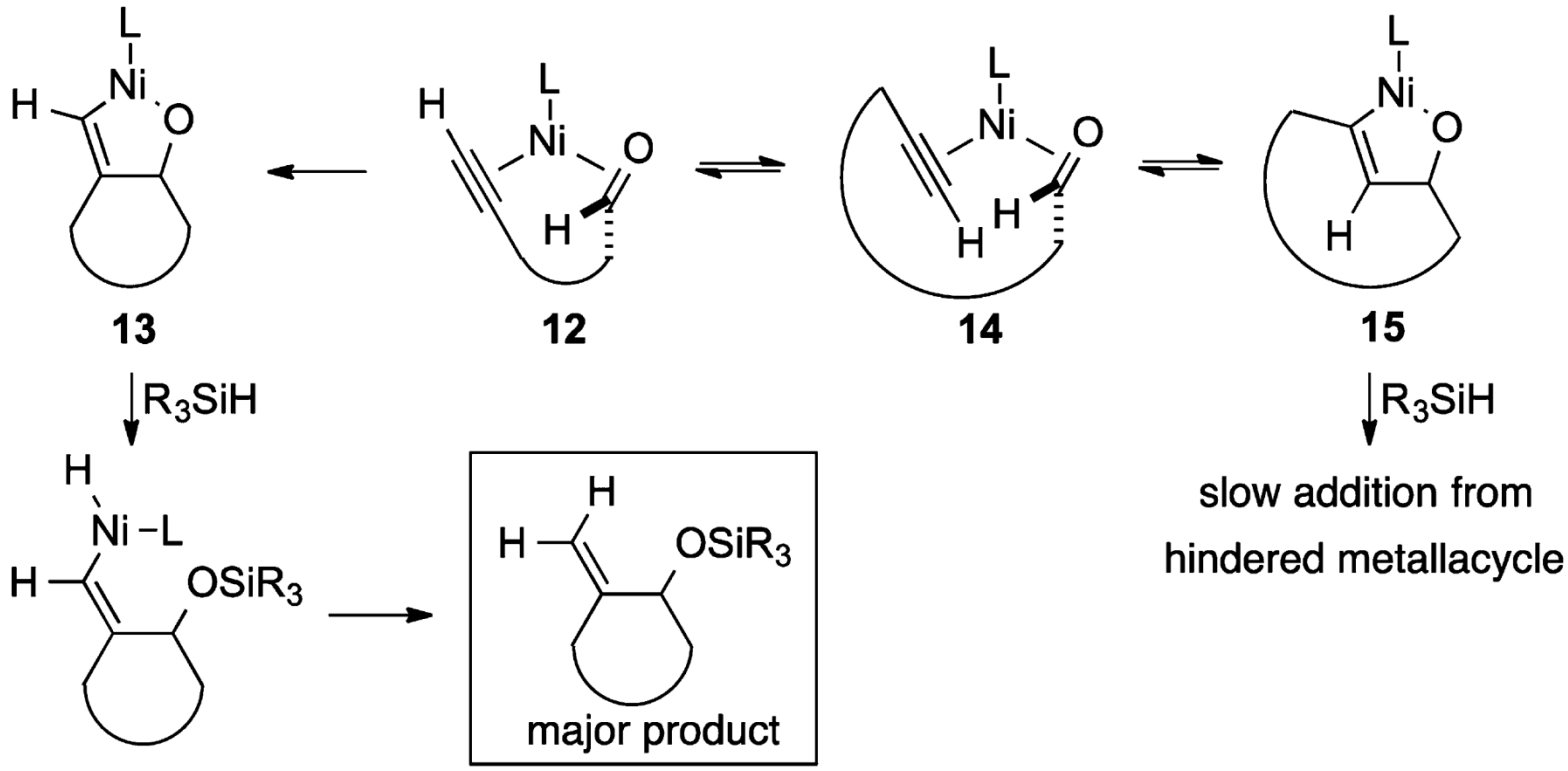
A. J. Frontier et al. *J. Am. Chem. Soc.* **2003**, *125,* 14278-14279

Conjugate Hydrocyanation



W. Nagata et al. *J. Am. Chem. Soc.* **1972**, *94,* 4672-4683

Exo-Selective Reductive Macrocyclization of Ynals



J. Montgomery et al. *Org. Lett.* **2015**, *17,* 1493−1496, *J. Am. Chem. Soc*. **2015**, *137*, 958−963