

# Journal Club

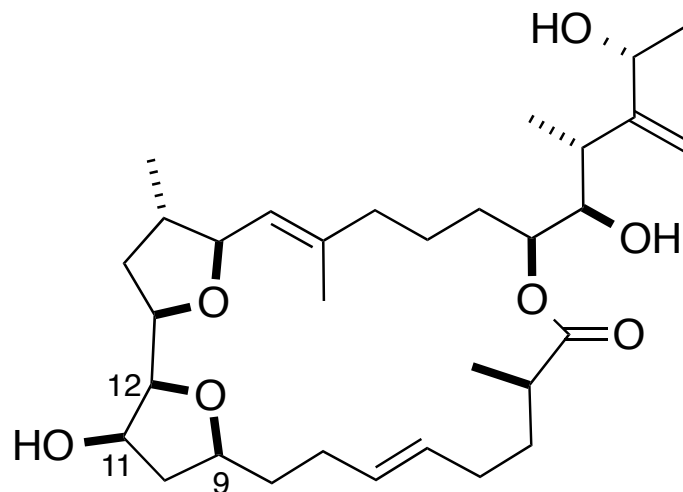
Nick Tappin  
Renaud Group  
15 March 2018

# Total Synthesis and Stereochemical Revision of Iriomoteolide-2a

Keita Sakamoto, Akihiro Hukamata, Masashi Tsuda, and  
Haruhiko Fuwa\*

*Angew. Chem. Int. Ed.* **2018**, 57, ASAP.

DOI: 10.1002/anie.201800507



**3: Iriomoteolide-2a**

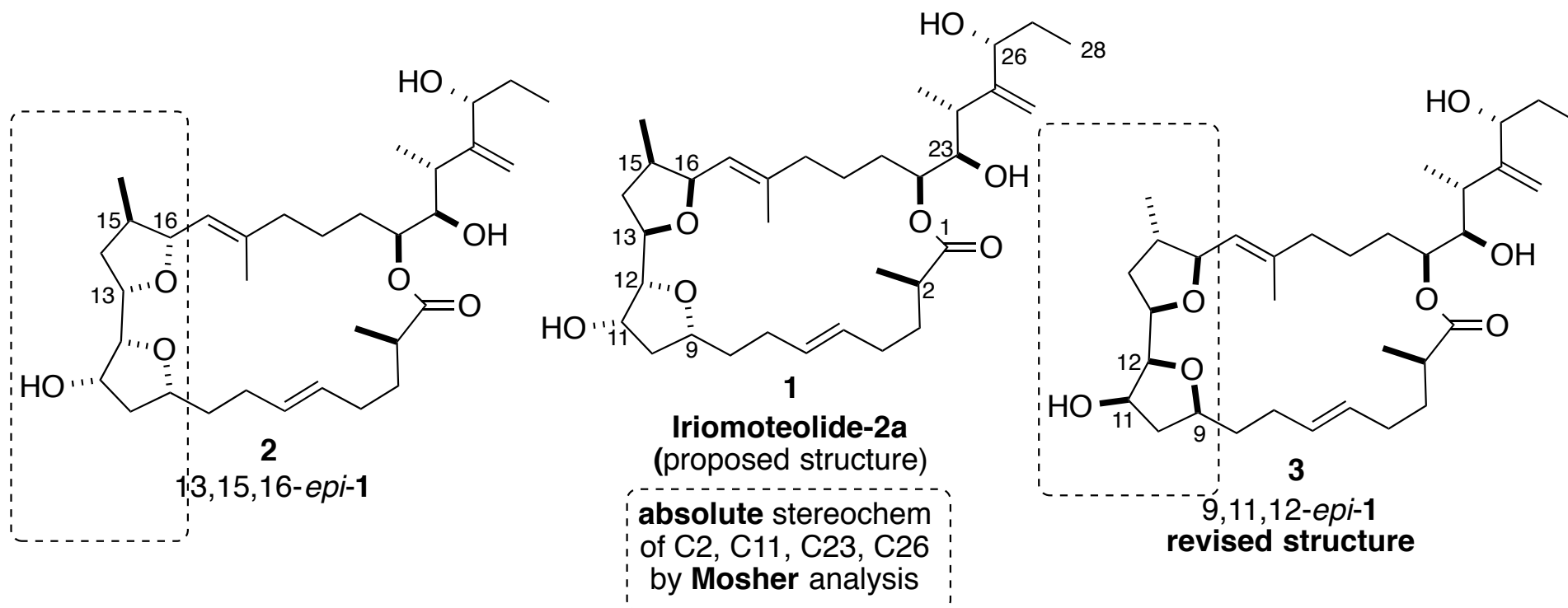
9,11,12-*epi*-1  
revised structure

# Haruhiko Fuwa

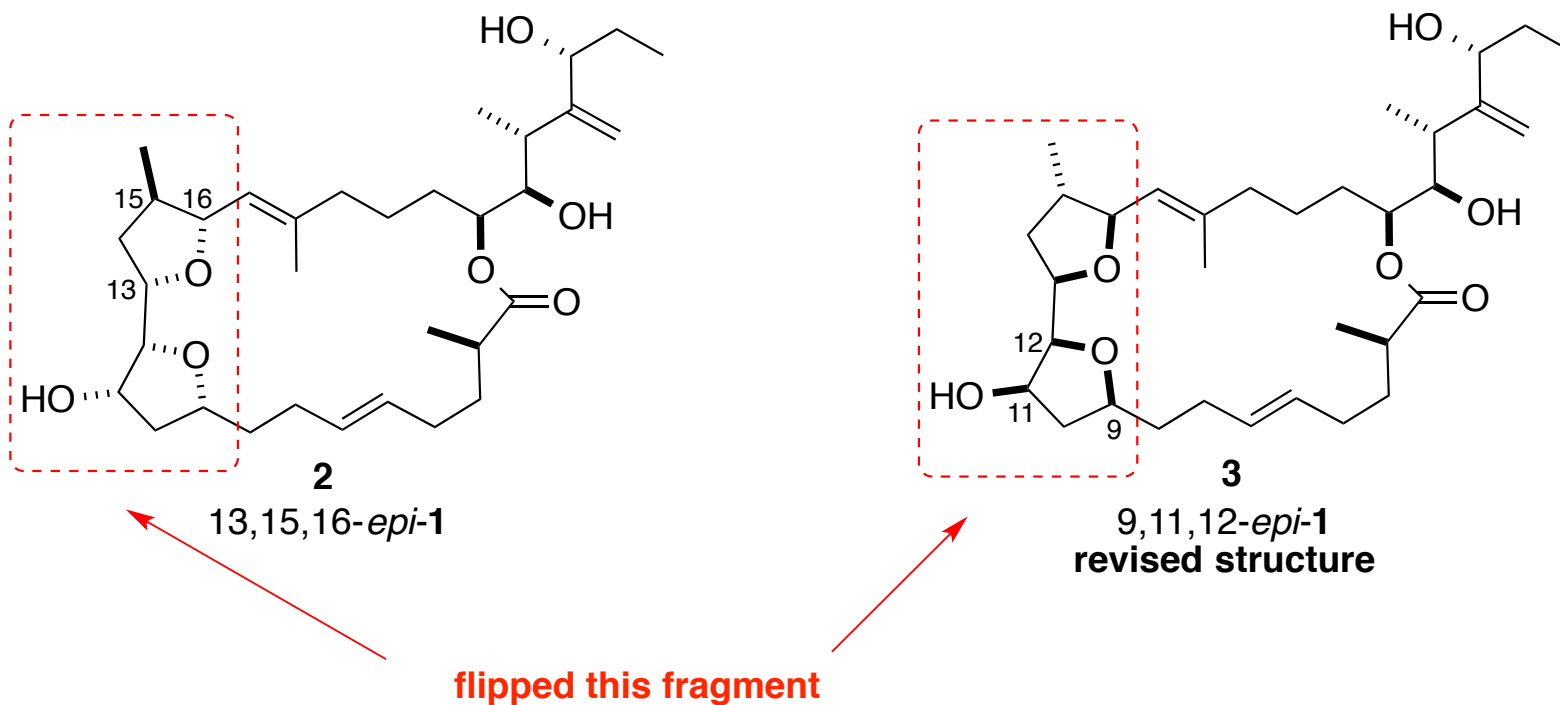


- **1993-1997: The University of Tokyo**, BSc in Chemistry,  
**1997-1999: The University of Tokyo**, MSc in Organic Chemistry,  
**1999-2002: The University of Tokyo** , PhD
- **Tohoku University (2006-2009)** Assistant Professor
- **Tohoku University (2009-2017)** Associate Professor, group of Makoto Sasaki
- **Chuo University (2017-)** Professor
- Working predominantly on marine natural products (>100 publications)

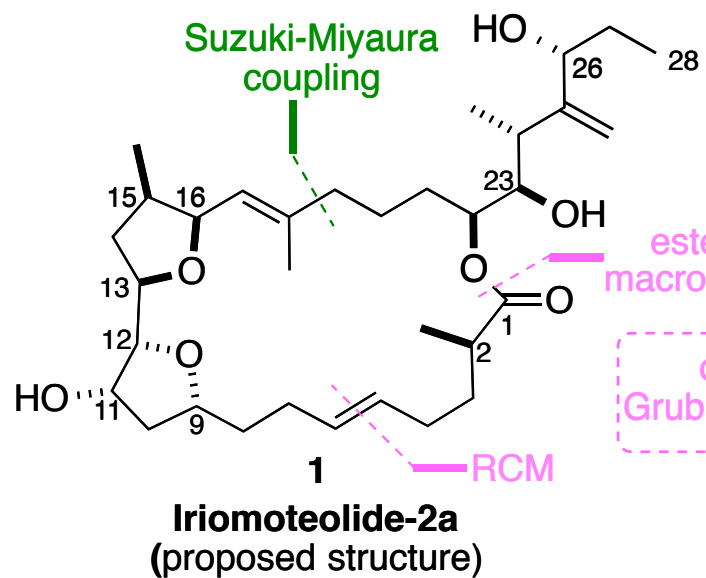
# Stereochemical concerns



# Stereochemical concerns



# Retrosynthetic analysis



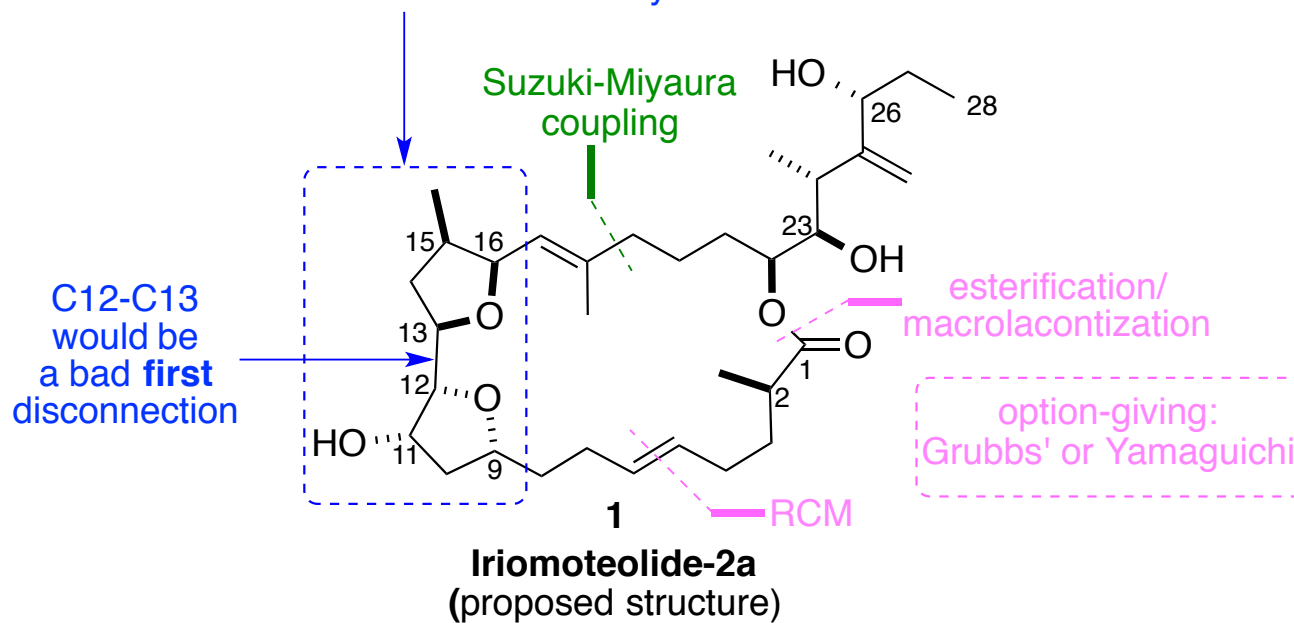
have separated the overall architecture containing problematic **relative** stereochemistry into its fragments (same strategy for analogues or diversity-orientated)

esterification/  
macrolactonization

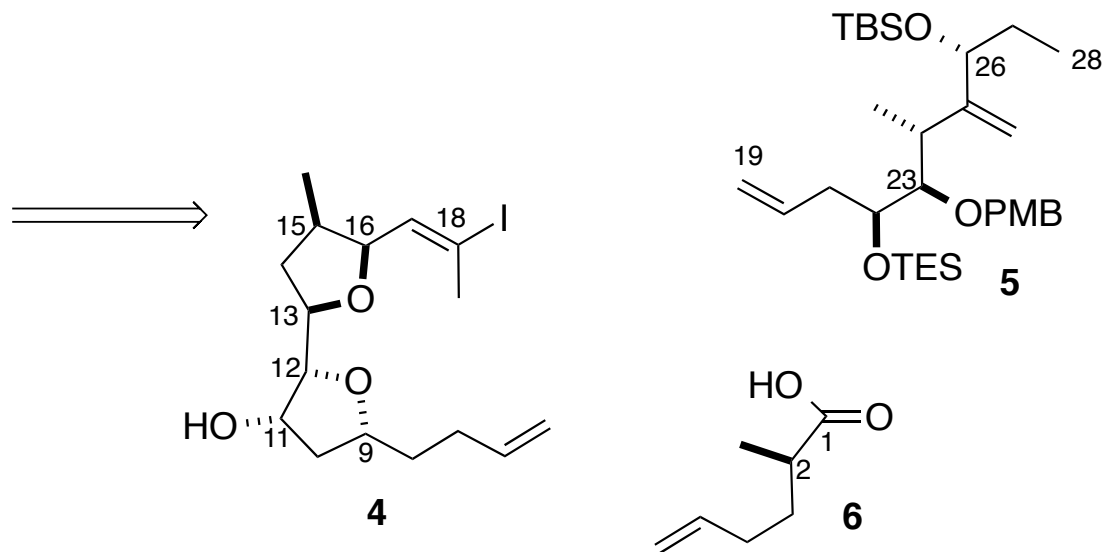
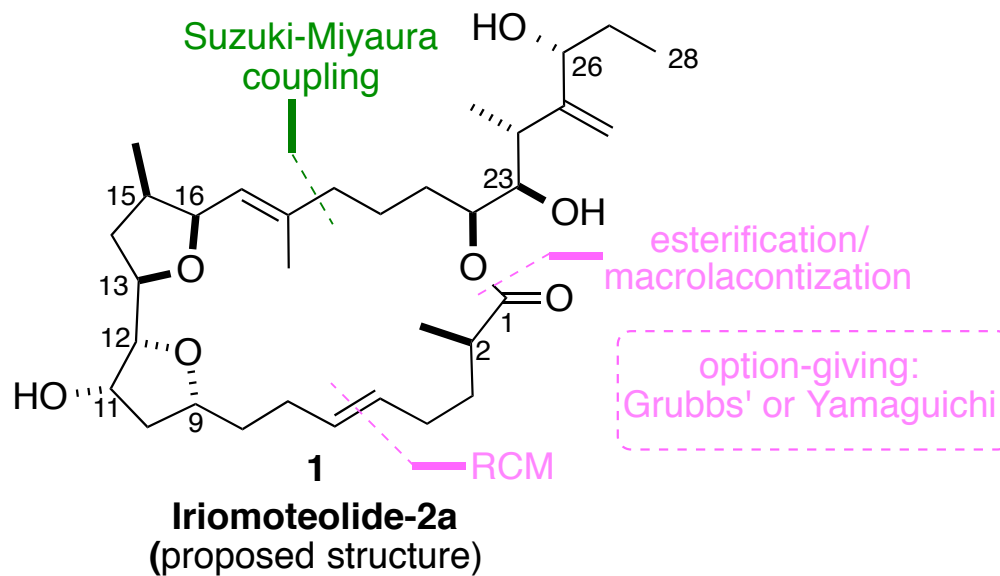
option-giving:  
Grubbs' or Yamaguchi

# Seperating the problems

The power of synthesis for structure assignment  
and how this influences retrosynthetic disconnections!

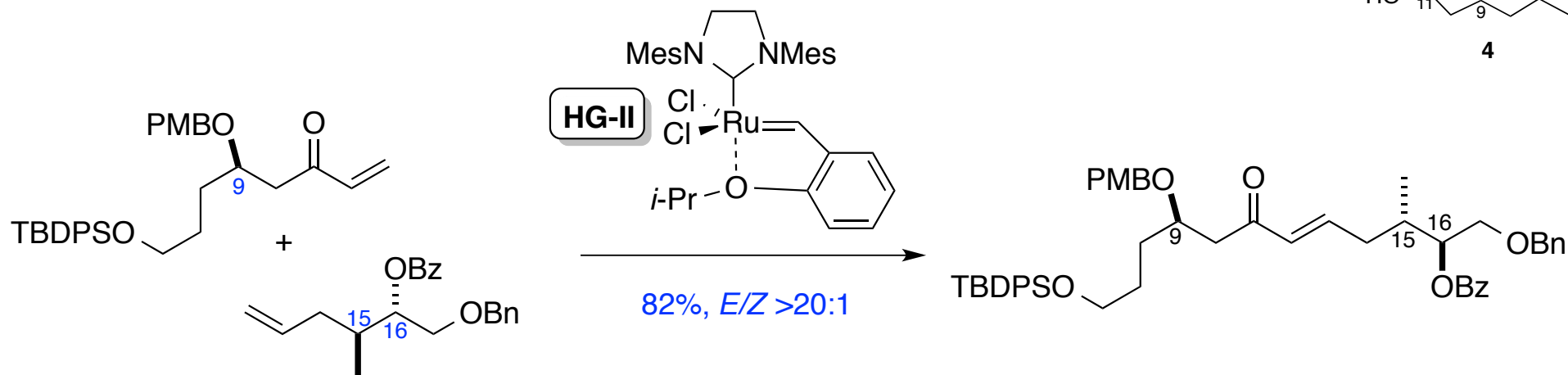
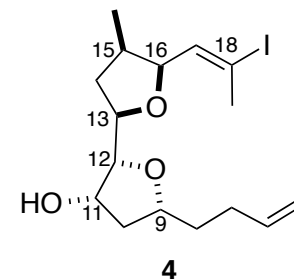


# Retrosynthetic analysis



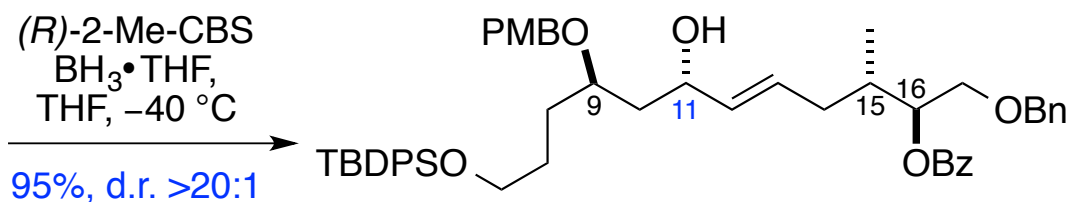


# Synthesis of vinyl iodide, 4

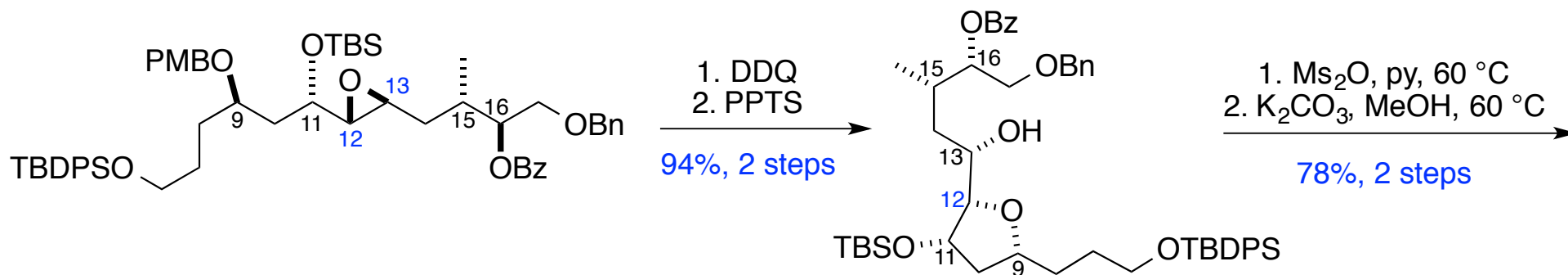


## Sharless asymmetric epoxidation

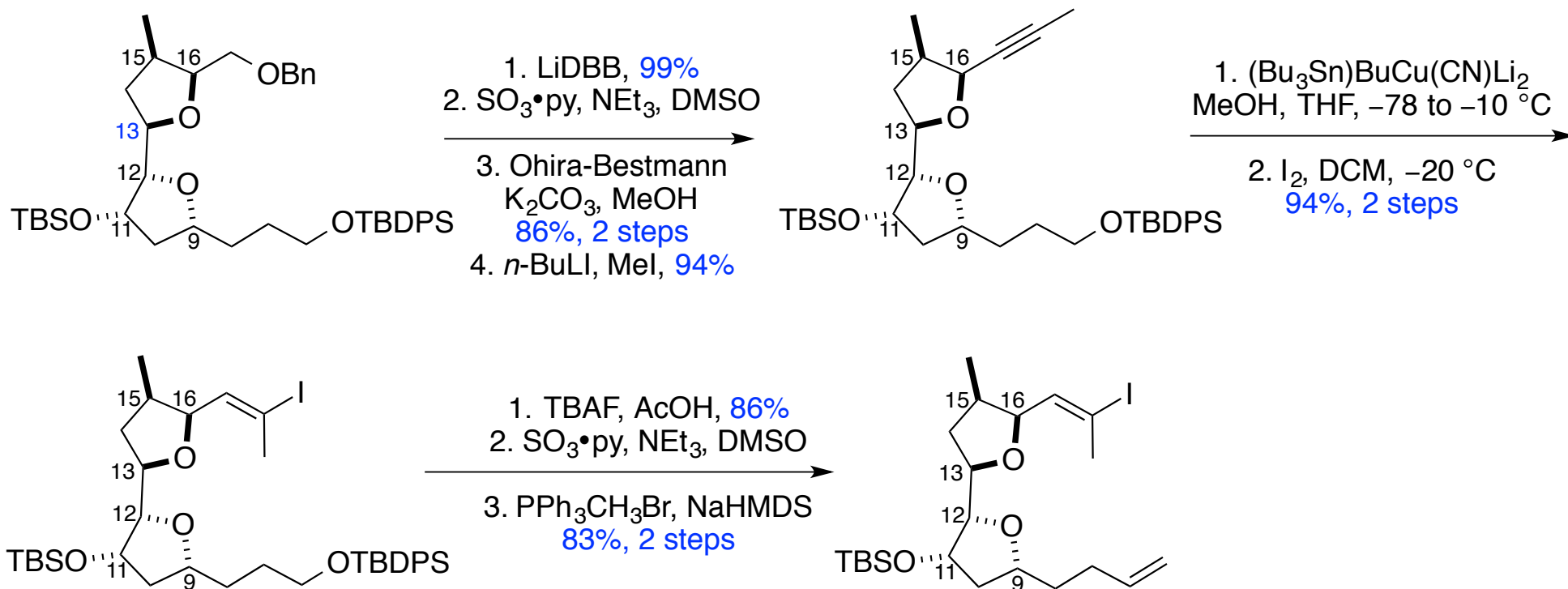
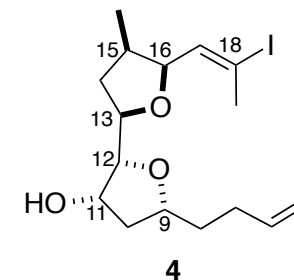
1. (+)-DIPT,  $\text{Ti}(\text{O}i\text{-Pr})_4$   
 $t\text{-BuOOH}$ , 4 Å MS,  
DCM,  $-40$  to  $-20$  °C



2. TBSCl, ImH  
**83%, 2 steps, d.r. >20:1**



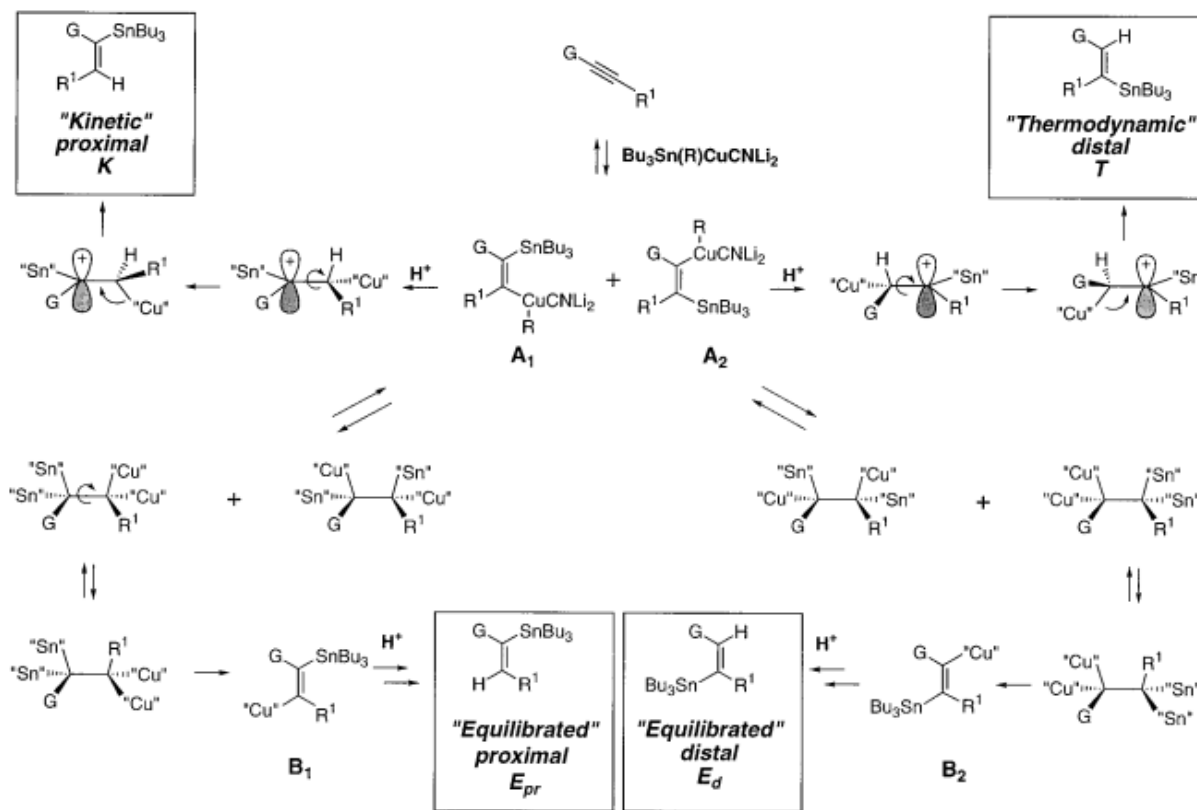
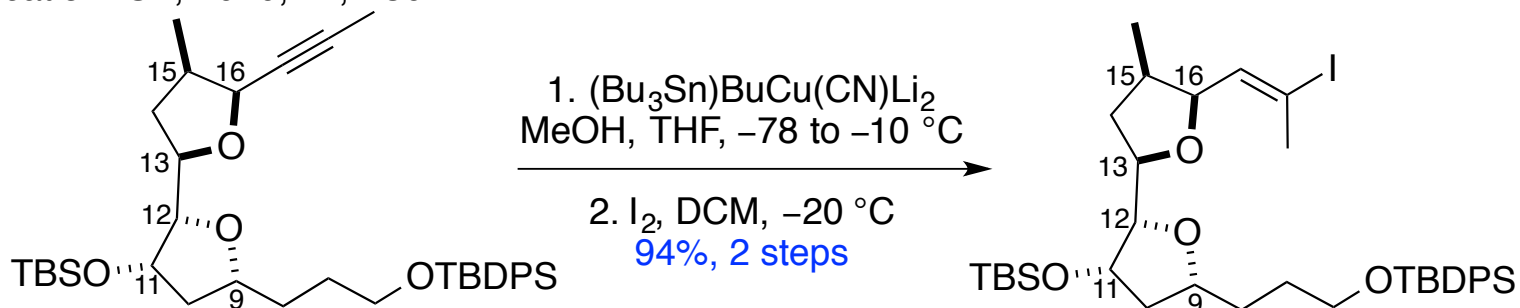
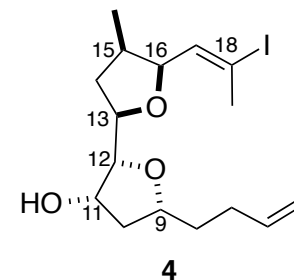
# Synthesis of vinyl iodide, 4



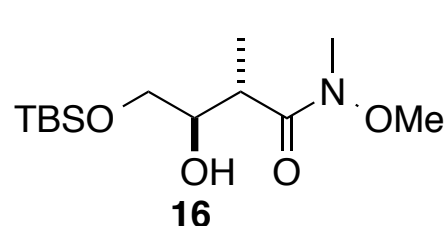
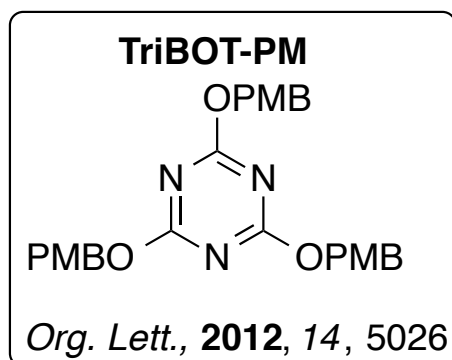
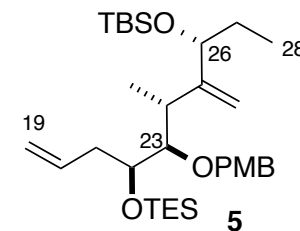
# Stannylcupration

mechanism: JOC, 1997, 62, 7768

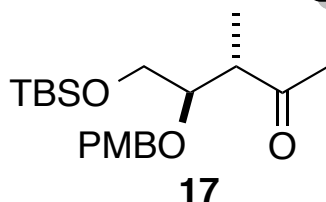
tot synth application: OL, 2010, 12, 2302



# Synthesis of *exo*-olefin, 5

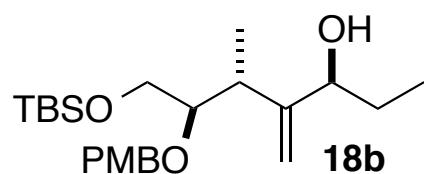
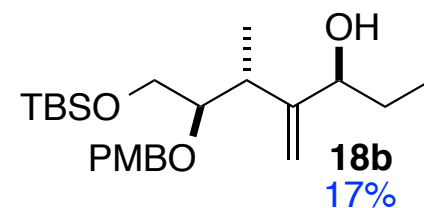
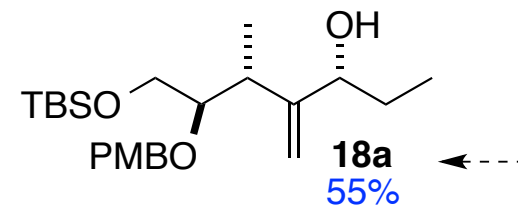


1. TriBOT-PM  
BF<sub>3</sub>•OEt<sub>2</sub>  
2. MeMgBr  
64%, 2 steps

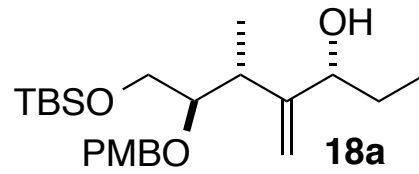


Nozaki-Hiyama-Kishi  
coupling

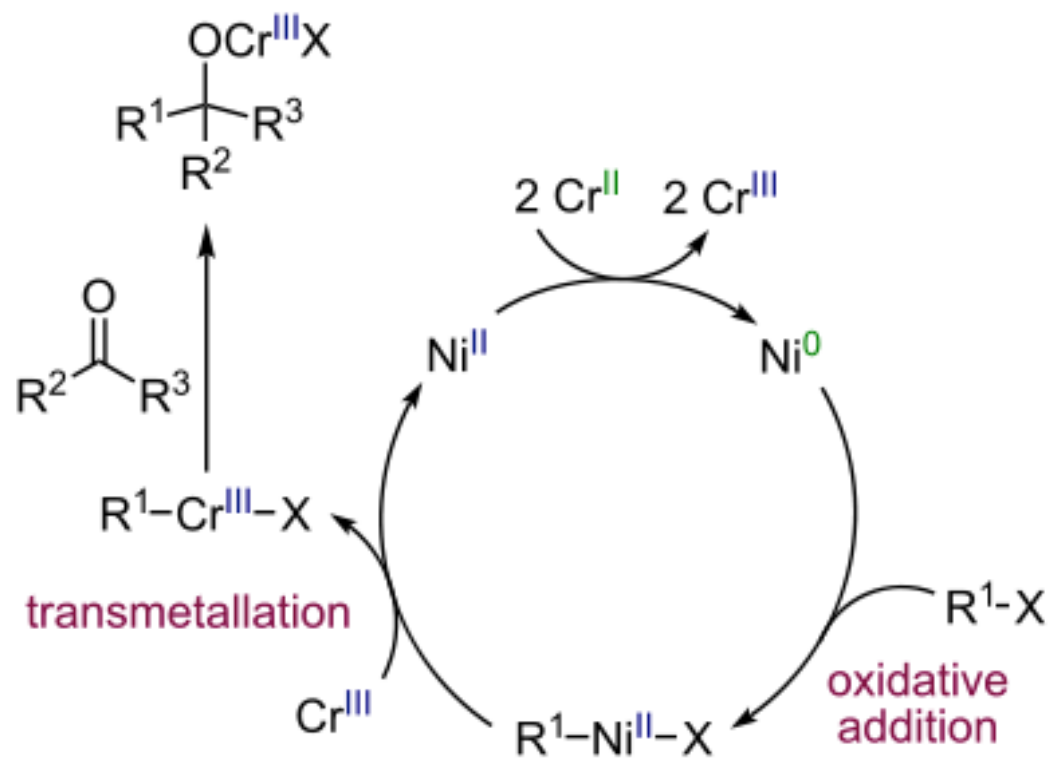
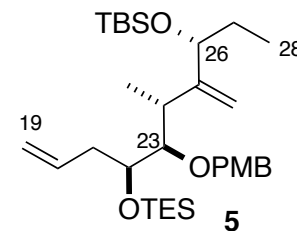
1. KHMDS, PhNTf<sub>2</sub>  
2. propanal, NiCl<sub>2</sub>,  
CrCl<sub>2</sub>, DMF



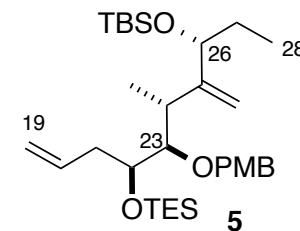
1. DMP, 94%  
2. (*R*)-2-Me-CBS  
BH<sub>3</sub>•THF, 91%



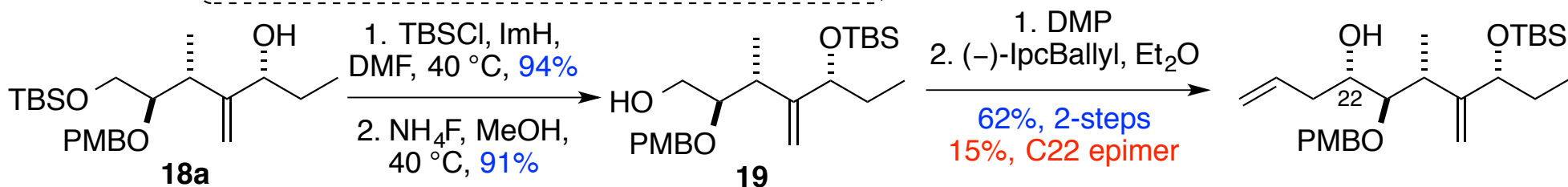
# NHK reaction



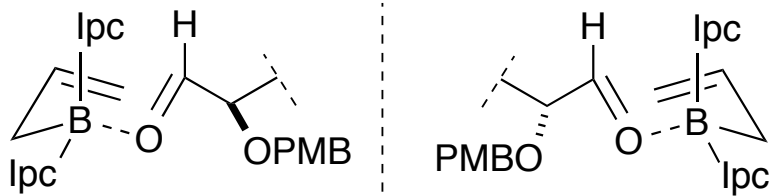
# Synthesis of *exo*-olefin, 5



deprotected 1° OTBS in presence of 2° OTBS!!!

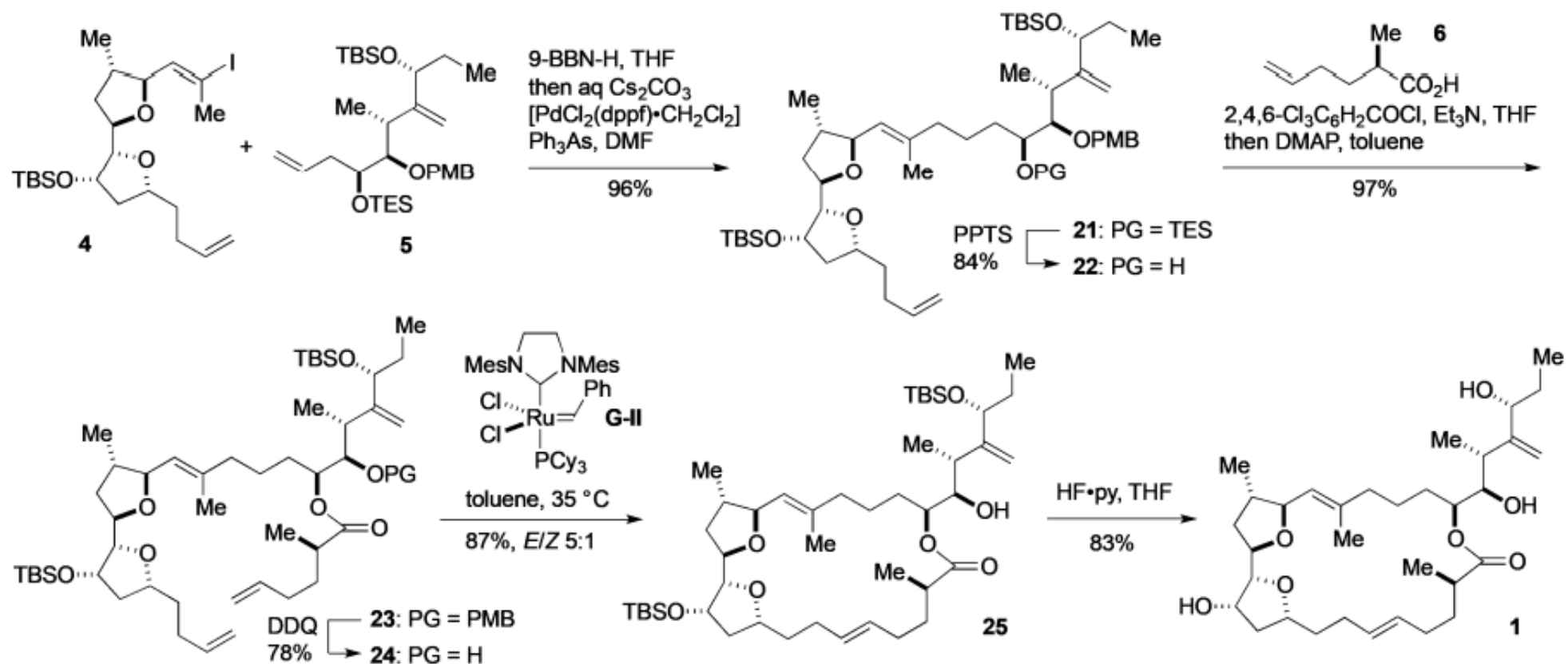


asymmetric Brown allylation

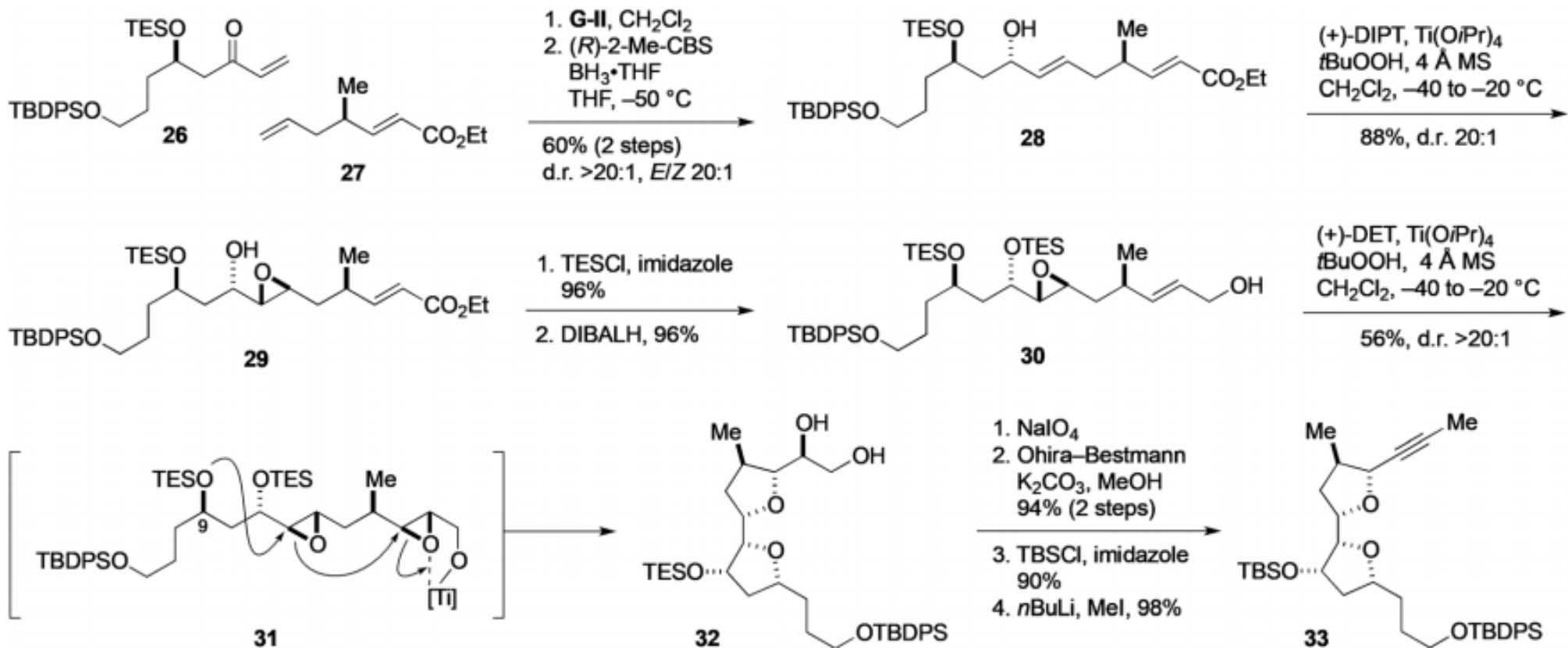


usually good selectivity (this may be a mis-match case...?)

# Endgame, wrong epimer

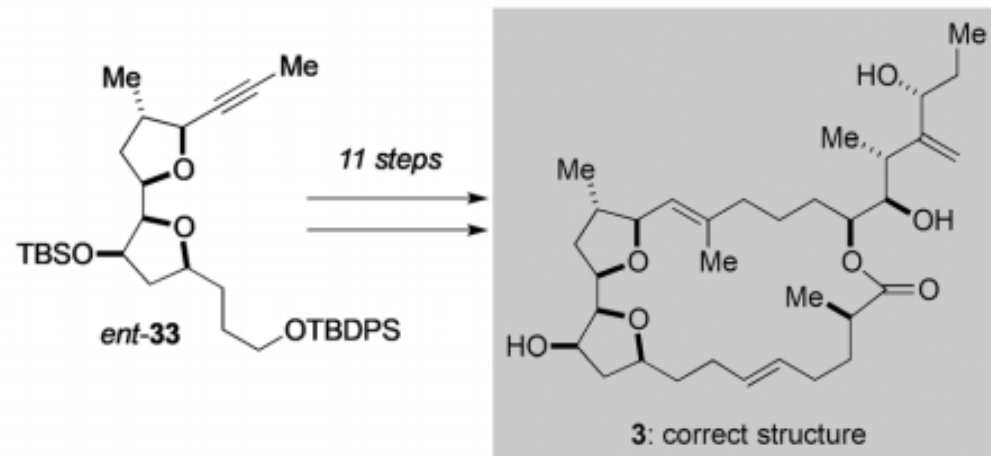
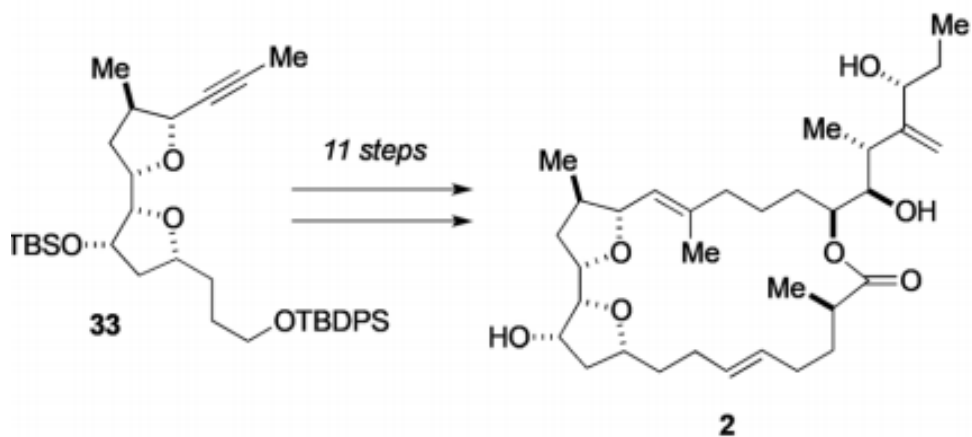


# Other epimer's fragment



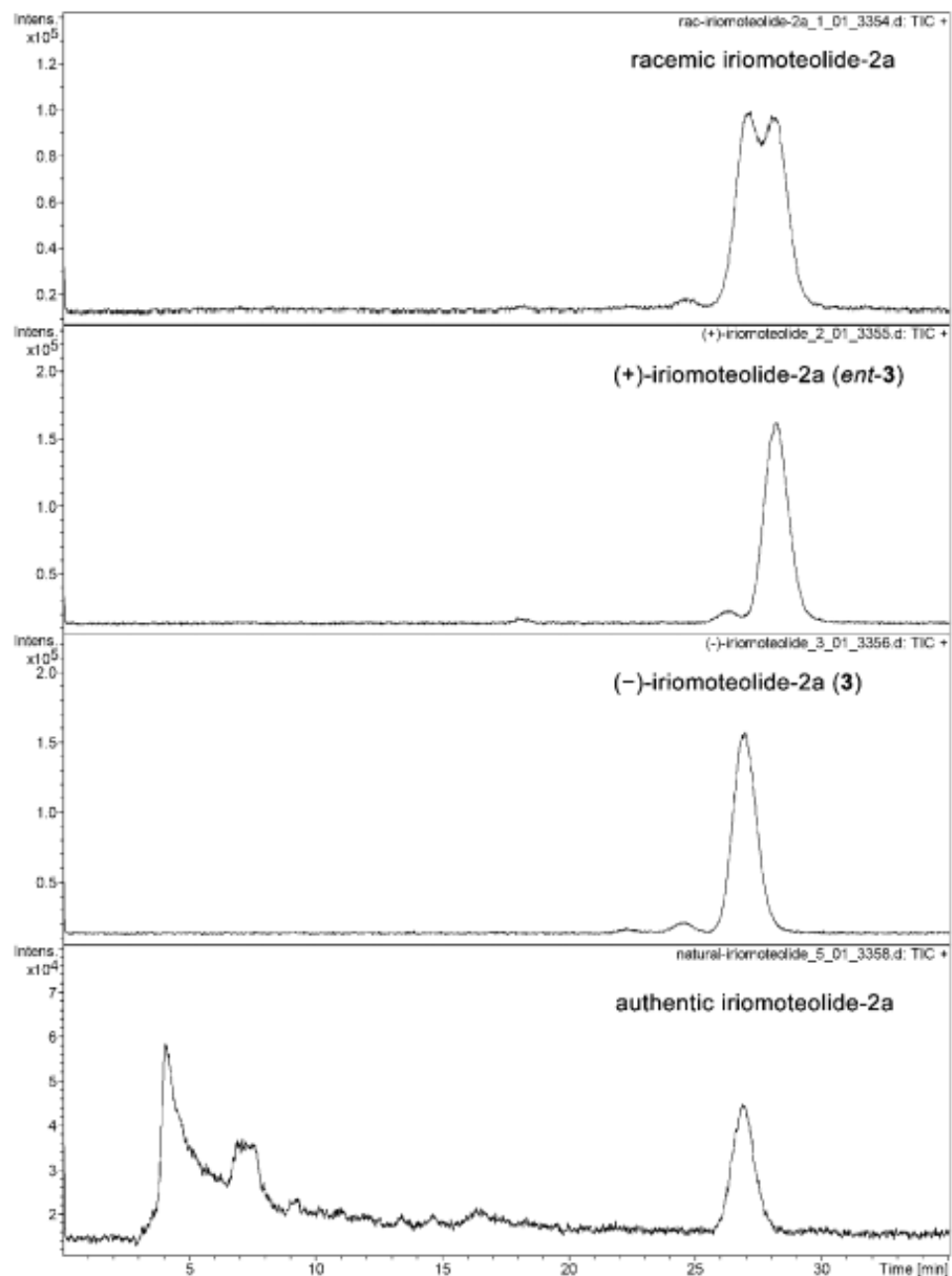


# Other epimers



# Correct epimer is **3**!

Specific rotation's were inaccurate (even by sign), so *ent*-**3** was synthesized!  
Looksee the chiral LC-MS

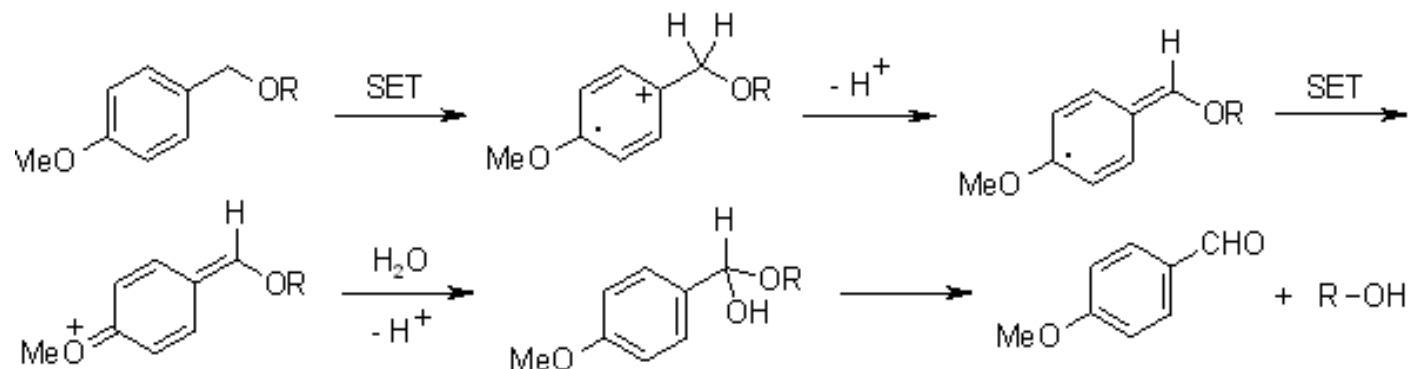


Thanks for attention!

And

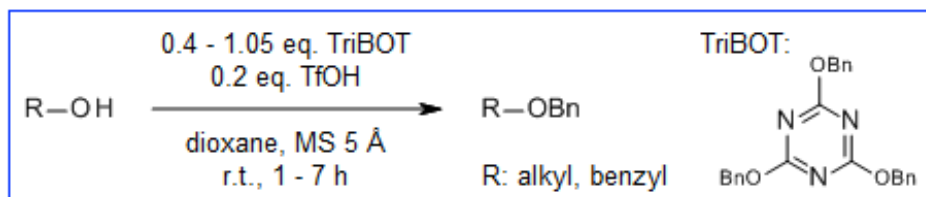
any questions?

# OPMB deprotection by Ox SET (c.f. Birch)



# OBn protection by TriBOT

## Protection of Hydroxyl Compounds



Inexpensive stable crystalline 2,4,6-tris(benzyloxy)-1,3,5-triazine (TriBOT) can be used as an acid-catalyzed *O*-benzylating reagent. The reaction of various functionalized alcohols with 0.4 equiv of TriBOT in the presence of trifluoromethanesulfonic acid afforded benzyl ethers in good yields. TriBOT, which is the formal trimerization of the smallest unit of benzyl imidate, offers high atom economy.

K. Yamada, H. Fujita, M. Kunishima, *Org. Lett.*, **2012**, *14*, 5026-5029.

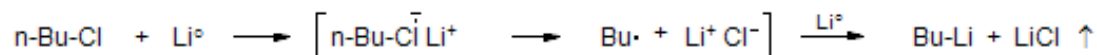
<http://www.organic-chemistry.org/protectivegroups/hydroxyl/benzyl-ethers.htm>

# OBn deprotection by red SET (c.f. Birch)

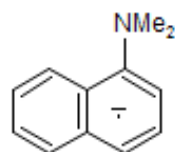
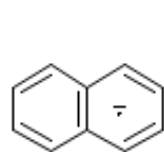
## from LiDBB

[J. Org. Chem. 81, 22, 10707-10714](#)

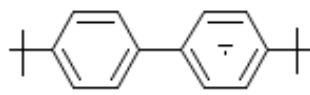
All of the simple hydrocarbon lithium reagents (*n*-BuLi, *s*-BuLi, *t*-BuLi, MeLi, PhLi) are prepared by reduction of RCl with Li<sup>0</sup>



These reductions are much improved if soluble lithium-arene radical anion solutions are used, instead of Li<sup>0</sup>.



LDMAN



LiDBB

T. Cohen, M. Bhupathy  
*Acc. Chem. Res.* **1989**, 22, 152.

P. K. Freeman, L. L. Hutchinson  
*J. Org. Chem.* **1980**, 45, 1924.

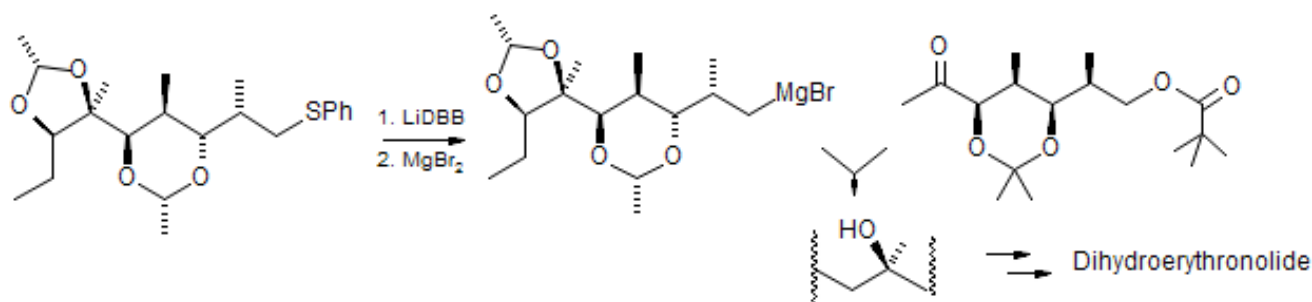
Alkyl phenyl sulfides and selenides can also be reduced:



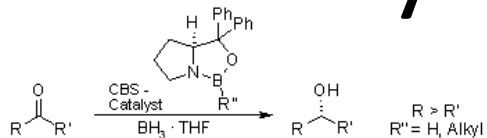
The relative stability of the two radicals (R<sup>•</sup> and Ph<sup>•</sup>) is a good predictor of which bond fragments. Thus, even though Ph<sup>•</sup> is more stable than R<sup>•</sup>, mostly or exclusively R<sup>•</sup> is formed.

The reaction can be used in quite complex systems:

**Dihydroerythronolide:** G. Stork, S. D. Rychnovsky, *J. Am. Chem. Soc.*, **1987**, 109, 1565.



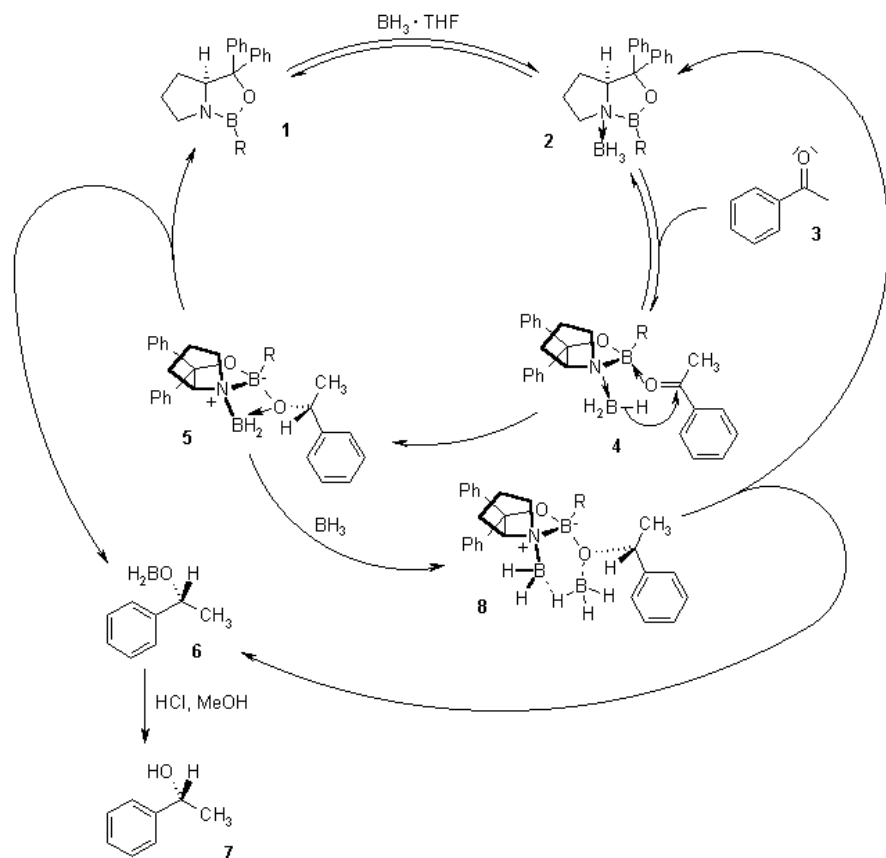
# CBS reduction (c.f. 1,2-metal hydride, Noyori, Midland Alpine Borane)



The enantioselective reduction of ketones using borane and a chiral oxazaborolidine as catalyst (CBS catalyst). Usually, MeCBS is used ( $\text{R}'' = \text{Me}$ , but selectivity may be increased by varying this substituent).

## Mechanism of the Corey-Bakshi-Shibata Reduction

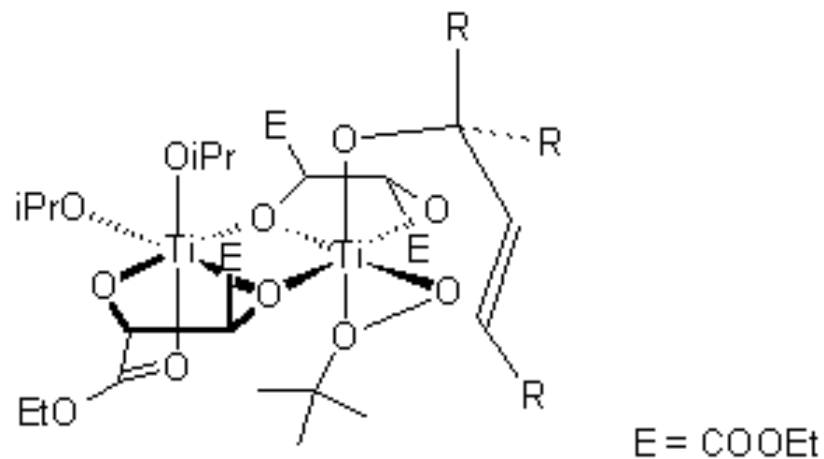
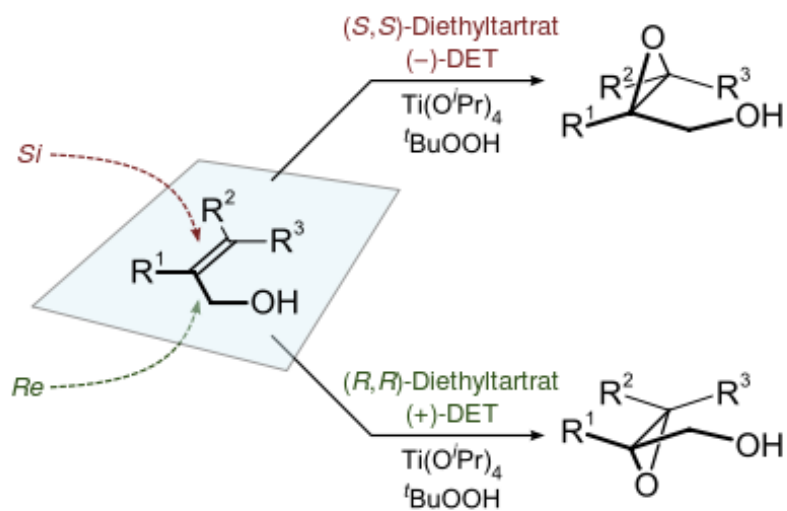
The mechanism depicted (E. J. Corey, C. J. Helal, *Angewandte Chem. Int. Ed.*, **1998**, *37*, 1986-2012. DOI) portrays the rationale for the enantioselectivity and high reaction rates, which are influenced only by the CBS catalyst. This catalyst is a combination of both a Lewis acid and a chiral auxiliary!



E. J. Corey, C. J. Helal, *Tetrahedron Lett.* 1995, *36*, 9153

<http://www.organic-chemistry.org/namedreactions/corey-bakshi-shibata-reduction.shtm>

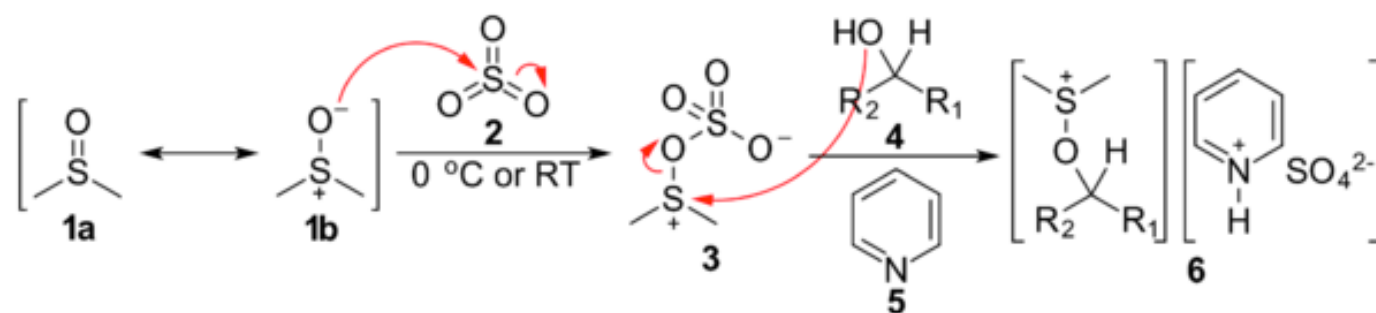
# Sharpless asymmetric epoxidation (c.f. dihydroxylation)



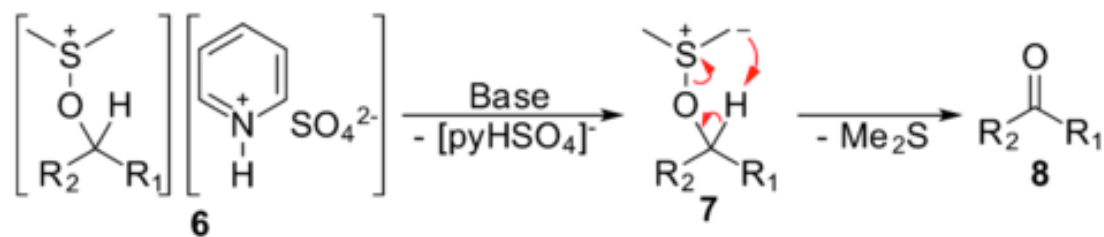
[https://en.wikipedia.org/wiki/Sharpless\\_epoxidation](https://en.wikipedia.org/wiki/Sharpless_epoxidation)

<http://www.organic-chemistry.org/namedreactions/sharpless-epoxidation.shtm>

# Backup slides: Parikh-Doering Oxidation (c.f. Swern Oxidation)

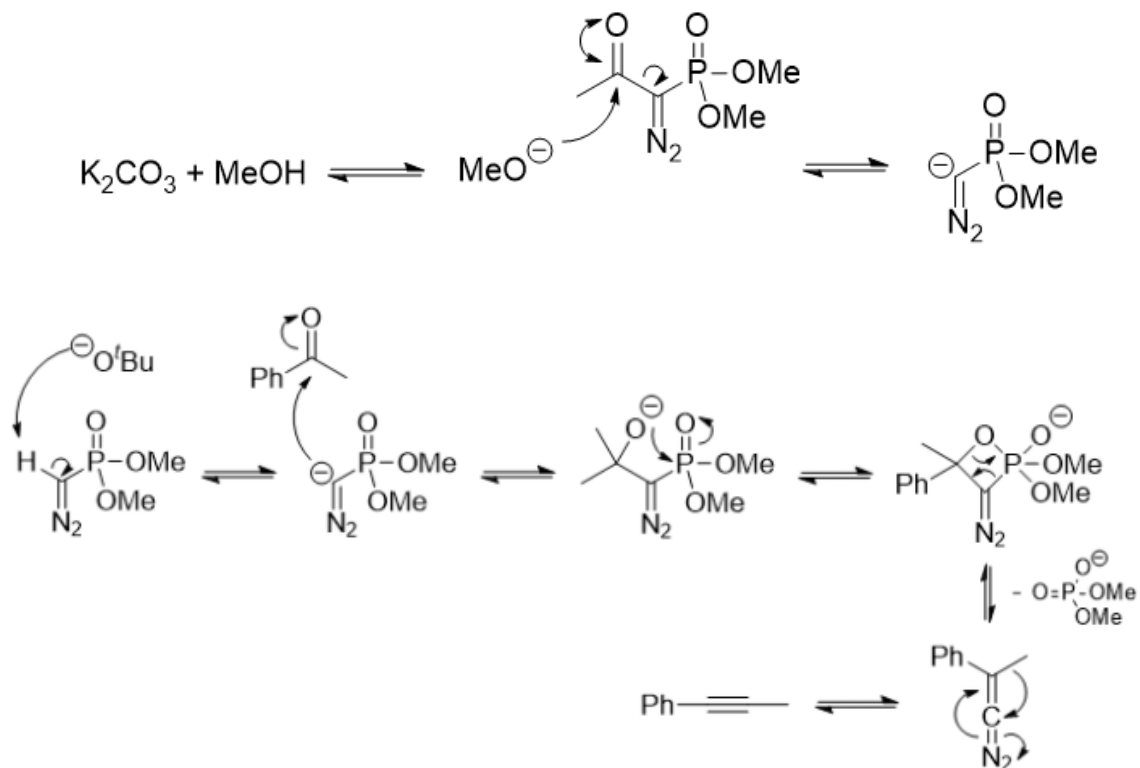


of base deprotonates the alkoxysulfonium ion to give sulfur ylide 7 and removes the pyridinium sulfate cation state to give the desired ketone or aldehyde 8, as well as an equivalent of dimethyl sulfide.





# Backup slides: Bestmann-Ohira (c.f. Seyferth-Gilbert and Corey-Fuchs)



<https://chemistry.stackexchange.com/questions/70653/mechanism-of-homologation-of-aldehyde-to-alkyne-ohira-bestmann-reaction>

