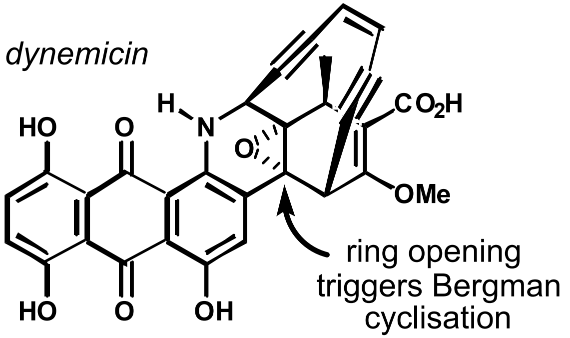
Importance of epoxides in organic chemistry

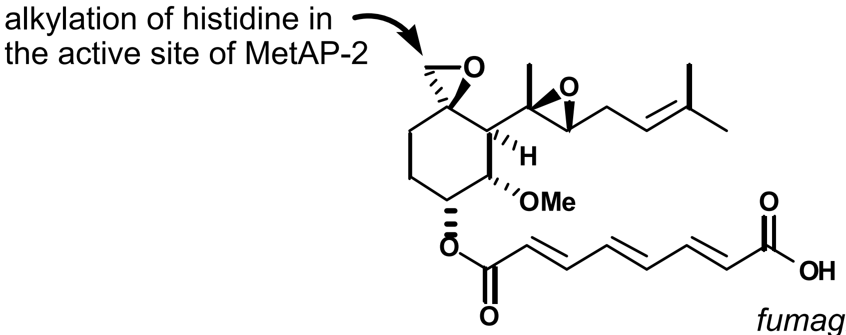
- As pharmacophores in bioactive natural products:

dynemicin



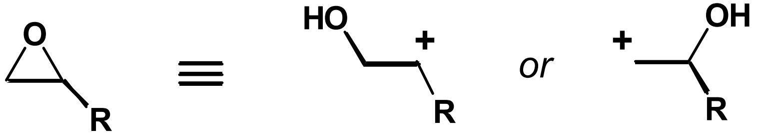
ring opening triggers Bergman cyclisation

alkylation of histidine in the active site of MetAP-2



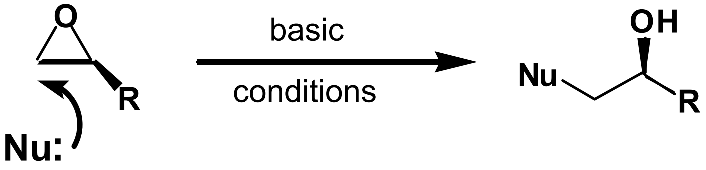
fumagillin

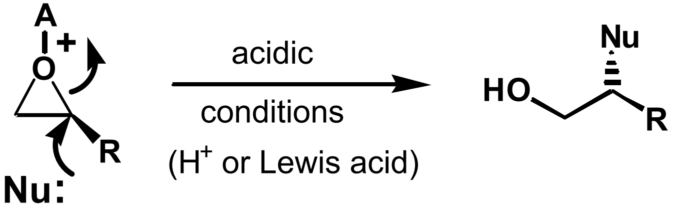
- Ring opening by nucleophiles



a^2 synthon

Nu = N,O,S, Se,C etc



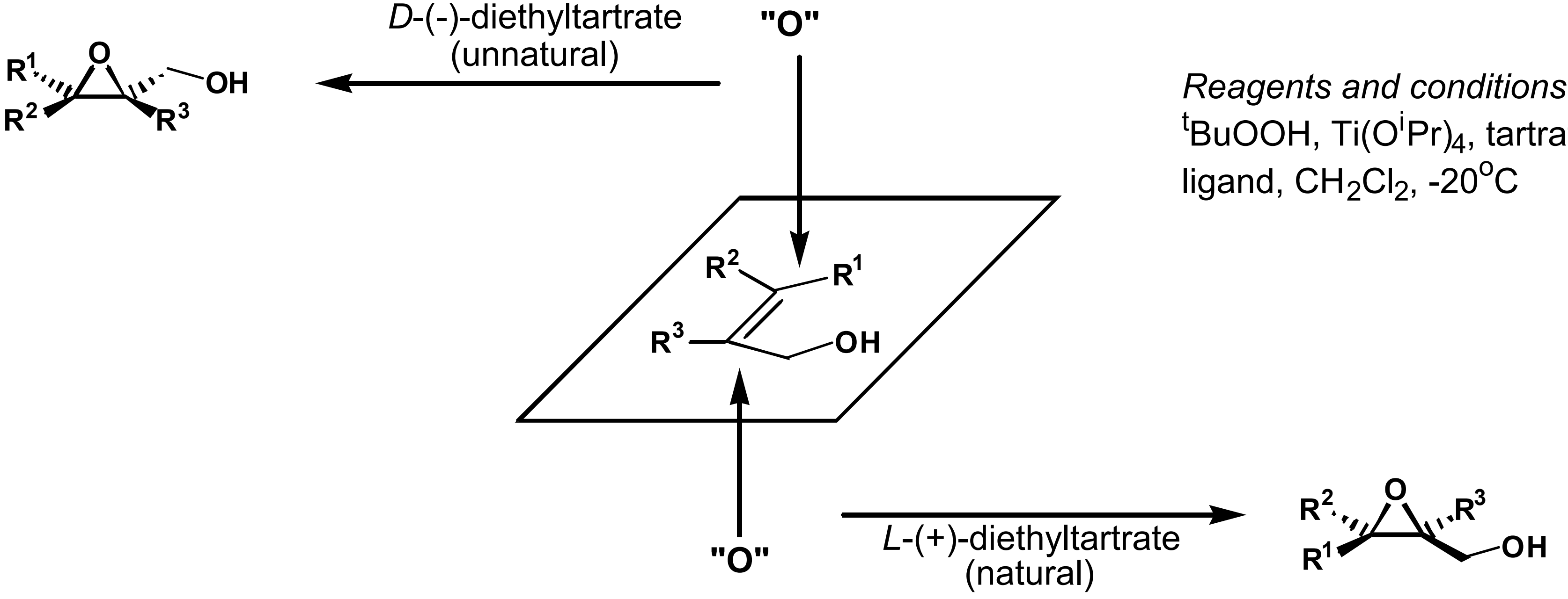


- attack at least hindered end

- attack at end which best stabilises δ+ charge

"If carbonyl compounds have been said to be virtually the backbone of organic synthesis, the epoxides correspond to at least one of the main muscles" - Professor D Seebach

Katsuki-Sharpless asymmetric epoxidation of allylic alcohols



Reagents and conditions:
^{t}BuOOH, Ti(O^{i}Pr)$_4$, tartrate ligand, CH_2Cl_2, -20^{o}C

Reviews:

Scope and mechanism:
Johnson/Sharpless, in *Comprehensive Organic Synthesis*, (Trost & Fleming, eds), Vol. 7, 1991, pp 389-436

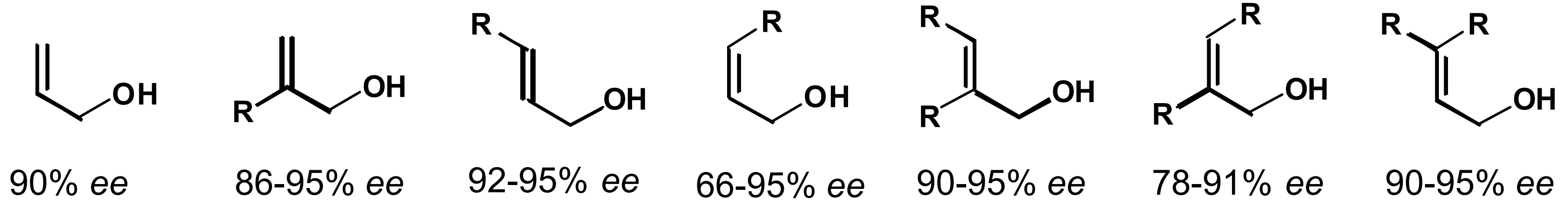
Synthetic applications: Hanson, *Chem. Rev.* **1991**, *91*, 431

For personal accounts by Sharpless see: *Aldrichim. Acta*, **1983**, *16*, 67; *Tetrahedron,* **1994**, *50*, 4235

- directed epoxidation of allylic alcohols with achiral reagents, *eg* V(O)(acac)$_2$: *J. Am. Chem. Soc.*, **1973**, *95*, 6136

Scope of the Katsuki-Sharpless asymmetric epoxidation

- *effect of olefin structure on enantioselectivity:*

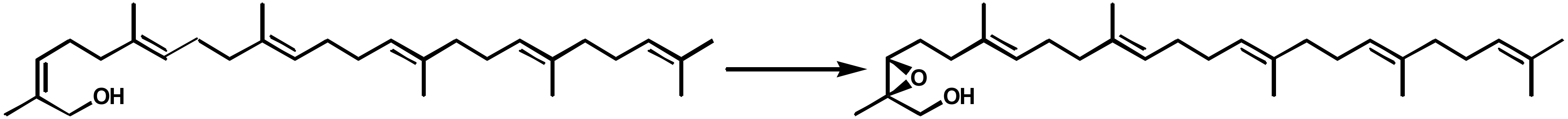


- *functional group compatibility:*

Reaction tolerates acetals, alkynes, alcohols, aldehydes, amides, azides, carbamates, epoxides, esters, ethers, hydrazides, ketones, nitriles, nitro, olefins, pyridines, silyl ethers, sulfones, sulfoxides, tetrazoles, ureas

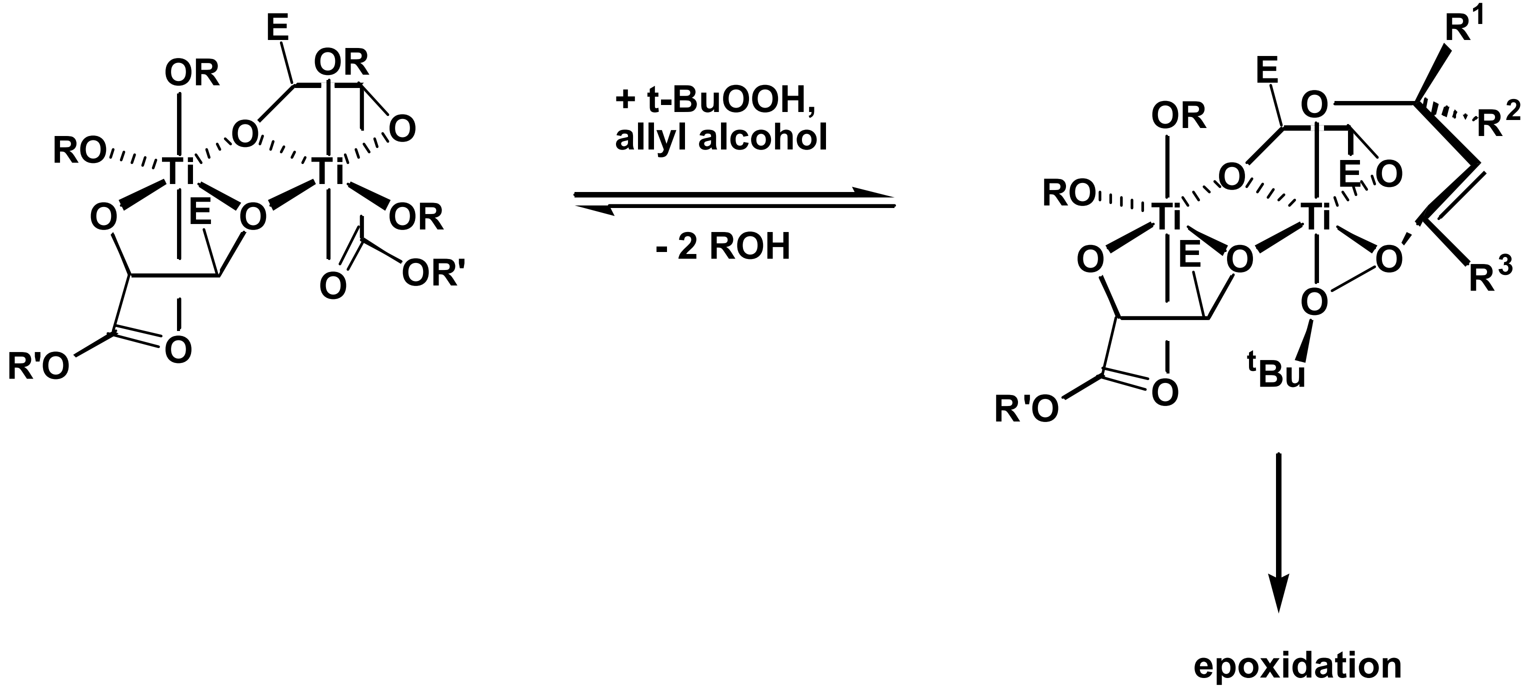
Reaction *does not tolerate:* amines, carboxylic acids, phenols, thiols, phosphines

- *selectivity for allylic alcohols over other olefins:*

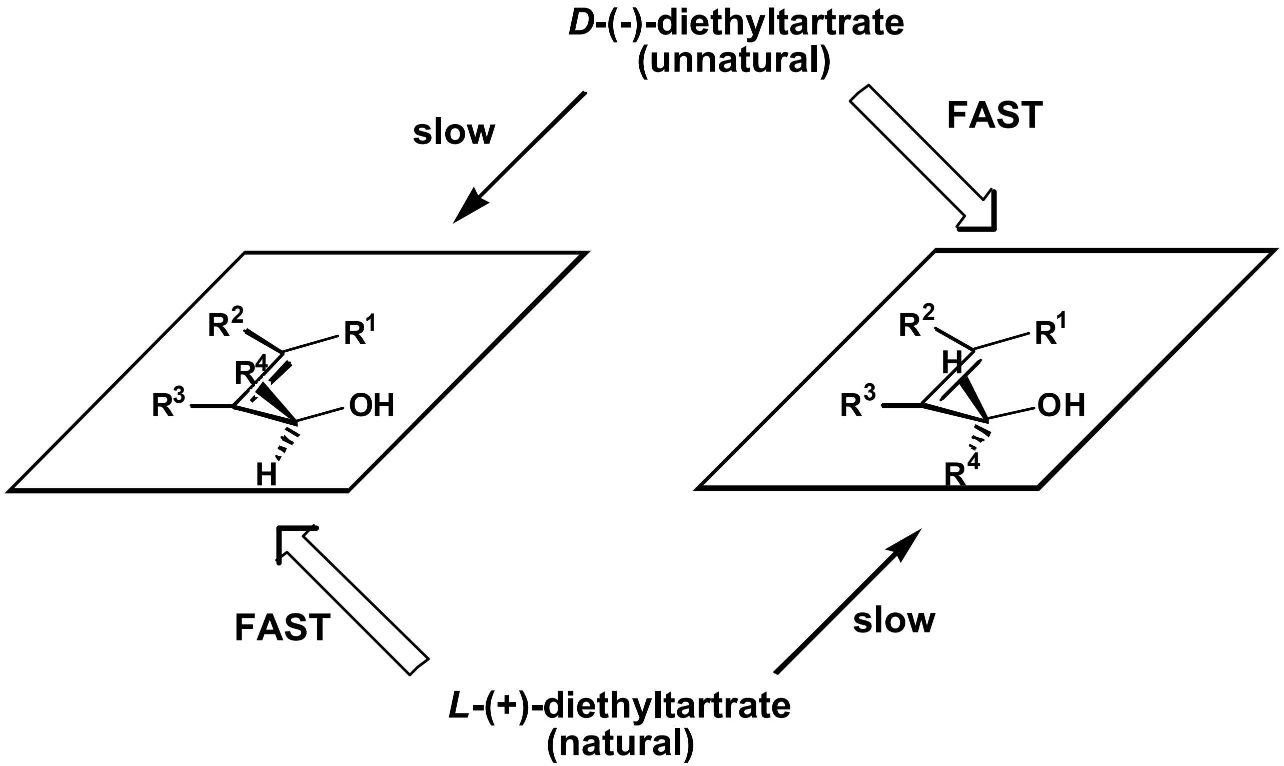


J. Am. Chem. Soc., **1988**, *110*, 4818

Active catalyst is believed to be a dimer



Katsuki-Sharpless asymmetric epoxidation in resolution mode



D-(-)-diethyltartrate
(unnatural)

slow

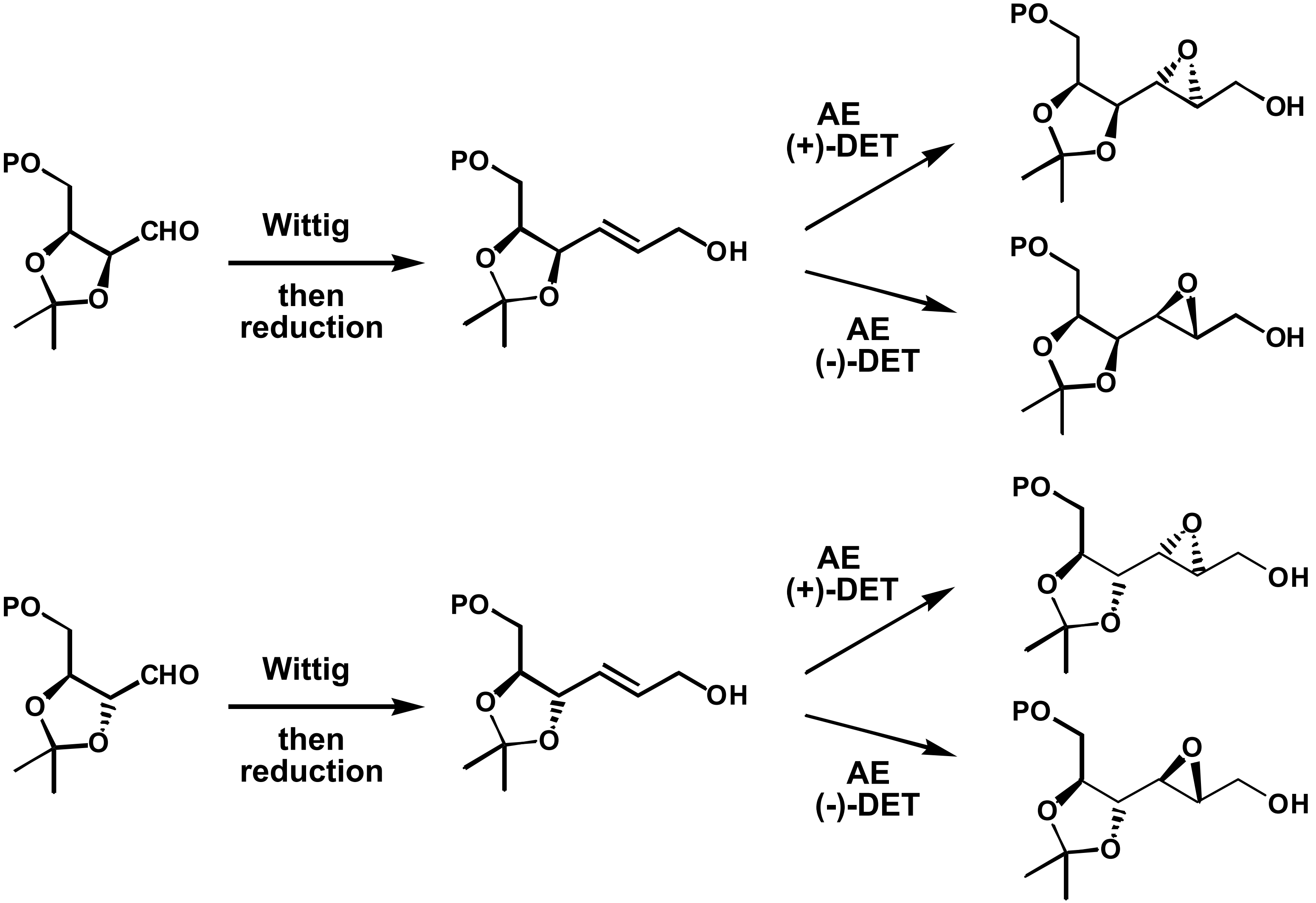
FAST

FAST

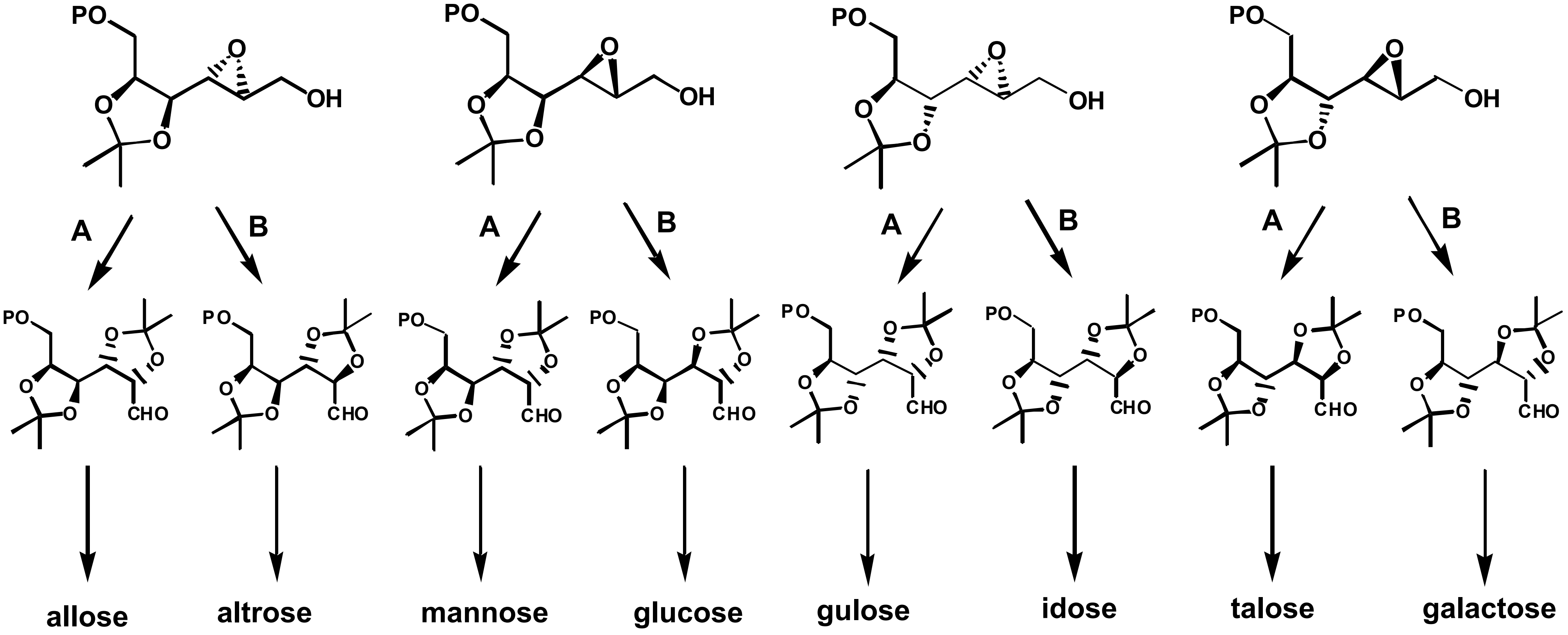
slow

L-(+)-diethyltartrate
(natural)

Masamune and Sharpless asymmetric epoxidation route to the hexose sugars



Masamune and Sharpless asymmetric epoxidation route to the hexose sugars

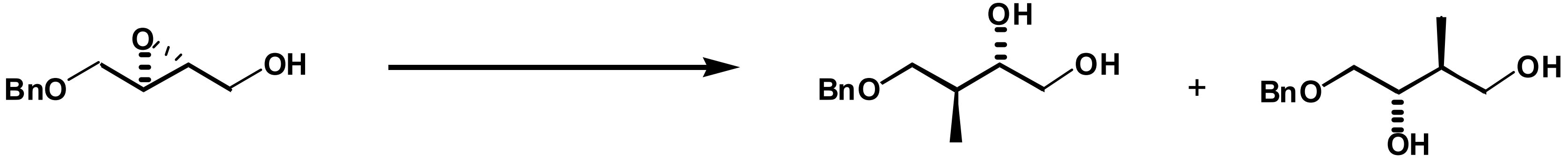


A = Payne/opening; ketalisation; Pummerer; neutral deprotection
B = Payne/opening; ketalisation; Pummerer; basic deprotection with epimerisation

***Science*, <u>1983</u>, *220*, 949**

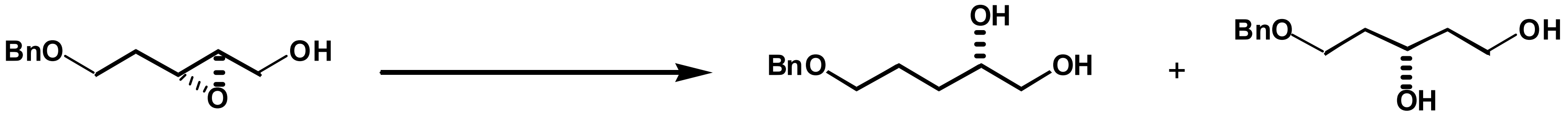
Regioselective ring-opening of epoxy alcohols from Sharpless protocols

- anionic nucleophiles favour the formation of the 1,3-diol by attack at the 2-carbon, whereas neutral (Lewis acidic) aluminium nucleophiles favour opening at the 3-position to generate 1,2-diols:



Me_2CuLi, Et_2O, -20°C	10 : 90
Me_3Al, CH_2Cl_2, 0°C	85 : 15

Tetrahedron Lett., **1983**, *24*, 1377

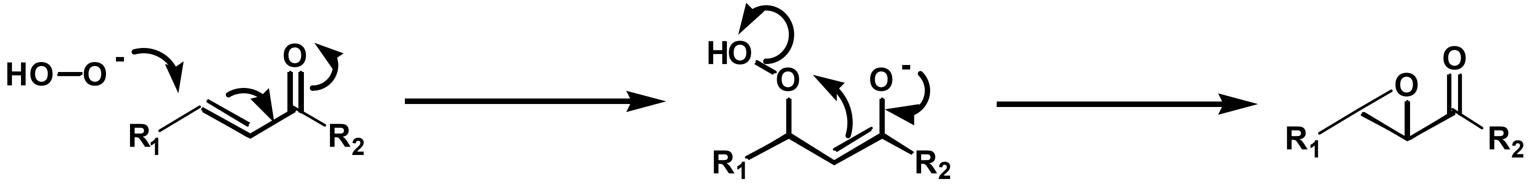


Red-Al, THF, -20°C	1 : 150
DIBAL, PhH, r.t.	13 : 1

Tetrahedron Lett., **1982**, *23*, 2719

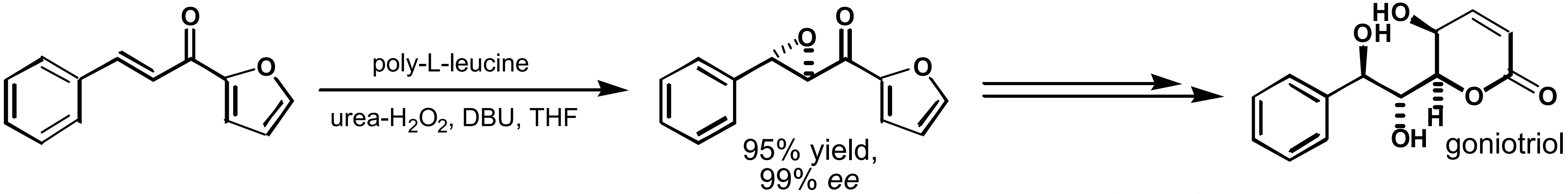
Poly-leucine mediated epoxidation of electron poor olefins

- peracids etc are poor oxidants for electron-deficient olefins; nucleophilic oxidation conditions are better:



- poly-amino acids such as polyleucine in triphasic (toluene/water/solid) systems catalyse the reaction(Julia, *Angew. Chem., Int. Ed. Engl*., **1980**, *19*, 929). Use of urea-H_2O_2 as co-oxidant facilitates reaction in biphasic (THF/solid) fashion, with increased rates and prolonged catalyst stability (Roberts, *Chem. Commun*., **1997**, 739)

- Limitation: no alkyl substituents at α' or β positions (enolisation), hence largely limited to diaryl substitution



Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1999, 103

review: *Tetrahedron Asymm*., **1997**, *8*, 3163
supported poly-leucine on polystyrene: *J. Org. Chem*., **1990**, *24*, 6067; or silica: *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1397

- other protocols include chiral phase-transfer catalysts (Lygo, *Tetrahedron*, **1999**, *55*, 6289) and chiral lanthanide binaptholates (Shibasaki, *J. Am. Chem. Soc*., **1997**, *119*, 2329).
  The latter two approaches are valuable since they tolerate β-alkyl substitution.