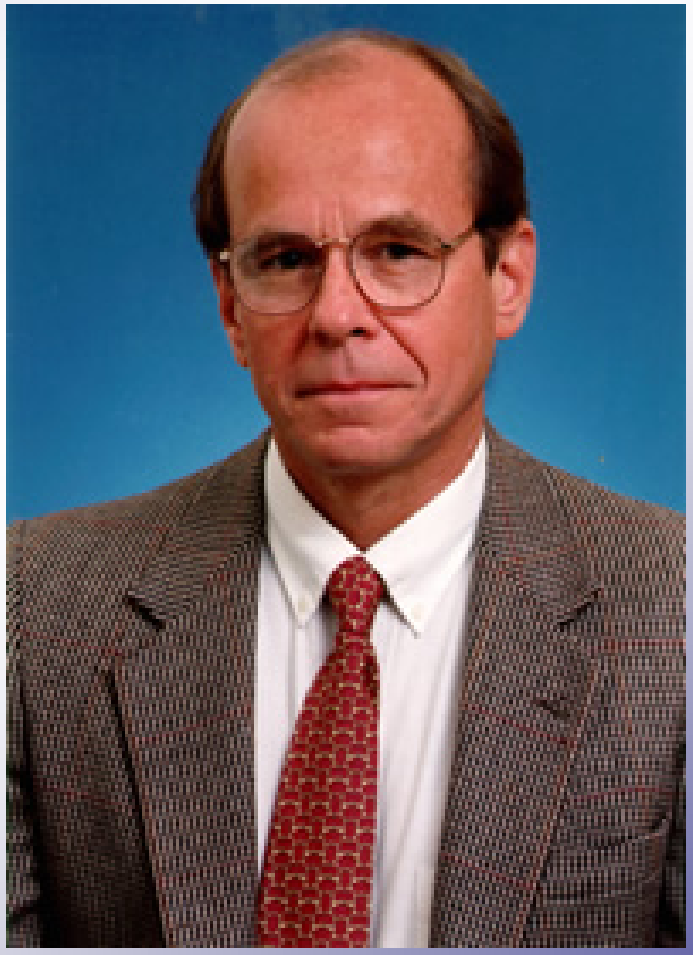
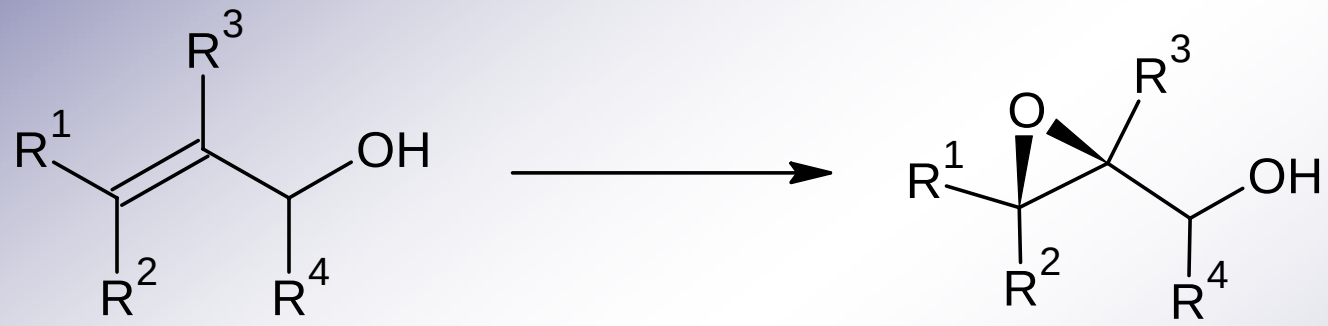
Sharpless Asymmetric Epoxidation

Karl Barry Sharpless

- Born in Philadephia in 1941
- Ph.D from Stanford University in 1968
- Postdoc at Harvard and at Stanford
- Research on chiral synthesis and catalysts at the Scripps Institute
- Received Nobel Prize in 2001 for his work on stereoselective oxidation reactions



Sharpless Asymmetric Epoxidation (SAE)

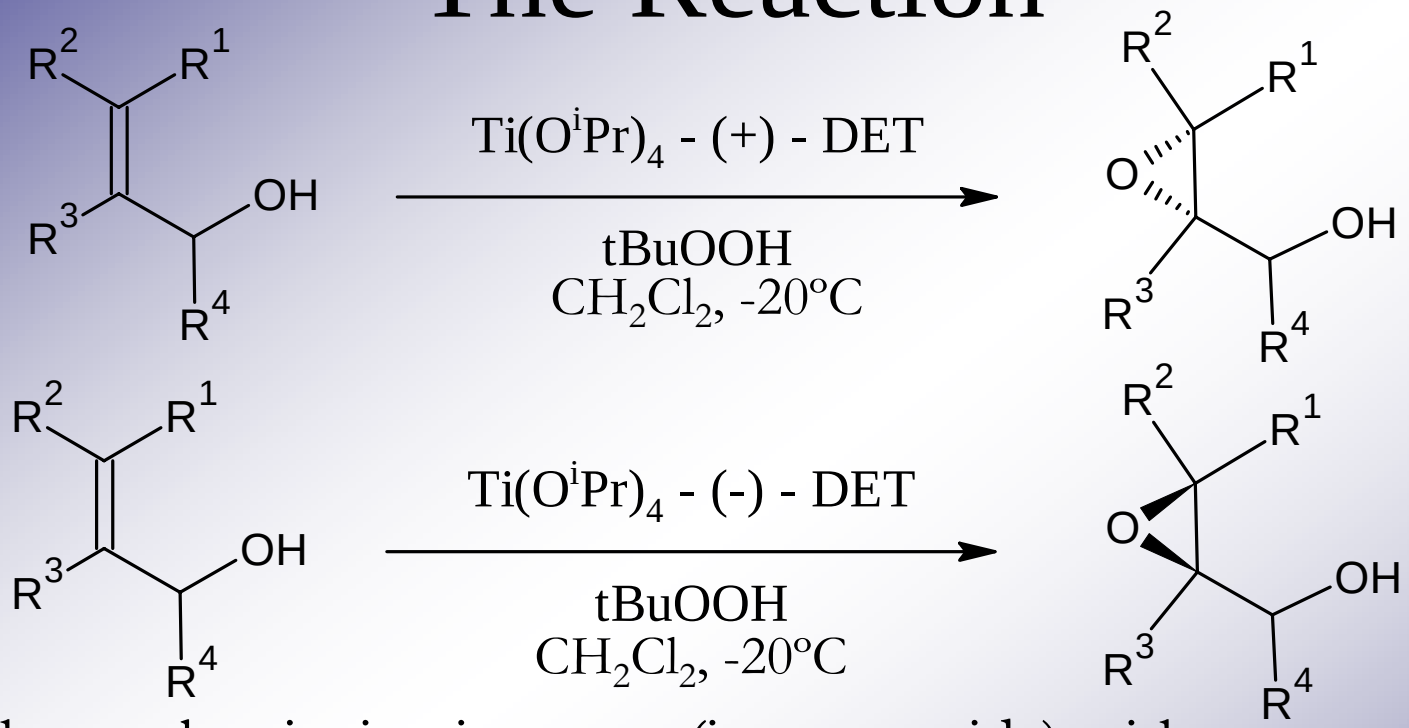


- Converts primary and secondary allylic alcohols into 2,3 epoxyalcohols

-The reaction is enantioselective (only one enantiomer produced)

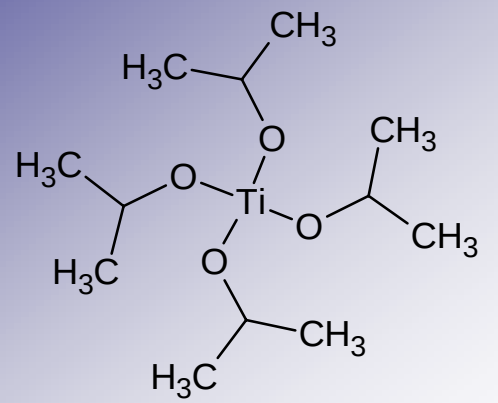
-Enantiomer formed depends on stereochemistry of catalyst

The Reaction

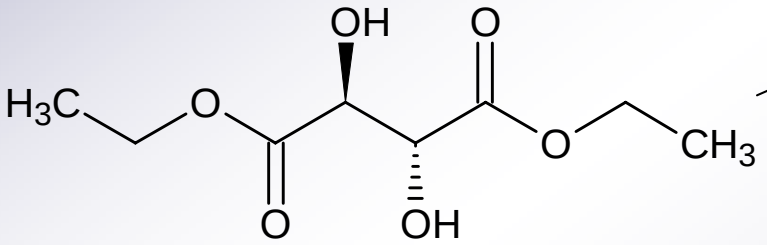


- The catalyst is titanium tetra(isopropoxide) with diethyltartrate.
- The use of + or – tartrate will yield different enantiomers
- Tertbutylperoxide is used as the oxidizing agent
- Dichloromethane solvent and -20ºC temperature

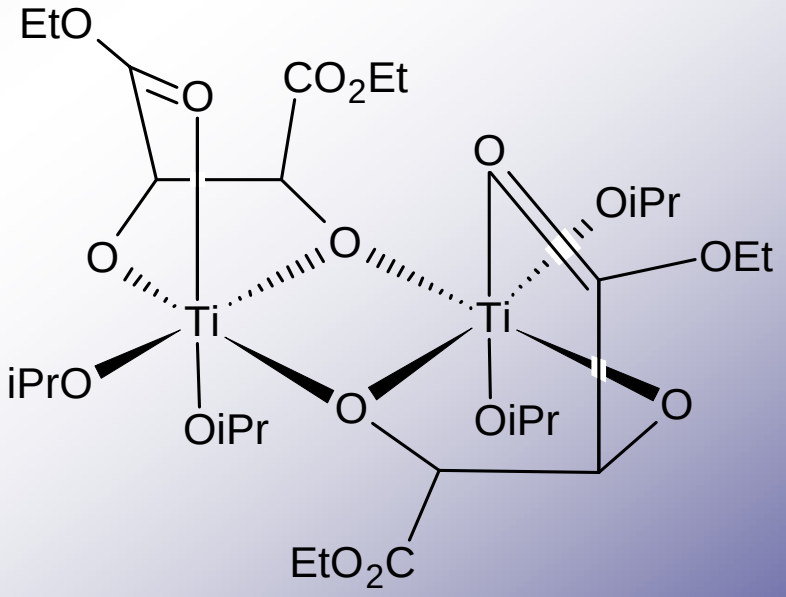
The Catalyst



$Ti(O^iPr)_4$ catalyst

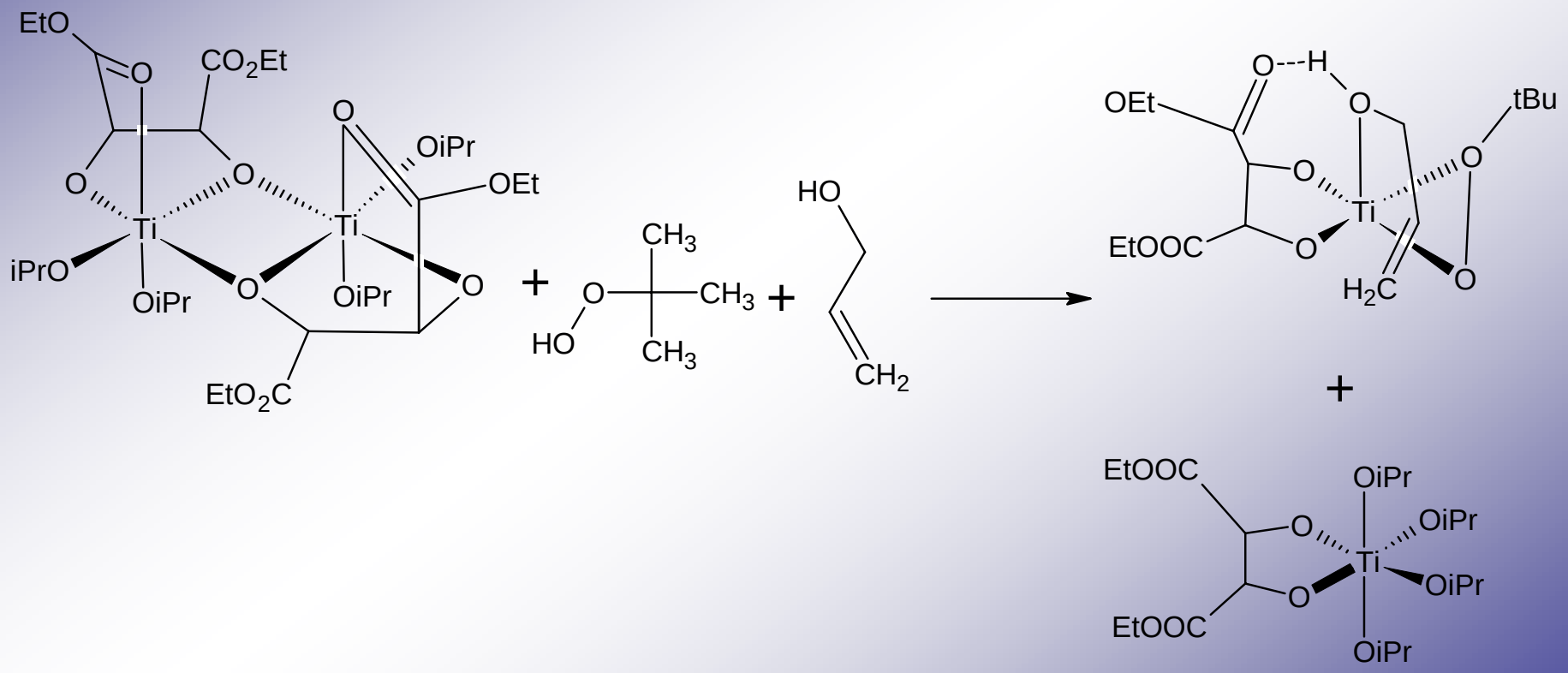


Diethyl Tartrate (DET)
Chirally controls reaction

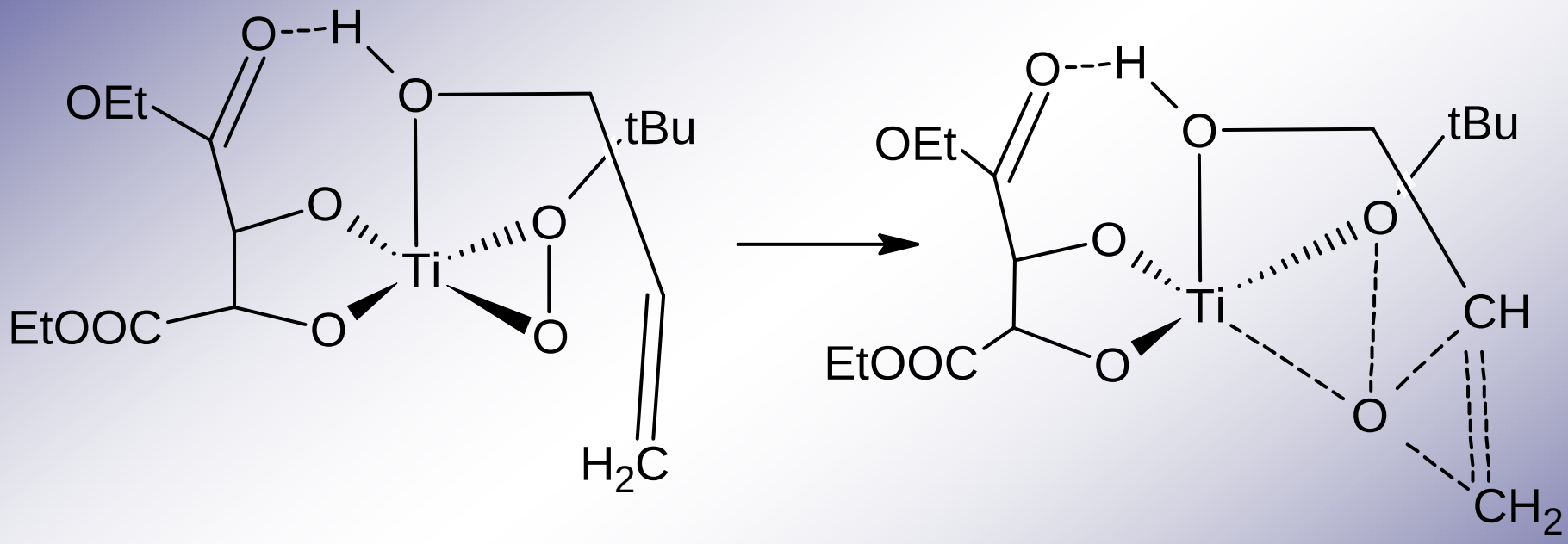


- Via rapid ligand exchange of O^iPr and diethyl tartrate

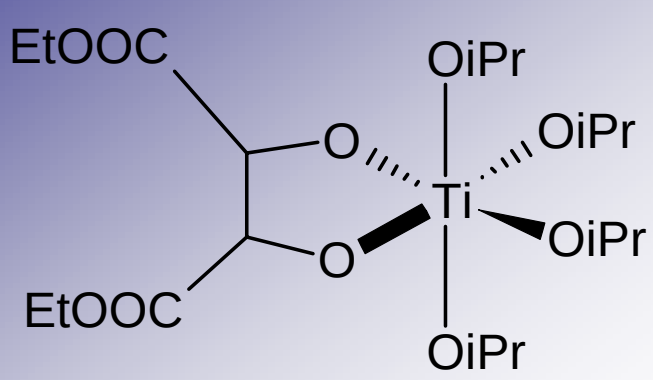
The Mechanism

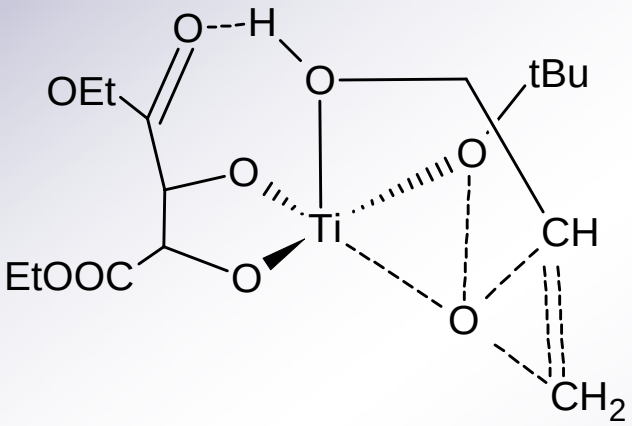


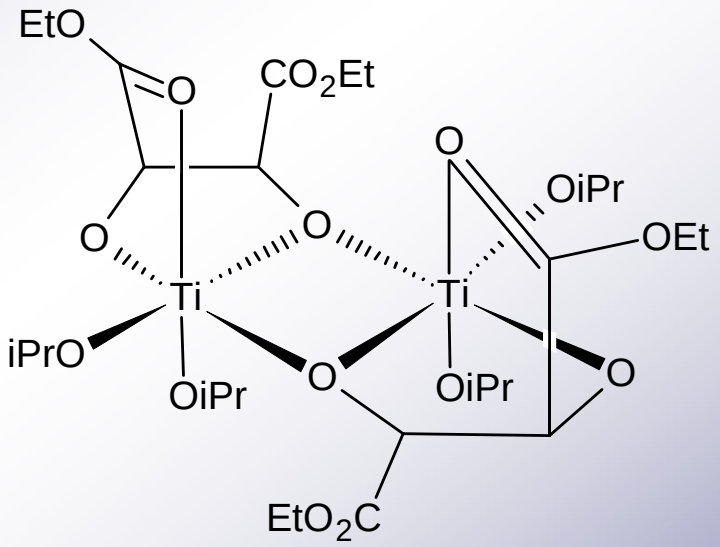
Transition State



Products



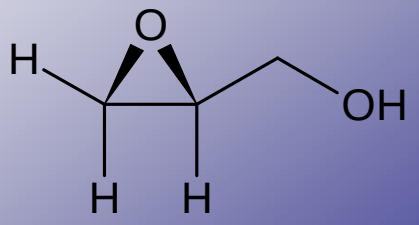


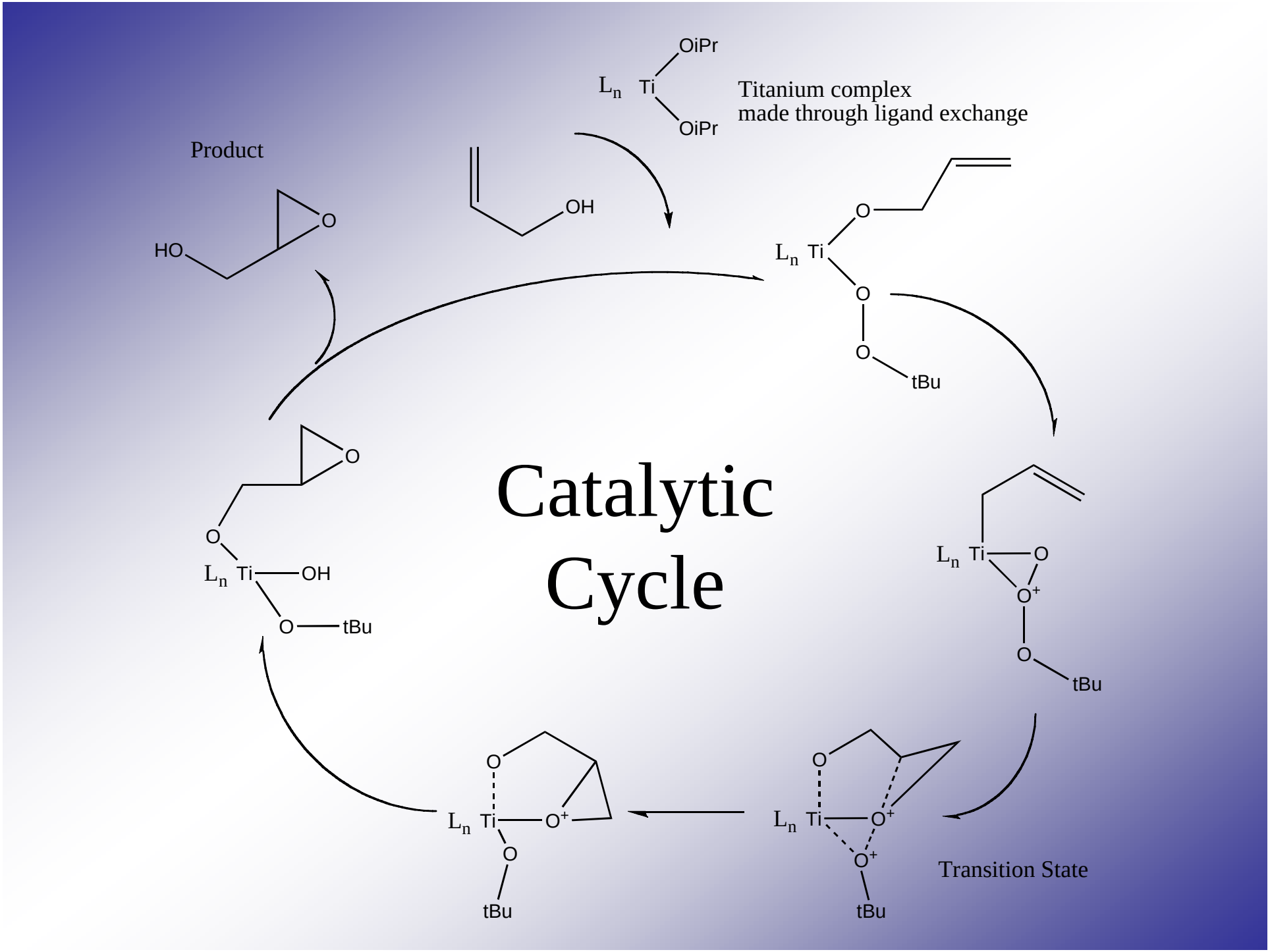


+

tBuOH

+




Catalytic Cycle
Titanium complex made through ligand exchange
Product
Transition State

Improvements

- Many potential areas of improvement to the original reaction
- Possible problems:
  - Stoichiometric amount of catalyst required
  - Water soluble substrates (Polymer Support) cannot be isolated after reaction
  - Requirement for low temperatures (high cost for SAE)
  - Some substrates react very slowly
  - Heterogeneous reaction?

Molecular Sieves

- Original reaction requires stoichiometric amount of $Ti(^{i}OPr)_4$ catalyst
- Very reactive allyl alcohols need 50% catalysts – still significant
- Major reasons for failure of SAE reactions:
  - Water destroys catalyst
  - Water ring-opens epoxide
- 3Å molecular sieves absorb water improving yield
- Requirement of Ti catalyst reduced to <10% and the tartrate ester to <13%
- Allyl alcohol concentration can be kept high since side reactions are minimized (no ring opening)

Molecular Sieves

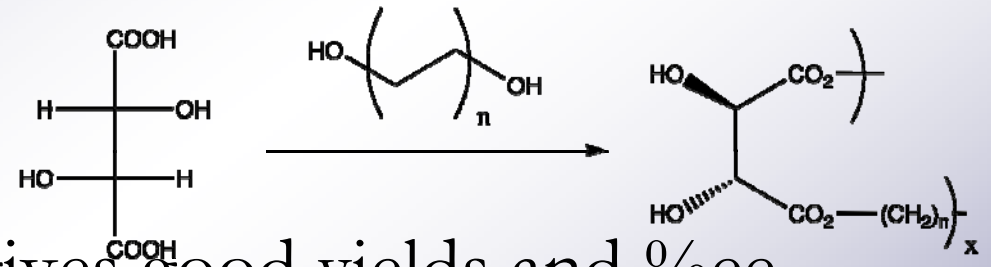
- Advantages:
  - Economy – less catalyst required
  - Somewhat milder conditions
  - Ease of isolation
  - Increased yields
  - Possible in-situ derivatization
- **Problem**: the substrate may not be soluble in the solvent (low propoxide ion concentration)

Polymer Support

- Metal catalyst is mounted on a polymer which makes it (usually) heterogeneous
- Advantages:
  - Lab scale: facilitate workup and isolation
  - Industry: continuous process
  - Minimizes catalyst loss during workup
- Possible Polymers:
  - silica gel (H_2O_2 catalysts)
  - alkaloid polymers
  - Polystyrene (heterogeneous Jacobson epoxidation)
- Polymer support vital with water-soluble substrates

Polymer Support

- Early work with polystyrene had low %ee
- A Scottish group used linear chiral poly(tartrate esters)
- Combining benefits of polymer support with the active functionality built in



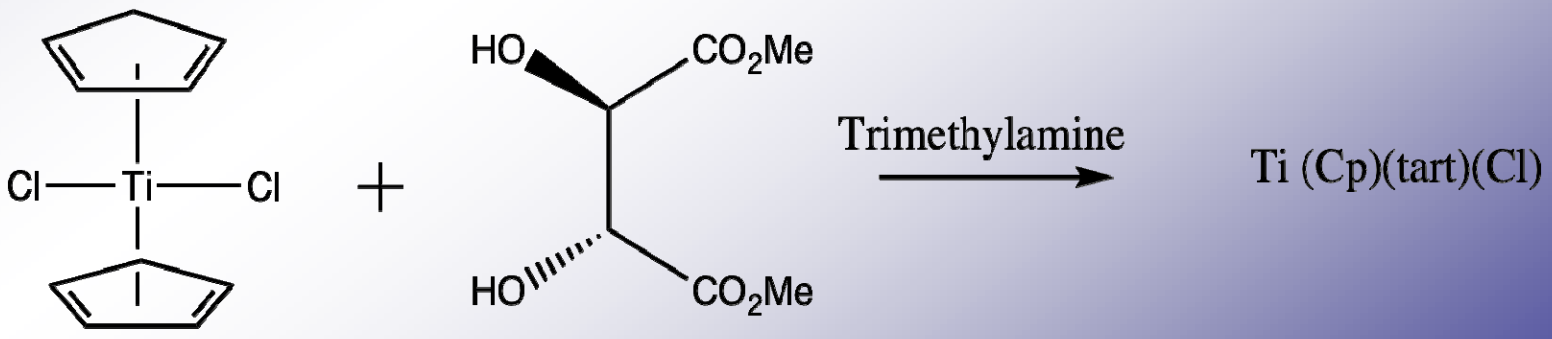
- Reaction gives good yields and %ee
- Branched poly(tartrate esters) were found to be even more selective and had higher yields

Higher Temperatures SAE

- **Problem:** High cost due low temperatures
- **Solution:** Titanocene-tartrate (TT) catalyst
- Very good catalytic activity and decent enantioselectivity at higher temperatures
- TT has bulky cyclopentadienyl rings which create steric hindrance, inducing chirality (compare with BINOL)
- In classic SAE, the tartrate-titanium complex forms through ligand exchange

Higher Temperatures SAE

- But the titanocene-tartrate cannot form through ligand exchange (Ti-halide stable)
- Titanocene tartrate is generated before the reaction:



In Situ Modification

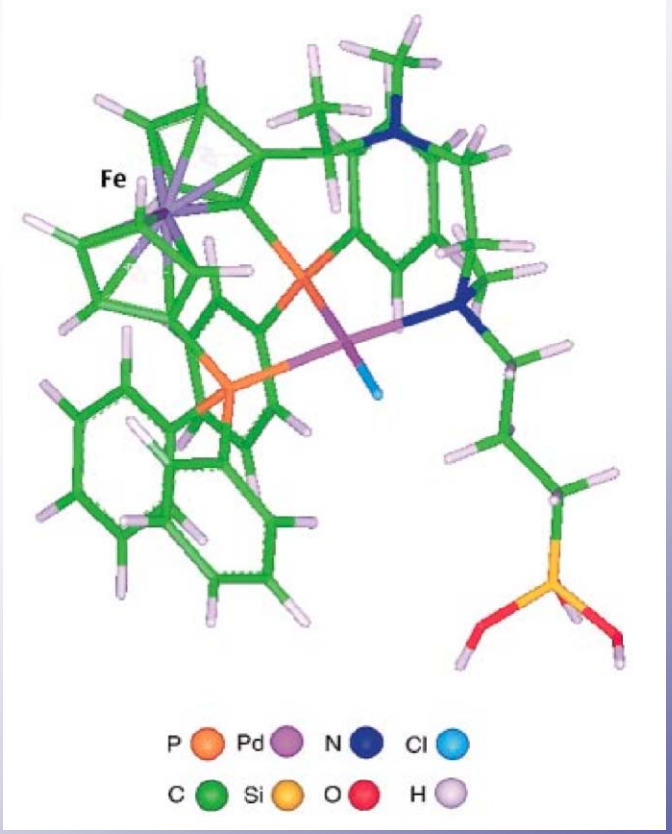
- Ideal use for SAE is to make low molecular weight chiral products – synthetic utility
- Low molecular weight substrates react slowly – product is lost during workup
- The epoxide formed may also be ring-opened during workup
- With molecular sieves, the catalyst concentration is reduced, so solubility of product also decreases
- Better solution is *in-situ* derivatization

In Situ Modification

- Epoxy-alcohol product is converted to an ester derivative:
  - *p*-toluene sulfonyl and 2-naphthalene sulfonyl
  - *t*-butyl diphenyl silyl and *t*-butyl dimethyl silyl
- The derivatives are
  - Easily un-doable (good leaving group)
  - Functionally equivalent to parent for reactions
- Further chemistry can be done on the epoxy-"alcohol" without loss of yield
- Derivative may be isolable in high yield and then converted back to alcohol

Other Modifications

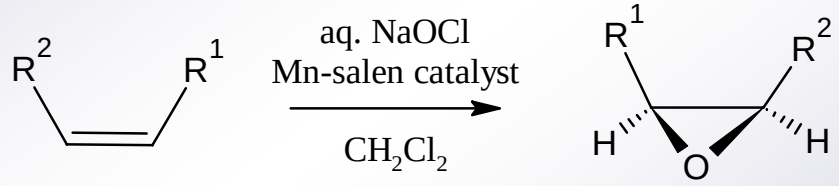
- Numerous minor modifications to the classic SAE
- Ageing the catalyst: the catalyst is synthesized fresh and "aged" for 30 minutes
- Alternative solvents: isooctane, toluene
- The ester: diethyl tartrate vs. diisopropyl tartrate
- Mesoporous silica support for heterogeneous catalysis (MCM-41)

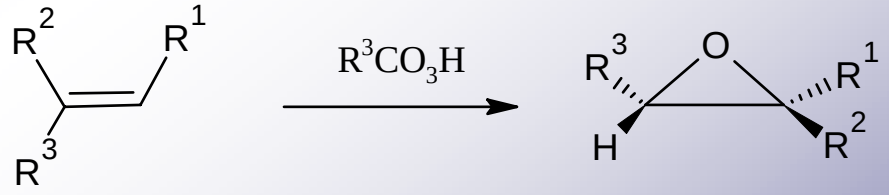


Structure of catalytic center of MCM-41

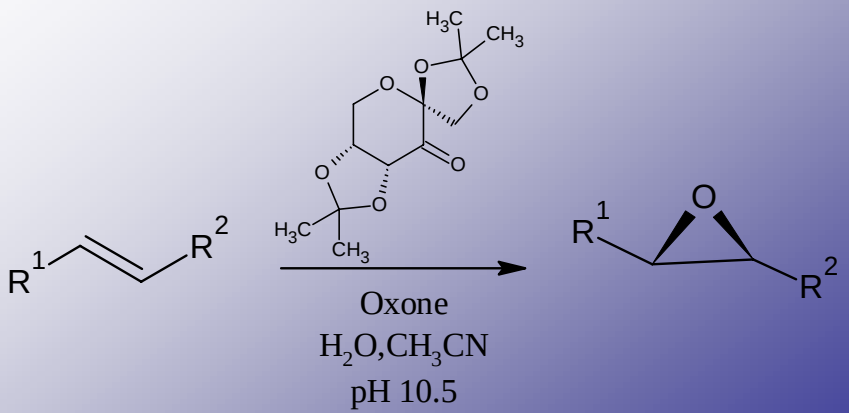
Competing Methods

- Many competing reactions for generating epoxides:



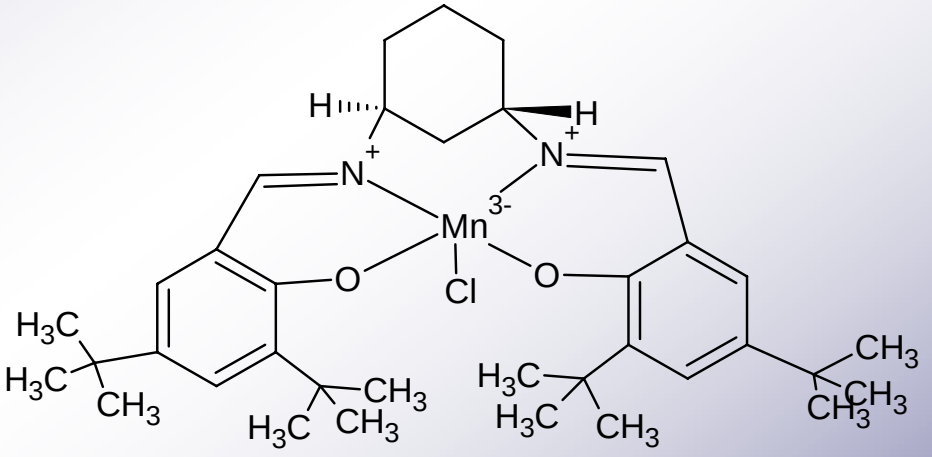


- Jacobsen-Katsuki epoxidation
- Prilezhaev reaction
- Shi expoxidation



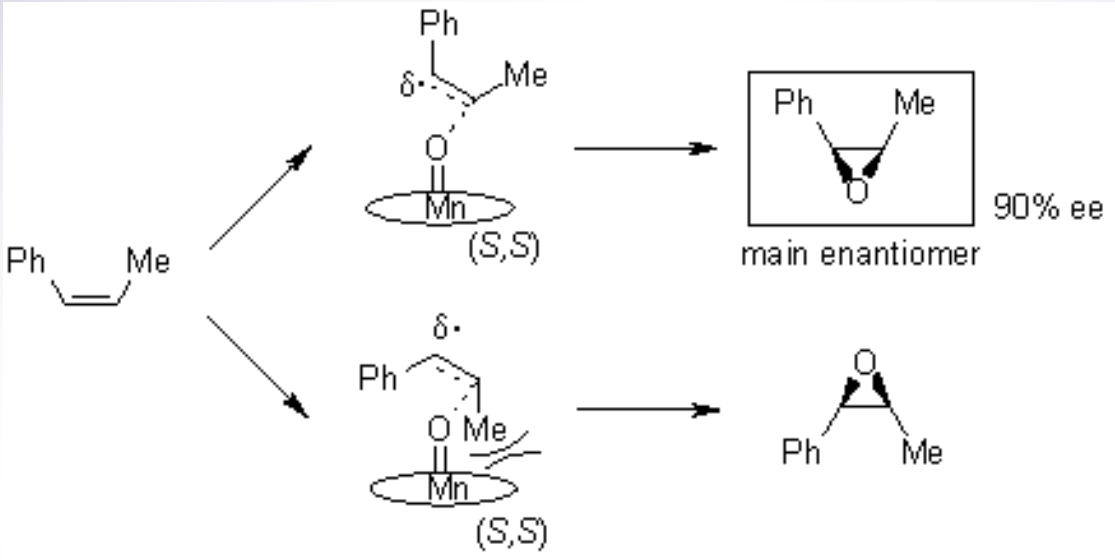
Jacobsen-Katsuki Epoxidation

- Uses cis alkene as a reactant
- Allows broader scope of substrate (R: Ar, alkenyl, alkynyl; R': Me, alkyl)
- Mn-salen catalyst and a stoichiometric oxidant



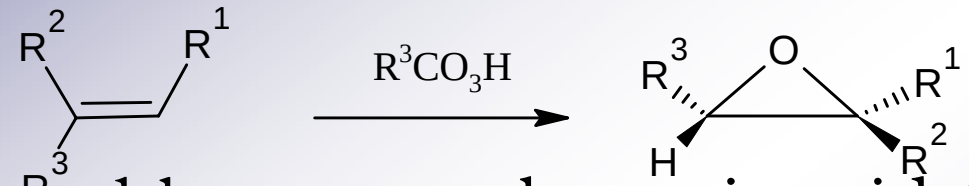
Jacobsen-Katsuki Epoxidation

- Mechanism's catalytic cycle shows the formation of an Mn(V)-oxo complex
- Good yields with high enatomeric excess



Prilezhaev Reaction

- Reaction of an alkene with a peracid

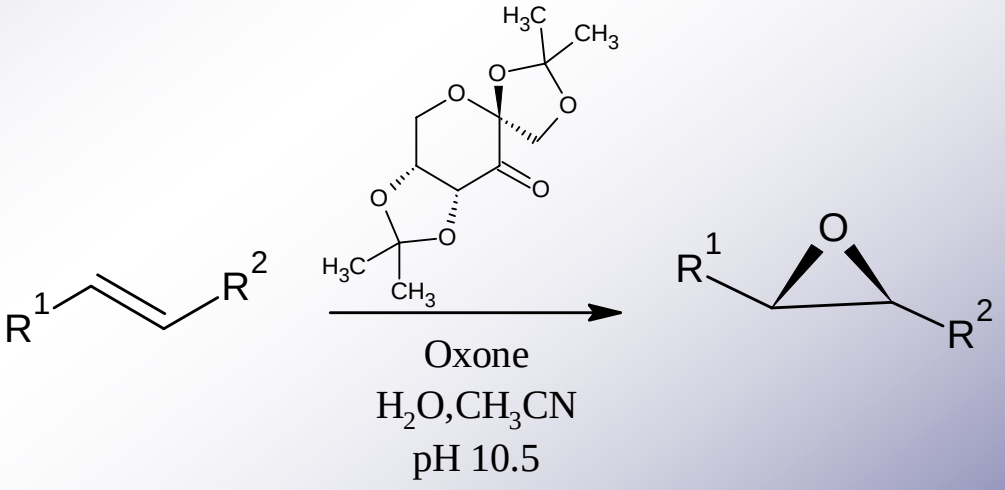


- meta-chloroperoxybenzoic acid (m-CPBA) is most commonly used as the peracid
- Magnesium mono-perphthalate and peracetic acid

N. K. Jana, J. G. Verkade, *Org. Lett.,* **2003**, *5*, 3787-3790.

Shi Epoxidation

- Reaction involving a trans alkene
- Oxone is another main component
- Fructose derived catalyst used
- High enatiomeric excess yields



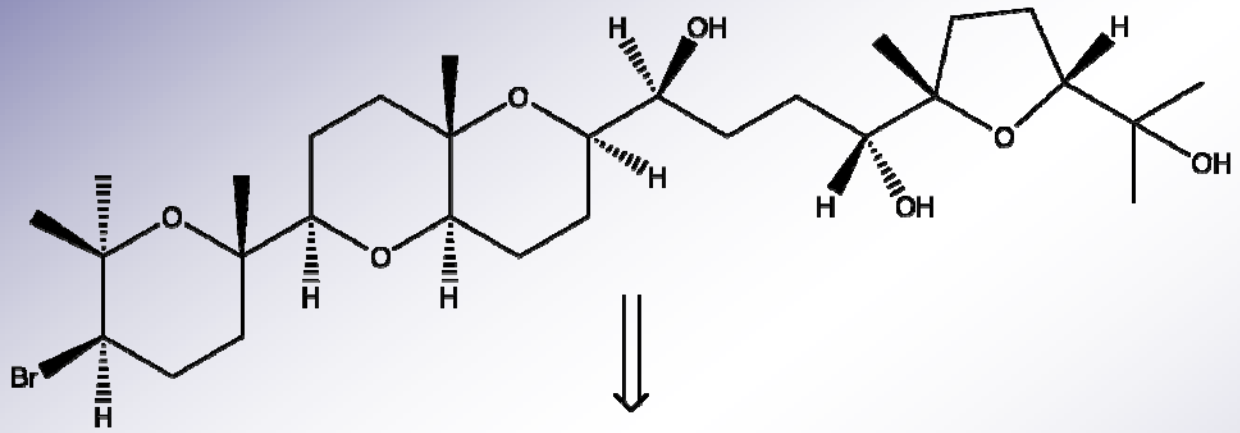
Uses of the Reaction

- The Sharpless Asymmetric Epoxidation converts alkenes into chirally active epoxides
- Innumerable syntheses published that use the SAE
- Chiral epoxides easily converted into:
  - 1,2 Diols
  - Make carbon-carbon bonds (stereospecifically)
  - Aminoalcohols
- Two examples considered:
  - A complex synthesis of **Venustatriol** by EJ Corey
  - Simpler synthesis of **Untenone** by Mizutani *et al.*

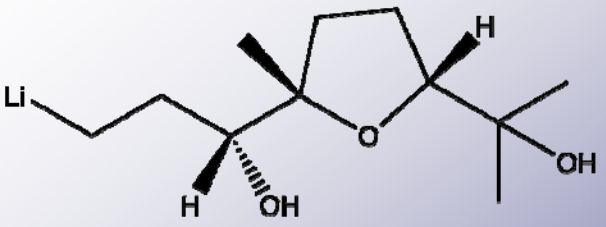
Venustatriol

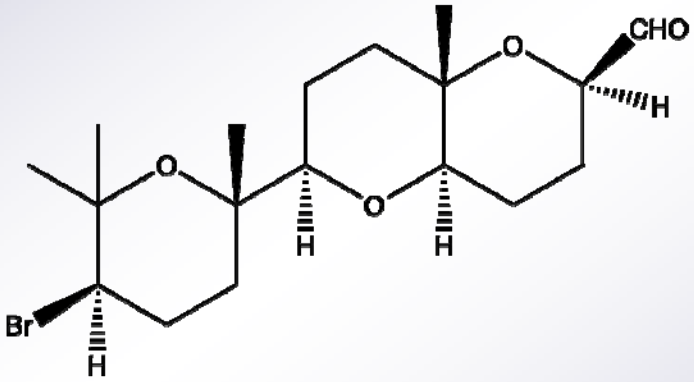
- Marine-derived natural product discovered initially in 1986
- Found in red alga Laurencia venusta
- Derived *in vivo* from squalene, made as a triterpene
- Shown to have antiviral and anti-inflammatory properties
- Structure contains repeated polyether moieties
- Key problems: multiple stereocenters and polyether moieties.
- Corey proposed a “simple and straightforward” disconnection

Venustatriol - Reterosynthetic Analysis

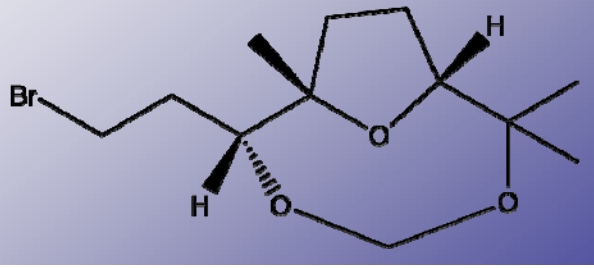


Fragment B

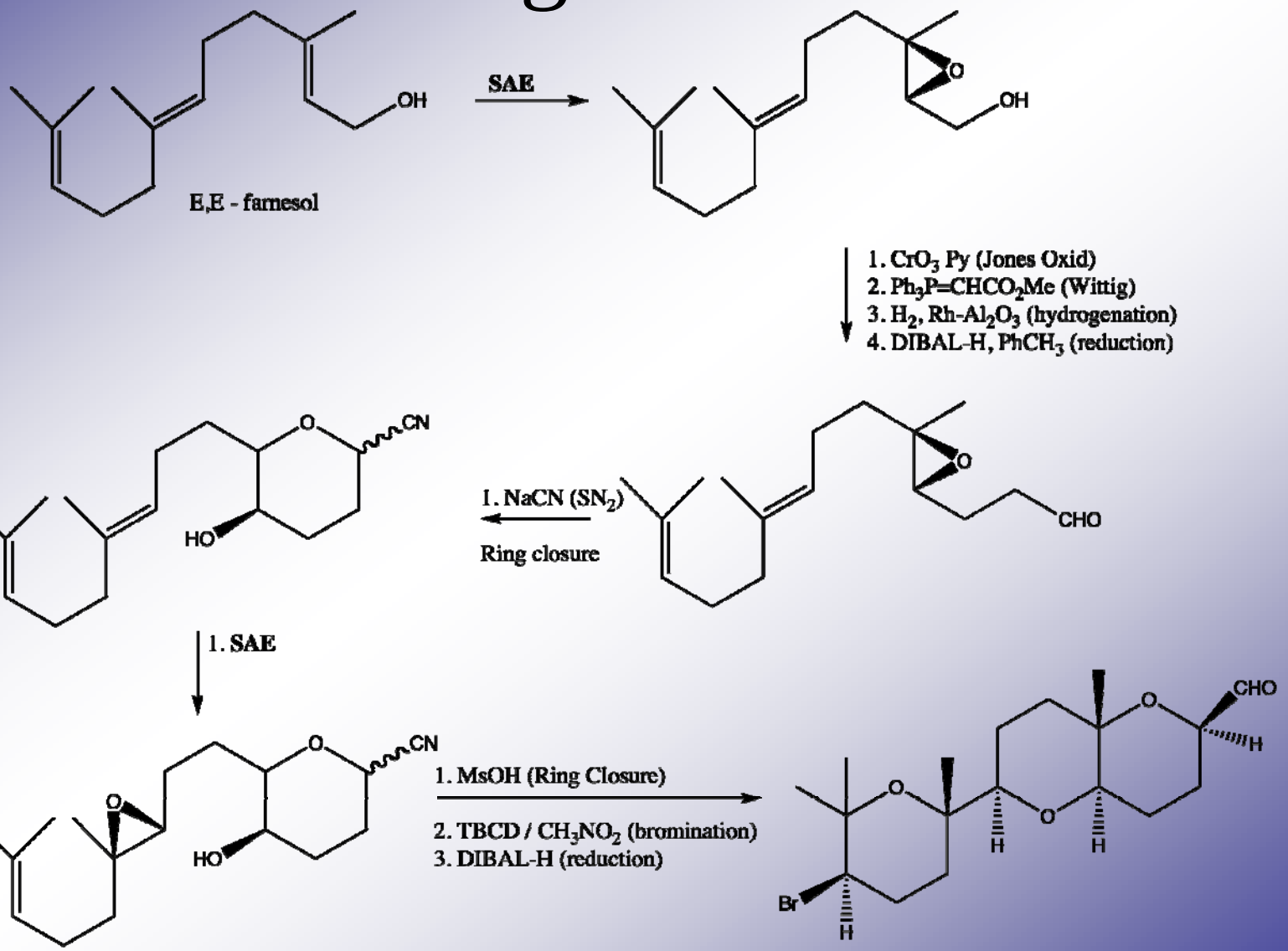




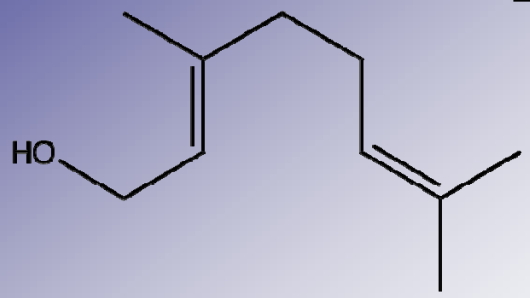
Fragment A



Fragment A

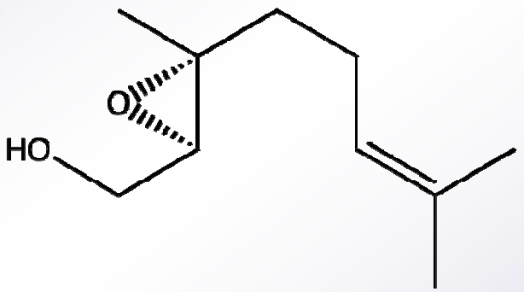

OH
SAE
O
OH
E,E - farnesol
1. CrO_3 Py (Jones Oxid)
2. $Ph_3P=CHCO_2Me$ (Wittig)
3. H_2, Rh-Al_2O_3 (hydrogenation)
4. DIBAL-H, $PhCH_3$ (reduction)
O
CN
HO
1. NaCN (SN_2)
Ring closure
O
CHO
1. SAE
O
CN
O
HO
1. MsOH (Ring Closure)
2. TBCD / CH_3NO_2 (bromination)
3. DIBAL-H (reduction)
CHO
O
H
O
O
H
H
Br
H

Fragment B

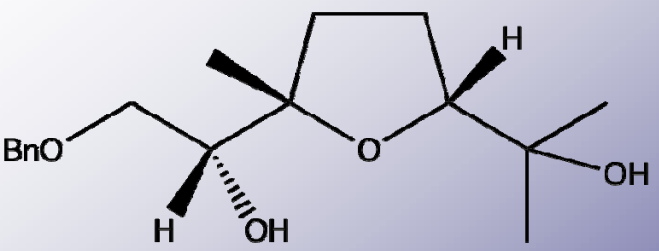


Geraniol

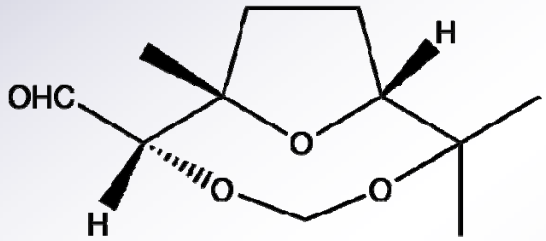
SAE



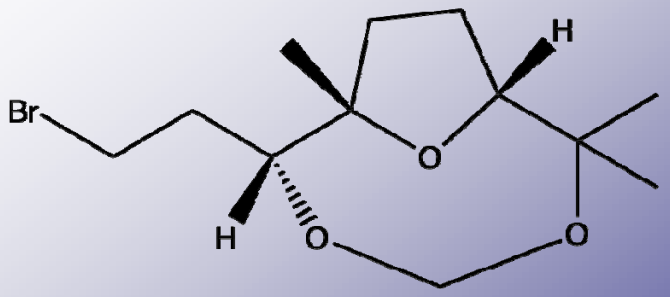
1. Hydride + BnBr (SN2)
2. $HClO_4$ (Open diol)
3. PCC/DCM (Ether Ring Close)



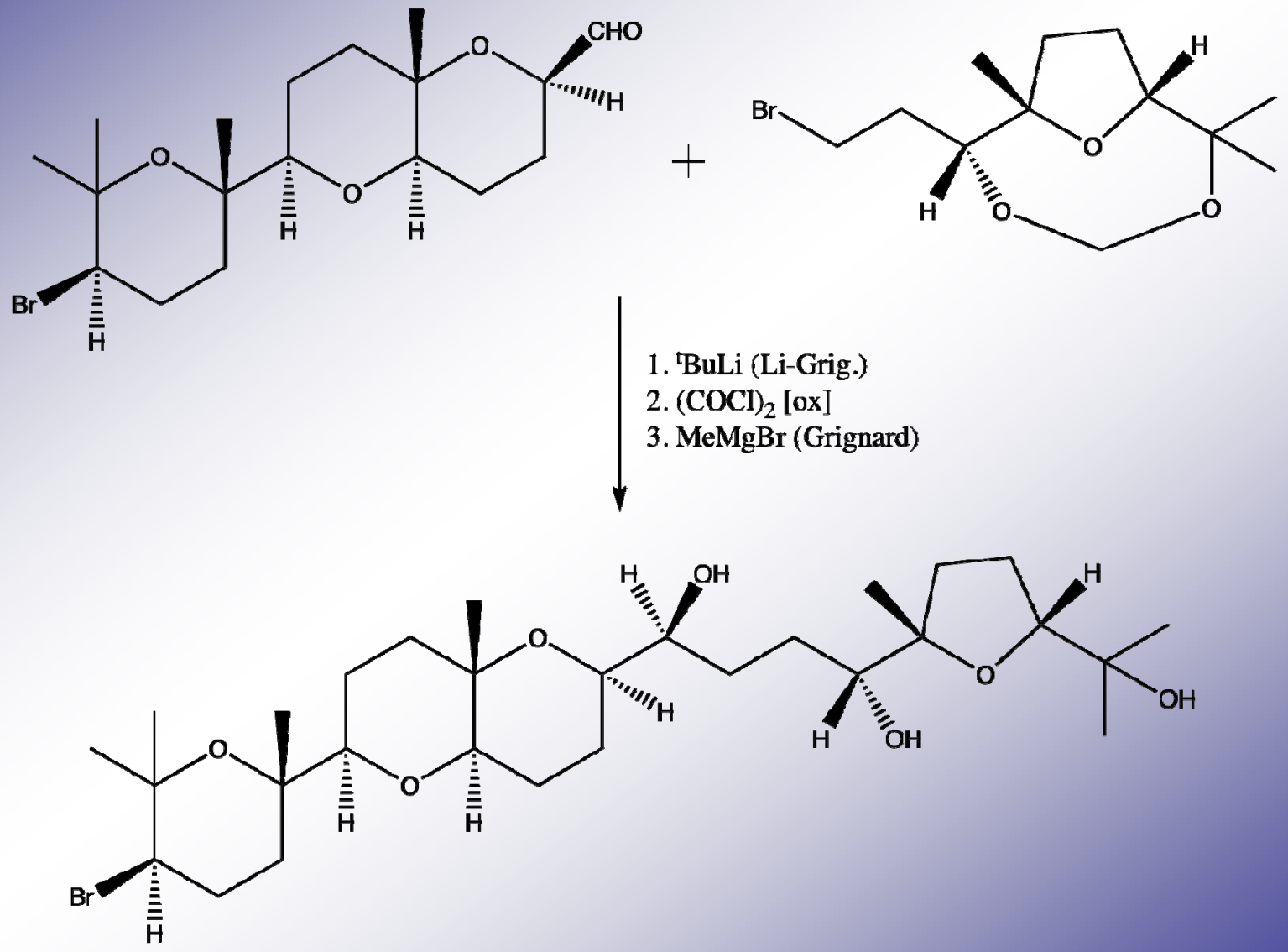
1. NaH
2. MOMCl (methyl ether)
3. $H_2/(COCl)_2$ (oxidize)



1. $Ph_3P{=}CH_2$ (Wittig)
2. 9-BBN/H_2O_2 (alcohol)
3. CBr_4 (bromination)



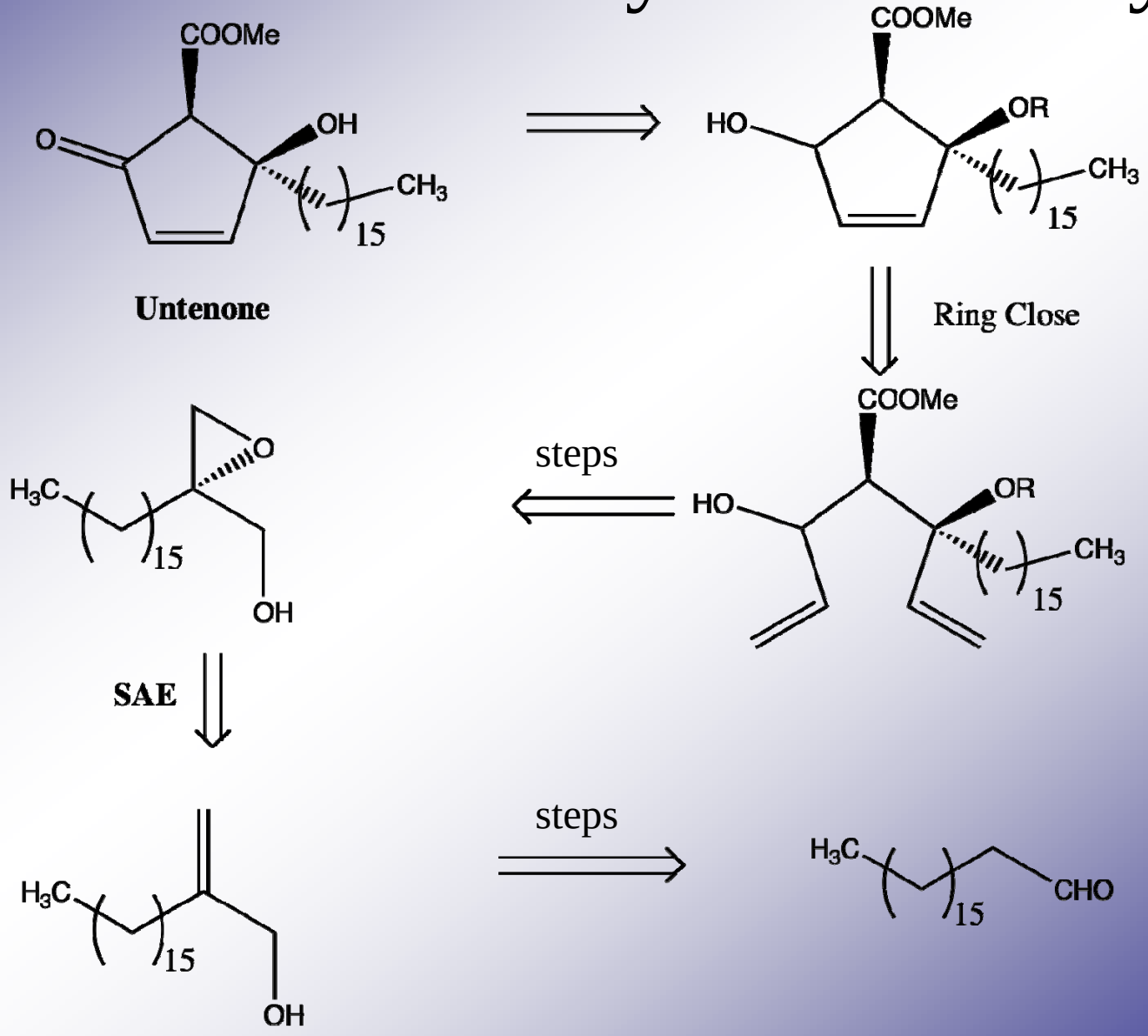
Final Step - Venustatriol



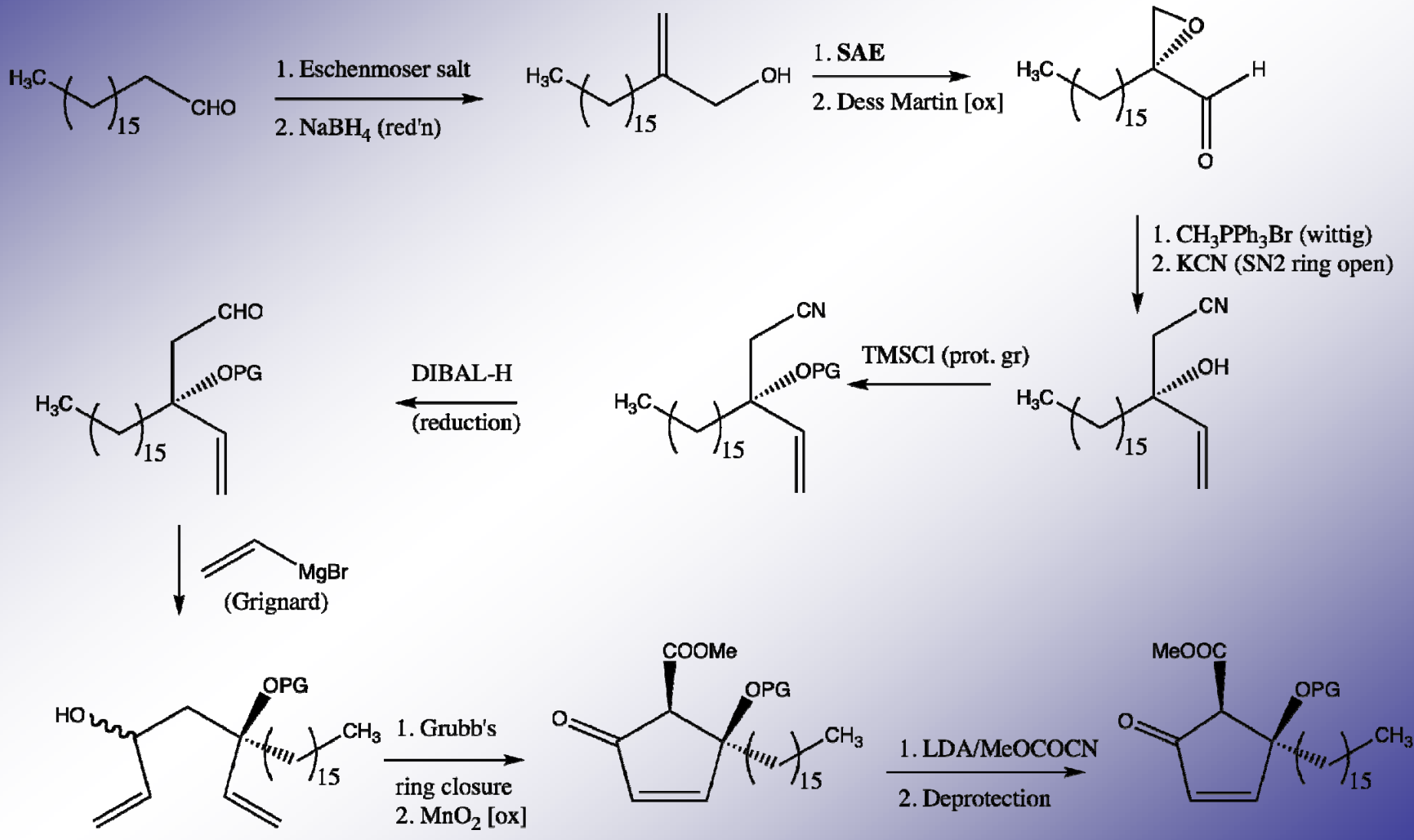
Untenone

- Isolated from a marine sponge in 1993
- Exhibits inhibitory activity against mammalian DNA polymerases
- These enzymes are important for DNA replication, repair and cell divisions (cancer implications)
- Biosynthetic pathway not investigated
- The critical part of the synthesis is the introduction of a quaternary carbon center (done via **SAE**)
- The total synthesis is 15 steps

Untenone - Reterosynthetic Analysis



Untenone Synthesis



References

- Kurti, L. and Czako, B. Strategic Application of Named Reactions in Organic Synthesis: Elsevier Academic Press, *2005*
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