

Organic Synthesis III

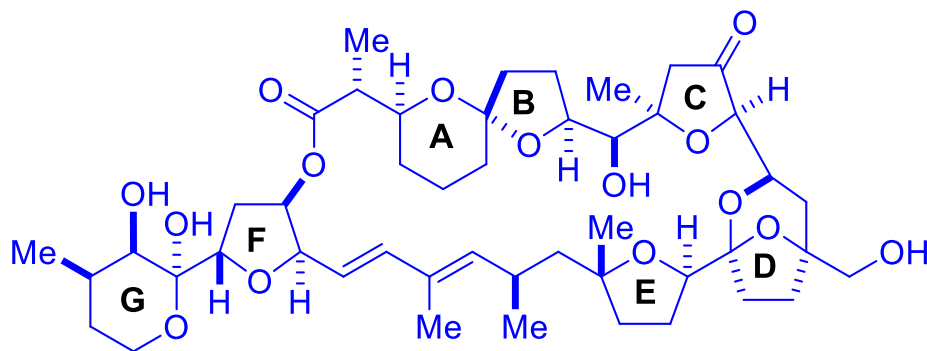
8 x 1hr Lectures: Michaelmas Term

Weeks 5-8 **2016**

Mon at 10am; Wed at 9am

Dyson Perrins lecture theatre

pectenotoxin 4



(D. A. Evans, *Angewandte Chemie, Int. Ed.* **2002**, 41, 4569)

Copies of this handout will be available at
<http://donohoe.chem.ox.ac.uk/page16/index.html>

Organic Synthesis III **Synopsis**

1) Introduction to synthesis:

- (i) Why do we want to synthesise molecules- what sort of molecules do we need to make?*
- (ii) What aspects of selectivity do we need to accomplish a good synthesis (chemo-, regio- and stereoselectivity)?*
- (iii) Protecting group chemistry is central to any synthetic effort (examples and principles)*
- (iv) What is the perfect synthesis (performed in industry versus academia)?*

2) The chiral pool: *where does absolute stereochemistry come from?*

3) Retrosynthesis- *learning to think backwards (revision from first and second year).*

Importance of making C-C bonds and controlling oxidation state.

Umpolung

4) Some problems to think about

5) Examples of retrosynthesis/synthesis in action.

6) Ten handy hints for retrosynthesis

7) Solutions to the problems

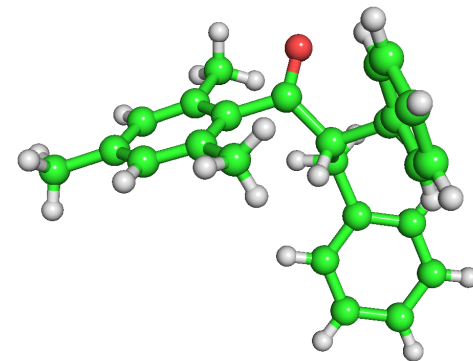
Recommended books:

General: Organic Chemistry (Warren et al)

Organic Synthesis: The Disconnection Approach (S. Warren)

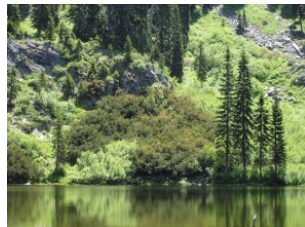
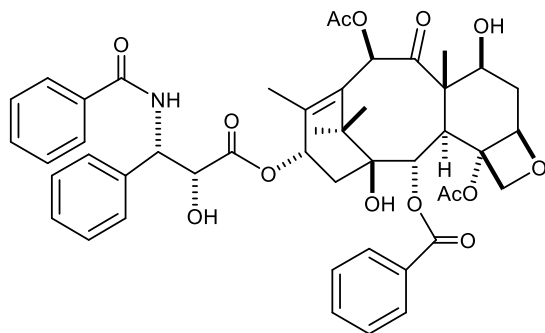
Classics in Total Synthesis Volumes I and II (K. C. Nicolaou)

The Logic of Chemical Synthesis (E. J. Corey)



(i) Why do we want to synthesise complex molecules?

Taxol



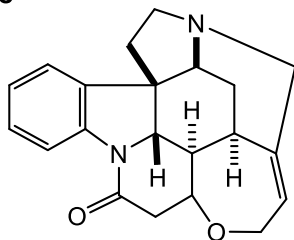
Isolated from the Pacific Yew in 1962

Prescribed for prostate, breast and ovarian cancer

Unique mode of action

1x 100 year old tree = 300 mg Taxol

Strychnine



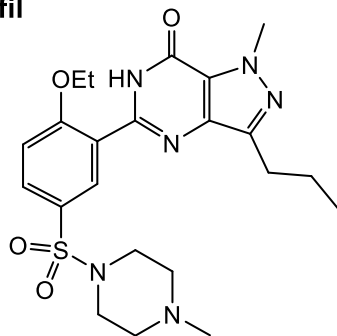
Isolated in 1818- poisonous

Structural elucidation took R. Robinson 40 years

Strychnine and Brucine. Part XLII. Constitution of the neo-Series of Bases and their Oxidation Products.

By L. H. BRIGGS, H. T. OPENSHAW, and SIR ROBERT ROBINSON.

Sildenafil



Developed in the UK (Pfizer)

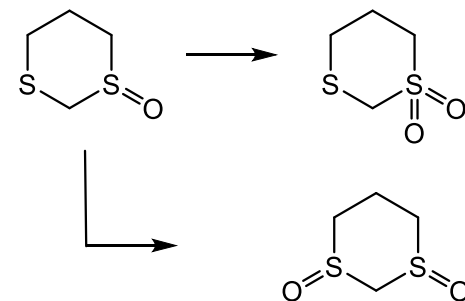
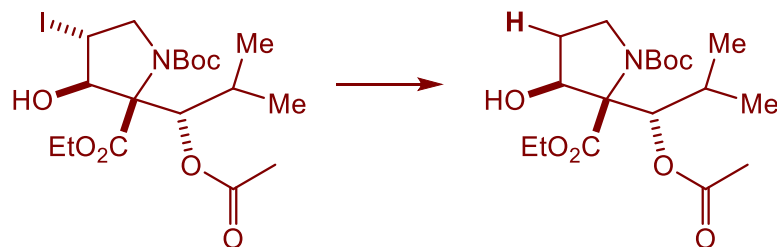
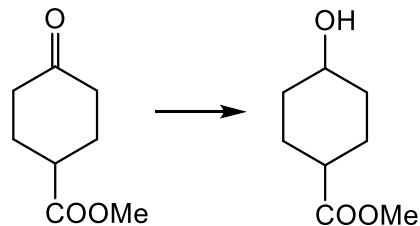
For a list of the structures of the top 200 band name drugs by retail dollars see:
<http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster>

(ii) In order to undertake the synthesis of a complex organic molecule, we need to control the following:

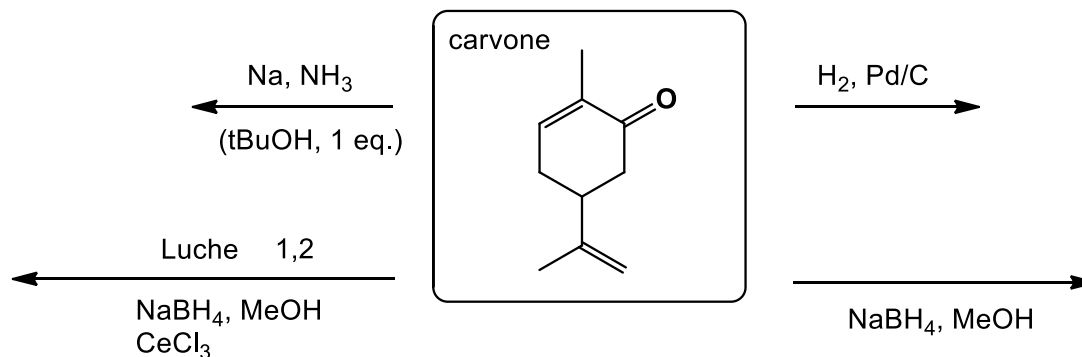
- 1) Carbon skeleton: ie the correct CONNECTIVITY
- 2) Functional groups: in the correct position
- 3) Stereochemistry: control of BOTH relative and absolute

In order to control 1) and 2) above we need the following aspects

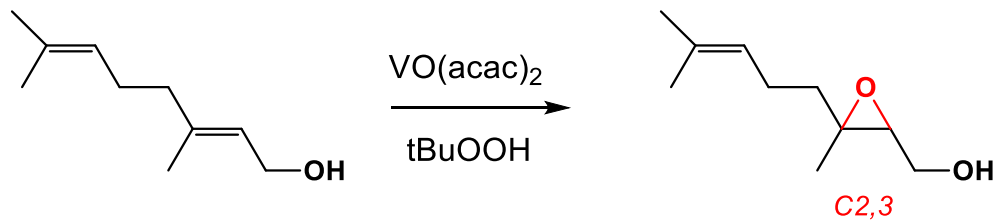
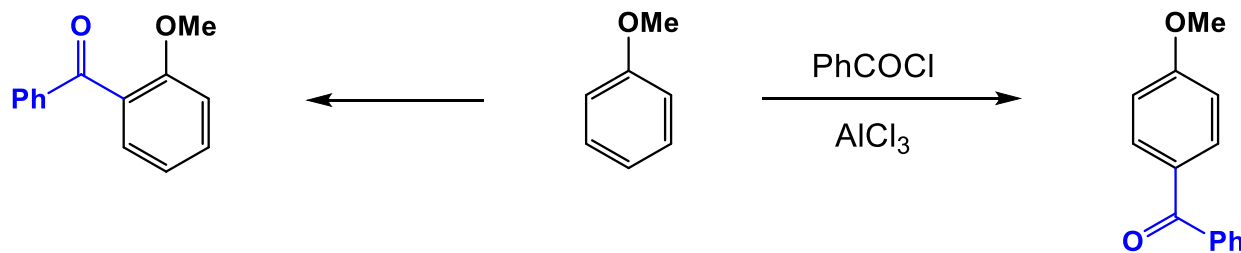
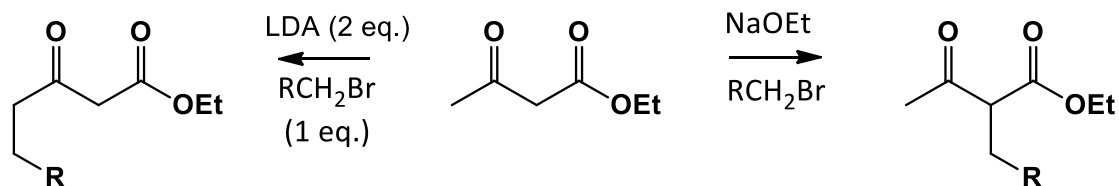
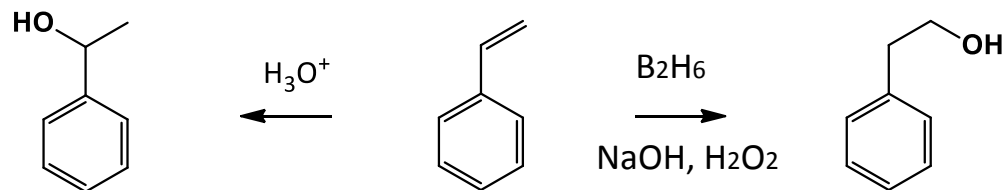
A) Chemoselectivity: Preferential reaction of one functional group over another



AND



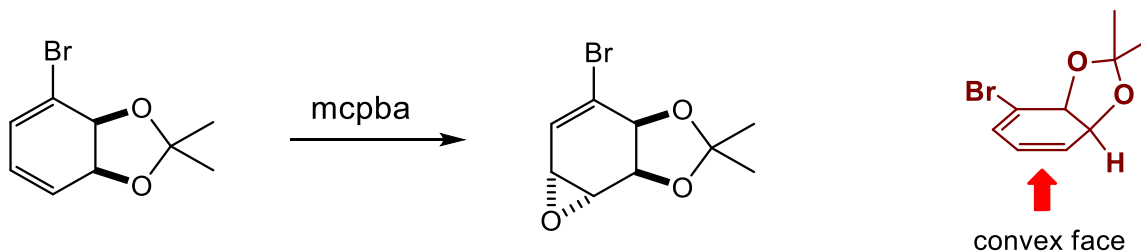
B) Regioselectivity: Preferential formation of one structural isomer over another; four examples



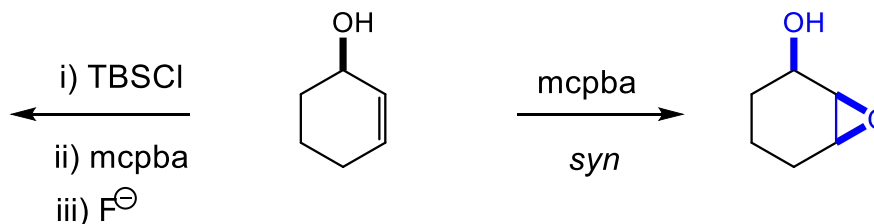
C) Stereoselectivity: Preferential formation of one stereoisomer over another

(i) Use the bias of the molecule:

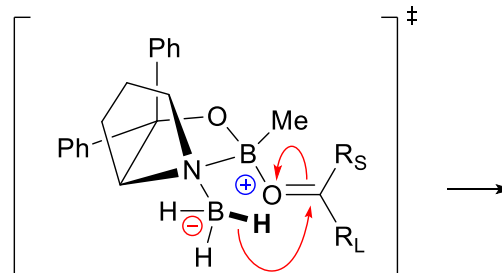
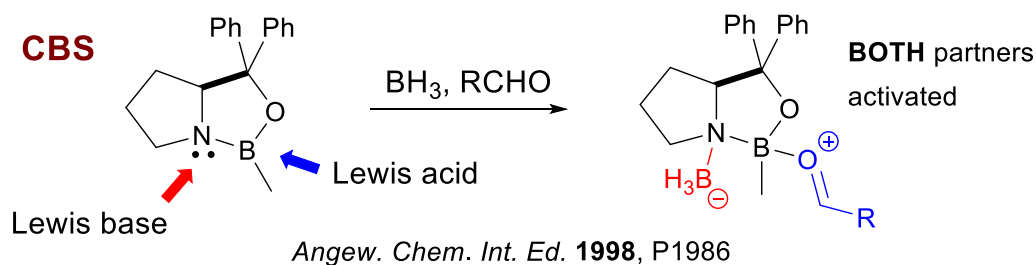
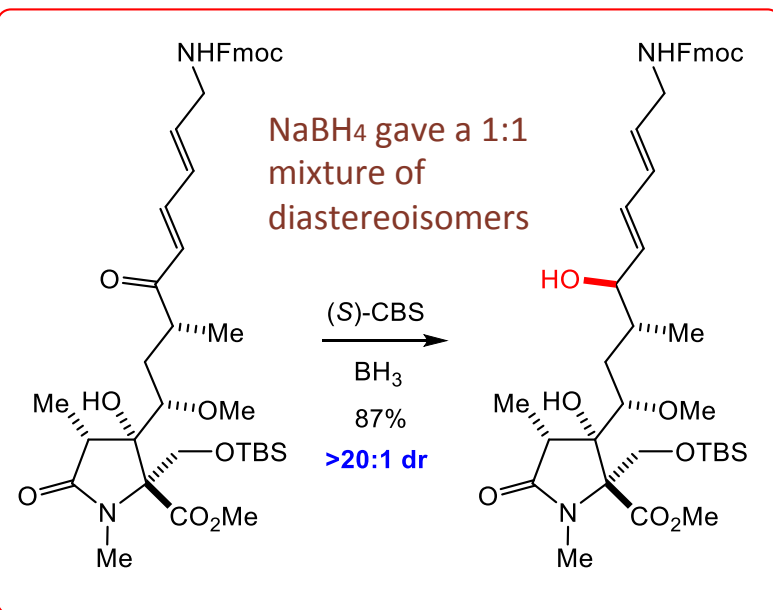
Sterics



Directing effects



(ii) Or an external chiral reagent to IMPOSE stereochemistry on the molecule

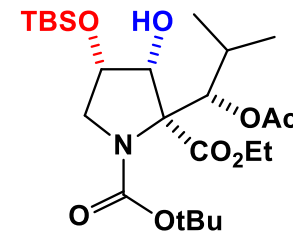
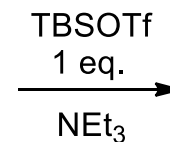
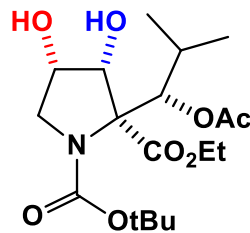
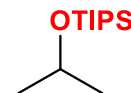
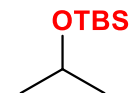
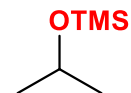


CC(O)CCC.O[Si](C)(C)C>CCN>CC(O)CCC[Si](C)(C)C
$$\text{R}_3\text{SiCl}$$
$$\text{Me}_3\text{SiCl}$$
$$\text{tBuMe}_2\text{SiCl}$$
$$\text{iPr}_3\text{SiCl}$$

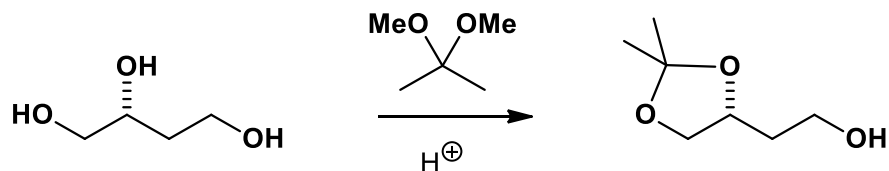
increasing
bulk of
silylating agent

$$1^\circ > 2^\circ > 3^\circ$$

use $\text{R}_3\text{Si-OSO}_2\text{CF}_3 = \text{R}_3\text{SiOTf}$



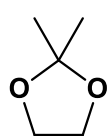
Cyclic protecting groups can be useful in achieving selectivity



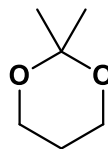
Primary OH is unable to form a stable, cyclic acetal and REMAINS unprotected

note:

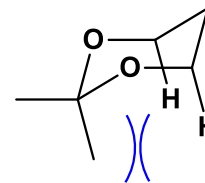
acetone protects
1,2 OVER 1,3 diols



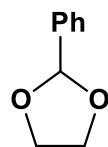
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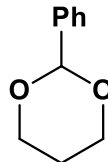
1,3- diaxial



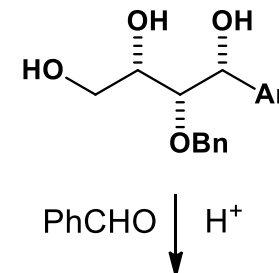
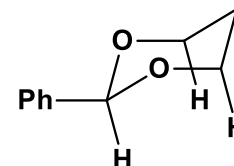
benzaldehyde protects
1,3 OVER 1,2 diols



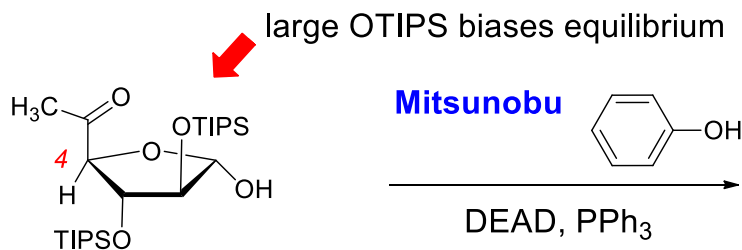
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6 ring is LESS strained than a 5 membered ring

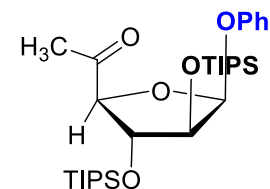


Sometimes their intrinsic properties can help



$\text{S}_{\text{N}}2$ INVERSION

large OTIPS
prevents epimerisation
at sensitive C-4



hygromycin A

(iii) What is the perfect synthesis (performed in industry versus academia)?

‘creates a complex molecule...in a sequence of only construction reactions involving no intermediary refunctionalizations, and leading directly to the target, not only its skeleton but also its correctly placed functionality.’

Ideally a synthesis would be

Length-
Non-
Commercially
Solvent
Mild
Atmosphere of
Purification
Yield
Waste



Academic researchers and medicinal chemists are highly focused on a target or analogs thereof and employ whatever means to get them made. Process chemists aim towards more "ideal" construction of molecules which tends toward minimization of steps/costs and an increased emphasis on yields and reproducibility.

Constraints on an industrial synthesis:

Amenable to
Reliable
Availability and cost of
Toxicity of
Purity of PRODUCTS;
Intellectual **PROPERTY** (no IP infringements)

Ideas such as, *atom economy*, *step economy*, *redox economy* have emerged.

For an in-depth discussion of the ‘ideal’ synthesis see:
J. Org. Chem. **2010**, 75, 4657.



2) The chiral pool: *where does absolute stereochemistry come from?*

Nature has provided a wide range of enantiopure compounds in great abundance

Amino acids, carbohydrates, terpenes.

Called the **CHIRAL POOL**

New compounds added by chemical synthesis- also available in scale.

These compounds can become the target themselves, or also the basis of reagents, ligands and chiral auxiliaries, to pass on their stereochemical information indirectly.

Advantages: **CHEAP**;

available on a large **SCALE**

Disadvantages: only one enantiomer

Functional group interconversions can lead to

Aminoacids

20 proteinogenic AAs

All amino acids found in proteins occur in the L-configuration about the chiral carbon atom.

Q. Work out the absolute configurations of the four amino acids shown above.

Representative prices

D-alanine- £3 per g (5g)

L- alanine -30p per gram (1 kg)

DL alanine is 6p per g (5Kg)

D-proline- £12 per g (5g)

L-proline-40p per gram (5 kg)

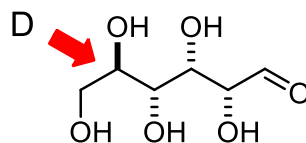
DL proline is £10 per g (5g)

Carbohydrates:

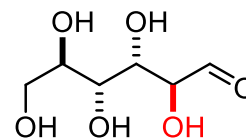
the D enantiomer tends to be found in Nature

D-glucose 1p per gram (>5Kg)

L-glucose- UNAVAILABLE



D- glucose



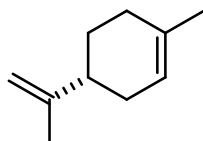
D- mannose

*Many different
diastereoisomers available*

However, L sugars ARE found in Nature

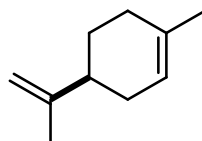
Terpenes

The class of terpene chemicals are abundant among natural products and many compounds have commercial applications, e.g. camphor. Other compounds of this class are used in pharmaceutical preparations or as fragrances, e.g. limonene from citrus fruit.



(+)-limonene

£0.03 per gram



(+)-limonene

£0.17 per gram

Miscellaneous others: α -hydroxy ACIDS and alkaloids: **Q look up the structures of mandelic acid, malic acid and quinine.**

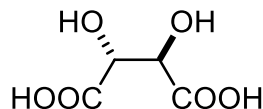
How else might we obtain enantiopure compounds?

RESOLUTION

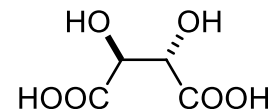
Tartaric acid: isolated from the salt in c. 800 AD. Naturally occurring acid is **CHIRAL**

Found in fruits and wine:

Unnatural enantiomer is made synthetically



(+)-tartaric acid

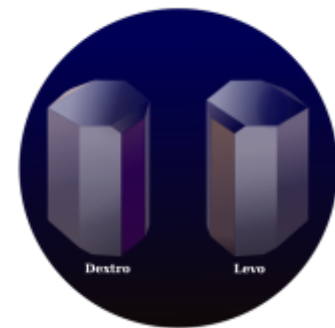


(-)-tartaric acid

Louis Pasteur (c. 1848)

A solution of tartaric acid derived from living things (specifically WINE) rotated the plane of polarization of light passing through it. However, tartaric acid derived by **chemical synthesis** had no such effect, even though its elemental composition was the same.

During an investigation of the shapes of ammonium sodium tartrate crystals, he found them to be **CHIRAL** (ie mirror images of one another)



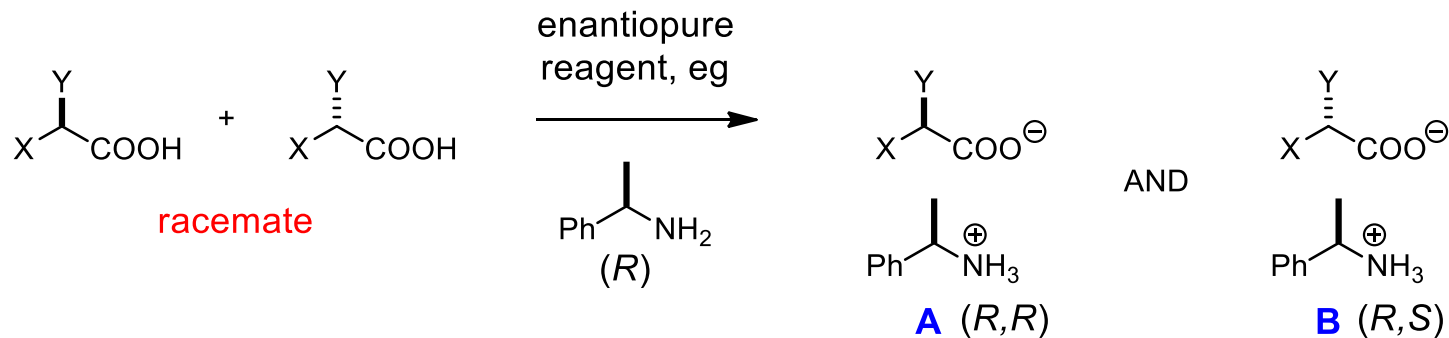
Manual sorting under a MICROSCOPE.

Allowed the production of both enantiomers of tartaric acid.

Happened because this salt crystallises as a **CONGLOMERATE**



A more **Classical Resolution** technique is shown below:



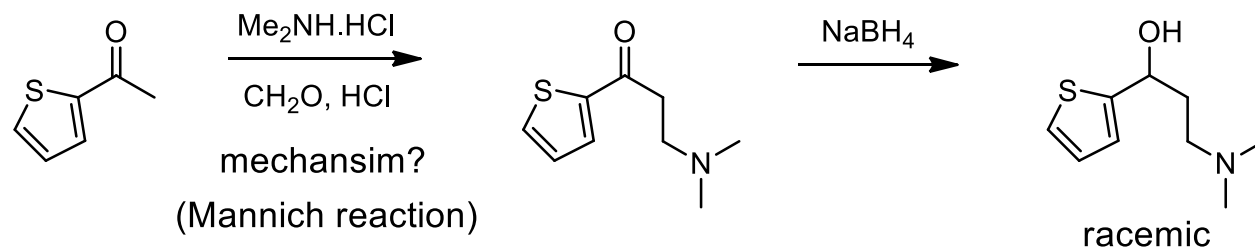
3 step guide to resolution:

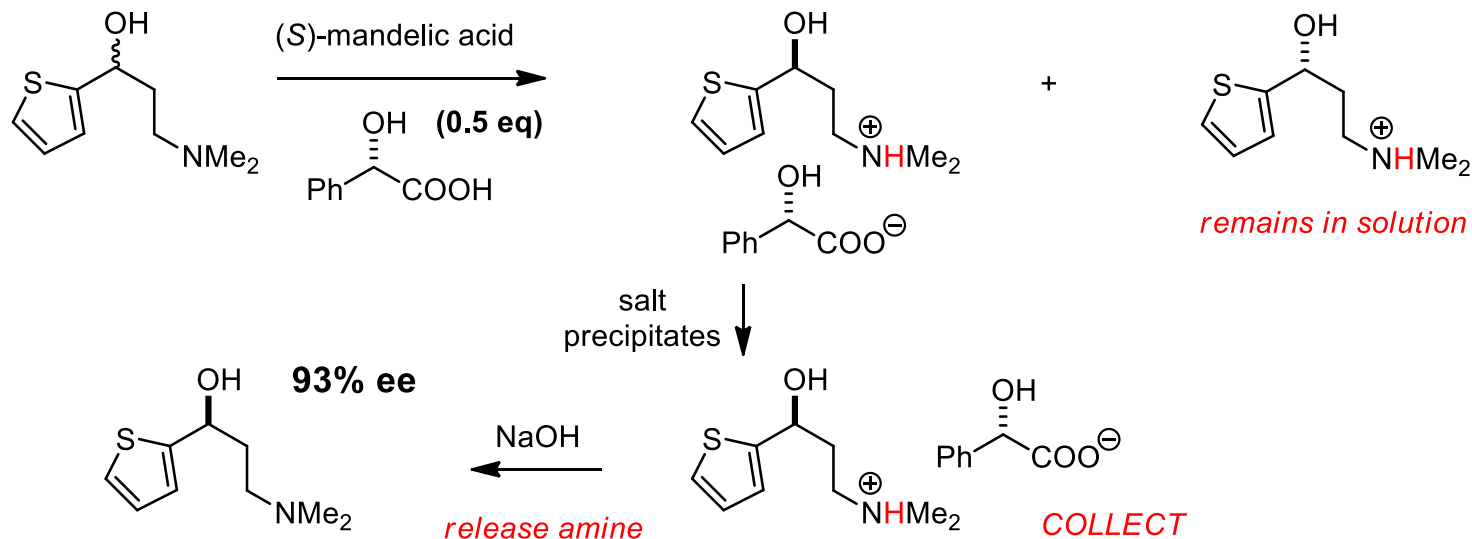
1) Make a derivative (use enantiopure reagent)

Products are DIASTEREOISOMERS (ie different compounds)

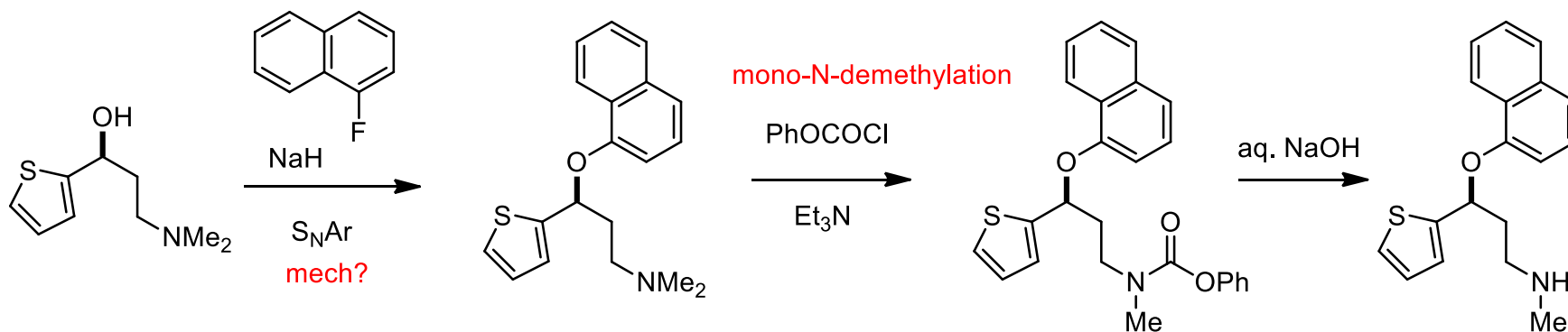
3) Release the original compound (eg by adding HCl to **A**). However, the maximum yield is 50%- wasteful

A more sophisticated example of this is found in an industrial variant of Lilly's synthesis of duloxetine (Cymbalta)
Used for the treatment of depression. Annual sales in 2010 were \$2.6 billion.

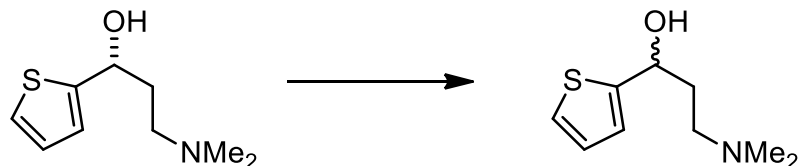




Completion of the synthesis



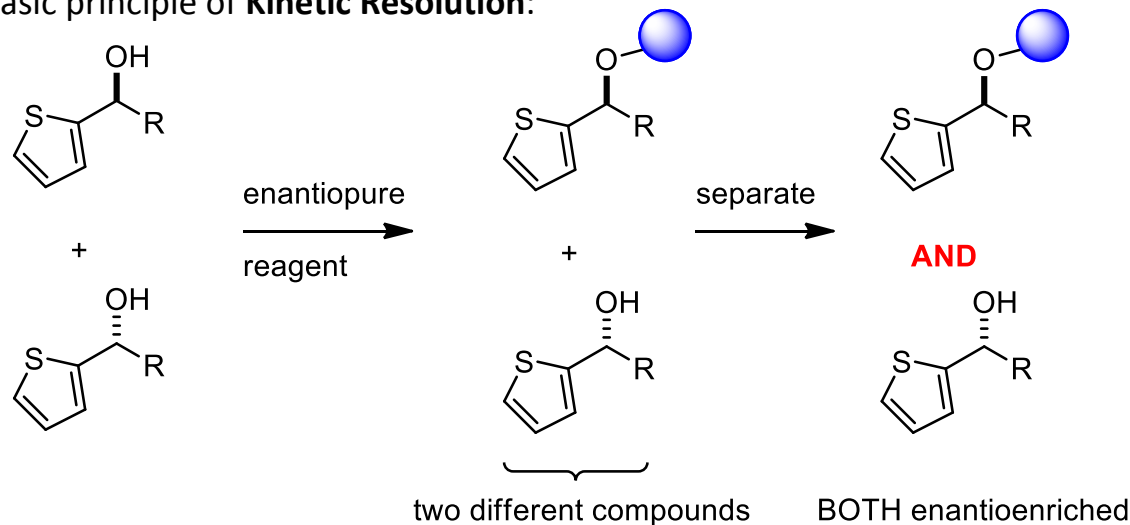
Recycling of the unwanted enantiomer?



See *Organic Process Research and Development*,
2006, 10, 905.

There are many variants of the resolution process including **Kinetic Resolution** (see the Sharpless Asymmetric Epoxidation and enzymatic resolution).

Basic principle of **Kinetic Resolution**:

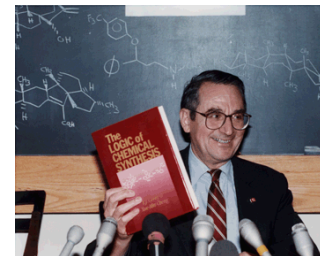
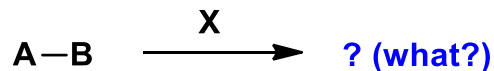
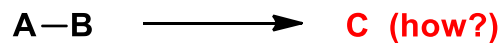


A chiral (and enantiopure) reagent, reacts faster with ONE enantiomer than the OTHER. Products are DIFFERENT and usually separable. The enantiomers are obtained as different compounds; both are enantioenriched (but not usually to the same degree).

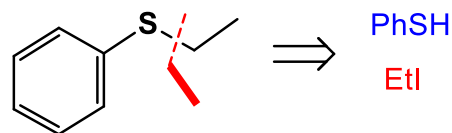
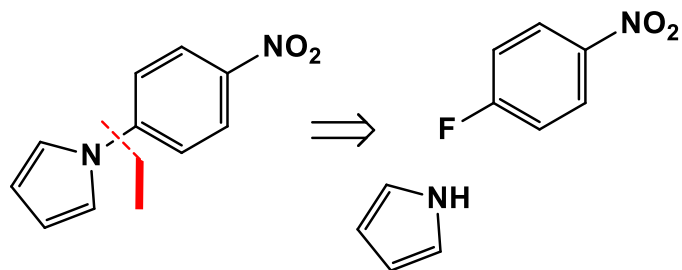
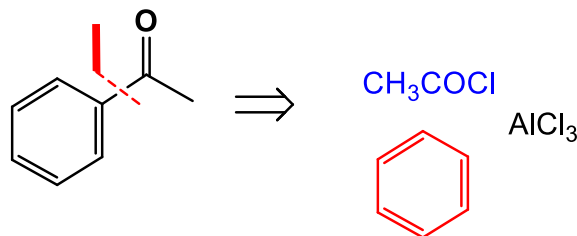
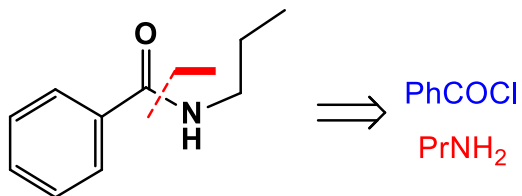
3) RETROSYNTHESIS

The theory (Corey- Nobel prize in 1990)

1) Think about reactions in reverse

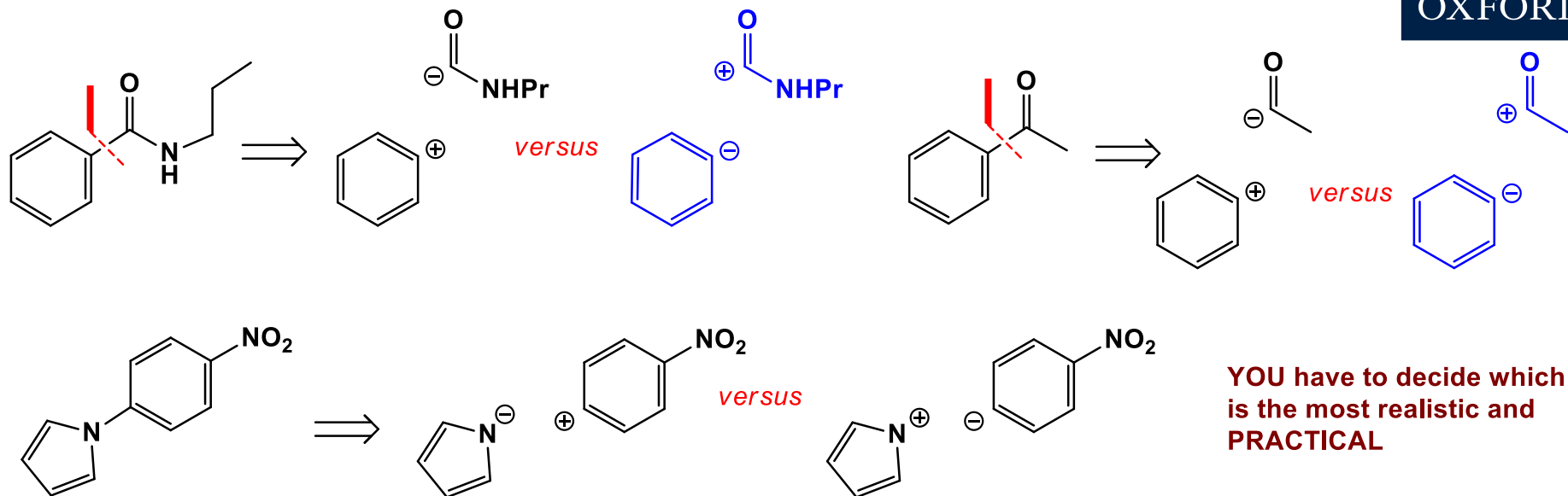


2) Use disconnections to break down molecules



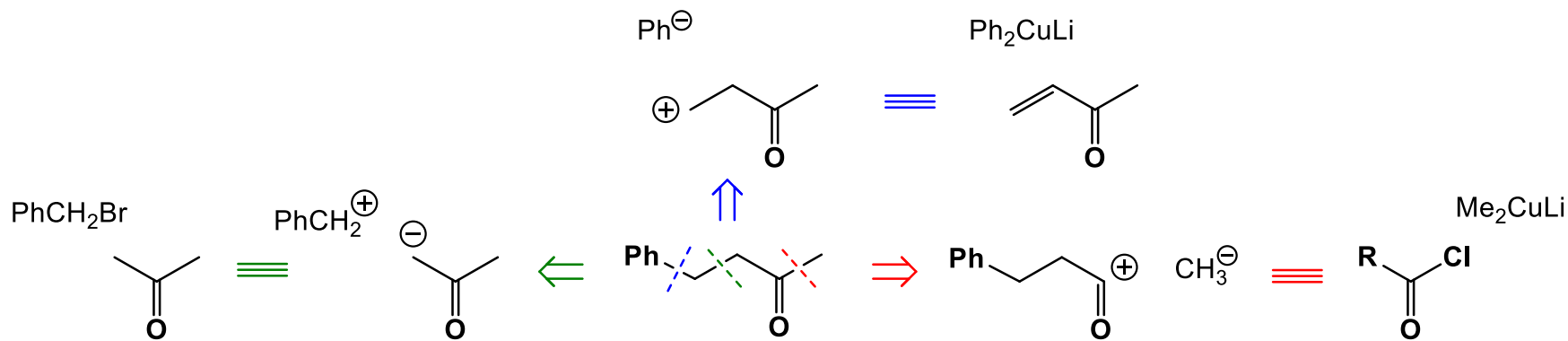
3) Synthons: These are simply hypothetical reaction intermediates

There are two ways of analysing a single disconnection



Remember the concept of **UMPOLUNG** is helpful (especially) with carbonyl groups:

1) Normal reactivity of the carbonyl group



Ph^+

\ominus

O

i) NaH
ii) R-X

mechanism?

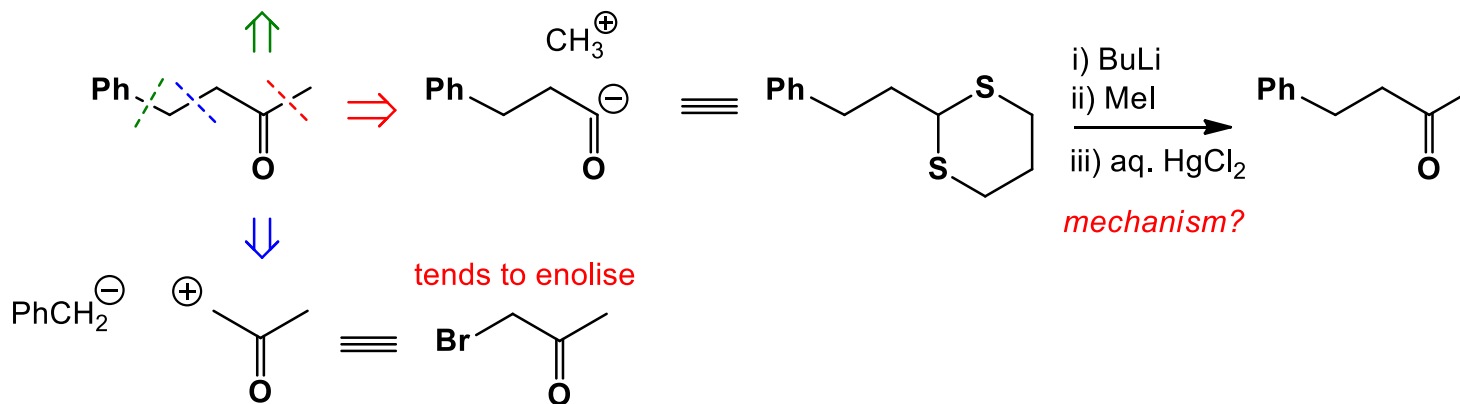
R

i) H₂/Pd
ii) H₃O⁺

but Ph⁺

mechanism?

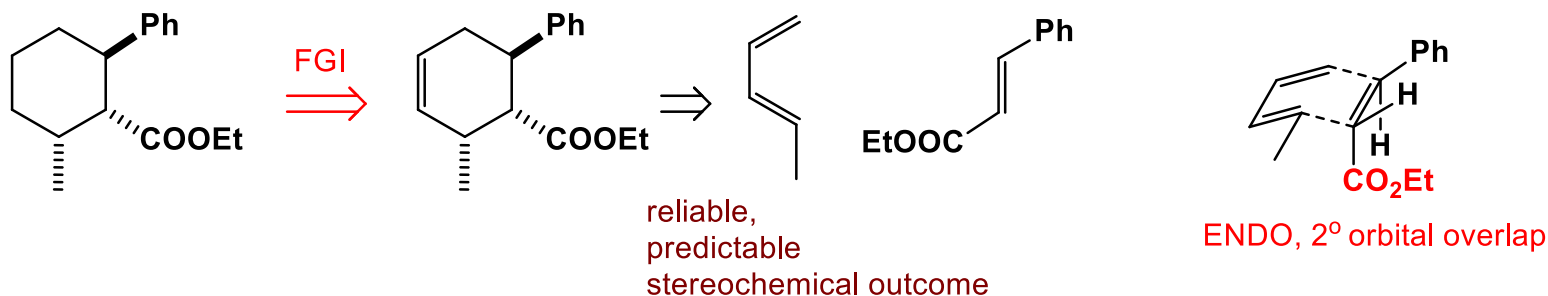
C



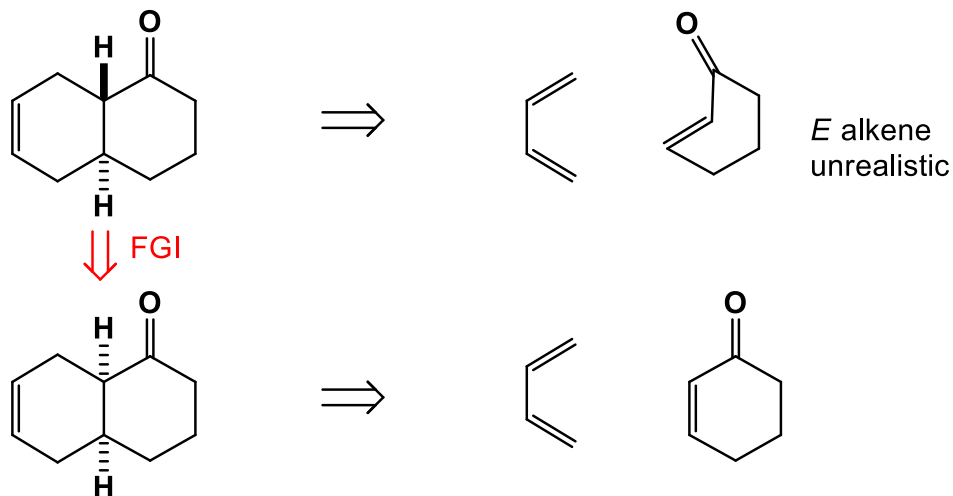
Simple

note: R-MgBr plus RCH_2I is not a good reaction

More difficult



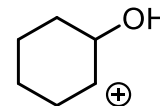
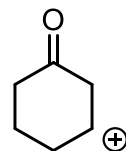
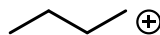
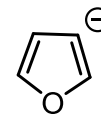
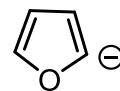
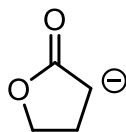
Even *stereochemistry* can be altered in this way.



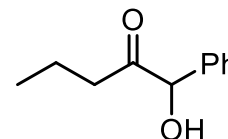
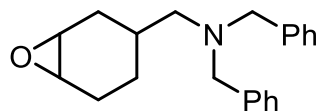
For advanced and further reading about the Diels Alder reaction in natural products synthesis see a review by K. C. Nicolau, *Angew. Chem. Int. Ed.* **2002**, 41, 1668-1698.

4) Some problems to think about

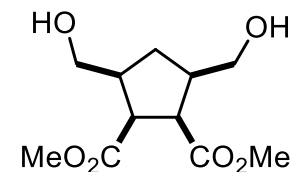
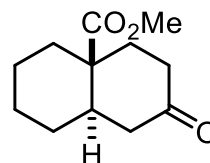
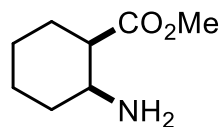
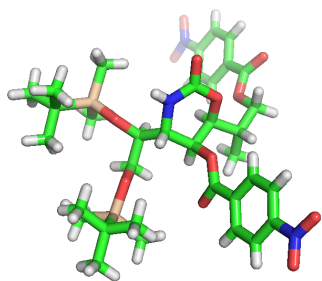
a) Suggest reagents for the following synthons



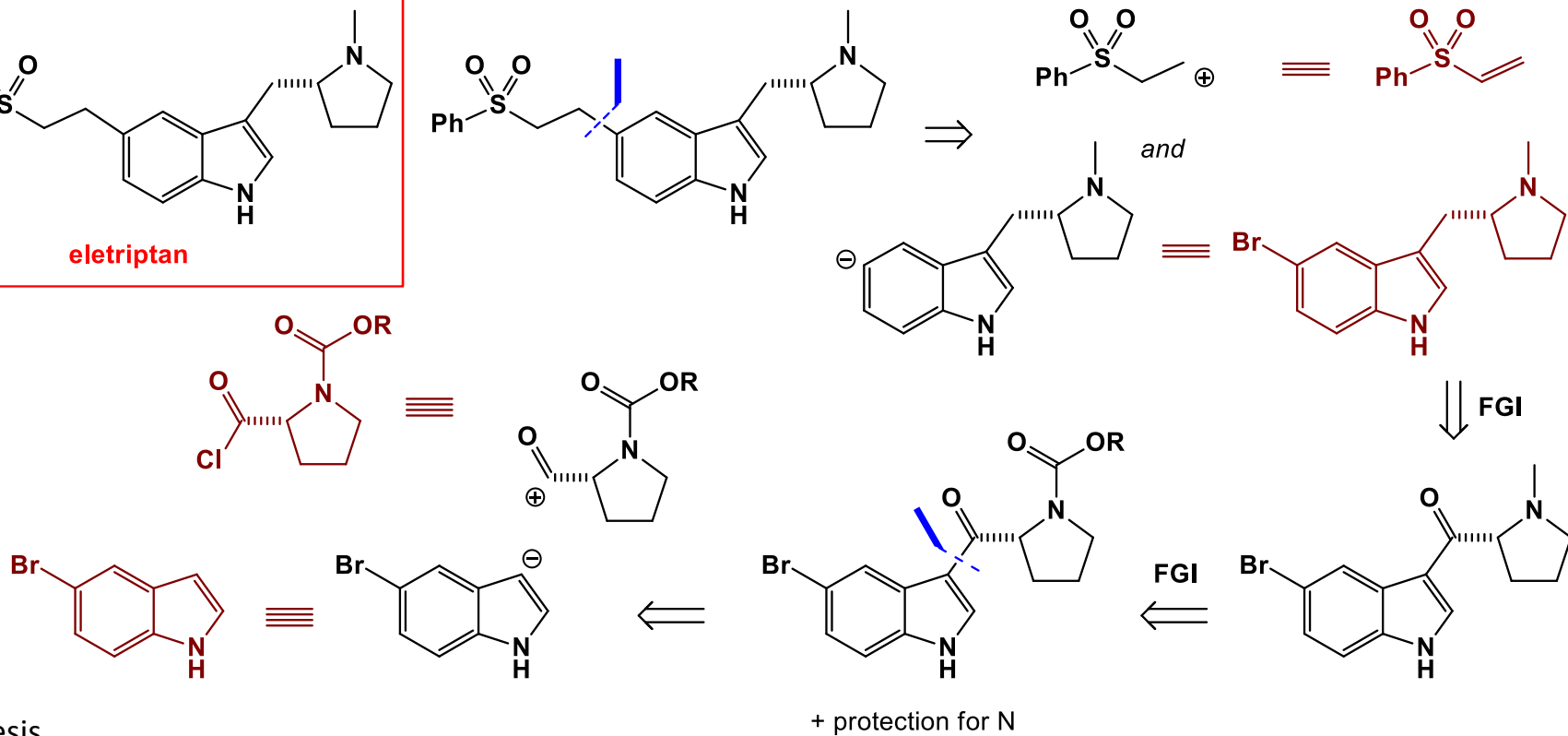
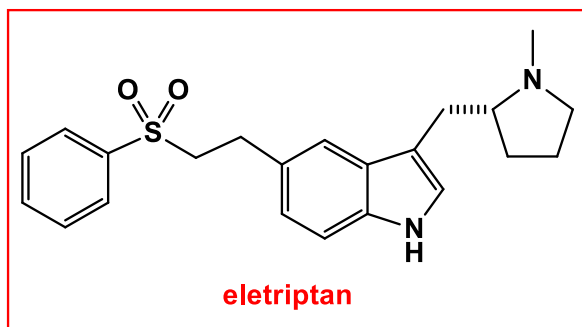
b) Suggest synthetic routes to the following five compounds using retrosynthetic analysis

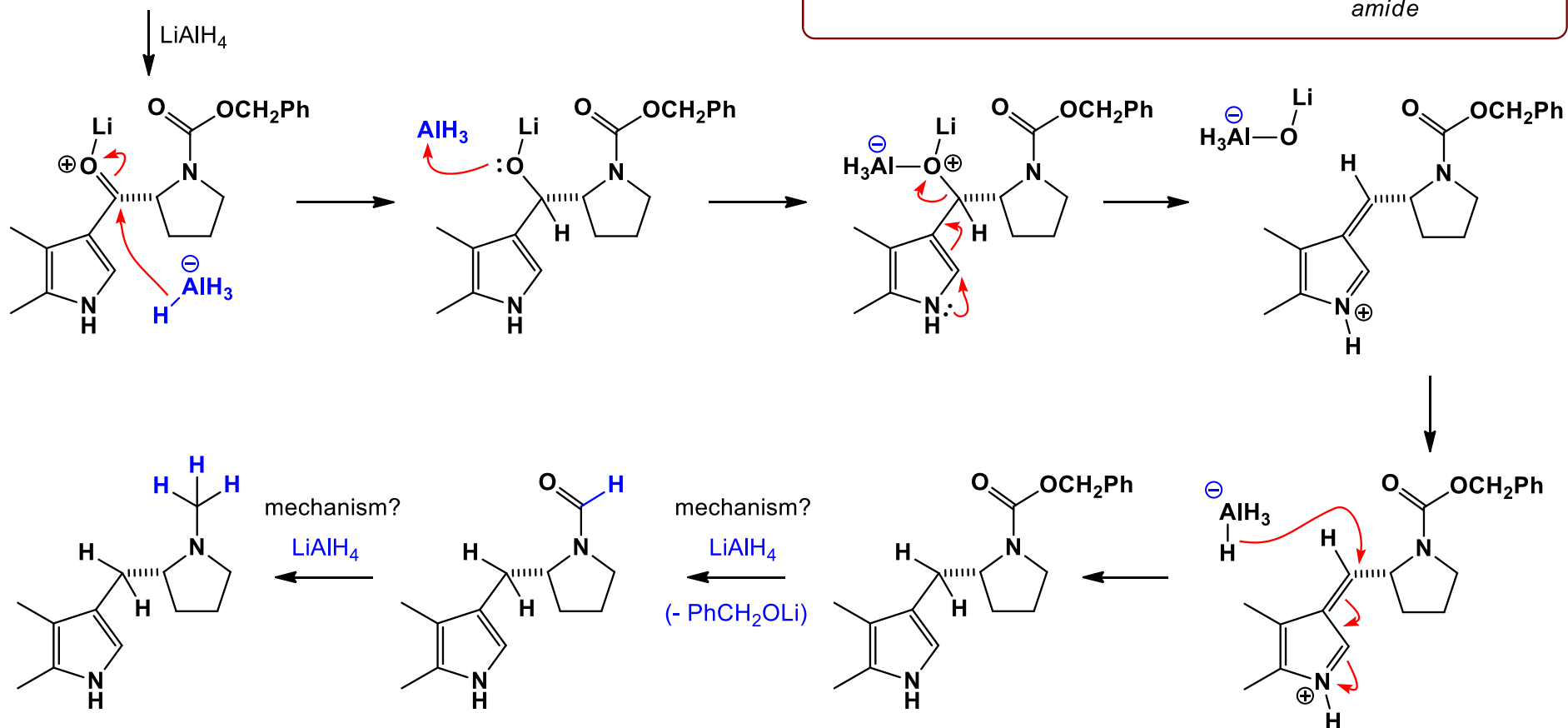
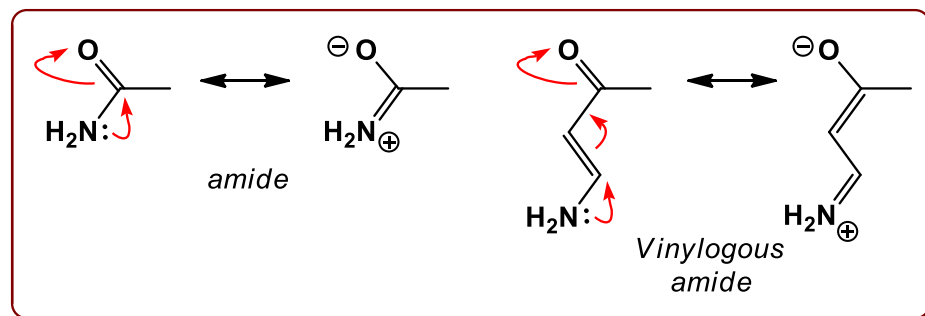


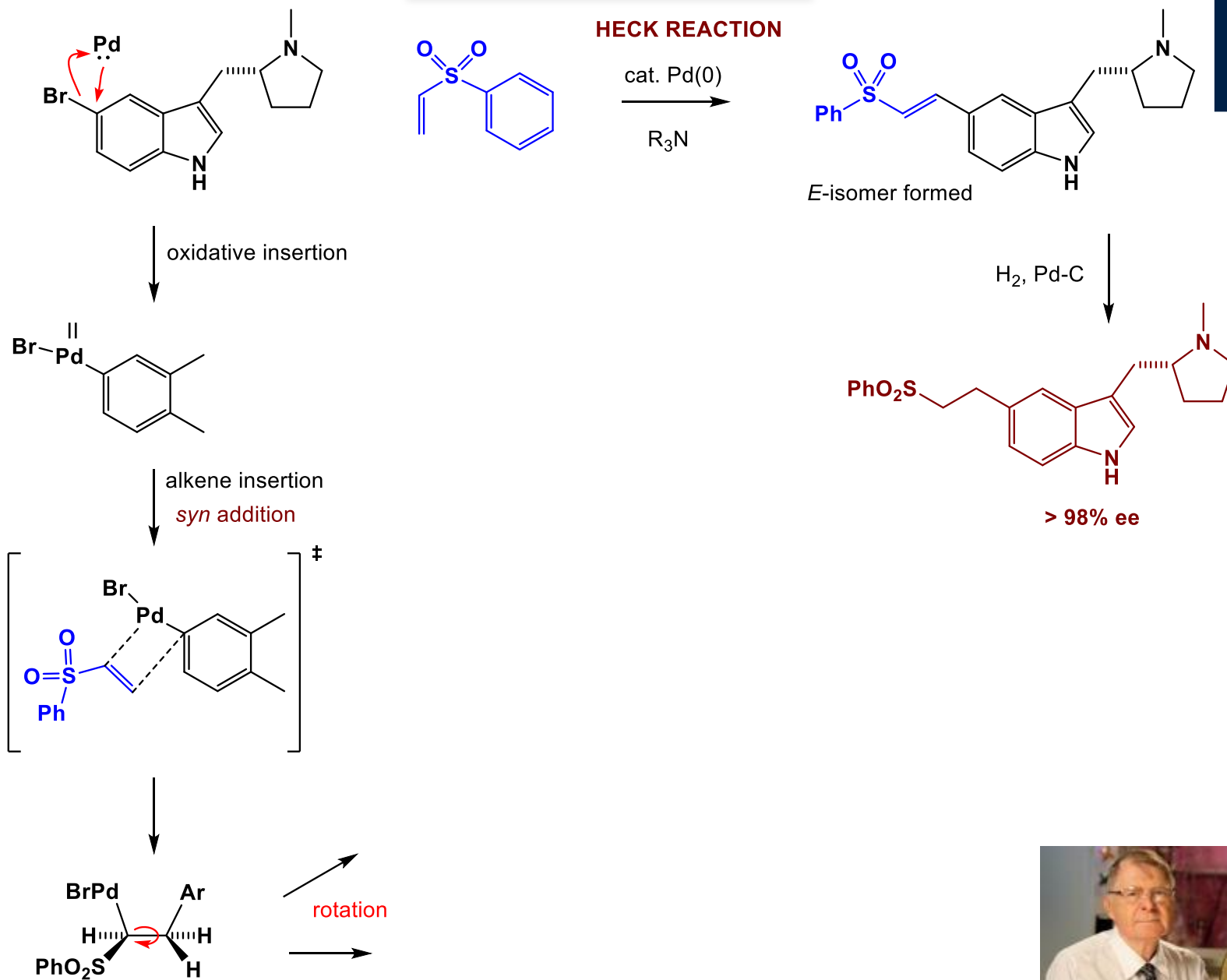
dont worry about stereochemistry



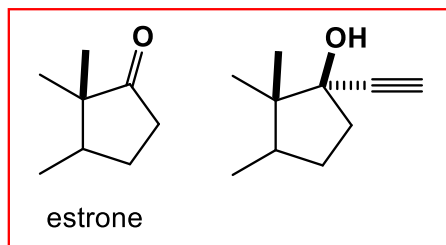
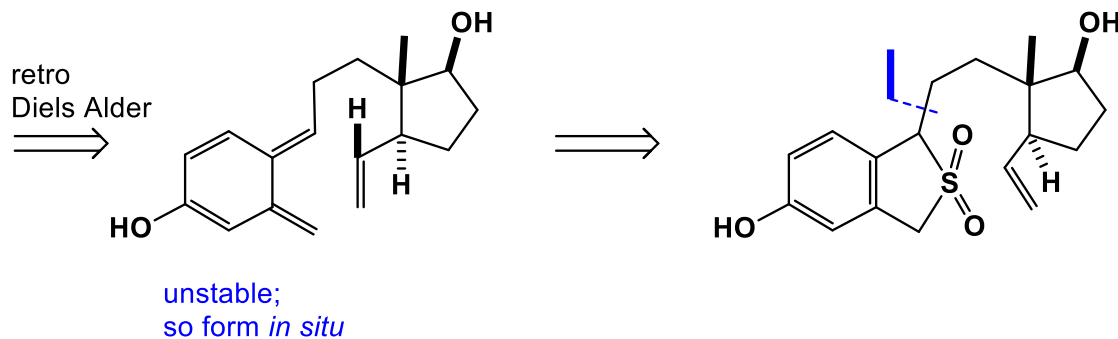
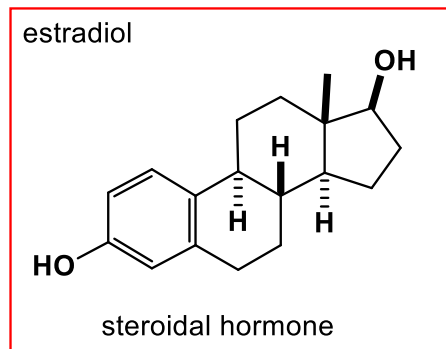
Synthesis 1) Eletriptan (Pfizer) Migraine (sales in 2008, \$0.21 billion)



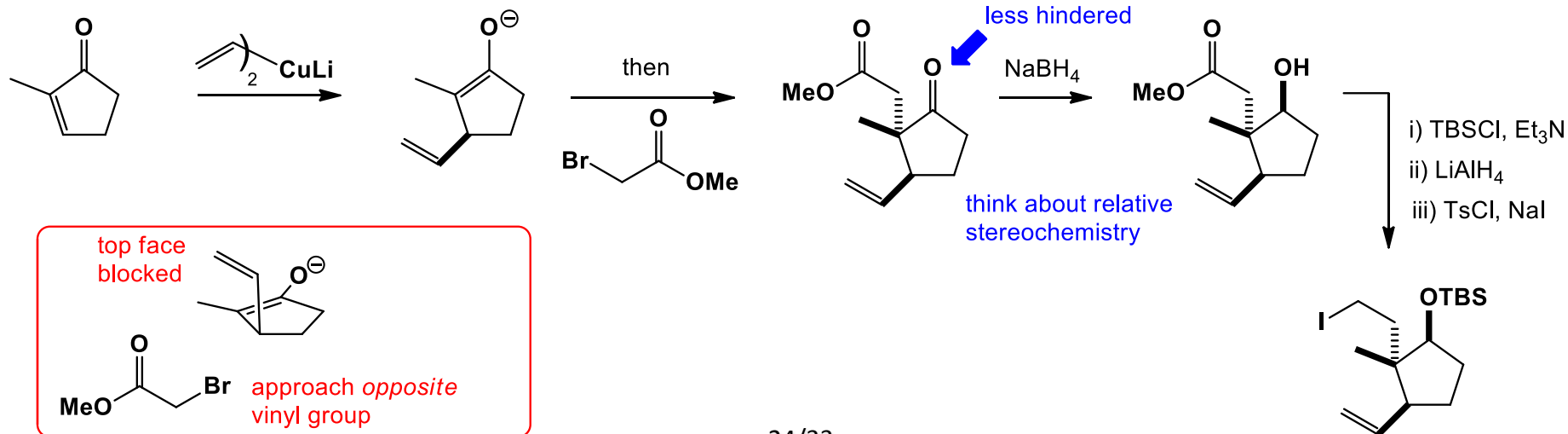


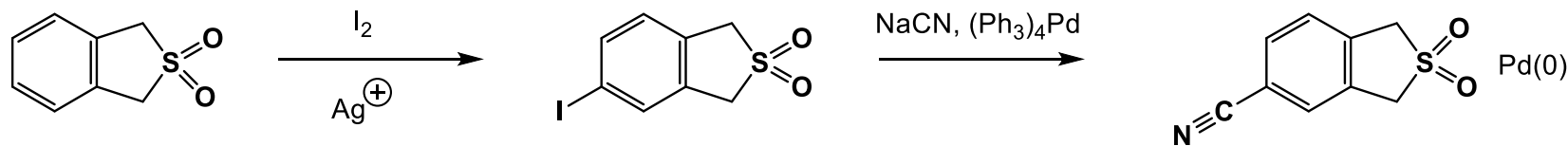


Synthesis 2) Estradiol (*Helvetica Chimica Acta*, 1980, 63, 1703)

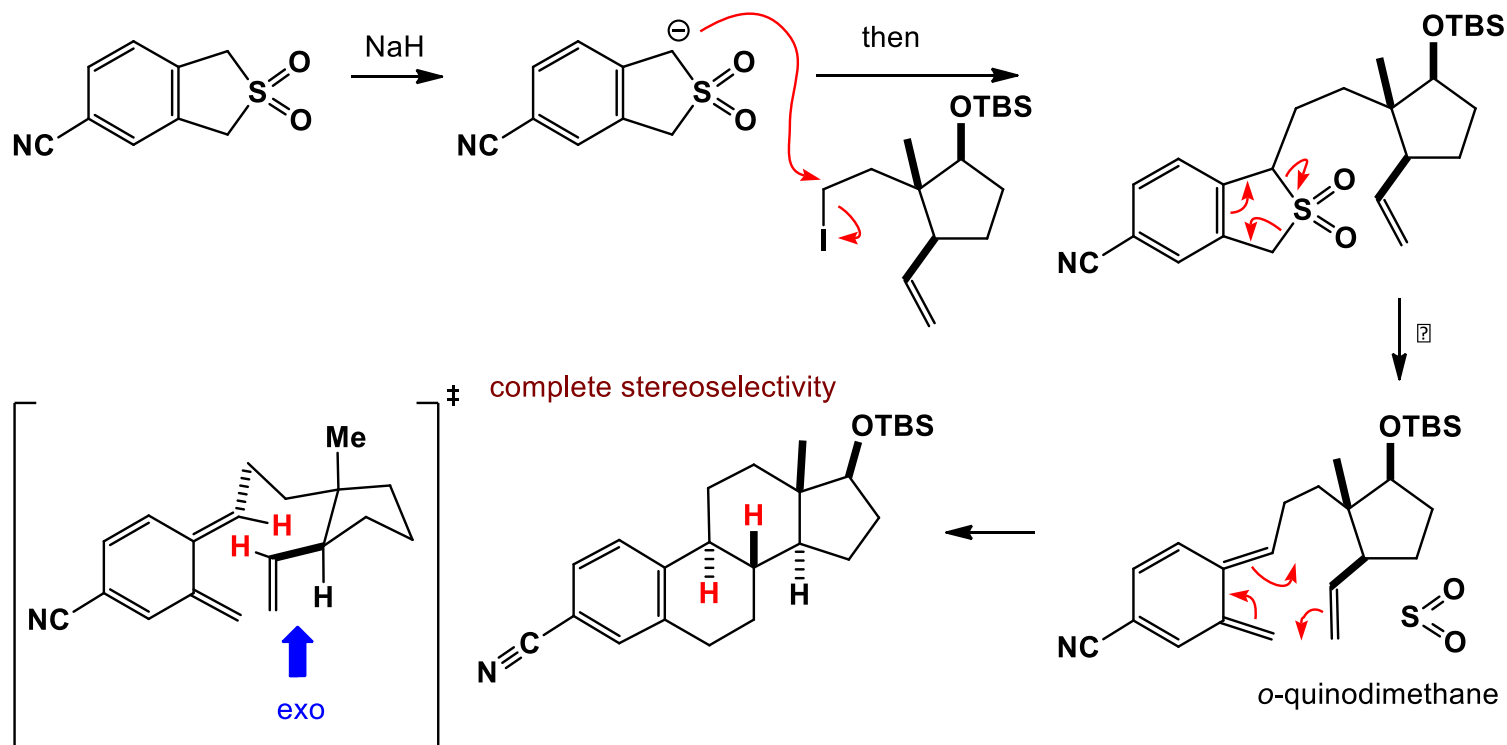


The synthesis

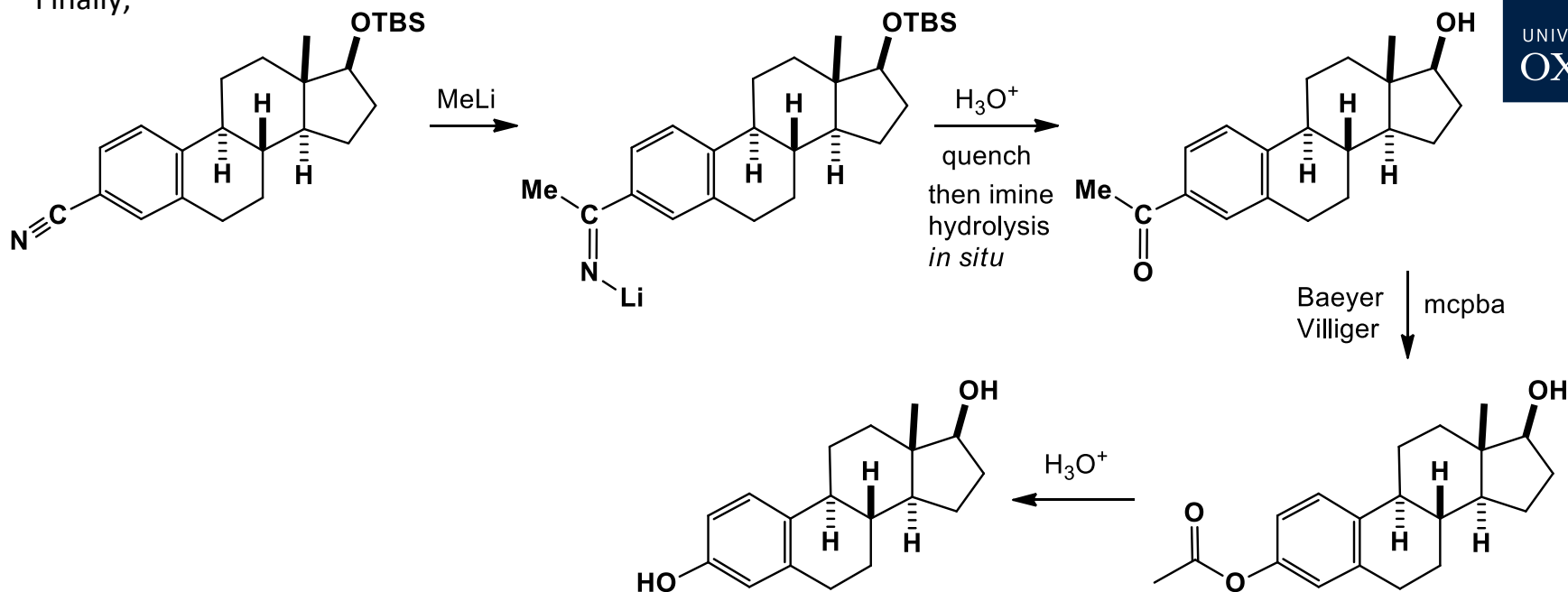




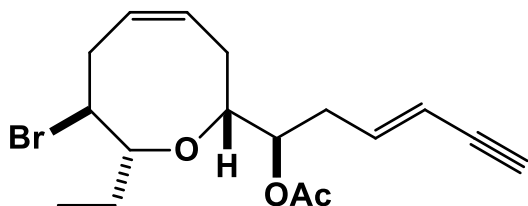
The end game



Finally,



Synthesis 3) (+)-Laurencin



(+)-laurencin

Isolated in 1965 from red algae- *Laurencia glandulifera*

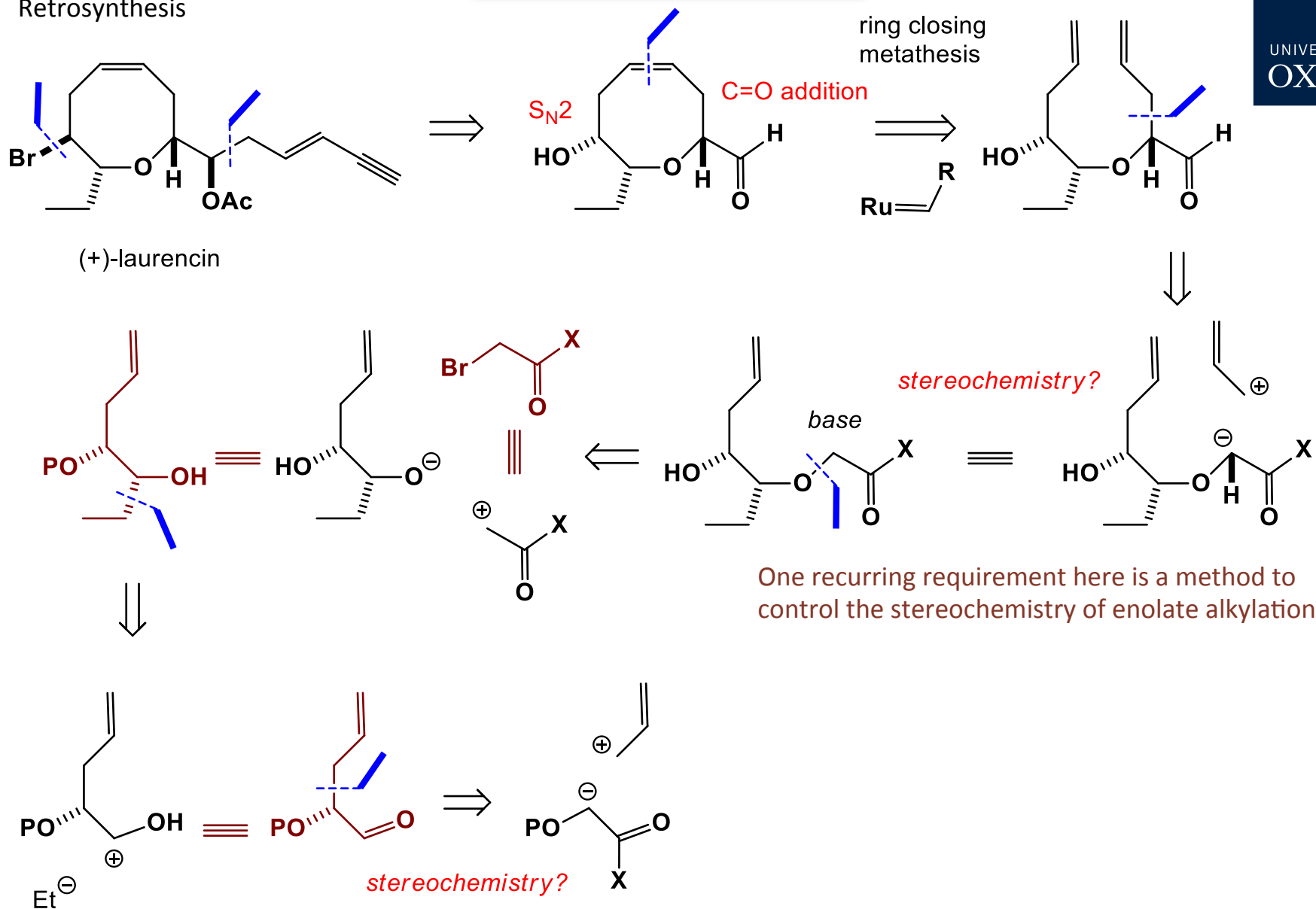
Structure proven by X-ray crystallography

Representative of a large number of medium ring marine metabolites found as natural products

Synthesis of the medium (here 8) membered ring is a formidable challenge

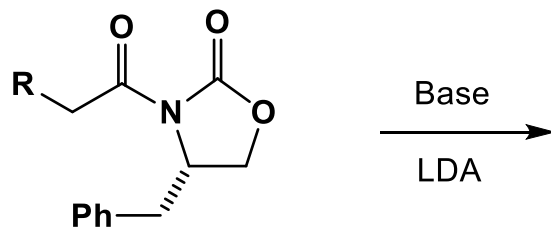
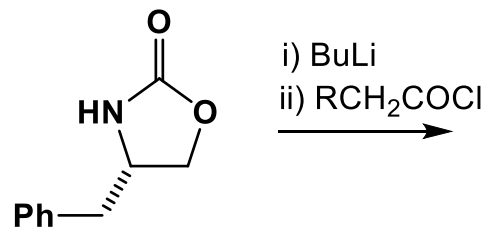


Retrosynthesis

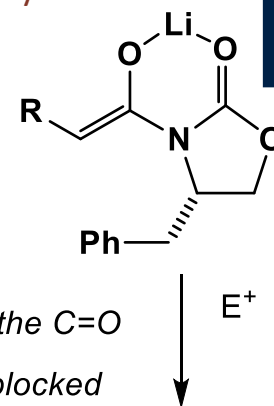




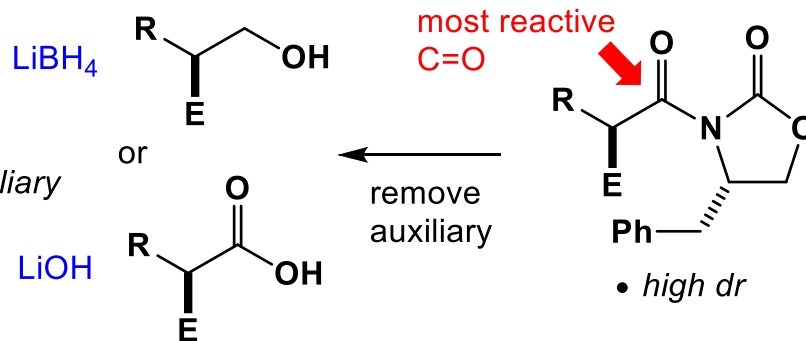
ASIDE; Evans chiral auxiliary (Xc) is a very GENERAL method which is used widely in organic synthesis



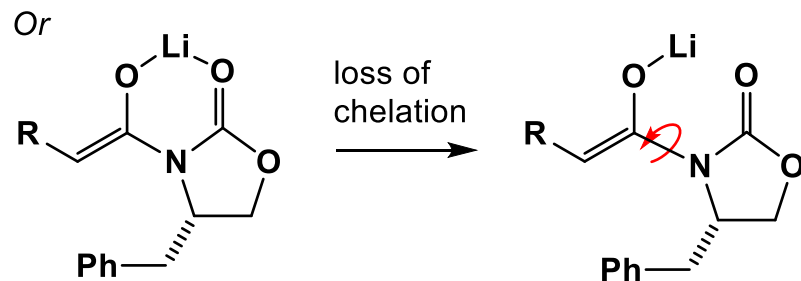
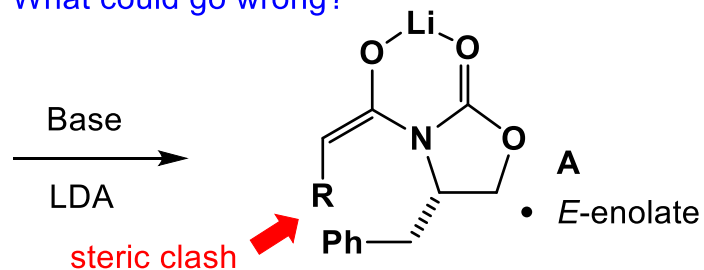
- Z-enolate
- *chelation to the C=O*
- *one face is blocked*

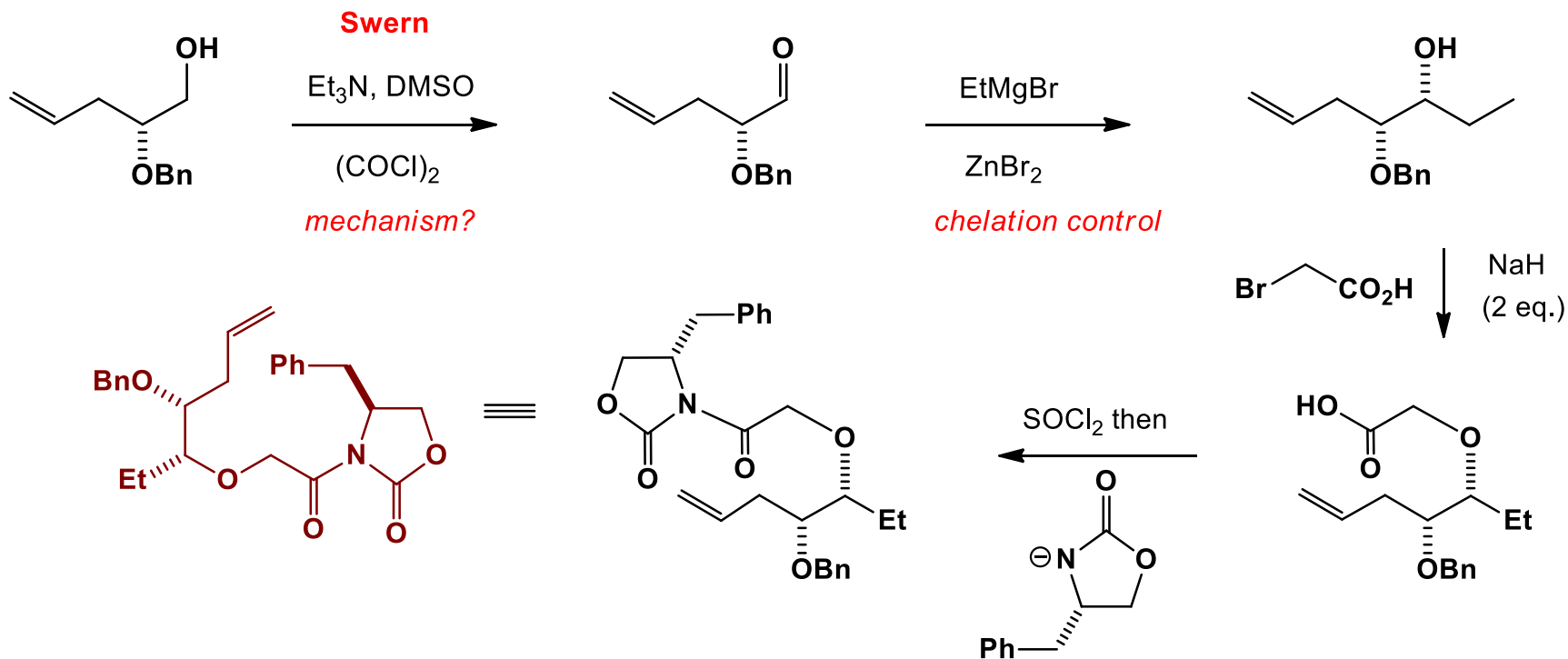


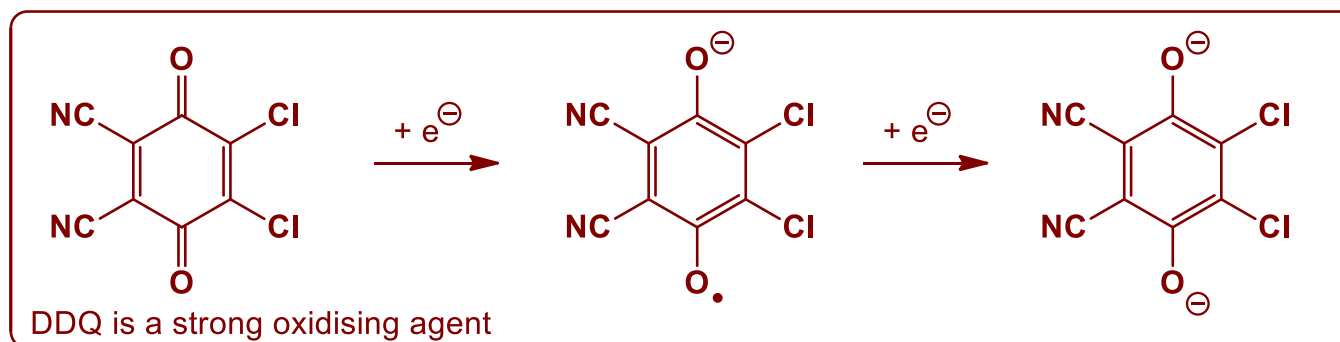
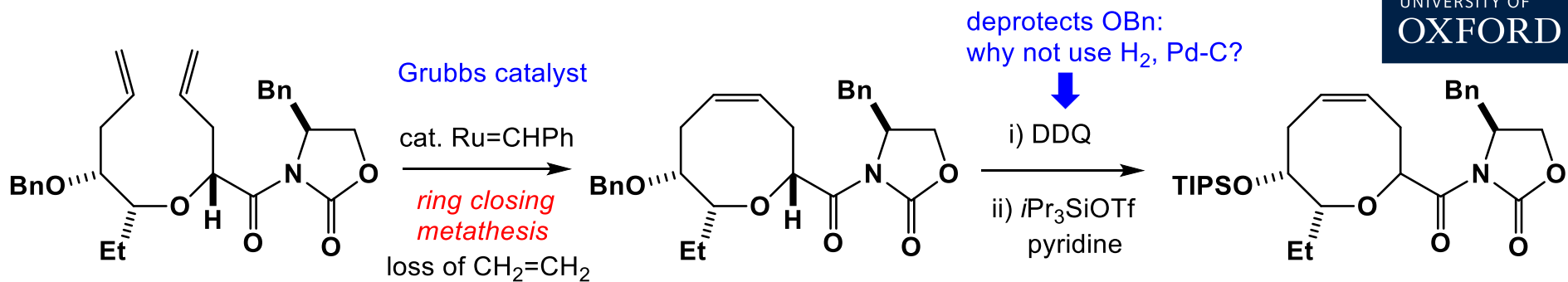
- other enantiomer is available
- other stereodirecting groups are possible, eg PhCH₂ vs *i*-Pr etc

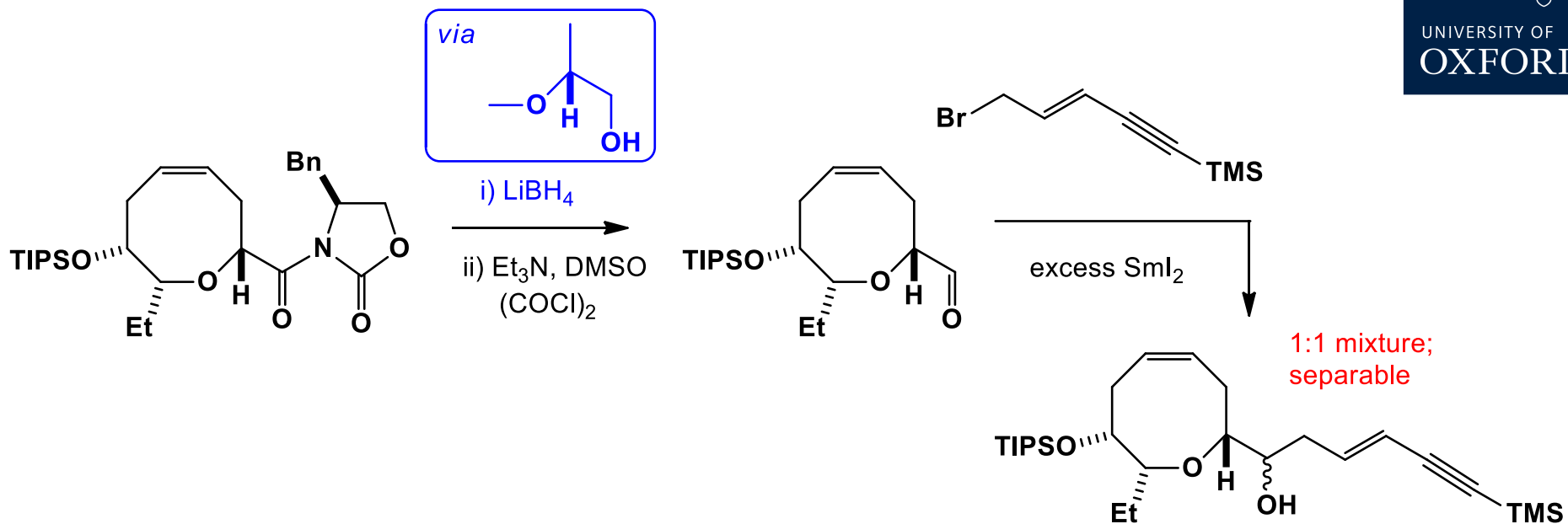


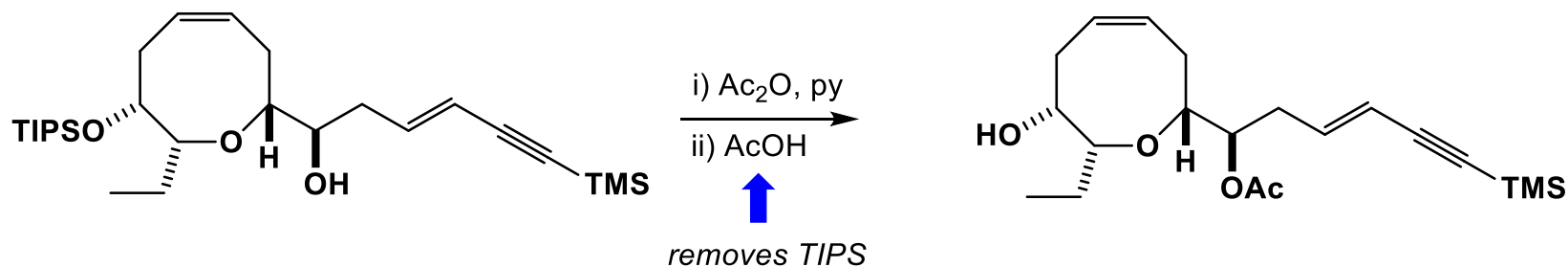
What could go wrong?



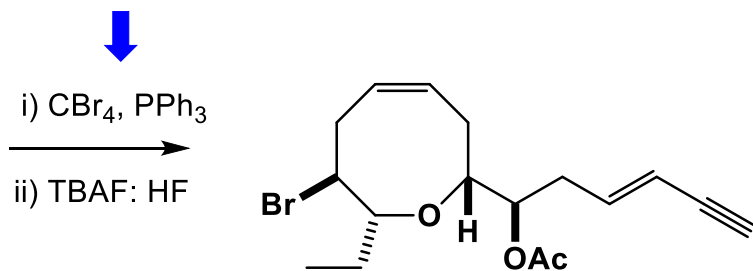








Appel reaction



Organic Letters, **1999**, 1, 2031; *Tetrahedron Letters*, **1992**, 33, 4345