UNIVERSITY OF OXFORD

# Organic Synthesis III

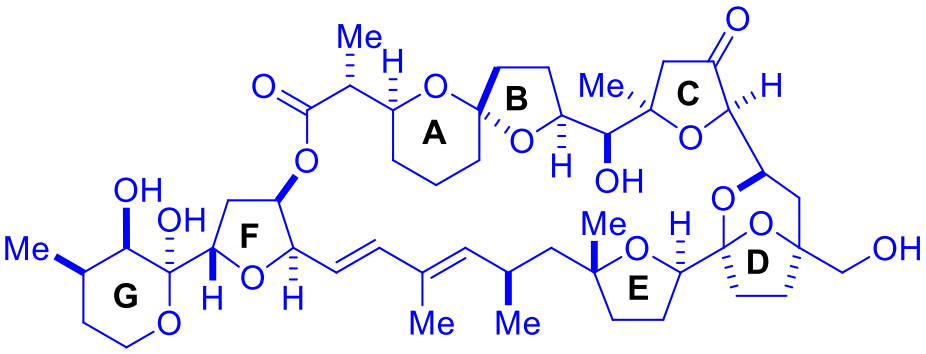
*8 x 1hr Lectures: Michaelmas Term*

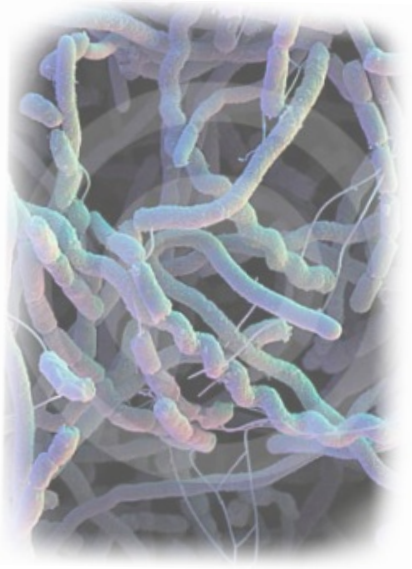
Weeks 5-8 **2016**

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

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**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**

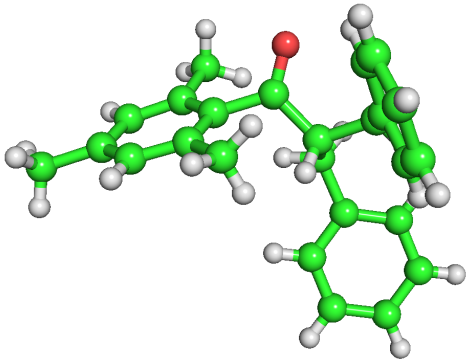
***Recommended books:***

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)



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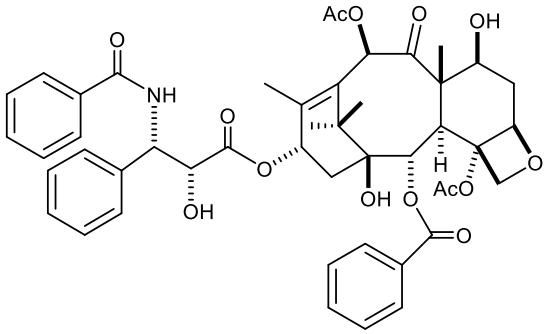
## (i) Why do we want to synthesise complex molecules?

**Taxol**



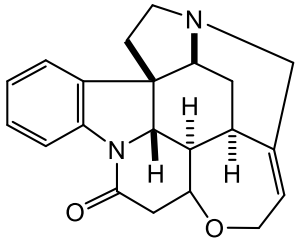

Isolated from the Pacific Yew in 1962

Prescribed for prostate, breast and ovarian cancer

Unique mode of action

1x 100 year old tree = 300 mg Taxol

**Strychnine**




Isolated in 1818- poisonous

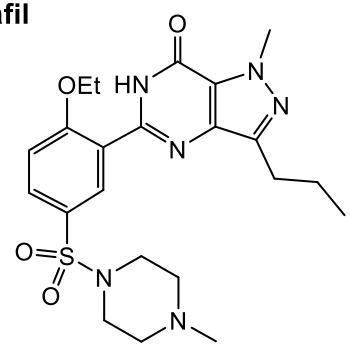
Stuctural elucidation took R. Robinson 40 years

'for its molecular size it is the most complex substance known'

*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.

**Sidenafil**




Developed in the UK (Pfizer)

Annual sales (2008)= $0.92 billion (ranked no. 39)

Lipitor ranked no. 1 (2009) sales = $13 billion with total sales of $141 billion

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:**

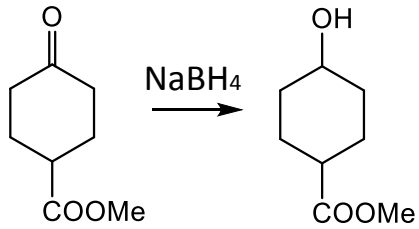
1) Carbon skeleton: ie the correct CONNECTIVITY

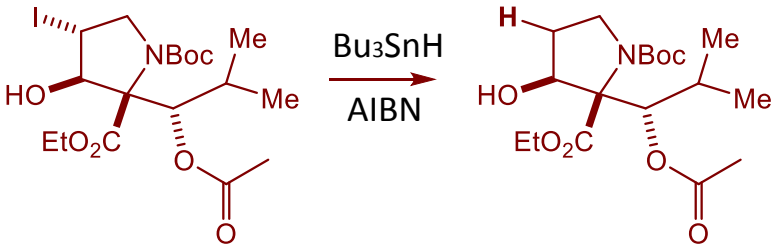
2) Functional groups: in the correct position

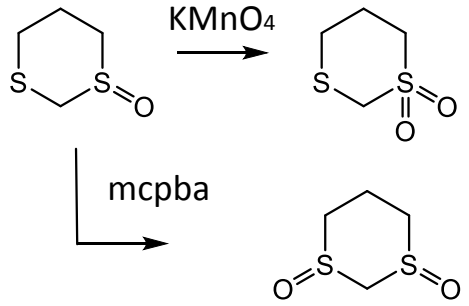
3) Stereochemistry: control of BOTH relative and absolute

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

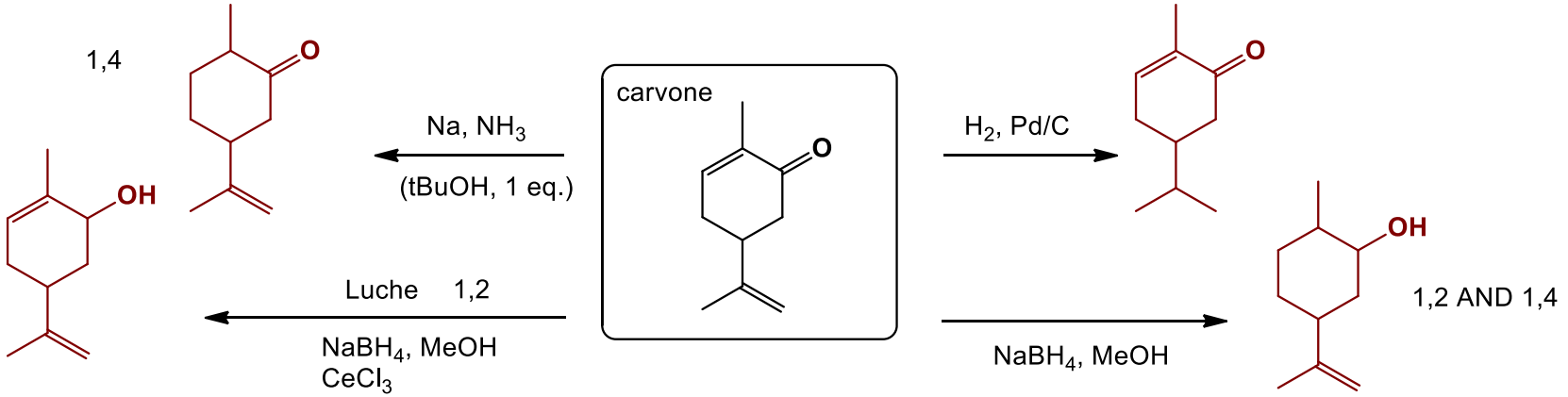
**A)** Chemoselectivity: Preferential reaction of one functional group over another



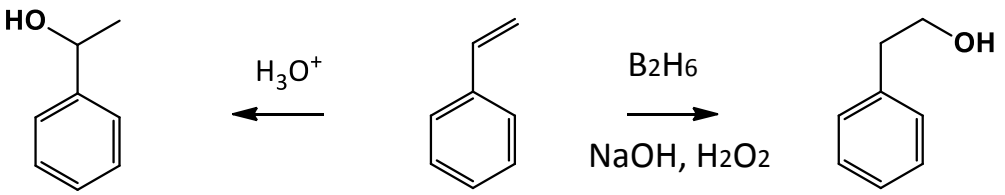



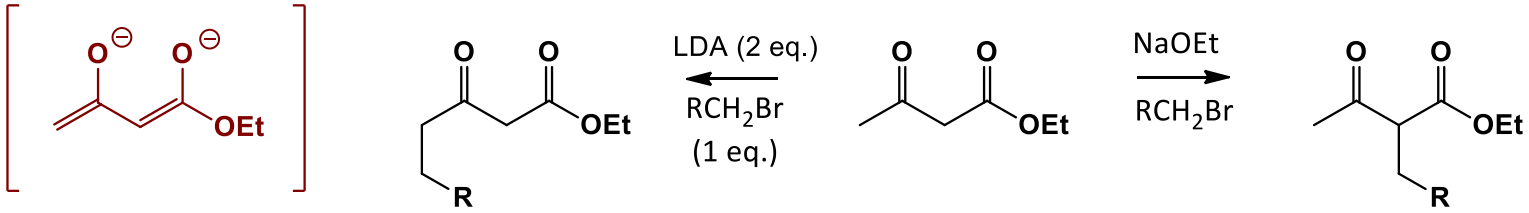



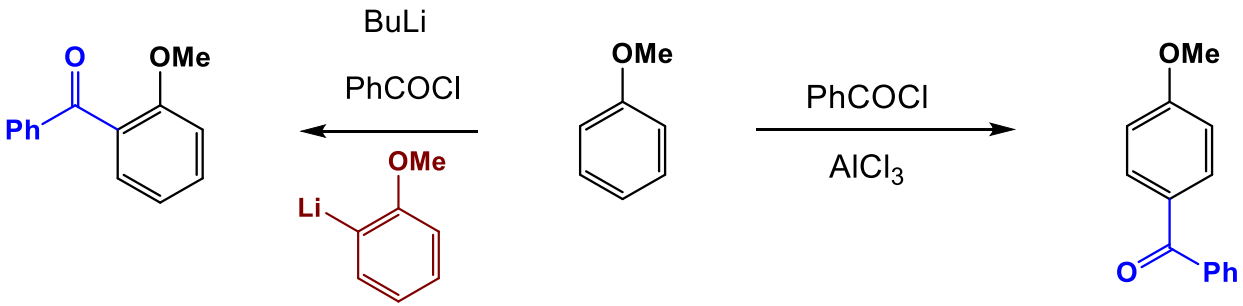

**AND**

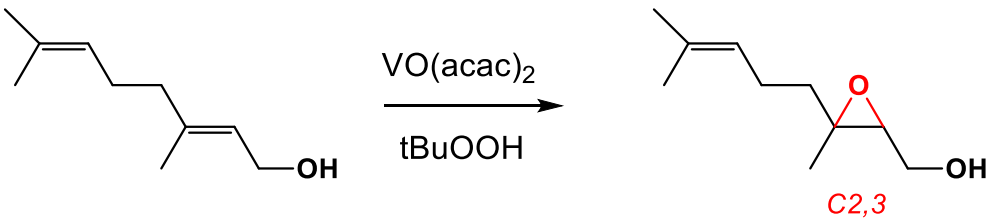


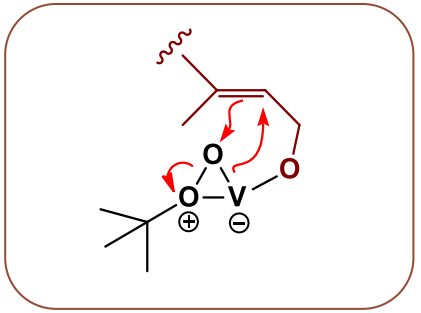
**B)** Regioselectivity: Preferential formation of one structural isomer over another; four examples



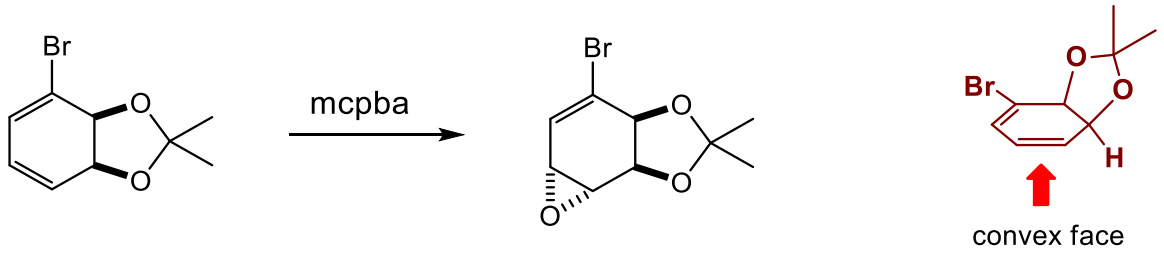



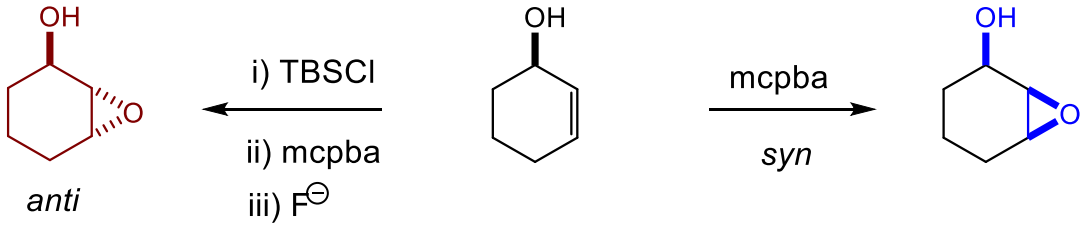
**C)** Stereoselectivity: Preferential formation of one stereoisomer over another

(i) Use the bias of the molecule:

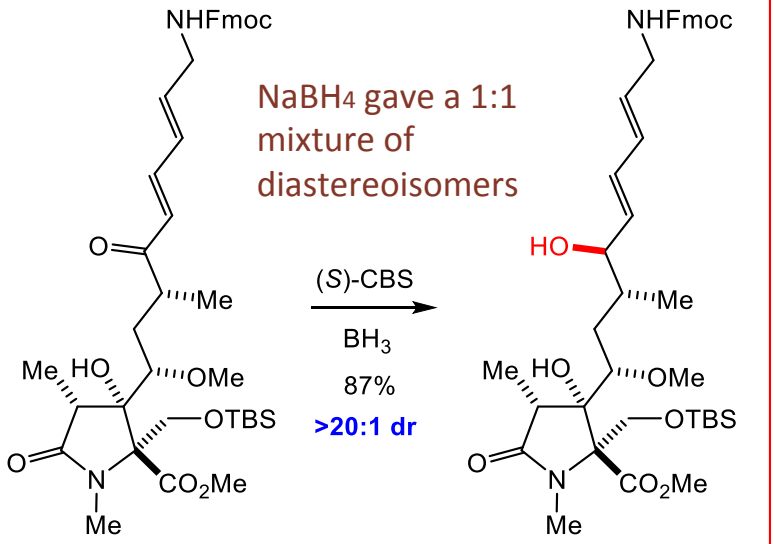
**Sterics**

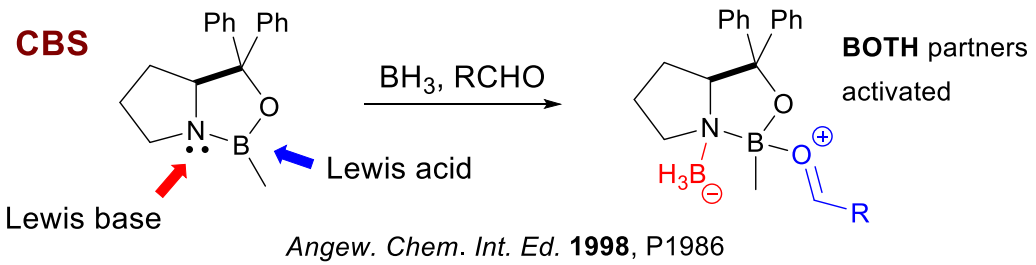


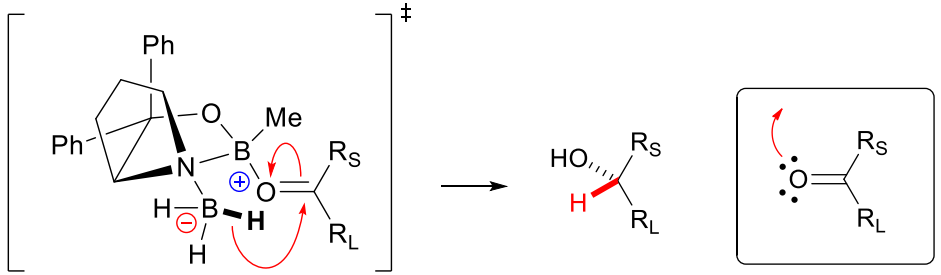

**Directing effects**



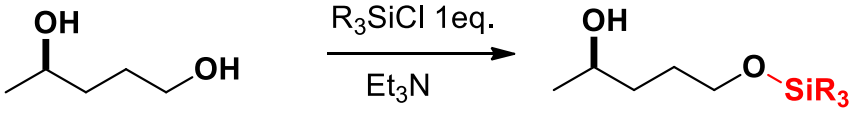

(ii) Or an external chiral reagent to IMPOSE stereochemistry on the molecule



**Protecting groups**: Sadly these are still essential to most chemical syntheses




| abbrev. | $R_3SiCl$ |
|---|---|
| TMS | $Me_3SiCl$ |
| TBS | $tBuMe_2SiCl$ |
| TIPS | $iPr_3SiCl$ |

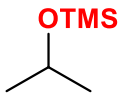
increasing bulk of silylating agent

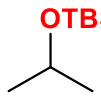
increasing preference to react at LEAST hindered site.

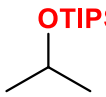
$1^o > 2^o > 3^o$

Bulker silicon groups may require a more reactive reagent:

use $R_3Si\text{-}OSO_2CF_3$ = $R_3SiOTf$

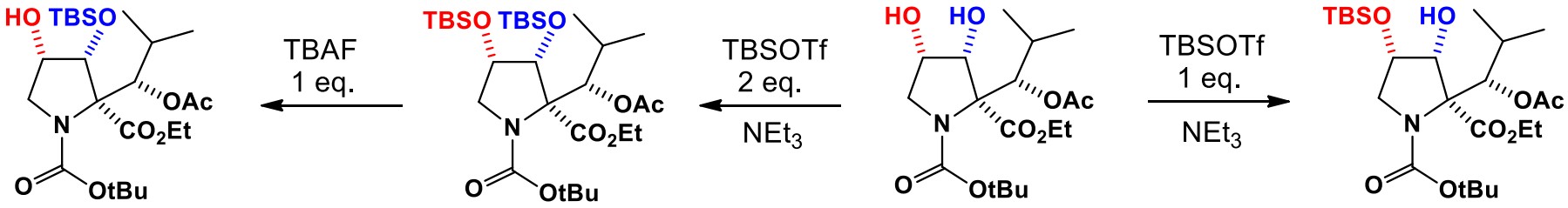


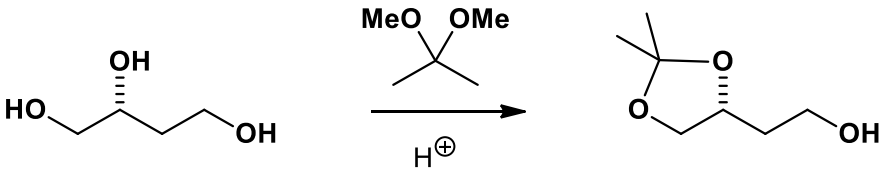




| relative rate of deprotection with fluoride | **1** | **20000** x slower | **100000** x slower |
|---|---|---|---|

There are tactics for protecting the **most** AND the **least** hindered functional groups, eg



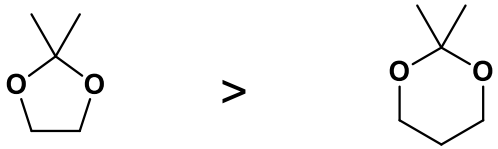
Cyclic protecting groups can be useful in achieving selectivity



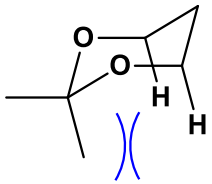

Primary OH is unable to form a stable, cyclic acetal and REMAINS unprotected

note:

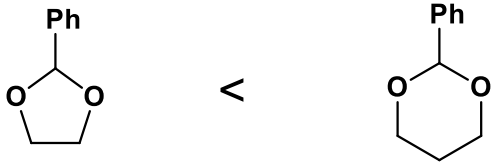
acetone protects
**1,2 OVER 1,3 diols**

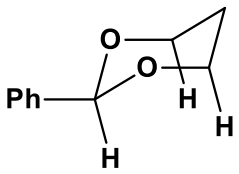



1,3- diaxial

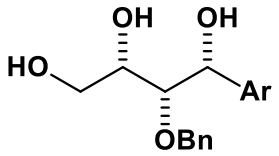



benzaldehyde protects
**1,3 OVER 1,2 diols**

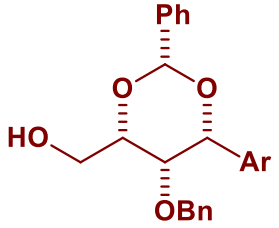



6 ring is LESS strained than a 5 membered ring



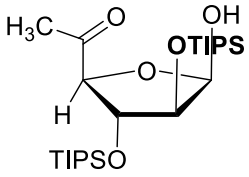

PhCHO | $H^+$



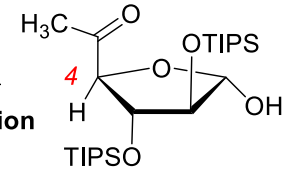

only has **ONE** 1,3 diol

Sometimes their intrinsic properties can help

large OTIPS biases equilibrium

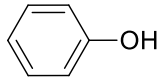



Mutarotation



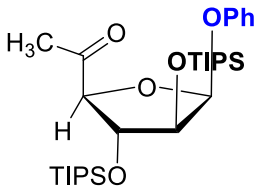

large OTIPS prevents epimerisation at sensitve C-4

**Mitsunobu**




DEAD, $PPh_3$

$S_{N2}$ INVERSION




hygromycin A

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**(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- ONE STEP
Non-TOXIC REAGENTS
Commercially AVAILABLE MATERIALS, CHEAP
Solvent WATER
Mild ROOM TEMPERATURE
Atmosphere of AIR
Purification NONE (but prefer recrystallisation to chromatography)
Yield 100 %
Waste NONE

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 LARGE SCALE
Reliable AND REPRODUCABLE
Availability and cost of STARTING MATERIALS
Toxicity of MATERIALS AND WASTE
Purity of PRODUCTS; LOW LEVELS, ESPECIALLY METALS
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?*

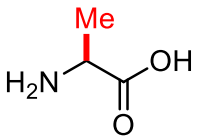
Nature has provided a wide range of enantiopure compounds in great abundance
Amino acids, carbohydrates, terpenes.
Called the **CHIRAL POOL**
New compounds added by chemical synthesis- also available in scale.
These compounds can become the target themselves, or also the basis of reagents, ligands and chiral auxiliaries, to pass on their stereochemical information indirectly.

**Advantages**: CHEAP;
available on a large SCALE
**Disadvantages**: only one enantiomer OFTEN AVAILABLE
Functional group interconversions can lead to LONG SEQUENCES

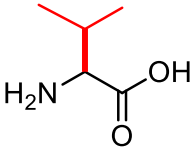
***Aminoacids***

20 proteinogenic AAs

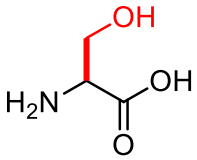
All amino acids found in proteins occur in the L-configuration about the chiral carbon atom.



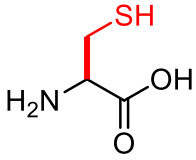

L- alanine




L- valine




L- serine




L- cysteine

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)

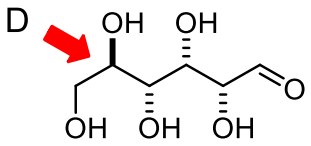
D-proline- £12 per g (5g)
L-proline-40p per gram (5 kg)
DL proline is £10 per g (5g)

***Carbohydrates:***

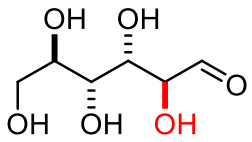
the D enantiomer tends to found in Nature

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

L-glucose- UNAVAILABLE



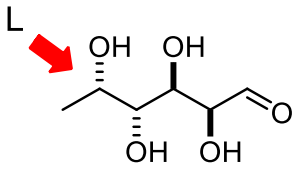

D- glucose



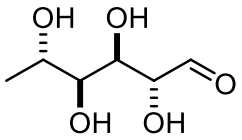

D- mannose

*Many different diastereoisomers available*

However, L sugars ARE found in Nature




L- fucose

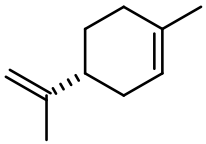



L- rhamnose

*All drawn in the open chain form*

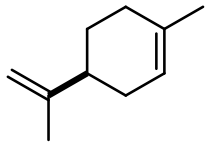
***Terpenes***

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 fragrants, e.g. limonine from citrus fruit.



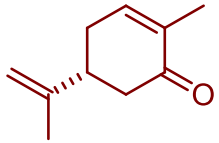
(+)-limonine

£0.03 per gram



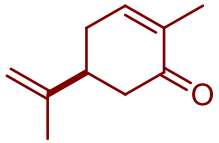
(+)-limonine

£0.17 per gram




(-)-carvone

£0.13 per gram




(+)-carvone

£1.64 per gram

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

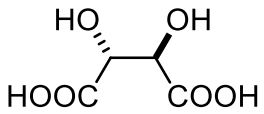
***How else might we obtain enantiopure compounds?***

**RESOLUTION**

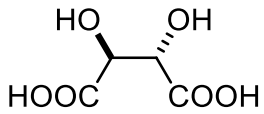
*Tartaric acid*: isolated from the salt in c. 800 AD. Naturally occurring acid is CHIRAL

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 amonaium sodium tartrate crystals, he found them to be CHIRAL (ie mirror images of one another)


Manual sorting under a MICROSCOPE.

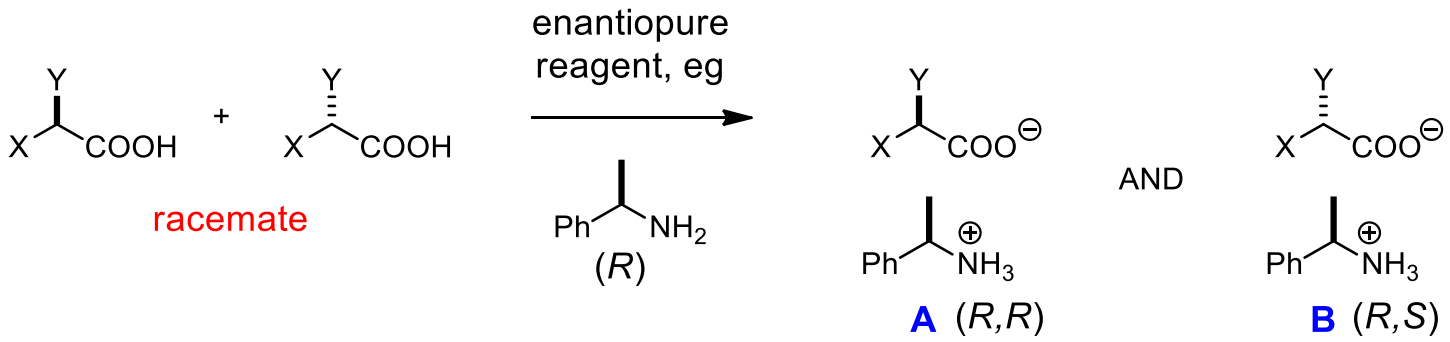
Allowed the production of both enantiomers of tartaric acid.

Happened because this salt crystallises as a CONGLOMERATE

An equimolar mechanical mixture of crystals, each one of which contains only **one** of the two enantiomers present in a racemic mixture.

However, it is estimated that only 5-10 % or organic solids are conglomerates, ie it is NOT GENERAL.

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




3 step guide to resolution:

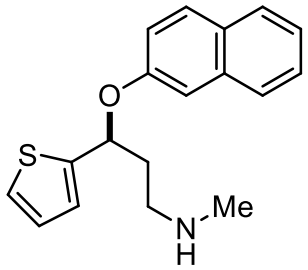
**1) Make a derivative (use enantiopure reagent)**

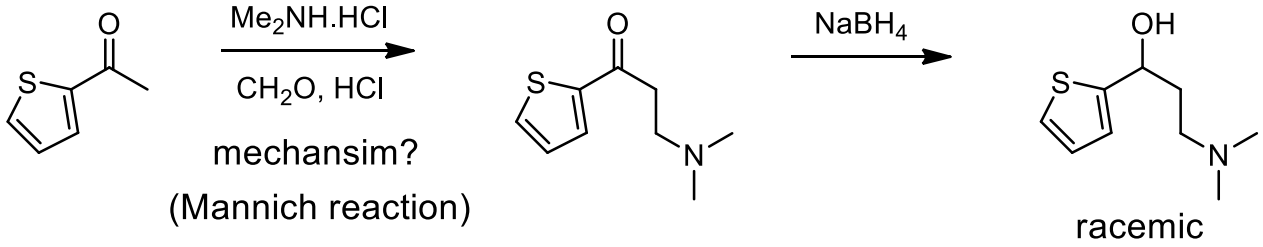
Products are DIASTEREOISOMERS (ie different compounds)

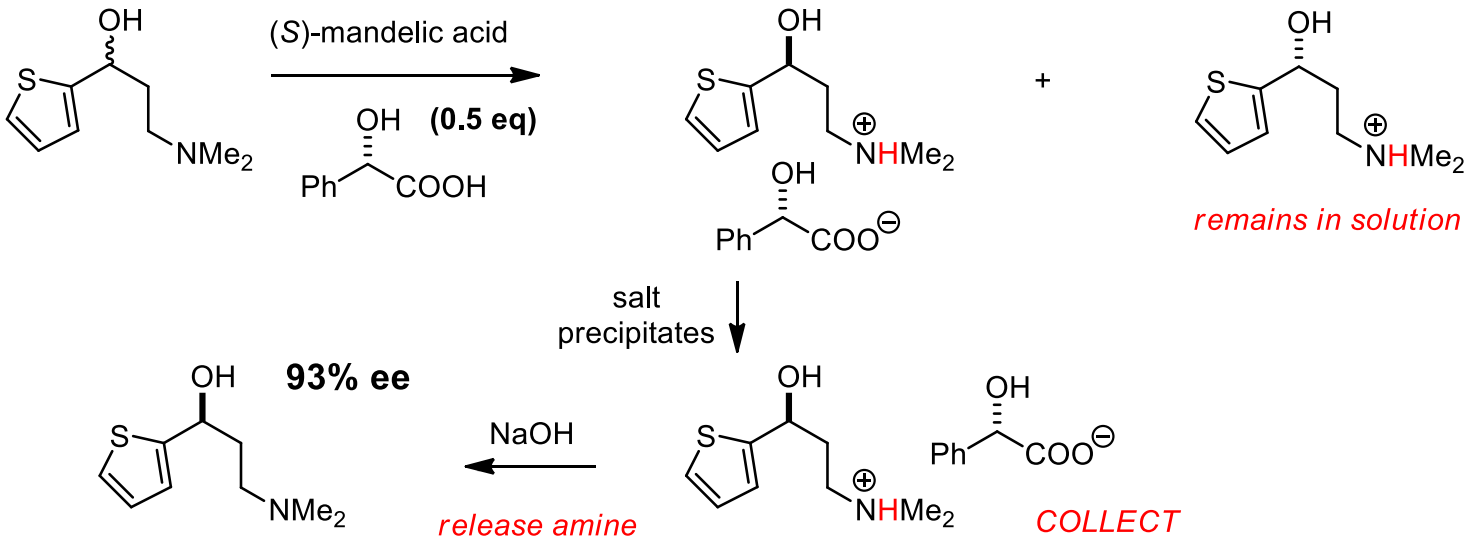
**2) Separate them (Recrystallisation is common)**

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

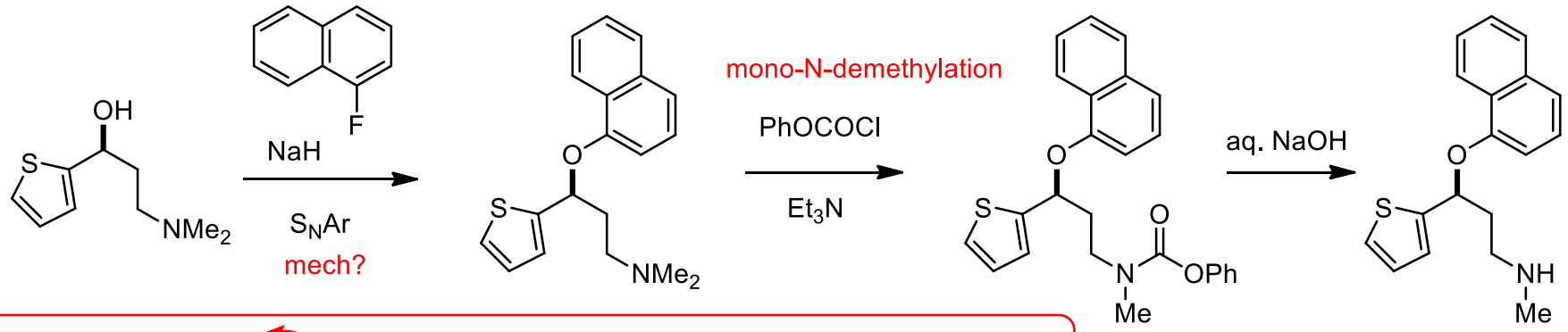
A more sophisticated example of this is found in an industrial variant of Lilly's synthesis of duloxetine (Cymbalta) Used for the treatment of depression. Annual sales in 2010 were $2.6 billion.

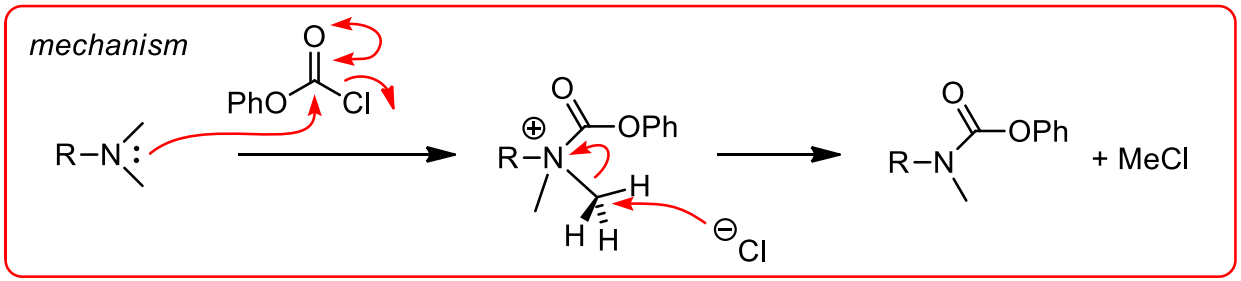

duloxetine



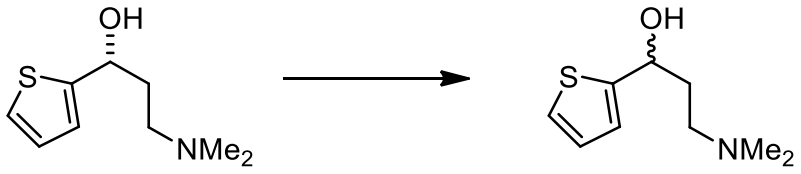



## Completion of the synthesis



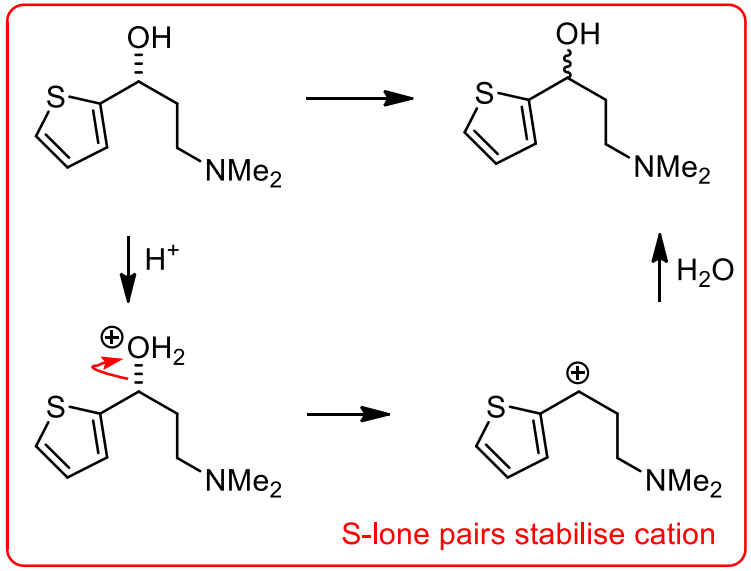



*Recycling of the unwanted enantiomer?*



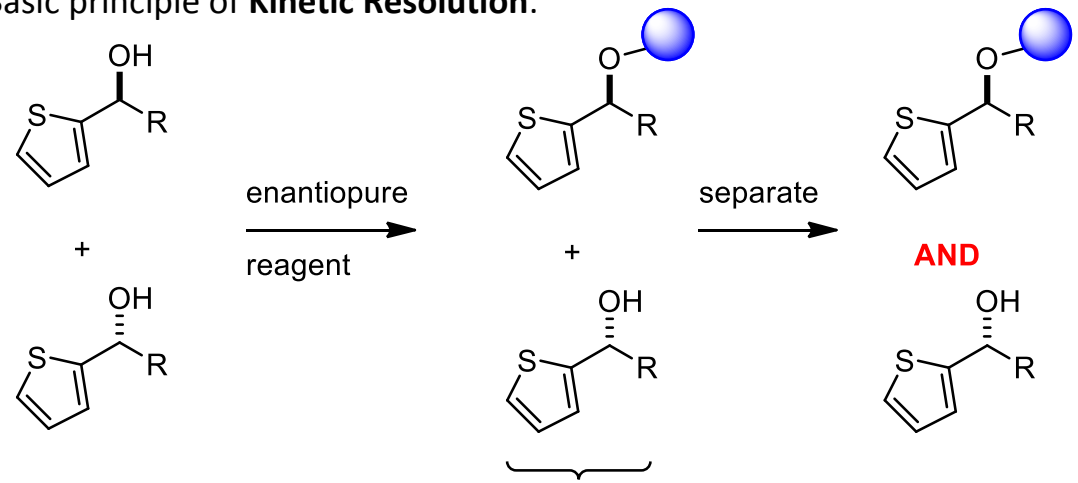

1) *Mitsunobu (ArCOOH, $PPh_3$, DEAD)*
2) *[O] then $NaBH_4$*
3) ***HCl***

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).

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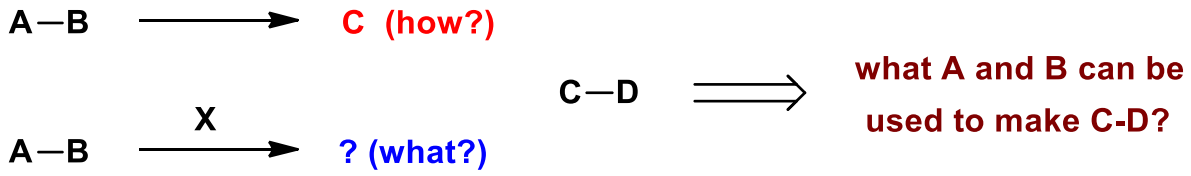
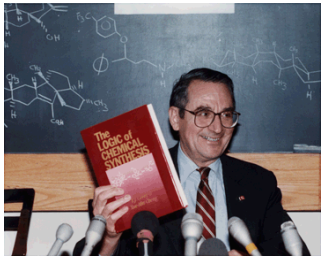
## 3) RETROSYNTHESIS

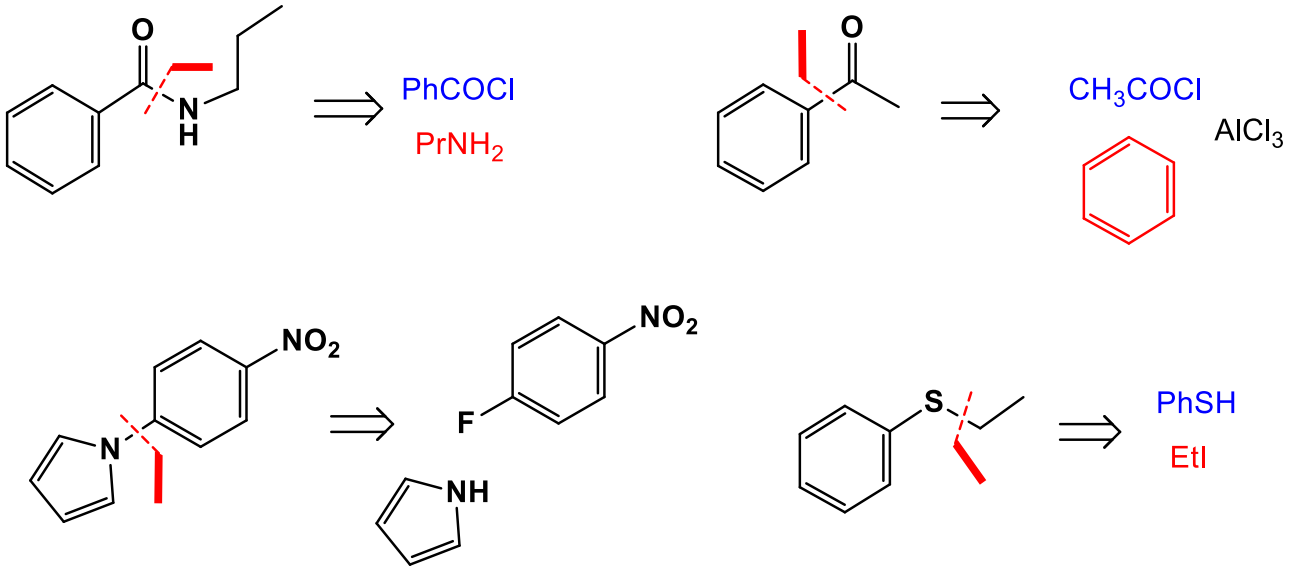
The theory (Corey- Nobel prize in 1990)

### 1) Think about reactions in reverse



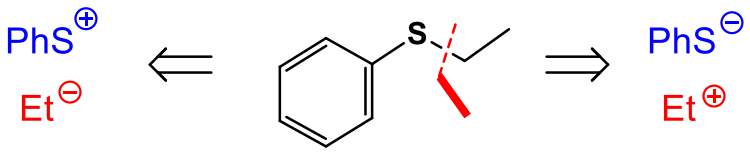
### 2) Use disconnections to break down molecules

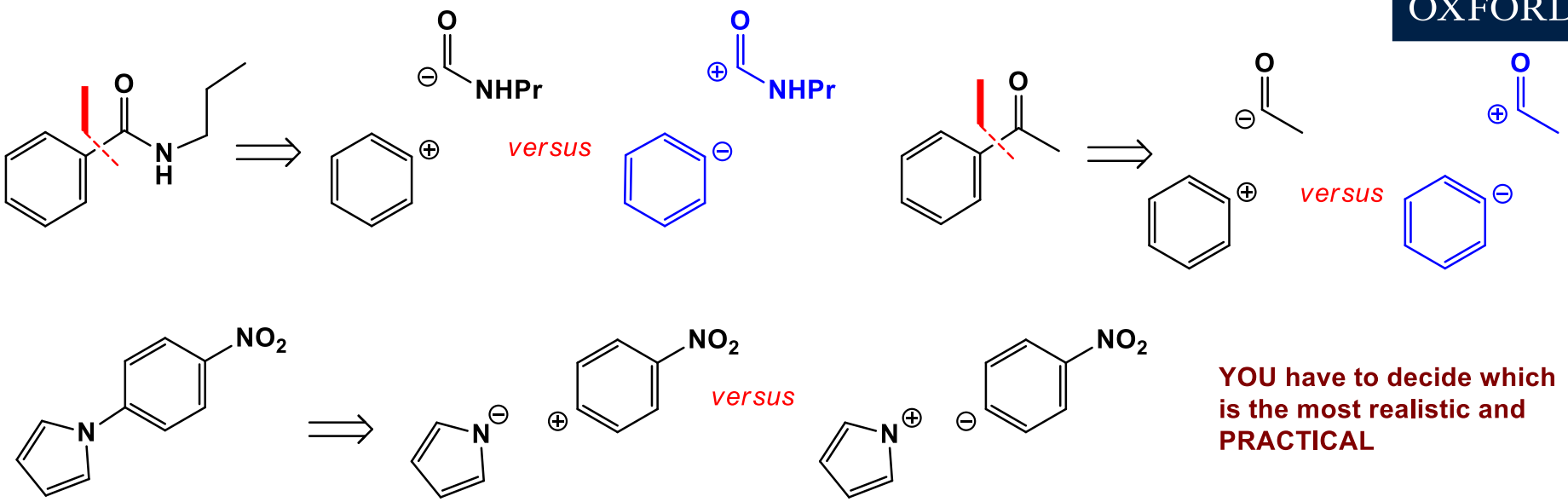



Make sure that your disconnections correspond to known and RELIABLE reactions

### 3) Synthons: These are simply hypothetical reaction intermediates

There are two ways of analysing a single disconnection

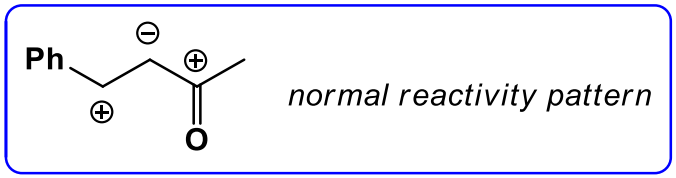


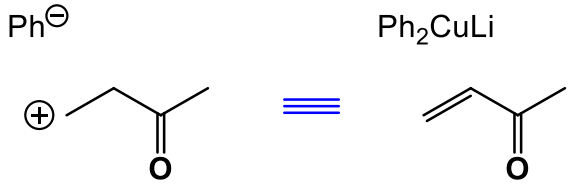


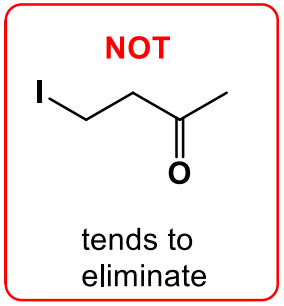

**YOU have to decide which is the most realistic and PRACTICAL**

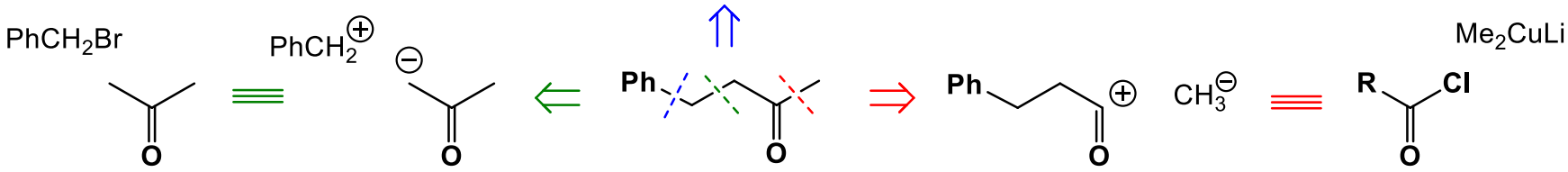
Remember the concept of **UMPOLUNG** is helpful (especially) with carbonyl groups:

1) Normal reactivity of the carbonyl group

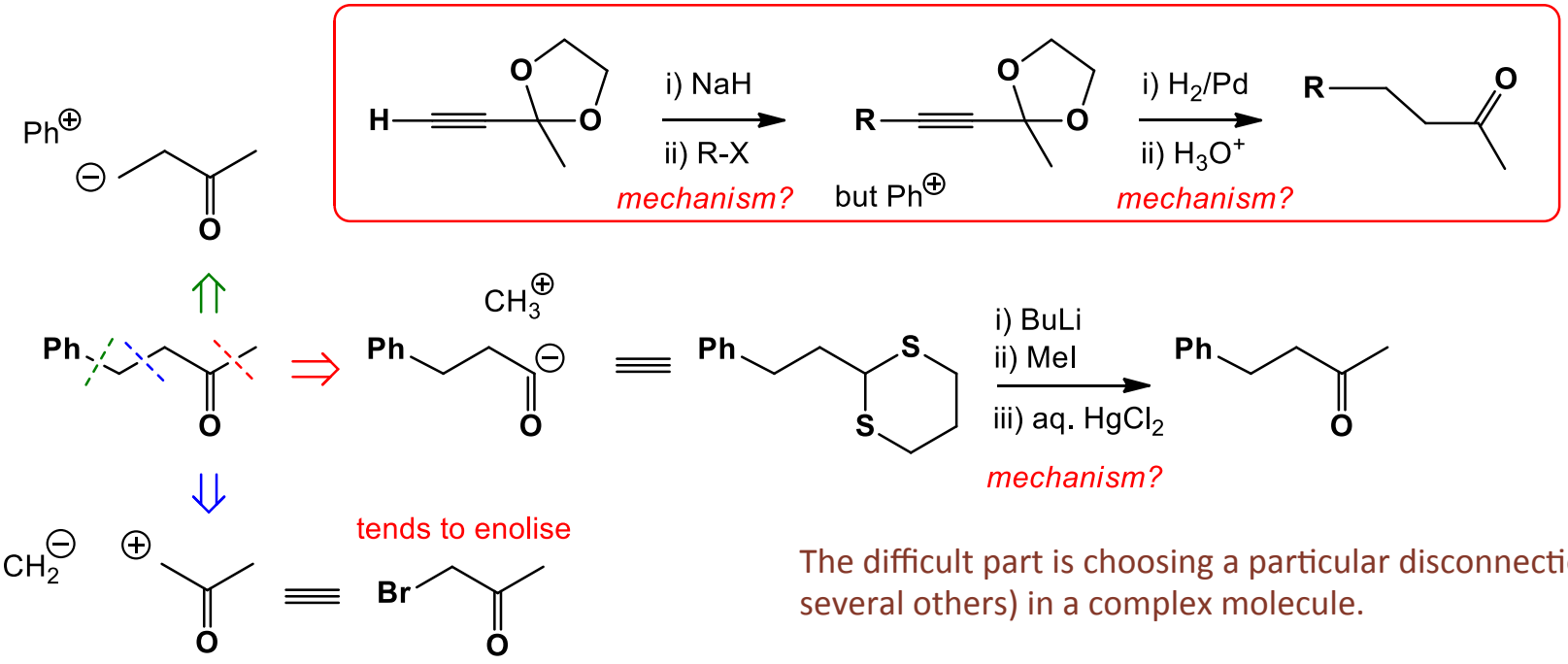


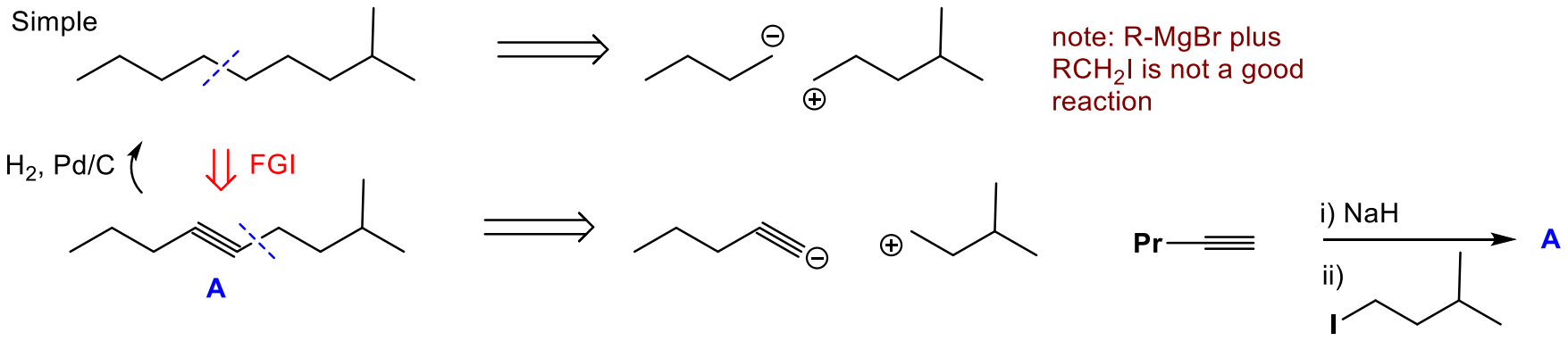



2) Use **UMPOLUNG** to reverse the reactivity of the carbonyl group

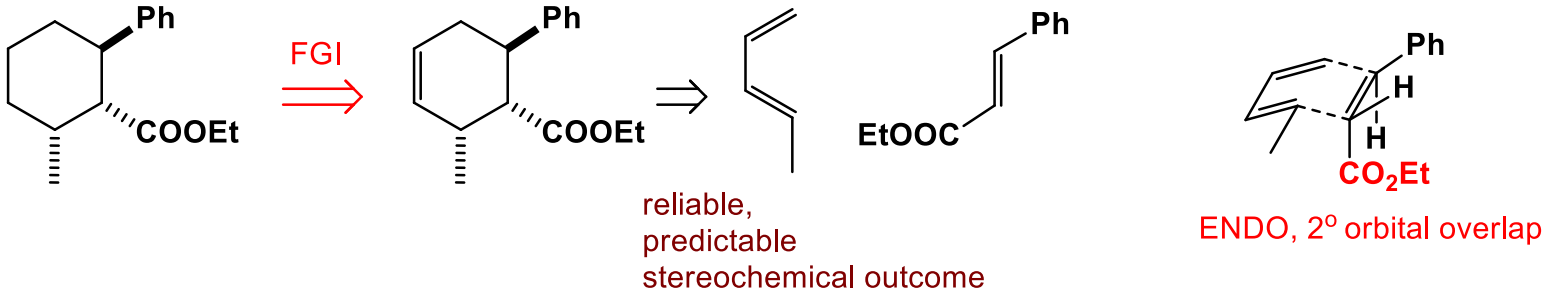



The difficult part is choosing a particular disconnection (from several others) in a complex molecule.

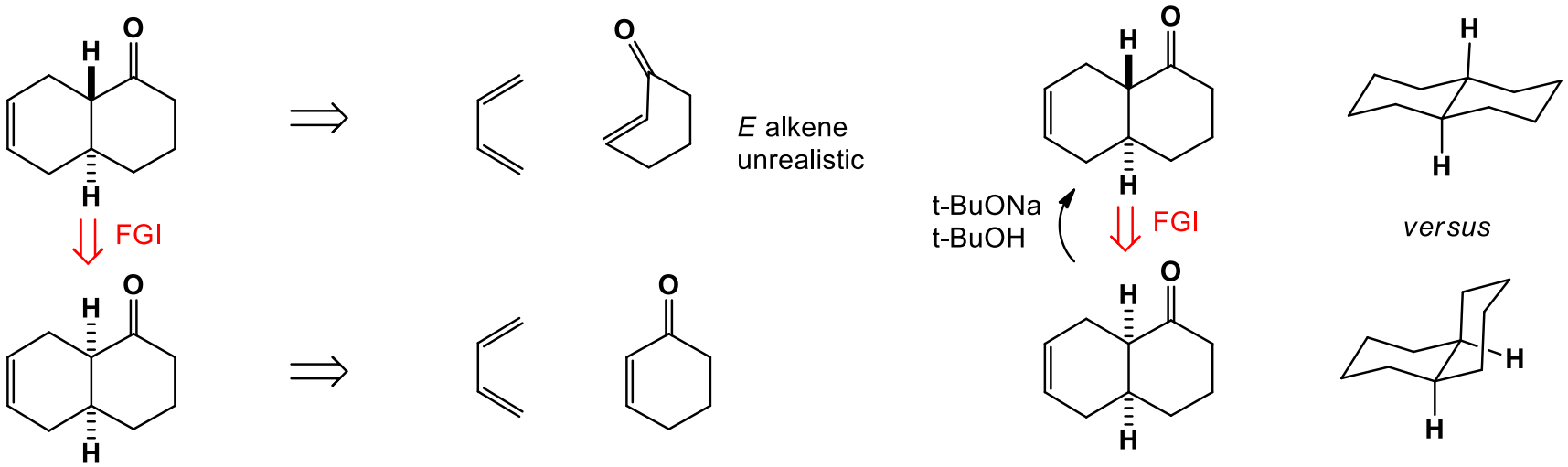
3) Sometimes functional group interconversion on the target helps



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. Nicoloau, *Angew. Chem. Int. Ed*. **2002**, *41*, 1668-1698.

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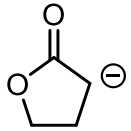
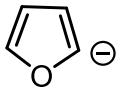
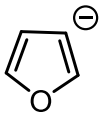
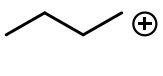
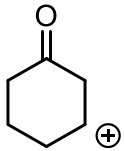
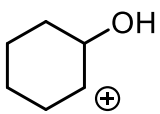
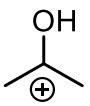
## 4) Some problems to think about

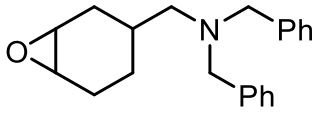
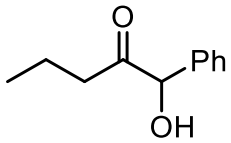
*a) Suggest reagents for the following synthons*

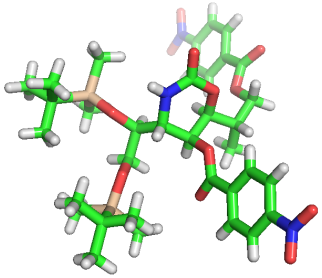
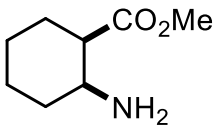
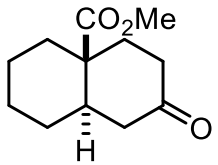
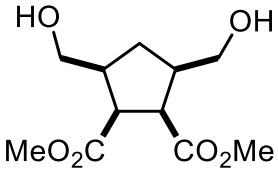






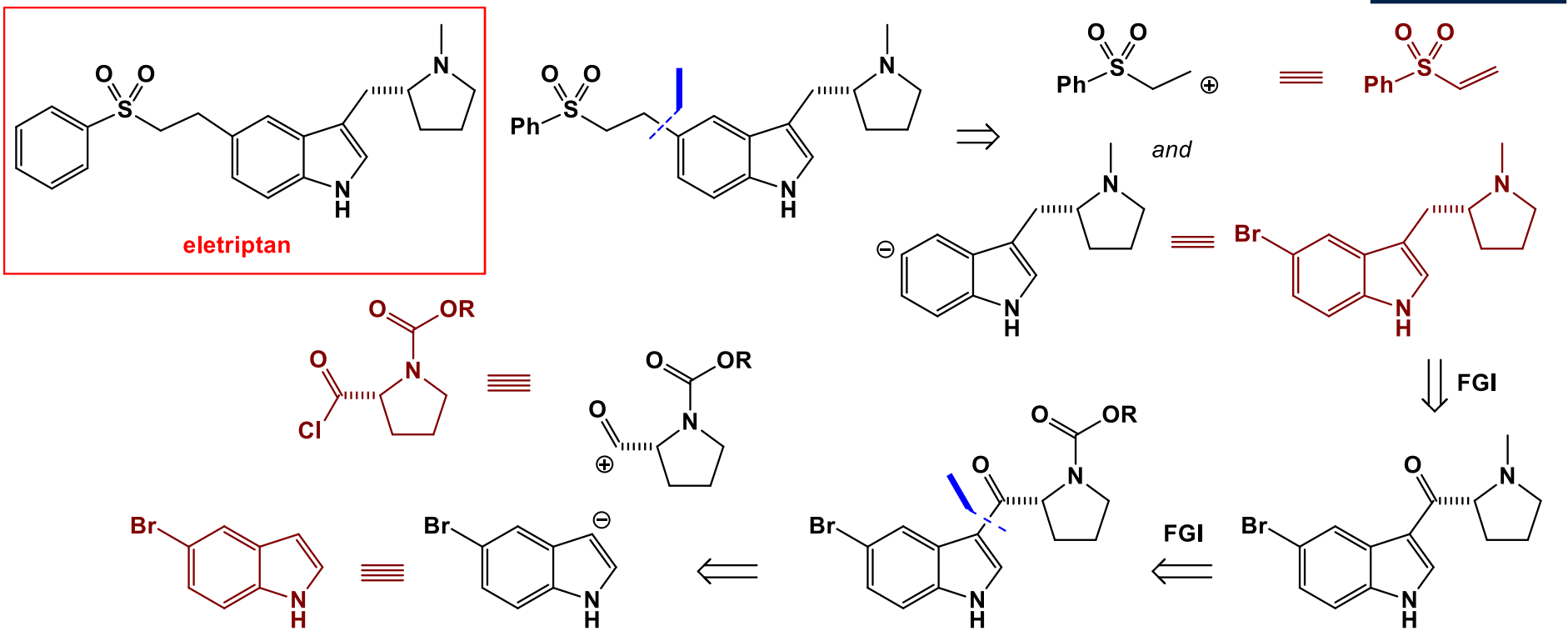
*b) Suggest synthetic routes to the following five compounds using retrosynthetic analysis*

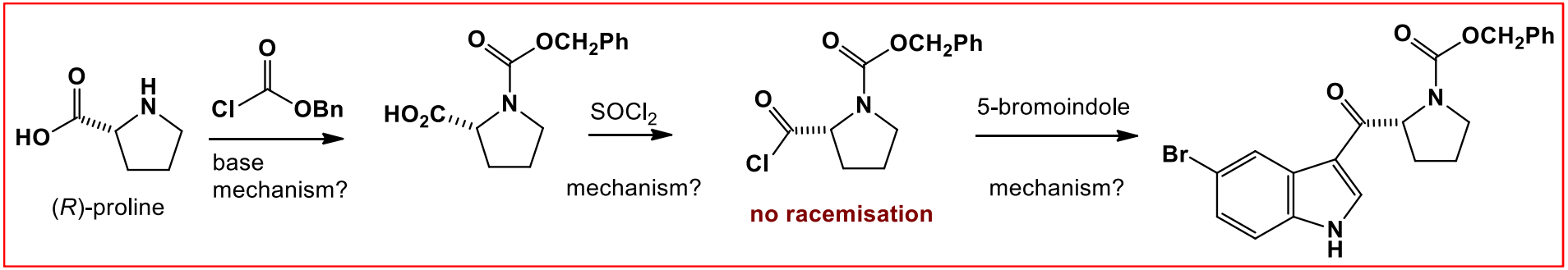
dont worry abut stereochemistry

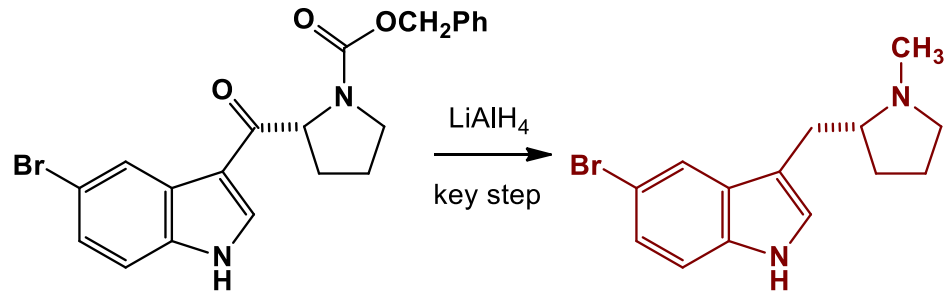





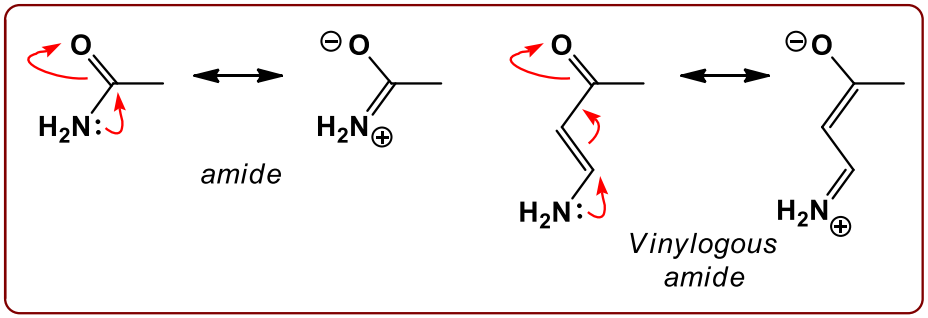
**Synthesis 1)** Eletriptan (Pfizer) Migraine (sales in 2008, $0.21 billion)

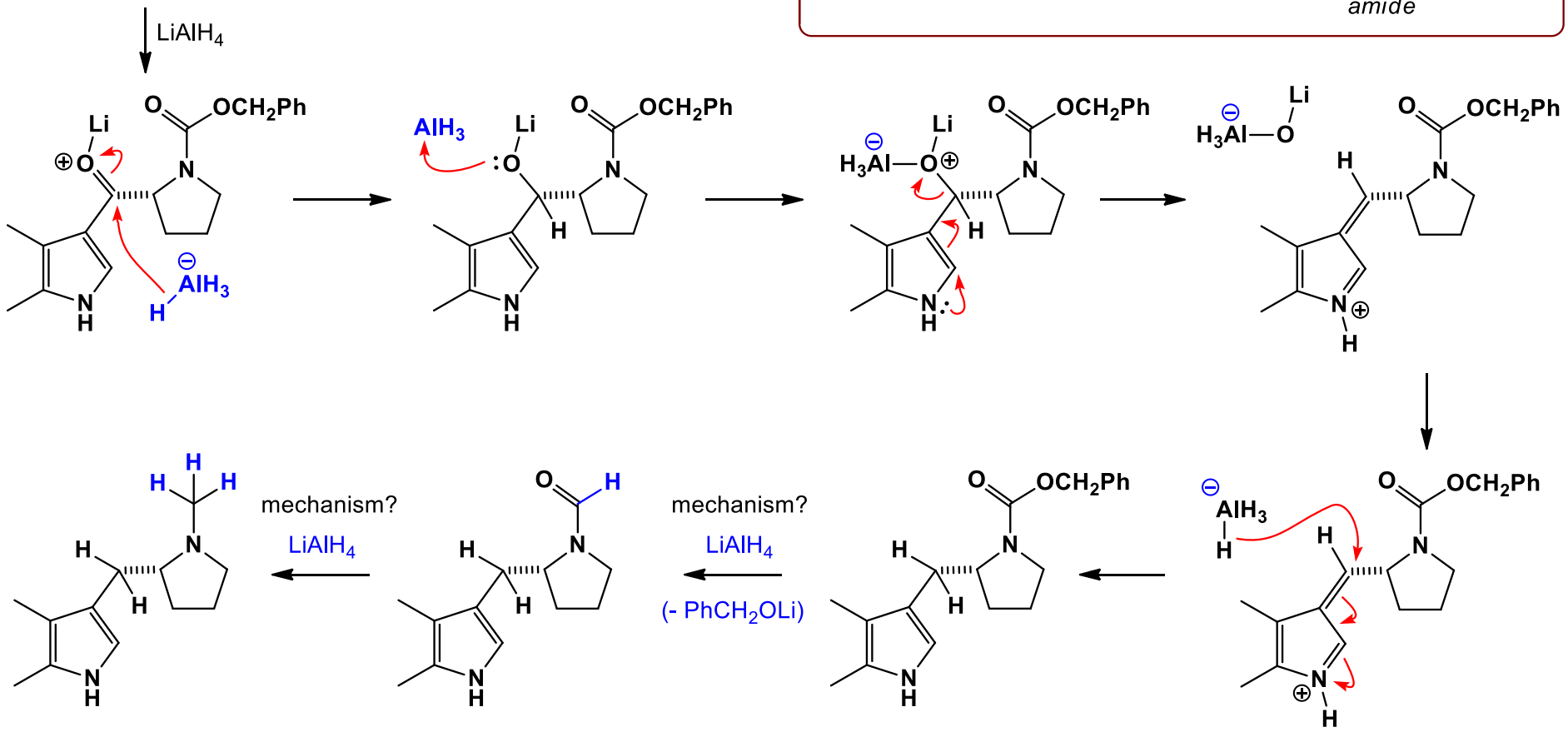



The synthesis

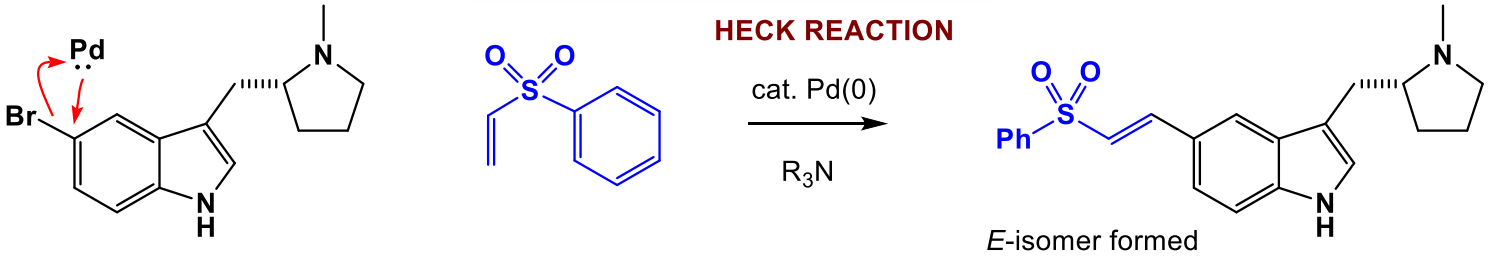



Br
O
OCH2Ph
N
H
LiAlH4
key step
CH3

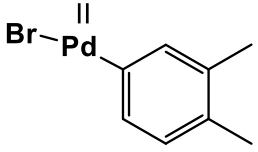

H2N:
amide
Vinylogous
amide


LiAlH4
Li
AlH3
H3Al—O
mechanism?
LiAlH4
(- PhCH2OLi)

## HECK REACTION

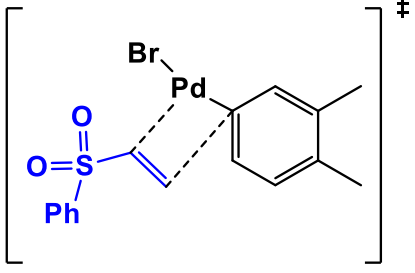


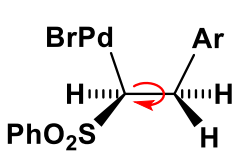

oxidative insertion



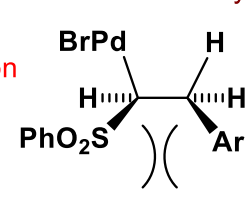

alkene insertion

*syn* addition

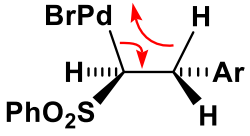


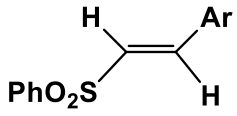

rotation




Z- alkene

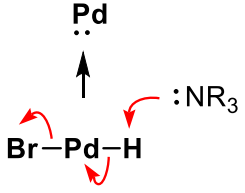



β-hydride elimination

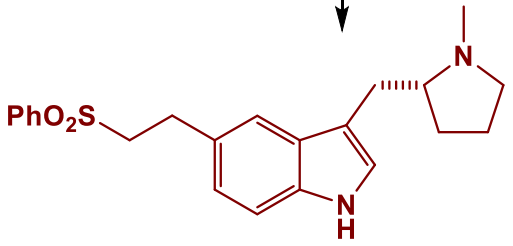



E- alkene

re-enters catalytic cycle




$H_2$, Pd-C




**> 98% ee**

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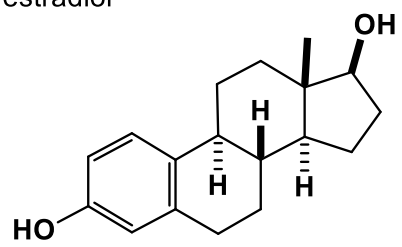
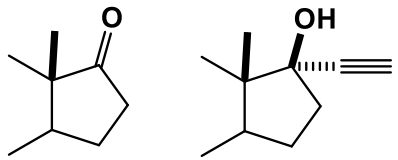
**Synthesis 2) Estradiol** (*Helvetica Chimica Acta*, **1980**, *63*, 1703)

estradiol

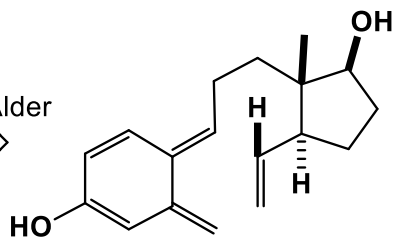


steroidal hormone

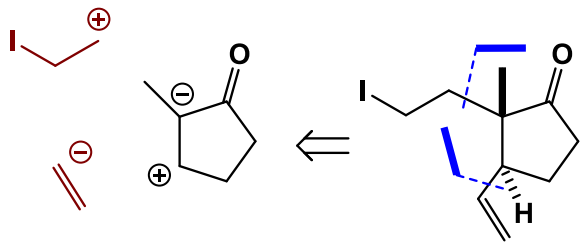


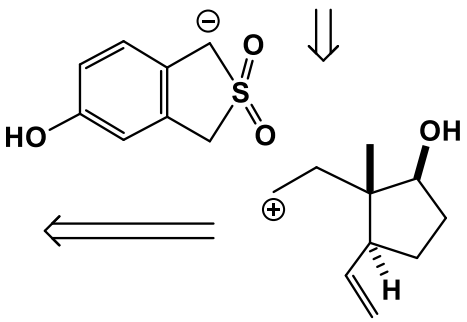
estrone

retro Diels Alder

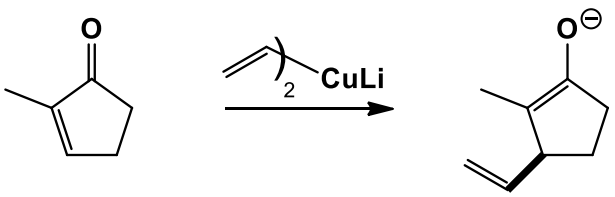


unstable; so form *in situ*

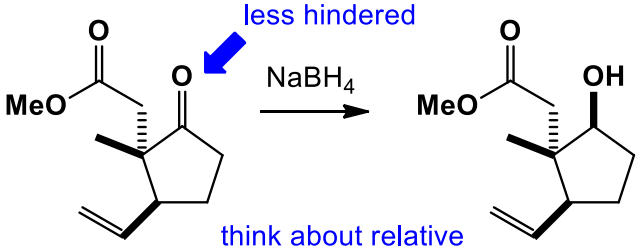




The synthesis

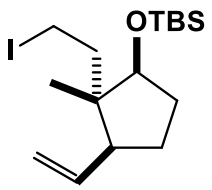


lower face is less hindered

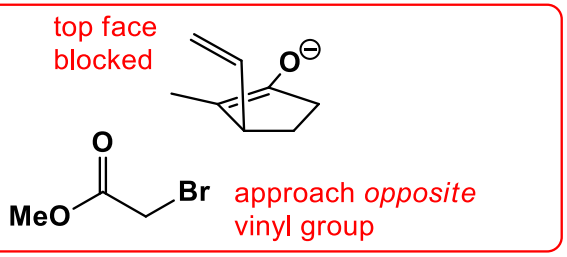


think about relative stereochemistry

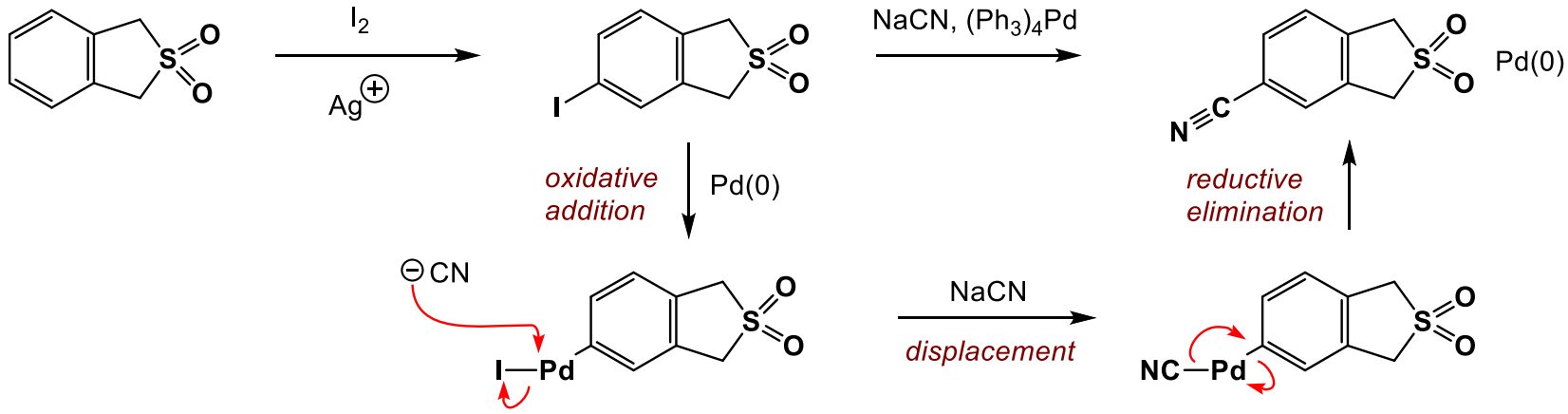
i) TBSCl, $Et_3N$
ii) $LiAlH_4$
iii) TsCl, NaI



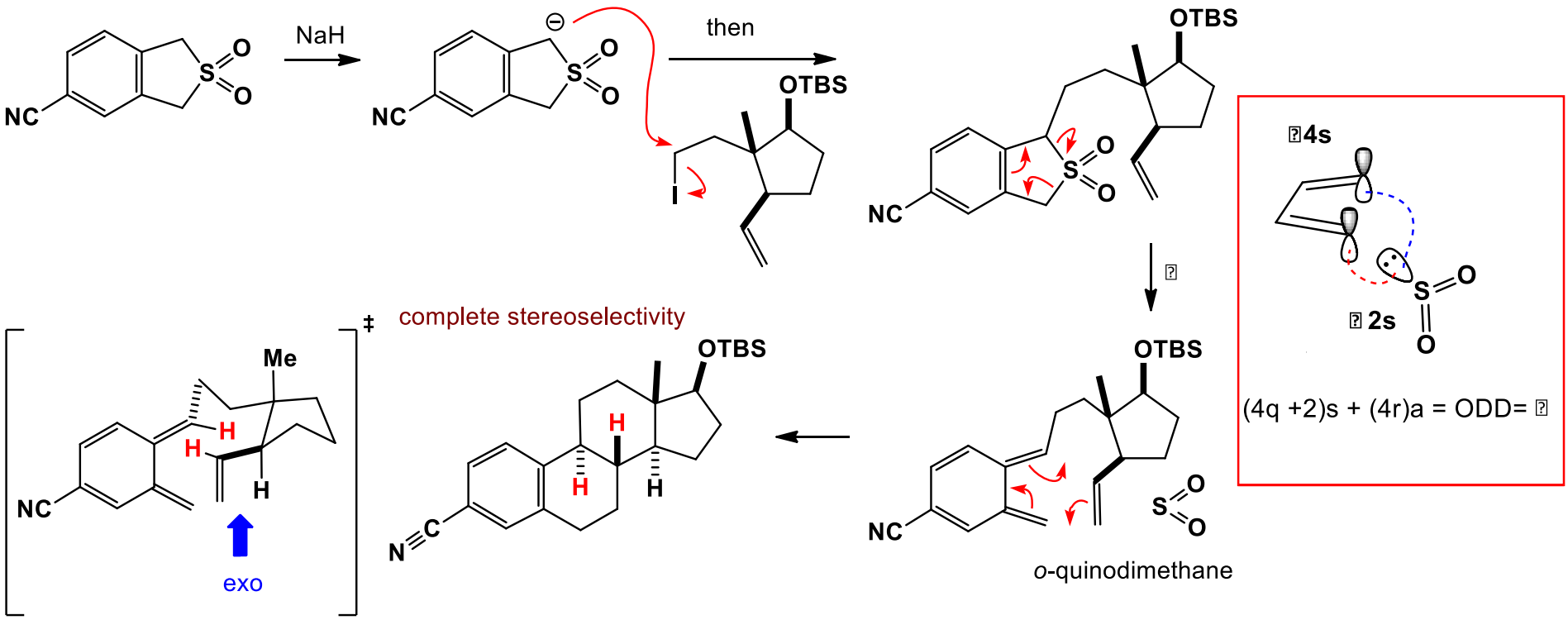
top face blocked



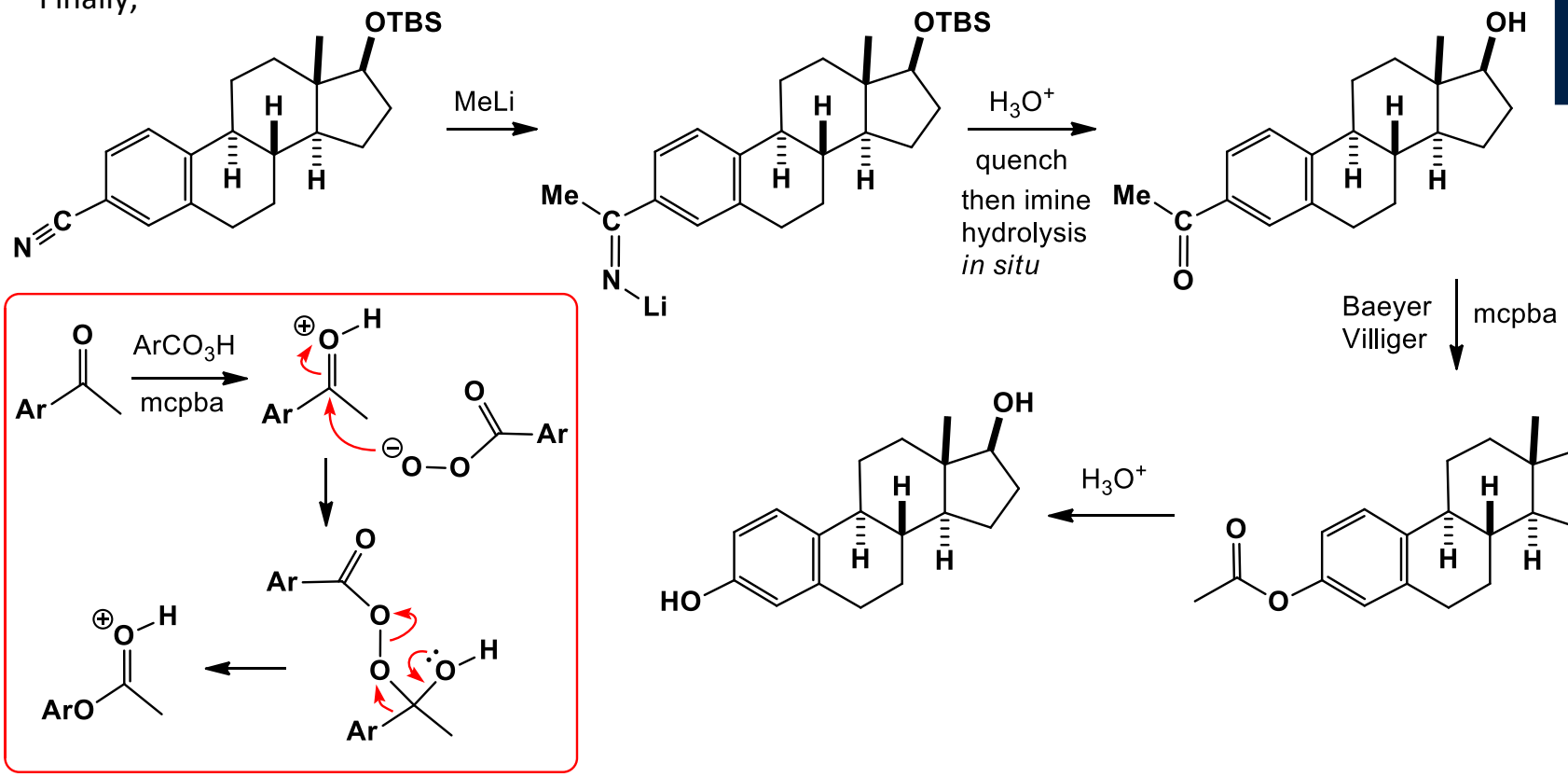
approach *opposite* vinyl group


I2
Ag⊕
NaCN, (Ph3)4Pd
Pd(0)
oxidative addition
Pd(0)
reductive elimination
⊖CN
NaCN
displacement

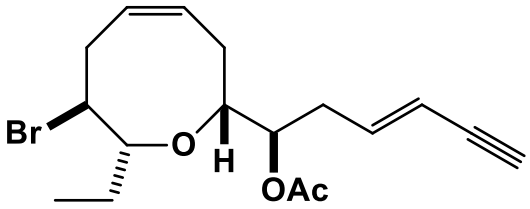
The end game


NaH
then
OTBS
complete stereoselectivity
Me
exo
‡
o-quinodimethane
[4s]
[2s]
(4q +2)s + (4r)a = ODD= [+]

Finally,




**Synthesis 3) (+)-Laurencin**



(+)-laurencin

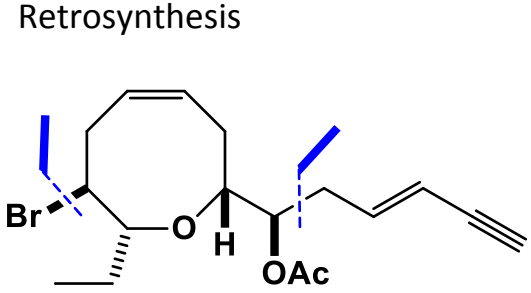
Isolated in 1965 from red algae- *Laurencia glandulifera*

Structure proven by X-ray crystallography

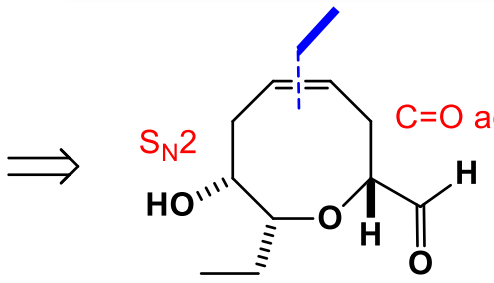
Representative of a large number of medium ring marine metabolites found as natural products

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

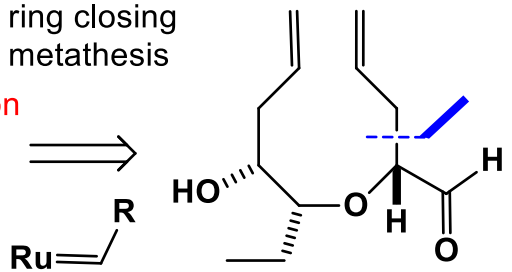
Retrosynthesis

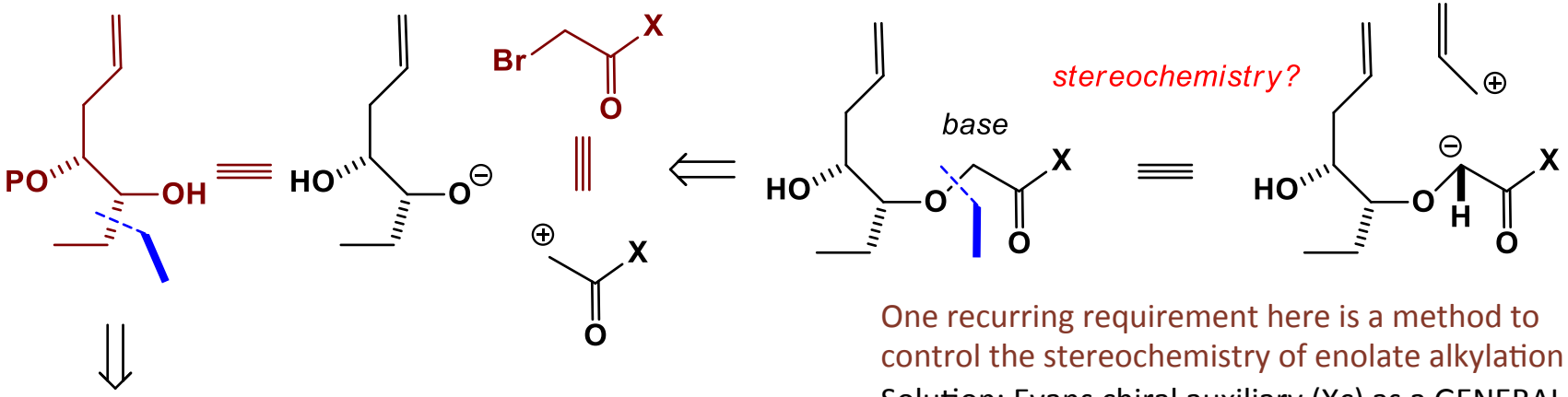



(+)-laurencin



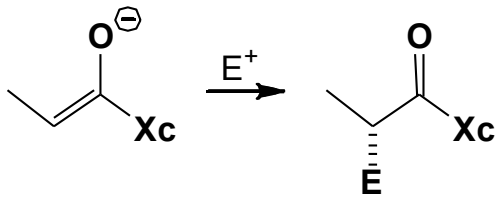

ring closing metathesis

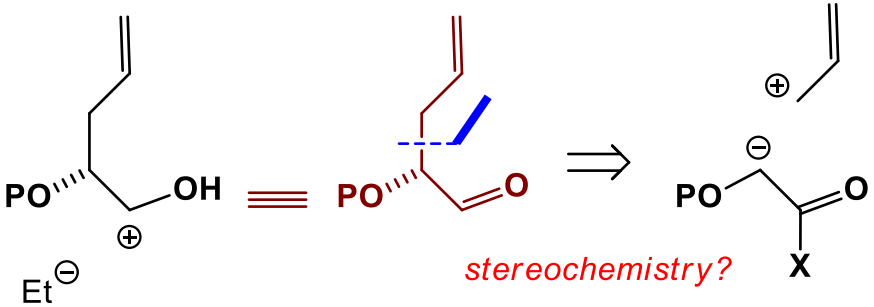


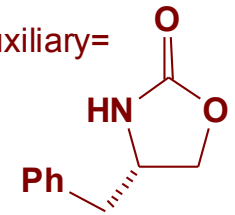

One recurring requirement here is a method to control the stereochemistry of enolate alkylation

Solution: Evans chiral auxiliary (Xc) as a GENERAL method

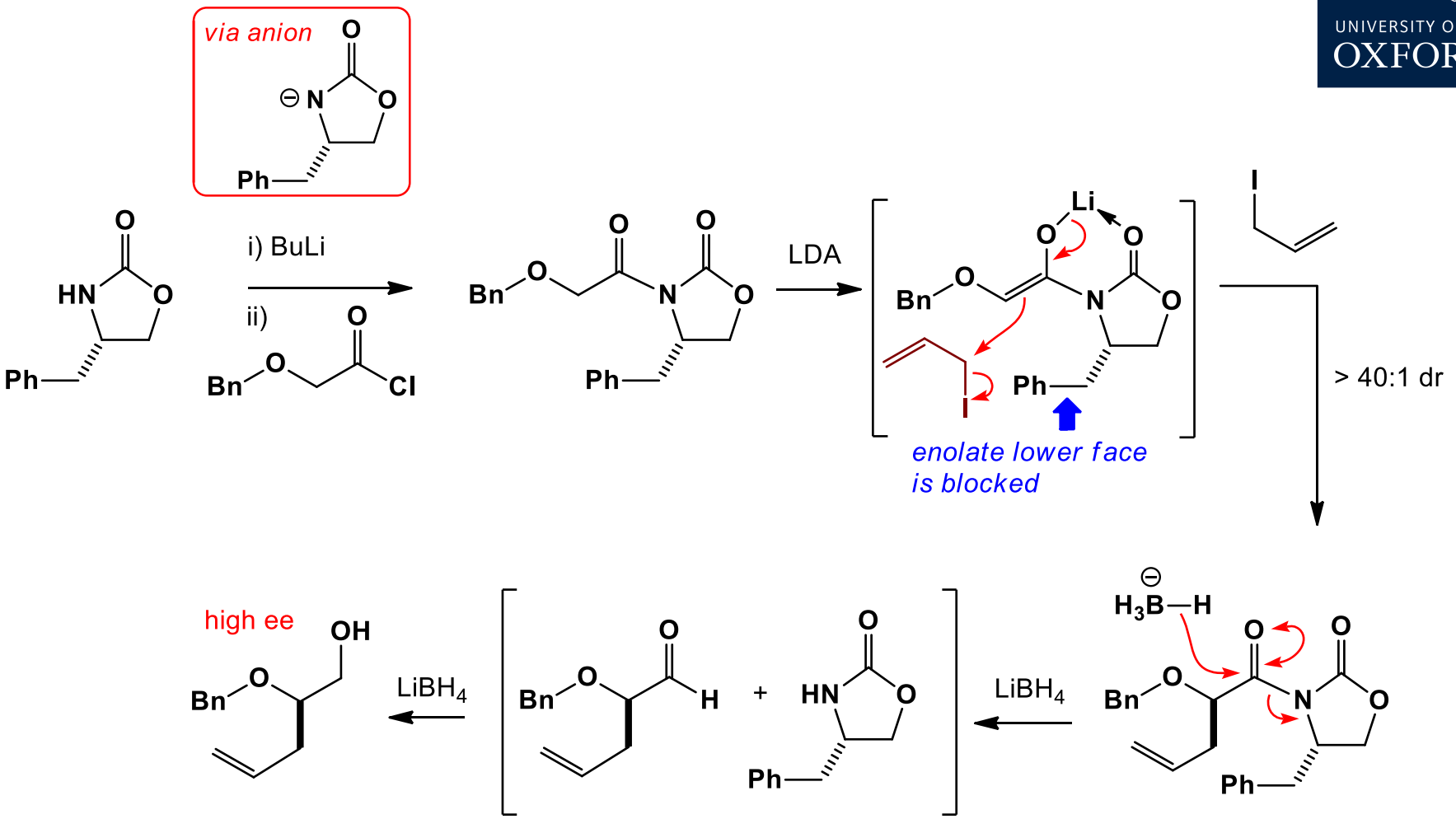



Xc= chiral auxiliary=

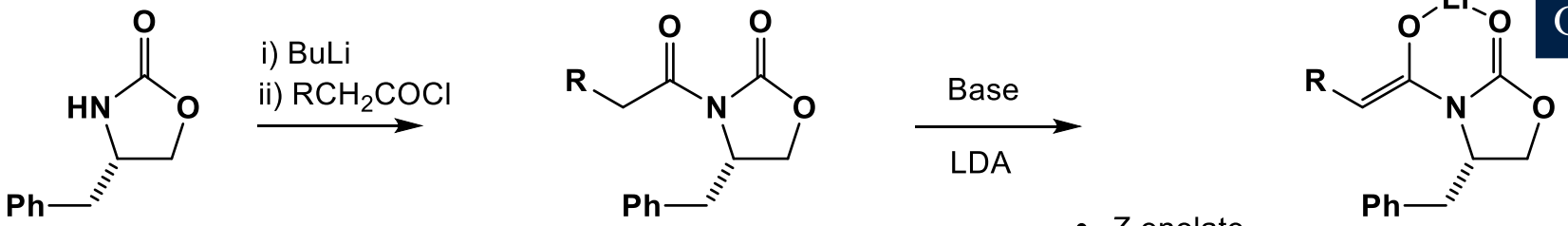



*commercially available, but how would you make it?*




Note:
Dr = diastereomeric ratio
Ee = enantiomeric excess

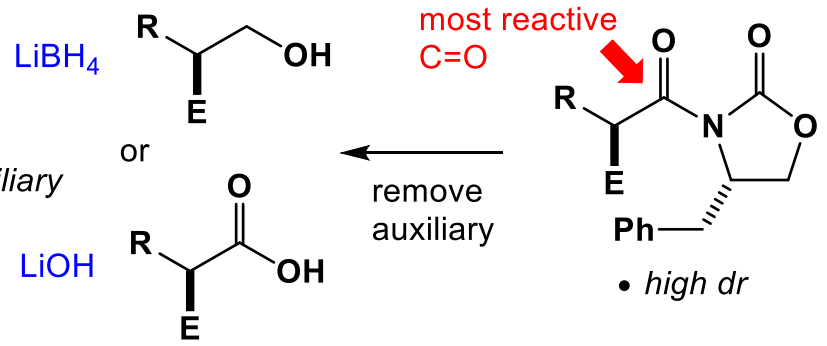
ASIDE; Evans chiral auxiliary (Xc) is a very GENERAL method which is used widely in organic synthesis




- other enantiomer is available
- other stereodirecting groups are possible, eg $PhCH_2$ vs *i*-Pr etc

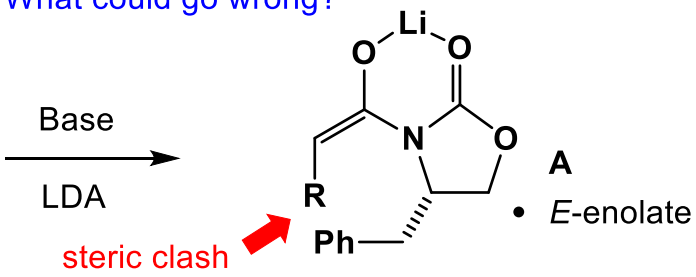
- *Z*-enolate
- *chelation to the C=O*
- *one face is blocked*

$E^+$

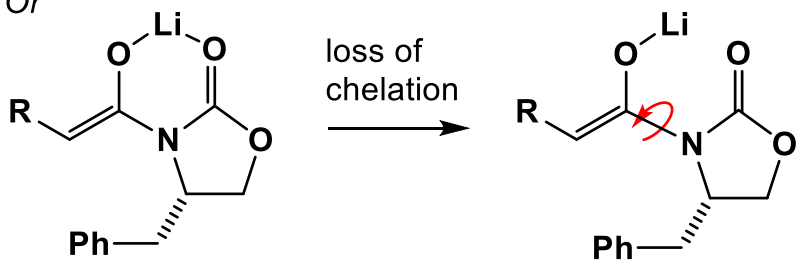



- *high dr*
- *high ee*
- *recycle auxiliary*

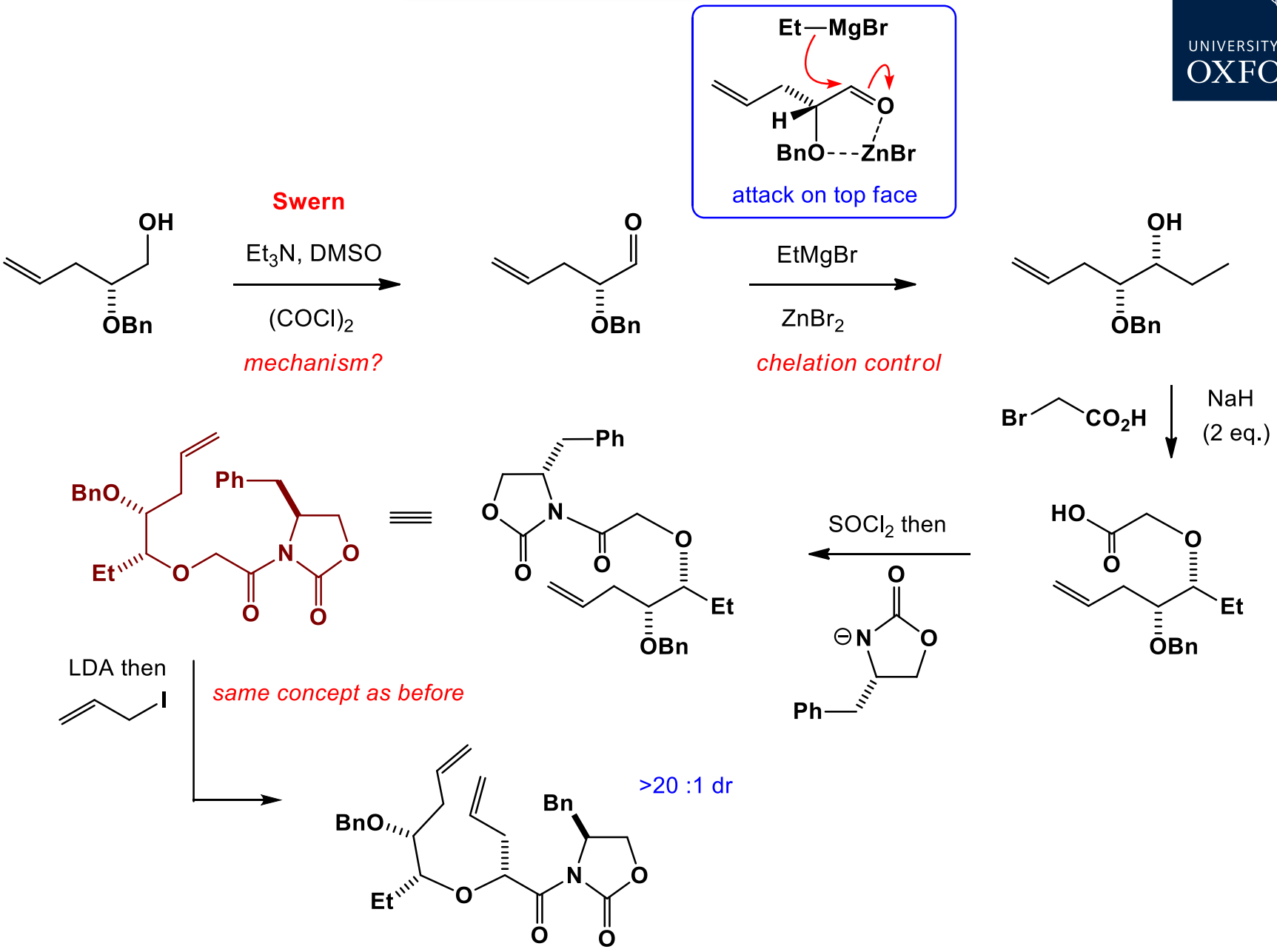
What could go wrong?

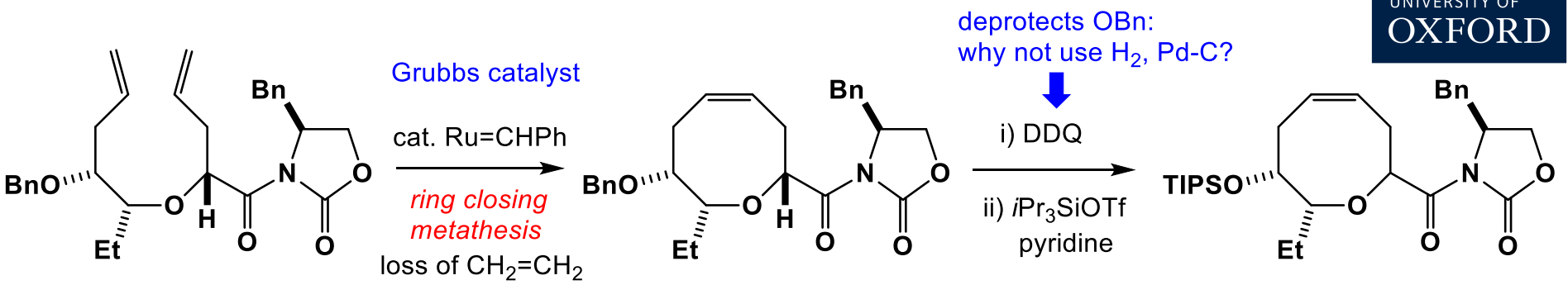


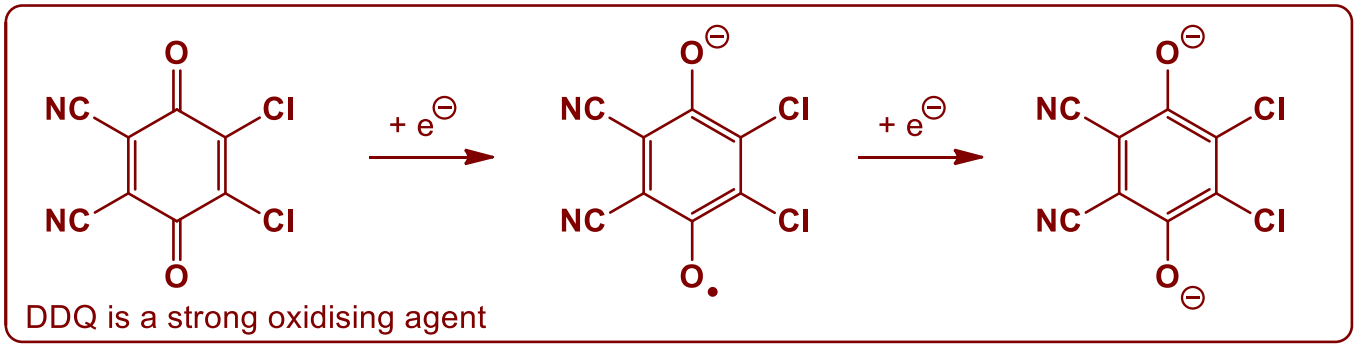

*Or*

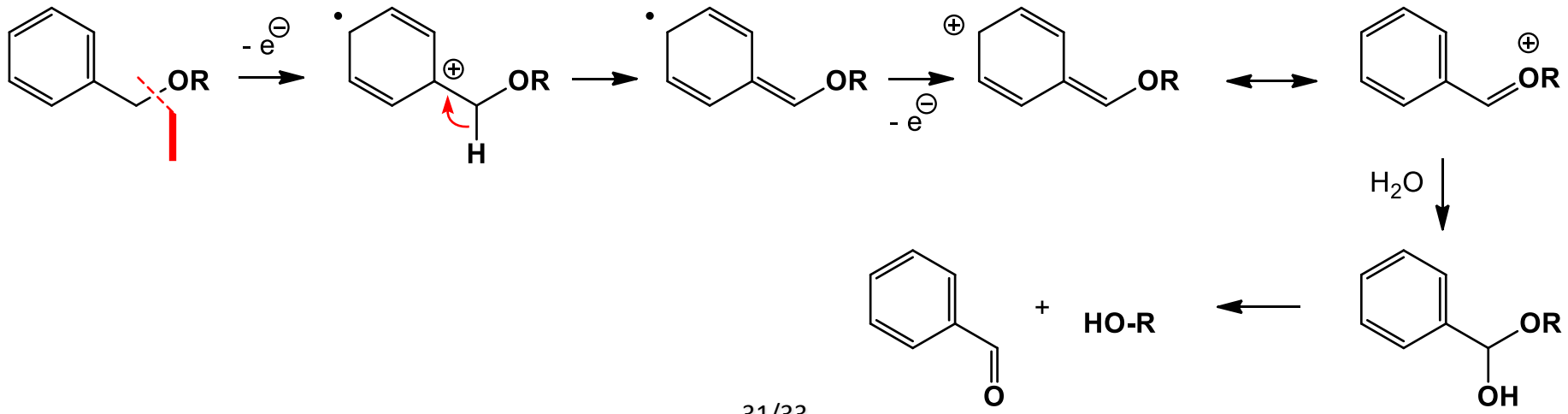


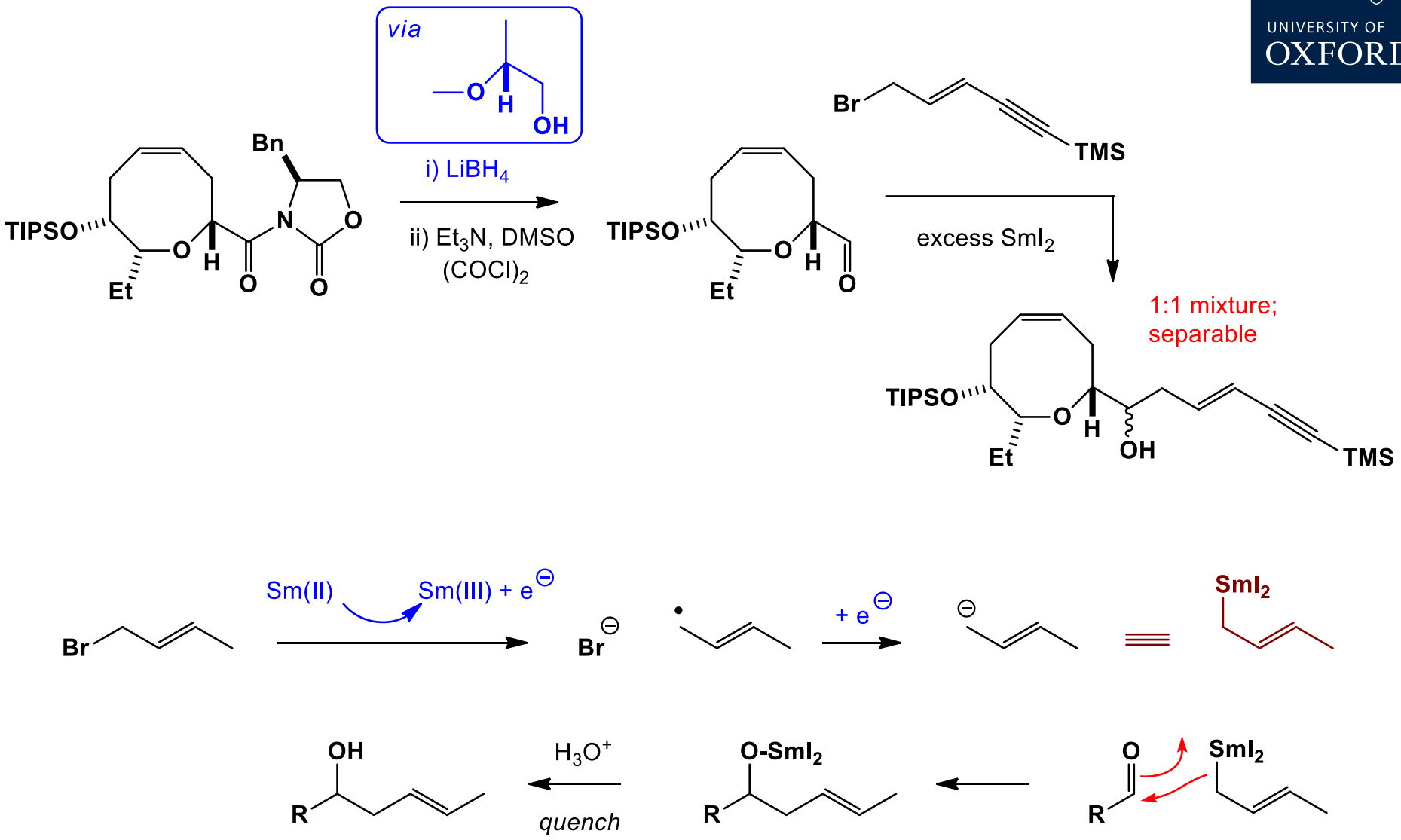

attack of **A** or **B** from the top face, leads to the OTHER diastereoisomer!

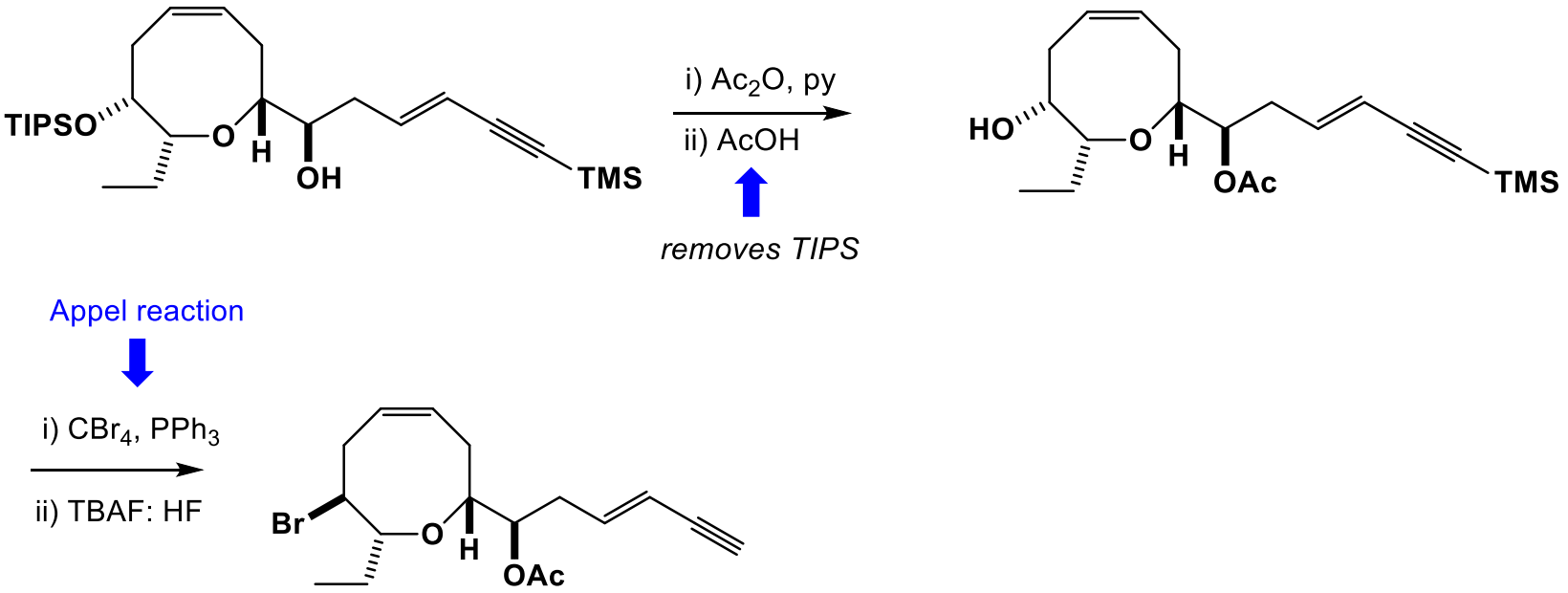

Et—MgBr
H
BnO---ZnBr
O
attack on top face
OH
OBn
Swern
Et3N, DMSO
(COCl)2
mechanism?
O
OBn
EtMgBr
ZnBr2
chelation control
OH
OBn
Br
CO2H
NaH
(2 eq.)
HO
O
O
Et
OBn
SOCl2 then
O
N
O
Ph
BnO
Ph
Et
O
N
O
O
O
Ph
O
N
O
O
O
Et
OBn
LDA then
I
same concept as before
BnO
Bn
Et
O
N
O
O
O
>20 :1 dr


Grubbs catalyst
cat. Ru=CHPh
ring closing metathesis
loss of CH2=CH2
deprotects OBn:
why not use H2, Pd-C?
i) DDQ
ii) iPr3SiOTf
pyridine
BnO
TIPSO
Bn
Et
H
N
O


NC
Cl
+ e⊖
DDQ is a strong oxidising agent


OR
- e⊖
H
H2O
HO-R
OH


via
i) LiBH4
ii) Et3N, DMSO
(COCl)2
excess SmI2
1:1 mixture;
separable
Sm(II)
Sm(III) + e
+ e
SmI2
H3O+
quench




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