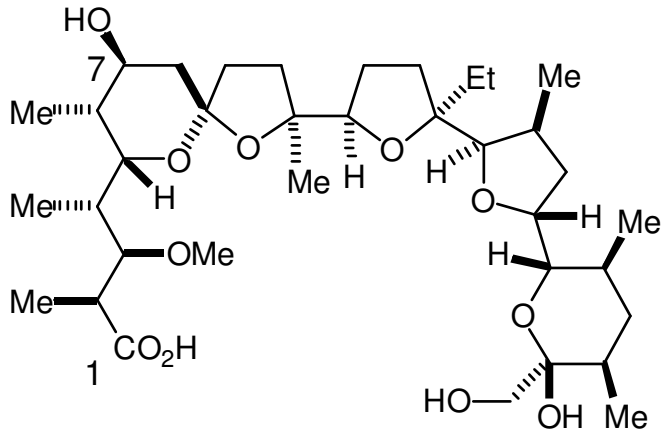
STRATEGIES IN SYNTHESIS

Professor T. J. Donohoe

MT 2006

6 Lectures: Tuesday at 10 am; Thursday at 9 am (weeks 6-8)
DP: Lecture Theatre

Monensin



Kishi *J. Am. Chem. Soc*, **1979**, *101*, 259.

A copy of this handout is available at:

http://users.ox.ac.uk/%7Emagd1571/finalpage/teaching2.html

Strategies in Synthesis

Synopsis

1) Introduction to synthesis: why do we want to synthesise molecules- what sort of molecules do we need to make?

What aspects of selectivity do we need to exert to accomplish a good synthesis (chemo-, regio- and stereoselectivity)

2) Protecting group chemistry is central to any synthetic effort (examples)

3) Retrosynthesis- learning to think backwards (revision from first year).
Importance of making C-C bonds and controlling oxidation state.
Umpolung

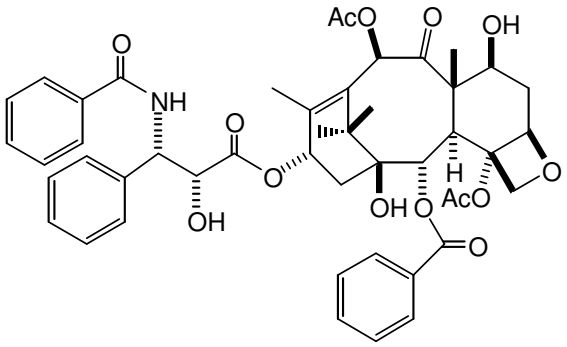
4) Examples of retrosynthesis/synthesis in action.

5) Handy hints for retrosynthesis

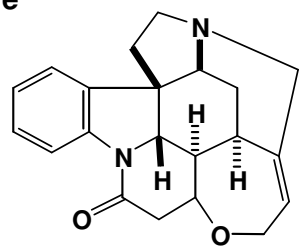
Recommended books:
General: Organic Chemistry (Warren et al)
Organic Synthesis: The Disconnection Approach (S. Warren)
Classics in Total Synthesis Volumes I and II (K. C. Nicolaou)
The Logic of Chemical Synthesis (E. J. Corey)

1) Why do we want to synthesise complex molecules?

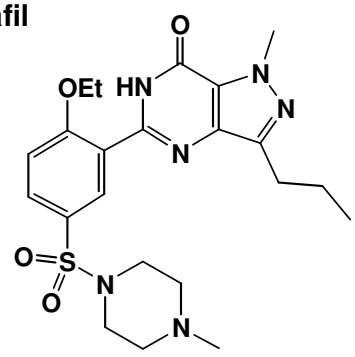
Taxol



Strychnine



Sidenafil



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

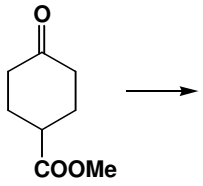
1) Carbon

2) Functional

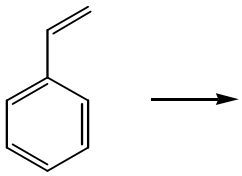
3) Stereochemistry

In order to control 1) and 2)

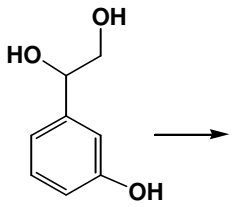
Chemoselectivity



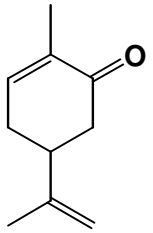
Regioselectivity



Protecting group strategy

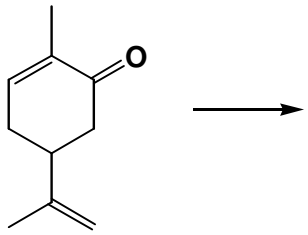


A) CHEMOSELECTIVITY

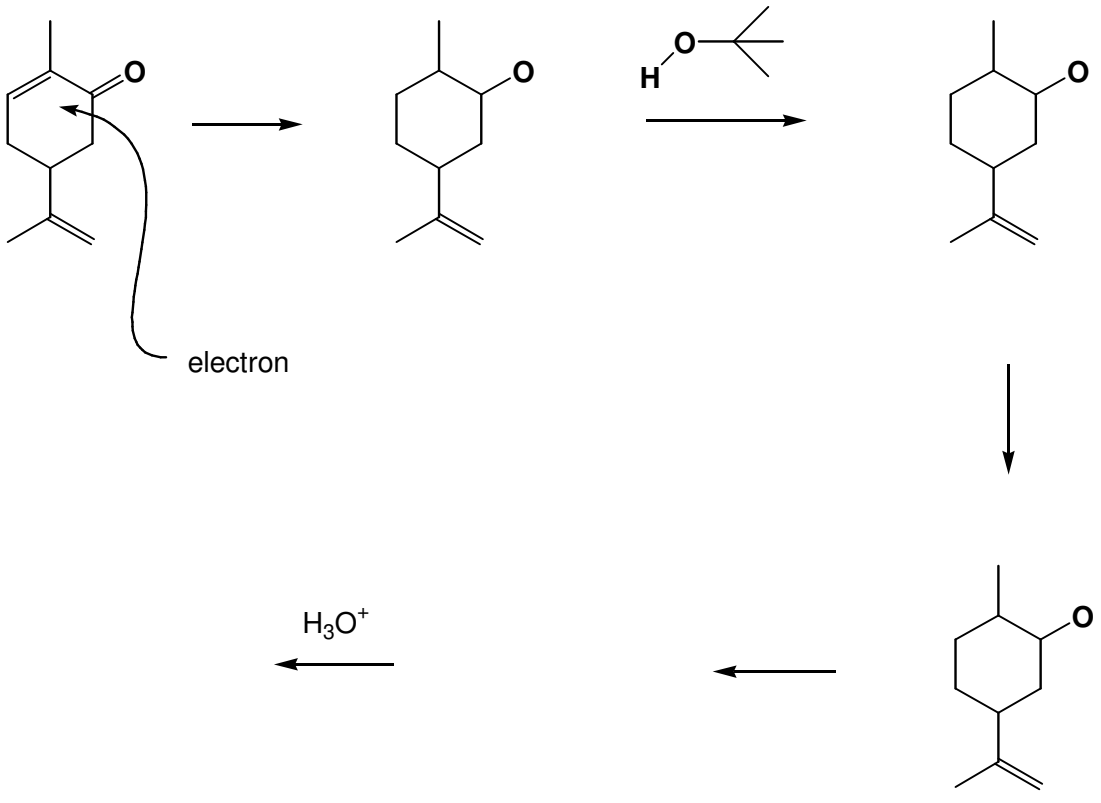


Using different tactics we can reduce each of the

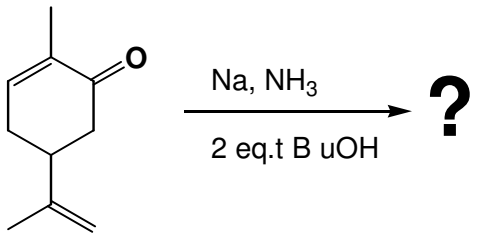
a) H_2, Pd-C. This reagent is sensitive to steric



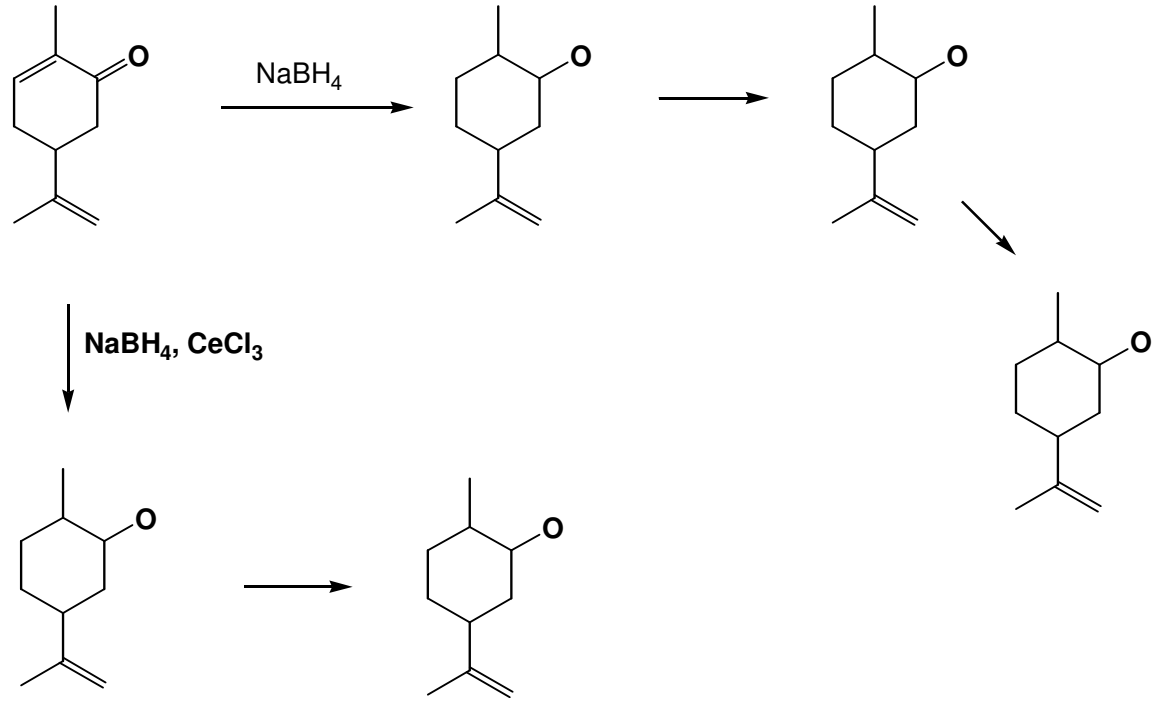
b) Na, NH_3, tBuOH (1 eq.)



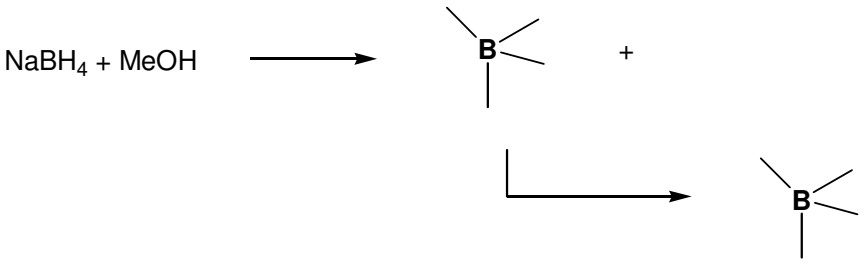
Q. What would happen if we added >2 eq. of tBuOH?



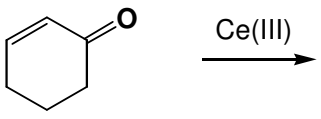
c) $NaBH_4$, $CeCl_3$ (Luche reduction)



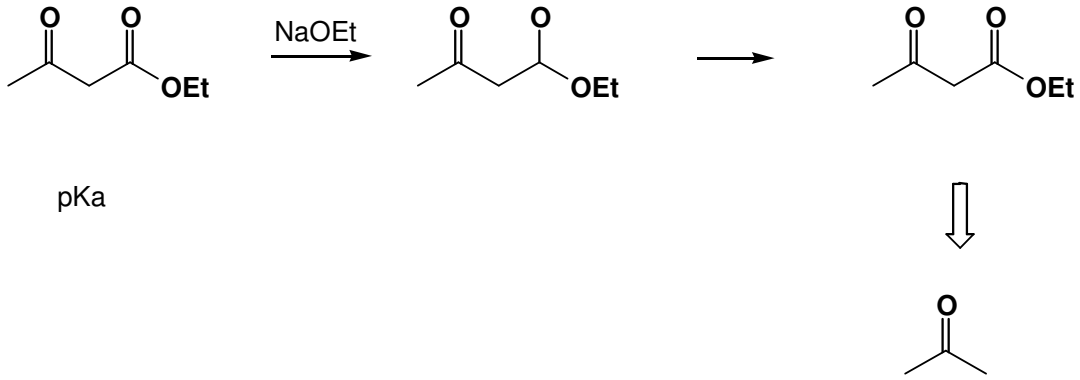
What does $CeCl_3$ do to sodiumborohydride?



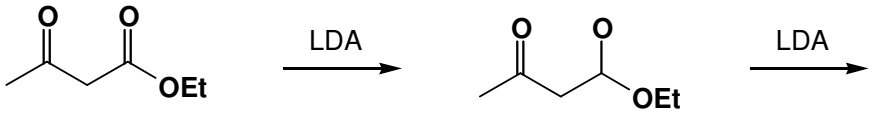
This process is promoted by

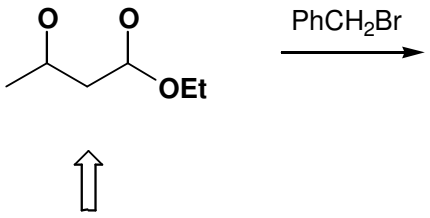


B) REGIOSELECTIVITY



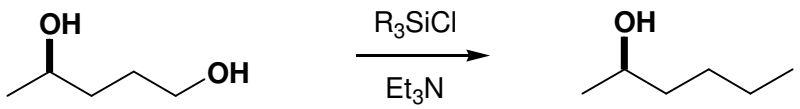
How to influence regioselectivity by

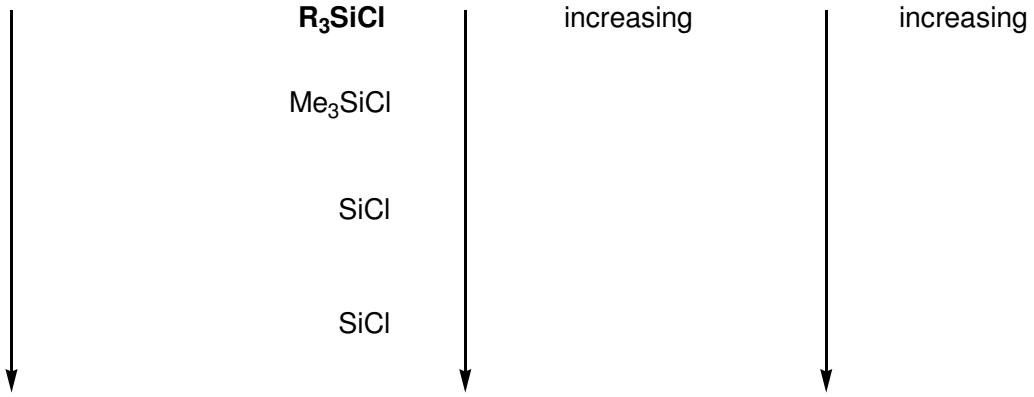




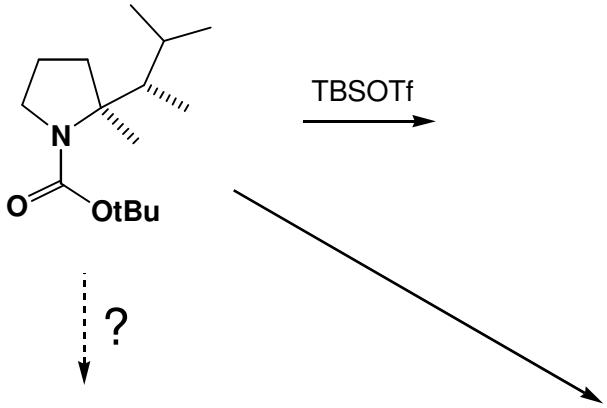
LDA=

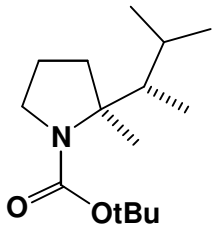
C) PROTECTING GROUPS (are essential to most syntheses)





There are tactics for protecting the least and the most hindered groups.



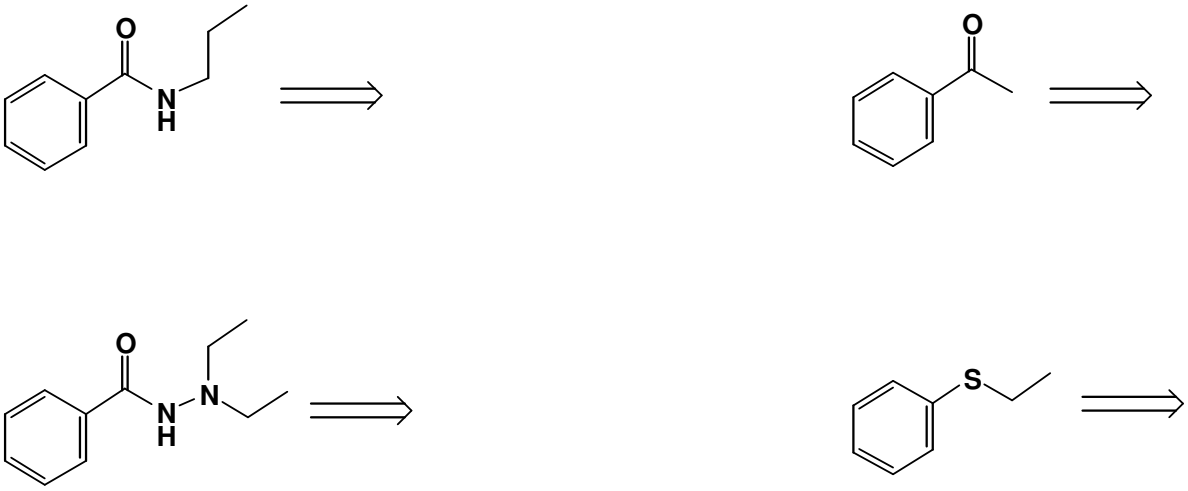


RETROSYNTHESIS

The theory (Corey- Nobel prize

1) Think about reactions in reverse

2) Use disconnections to break down molecules

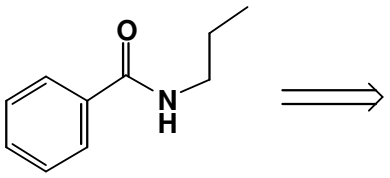


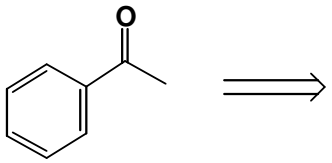
Make sure that your disconnections correspond to known and

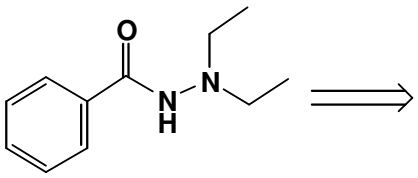
3) Synthons: These are simply

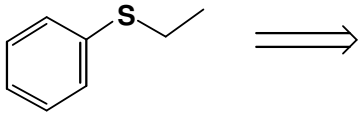
There are two ways of analysing a single

A number shows the position of the charge relative to the





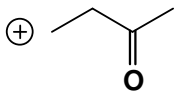


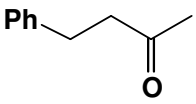


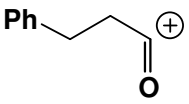
You have to decide which synthon is realistic and

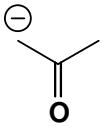
Remember the concept of UMPOLUNG is helpful (especially) with carbonyl groups:

1) Normal reactivity of the carbonyl group

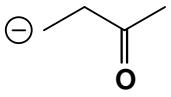


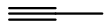


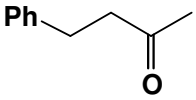


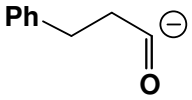


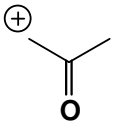
2) Use **UMPOLUNG** to reverse the reactivity of the carbonyl group







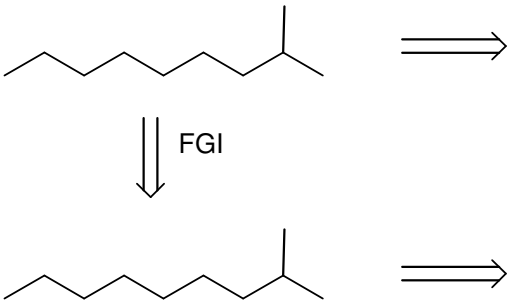




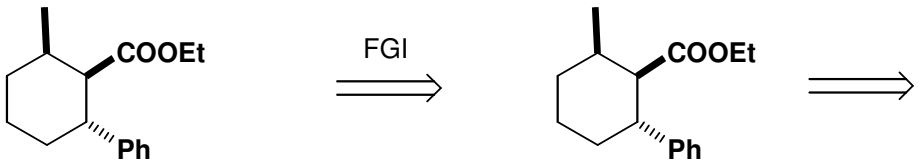
The hard part is choosing a particular disconnection (from several others) in a complex molecule.

4) Sometimes functional group interconversion on the target helps

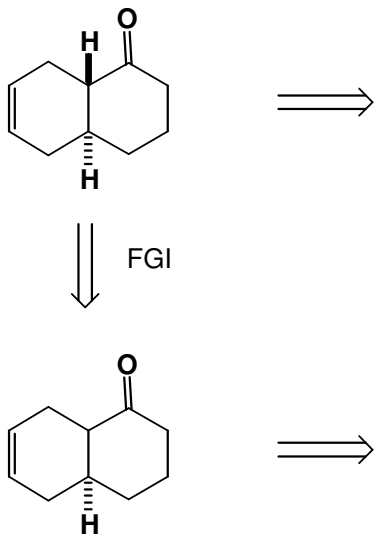
Simple



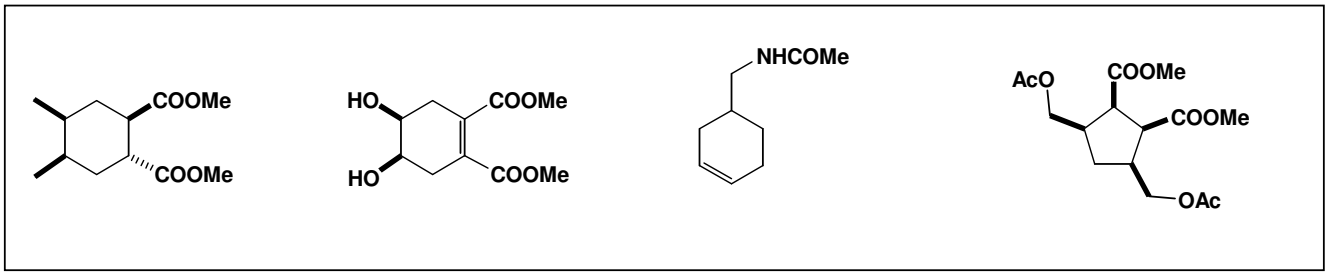
More difficult



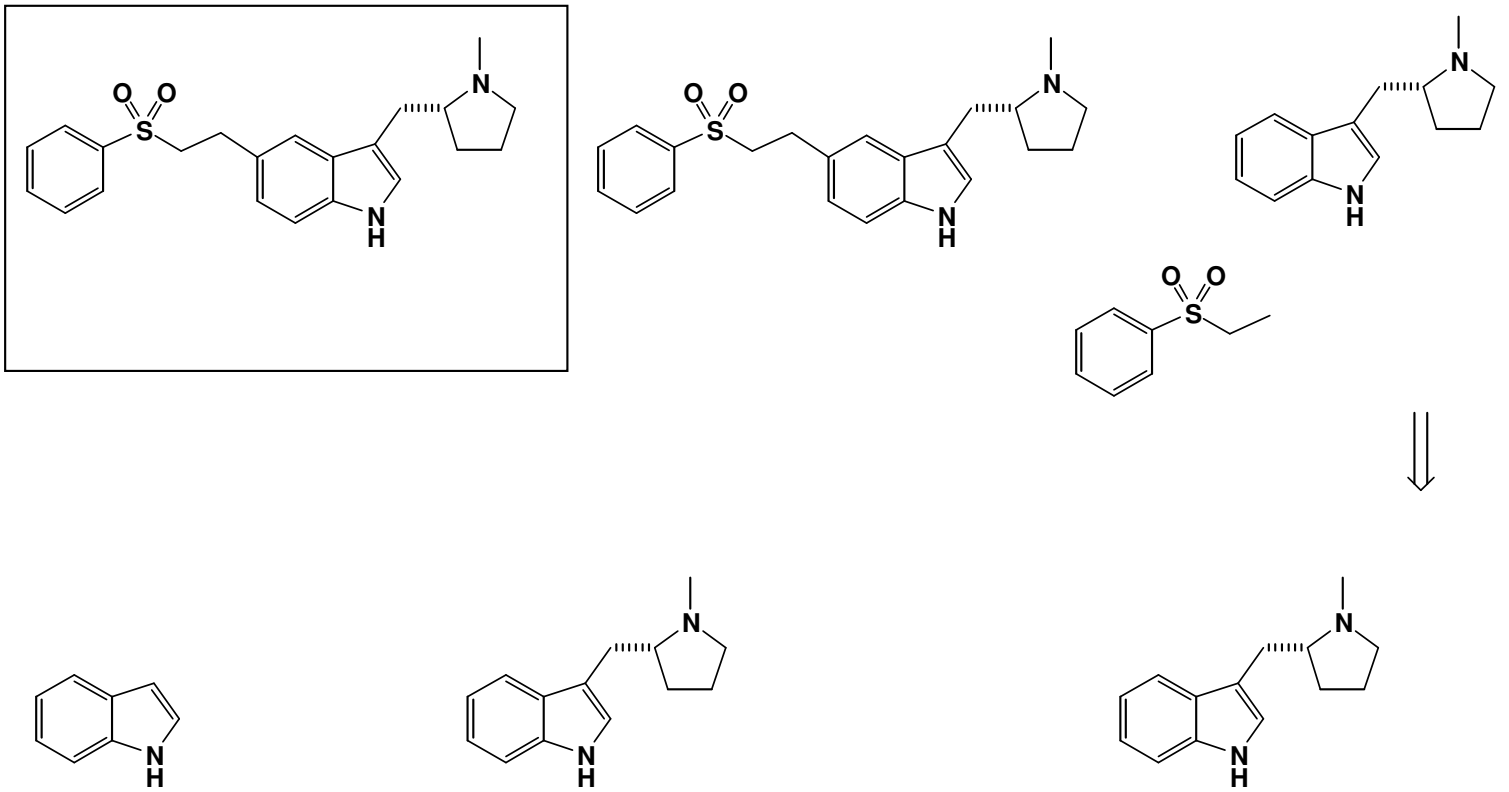
Even stereochemistry can be altered in this way.



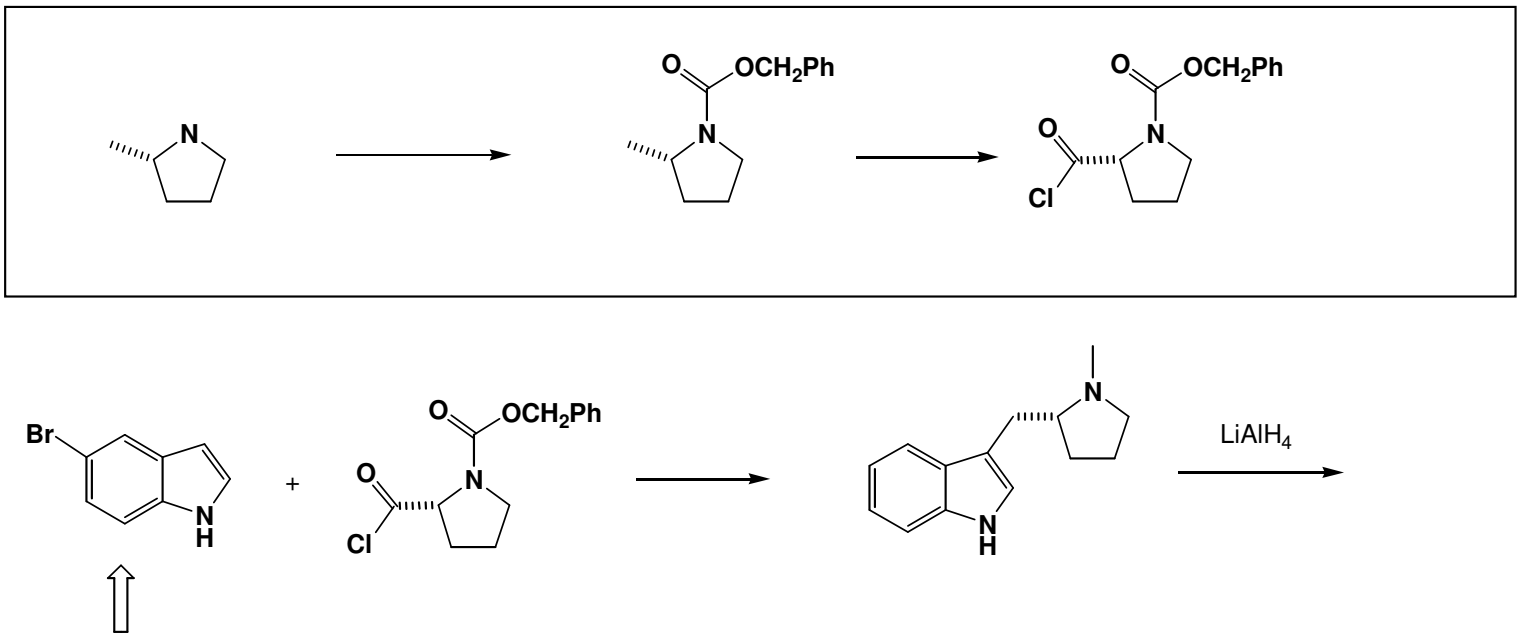
Some problems: How would you synthesise the following? (Hint: think about Diels Alder)

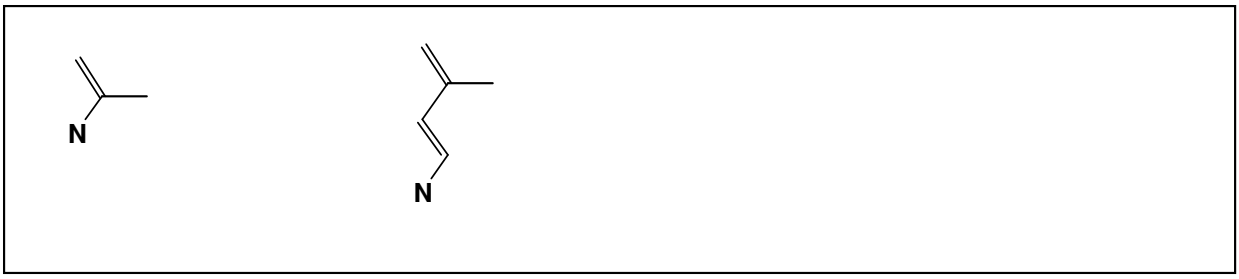


Synthesis 1) Eletriptan (Pfizer) Migraine

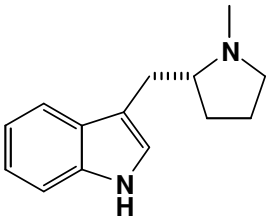
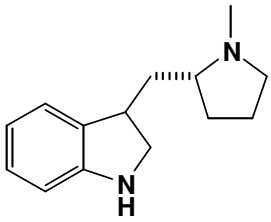
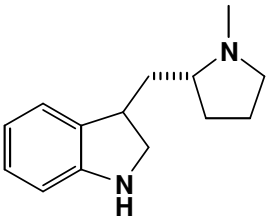
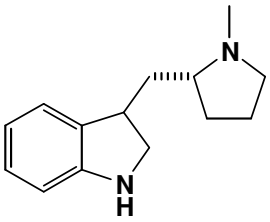
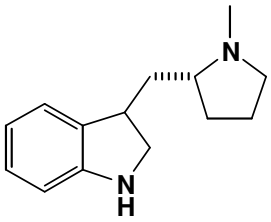
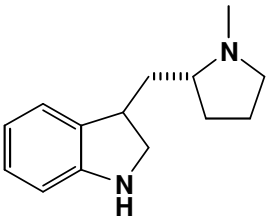
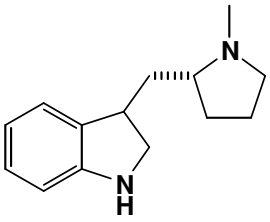
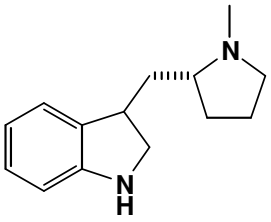
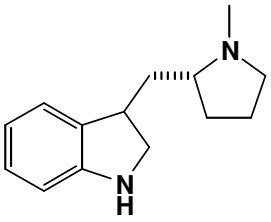


The synthesis:

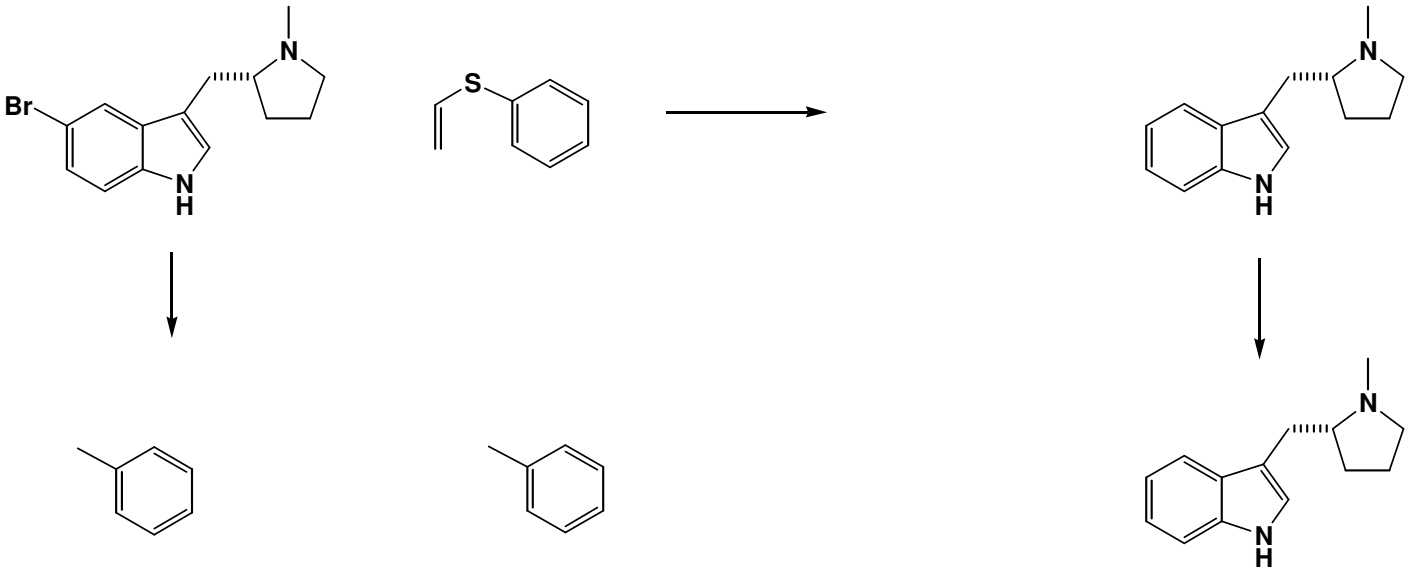




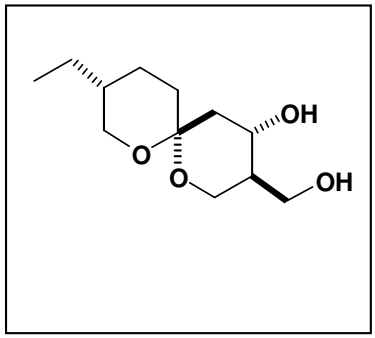
Mechanism for this step is:

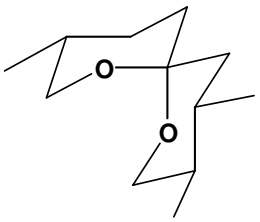










To finish the synthesis



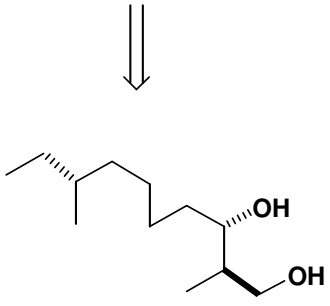
Synthesis 2) Talaromycin B (Schrieber, *Tetrahedron Letters*, 1983, P4781)



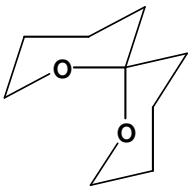


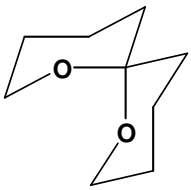
1) Most substituents on each ring are

2) The only axially disposed groups are

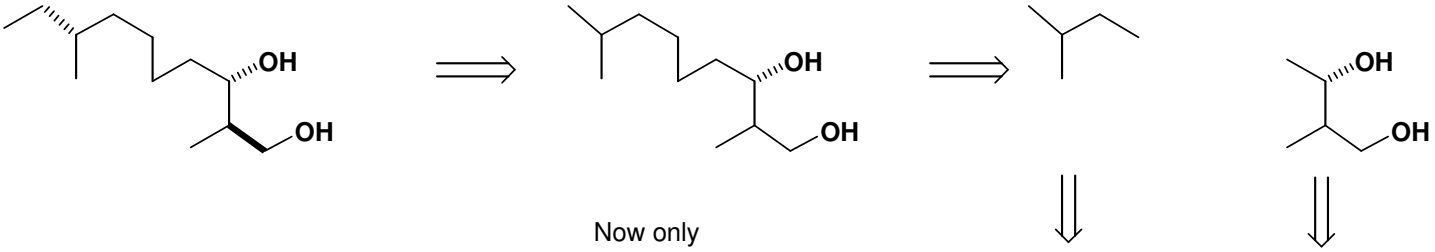


3) The ANOMERIC



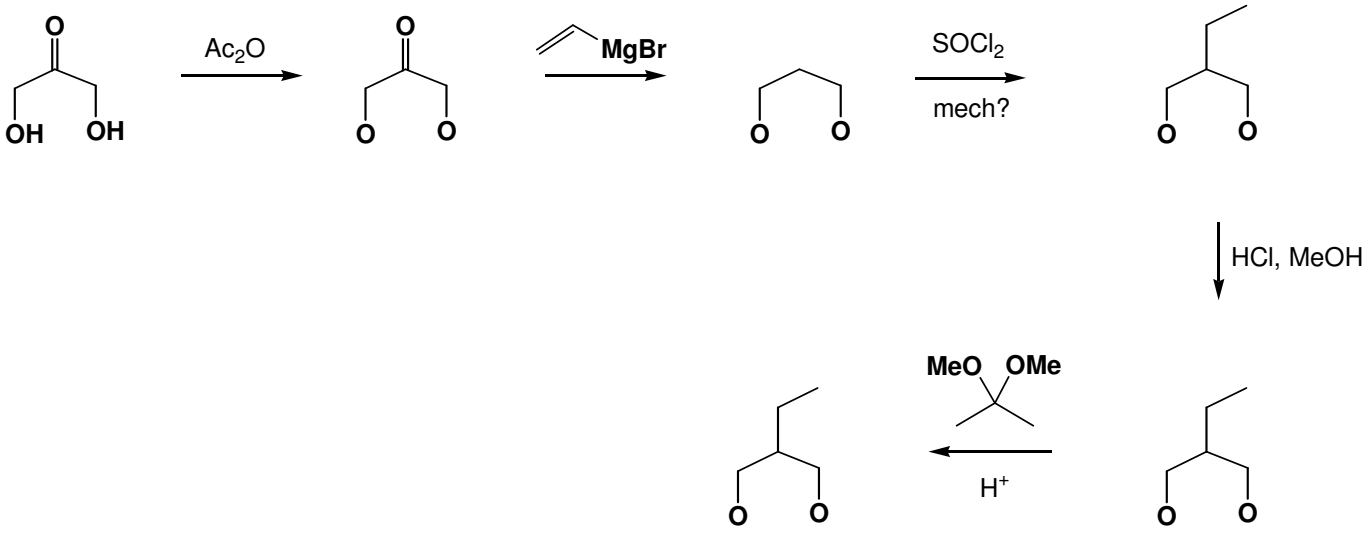


Further disconnections are possible

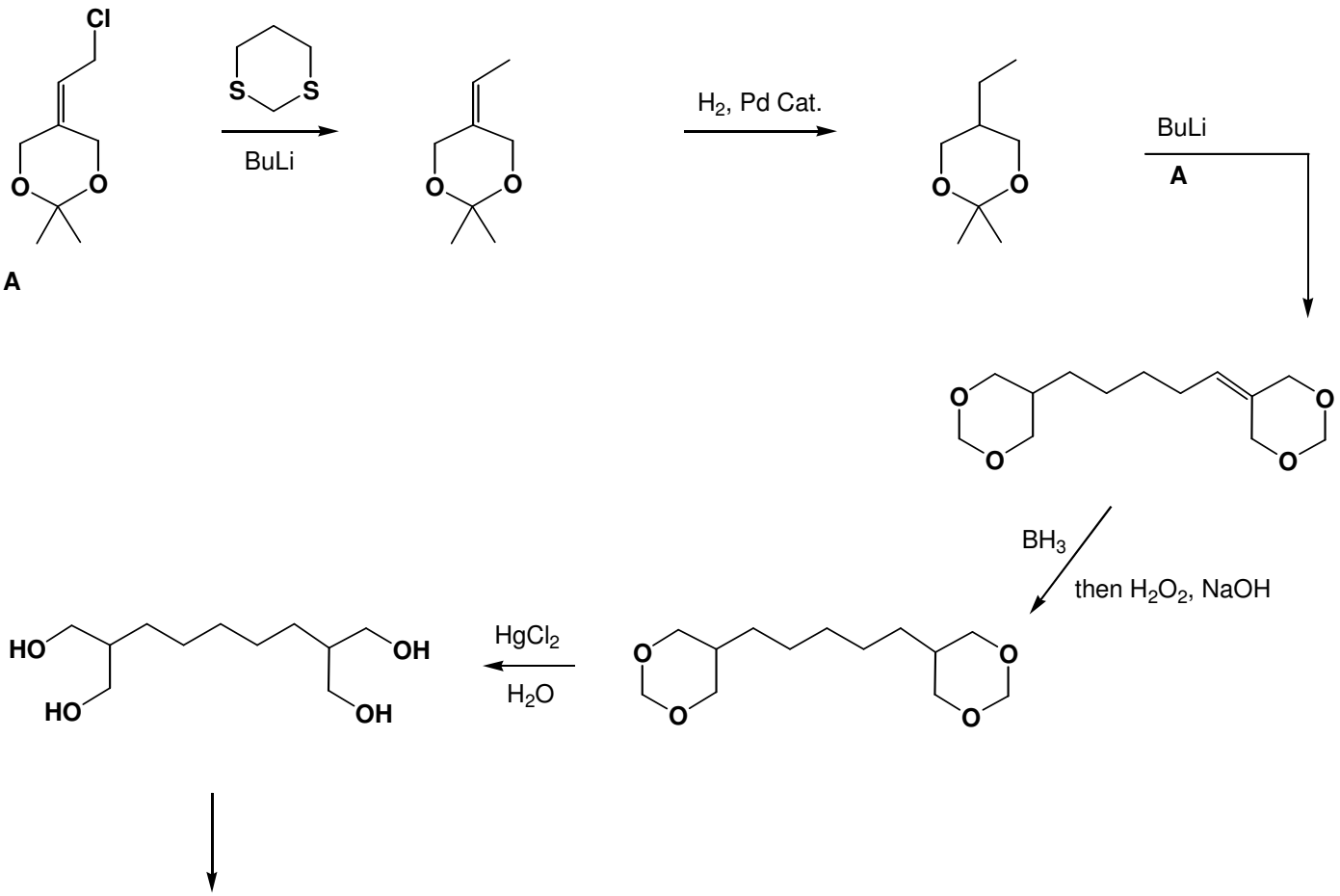


The synthesis in full:

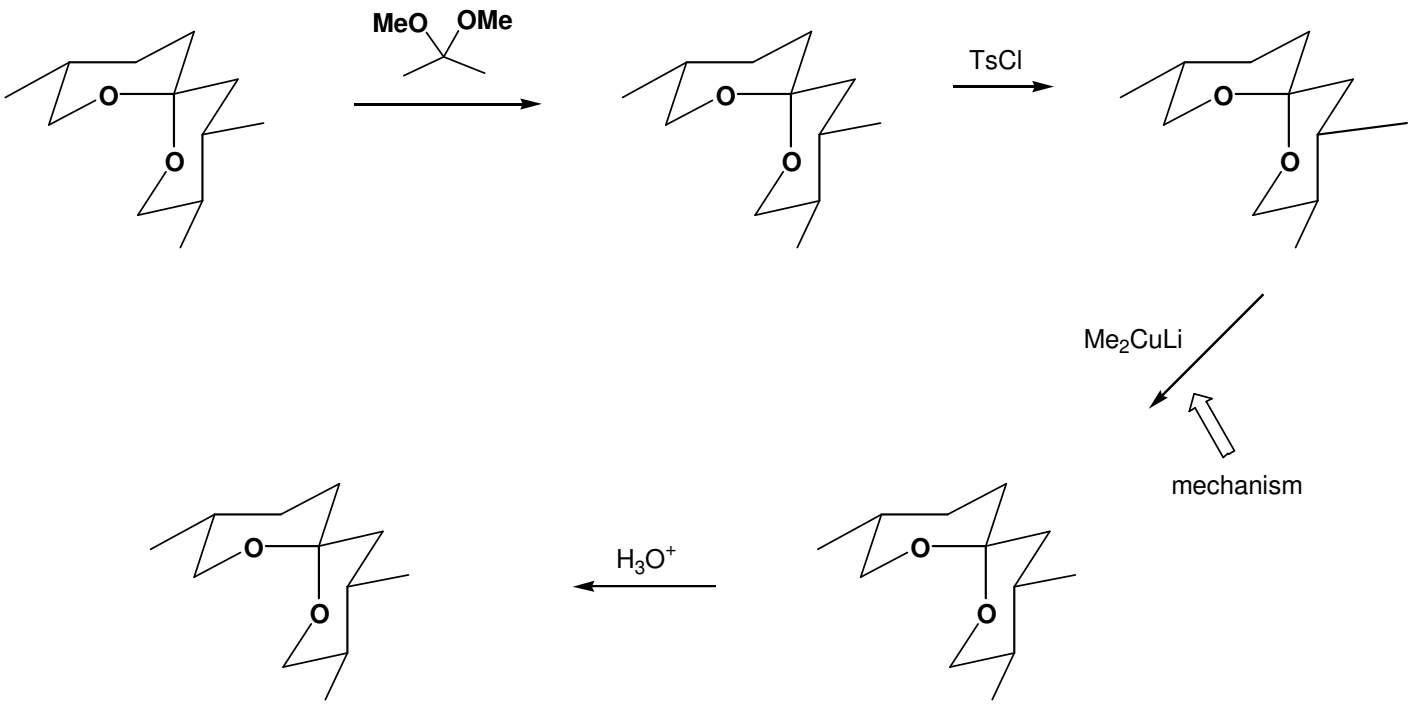
1) Preparation of the starting materials



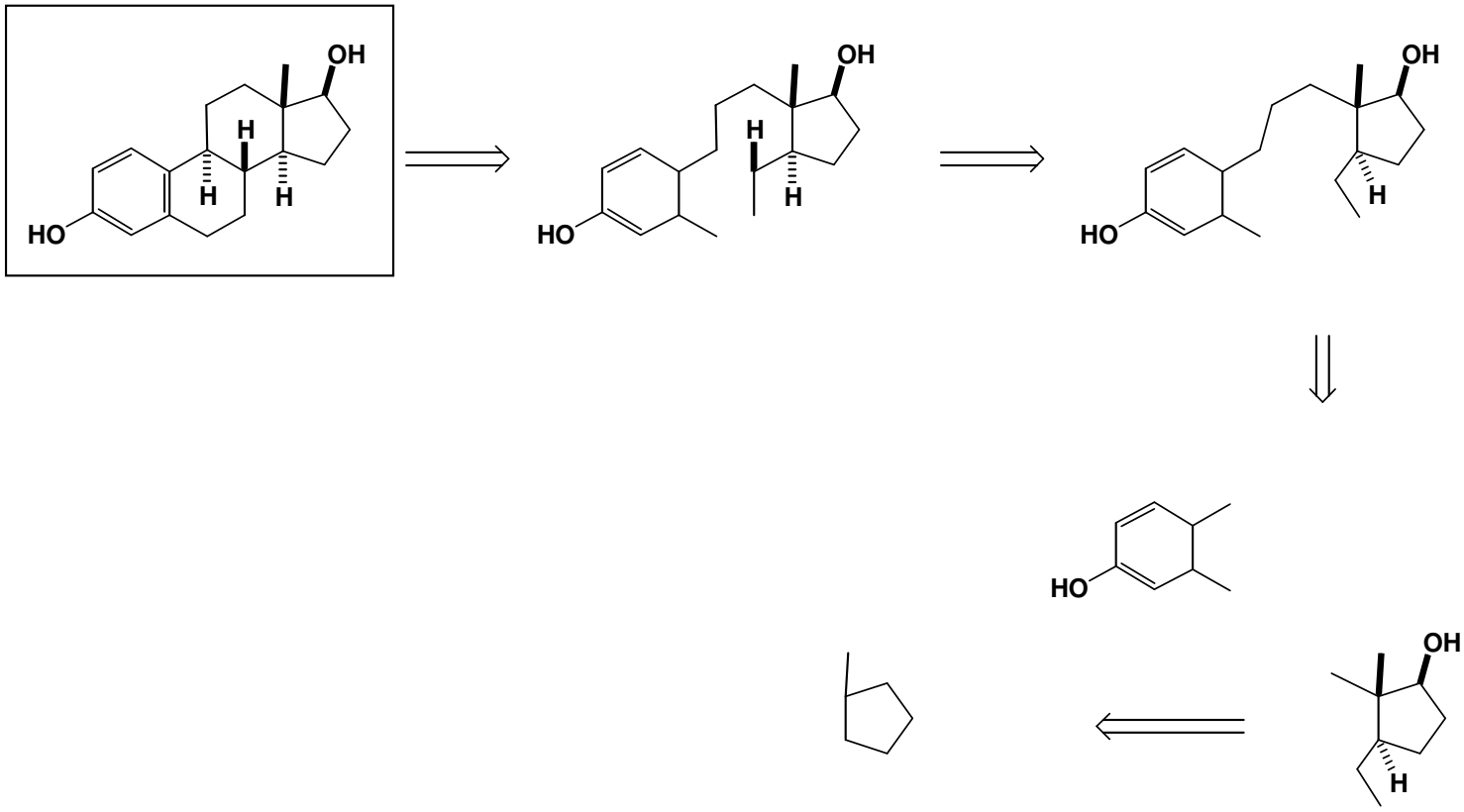
Putting these pieces together:


Cl
A
S
S
BuLi
O
O
H2, Pd Cat.
BuLi
A
BH3
then H2O2, NaOH
HO
OH
HO
OH
HgCl2
H2O

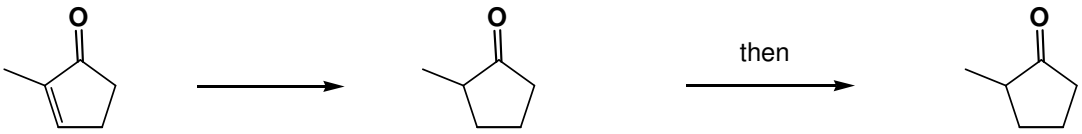
And finally,


MeO
OMe
TsCl
Me2CuLi
mechanism
H3O+

Synthesis 3) Estradiol (*Helvetica Chimica Acta*, 1980, **63**, 1703)

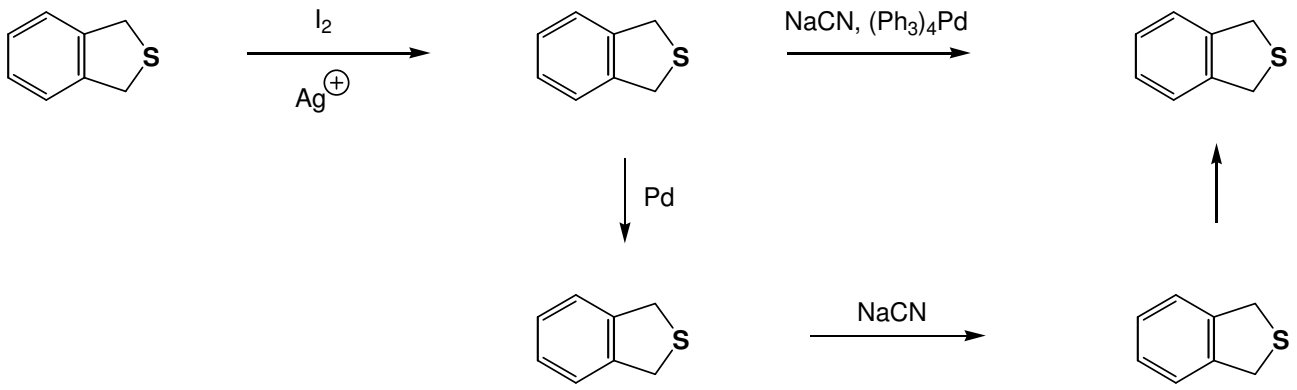


Now the synthesis.

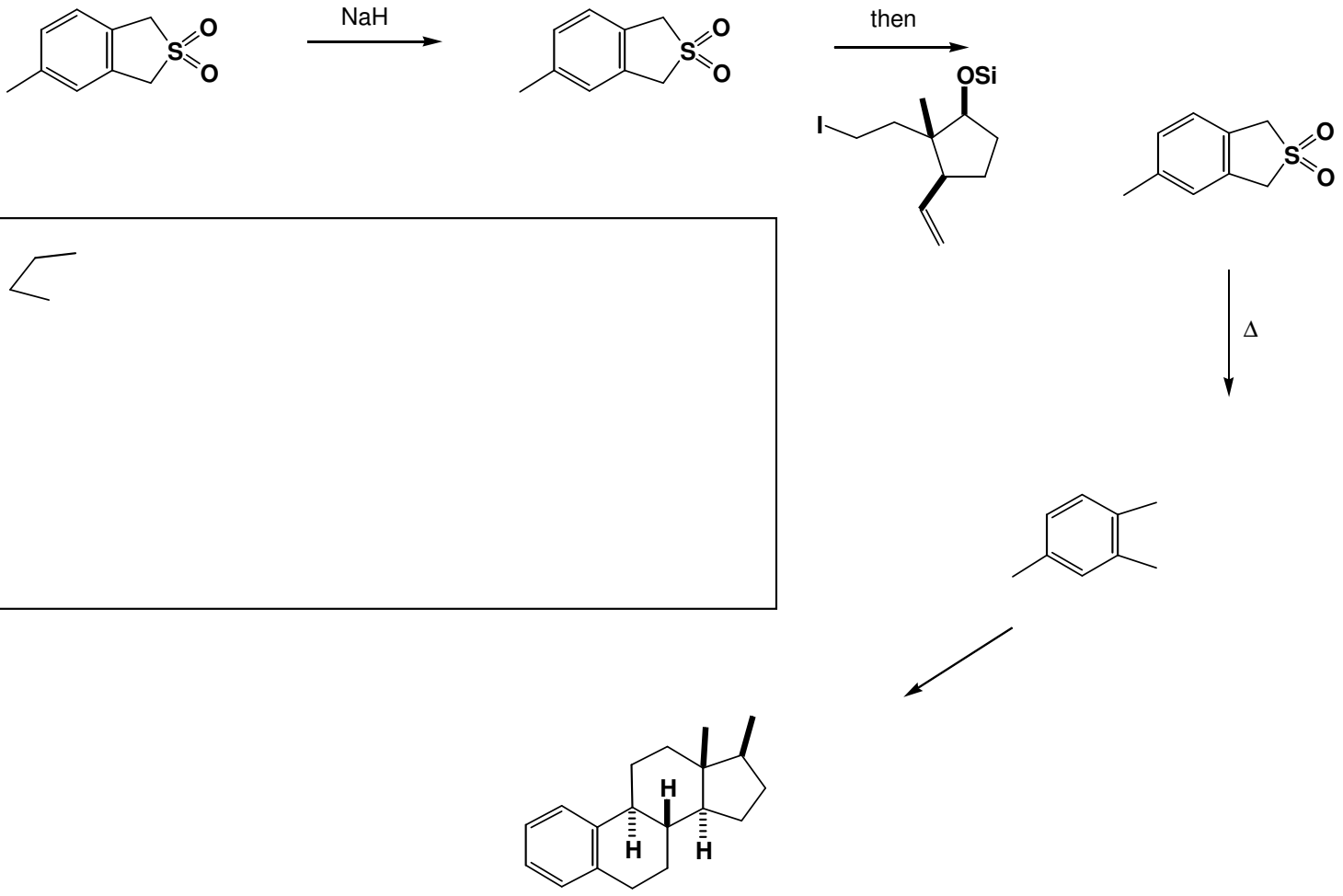


think about relative

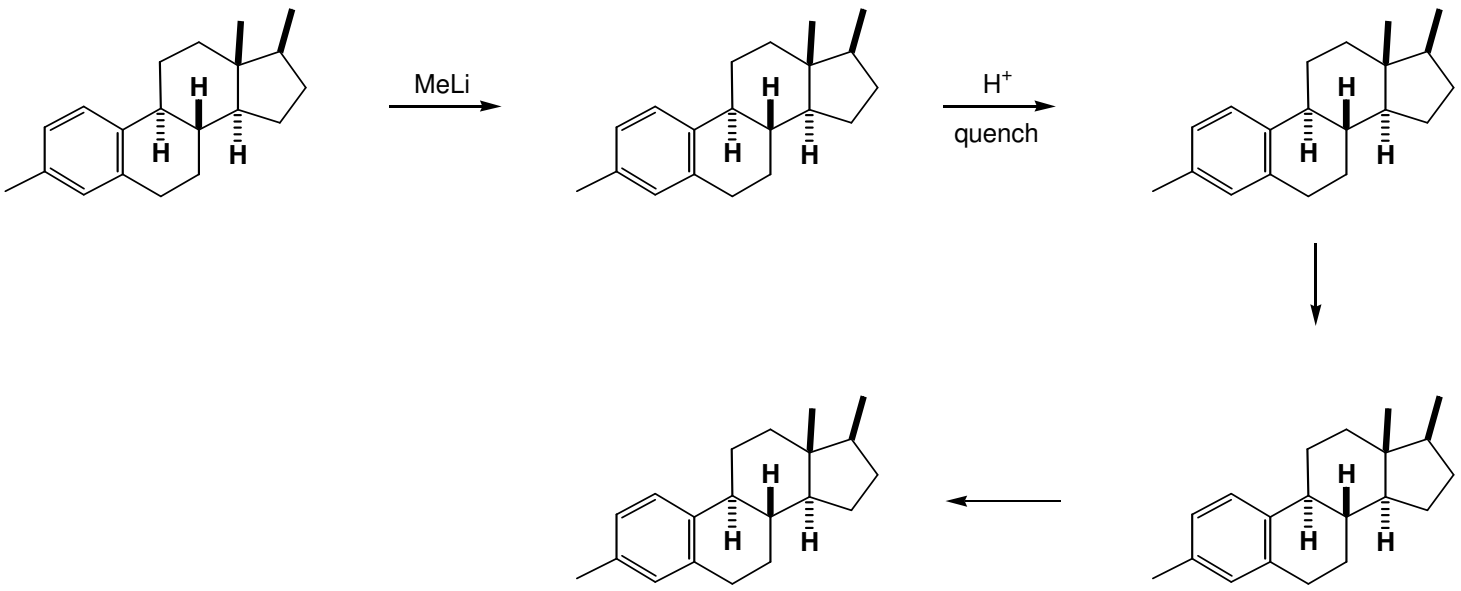
The other half:



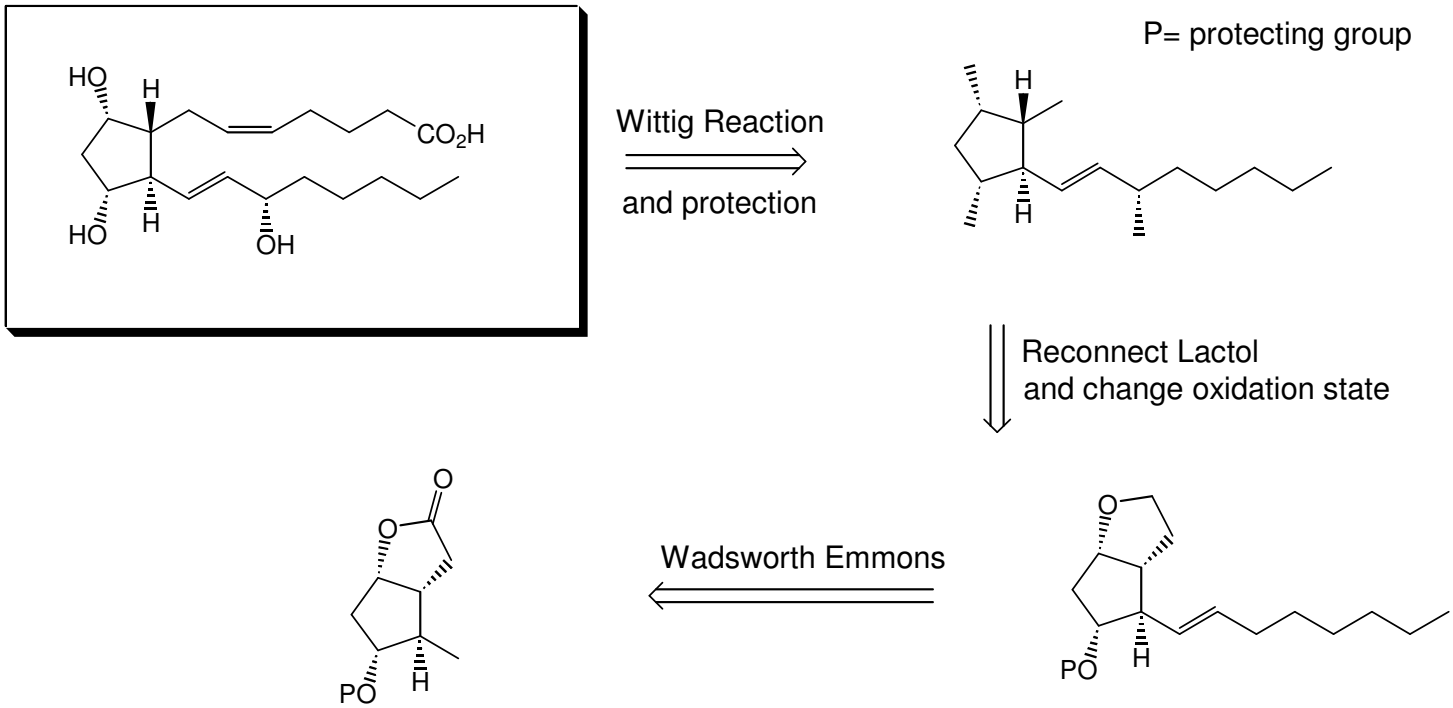
The end-game



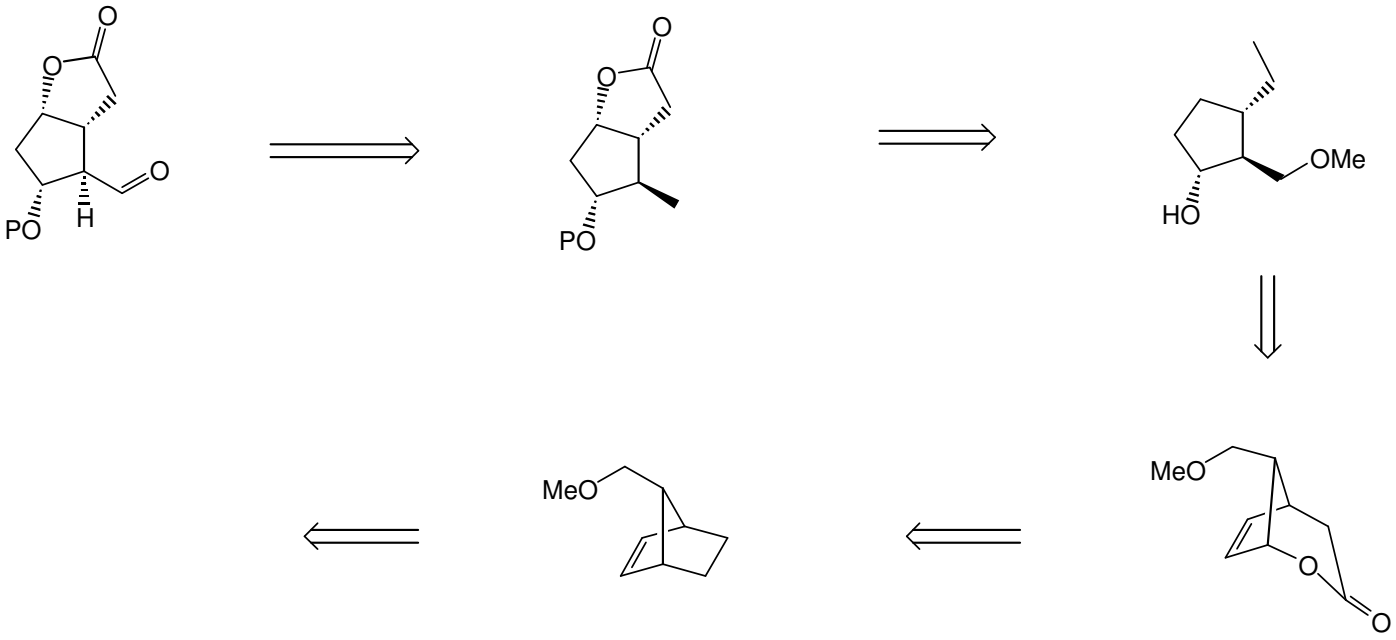
And finally,



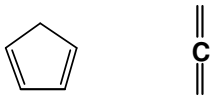
Synthesis 4) Prostaglandin $F_{2\alpha}$ (*Journal of the American Chemical Society*, 1969, P5675) E. J. Corey



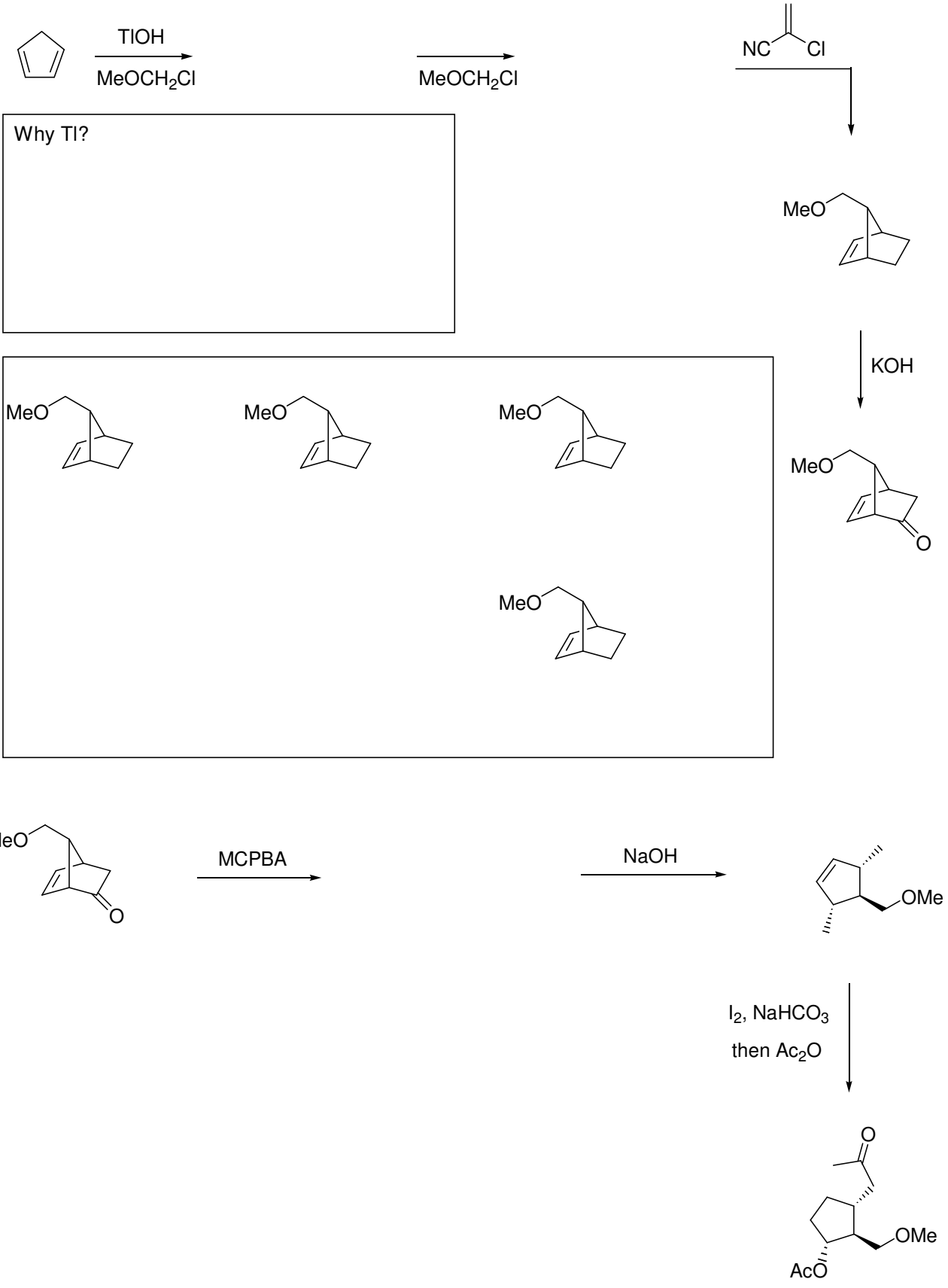
AND



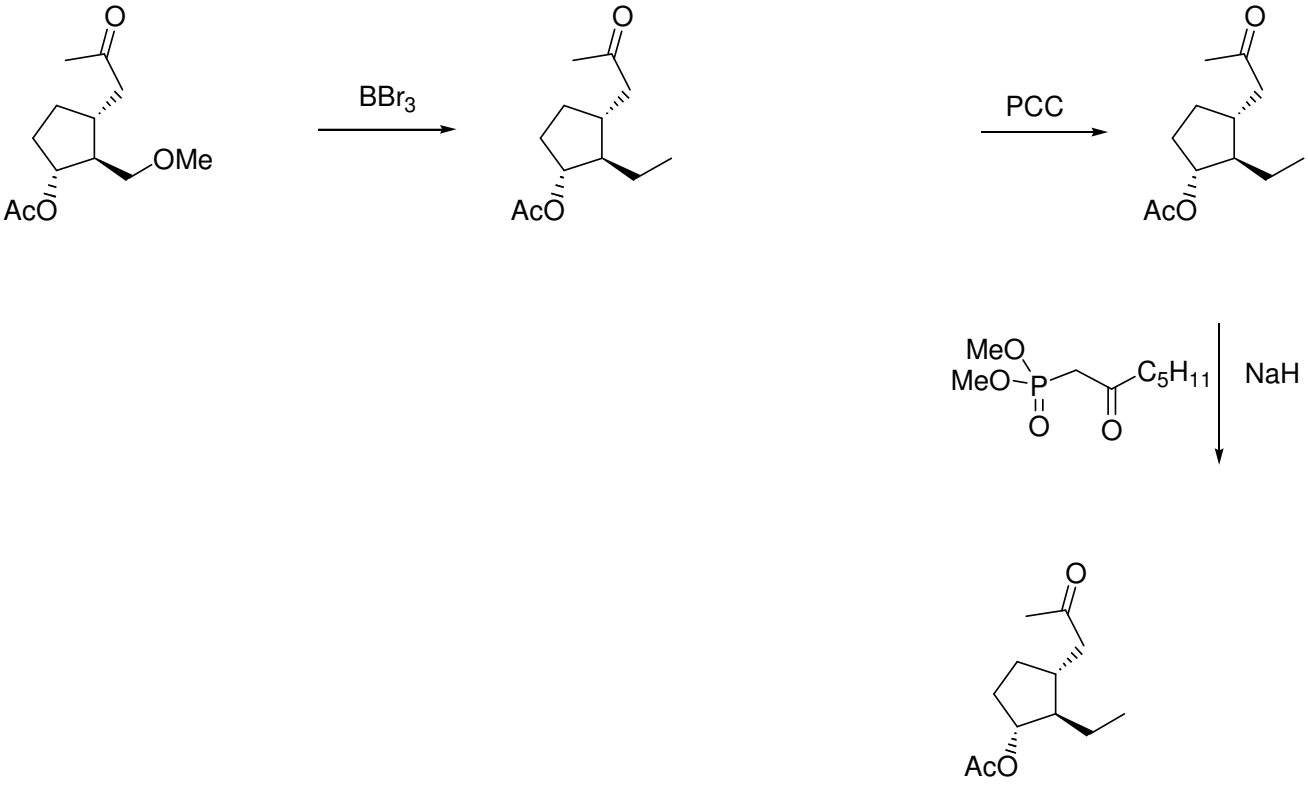
Problem:



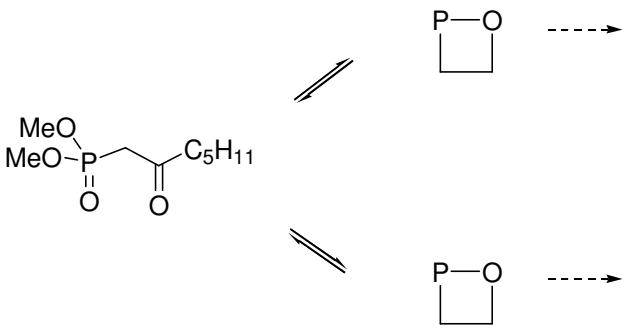
The synthesis:


TlOH
MeOCH2Cl
MeOCH2Cl
NC
Cl
Why Tl?
MeO
KOH
MeO
MeO
MeO
MeO
MeO
MeO
O
MCPBA
NaOH
OMe
I2, NaHCO3
then Ac2O
O
OMe
AcO

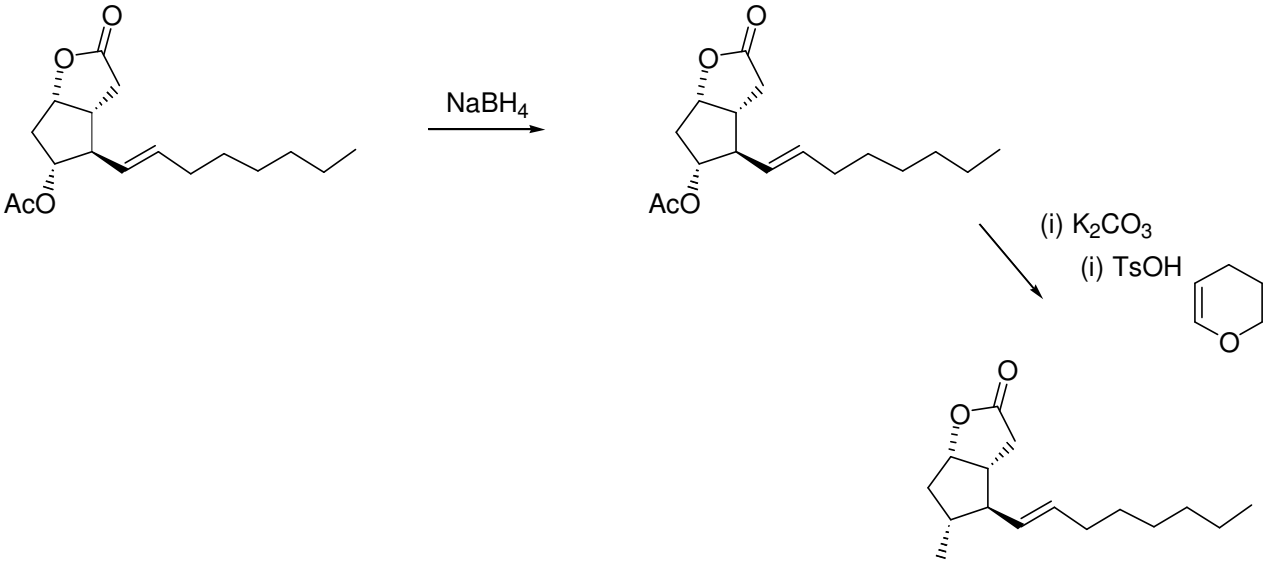
mechanism of iodide reduction:

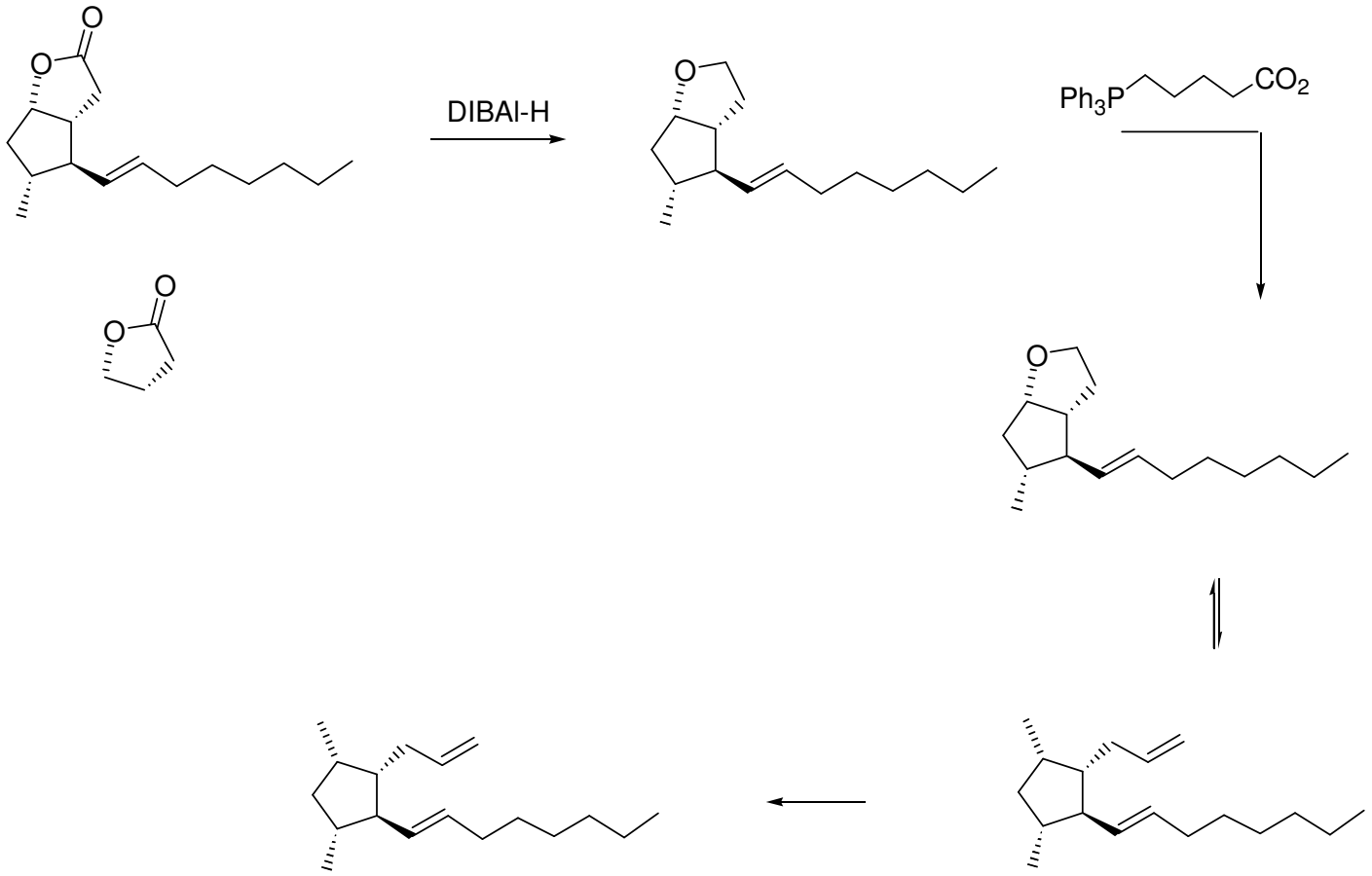


Why do

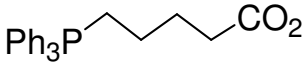


Reduction of the C=O bond

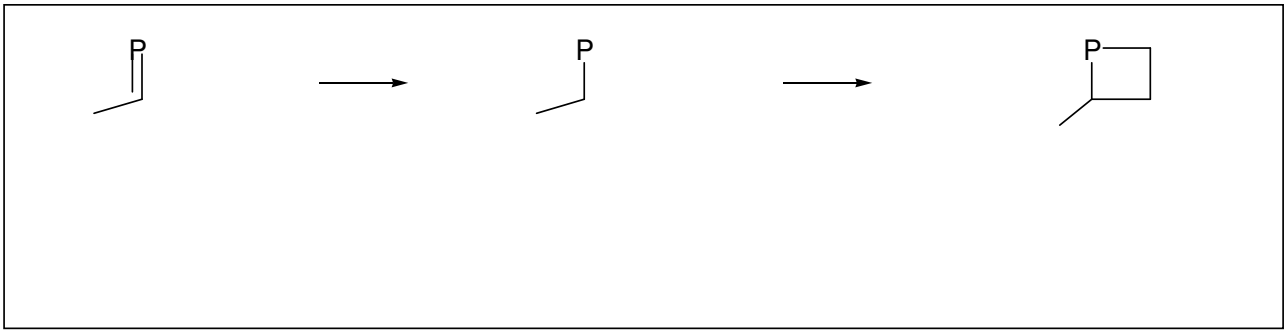




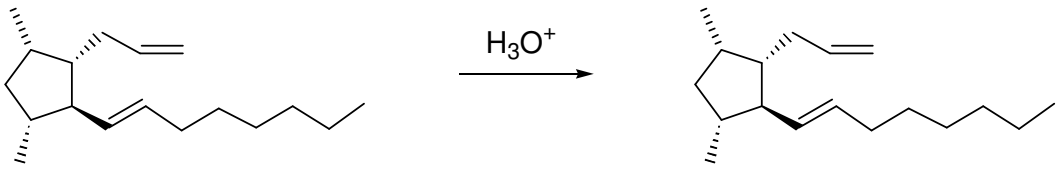
How do you make the ylid?



Why do non-stabilised



Finally, to complete the synthesis:

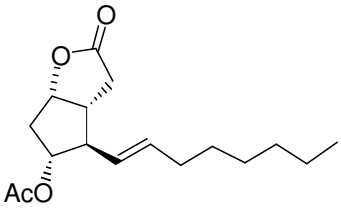


Some handy hints for retrosynthesis

1) Make the synthesis

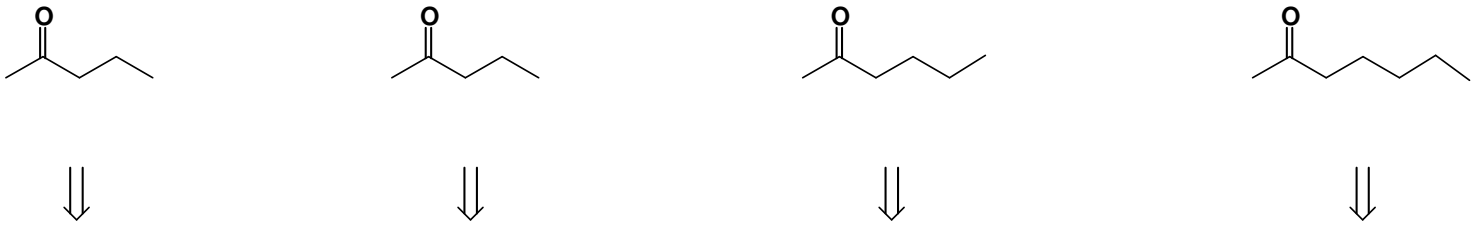
Use convergent rather than

2) Use only disconnections corresponding to

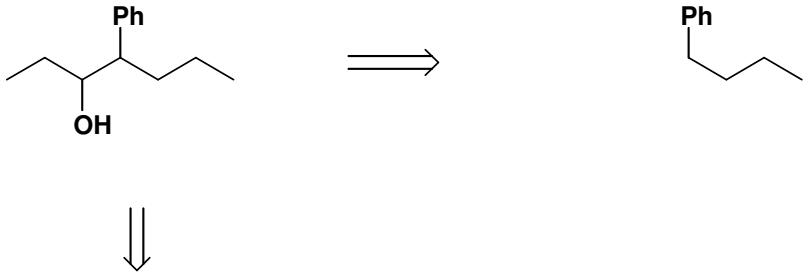


3) Disconnect C-X bonds wherever possible (this includes RCO

4) Disconnect C-C bonds by using nearby functional groups or by



Also, it makes more sense to disconnect in the middle



5) Disconnect back to readily recognisable

Some problems to think about:

Disconnect the following and then devise forward syntheses: