Strategy of Synthesis

How do we assess the quality of a synthesis?

- **Number of steps** - lower the better (usually) - there are various methods for decreasing the number of reaction steps.
    - **Two directional synthesis** performs two identical reactions simultaneously which can be useful if there is useful symmetry in the molecule.
    - **Tandem or cascade reaction sequences** are those where reactions occur in succession without the need to isolate individual intermediates. These processes are even better when they can be performed in 'one-pot'.
- **High yielding reactions** - clearly the higher the yield of each step, the higher will be the overall yield across the reaction sequence.
- **High levels of selectivity** - the more chemo-, regio- and stereoselective each step the better.
- **High levels of *atom economy***. This term was introduced by Trost and refers to the fact that it is desirable to maximise the number of atoms from *all* raw materials which end up in the final product.
    - A reaction is highly atom economical if equimolar amounts of reagents react to form exclusively the desired product with no by-products *and* that all the atoms incorporated in the product are required - the Diels Alder reaction is a good example.
    - Compare two methods of enantioselective synthesis:
        1. Chiral auxiliary approach. First attach the auxiliary to the substrate, then carry out the stereoselective reaction and finally remove the auxiliary (recycle if possible).
        2. Use of a chiral catalyst. No modification of the substrate is required (reduces steps) and the stereodirecting group (the catalyst) is used in sub-stoichiometric amounts (and is even better if it can be recycled). This is clearly the more atom economical process.
- **Low cost** - it is clearly desirable to carry out reactions using readily available, cheap reagents and under mild reaction conditions. This last point is becoming more important in large scale synthetic processes.

More Subjective Answers

- Creativity and elegance of synthesis
- The approach involves practical and convenient steps
- Flexibility - difficult to quantify but very desirable
- Environmentally friendly - 'green' chemistry is becoming increasingly important. Synthetic routes which avoid the use of large excesses of toxic compounds and laborious purification procedures requiring large volumes of solvents and silica gel are desirable. Production of unwanted side-products should be avoided. This becomes more important on scale-up, but processes should be designed “green” from the beginning in the research lab.

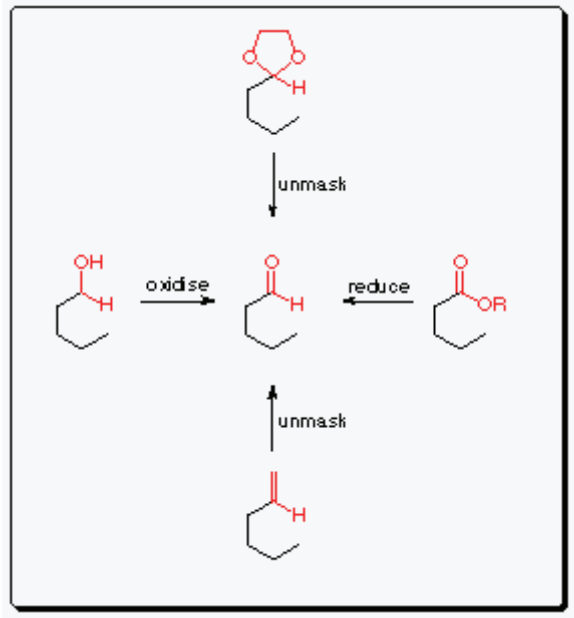
Retrosynthetic analysis

The constant goal of a retrosynthetic analysis should be to reduce the molecule to similarly sized building blocks of lower or similar complexity. This simplification should be continued until you reach molecules which are commercially available.

The two main operation of a retrosynthetic analysis are: 1) Functional group interconversions (FIG) and 2) bond disconnections.

Functional group interconversion (FGI)

Many functional groups can be interconverted into each other, e.g. oxidation of an alcohol gives an aldehyde, further oxidation a carboxylic acid. Many organic transformations can be used to do FGIs. Carbonyl groups are particular useful in this respect. The reactivity of the carbonyl group can be masked during synthesis as double bond (ozonolysis for FGI into aldehyde) or dioxolane until needed.



Disconnection of covalent bonds

The key step(s) in many syntheses is (are) bond formation. In planning a synthesis the reverse bond disconnection helps to identify suitable synthetic routes. There is no general way to disconnect a molecule; each retrosynthetic problem requires its individual creative solution. Retrosynthetic analysis and planning of syntheses needs experience and training. The more reactions and their scope someone knows, there more options for synthetic routes he or she has.

There are some general features of a molecule that can guide the analysis:

1) **Pattern of oxygenated carbon atoms.** If Carbonyl- and/or hydroxgroups are found in a 1,3 or 1,5 pattern, this gives a hint to use one of the classical carbonyl reactions for synthesis. Aldol reaction and Claisen condensation give 1,3 dioxygenated structures, Michael additions lead to 1,5 dioxygenation patterns. If the molecule to be synthesized has oxygenated carbons

in 1,2 or 1,4 position, only Umpolung or the use of cyanide anions, as a C_1 equivalent yield the desired structure.

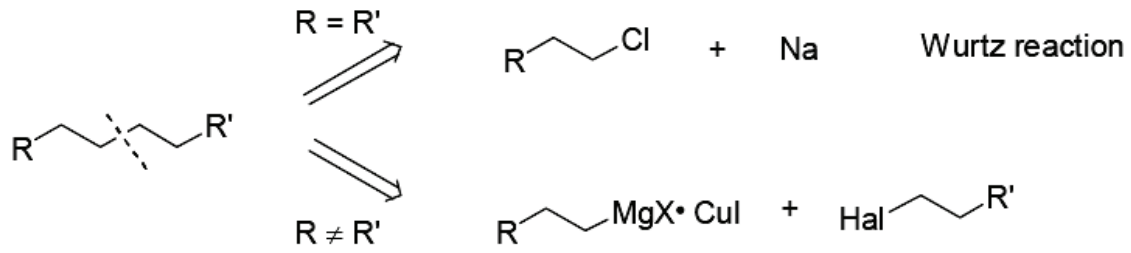
2) **Six-membered rings in the molecule**. The Diels-Alder reaction leads to a six membered ring by connection of diene and dienophile. A disconnection using a retro Diels-Alder reaction can drastically reduce the complexity of a molecule.

3) **Double bonds** or their equivalents can serve as points of disconnection, because many reliable methods to synthesize C=C double bond are known.

Basic retrosynthetic key steps

Disconnection of molecules according to the functional groups present in the target molecule.

a) *C-C bond with no functional group present:*

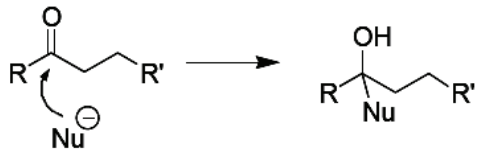


Difficult, only limited set of connecting reactions available, e.g. radical combination, aliphatic nucleophilic substitution. Sometimes a detour is necessary, e.g. formation of a double bond and subsequent hydrogenation.

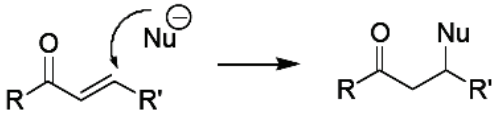
b) *One-group disconnections based on normal carbonyl reactivity.*

Normal carbonyl reactivity:

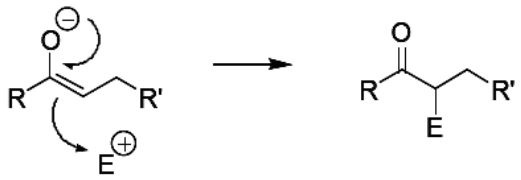
ACCEPT electrons at the C=O carbon



ACCEPT electrons at the β-carbon of the enone



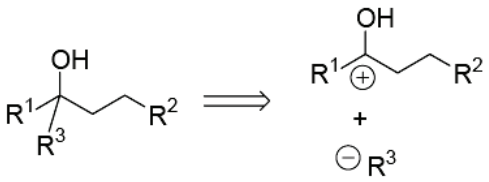
DONATE electrons to the α-carbon *via* the enolate



Synthetic planning should show an analysis of the problem followed by synthetic solution.

Alcohols

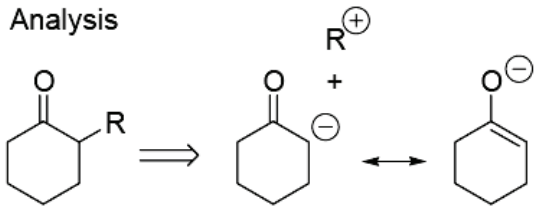
Analysis



Synthesis

Carbonyl compounds brunched at α-carbon.

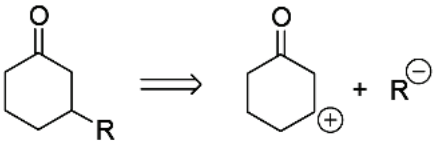
Analysis



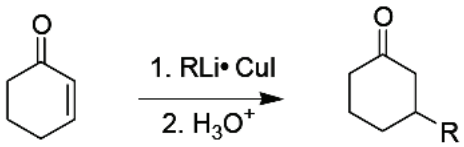
Synthesis

Carbonyl compounds branched at β-carbon.

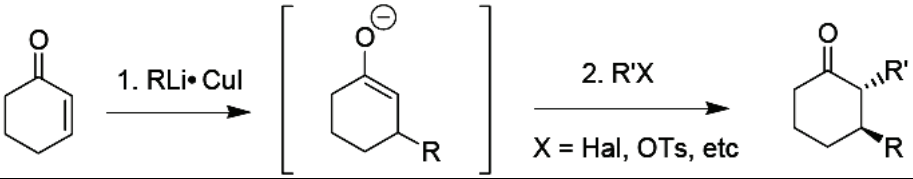
Analysis



Synthesis: Michael addition



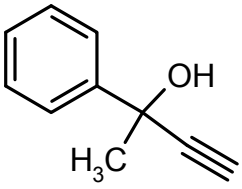
Combination of the last two synthetic approaches allows the introduction of two new groups:

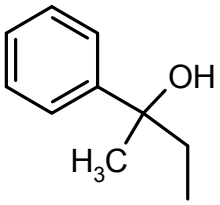


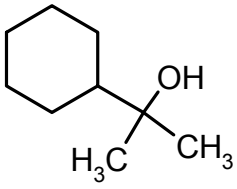
Retrosynthesis training

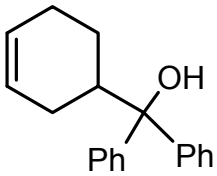
Propose syntheses – discuss alternative routes !

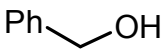
Simple alcohols

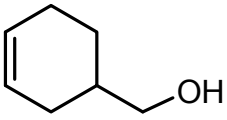
1) 

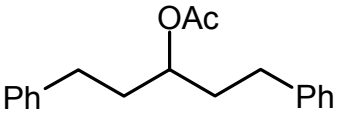
2) 

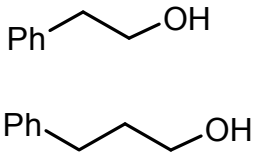
3) 

4) 

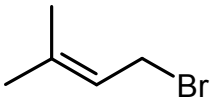


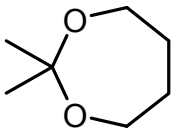
5) 

6) 

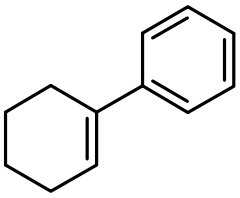
7) 

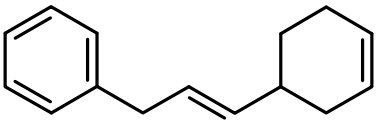
Exercises

8) 

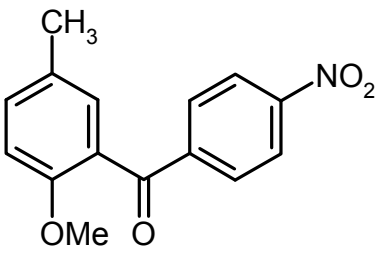
9) 

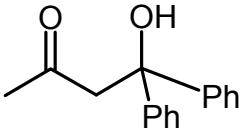
Simple Alkenes

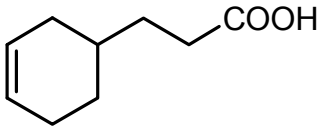
10) 

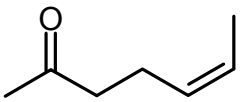
11) 

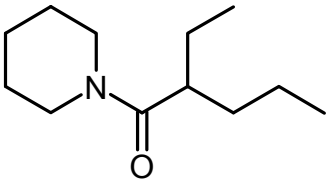
Simple Carbonyl Compounds

12) 

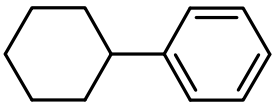
13) 

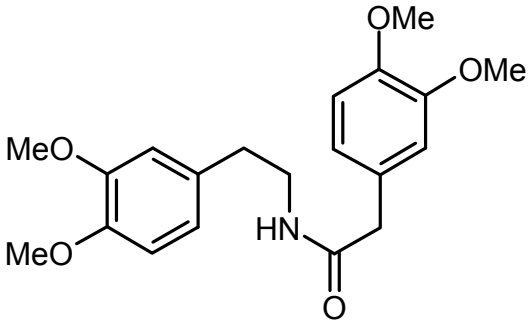
14) 

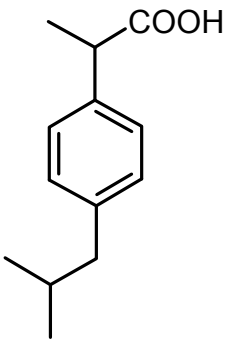
15) 

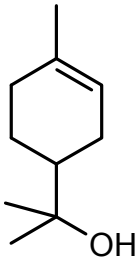
16) 

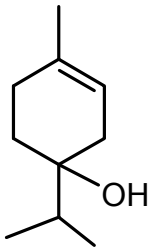
Exercise

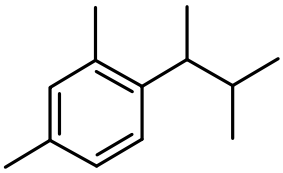
17) 

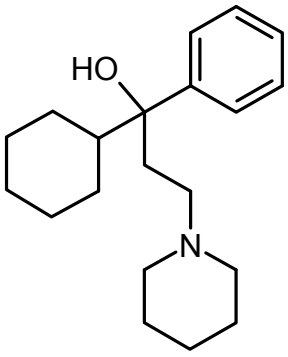
18) 

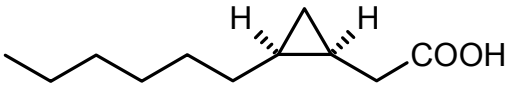
19) 

20) 

α-terpinol isomers 21) 

20) 

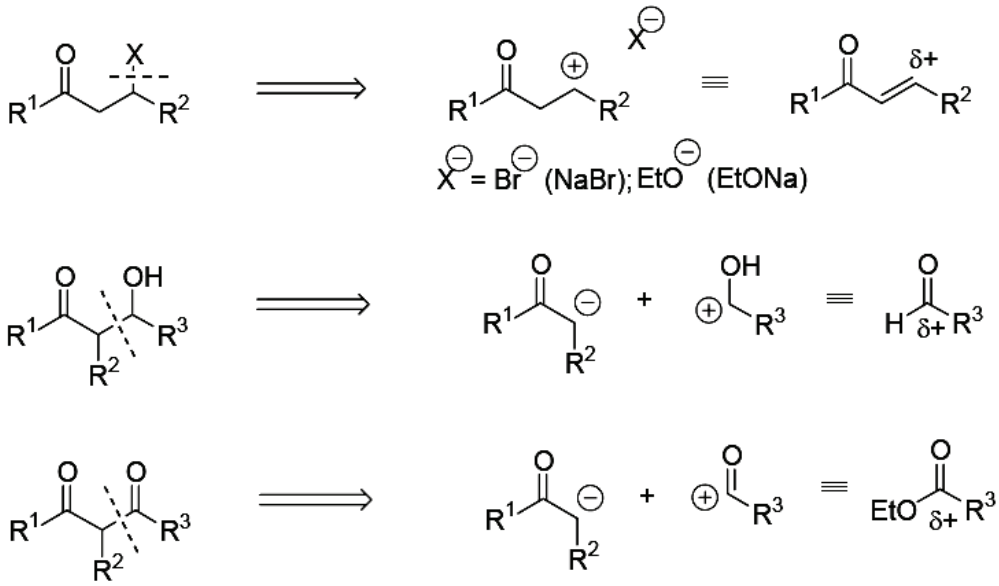
23) 

24) 

Cascarillsäure aus Wolfsmilchgewächsen

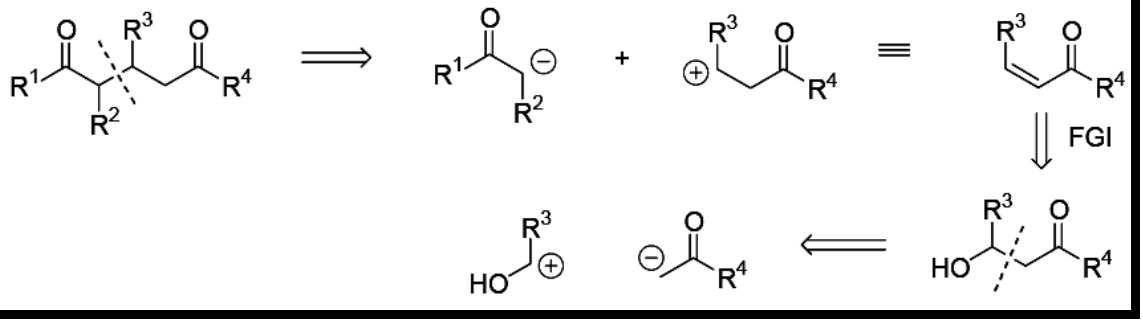
c) *Two-group disconnections based on normal carbonyl reactivity.*

1,3-Difunctionalised compounds

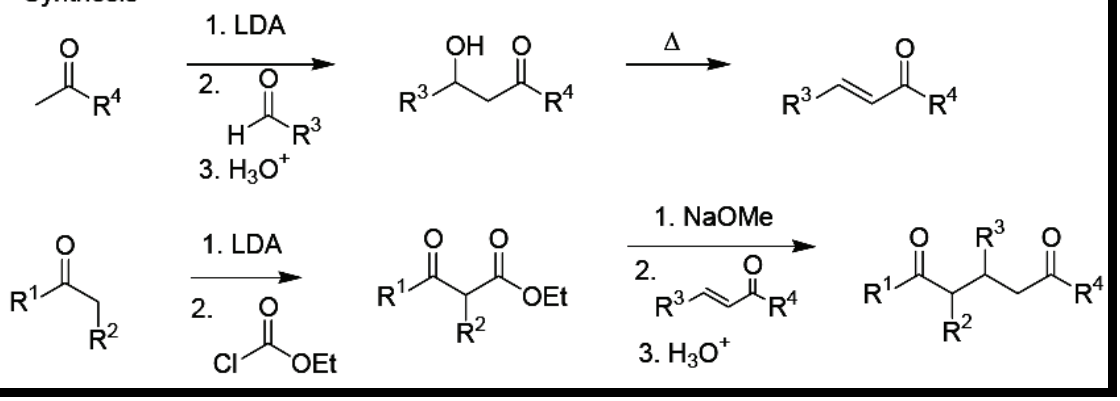


1,5-Difunctionalised compounds

Analysis



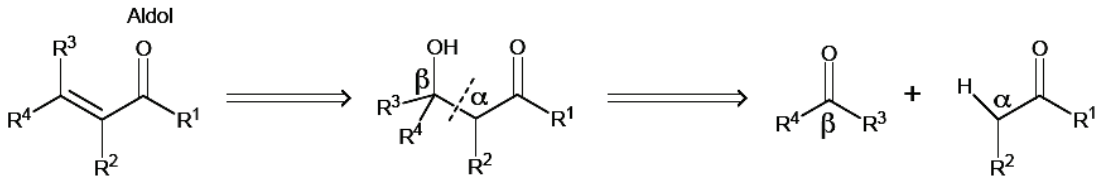
Synthesis



1,3- and 1,5-dioxygenated compounds can be prepared from classic carbonyl reactions.

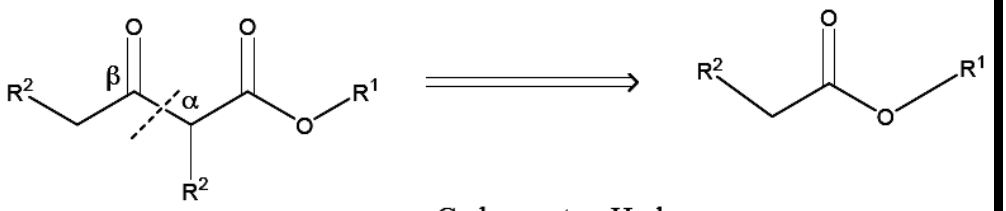
Retrosynthesis with classic carbonyl reactions - overview

Aldol Condensation:



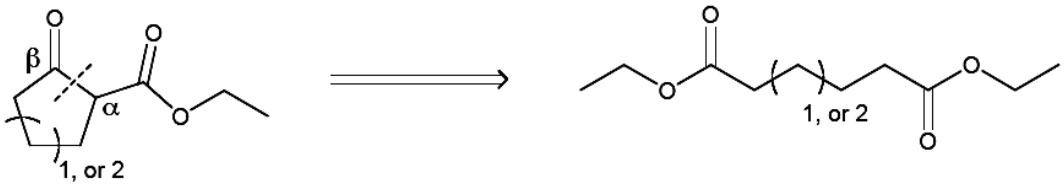
α-Carbon gets a Hydrogen
β-Carbon becomes a carbonyl

Claisen Condensation:

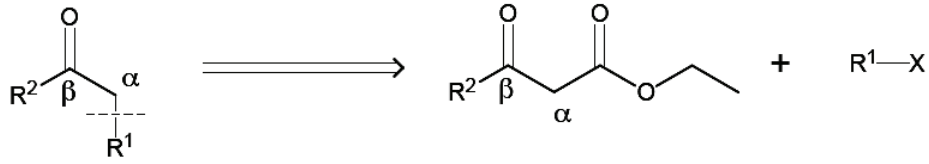


α-Carbon gets a Hydrogen
β-Carbon becomes an ester

Dieckman:

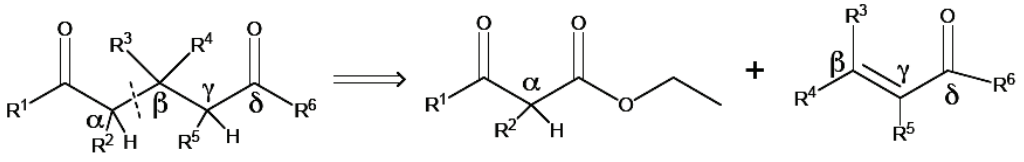


Acetoacetic Ester Type Synthesis:



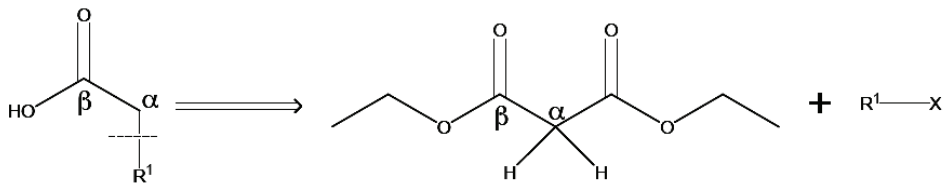
R^1-X : R^1 must be able to do S_N2
α-Carbon gets an attached ester
R^1 comes from R^1-LG
R^2 can derive from a Claisen Reaction

Acetoacetic Ester-Type Conjugate Addition:



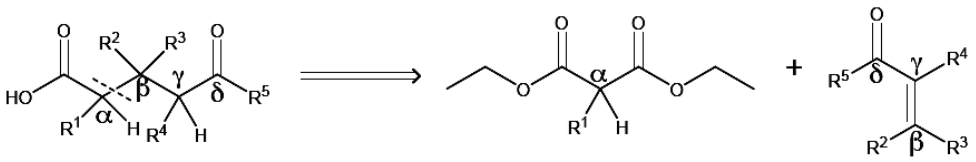
α- carbon gets an ester
β-γ carbons become an alkene

Malonic Ester Synthesis:



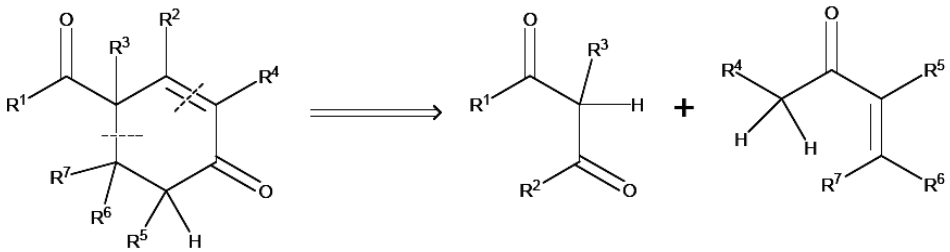
α-carbon gets an attached ester
β-carbon becomes an ester
R^1 comes from R^1-LG

Malonic Ester Conjugate Addition:



α-carbon gets an attached ester
β-γ carbons become an alkene

Robinson Annulation:

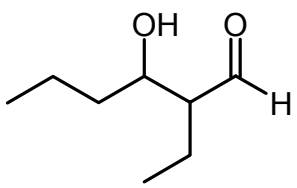


Retrosynthesis training

Propose syntheses – discuss alternative routes!

β-Hydroxycarbonyl compounds

1)



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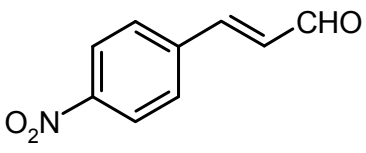
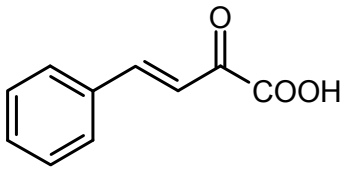
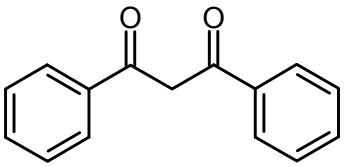
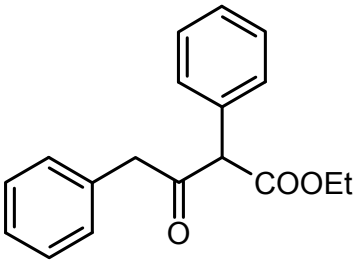
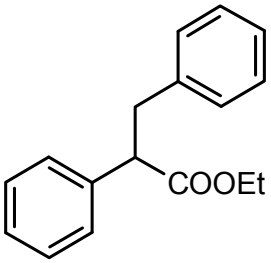


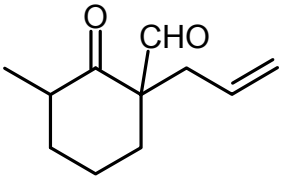
3)

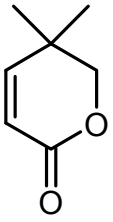


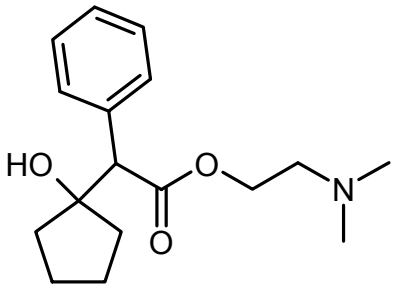
4) 

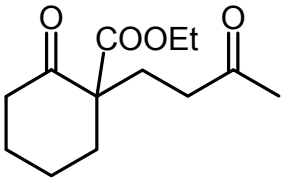
5) 

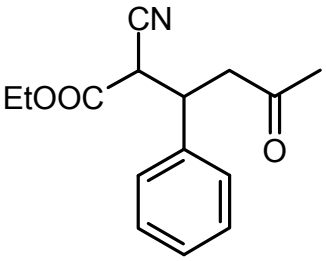
6) 

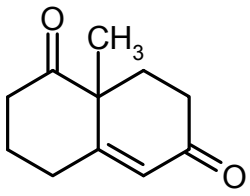
7) 

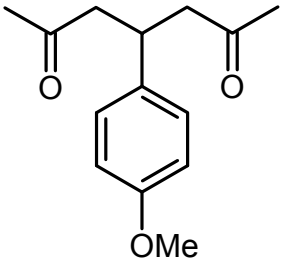
8) 

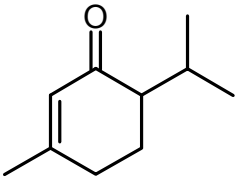
9) 

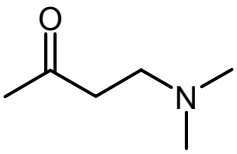
10) 

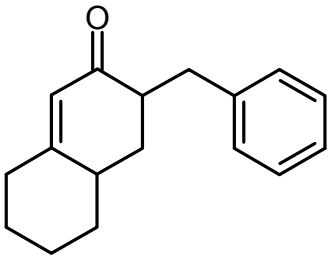
11) 

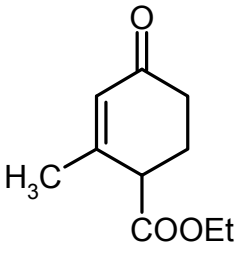
12) 

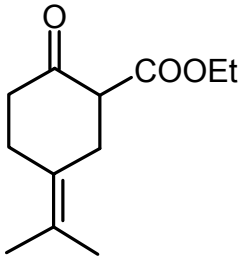
13) 

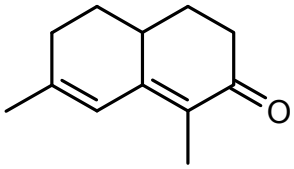
14) 

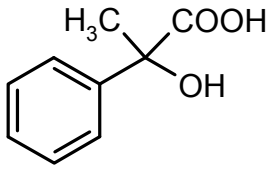
15) 

16) 

17) 

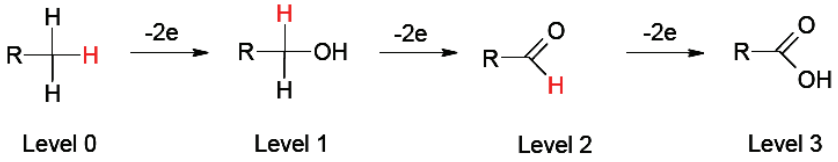
18) 

19) 

20) 

Functional group interconversions (FGIs)

Based on the oxidation level of carbon there are two main types FGIs: Without change of the carbon oxidation level and with change of the oxidation level.



Oxidation level 1 (alkane – 2e):

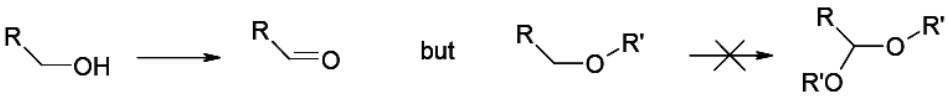
C-X (X = Hal, OH, OR, OAc, OTs, NR_2, NO_2, SR, *etc*);
C=C

Oxidation level 2 (alkane – 4e):

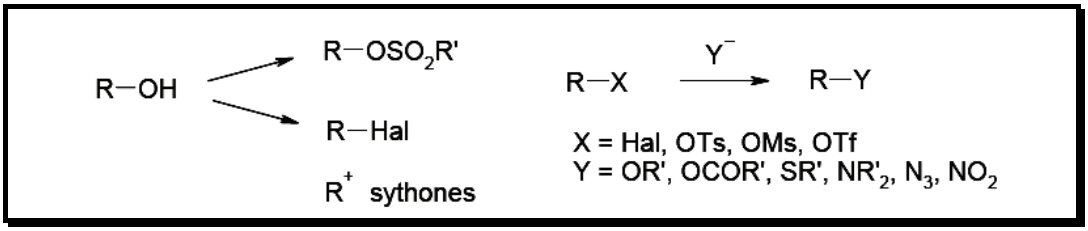
C=X (X = O, NR); CXY (X, Y = Hal, OR, SR); C=C-X (X = Hal, OR, $OSiR_3$); C≡C; X-C-C-Y; epoxides.

Oxidation level 3 (alkane – 6e):
COOH, COX (X = OR, Hal, OCOR, NR_2); C≡N, C=C-C=O, C=C-C≡C

With chance of oxidation level, but not all are possible:



Same oxidation level:

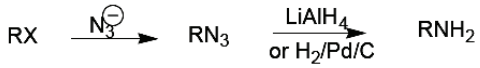


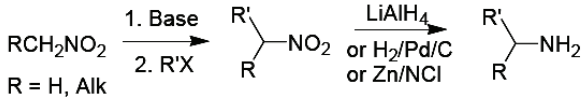
Amino groups are of particular importance in many molecules. Therefore many methods for their preparation from other functional groups have been developed.

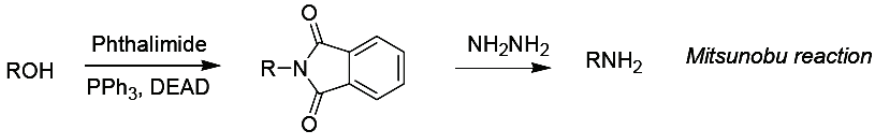
Primary amines:

Primary amines at primary carbon

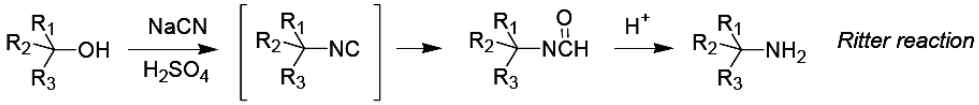
Primary amines at primary or secondary carbon







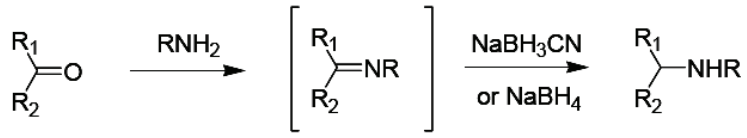
Primary amines at secondary or tertiary carbon



The Ritter reaction with alkylnitriles produces secondary amines

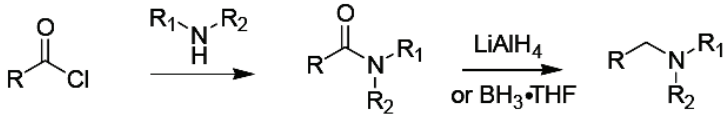
Secondary amines:

Reductive amination



If hydroxylamine (NH_2OH) is used in the place of RNH_2, reduction of the corresponding oxime gives primary amine.

Secondary and tertiary amines:



The method is also suitable for the preparation of primary amines ($R_1 = R_2 = H$).

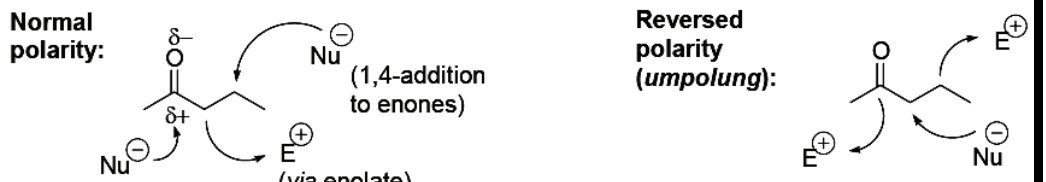
Removal of functional groups – Hydrocarbon synthesis

FG	Conditions for FG removal
C≡C C=C	H_2/Pd
OH	a) TsCl, MsCl – $LiAlH_4$, BH_3 b) Barton reaction (radical Bu_3SnH)
C=O	a) $NaBH_4$ and then as with OH group b) Kizhner reduction(NH_2NH_2) c) Clemence reduction(Zn/Hg; HCl)
SH	Ranney Ni
Br	Radical Bu_3SnH
NH_2	HNO_2 diazotisation

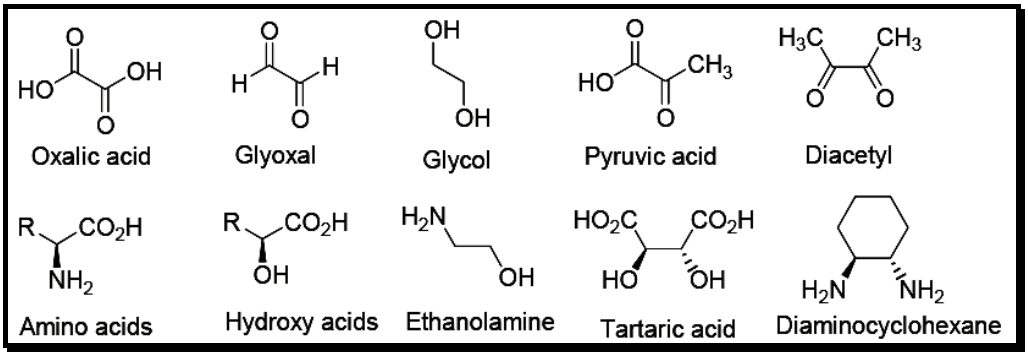
Two-group Disconnections:

"Illogical" disconnections, "unnatural" reactivity patterns

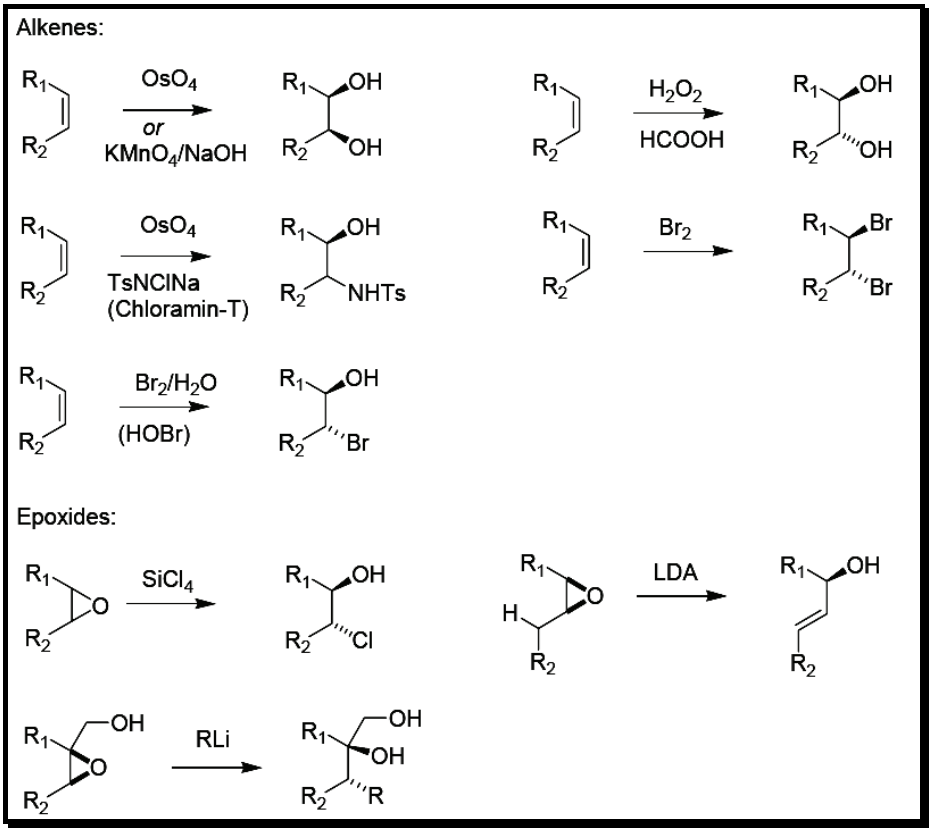
Unnatural or reversed polarity carbonyl reactivity reverses the normal patterns attributable to carbonyl compounds.



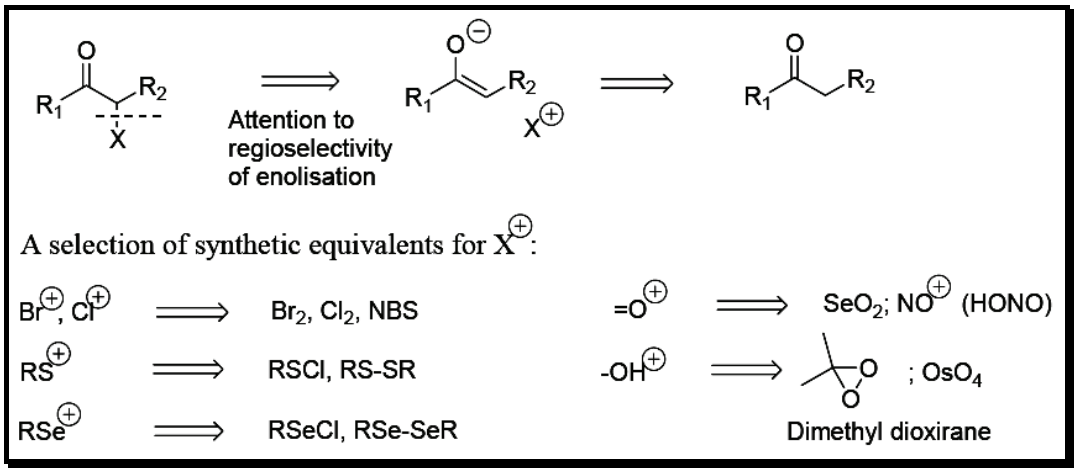
Use of 1,2-difunctionalysed starting materials



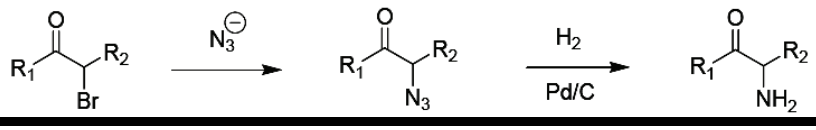
Difunctionalisation of alkenes and epoxide opening

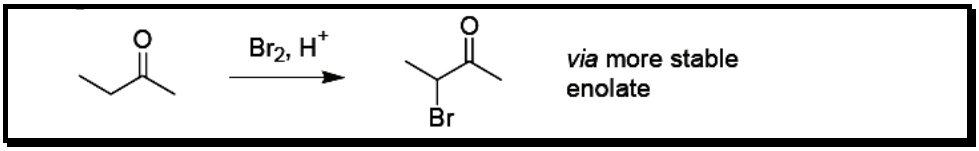


α-Functionalisation of carbonyl compounds

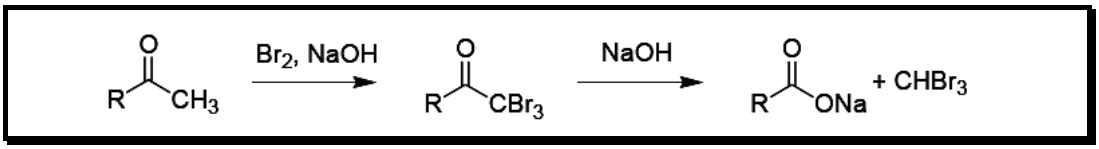


Amines can be introduced by FGI, *e.g.* from α–halocarbonyl compounds *via* azides followed by reduction:

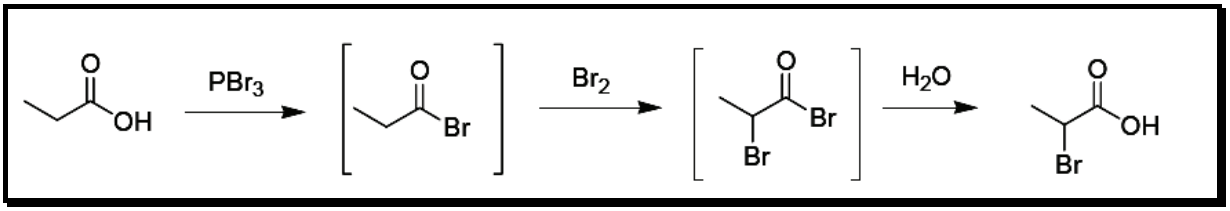




Be aware of the haloform reaction!



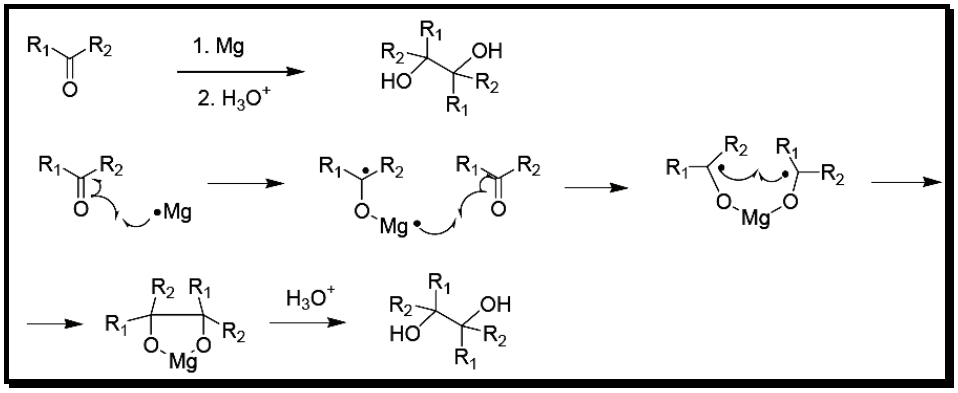
Carboxylic acid:



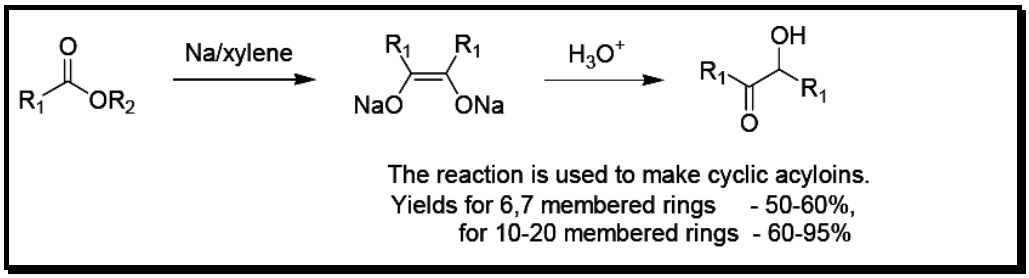
Radical coupling

Radical coupling is only good when two identical molecules are being coupled or when the reaction proceeds intramolecularly.

Pinacol reaction:



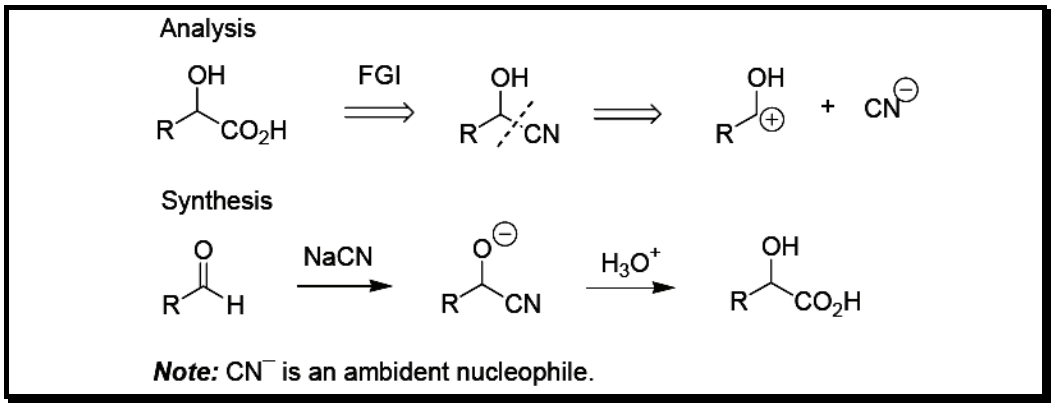
Acyloin condensation:



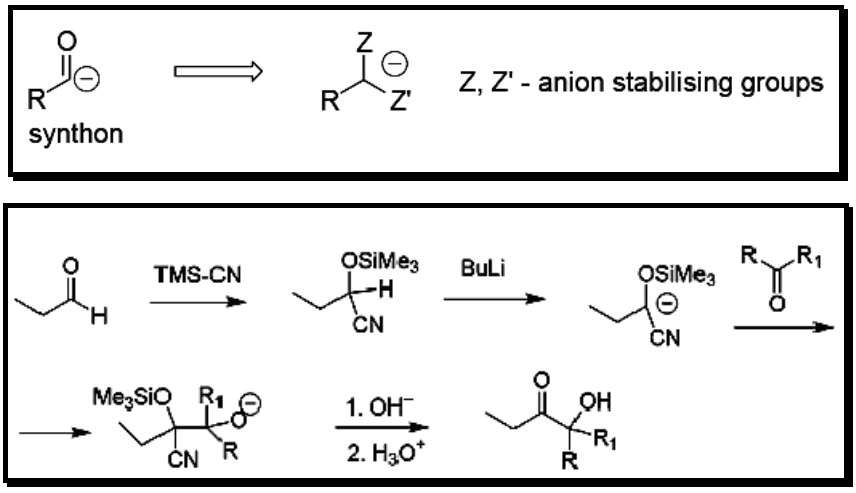
Umpolung strategies

A synthetic equivalent of a reagent which cannot be prepared, e.g. an acyl anion, is called a **synthon**. Dithiane, cyanohydrin and sulfone are latent carbonyl groups; the carbonyl functionality is masked in a different form and can be released at a later stage when required. This process is called "*Umpolung*", because the usually partially positively charged carbonyl carbon is temporarily transformed into a carbanion. So the polarity is reversed. After the reaction of the acyl anion equivalent the carbonyl functional group can be restored.

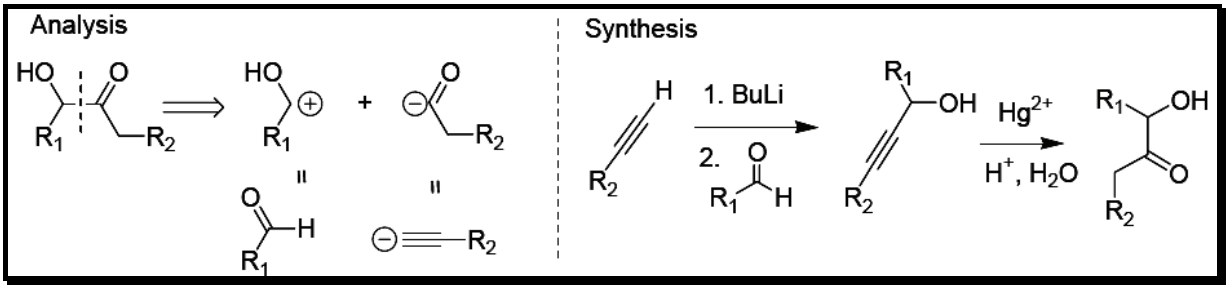
Cyanide anion + electrophilic carbonyl compound:



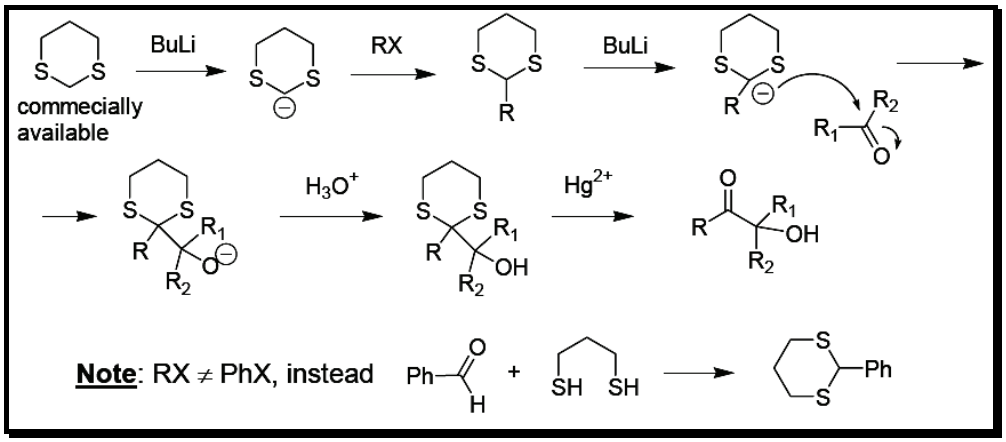
Cyanohydrins



Alkyne nucleophile + electrophilic carbonyl



Dithians (thioacetal) nucleophile + electrophilic carbonyl

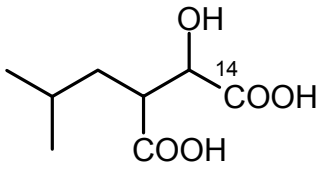


Retrosynthesis training

Propose syntheses – discuss alternative routes

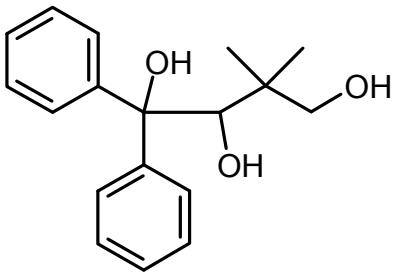
α-Hydroxycarbonyl compounds

1)



Note that one of the carbon atoms is labelled!

2)



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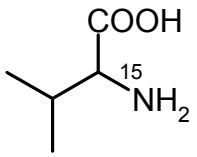
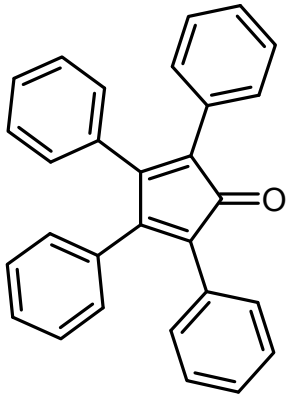


Note that the nitrogen atom is labelled!

4)



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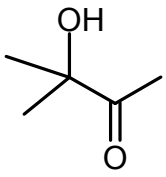

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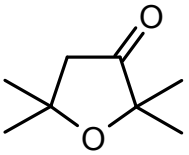

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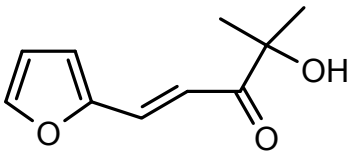

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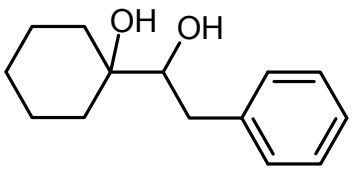
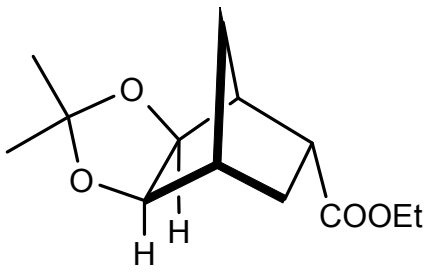
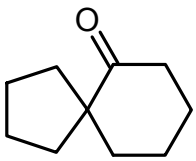
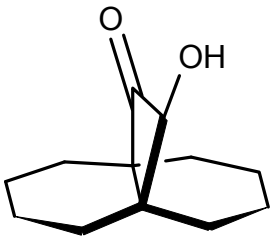
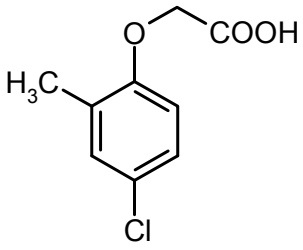


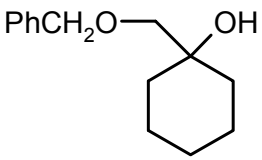
9) 

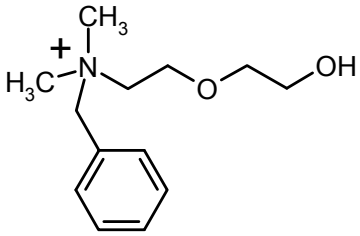
10) 

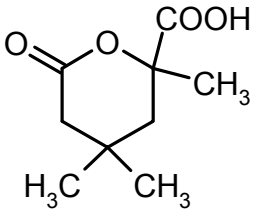
11) 

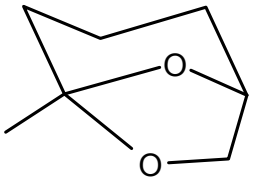
12) 

Insecticide

13) 

14) 

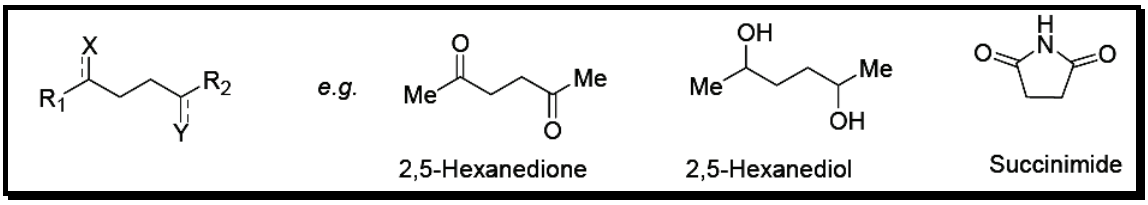
15) 

16) 

Beatle Pheromone

Synthetic strategies for 1,4-difunctionalysed compounds

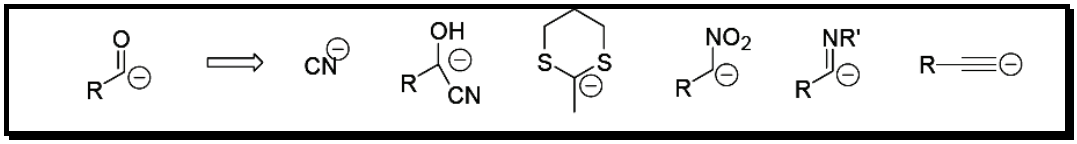
Approaches to the synthesis of 1,4-difucntionalized compounds share a lot of common features with methods for the preparation of 1,2-analogues. Again, a few commercially available derivatives can serve as starting materials.

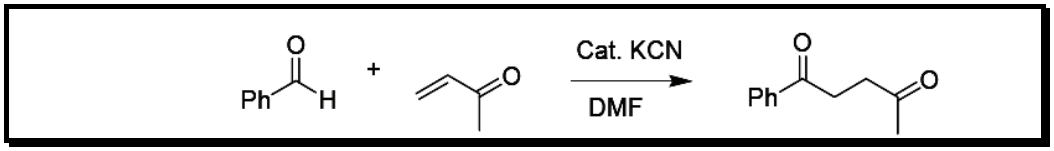


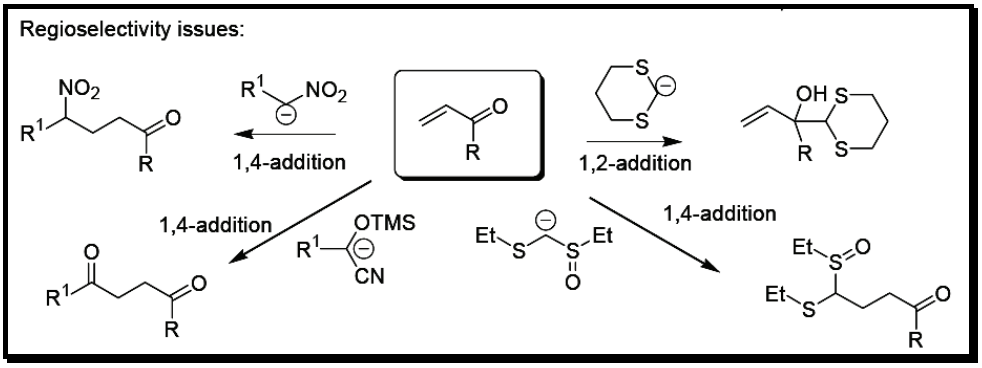
Acyl equivalent + Michael acceptor

This approach is analogues to the preparation of 1,5-dicarbonyl compounds *via* addition of enolates to α,β-unsatuarted carbonyl compounds. However, this time, acyl-anion synthons are used as nucleophiles. A selection of such reagents has been discussed previously.

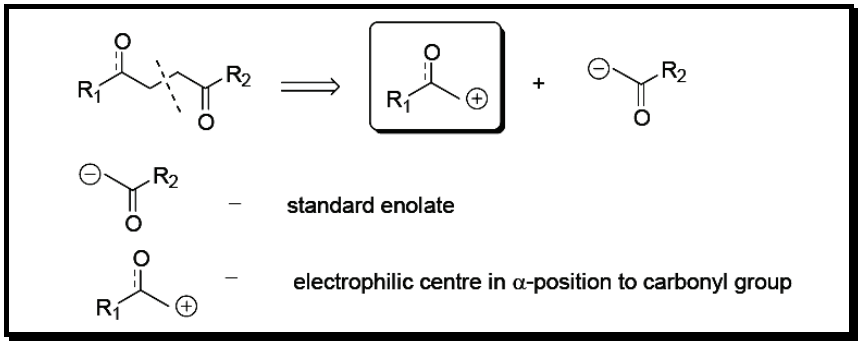
Acyl anion synthons:

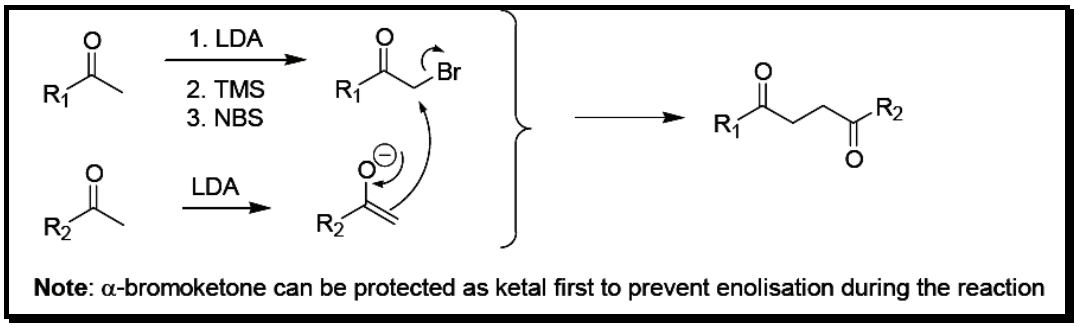






Additional Umpolung strategies

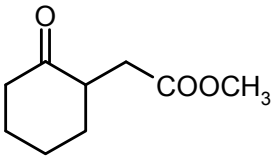


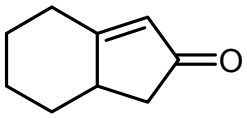


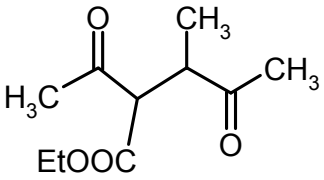
Retrosynthesis training

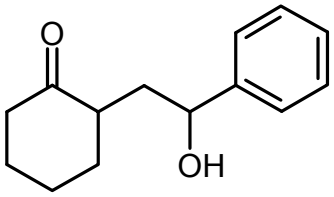
Propose syntheses – discuss alternative routes!

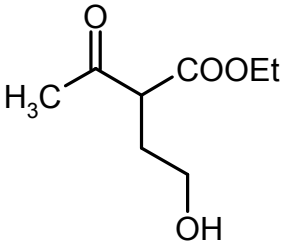
1,4-Difunctionalized compounds

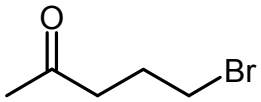
1) 

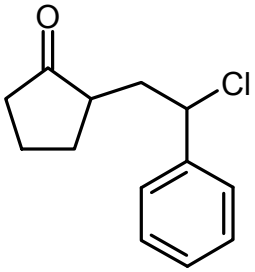
2) 

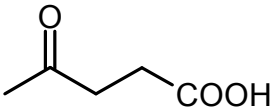
3) 

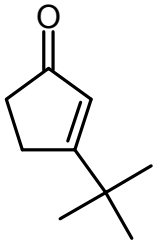
4) 

5) 

6) 

7) 

8) 

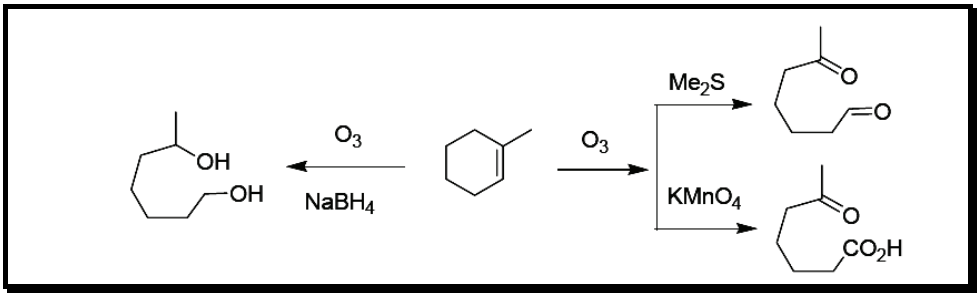
9) 

Reconnection strategies for 1,6-difunctionalysed compounds

In retrosynthetic analysis, open chain 1,6-difunctionalised compounds can be linked to appropriate cyclic precursors. We call this *reconnection strategies*, which can also be used to make compounds with two functional groups related to each other as 1,5-, 1,7- etc.

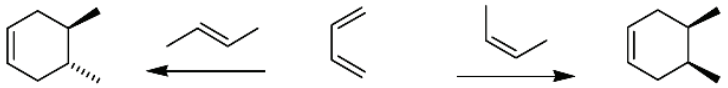
Ozonolysis of cycloalkenes

Functional groups with 1,6-relationship are too far apart for any conventional disconnection strategies. However, ozonolysis of cyclohexene creates two functional groups which are 1,6-related.



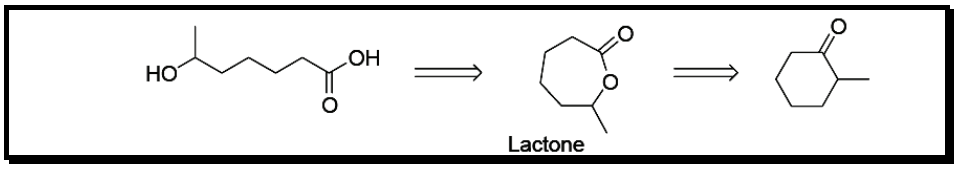
This strategy requires synthetic access to 6-membered unsaturated rings. The best way to make such precursors is Diels-Alder cycloaddition reaction (see above in the course):

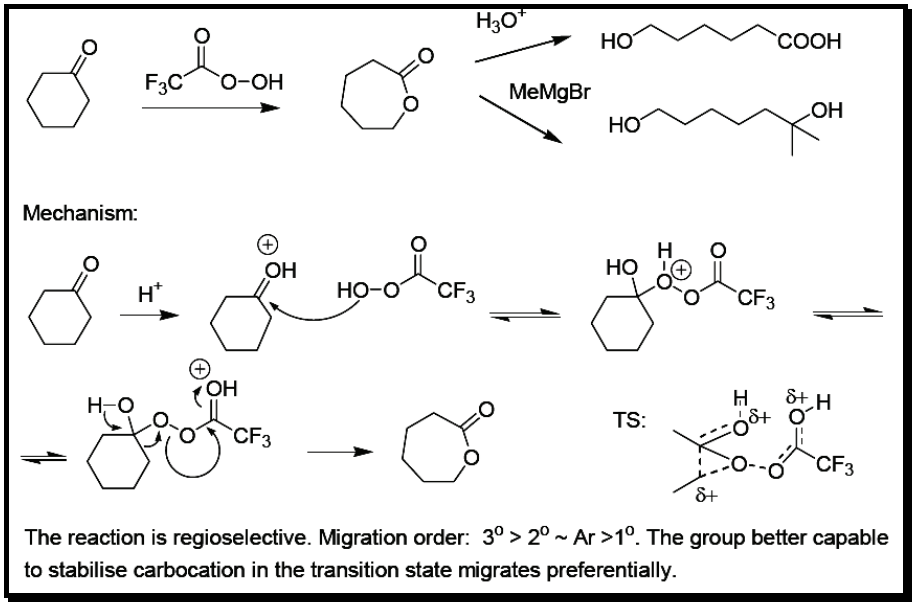
The reaction is stereospecific



Baeyer-Villinger rearrangement

Another type of reconnection strategies is the hydrolysis of lactones. The required lactones can be prepared from cyclic ketones by a ring expansion reaction, the Bayer-Villinger rearrangement.

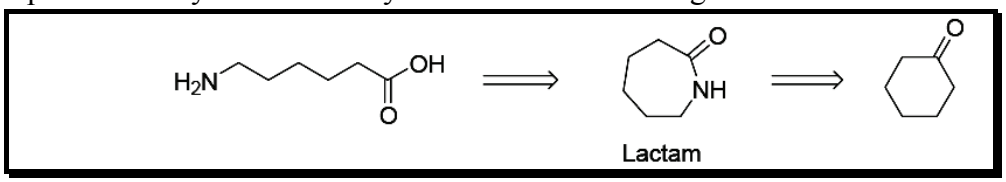


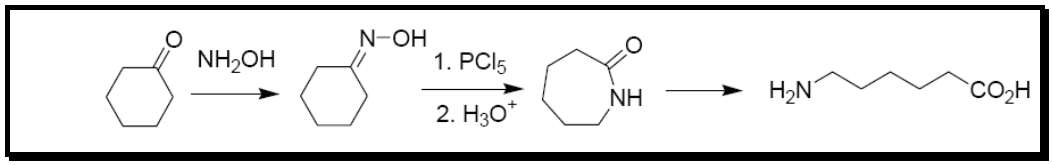


The reaction is regioselective. Migration order: $3^o > 2^o \sim Ar > 1^o$. The group better capable to stabilise carbocation in the transition state migrates preferentially.

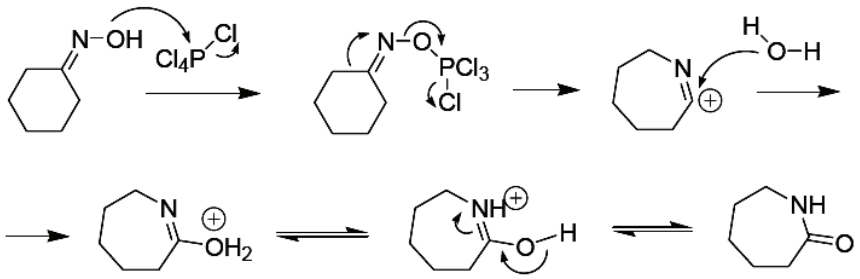
Beckmann rearrangement

Analogously, a reconnection strategy for 6-amino acids is the hydrolysis of lactams. Lactams can be prepared from cyclic ketones by the Beckmann rearrangement.



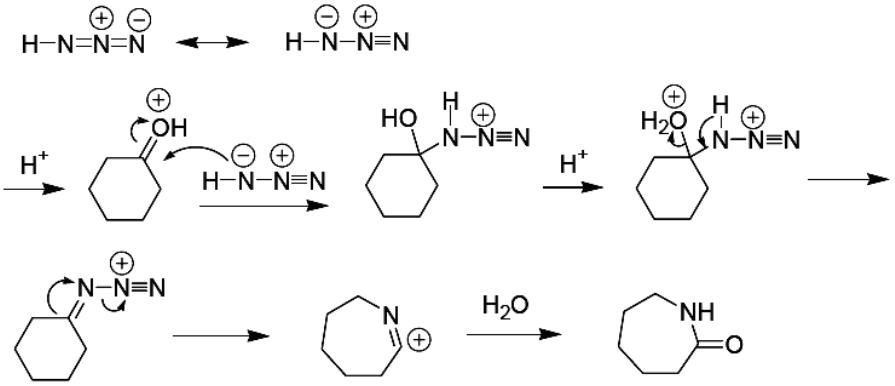


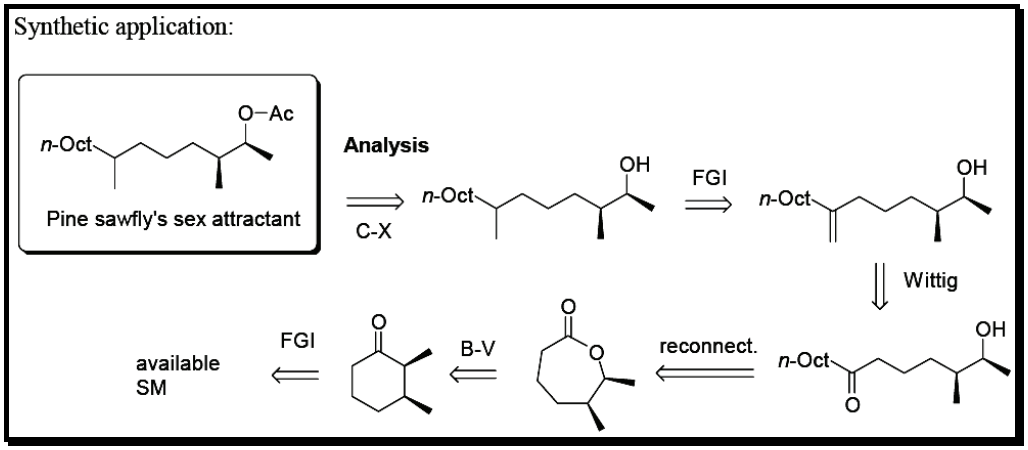
Reaction mechanism:

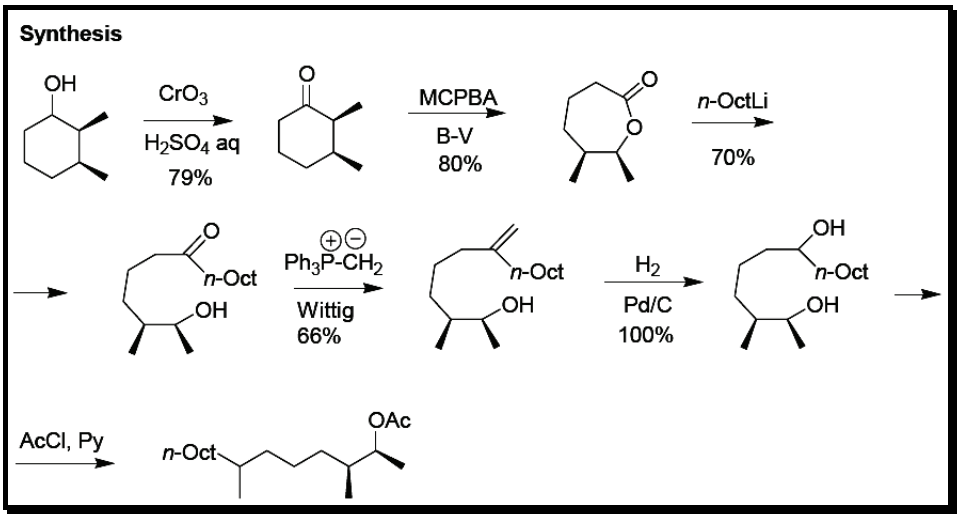


Usually, the group positioned *anti* to oxime is migrating.

A related process which involves addition of hydrazoic acid to carbonyl compounds catalysed by sulphuric acid is called **Schmidt reaction**:







Retrosynthesis training

Propose syntheses – discuss alternative routes!

1,6-Difunctionalized compounds and Lactones

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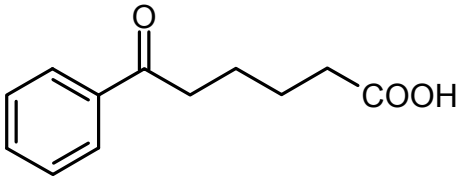

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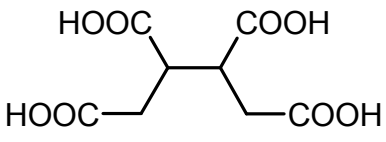

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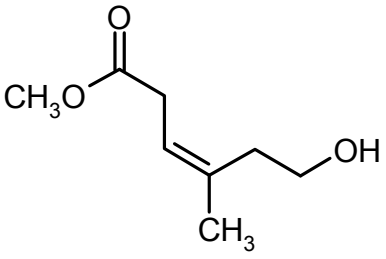

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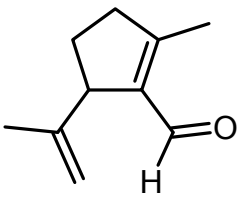

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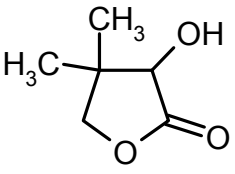

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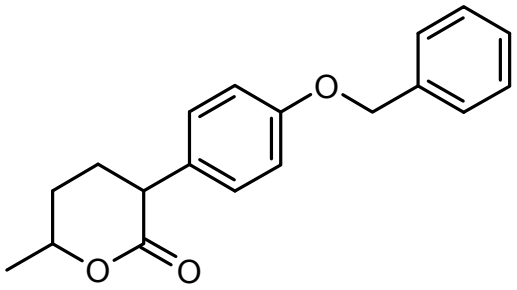

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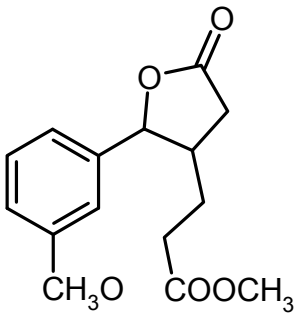

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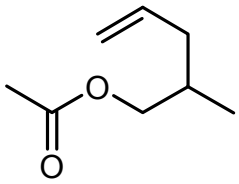

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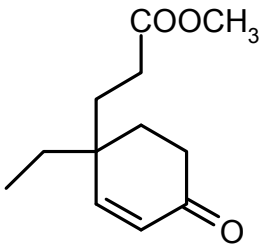

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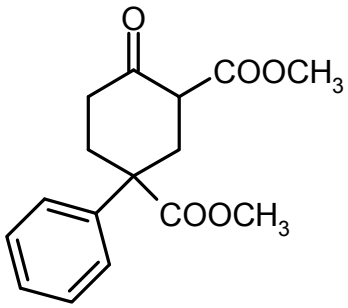

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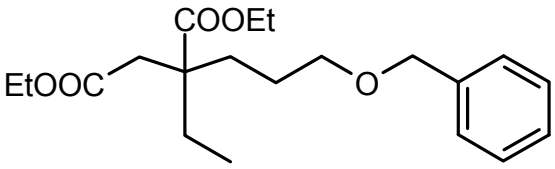

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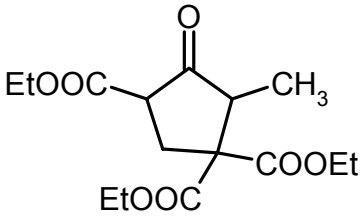
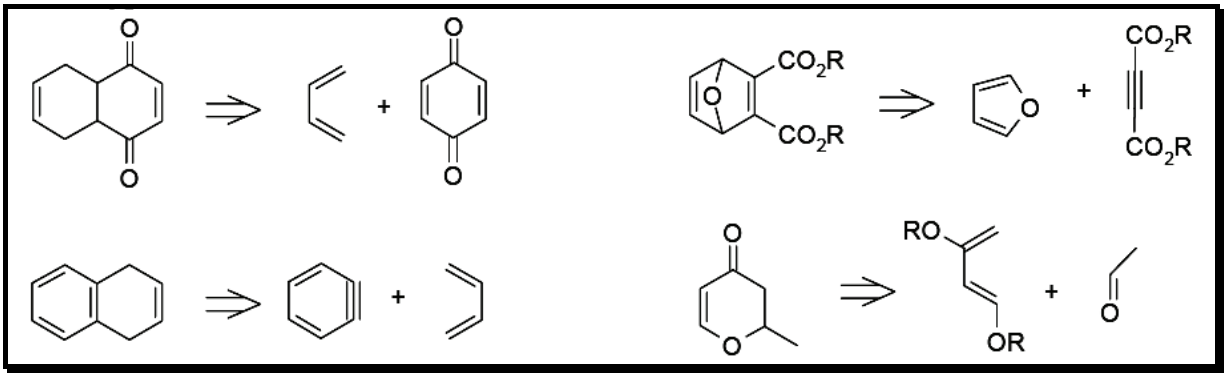
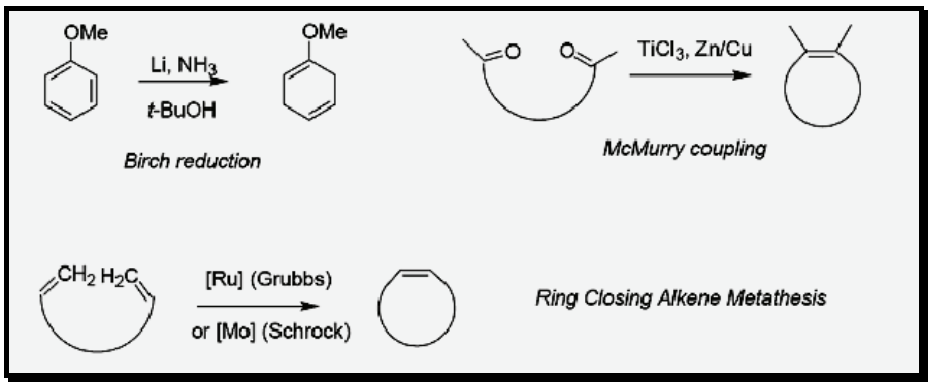


Synthesis of carbocyclic compounds

Diels-Alder disconnections:



Other methods of carbocycle synthesis:



Retrosynthesis training

Propose syntheses – discuss alternative routes!

Carbo- and heterocyclic compounds

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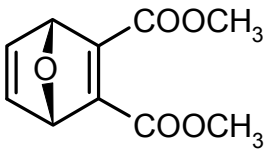

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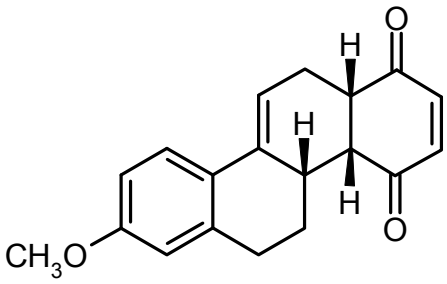

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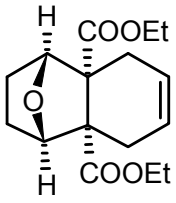

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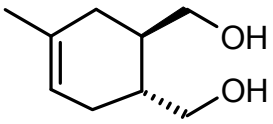

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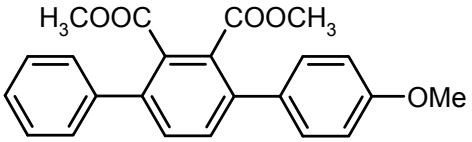

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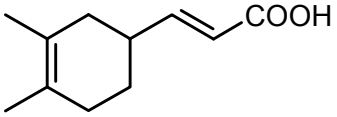

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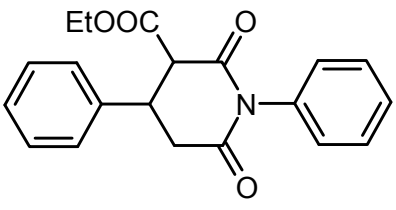

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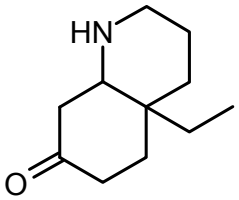

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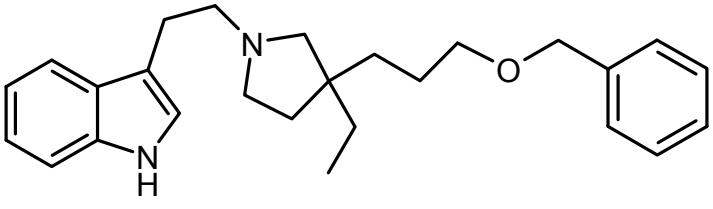

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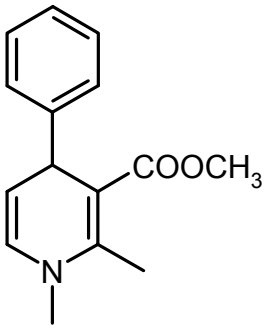

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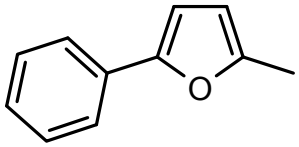

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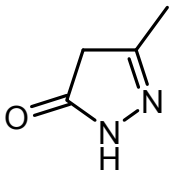

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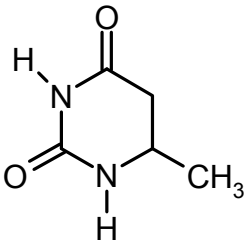

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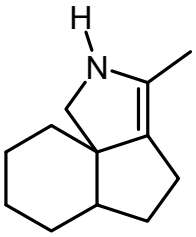

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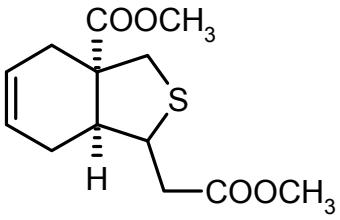

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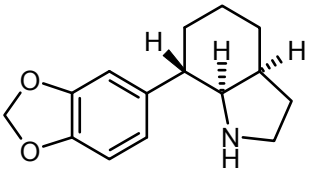

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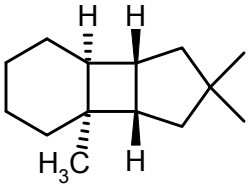

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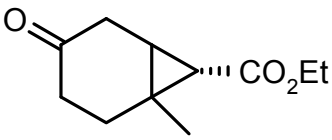
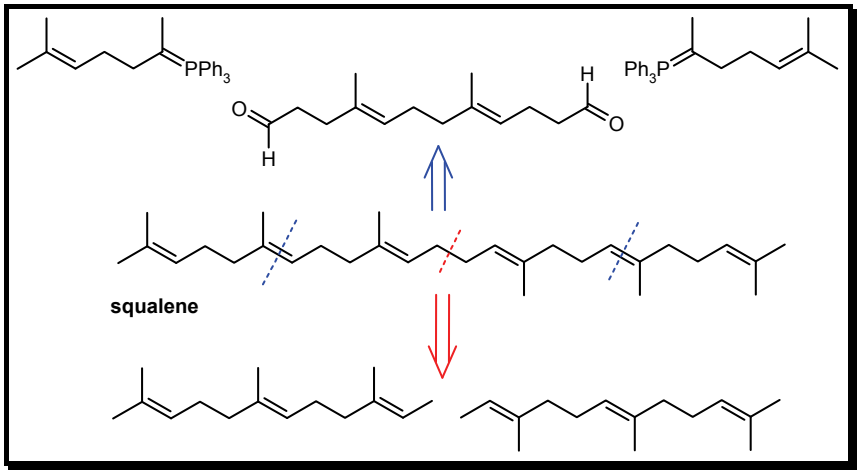


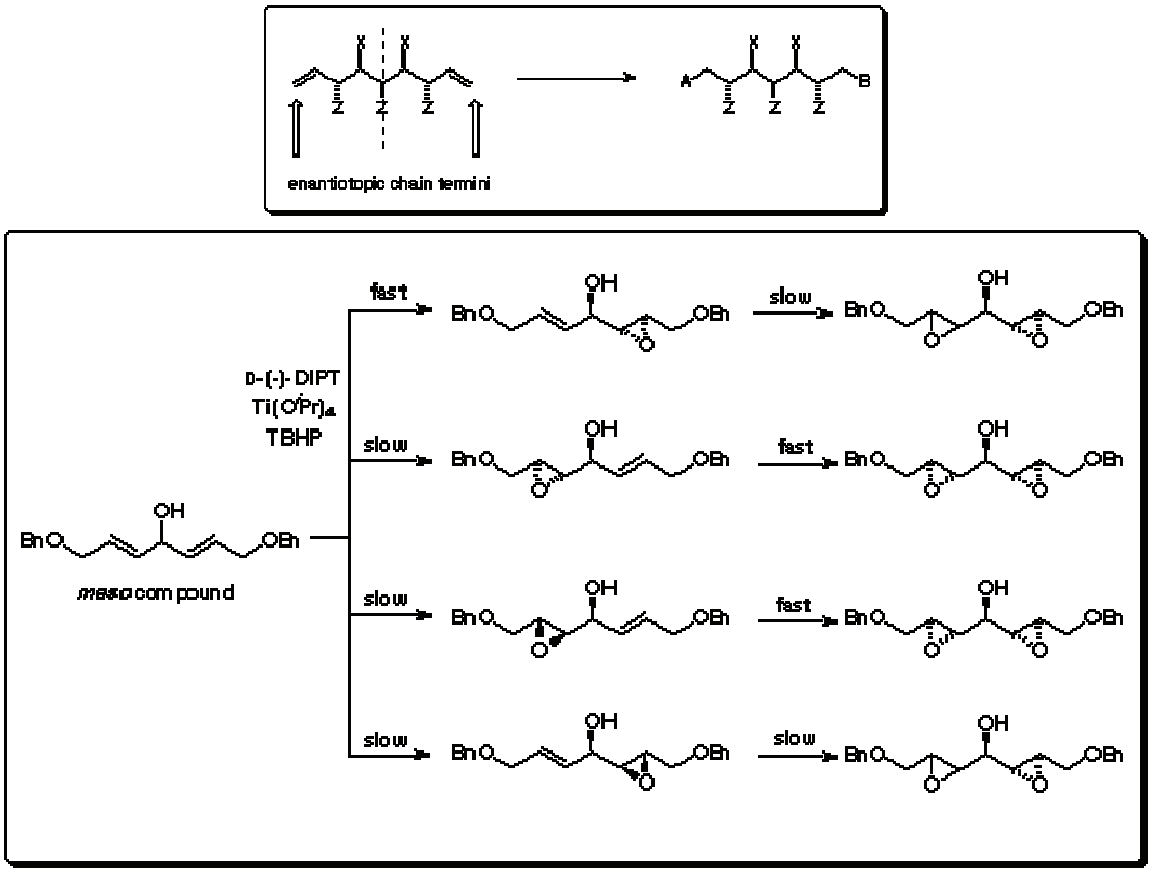
Taking advantage of symmetry

The symmetry of the target molecule structure may facilitate the synthesis. Instead of a stepwise linear synthesis a convergent approach can be used. Simultaneous formation of two or more bonds can save steps and allows building up the target molecule from similar sized building blocks. An example is the retrosynthetic analysis of squalene. Linear and convergent syntheses need typically different numbers of synthetic steps.

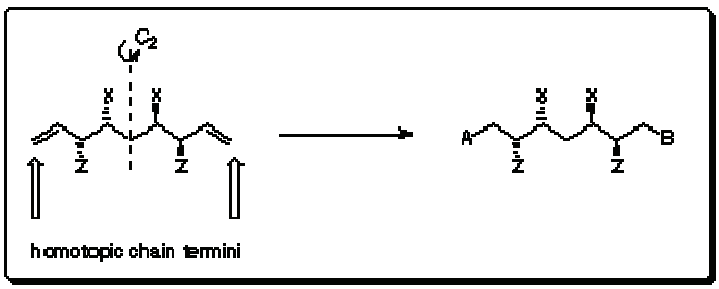


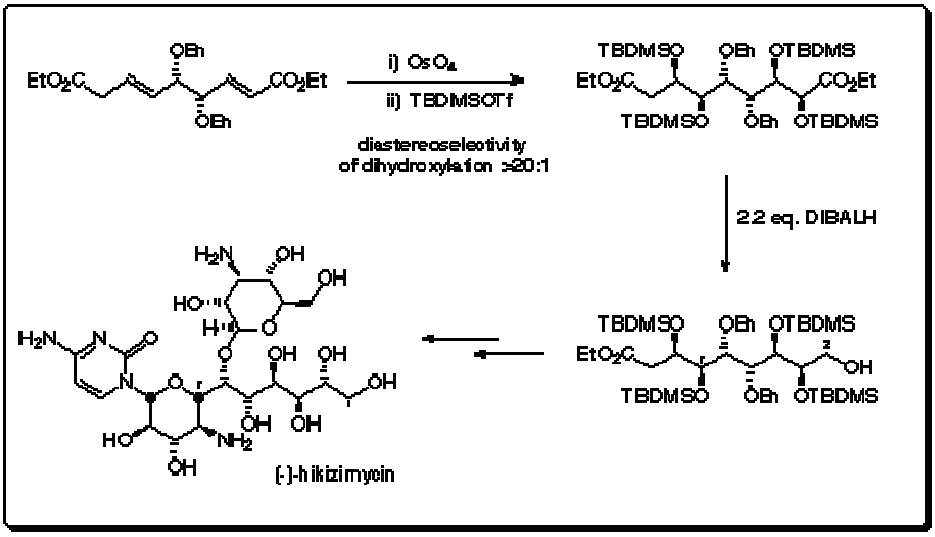
"Meso trick"

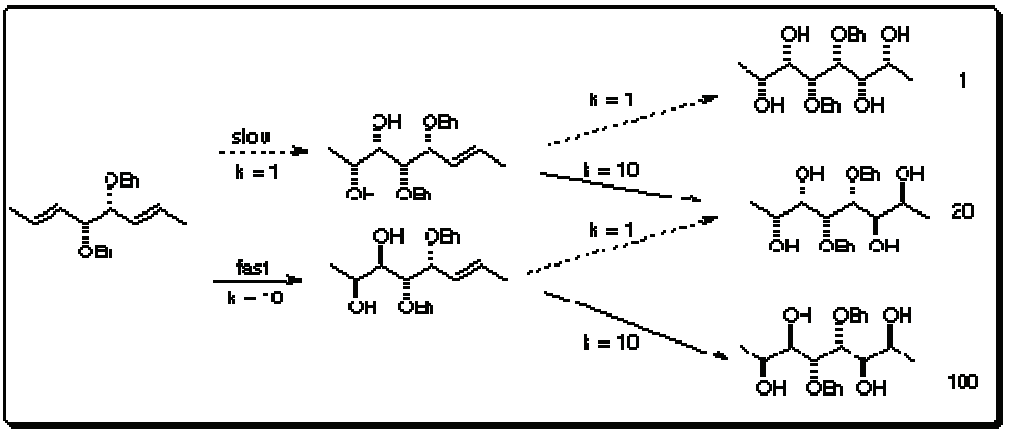
The stereochemistry of the starting material of a synthesis can be used to build up complex stereochemical patterns quick and efficient. Starting form an achiral *meso* compound chiral intermediates are obtained by enantioselective reactions. The "meso trick" uses the different reaction rates of symmetric prochiral groups. The Sharpless epoxidation of a meso bis-allyl alcohol illustrates the different reaction pathways.



The situation is different in C_2 symmetric chiral starting materials. Now reactions may proceed diastereoselective giving C_2 symmetric chiral intermediates. The diastereoselectivity of a reaction is determined by the difference in reaction rate for the different pathways.




i) OsO4
ii) TBDMSOTf
diastereoselectivity of dihydroxylation >20:1
2.2 eq. DIBALH
(-)-hikizimycin


slow
k = 1
fast
k = 10
1
20
100

Enzymes in synthesis

Advantages of using Enzymes and other Biological Methods (e.g. whole organisms)

- rate of reaction is increased
- reaction proceeds under very mild conditions
- green chemistry - very low environmental impact (increasingly important)
- can be extremely selective
- a wide variety are commercially available although some are very expensive
- chiral catalysts and can show exceptional levels of enantio- and diastereodifferentiation on natural *and* unnatural substrates.
- can be exceptionally efficient catalysts - very few synthetic catalysts compare
- can achieve transformations not possible using conventional chemical reagents

Disadvantages and Some Solutions

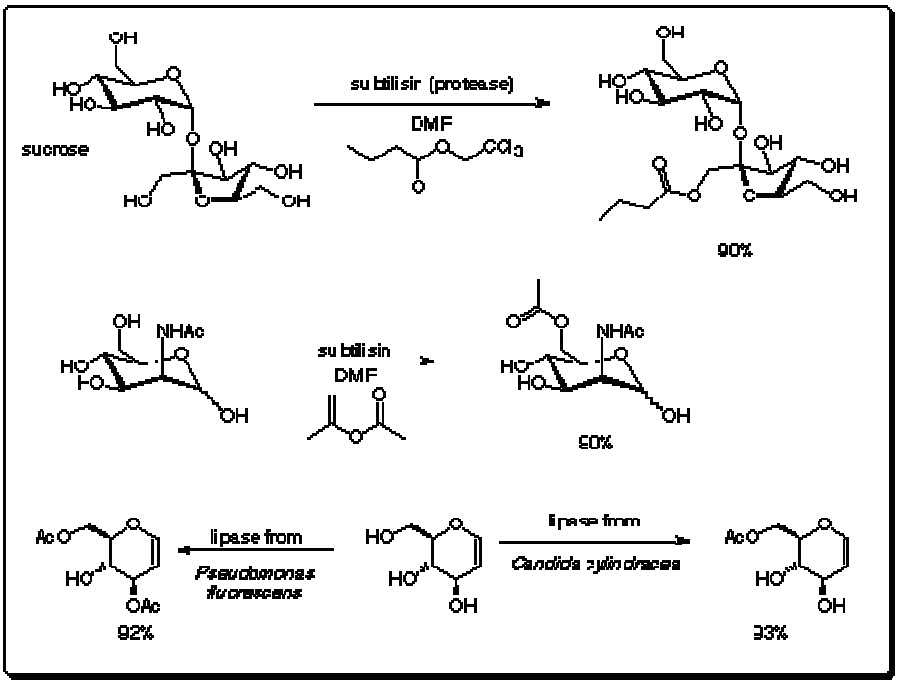
- can be extremely selective - this can be a problem if the enzyme doesn't accept your substrate:
    - if the reaction is sufficiently important it is usually possible to find a suitable enzyme which will accept the substrate by screening.
- can be unstable in organic solvents which are required to solubilise the substrate:
    - the stability of enzymes in organic solvents depends on the hydrophilicity of the enzyme - hydrophilic enzymes tend to be less stable
    - the solvent used can be important - immiscible, non polar solvents often give the best results
    - immobilising the enzyme on a support can increase stability (and also simplify purification procedures - the enzyme can be filtered off and recovered).
- some enzymes require co-factors to operate - co-factor recycling is possible but not always easy.
- Water is required for enzymes to maintain catalytic activity - some substrates are water sensitive. It is often possible however to use very small amounts of water and still maintain activity.
- some enzymes are very very expensive

I. Hydrolytic Enzymes - Lipases, Esterases, Proteases and Amidases

- catalyse the hydrolysis of ester and amide bonds
- reaction is reversible so they can also be used to catalyse the formation of ester and amide bonds depending on the conditions
- this is the most commonly used class of enzymes
- require no co-factor so no need for co-factor recycling
- reactions are simple to carry out
- many 1000's of these enzymes are known; a large number are commercially available and relatively inexpensive

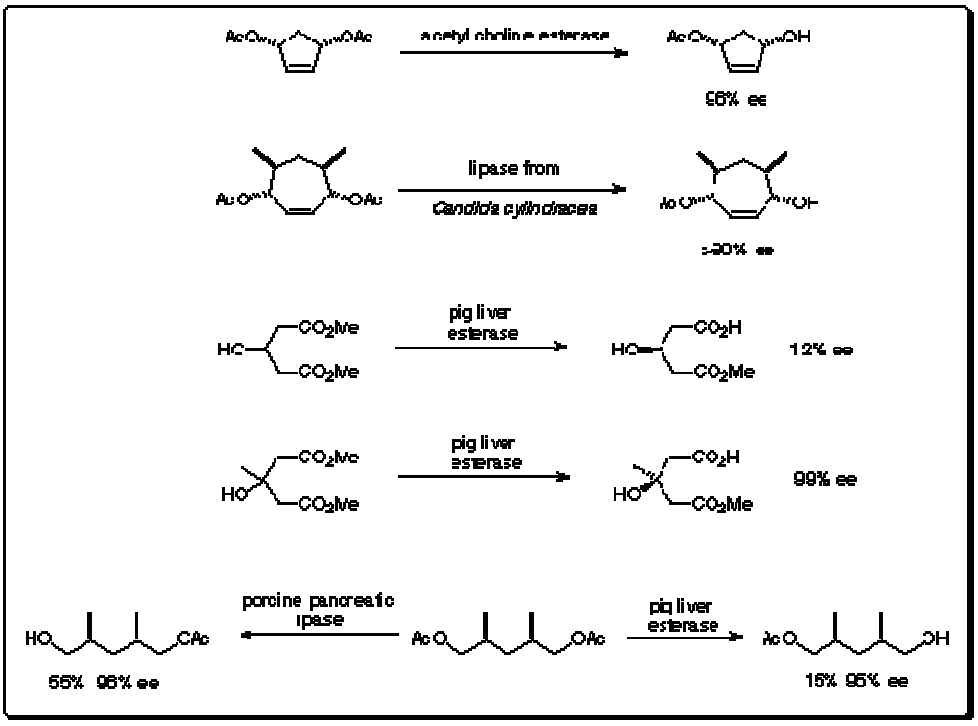
Regioselective Protection of Alcohols

Enzymes have been used for highly regioselective protection of alcohol functionality (as esters) in carbohydrates.



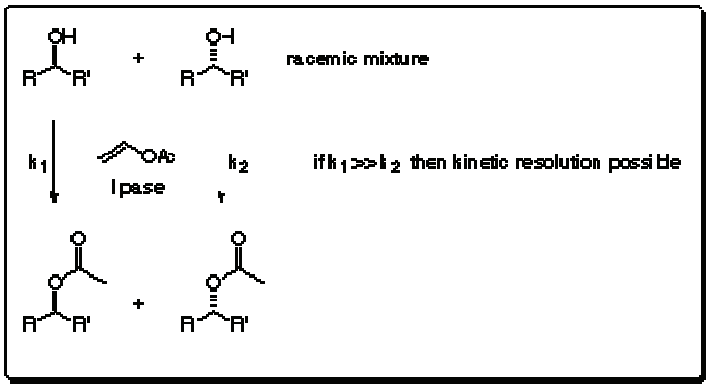
Desymmetrisation of *Meso* Systems

- a very useful method for accessing chiral compounds
- complete conversion possible (see kinetic resolution below) although lower yields are often obtained when hydrolysis of the remaining acetate becomes competitive.



Kinetic Resolution of Racemic Alcohols and Esters

- a very useful method for accessing enantiomerically enriched molecules
- Start with a racemate. Providing one enantiomer reacts faster than the other there is the potential for resolution. The greater the difference in rates, the more efficient the resolution.
- the maximum yield is 50%
- need to separate unreacted starting material from product



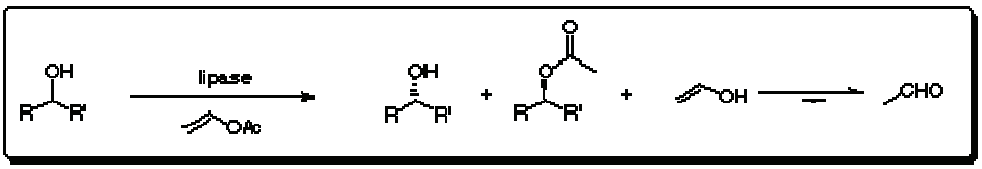
Problems with enzymatic kinetic resolutions of alcohols

- The reaction is reversible. This is a problem in a kinetic resolution. The major product in the forward reaction is also going to be the faster reacting of the two enantiomeric products in the reverse reaction. Hence there will be a loss in the enantioselectivity as the reverse reaction proceeds.
- product inhibition caused by the release of an alcohol during the transesterification reaction.

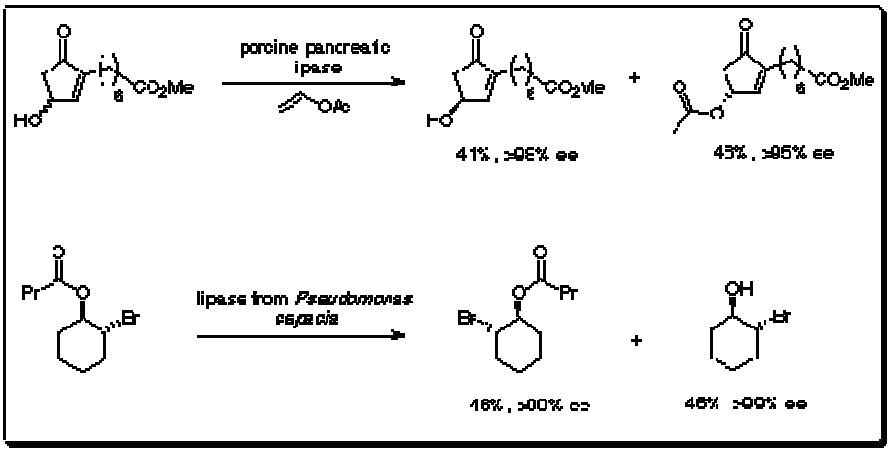
Solution: make the desired reaction *irreversible* and remove the alcohol transesterification product.

These problems can be avoided using activated esters especially enol esters (*e.g.* vinyl acetate):

- the increased reactivity of the ester facilitates the forward reaction
- the equilibrium is pushed over to the right if the ester is used in excess - vinyl acetate is cheap and volatile so it can be used as the solvent.
- the product is an enol and therefore rapidly tautomerises to the aldehyde thereby removing the product alcohol and rendering the reaction irreversible.



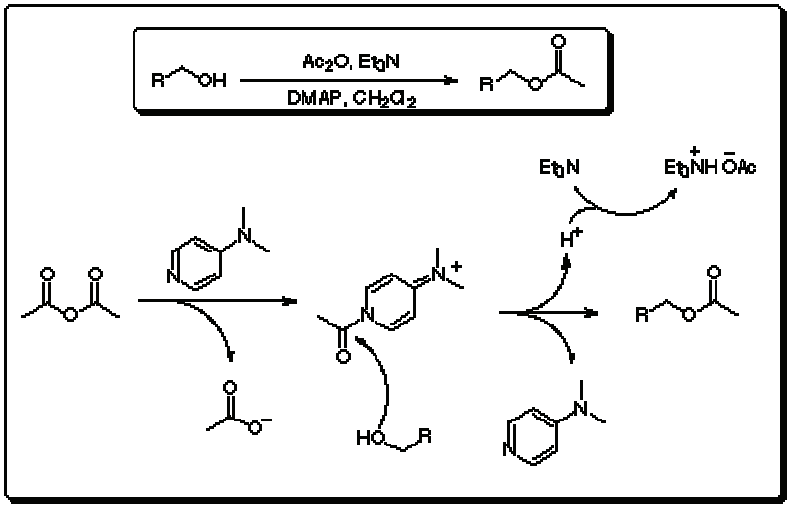
Examples:



A comparison with chemical catalysis – towards a biomimetic artificial enzyme

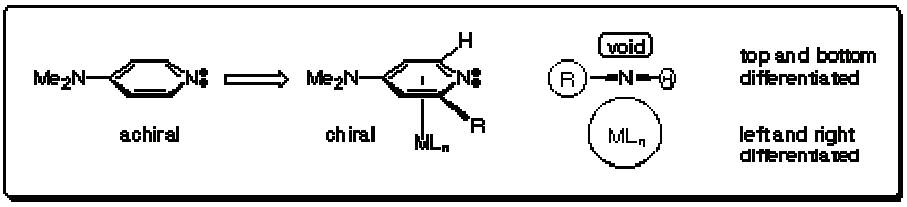
The standard method of acylating alcohols uses 4-dimethylaminopyridine (DMAP) as a catalyst.

- DMAP (4-dimethylaminopyridine) acts as a **nucleophilic catalyst** and increases the rate of acylation by greater than 10000.
- Reaction is very general - very broad substrate selectivity.
- Rapid and high yielding.
- The active acylating reagent is the acyl pyridinium species.

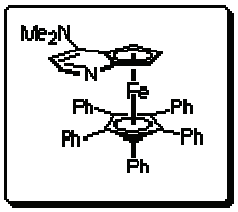


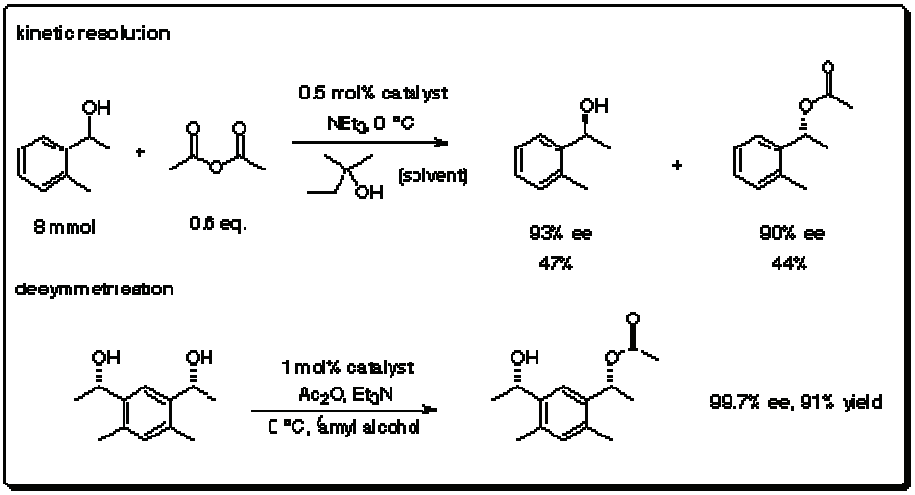
Design of a chiral nucleophilic catalyst:

DMAP contains two mirror planes and therefore is achiral. If we can eliminate these mirror planes then we can generate a chiral molecule.



Solution:





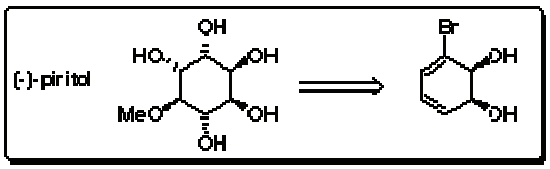
Review: G. C. Fu, *Acc. Chem. Res*., 2000, **33**, 412-420.

II. Enzymatic Oxidation

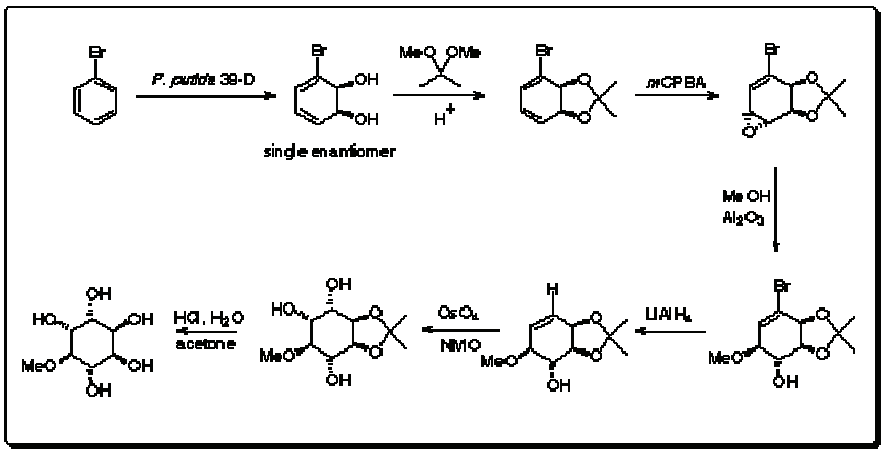
Oxidation of Benzene

It is impossible to perform this transformation using standard chemical dihydroxylation (e.g. OsO_4). Use in the synthesis of (-) pinitol.

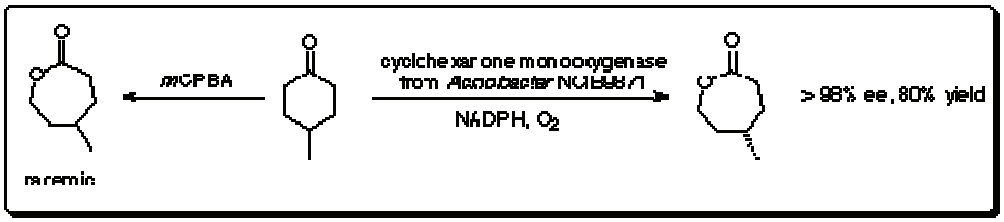
Retrosynthetic analysis:



Forward synthesis:



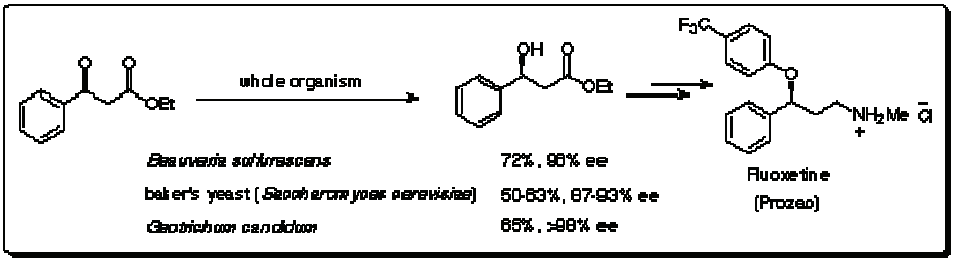
Enantioselective Baeyer-Villiger Oxidation



- This enzyme requires a cofactor (NADPH) for activity.
- Olefins are NOT epoxidised - this can be a competing process using chemical methods (chemoselectivity).
- Oxidation is highly enantioselective and generates a synthetically useful product.

III. Reduction Reactions

Yeast reduction



- β-ketoesters are good substrates for yeast reduction
- the active enzyme is an alcohol dehydrogenase
- the reaction usually does not require the use of purified enzyme
- instead, the whole organism is used
- this can lead to problems if the substrate is accepted by two enzymes (an organism will obviously contain thousands of enzymes) which impart opposing facial selectivities in the reduction - if both enzymes react at similar rates there will be an erosion in the enantioselectivity of the reaction - in this case it is better to use a purified enzyme.