RETROSYNTHETIC ANALYSIS

Retrosynthetic Analysis and Synthetic Planning

Definitions

Retrosynthetic analysis is a technique for planning a synthesis, especially of complex organic molecules, whereby the complex target molecule (TM) is reduced into a sequence of progressively simpler structures (retrons) along a pathway which ultimately leads to the identification of a simple or commercially available starting material (SM) from which a chemical synthesis can then be developed.

The synthetic plan generated from the retrosynthetic analysis will be the roadmap to guide the synthesis of the target molecule.

Synthetic Planning

Linear Synthesis

In linear synthesis, the target molecule is synthesized through a series of linear transformations.

$$A + B \xrightarrow[1]{} C \xrightarrow[2]{D} G \xrightarrow[3]{E} G\text{-}E \xrightarrow[4]{F} G\text{-}H \xrightarrow[5]{I} G\text{-}H\text{-}I$$

Longest sequence is 5 steps

$$\text{Overall yield} = \frac{90}{100} \times \frac{90}{100} \times \frac{90}{100} \times \frac{90}{100} \times \frac{90}{100} = \frac{59}{100}$$

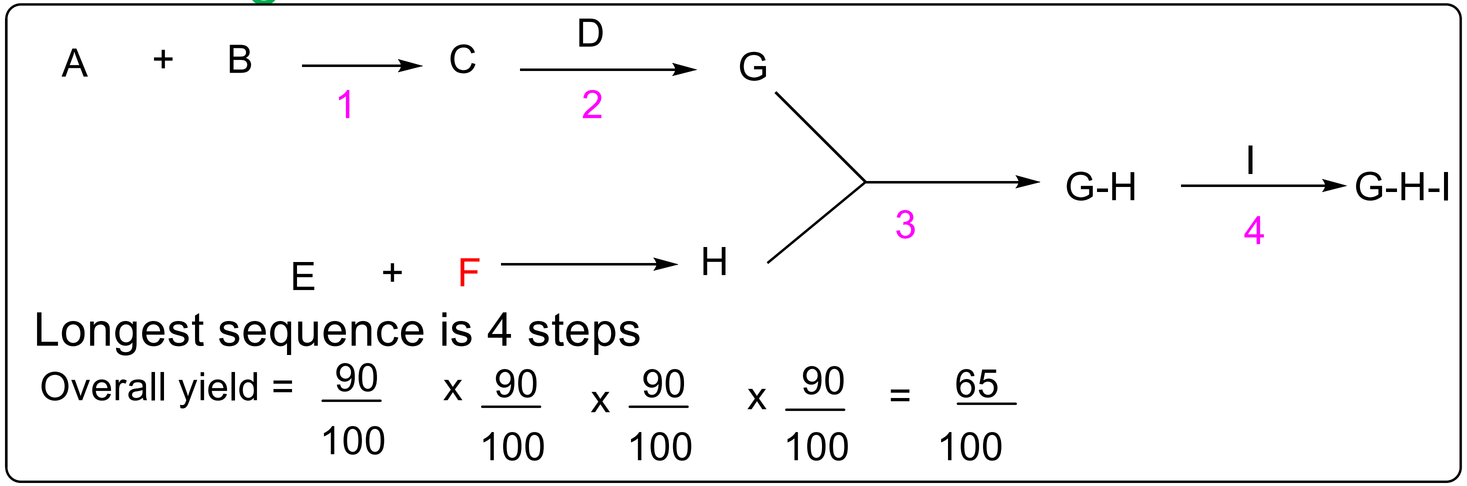
The linear synthesis is fraught with failure for its lack of flexibility leading to potential large losses in the material already invested in the synthesis at the time of failure.

A linear synthesis is longer and thus suffers lower overall yields compared to a convergent synthesis.

Synthetic Planning

Convergent Synthesis

In convergent synthesis, key fragments of the target molecule are synthesized separately or independently and then brought together at a later stage in the synthesis to make the target molecule.

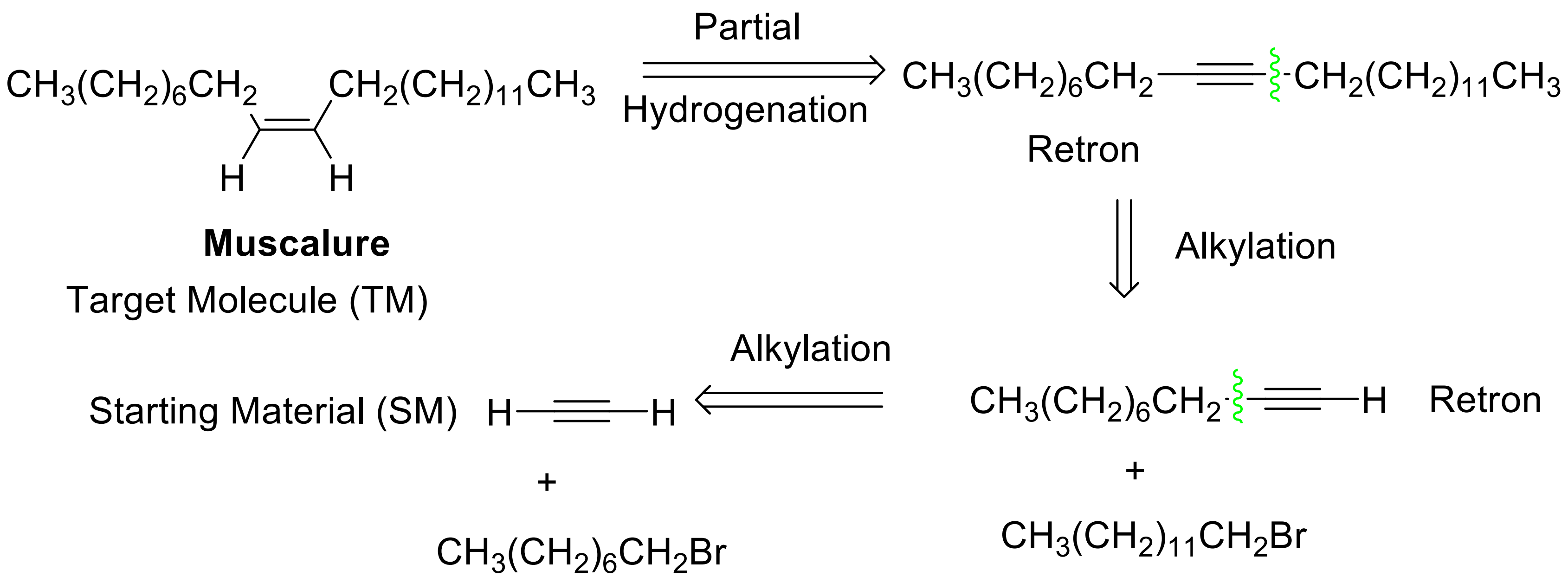


A convergent synthesis is shorter and more efficient than a linear synthesis leading to a higher overall yield.

It is flexible and easier to execute due to the independent synthesis of the fragments of the target molecule.

Retrosynthetic Analysis

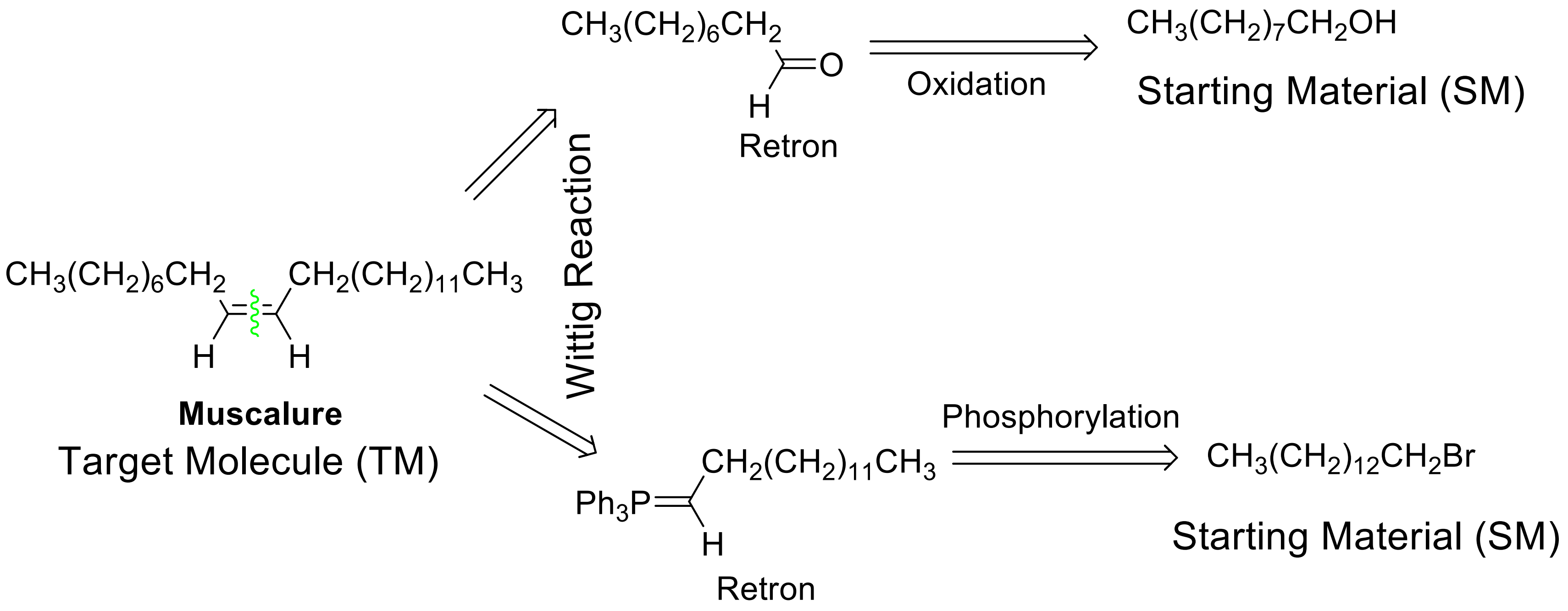
Consider the retrosynthetic analysis of Muscalure, the pheromone of the domestic housefly, for illustration of the concept of retrosynthetic analysis:



The retrosynthetic analysis of any target molecule must be based on known chemical reactions for it to stand a realistic chance of being translated to a chemical synthesis.

Retrosynthetic Analysis

Muscalure can also be deconstructed based on the Wittig reaction.

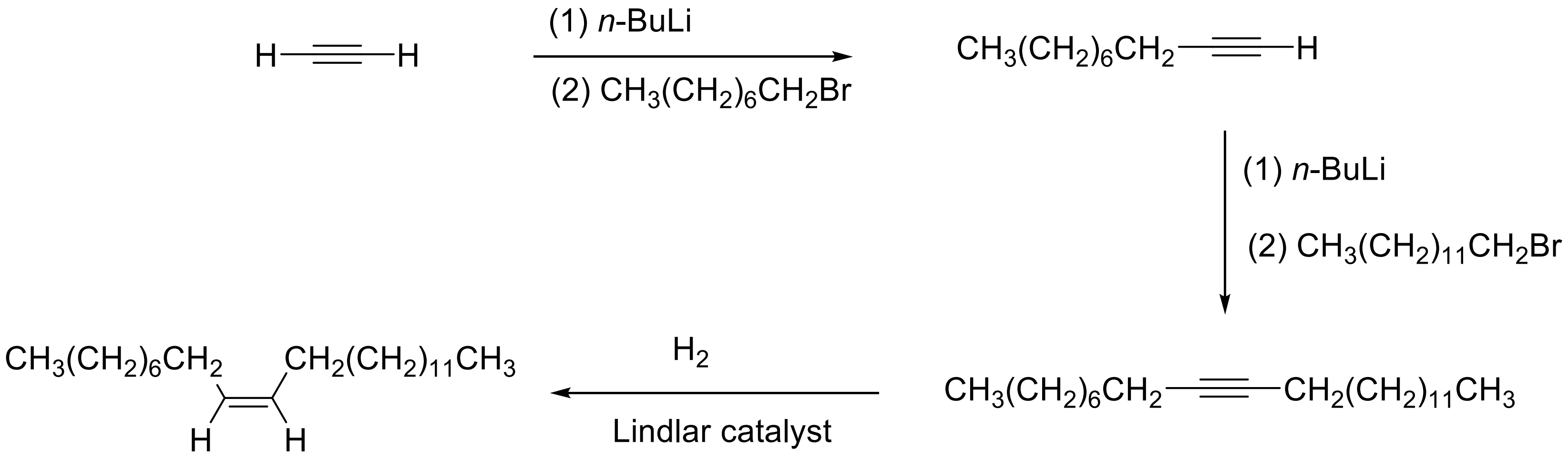


A thorough evaluation of all alternative retrosynthetic pathways should be made to identify the pathway that best stands a realistic chance of being translated to an efficient chemical synthesis.

Synthetic Planning

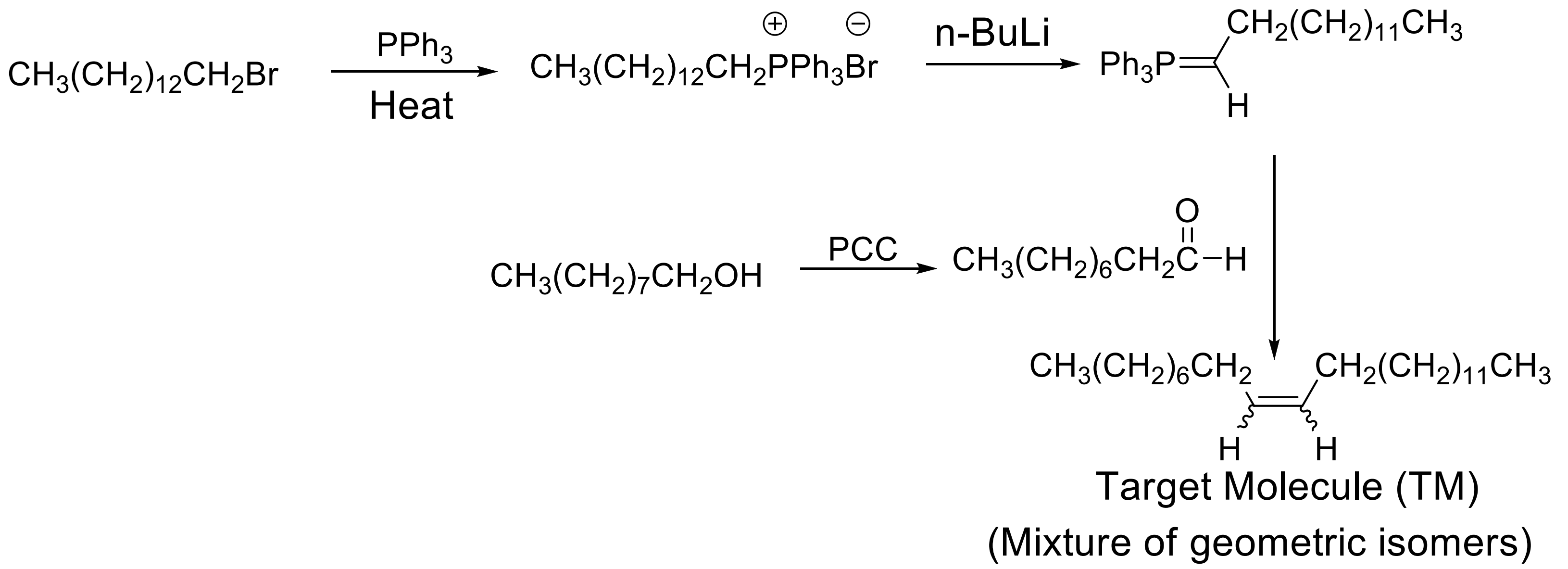
Synthesis is a construction process that involves converting simple or commercially available molecules into complex molecules using known reagents.

Consider the chemical syntheses of Muscalure to appreciate how the two retrosynthetic plans fit in, but most importantly, note the use of specific reagents that transform the intermediates in the retrosynthetic scheme eventually to the target molecule.



Synthetic Planning

Synthesis of Muscalure via the Wittig reaction.



Comparing the two synthetic pathways shows that while the Wittig route is convergent, the stereochemistry of the double bond is not stereospecifically controlled.

The linear pathway of the stereospecific partial reduction of a terminal alkyne is the preferred route to Muscalure.

Synthetic Planning

Retrosynthetic analysis and synthetic planning requires training (knowledge of chemistry) and experience (practical application of the chemistry).

The wider someone's knowledgebase is in organic chemistry, the more the options one has to develop a variety of synthetic routes to a target molecule. One of these retrosynthetic pathways may turn out to be more practical and executable than the others.

A good synthetic plan should consider taking into account the advantage of a convergent synthesis, if possible, over a linear synthesis.

Terminology of Retrosynthetic Analysis

Disconnection

During retrosynthetic analysis the target molecule is systematically broken down by a combination of functional group interconversion (FGI) and disconnection.

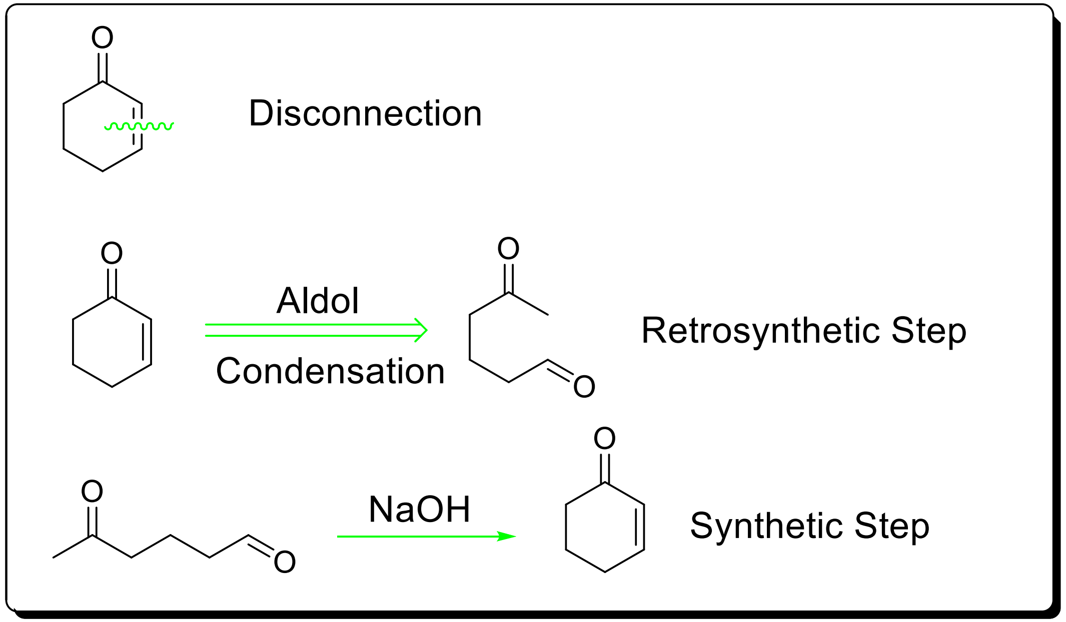
The term disconnection relates to breaking a carbon-carbon bond of a molecule to generate simpler fragments.

A good disconnection must achieve the greatest simplification of the target molecule. For a complex organic molecule, this basic disconnection process is repeated until the target is reduced to simple starting materials.

The complete set of disconnections and functional group interconversions for a specified target molecule is what constitutes a retrosynthesis or retrosynthetic plan.

Symbols of Retrosynthetic Analysis

- A disconnection is represented by a wavy (⌇) line through the bond being disconnected,.
- A retrosynthetic arrow (⇒) represents going from the target molecule "backwards" to simpler molecules (retrons).
- A synthetic arrow (⟶) represents going in the forward direction.



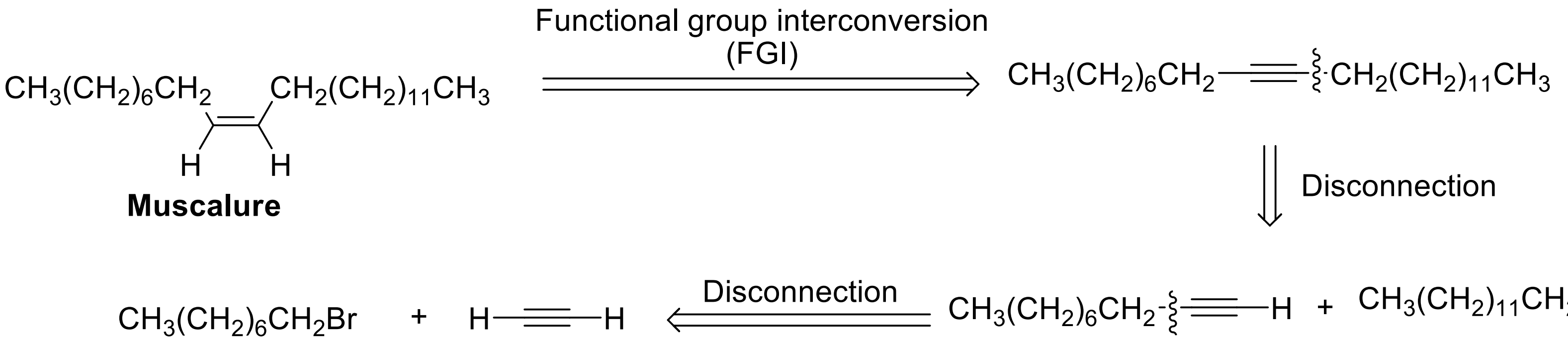
Terminology of Retrosynthetic Analysis

Functional Group Interconversion

Functional group interconversion (FGI) describes a process of converting one functional group to another: e.g. an alcohol to an aldehyde, alkyne to alkene etc.

Although FGI doesn't offer much gain to a synthesis, it facilitates subsequent disconnection of the intermediate.

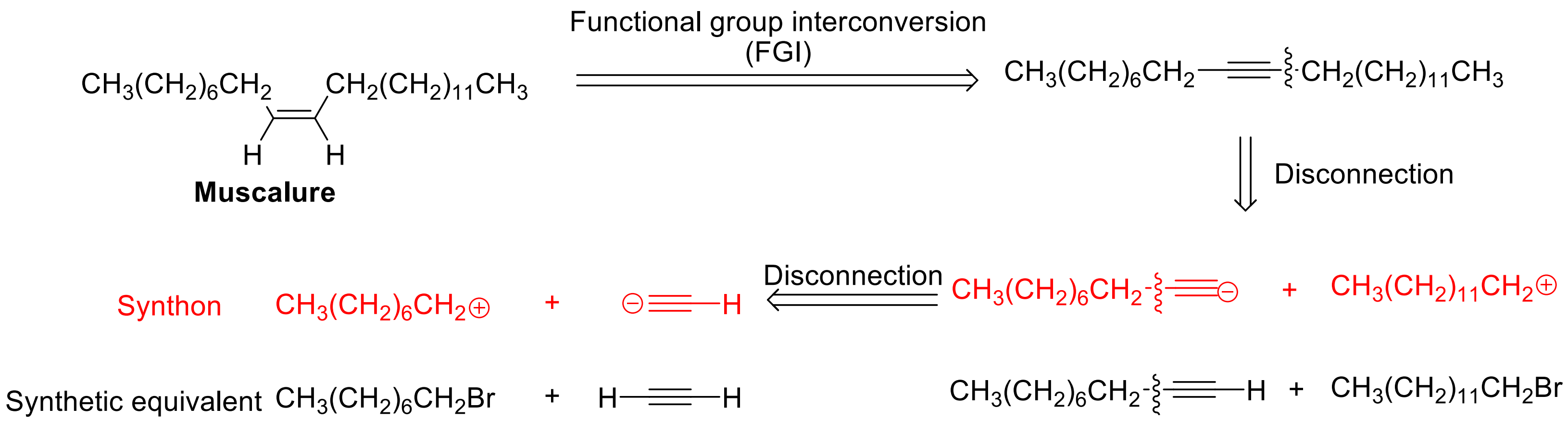
Revisit the retrosynthetic analysis of Muscalure to identify the disconnections and Functional group interconversions.



Retrosynthetic Strategy

The concept of bond polarity within functional groups is of prime importance in disconnections.

The disconnection of a bond based on this innate polarity may lead to two pairs of idealized (imaginary) fragments called synthons from which a functional group may be generated.

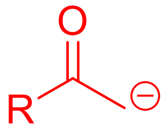
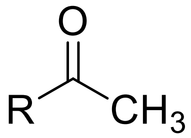


Terminology of Retrosynthetic Analysis

A synthon is an idealized fragment or species (e.g. CH_3^+ or CH_3^-) generated from a bond disconnection during retrosynthetic analysis. It may not necessarily correspond to a real molecule.

A synthetic equivalent is a real molecule or reagent (e.g. CH_3Br or CH_3MgBr) that can be ascribed to a synthon and can be employed in a synthetic step.

Other Synthons and their Synthetic equivalents

Synthon	$R^{\oplus}$	$R^{\ominus}$	
Synthetic equivalent	RI, RBr, ROTs	RMgX, RLi	

Strategies in Synthetic Planning

(a) Strive for success and good cost management

In planning a synthesis generate a large number of retrosynthetic pathways to the target molecule: Examine these retrosynthetic pathways to identify among them an optimal synthetic route for which reagents are readily available and inexpensive.

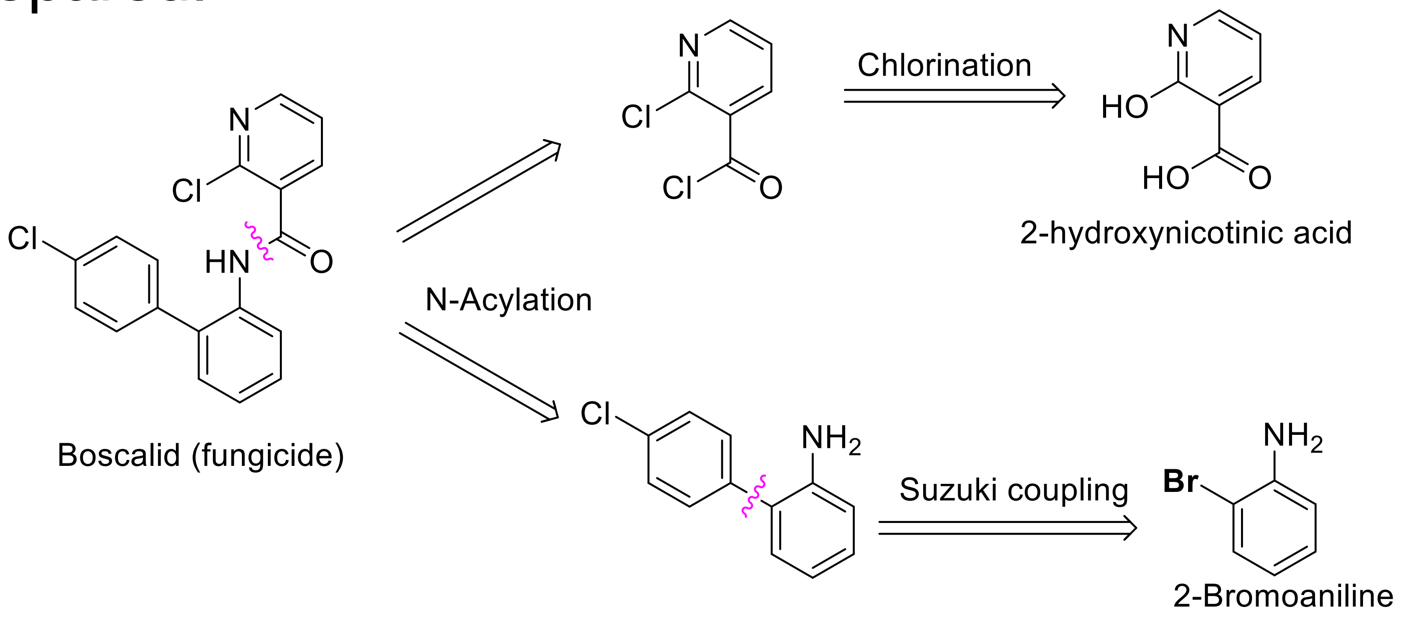
(b) Convergent vs Linear synthesis

When considering a disconnection in the retrosynthetic analysis of a complex target molecule, try (if possible) to divide the molecule into halves at convenient bonds. This will make possible the formulation of a convergent synthesis with several mini-syntheses leading to the target molecule.

Strategies in Synthetic Planning

(c) Aim for disconnections that lead to the greatest simplification of the target molecule

Given a choice of possible disconnections, those located at branch points or on rings are more strategic as they usually give straight chain fragments which are more likely to be commercially available or simply prepared.

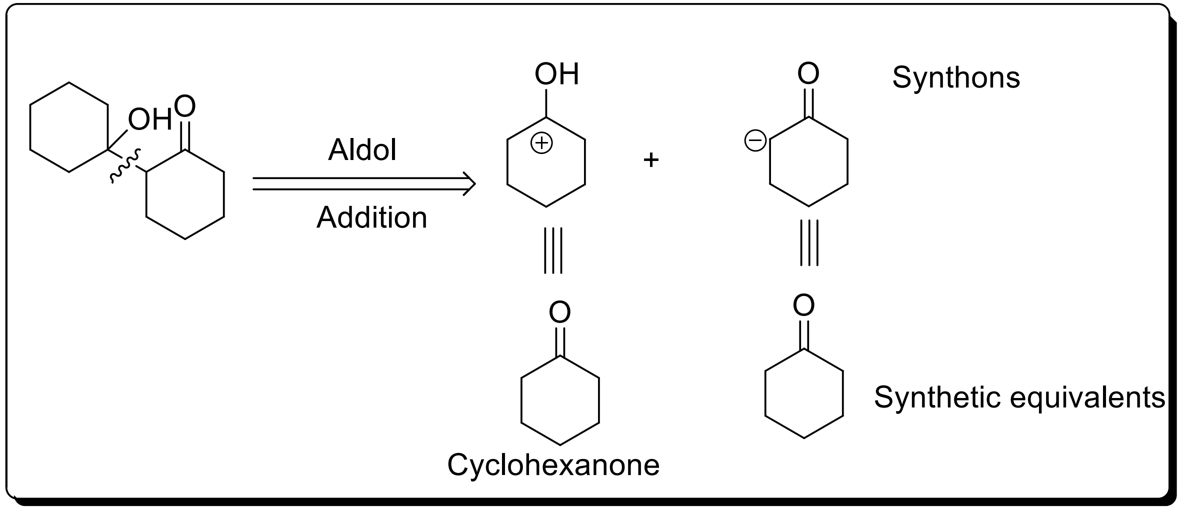


Strategies in Synthetic Planning

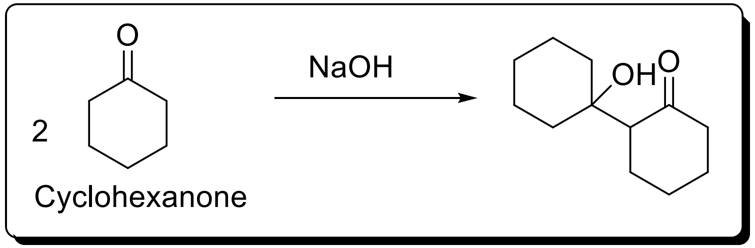
(d) Identify and exploit any inherent symmetry in a target molecule

Exploiting any symmetry in a TM or its intermediate can dramatically simplify its retrosynthesis. This may also provide an opportunity to identify a convergent pathway in the synthesis.

Retrosynthetic Plan



Synthetic Plan



Self-Aldol Addition

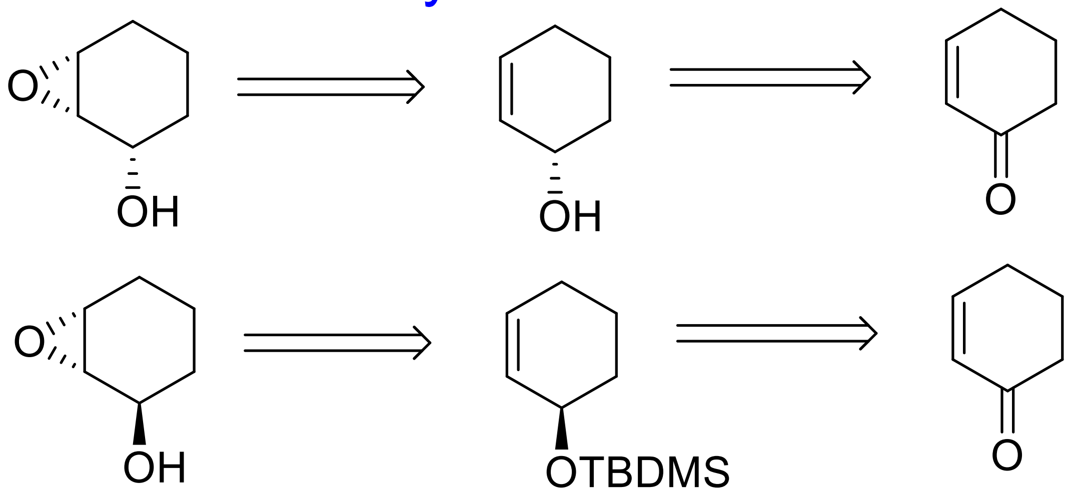
Strategies in Synthetic Planning

(e) Introduce reactive functional groups at a late stage in the synthesis

It is often difficult to selectively react at a less reactive functional group when a more reactive functionality is present within the same molecule. Such reactive functional groups are usually among the first to be disconnected during retrosynthetic analysis.

Consider the retrosynthetic analysis of two epoxy alcohols shown below:

Retrosynthetic Path

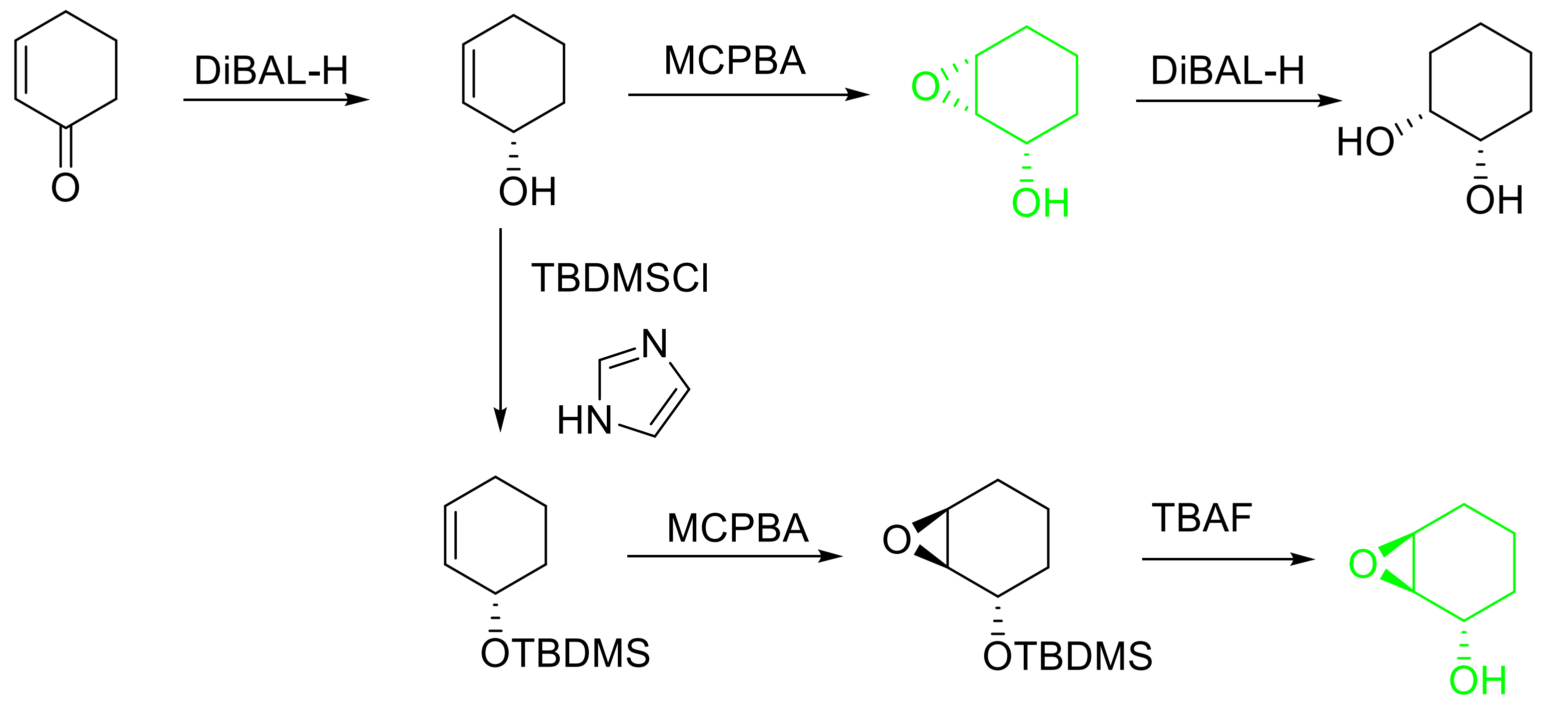


Strategies in Synthetic Planning

Synthesis of the Epoxy Alcohol

Based on the preceding retrosynthetic plans, the epoxy alcohols can be synthesized as shown below:

Synthesis



Ring opening of epoxide occurs readily, consequently epoxides must be introduced last in the synthesis

Strategies in Synthetic Planning

(f) During retrosynthetic analysis introduce additional functional groups, if necessary, to direct bond formation: Functional group addition (FGA) strategy

The functional group addition strategy in retrosynthetic analysis involves introducing additional functional groups at strategic locations in a retron, if necessary, to guide further disconnections based on known powerful bond making reactions.

Addition of functional groups such as double bonds or carbonyl groups can serve to direct reactivity to specific locations of a molecule and allow disconnection based on dependable reactions.

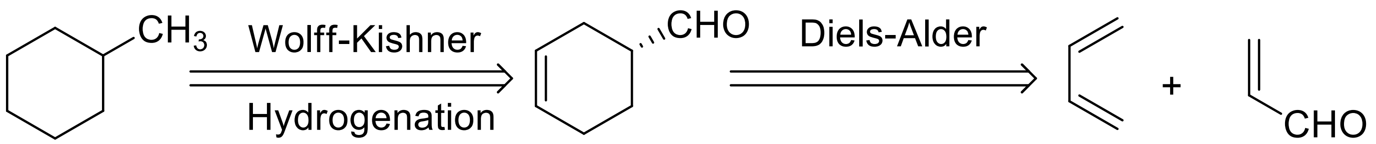
This can significantly simplify a synthesis.

Strategies in Synthetic Planning

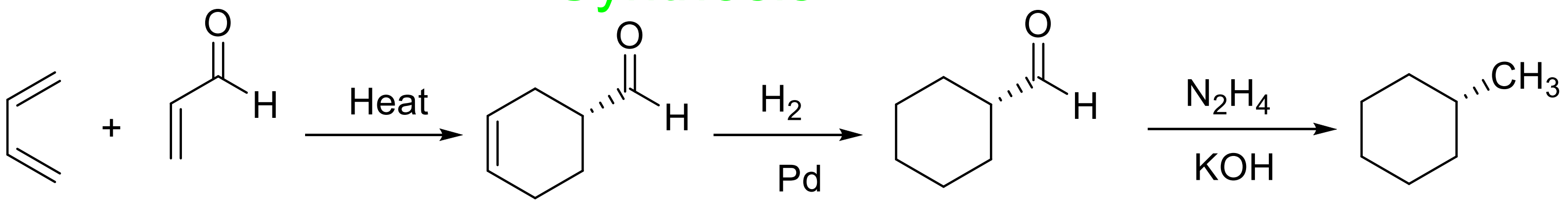
Functional Group Addition Strategy

For example, introduction of a double bond in a cyclohexane target molecule may help key a disconnection based on a Diels Alder reaction, a powerful carbon-carbon bond forming reaction.

Retrosynthesis



Synthesis



Strategies in Synthetic Planning

(g) Use protecting groups if inevitable

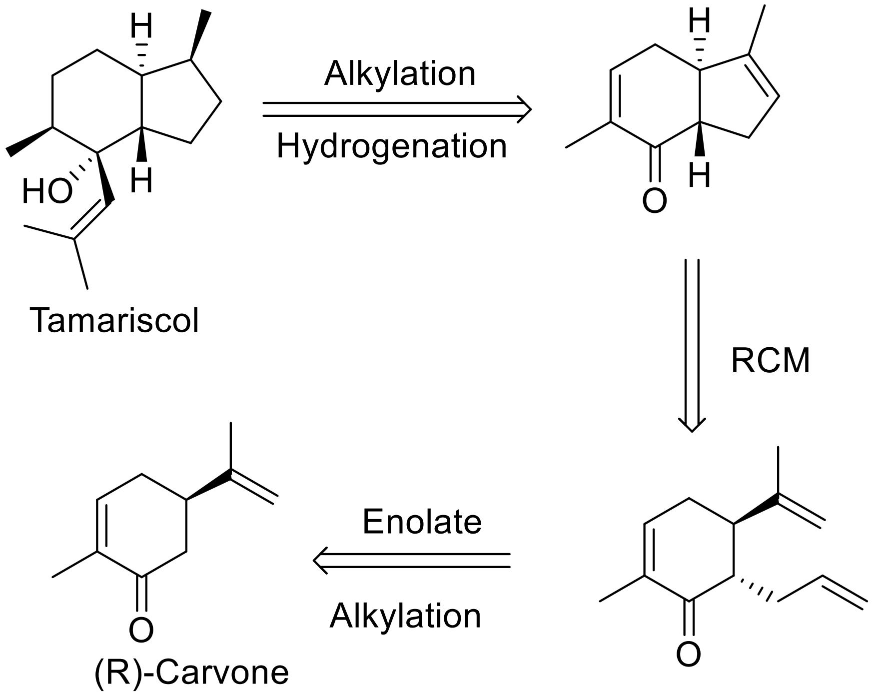
Given that the use of protecting groups adds to the number of steps of a synthesis, use them only when it is absolutely necessary.

Sample Retrosyntheses and Syntheses

Retrosynthetic Analysis of Tamariscol

Tamariscol belongs to the pacifigorgiane class of sesquiterpenes found in both marine and terrestrial sources.

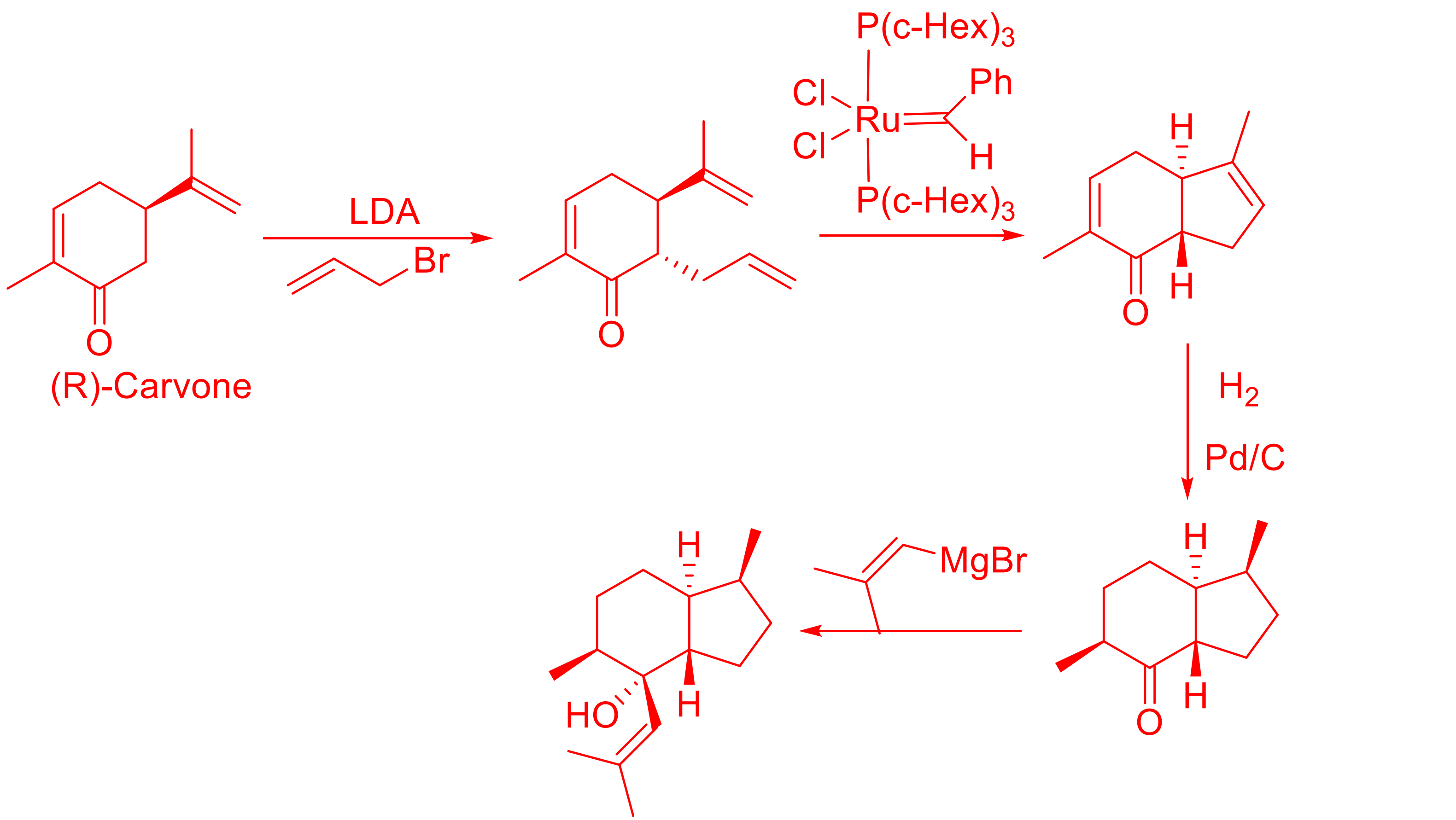
The retrosythesis based on ring closing metathesis is highlighted below:



Sample Retrosyntheses and Syntheses

Synthesis of Tamariscol based on RCM

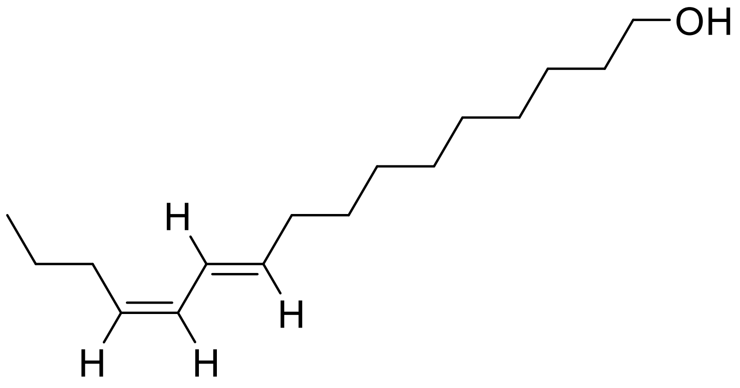
The synthesis of tamariscol based on ring closing metathesis is highlighted below:



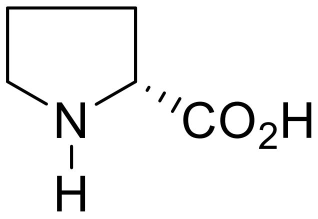
Sample Retrosyntheses and Syntheses

Sample Problems

(1) Propose retrosynthetic and synthetic schemes for bombykol, a pheromone released by the female silkworm to attract males.



(2) Proline is an essential amino acid. Develop a retrosynthetic strategy and then synthesis from serine as a starting material using RCM.



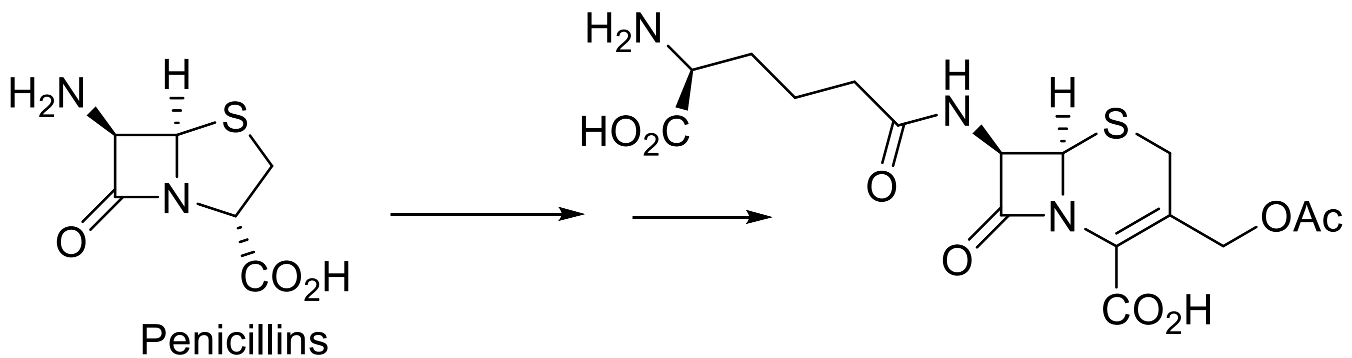
Terminology in Synthesis of Natural Products

(a) Total synthesis

Total synthesis refers to the synthesis of complex natural compounds from simple common starting materials that are commercially available.

(b) Partial synthesis

Partial synthesis relates to the synthesis of complex natural products beginning from a naturally occurring compound or an advanced intermediate and then independently converting it to the target natural product. Note that a portion of the molecule is therefore biosynthesized and the other chemically synthesized.



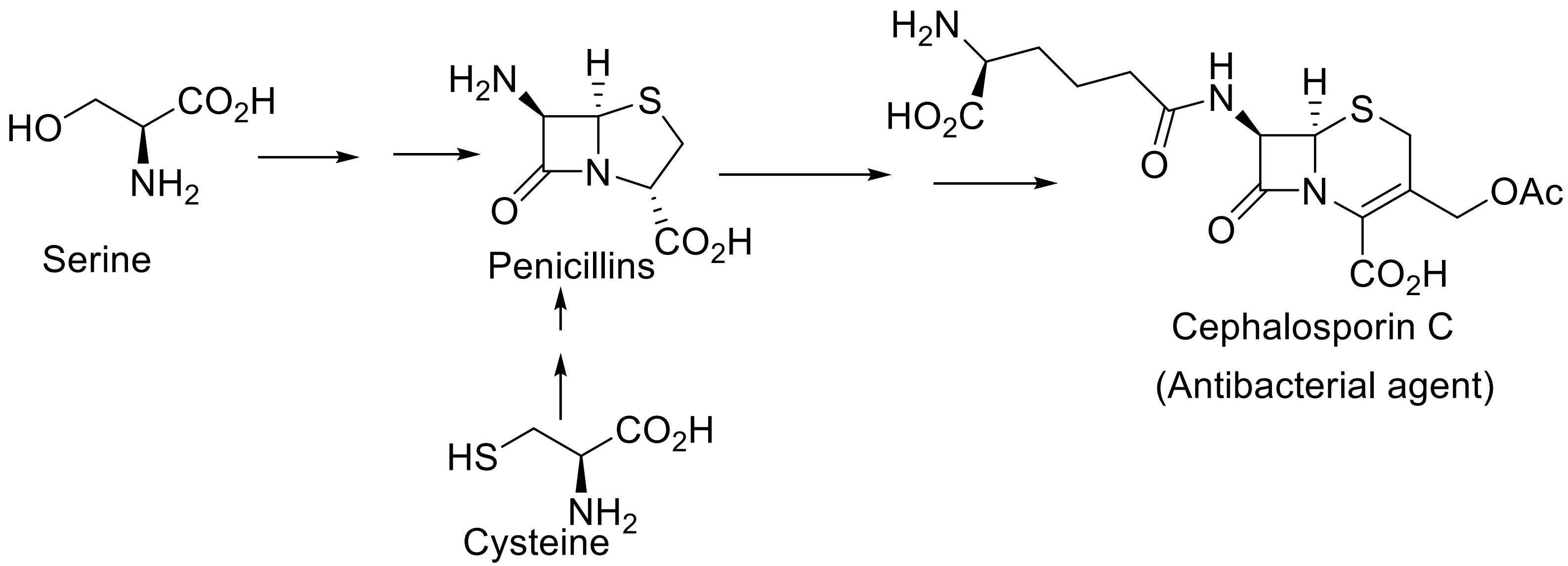
Penicillins
(Available by fermentation)

Cephalosporin C

Terminology in Synthesis of Natural Products

(c) Formal synthesis

Formal synthesis refers to the independent synthesis of an advanced precursor of a natural product, whose synthesis has previously been accomplished. The independent synthesis of that advanced precursor must also have been reported in the literature.



CAT 2
ORGANIC SYNTHESIS

THURSDAY, 6TH APRIL 2016

10.00 – 11.30 AM

G14