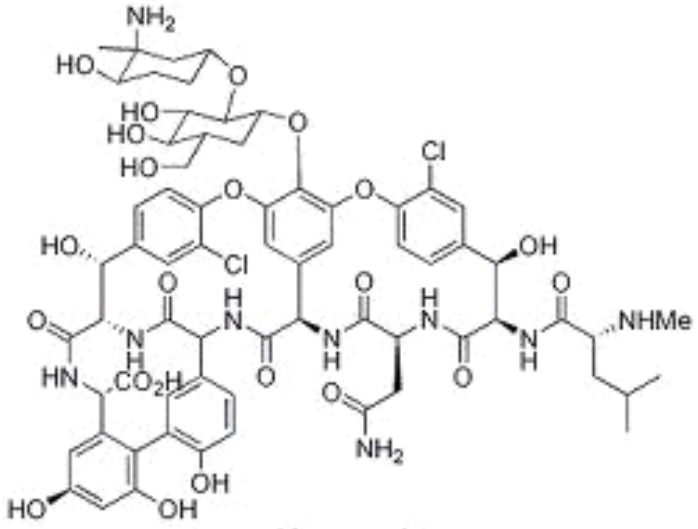
Retrosynthetic Analysis and Synthetic Planning

Simple Starting Material for Synthesis

?



Vancomycin

Complex Target Molecule to be synthesized

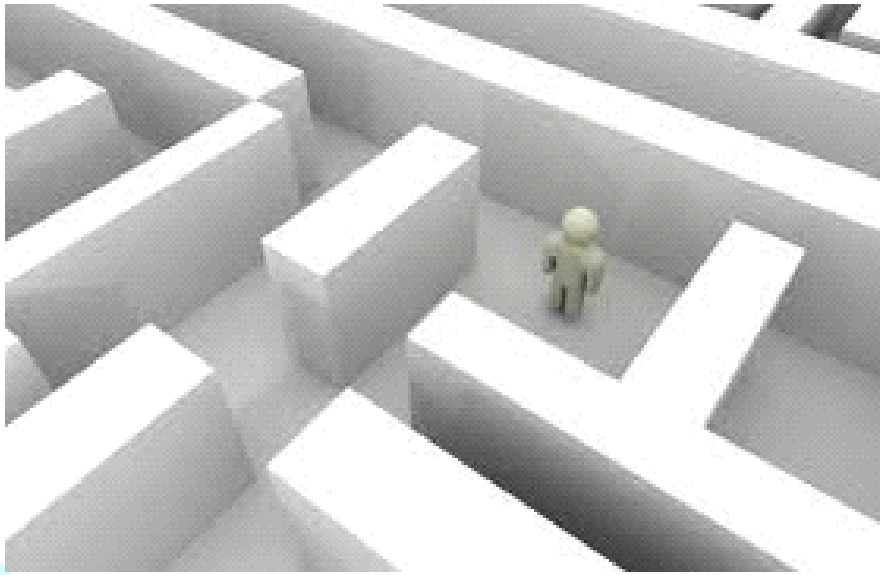
Vancomycin is an antibiotic used against bacteria that cause food poisoning.

Life's Perspectives

Planning a Journey to the Unknown

"I am now lost, I have been wandering"

Destination



Origin

"I am not lost, I am just wondering"

Retrosynthetic Analysis

Definition

Retrosynthetic analysis (retrosynthesis) 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 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.

Retrosynthetic analysis is based on known reactions (e.g the Wittig reaction, oxidation, reduction etc).

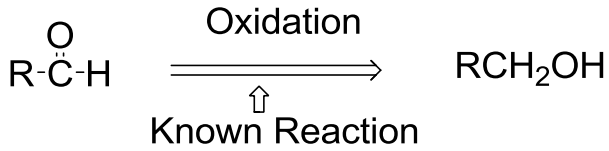
The synthetic plan generated from the retrosynthetic analysis will be the roadmap to guide the synthesis of the target molecule.

Synthetic Planning

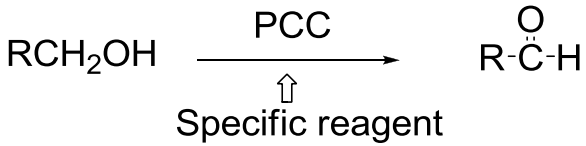
Definition

Synthesis is a construction process that involves converting simple or commercially available molecules into complex molecules using specific reagents associated with known reactions in the retrosynthetic scheme.

Retrosynthetic Scheme



Synthetic Scheme



Syntheses can be grouped into two broad categories:

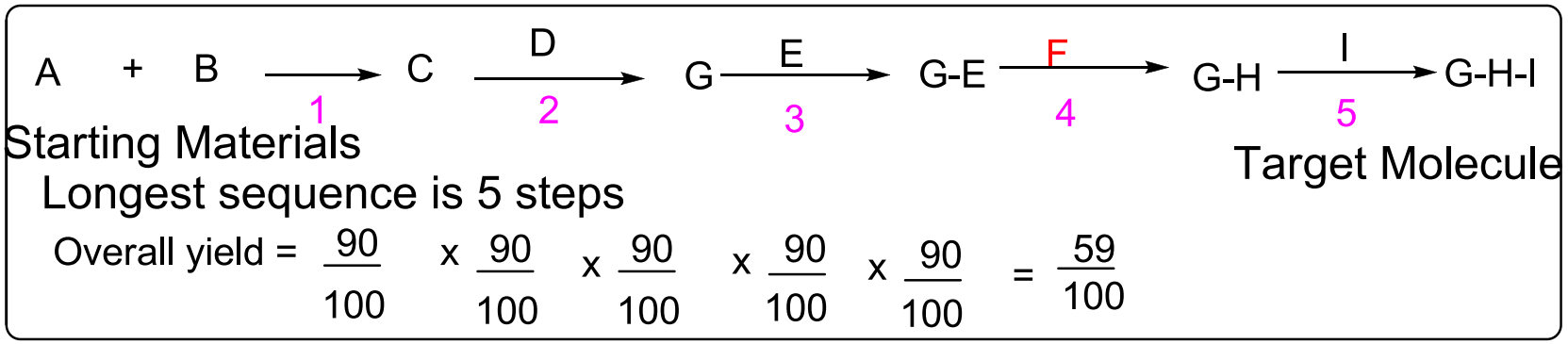
(i) Linear syntheses

(ii)Convergent syntheses

Linear Synthesis

Definition

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



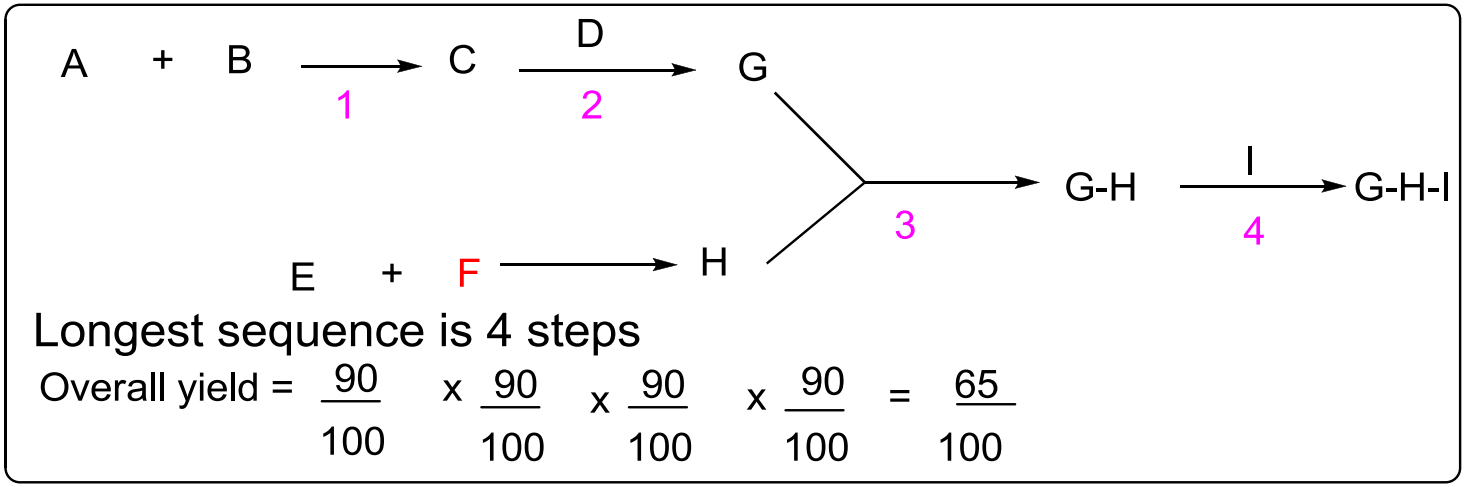
Since the overall yield of the synthesis is based on the single longest route to the target molecule, by being long, a linear synthesis suffers a lower overall yield.

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.

Convergent Synthesis

Definition

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.

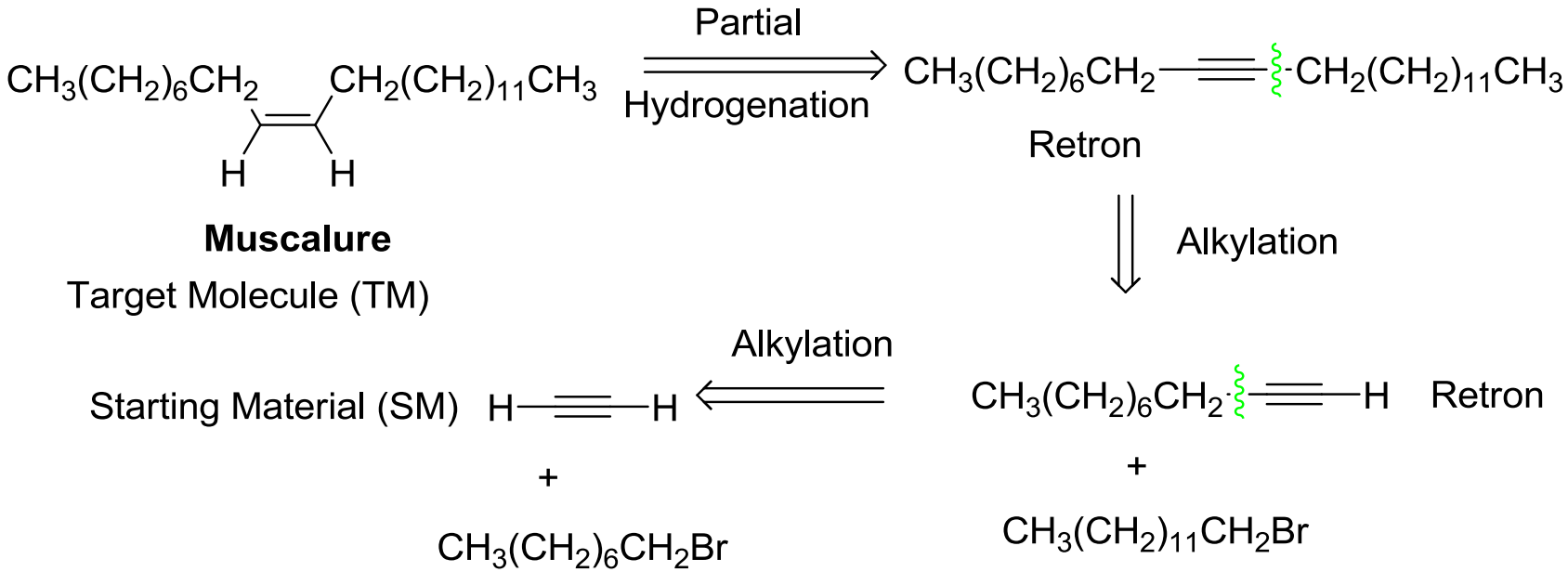


A convergent synthesis is shorter and more efficient than a linear synthesis leading to a higher overall yield.

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

Retrosynthetic Analysis

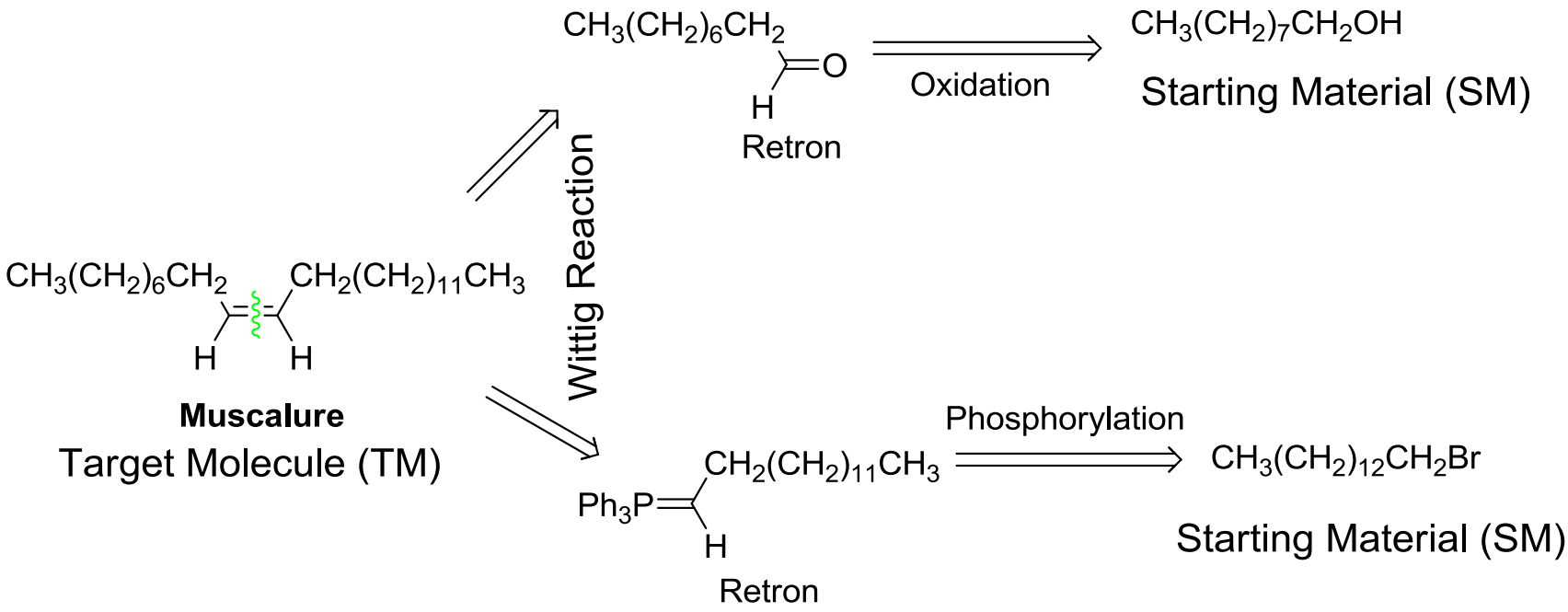
Consider the retrosynthetic analysis of Muscalure, the pheromone of the domestic housefly, to illustrate the concept of retrosynthetic analysis:



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.

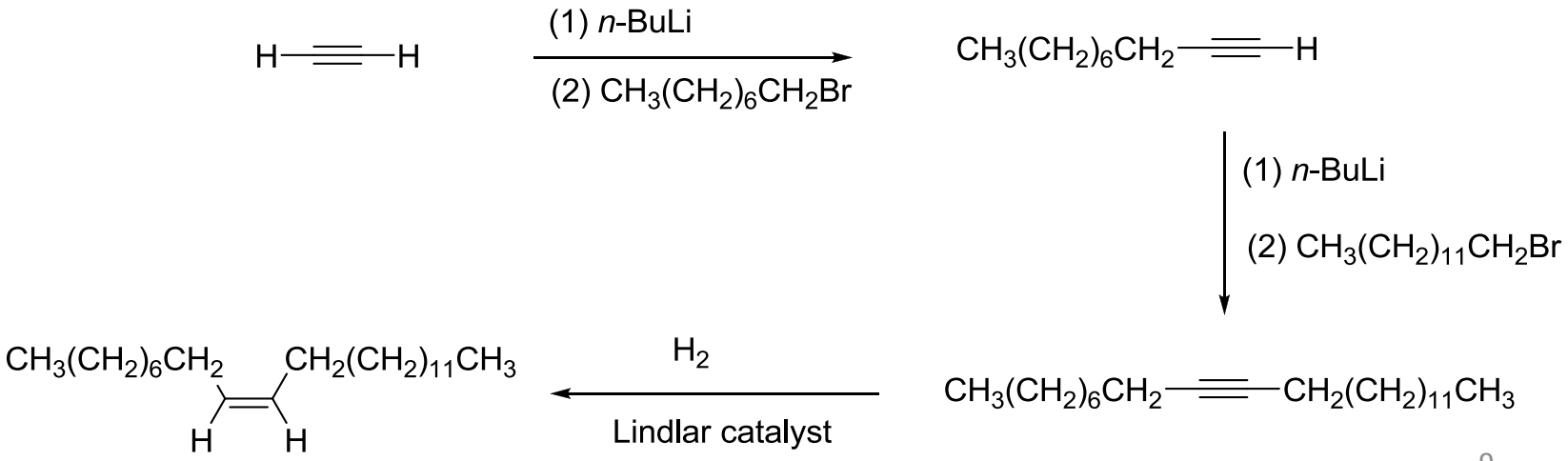


A thorough evaluation of the alternative retrosynthetic pathways should be made to identify the pathway that best stands a realistic chance of being translated to an efficient chemical synthesis.

Synthetic Planning

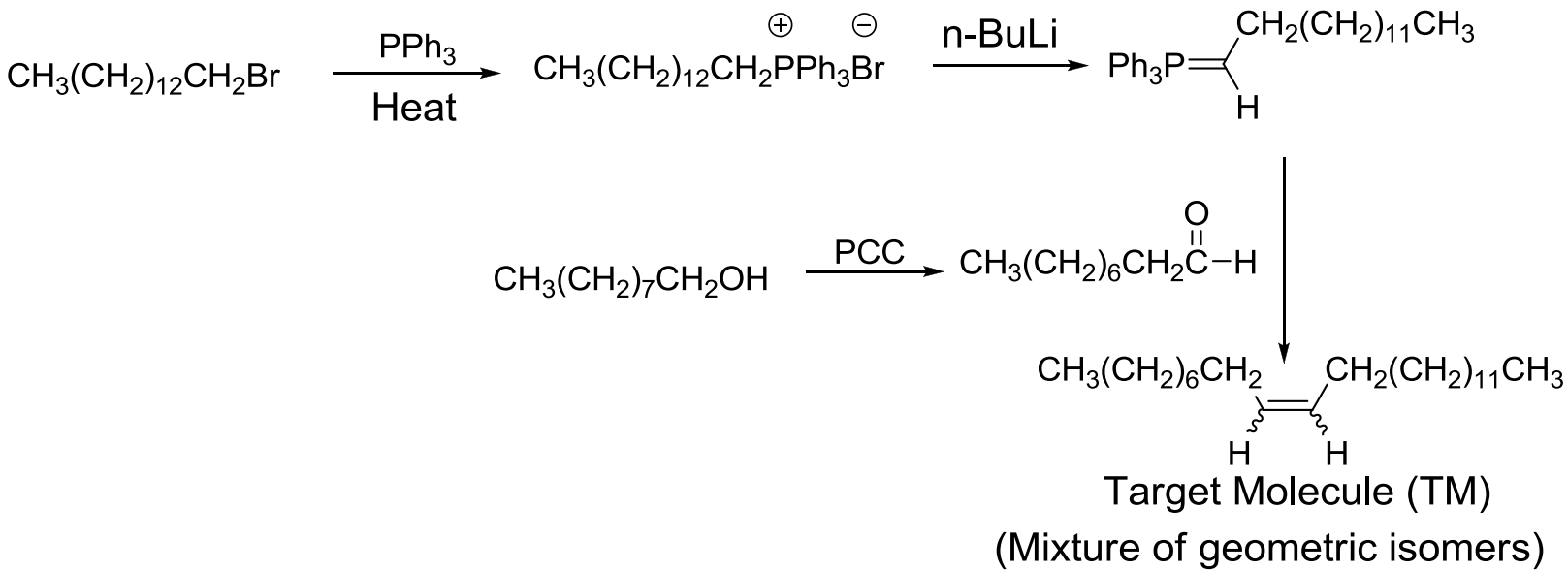
When evaluating the various retrosynthetic schemes of the target molecule, it is important to recognize the strategic features of the molecule that the synthesis must address.

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 available to one 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

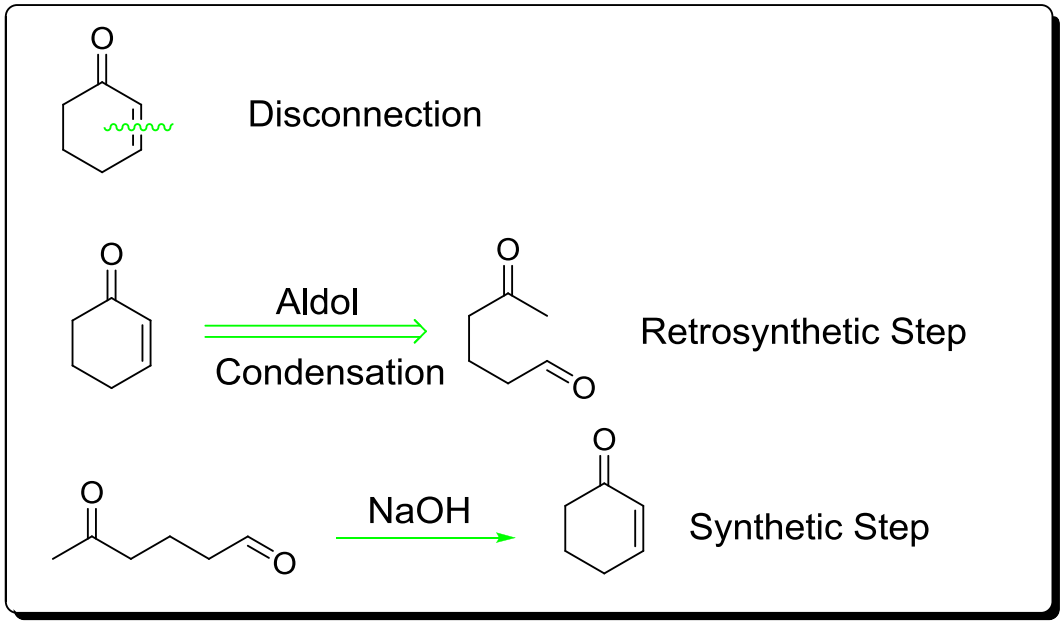
During retrosynthetic analysis the target molecule is systematically broken down by a combination of disconnection and functional group interconversion (FGI).

The term disconnection relates to breaking a carbon-carbon bond of a molecule to generate shorter or simpler fragments. A good disconnection must achieve the greatest simplification of the target molecule. For a complex 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 retrosynthetic pathway or plan.

Symbols of Retrosynthetic Analysis

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



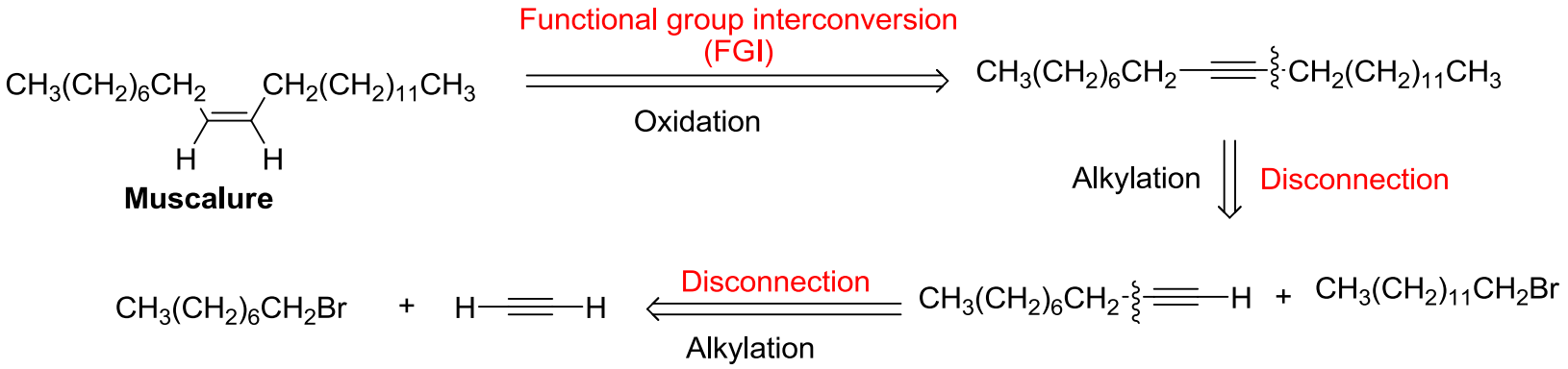
Terminology of Retrosynthetic Analysis

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 sets the stage for subsequent disconnection of the intermediate.

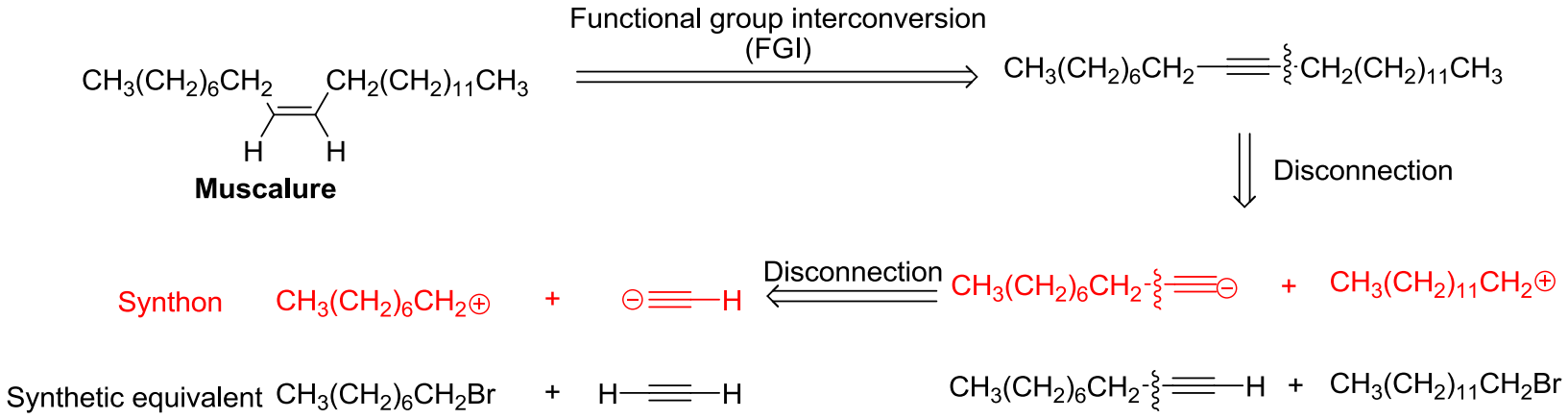
Revisit the retrosynthetic analysis of Muscalure to identify the disconnections and Functional group interconversions.



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.

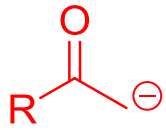
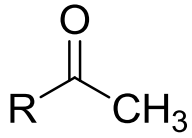


Terminology of Retrosynthetic Analysis

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.

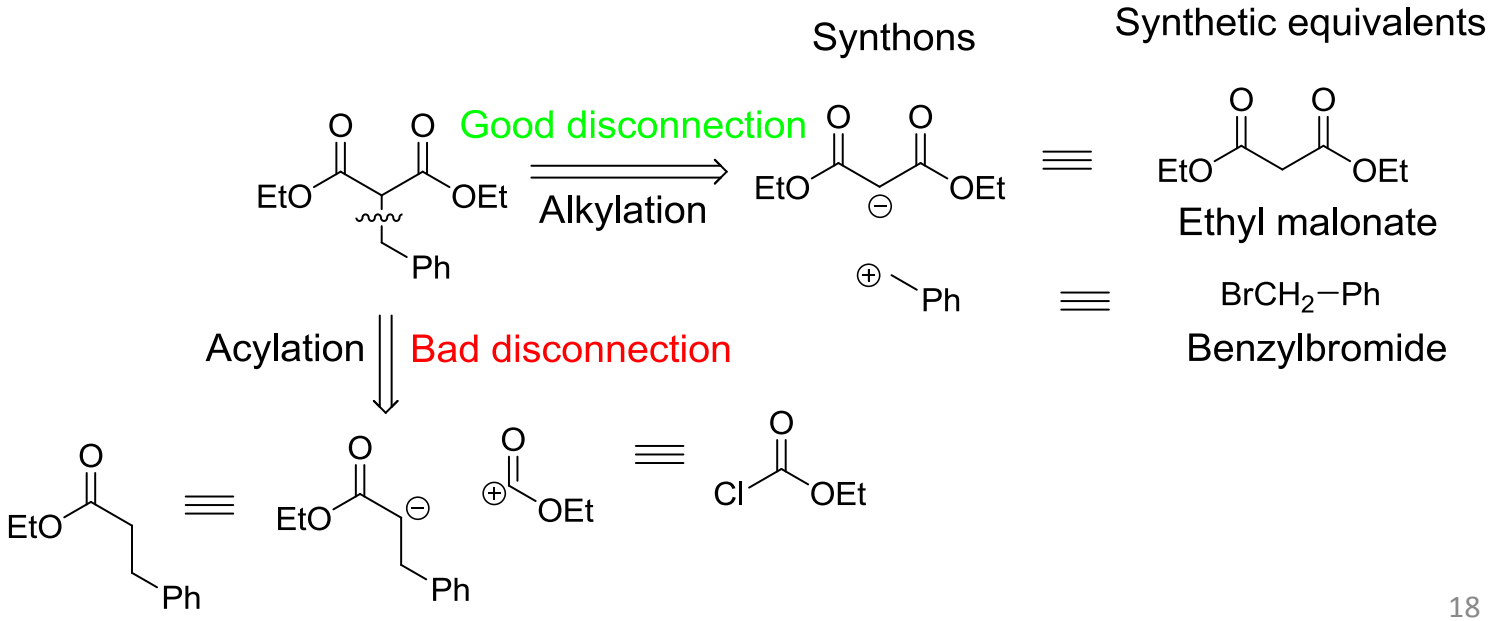
(b) Convergent vs Linear synthesis

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.

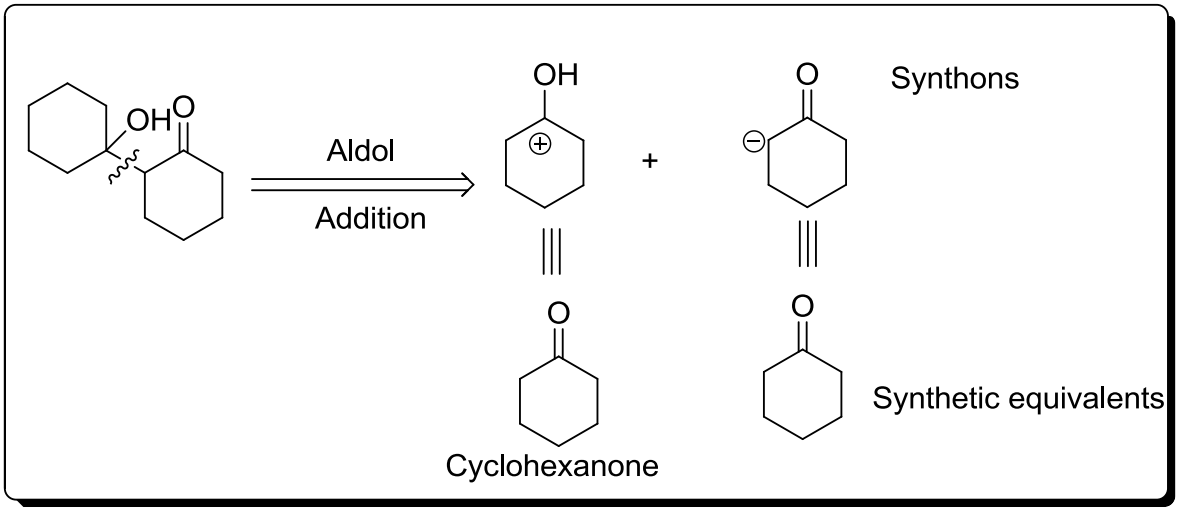


Strategies in Synthetic Planning

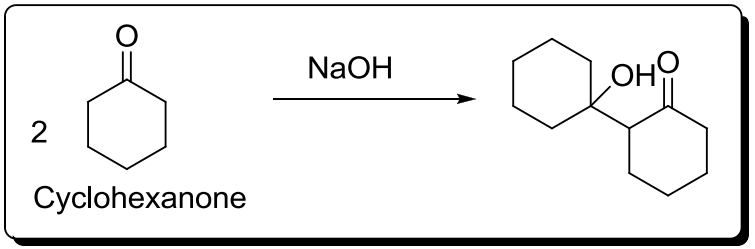
(d) Identify and exploit any inherent symmetry in a target molecule

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

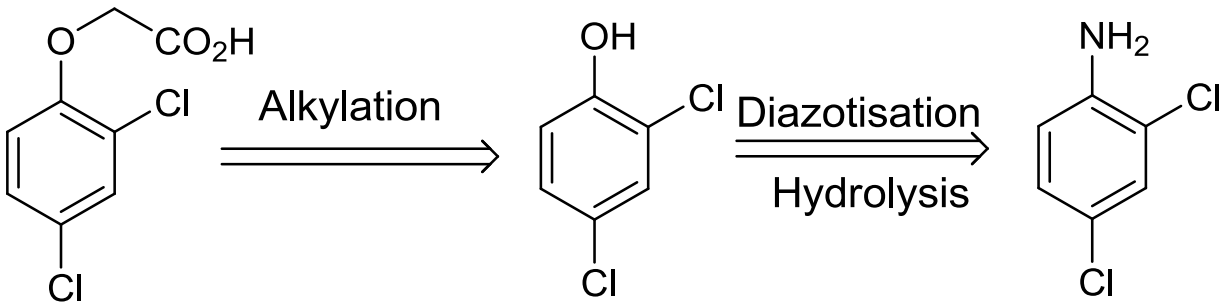
Strategies in Synthetic Planning

(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.

The retrosynthetic analysis of 2,4-dichlorophenoxyacetic acid (2,4-D), a common herbicide for the control of broadleafed weeds, is shown below:

Retrosynthetic Plan



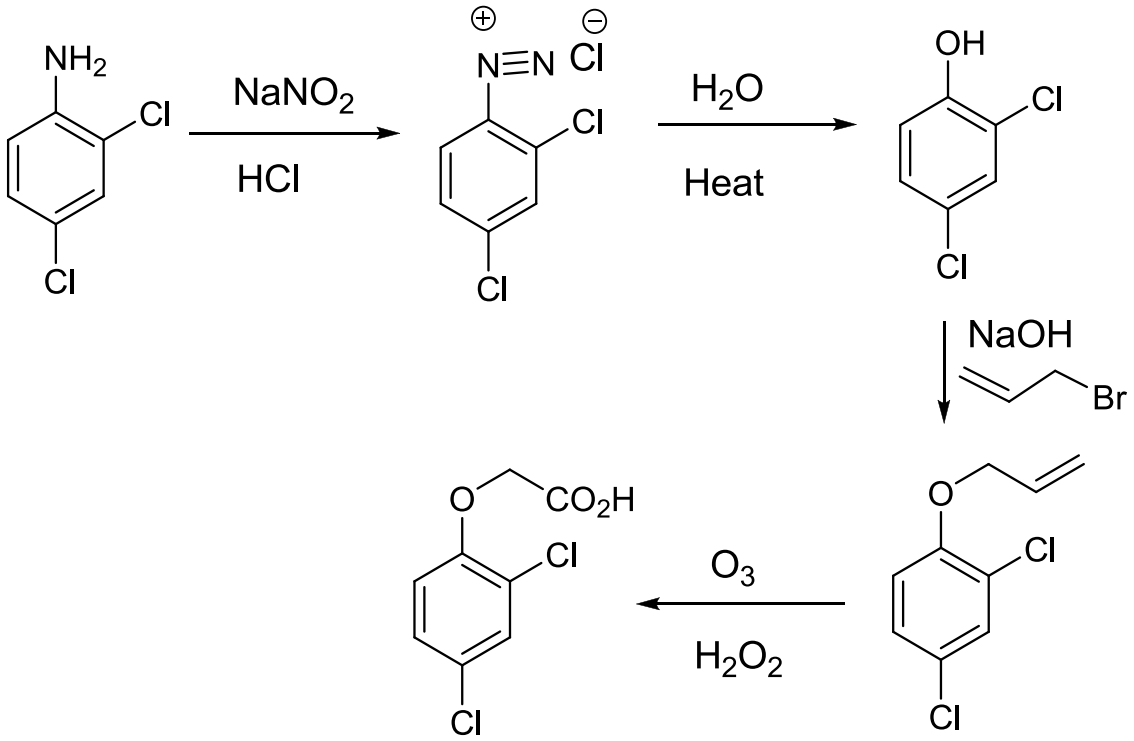
2,4-D

Strategies in Synthetic Planning

Synthesis of the Weed-Killer, 2,4-D

Based on the preceding retrosynthetic plan, 2,4-dichlorophenoxyacetic acid (2,4-D) can be synthesized as shown below:

Synthetic Plan

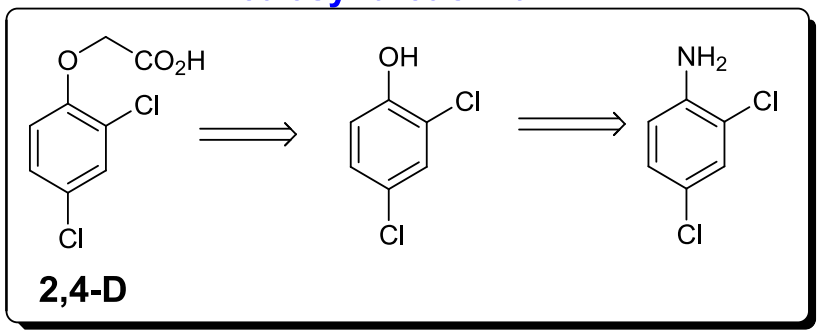


Strategies in Synthetic Planning

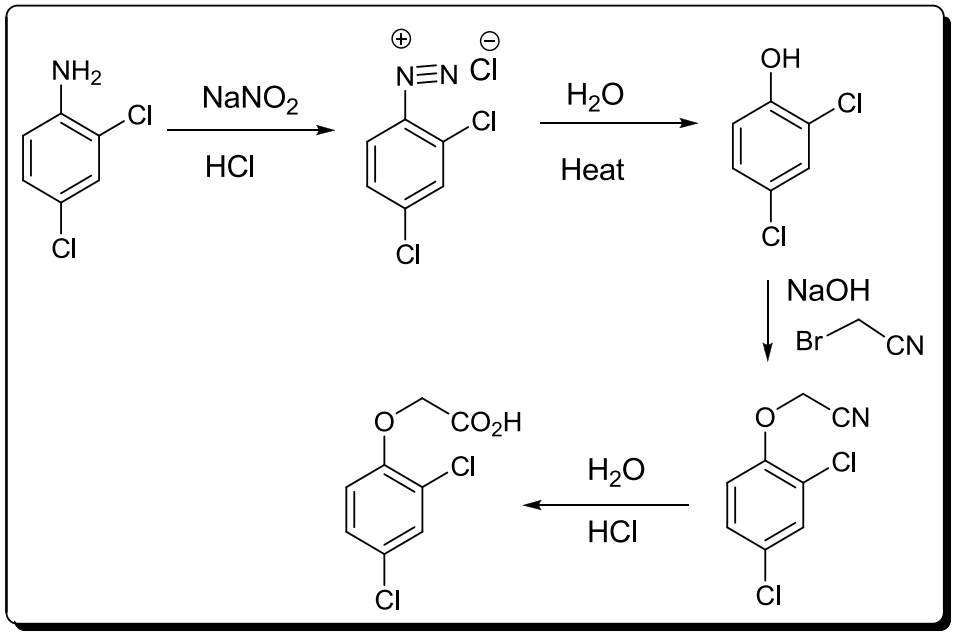
Alternative Synthesis of the Weed-Killer, 2,4-D

The synthesis of 2,4-D can also be approached based on the alternative retrosynthetic and synthetic plan highlighted below:

Retrosynthetic Plan



Synthetic Plan



Strategies in Synthetic Planning

(f) During retrosynthetic analysis introduce additional functional groups, if necessary, to facilitate further disconnection: 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.

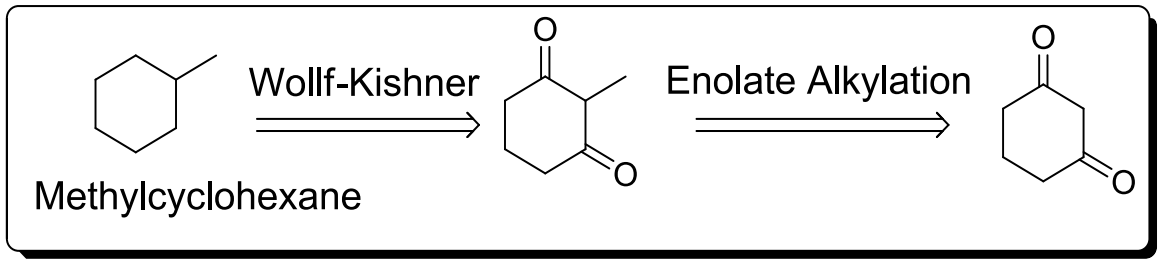
Addition of functional groups e.g. double bonds or carbonyl groups can serve to direct reactivity to specific sites of a molecule significantly simplifying a synthesis.

Strategies in Synthetic Planning

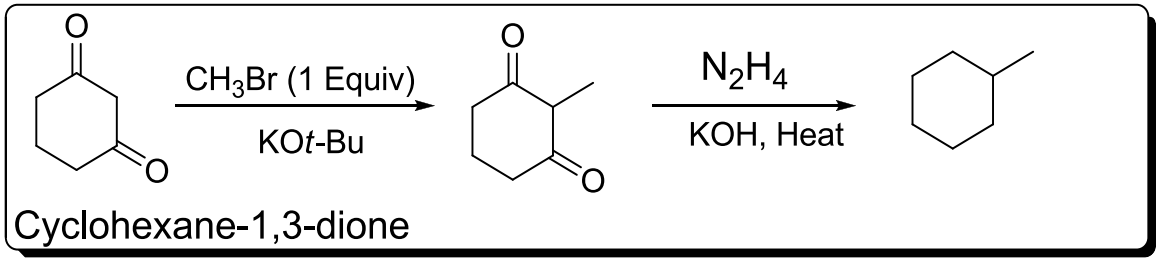
Functional Group Addition Strategy

For example, one may introduce a carbonyl group in a substituted cyclohexane target molecule which may help guide introduction of a substituent through enolate alkylation.

Retrosynthetic Plan



Synthetic Plan



Strategies in Synthetic Planning

(g) Use protecting groups if inevitable

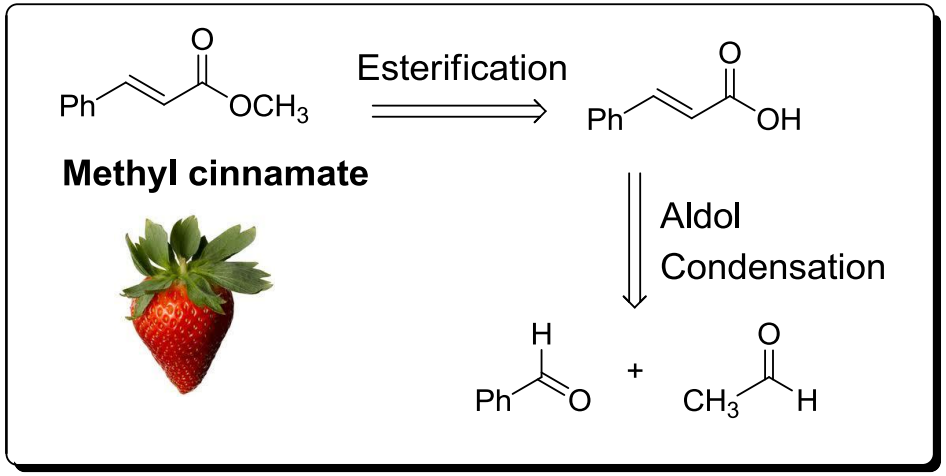
Given that the use of protecting groups adds to the number of steps of a synthesis, use them only when it is absolutely necessary.

Sample Retrosyntheses and Syntheses

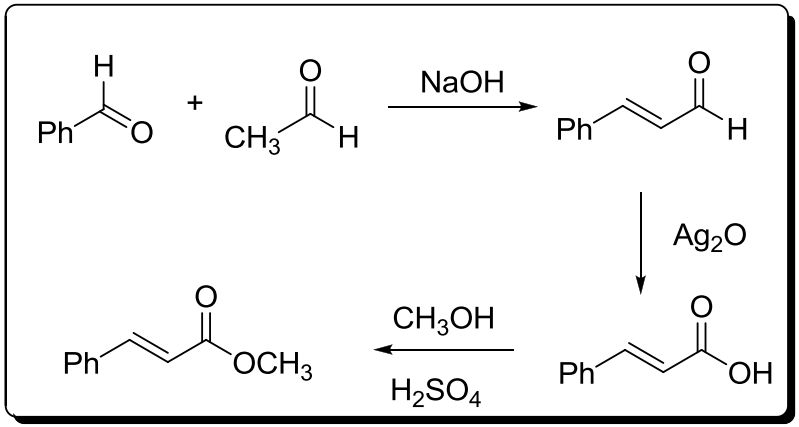
Retrosynthetic Analysis of Methyl Cinnamate

Methyl cinnamate is found naturally in fruits, like strawberry. It is used in the flavor and perfume industries.

Retrosynthetic Plan



Synthetic Plan for Methyl cinnamte



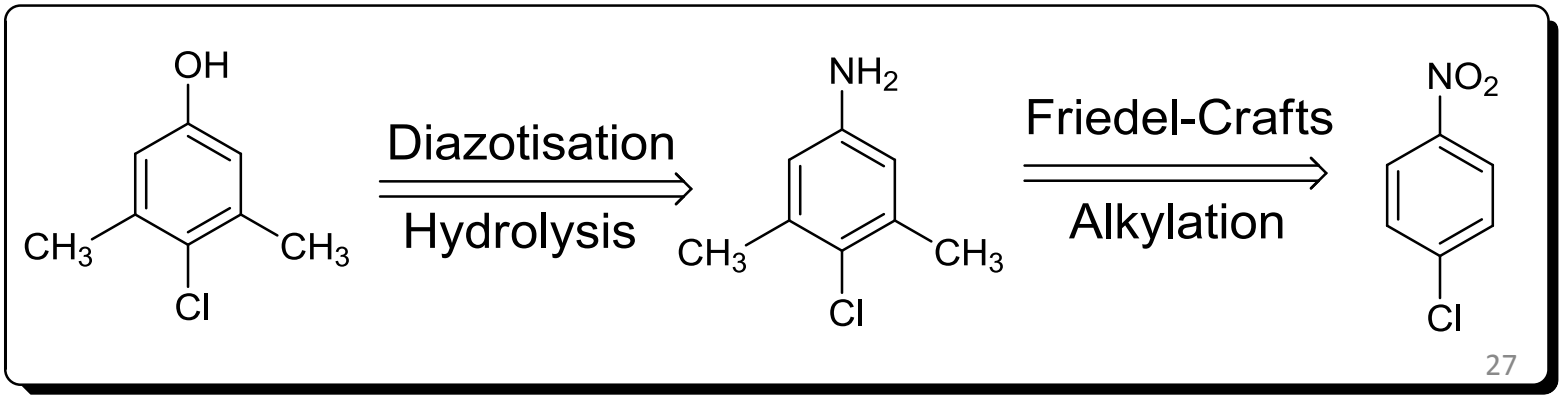
Sample Retrosyntheses and Syntheses

Retrosynthetic Analysis of Dettol

4-Chloro-3,5-dimethylphenol is the active ingredient responsible for the antiseptic properties of Dettol.

The retrosynthetic analysis of Dettol from 4-chloronitrobenzene is outlined below:

Retrosynthetic Plan

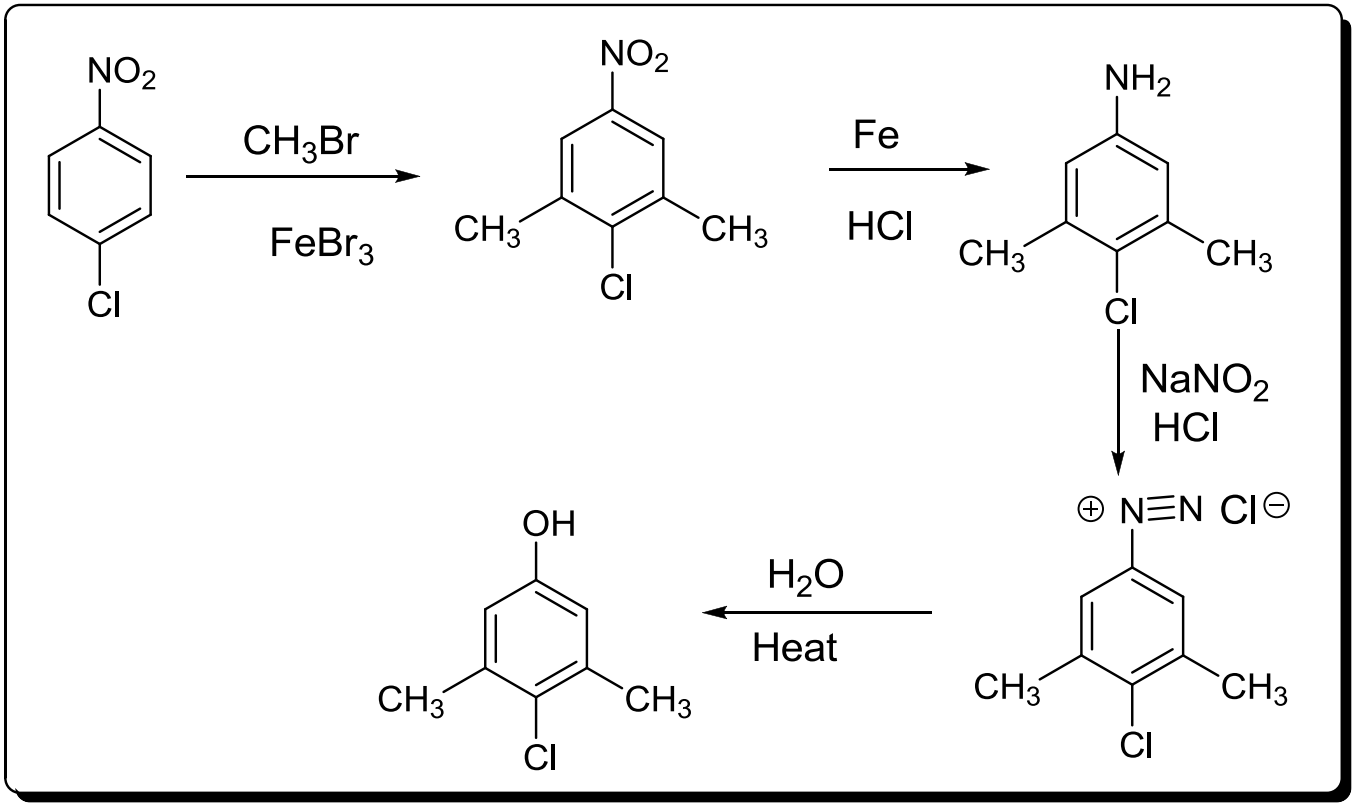


Sample Retrosyntheses and Syntheses

Synthesis of Dettol

The synthesis of Dettol from 4-chloronitrobenzene is outlined below:

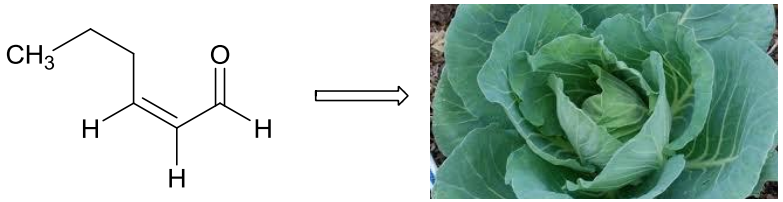
Synthetic Plan



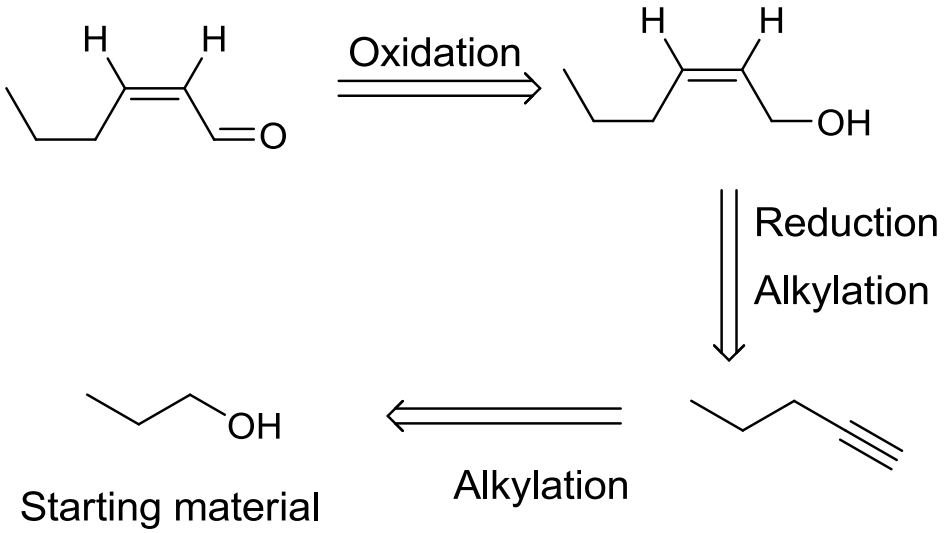
Sample Retrosyntheses and Syntheses

Retrosynthetic Analysis of Z-Hex-2-enal

Z-Hex-2-enal provides the aroma reminiscent of cabbages, but has also found application as an insect repellent.

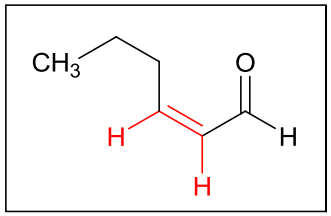


The synthesis of Z-hex-2-enal can be approached based on partial syn-hydrogenation as shown below:

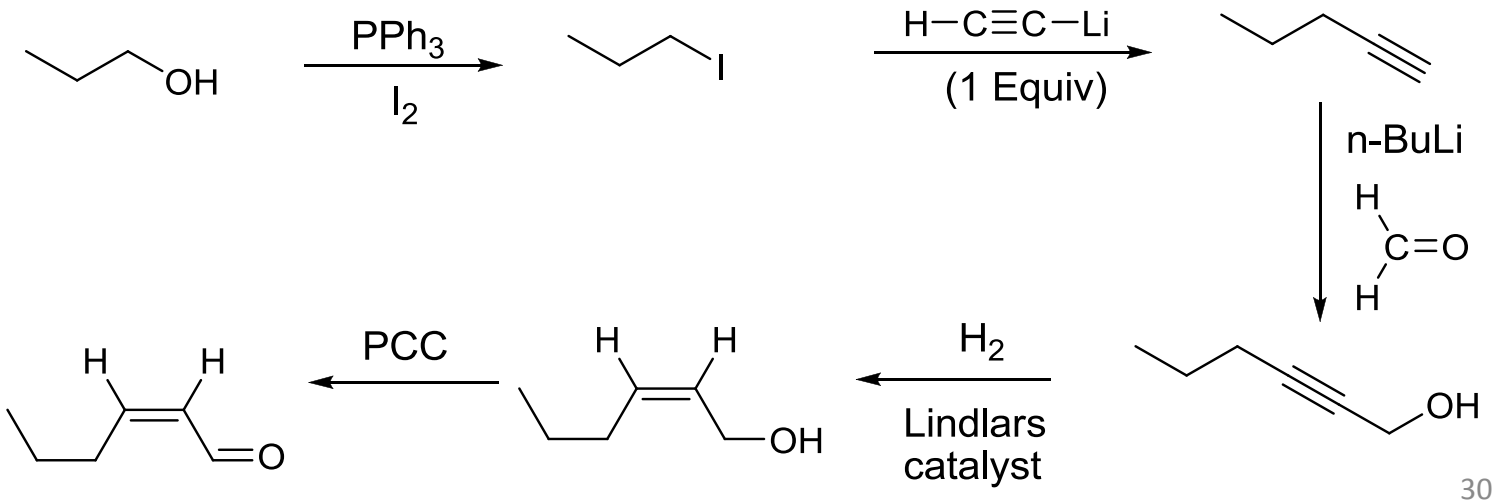


Sample Retrosyntheses and Syntheses

Synthesis of Z-Hex-2-enal



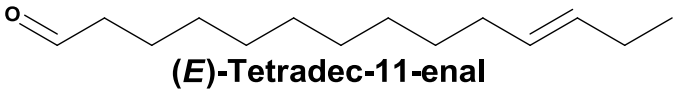
The key feature in the synthesis of Z-hex-2-enal is stereochemistry of the double bond that can stereospecifically be achieved by partial syn-hydrogenation of an alkyne.



Sample Retrosyntheses and Syntheses

Retrosynthetic Analysis of(E)-Tetradec-11-enal

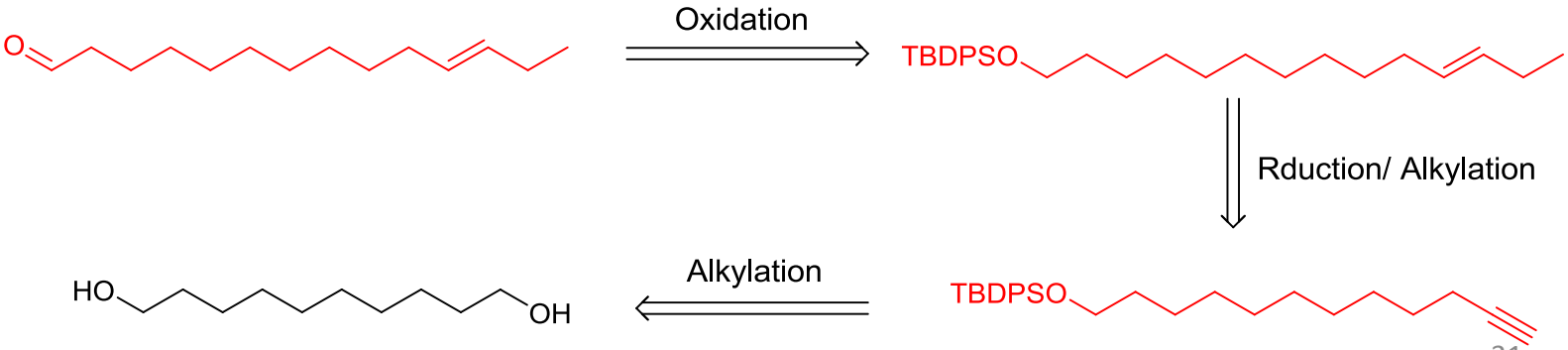
(E)-Tetradec-11-enal is the pheromone of the spruce budworm



(*E*)-Tetradec-11-enal

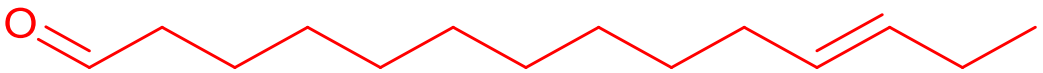
Spruce budworm

The synthesis of (E)-tetradec-11-enal can be approached based on partial trans-hydrogenation as shown below:

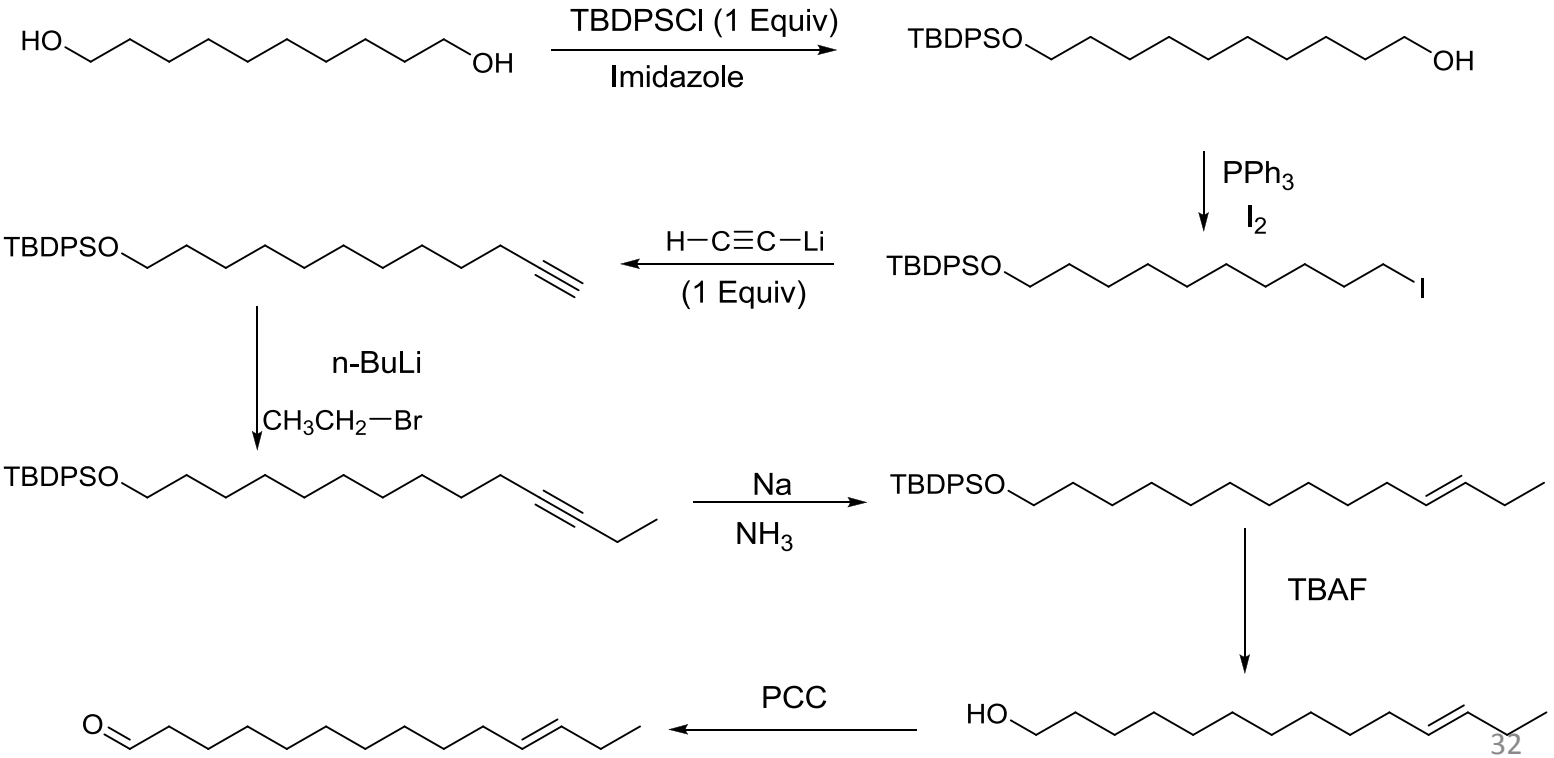


Sample Retrosyntheses and Syntheses

Synthesis of (E)-Tetradec-11-enal



The synthesis of (E)-tetradec-11-enal must address the stereospecific synthesis of the E-double bond and ensure that the reactive aldehyde group is generated last.



CAT 2

ORGANIC SYNTHESIS

MONDAY, 1ST DECEMBER 2014

8.00 AM

CHEMLAB 1