

## 2B Synthesis

### Organic synthesis of aliphatic and aromatic compounds

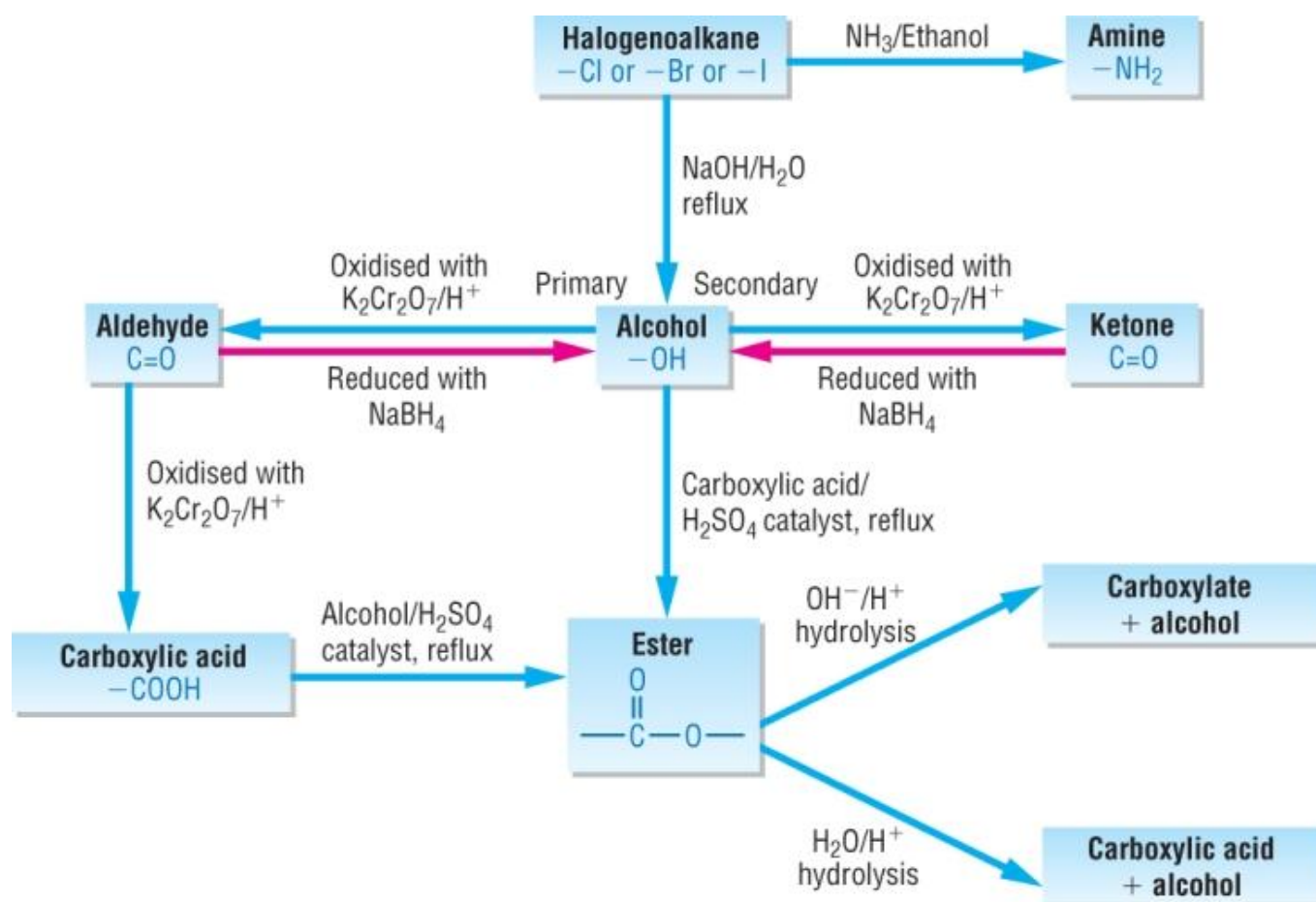
#### What is organic synthesis:

- This is a part of chemistry dedicated to producing organic compounds.
- Usually starting from crude oil, a cheap raw starting material to make complex molecules / pharmaceuticals which are sold at a profit
- It may be a simple one step reaction or a multi step synthesis requiring many steps.
- Synthesis is useful to copy nature's compounds that may be expensive to extract or in low abundance.
- A synthesis can take many steps – In 1951 Woodward synthesized cortisone in 40 steps.
- This shows manipulation of bond breaking/forming and knowledge of organic reactions to change functional groups.
- Synthesis is seen as a puzzle. In order to be good at these puzzles you must know your organic chemical reactions

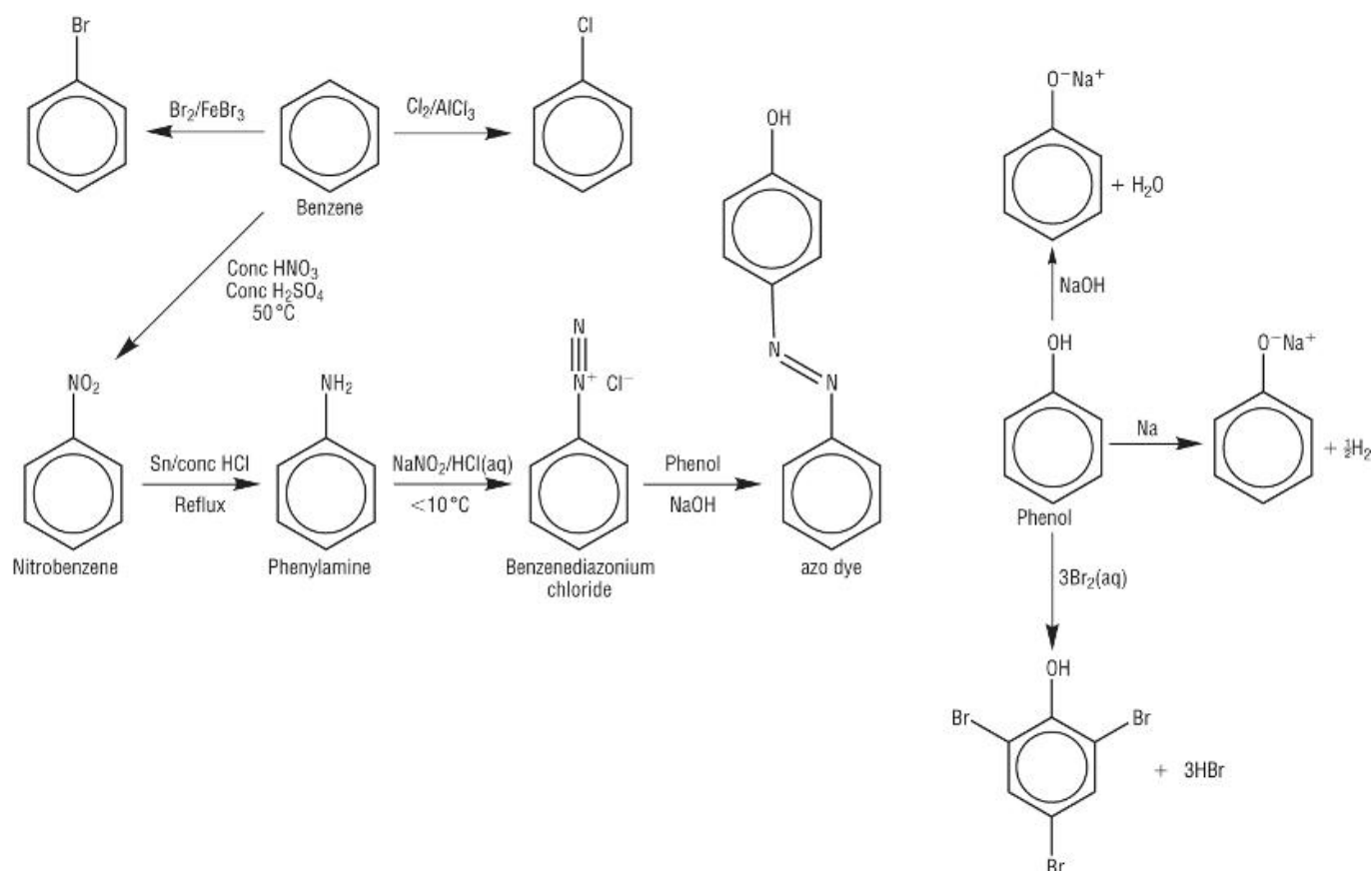
#### Synthetic routes in aliphatic / aromatic chemistry:

- You will be required to solve synthesis routes involving reactions from **AS and A2** plus any new reactions that you may be given in an exam.
- You need to start by collating all your organic reaction spider diagrams.
- If you haven't done this as you have gone through the A level course, you have a massive task ahead of you.
- You will need **2 Charts: Aliphatic and Aromatic**.
- You will need to learn all the **reactions: with reagents and conditions**.

#### Aliphatic routes:



## Aromatic routes:



## The general approach:-

• For a 2 step synthesis:-

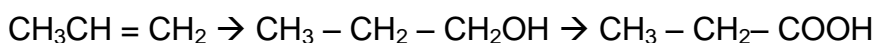
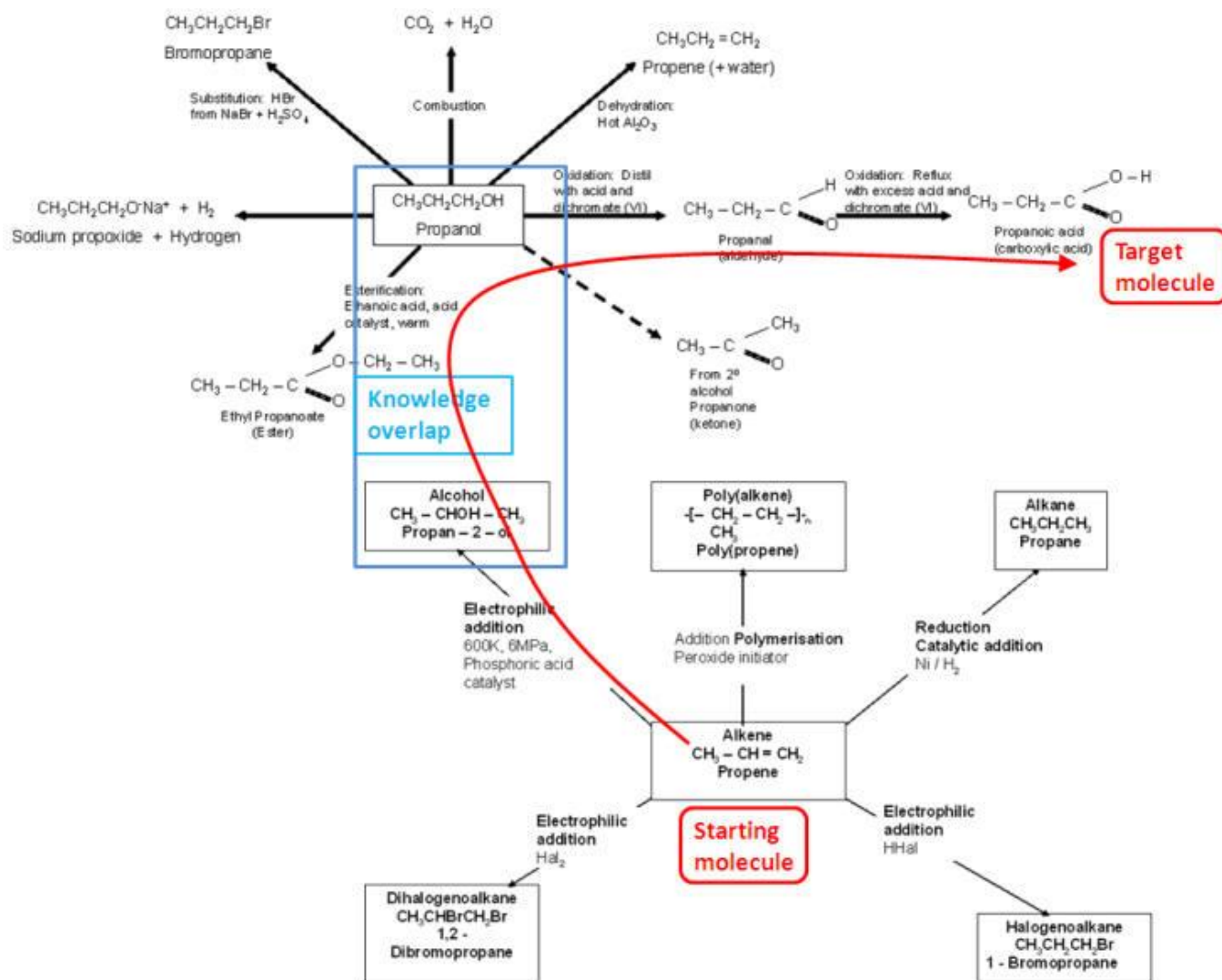
1. Examine the **starting molecule's functional group**.
2. Examine the **target molecules functional group**.
3. Note which functional group has been changed on the starting molecule.
4. Note what that functional group has been changed to in the target molecule.
5. Using your knowledge maps, find the intermediate functional group that the starting molecule can be changed to and the target molecule can be made from.
6. Apply the conditions and you have a 2 step synthesis.

## Example 1:

**Starting molecule:**– propene

**Target molecule:**– propanoic acid

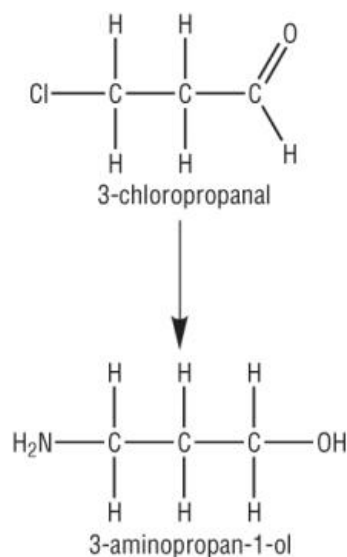
### 2 – step synthesis:-



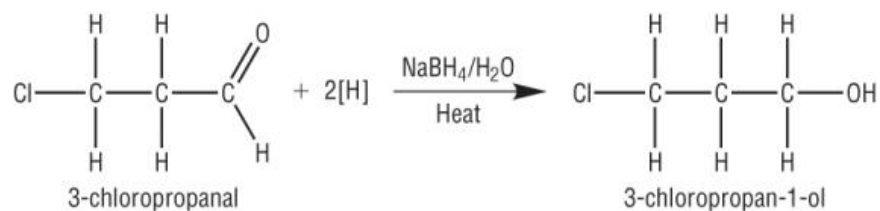
**Step 1:-** Steam and phosphoric acid

**Step 2:-** Reflux with sulphuric acid and potassium dichromate

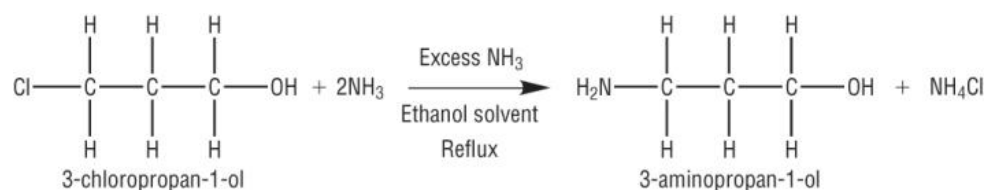
### Example 2:



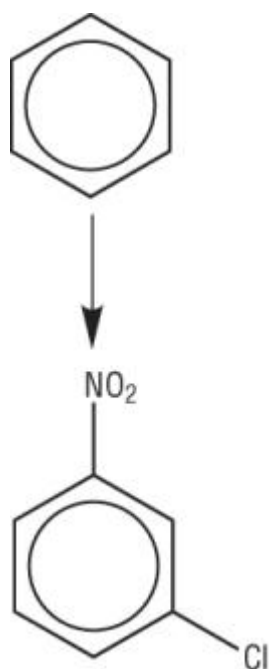
#### Step 1:



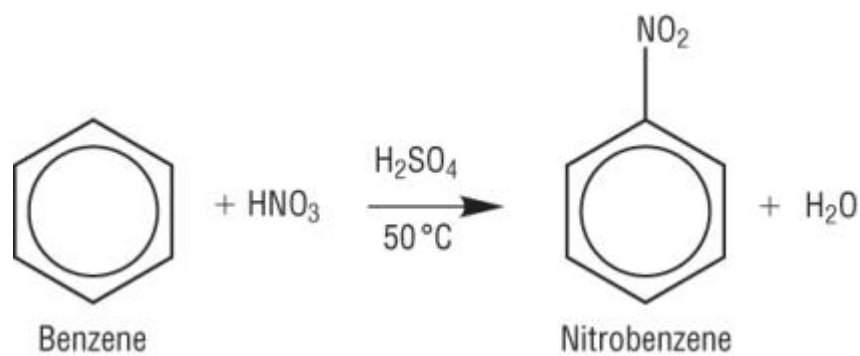
#### Step 2:



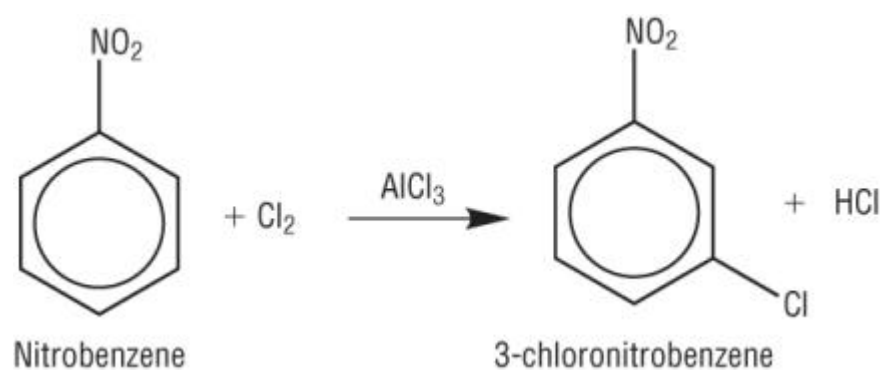
### Example 3:



#### Step 1:



#### Step 2:



**Task: Collate all your organic reactions diagrams from AS and A2 (include reagents and conditions)**

Once you have completed the task above:

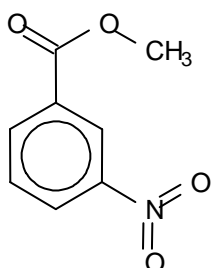
Have a go at synthesising:

- 1,2-Dibromobutane from butan-1-ol
- Butanoic acid from 1-bromobutane
- Ethane from ethanol
- Ethyl ethanoate from ethene
- Ethylamine from ethanol
- phenylamine from benzene
- 3 - chloronitrobenzene from benzene

Qu 1 P63 1,2 P65

Designing a two step synthesis:

- Your task is to design a two step synthesis to make Methyl 3-nitrobenzoate from benzoic acid:



- Checked your 2 step synthesis with your teacher. You will then be given you a procedure to follow.

### Optical isomerism

Task:

**Build a molecule using:**

**Black molymod in the centre**

**Attach a green, blue, red and white molymod to the central black molymod:**

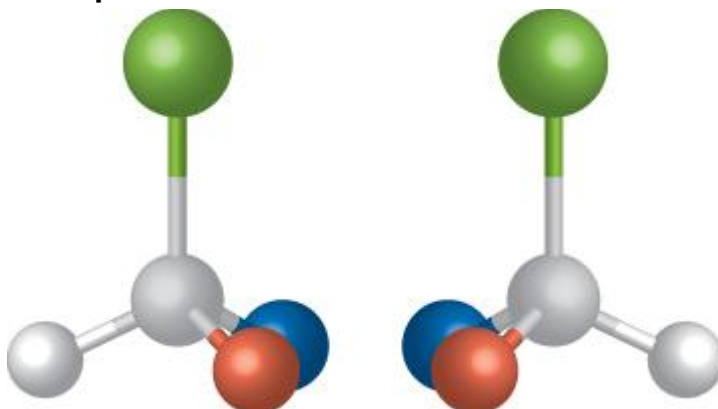
**Your teacher will guide you what to do from here.**

**Stereoisomerism:**

- You are already familiar with stereoisomers from AS - E/Z Cis and Trans with alkenes.
- There is a second type of stereoisomers called **optical isomers**:

**Optical isomers:**

- Mirror images **cannot** be superimposed upon each other.
- These are called **optical isomers**:

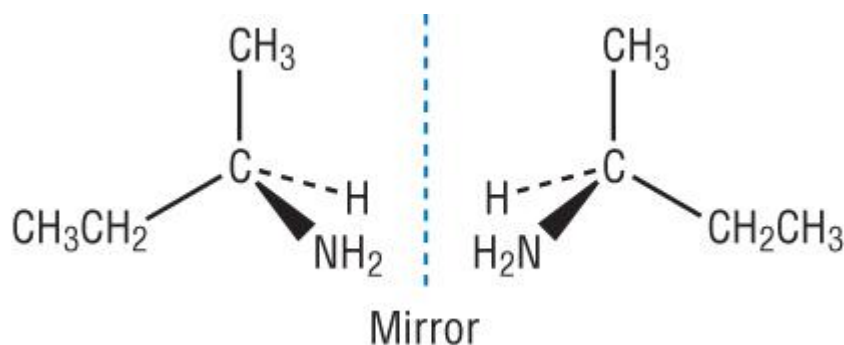


- Your hands are optical isomers of each other. Both are the same but are not super imposable.

- A mirror image of one hand makes it possible to super impose it upon the other.

**When a carbon atom has 4 different groups attached to it, you get 2 shapes that are mirror images of each other, known as optical isomers. The carbon atom is called the 'Chiral Centre'.**

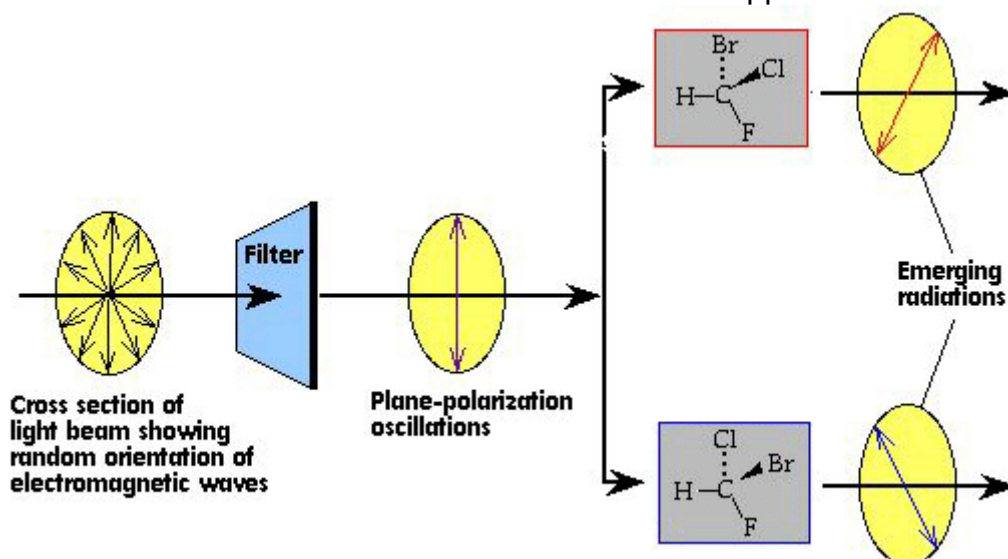
- The chiral carbons often have an asterisk on to show the chiral centre.
- Compounds that do not have 4 different groups around a carbon atom are said to be **achiral**. (most compounds are these).
- The 2 isomers are called **enantiomers**.
- You must draw them in 3D and a mirror line is often drawn to help with this:



- The  $\alpha$  in amino acids represents one of the enantiomers (or mirror images) This makes them join together in particular shape / way (biology).

#### Properties of optical isomers:

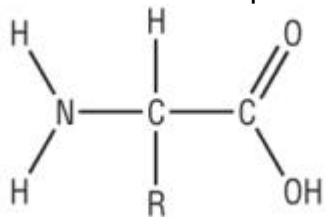
- They rotate plane polarised light.
- One isomer rotates it in one direction and the other in the opposite direction.



- An equal mixture of the 2 isomers will not rotate plane polarised light as each isomer cancels the other out. This mixture is known as a **racemic** mixture.

## Optical activity and amino acids:

- Amino acids are optically active:



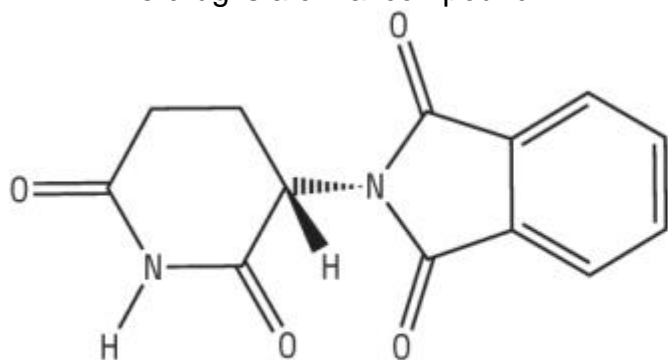
- The only one that isn't is glycine as this has 2 hydrogen's on the same carbon.
- Optical activity is important in biological systems as only one of the isomers will interact with enzymes..
- These are described as **stereospecific**

## Chirality in pharmaceutical synthesis

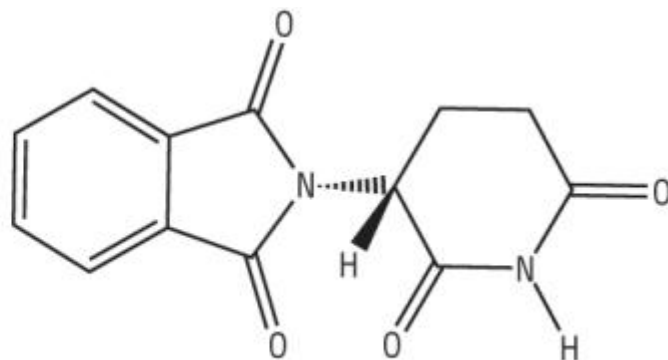
### The importance of chirality in drug synthesis:

#### Thalidomide:

- In the 1950's a drug called thalidomide was produced to combat the effects of morning sickness in pregnant women.
- The drug is a chiral compound:



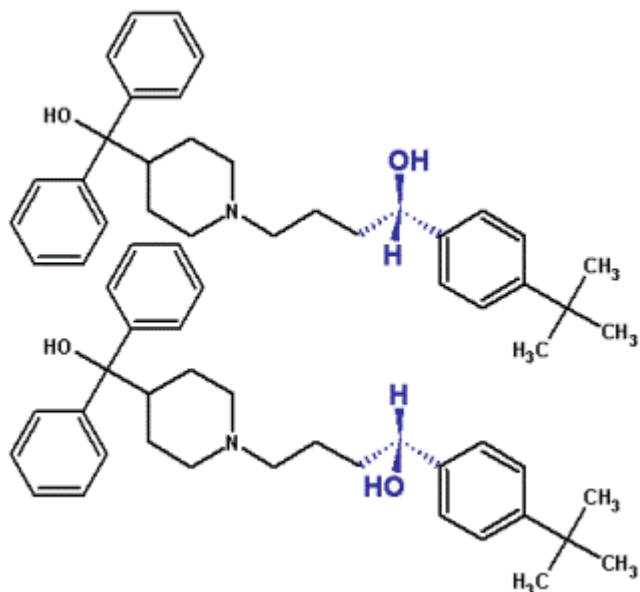
(-)-Thalidomide



(+)-Thalidomide

- While one stereoisomer gave the desired effects - relieving morning sickness.
- The other gave undesirable side effects that lead to deformities in an estimated 10000 babies.

#### Seldane:

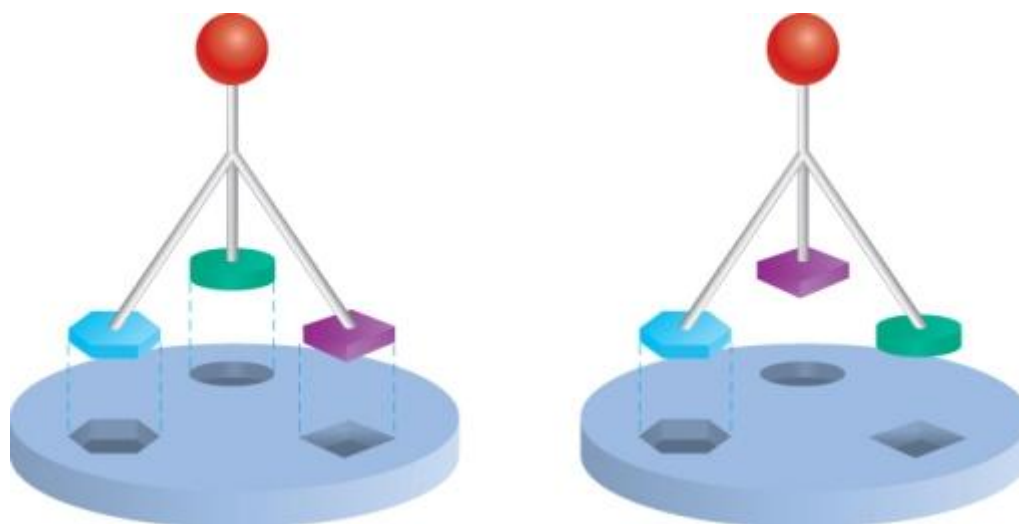


- Seldane was the first antihistamine on the market to combat hay fever.
- The drug is chiral.
- One stereoisomer relieved hay fever.
- The other caused potentially fatal heart conditions.

- Rigorous testing is now carried out on each of the stereoisomers separately, and this is costly.
- It has led to the development of synthesis of just one of the stereoisomers.

### Synthesising pharmaceuticals:

- Drugs and medicines interact with biological molecules such as proteins etc.
- These have a complex 3D structure that will only bind to a drug molecule with a specific shape.
- The 3D structure of the drug has to 'fit' with the **receptor site** in a biological system:



- This will determine the **pharmacological activity** and whether it will have the desired effect or not.

### Synthesis Vs Nature:

	Synthesis	Nature
	<p>Both equally likely so 50:50 mixture of both isomers made</p>	<p>The enzyme holds the molecule in place blocking one side off for attack - 1 isomer made</p>
<b>Isomers</b>	<b>Both</b>	<b>one</b>
<b>Made</b>	<b>In the laboratory</b>	<b>In the body</b>
<b>Dose</b>	<b>Twice needed</b>	<b>Half needed</b>
<b>Side effects</b>	<b>Probably</b>	<b>None</b>
<b>Cost</b>	<b>Cheaper</b>	<b>More expensive</b>
<b>Separation in lab</b>	<b>Usual chemical difficult - isomers have same physical and chemical properties</b>	<b>Using enzymes - costly and time consuming</b>



## Modern chiral synthesis:

### 1) Using enzymes as biological catalysts:

- Nature is stereospecific, if this can be used only one isomer will be produced.
- If a biocatalyst is used it will only catalyse the production of one isomer.

### 2) Chiral pool synthesis:

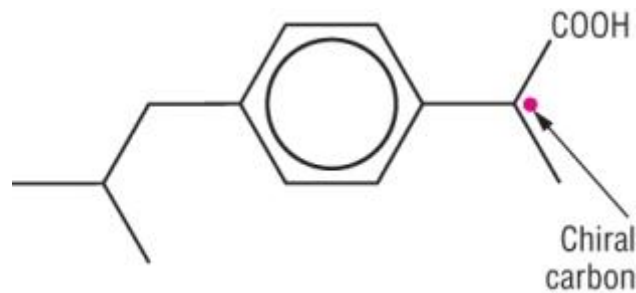
- This starts the synthesis pathway with a stereospecific enantiomer (one stereoisomer)
- All of the following synthesis steps should lead to a pure optical isomeric drug

### 3) Use of transition metal complexes:

- Some transition metal complexes act as catalysts that will produce only one optical isomer

## Chiral drugs at home:

- Ibuprofen - anti - inflammatory. It works by blocking the pain messages to the brain:



- As a chiral molecule, one isomer blocks the pain more effectively than the other.
- Unusually - the body converts the less active isomer into the active isomer.
- This minimises side effects and means that the whole dose is effective.

Qu 1 - 3 P67 / Qu 3 P 69 / Qu 1b,7,8 P72