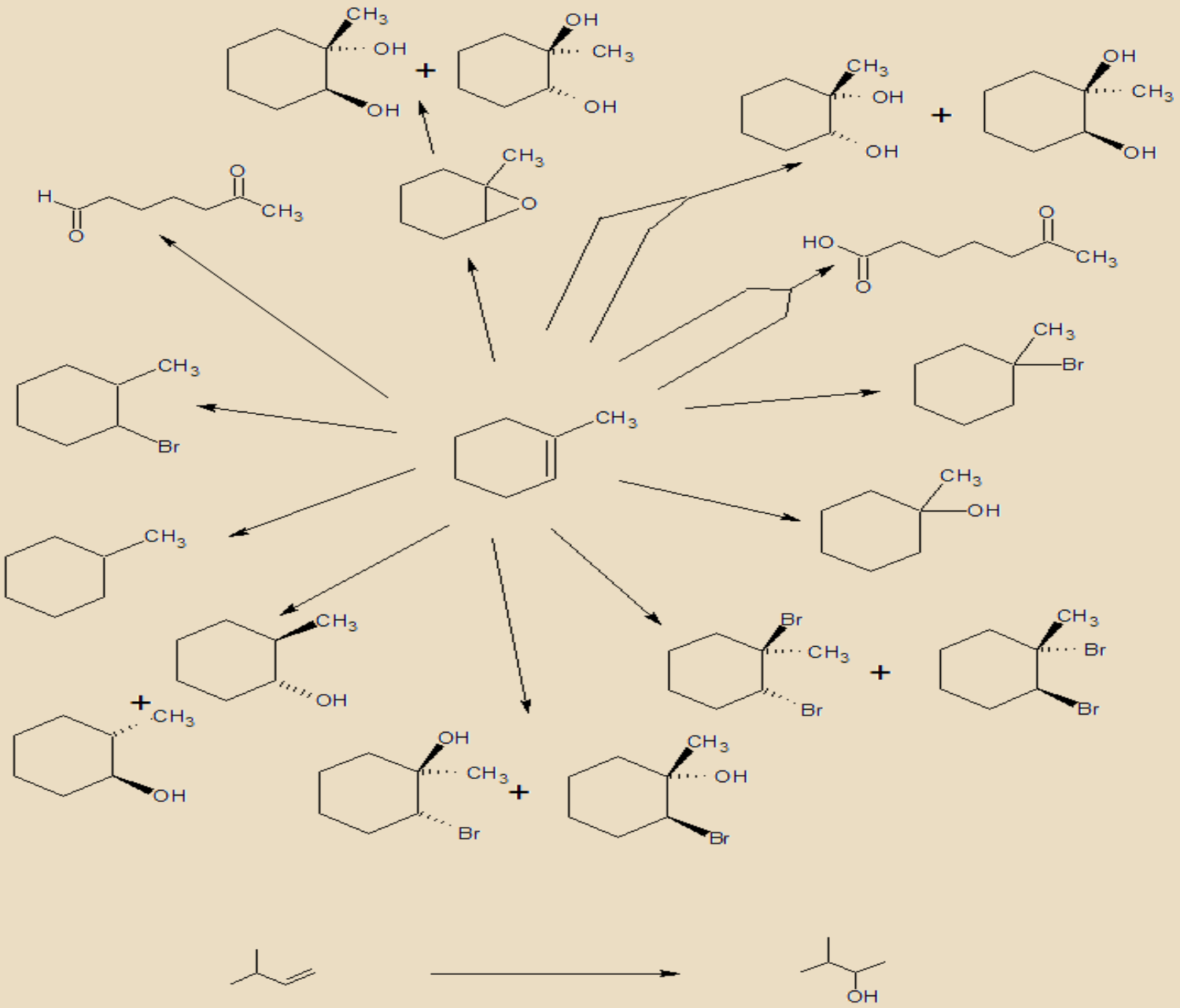
MULTISTEP SYNTHESIS

- The study of organic chemistry introduces students to a wide range of interrelated reactions.
- Alkenes, for example, may be converted to structurally similar alkanes, alcohols, alkyl halides, epoxides, glycols and boranes; cleaved to smaller aldehydes, ketones and carboxylic acids; and enlarged by carbocation and radical additions as well as cycloadditions.
- Most of these reactions are shown in the Alkene Reaction Map below. All of these products may be subsequently transformed into a host of new compounds incorporating a wide variety of functional groups.

- Consequently, the logical conception of a multi-step synthesis for the construction of a designated compound from a specified starting material becomes one of the most challenging problems that may be posed.
- Functional group reaction maps like the one below for alkenes can be helpful in designing multi-step syntheses. It can be helpful to build and design your own reaction maps for each functional group studied.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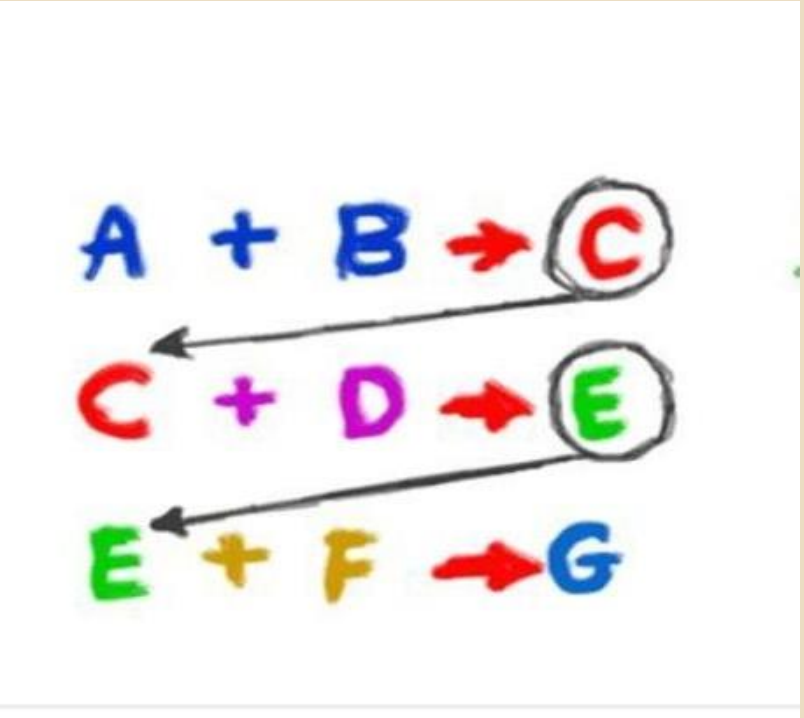
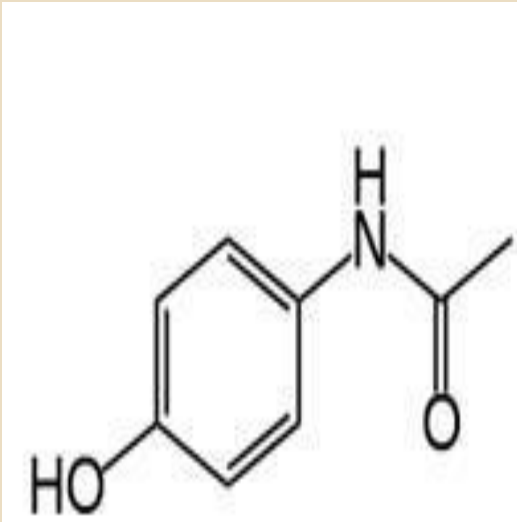
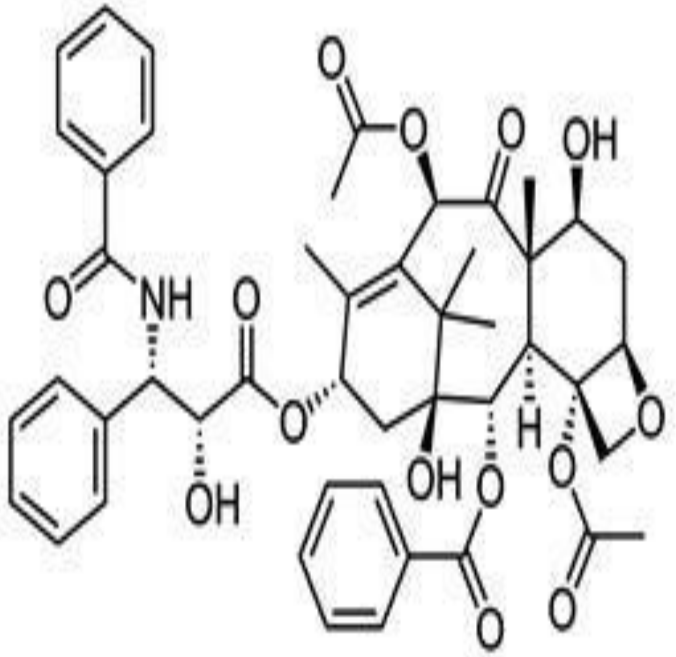
- **Multistep synthesis** is the process of taking a readily available compound (one you can buy) and converting it into the compound you need using chemical reactions.
- Multistep syntheses require more than one step (reaction), and so one or more intermediate compounds are formed along the way. This process is illustrated below:



- In chemistry, the synthesis of most compounds of interest (Drugs, polymers, dyes…) cannot be done in a single step.
- Some synthesis are relatively short (2-4 steps), others can be very long (35-55 steps).
- For example, paracetamol (IUPAC: N-(4-hydroxyphenyl) ethanamide), a relatively simple molecule, can be prepared in one, two or three steps depending on the **starting material** you choose (what chemists call starting material is the very first chemical compound they will use to start a synthesis, the one they will use in the first step (or reaction) of the synthesis they want to make).
- Taxol (an anti-cancer drug) is a natural compound with a very complex structure whose total synthesis requires at least 40 steps.



Paracetamol



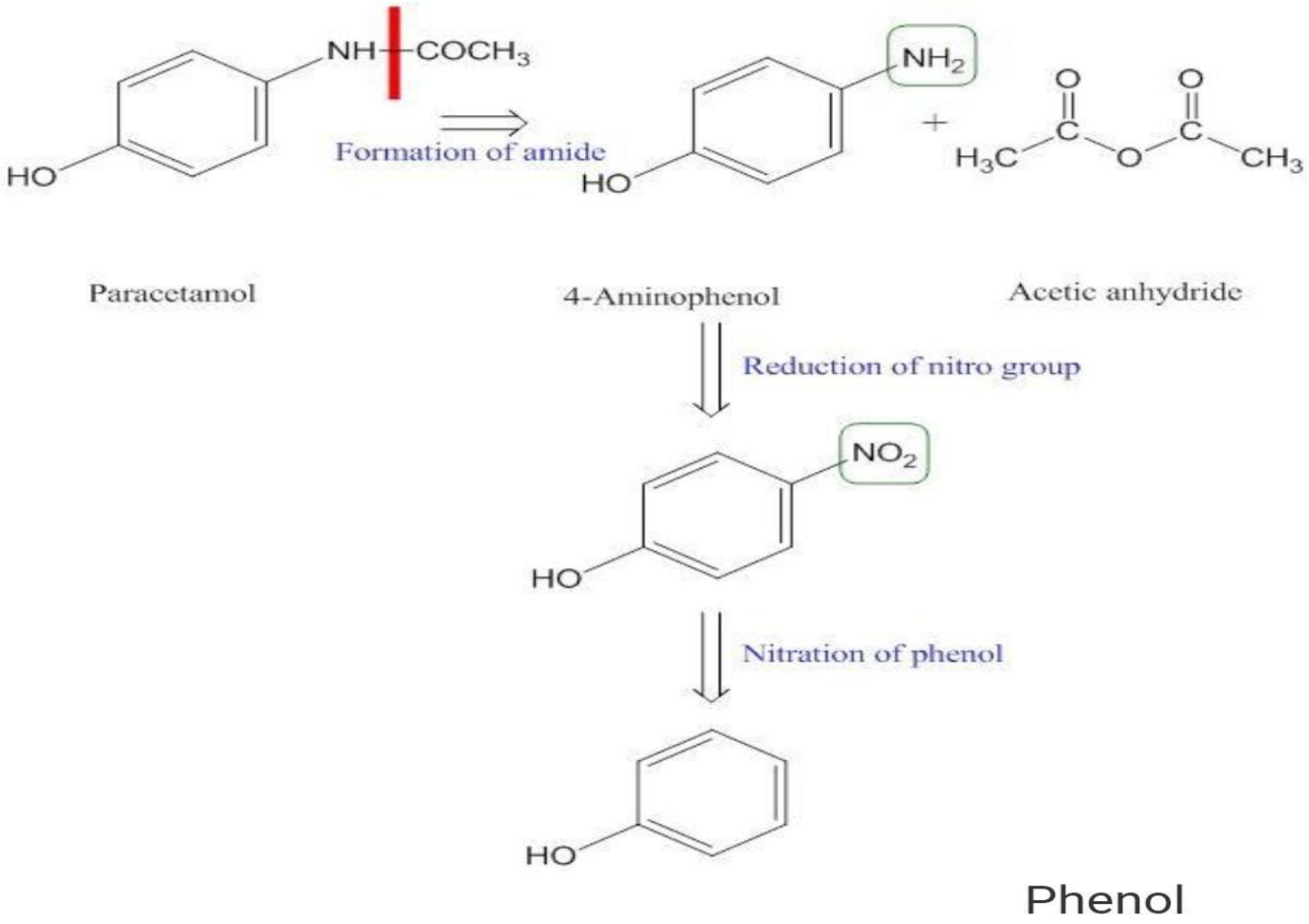
Taxol

1 - 3 steps

40 steps

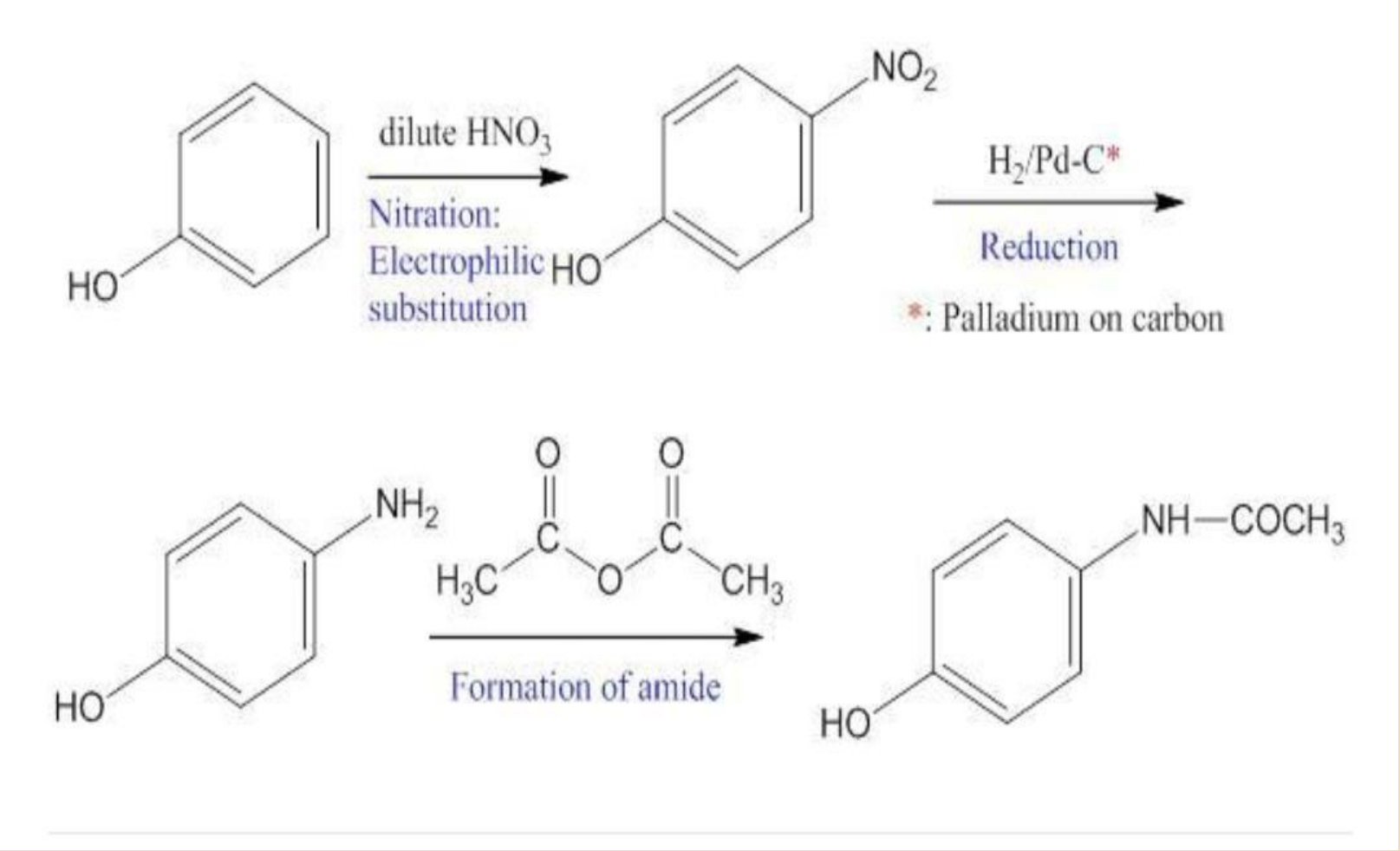
- How do chemists decide the chemical route they will use to prepare a compound? They use what is called **retrosynthesis.**
- Retro means going backward therefore in planning their synthesis, chemists start from the compound they want to make and cut it in smaller pieces, going backward, until they can reach the starting material they want to use (something they can easily buy and that is not too expensive).
- Each of these smaller pieces corresponds to at least one reaction (or step). To clarify, let’s see an example with paracetamol:

- Paracetamol contains an amide functional group and amide can be made from an amine and an acid chloride or an anhydride therefore we can prepare paracetamol in one step starting from para-aminophenol (IUPAC: 4-Aminophenol) and acetyl chloride (IUPAC: Ethanoyl chloride) or acetic anhydride (IUPAC: Ethanoic anhydride):



Retrosynthesis (Backward synthesis) of paracetamol

- Now see how the forward synthesis (the synthesis the chemist will perform in the lab) looks like compared to the retrosynthesis we just did:



- However, how can we be sure that the nitration will take place on the carbon opposite the OH of phenol and not anywhere else?
- The -OH can activate the benzene ring due to one of the lone pair of electrons on the oxygen group The donation of the oxygen's lone pair into the ring system increases the electron density around the ring. Phenol has more activating effect on some positions around the ring than others.That means that incoming groups will go into some positions much faster than they will into others.You will learn why at university

- The -OH group has a **2,4-directing effect (also called ortho/para)**. That means that incoming groups (like the nitro group in our paracetamol example) will go into the 2- position (next door to the -OH group) or the 4- position (opposite the -OH group).

- **How to Plan a Synthesis?**
- The ideas collected here are based on the work of E.J.Corey (Nobel Prize 1990) who was one of the pioneers at trying to design strategies for the synthesis of complex organic molecules.
- **Retrosynthesis**" means planning a synthesis backwards, by starting at the product, the "target" and taking it back a step at a time to simple, available starting materials or precursors.

  In general students dislike these problems because it requires "thinking backwards", good problem solving skills, and a good knowledge of their organic reactions.

  In order to "plan" a synthesis, we can break the target down by making a series of "disconnections" - these steps are the reverse of synthetic steps or reactions.

Basic Concept