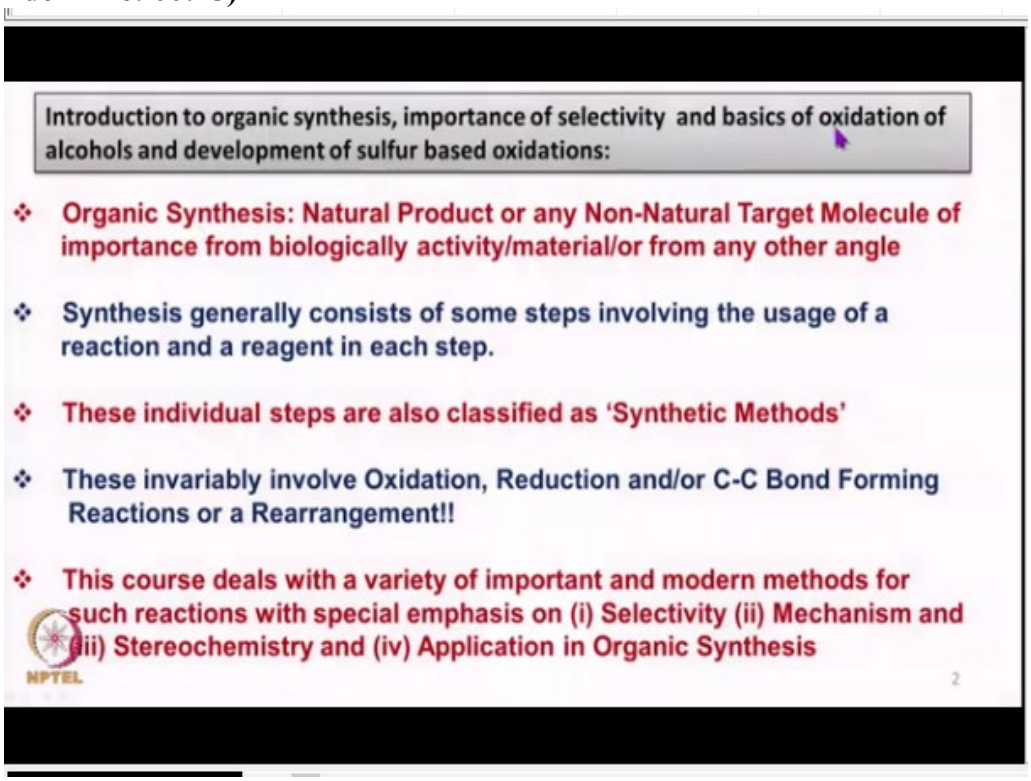
Essentials of Oxidation, Reduction and C-C Bond Formation Application in Organic Synthesis

Prof. Dr. Yashwant D. Vankar
Retired from Department of Chemistry
Indian Institute of Technology-Kanpur

Lecture-01
Introduction to Organic Synthesis-Importance of Selectivity, Stereochemistry and Mechanism

Hello everyone, I welcome you all to the first lecture of this particular course, as you know that the title of this course is essentials of oxidation, reduction and C-C bond formation, application in organic synthesis.

(Refer Slide Time: 00:45)

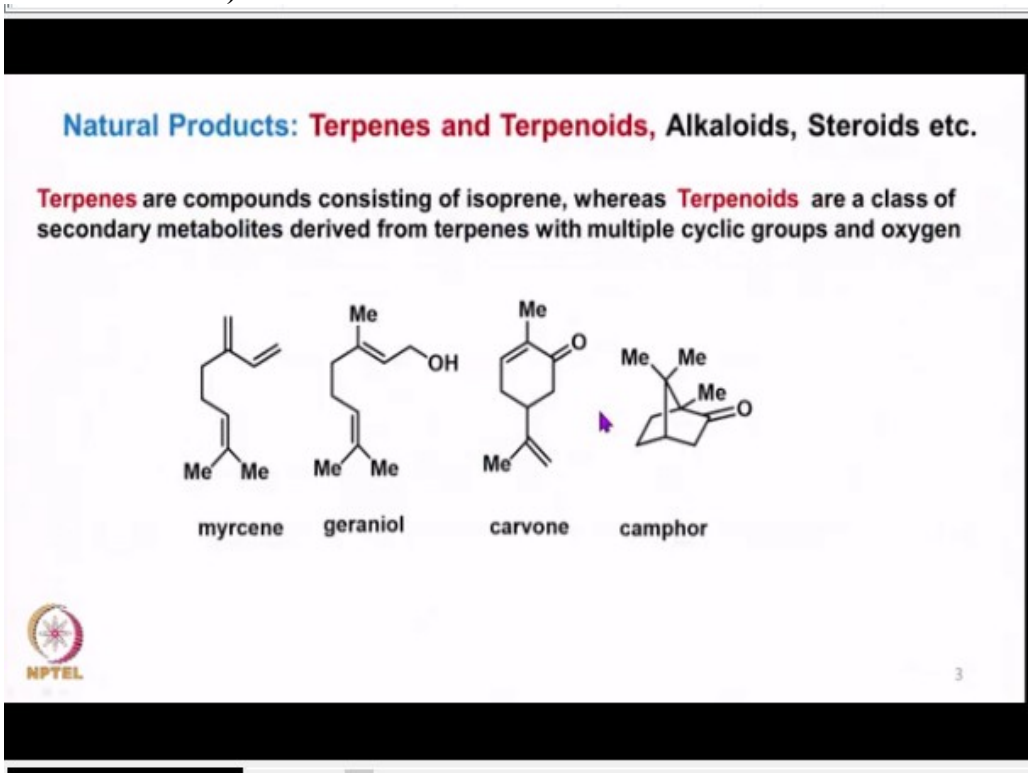


Now, to start with, I would like to give a brief introduction to organic synthesis, importance of selectivity and basics of oxidation of alcohols and development of sulfur based oxidations to start, with the organic synthesis that we generally talk about involves the synthesis of natural products or any other non natural target molecule of importance, which have biological importance or synthesis of some materials or synthesis from any other angle.

So, this is what is organic synthesis. Generally synthesis consists of some steps that involve the usage of different types of reactions and reagents and sometimes of course rearrangements. Now, these individual steps are also classified as synthetic methods. These synthetic methods involve as I said many steps. Now, each step can be involving an oxidation, reduction and or C-C bond forming reaction or also an rearrangement.

The rearrangement can involve acid base or light or heat or even in reagent. This course deals with a variety of important and modern methods for such synthetic methods with special emphasis on selectivity, mechanism and stereochemistry and then application in organic synthesis.

(Refer Slide Time: 02:35)

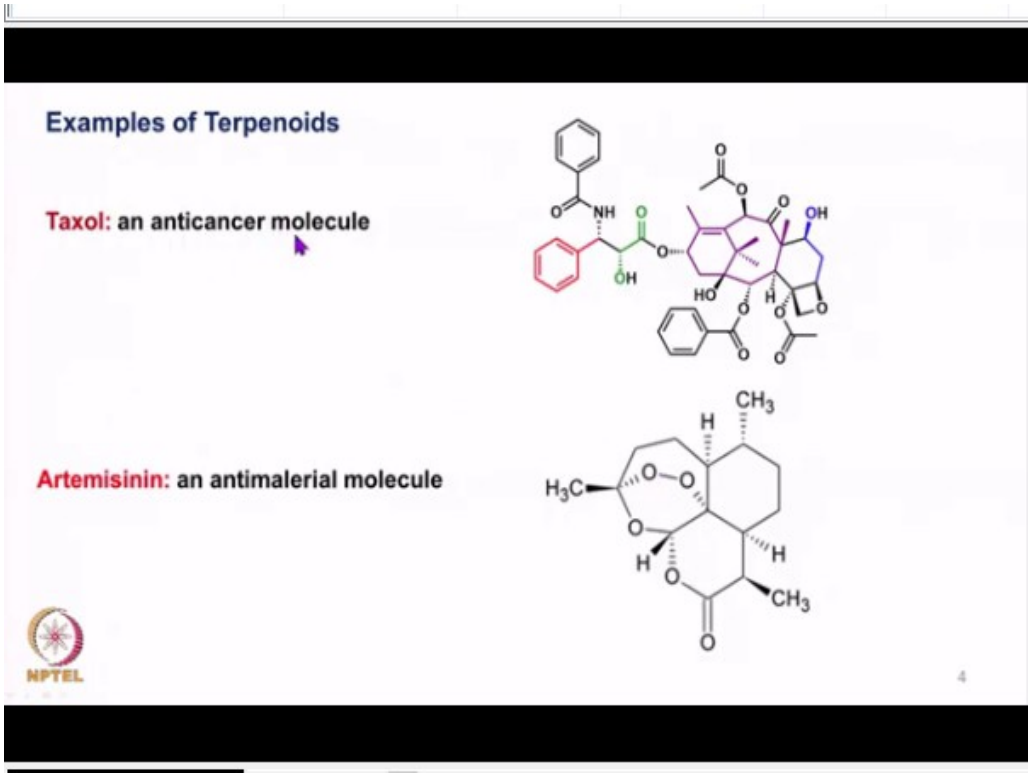


Now, if you look at the natural products, you know, many of these natural products already say we have terpenes, terpenoids, alkaloids, steroids and many more. So, we know that the terpenes are compounds that consist of isoprene, whereas terpenoids are the class of secondary metabolites, which are derived from terpenes. And we will have some cyclic groups and oxygen.

Let us take some examples of terpenes of course, we know that there are monoterpenes, there are diterpenes, then sesquiterpenes, then triterpenes etc. If you examples of them are like here like this is a monoterpene which is myrcene, then of course, we have geraniol, all of this kind of course, if the double bond here would be having the CH_2OH group pointing below and that means it is trans to the methyl group, then that will be nerol.

Then we have carvone of course, here there is an asymmetric center, then of course, we have camphor. So, there are many such type of molecules which are classified as terpenes.

(Refer Slide Time: 03:57)

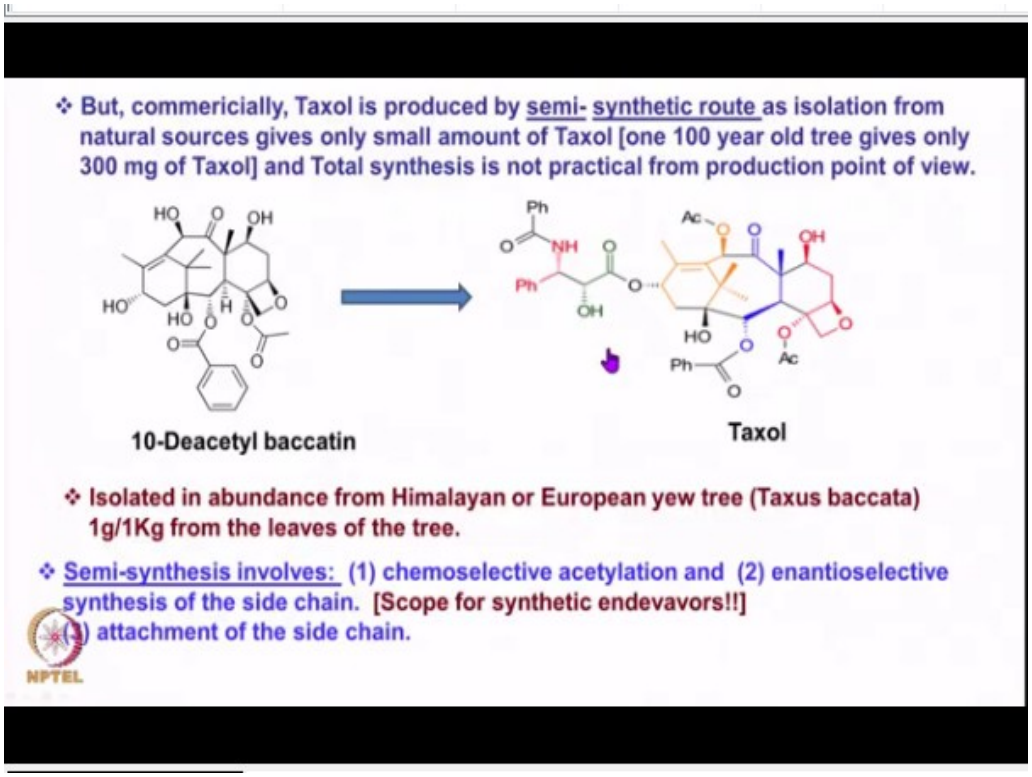


Then we have an example of terpenoid. Now, this is a very interesting molecule which is called as Taxol, it is an anticancer molecule, is a very important anticancer molecule. The structure of Taxol is like this is one of the natural products isolated from a tree call yew tree and as you can see that there is 3 rings here, fourth one is a oxygen containing ring, then of course, we have side chain here.

So, particular molecule has a number of asymmetric centers. This also has a side chain which has 2 asymmetric centers. That means the synthesis of this entire molecule is quite complicated, not only complicated but needs to be made in optically pure form. But since it is a very important anticancer molecule, a lot of work has been done a lot of synthesis has been reported, some total synthesis and some partial or semi synthesis.

Now, artemisinin is an antimalarial molecule which structure is like this. Now, as you can see that it has 3 basic rings, but at the same time there is a bridge here having a peroxide bond. Again, it is a very difficult molecule to synthesize, but then many derivatives of these Taxol and artemisinin have been synthesized and assessed for their biological activity.

(Refer Slide Time: 05:50)



The commercially applicable synthesis of Taxol is very difficult. Therefore, semi synthetic route to Taxol has been basically utilized. Since isolation of the Taxol from natural source gives only a very small amount of the product that is the Taxol. As you can see, 100 year old tree gives only 300 milligrams of Taxol. So, you can imagine how you had to grow a tree for 100 years and then you can at the most get 300 milligrams of the molecule that is Taxol.

At the same time as I mention that the structure of the Taxol molecule which is shown here is very complicated and therefore, total synthesis that means synthesis starting from a very easily available starting material is very difficult, because it will involve a large number of steps. And therefore, the semi synthetic route has been developed, which is now from this particular molecule, which is naturally available.

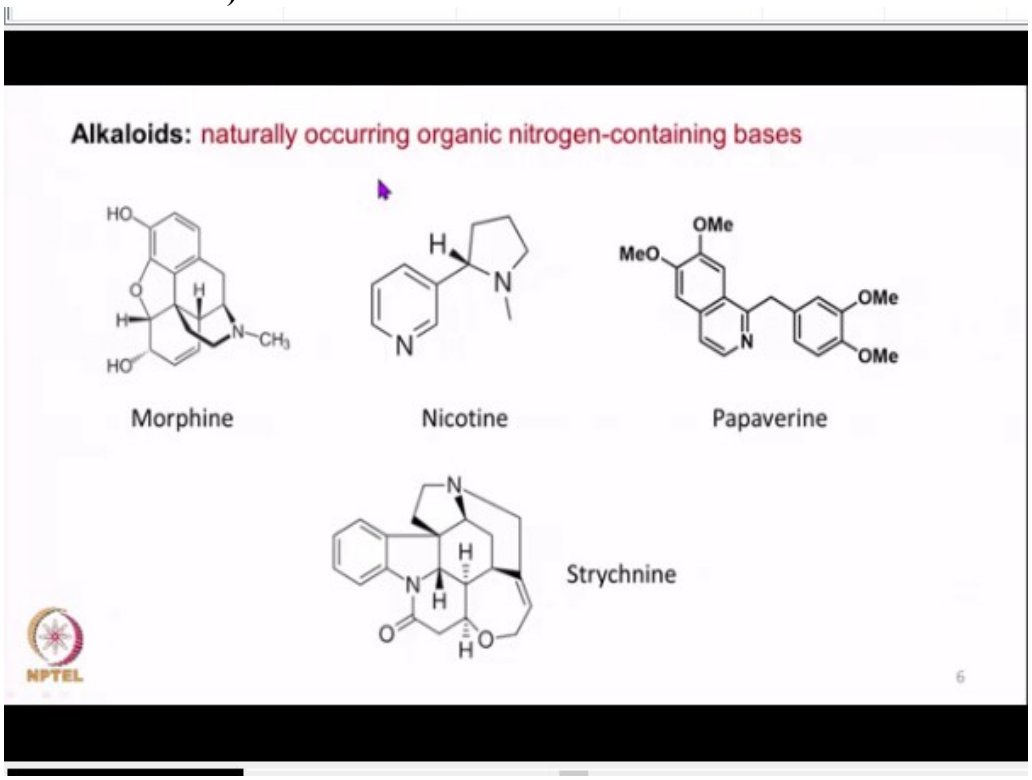
It is called 10-Deacetyl baccatin. Now, as you can see that this particular acetate group is present in the Taxol molecule. Whereas, if you compare the structure of this 10-Deacetyl baccatin with this particular part here, then you can say that 10-Deacetyl baccatin is a starting material for the synthesis of Taxol and it has no acetyl group at the 10th position. Now, this 10-Deacetyl baccatin has been isolated in abundance from Himalayan or European yew tree, which is called Taxus baccata.

And it gives 1 gram from 1 kilogram of the leaves of this tree, that is Himalayan or European yew tree. So, it is much easier to isolate about 1 gram of such a molecule from 1 kilogram of the leaves and then convert into the Taxol molecule. So, if we start with this naturally occurring 10-Deacetyl baccatin. The semi synthesis would involve chemo selective acetylation, that means, this particular hydroxy group has to be acetylated.

Otherwise, the rest of the things are there except the side chain here. So, we have to do the chemo selective acetylation at this particular position and then we need to introduce a side chain. Now, already there is a hydroxy group here. So, now, that hydroxy group has to be converted to this particular side chain which has 2 asymmetric centers. That means we have to make sure that we attach the side chain to this hydroxy group with appropriate stereochemistry and also absolute configuration. So, this attachment has to be done.

Now, you can see that, first of all we have to make sure that we introduce the acetyl group at this particular position. And then the remaining 3 hydroxy groups are still there, to which, at this particular position, we have to make sure that we attach the side chain. So, attachment of a side chain is also a very challenging task. So, there is a scope for synthetic endeavours even after having obtained this particular 10-Deacetyl baccatin.

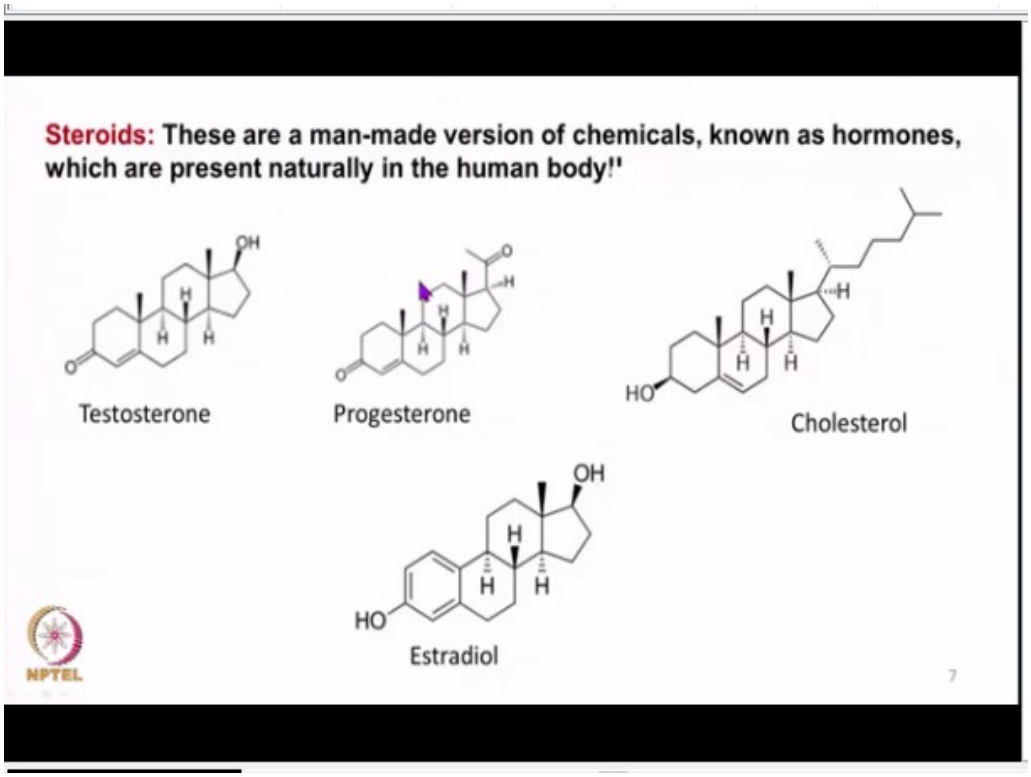
(Refer Slide Time: 10:17)



Now, we look at alkaloids, there are many alkaloids and there are all naturally occurring organic nitrogen containing basis. For example, this morphine which has these 5 rings attached to it and a nitrogen here.

Similarly, we have this nicotine, which contains these 2 rings, one of them is of course, piperidine ring and the other is pyrrolidine ring, then we have this papaverine which has this aromatic structures attached to each other and then we have the strychnine. Now, these are 4 types of alkaloids that I have shown here, but then there are many of them. For example, ((Yohimbine)) (11:15) reserpine and vinblastine, vincristine, there are many such alkaloids, which are naturally occurring and they are all biologically important.

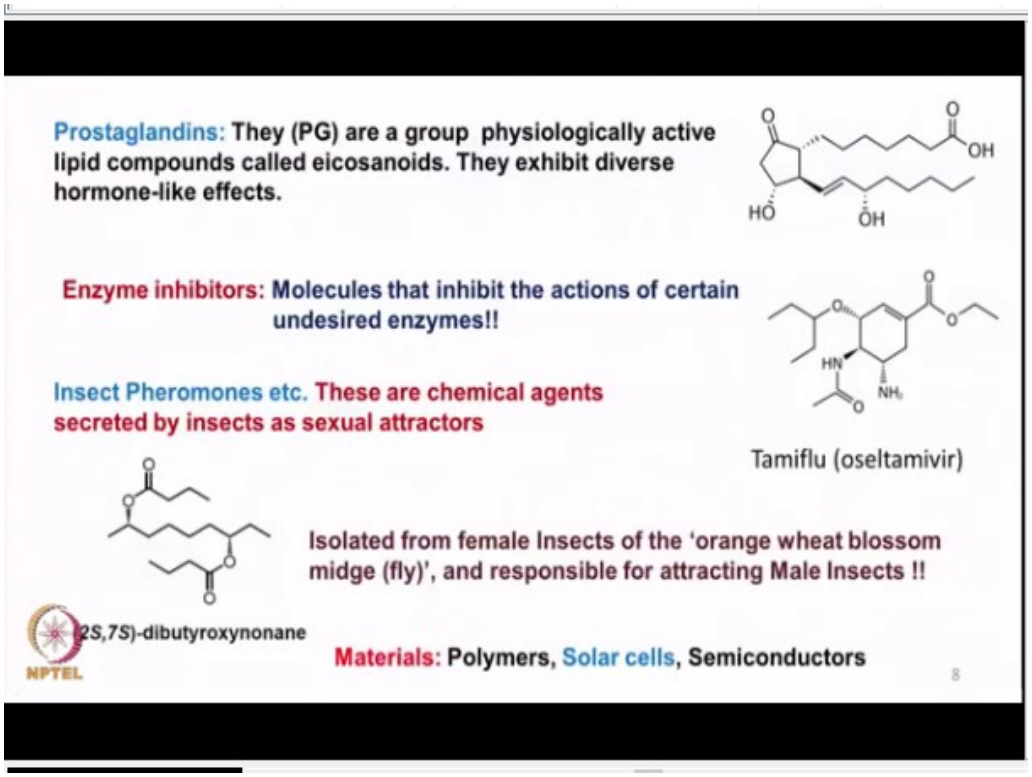
(Refer Slide Time: 11:27)



Now, there are steroids, these are manmade version of chemicals known as hormones, which are presented naturally in our body. The hormones which are present in our body play a very important role. For example, testosterone has a structure like this, which is a male sex hormone, then we have this progesterone which is female sex hormone, then we have cholesterol which is structurally quite similar, as you can see.

And we know that cholesterol is bad for health if it is in large quantity, but is required for the body because then these hormones are actually biosynthesized. Now similarly, we have estradiol which is important from both male as well as female sex hormones point of view. As you can see that these hormones or the steroid type of skeletons have 4 rings A B C and D. The A B and C rings are 6 members and fourth ring is 5 membered ring. As you can see also that the junctions are trans -oriented and that is the common feature in all the cases. Therefore, synthesis of these steroids molecules or the hormones becomes very important.

(Refer Slide Time: 13:07)



Now we have other set of molecules which are called as prostaglandins. They are a group of physiologically active lipid compounds called eicosanoids. And they exhibit a lot of different types of hormone like effects. The structure of prostaglandins is somewhat like this. This is one example but there are many similar type of prostaglandins. A common feature in all the prostaglandins is that it contains a 5 membered ring with substitutions which are contiguously like this as shown here.

There are 2 side chains and there is a either a hydroxy or a ketone and the hydroxy group here and the side chains would have of course, different double bonds and different hydroxy groups and at the end, there is a carboxylic acid group. Now, these are all very important molecules and they are not very stable molecules and synthesis becomes very challenging. However, a lot of synthetic efforts have been reported in the literature.

And synthesis for many of these compounds have been improvised and does involving shorter steps to procure these molecules. There are also enzyme inhibitors of different kinds, which basically are molecules that inhibit the actions of certain undesired enzymes. For example, this Tamiflu, which is oseltamivir is a actually a drug or an enzyme inhibitor against swine flu.

So, that means it inhibits the enzymes of the virus, which is causing the swine flu. Now, there are many pheromones which are called as insect pheromones, these are all chemical agents secreted by insects as sexual attractors, that means, male insects will have certain pheromones, the smell of that will attract the female insects and likewise female insects will have pheromones which will attract the males.

So, now what happens is when in certain fields or certain agricultural lands and there are different kinds of insects which are present and spoiling the field then that becomes a problem.

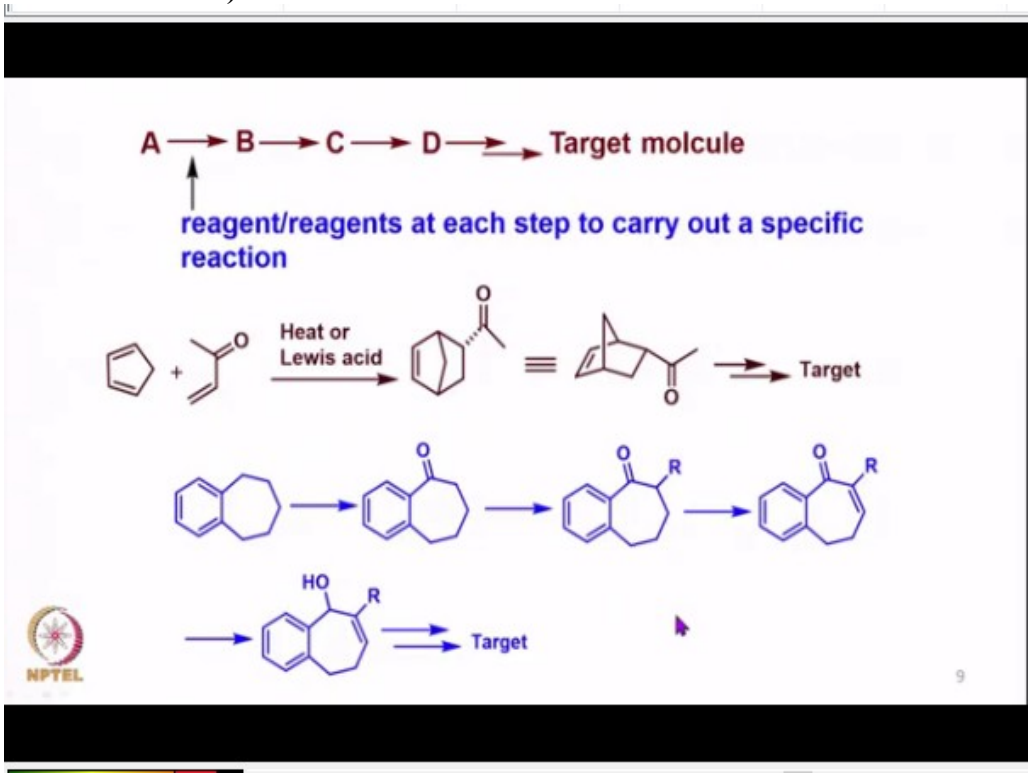
For example, this particular compound is isolated from female insects of the orange, wheat blossom midge, that means, this compound is isolated from the female insects, which remain close to the wheat and spoil the wheat.

And therefore, if we take this particular molecule and synthesize and put it in the field where wheat is grown, then since this is isolated from female insects, and if we are keeping this in a corner of the field, then all the males will be attracted towards this particular compound. And then with a small amount of insecticides you can kill the male insects and not spoil the wheat.

Likewise, if we isolate the pheromone from the male insects and synthesize and keep it in the field, where this wheat is grown, then all the females will be attracted towards that male insect pheromone and then of course, we can spray the insecticide and kill all the female insects. So, basically these are all molecules which can attract the female or male insects depending on which one we are using.

And of course, instead of spraying the insecticide over the entire field and spoiling the weed in this particular case, and thus we can avoid spoiling the wheat. Now, there are synthesis of various kinds of materials like polymers, solar cells, semiconductors that required organic synthesis.

(Refer Slide Time: 18:17)



Now, organic synthesis of course, of a target molecule whether it is a natural product or a non natural product would involve a number of steps. Say, if we start with a starting material like A and then go to the target molecule with different kinds of intermediate steps. Now, each step in this particular endeavour would need a reagent or a combination of reagents.

And of course, then it allows a reaction to carry out of course, as I mentioned earlier, it can also be a rearrangement, but it requires a reagent or a set of reagents or certain conditions. So, basically synthesis of target molecule is actually composed of a number of steps. Say for example, if we start with cyclopentadiene and react with an alpha beta unsaturated ketone, like methyl vinyl ketone.

Then either with the help of heat or a Lewis acid we can carry out these deals order reaction to form these bicyclic molecule which can be written up like this. As we can see that it has a double bond which can be functionalized or cleaved then it has a carbonyl group. And of course, there is a alpha hydrogen next to the carbonyl and there are 3 hydrogens here which are alpha 2 carbonyl group here.

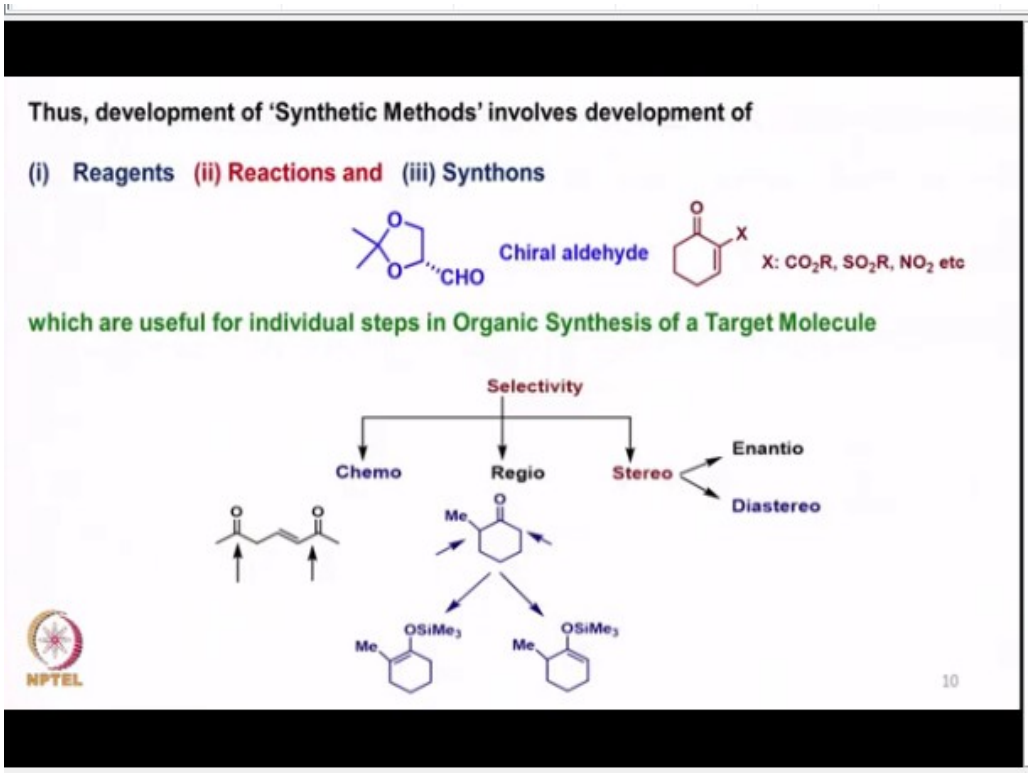
And therefore, they are activated hydrogens and can be functionalized. So, depending on what the target molecule is, we can carry out different reactions on this particular bicyclic molecule because it has a potential to functionalize double bond, functionalized ketone, functionalized alpha positions of the ketone. So, obviously, one can carry out several steps in between.

Likewise, if we start with this particular molecule, which is a bicyclic molecule having an aromatic ring of course, we can have different substitutions on the aromatic range depending on what is the target molecule, but just to show what steps could involve is we can do the benzylic oxidation here to go to the corresponding ketone, then we can functionalize the alpha position of the ketone to the introduction of an R group here.

And then we can introduce a double bond. This is further functionalisation we can reduce the ketone to the alcohol in a stereo selective fashion or if it is required, then any non selective fashion, then now, we are still left out with a double bond here and then R group. Now, depending on what R group is, we can then functionalize the hydroxy group here, the double bond here part of the R group here and of course, reach eventually to the target molecule.

So, it means that we can start with a molecule like this and go to the target molecule like this with several different steps. These are just 2 examples of how the synthesis can be done of a target molecule starting from this small simple molecule like here cyclopentadiene or something like this here. So, it involves a number of steps and each step as I mentioned earlier is of course, a synthetic method.

(Refer Slide Time: 22:08)



Now, development of synthetic methods therefore, involves development of reagents and reactions and synthons. Development of reagents that means, we need to develop reagents which are of general use or a specific use then we have different reactions using those reagents which we can improvise or develop new reactions and what is called as synthon. What is the synthon?

Basically synthol is a synthetic intermediate. Say for example, if we start with a molecule like this, which can be easily prepared from say D-mannitol or maybe from many other sources, it is a chiral aldehyde is optically pure aldehyde, it is a 1 2 protected dye all having a aldehyde moiety at this particular position. So, one can start with this it is a synthetic intermediate and can be converted to the target molecule.

Likewise, if we have an enone of this kind, which has an X group here that can be an ester or SO_2 R, or NO_2 or a cyano anything that we can put it here or even an aldehyde and then that becomes a very important molecule which is a synthol or which is a synthetic intermediate. Now, the individual steps in organic synthesis of a target molecule can make use of these reagents, reactions and synthons.

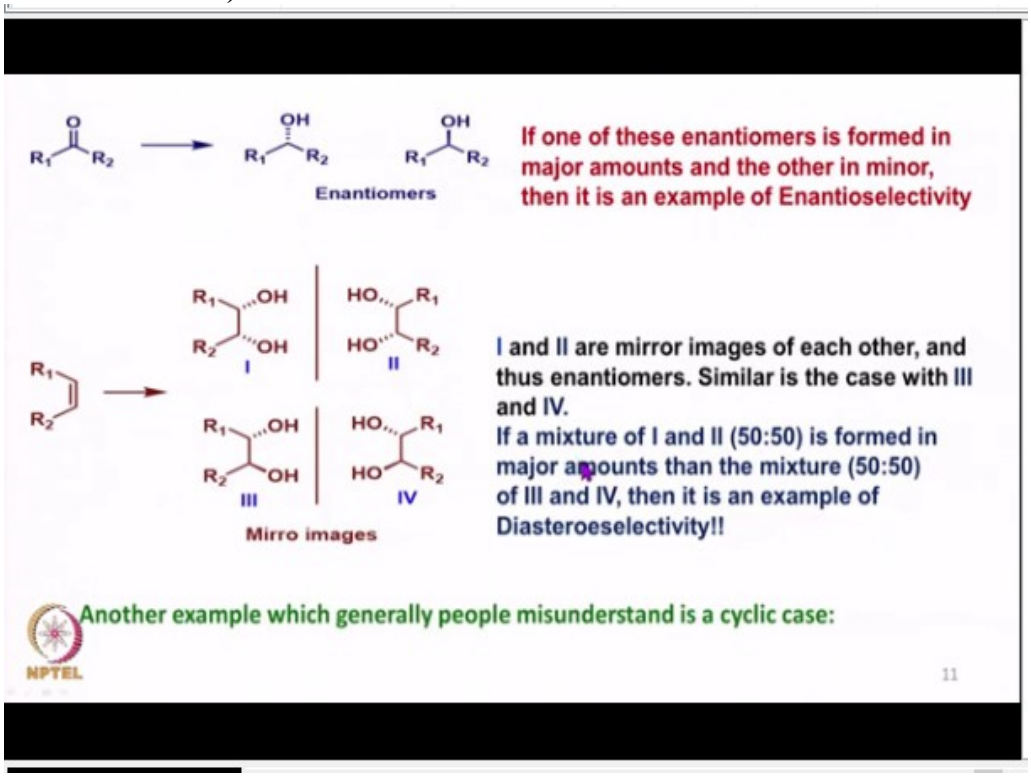
But then we also need to address selectivity. Now, we have chemo selectivity regio selectivity and stereo selectivity. So, if we have a molecule like this, which has 2 different ketones as you can see, this is a saturated ketone and this is an unsaturated ketone. So, if we do a reaction on this and allow this particular ketone to remain unaffected or do a reaction on this particular ketone and let this ketone be unaffected then this is a chemo selective reaction.

Now, in this particular ketone, when there is a methyl group on the left side and there is no substitution on the right side then of course, if we carry out the formation of ((enol silyl etther)) (24:49) by removing this proton here, then this is a regioselective deprotonation and

regioselective formation an ((enol silyl etther))) (25:00). On the other hand, if we deprotonate on the right side and lead the ((enol silyl etther)) (25:06) we made in this way then of course also this is a regioselective ((enol silyl etther))) (25:13) preparation.

So, these are the examples of regioselectivity and of course, we have stereoselectivity where we can have enantio and diastereo selectivity.

(Refer Slide Time: 25:25)

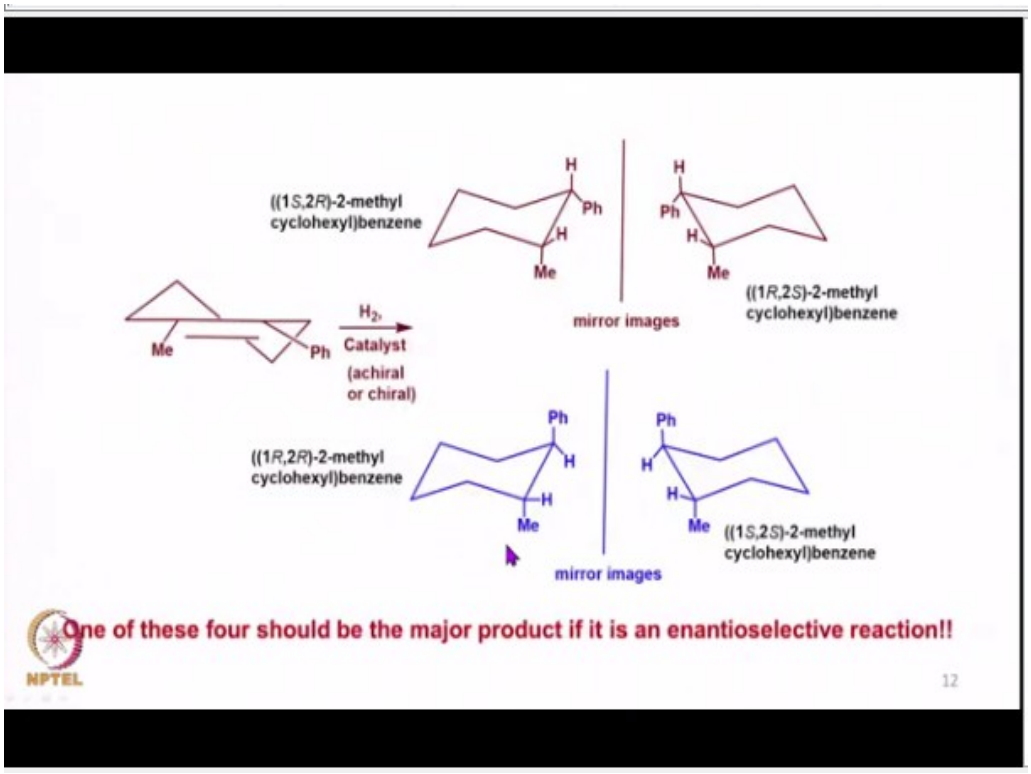


For example, if we start with a ketone like this, which is a prochiral ketone and when we reduce it and we can get a mixture of 2 enantiomers which are mirror images, but if we can have reaction conditions in such a way that we get only one of the enantiomers as the major product then of course we call it as an enantioselective reaction. In a similar fashion if we start with a double bond like this, which is kind of prochiral double bond and do dihydrooxylation.

So, if we do sis diode oxidation, we get these 2 molecules, which are mirror images of each other and if we do trans, dihydrooxylation then of course, we get these 2 molecules, which are again mirror images of each other. So, if I and II are mirror images of each other and II and IV are mirror images of each other, then if a mixture of I and II, which is a 50 50 mixture, that is an enantiomers.

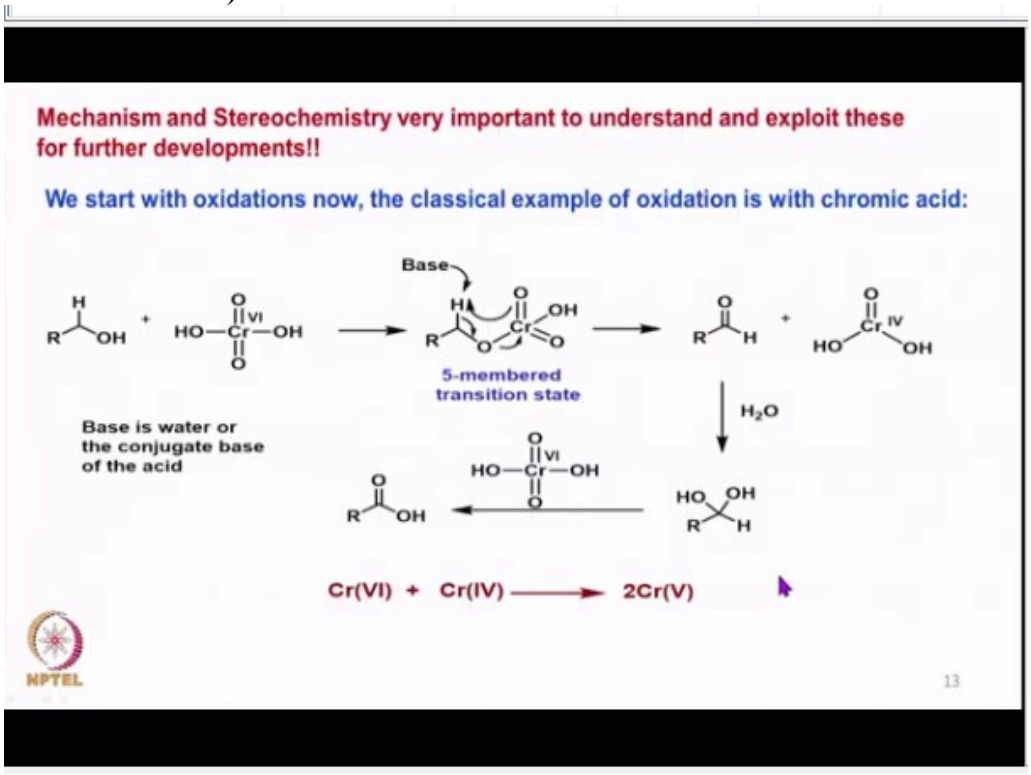
If this mixture is formed in major amount that means, if these compounds are formed in major amount than this that means, dihydrooxylation is specifically since dihydrooxylation then we call that this is an example of diastereoselectivity that means these are form in major amount and this is for minor amount, that means is example of a diastereoselectivity.

(Refer Slide Time: 26:57)



In a similar fashion, if we do the hydrogenation of this double bond, then we can get these 4 types of molecules again, sis or say trans hydrogenation. If one of these 4 is formed as a major product, then of course, we will call that as enantioselective reaction and also a diastereoselective reaction.

(Refer Slide Time: 27:22)

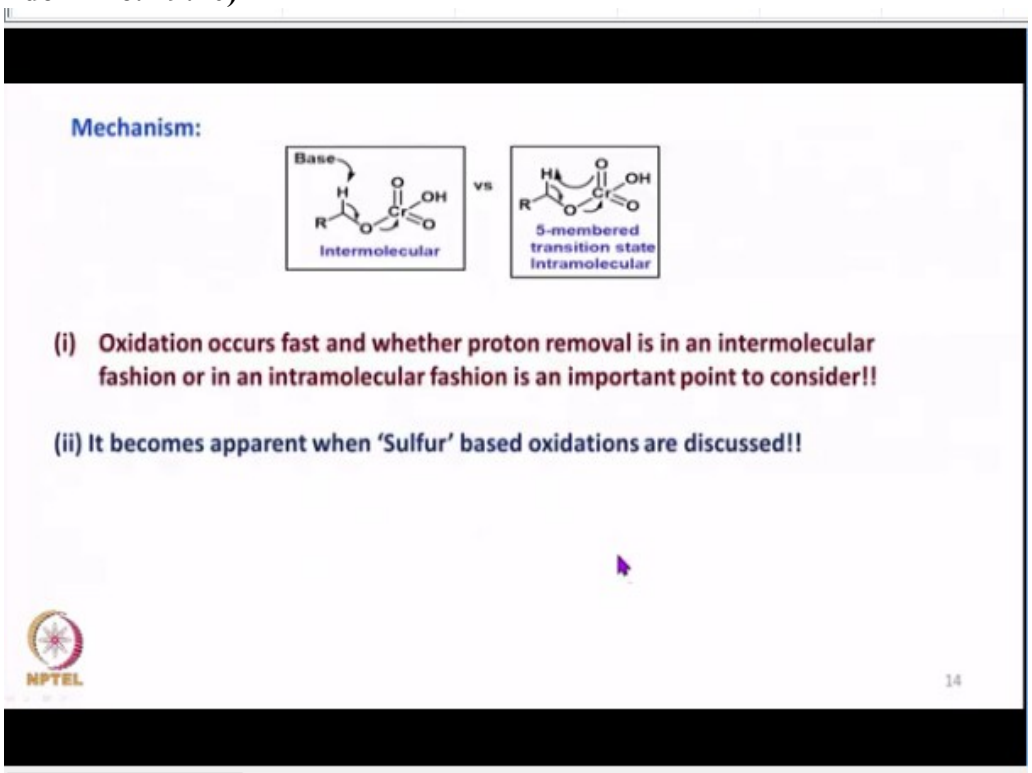


Now, we go to the last part of it of today's lecture and which will be then carried on to the next class is now, to see how oxidations can be carried out. Now, in all the oxidation that we are going to discuss or reductions or C-C bond formations that we are going to discuss, we will be basically talking about mechanism, stereochemistry because, that becomes very important to exploit for further developments.

Now, suppose we carry out an oxidation of an alcohol with chromic acid. So, we would get an intermediate of this kind. So, because alcohol here reacts with the electrophilic chromium VI species which leads to the formation of this particular chromate ester. Now, it can undergo cleavage of this kind to lead to the formation of an aldehyde either by the removal of the proton by base which is presented as a medium like water or it can undergo 5 member transition state like this to form aldehyde and release chromium IV species.

If this aldehyde reacts with water, then you get this terminal geminal diol which then can undergo oxidation to form the corresponding carboxylic acid. Of course, the chromium IV and chromium VI species can combine to form chromium Vspecies.

(Refer Slide Time: 29:10)



Now, the mechanism of this reaction whether it is an intermolecular like this, where base like water takes up the proton in this particular fashion to release aldehyde or whether it involves a 5 membered intermolecular transition state of this kind to remove the chromium species and release aldehyde is something that needs to be debated. It is difficult in this particular case to assess whether it is intermolecular or intramolecular because oxidation occurs fast.

And therefore, it is not easy to find out whether the reaction is proceeding in this particular fashion or in this particular fashion. But it becomes apparent when we do various kinds of sulfur base oxidations which we will discuss in the next class. So, we will stop it here today and then

start sulfur based oxidations in the next class, till then you take care of this particular lecture, whatever I have taught today and then we will continue in the next class. Thank you and bye