Classics in Total Synthesis-I
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Lecture - 03
Introduction History and Retrosynthesis

So, good morning and welcome back to this course on Classics in Total Synthesis Part 1. In the last lecture we briefly talked about the need for synthesis and basic requirements to become a synthetic chemist. Now, we will continue our discussion on brief history of organic synthesis and also little bit about retro synthesis ok.

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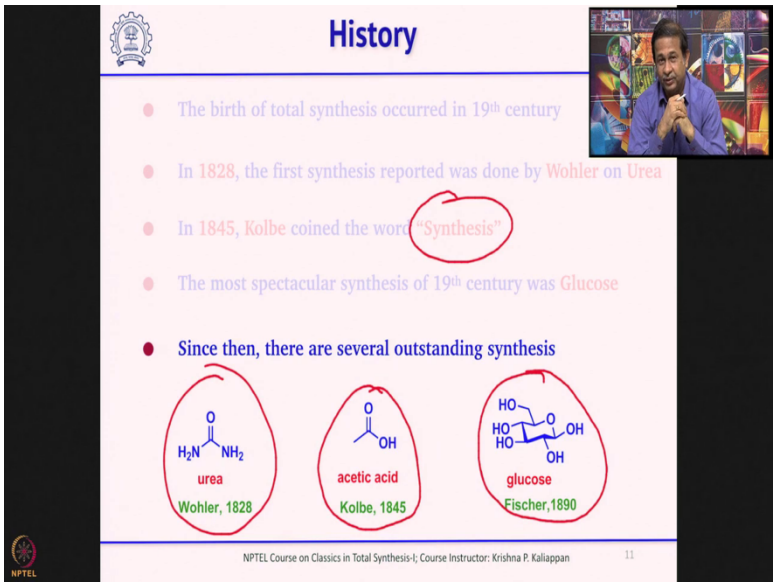

So, when you talk about history, the first synthesis of a natural product or any other molecule molecule, organic molecule was reported in 19th century. In fact, in 1828 the first synthesis was reported by Wohler on Urea. Interestingly, if you look at this, this urea was made from an inorganic compound and it was 100 percent atom economy reaction.

Then Kolbe was the one who made acetic acid and he was the first person to use the term synthesis. And afterwards you know people you started using synthesis, I will come back a little later the difference between preparation and synthesis and many times still people make mistake where to use synthesis and where to use preparation.

And in 19th century the most spectacular synthesis reported was by Fischer and Fisc her who made glucose that was the first time a natural product with chiral centers were made ok. So, it was you know spectacular landmark synthesis in the history of synthesis ok. So, if you look at 19th century these three are great landmarks.

First Wohler's urea, then Kolbe made acetic acid and also coined the word synthesis and towards the end of the century Fischer made glucose with five chiral centers. Then of course, you know there are many many outstanding synthesis of natural products and natural products like molecules. It is very difficult to compile all or compile most of them.

So, what I will do I will try to do it in two to three slides and how the history evolved over the next century or so on total synthesis.

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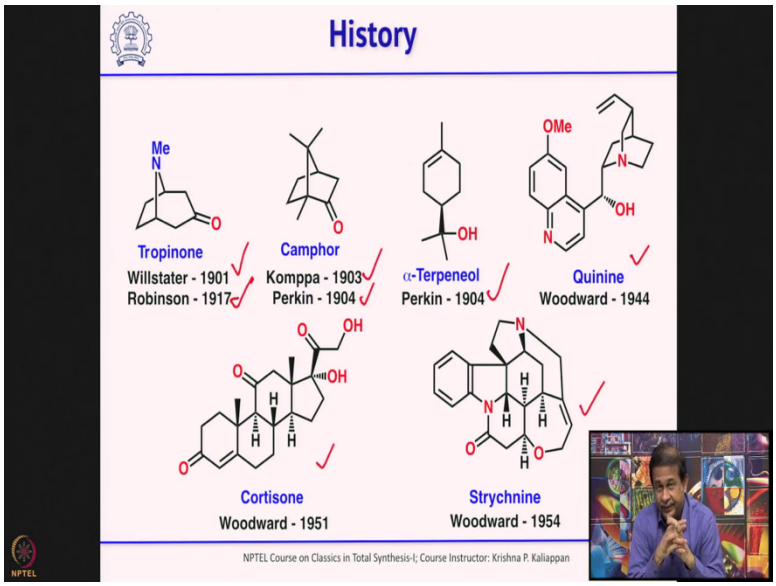

The in the 20th century the first molecule which was reported was tropinone. So, tropinone was an alkaloid and 1901 Willstater reported the synthesis of tropinone and 16 years later Sir Robert Robinson reported the synthesis of tropinone. Interestingly when Robert Robinson reported the synthesis of tropinone, it involved two important concepts, one is green chemistry because all the reactions were done in water ok one. Two he also involved a multi component reaction to make these natural products.

So, the two important concepts he introduced almost 100 years ago green chemistry and multicomponent reaction in the synthesis of tropinone. And two years later camphor which we all know is a monoterpene, so he was reported by Komppa and year later Perkin also synthesized camphor.

So, the first decade of 20th century saw three reasonably complex molecule considering the time frame the third molecule again Perkin reported was the synthesis of α-terpeneol another monoterpene ok. And three or four decades later the father of modern synthetic chemistry Robert Robinson synthesized the alkaloid called quinine, it was a formal synthesis and that got major attraction.

I and this is one of the molecules which I will discuss in details, a few weeks later and I will share lot of stories about this molecule as well as you know other related molecules. And 7 years later he synthesized the famous steroid called cortisone. This also we will discuss in our synthesis.

And 3 years later he completed and reported the total synthesis of an alkaloid called strychnine, which I already mentioned there were 400 papers, there were 400 papers on the isolation and structural elucidation of strychnine. So, he took several years to even report the correct structure of strychnine those days. And finally, in 1954 Woodward was the first one to complete the total synthesis of strychnine.

So, since then there are many synthesis we will try to cover at least two or three total synthesis of strychnine in this course.

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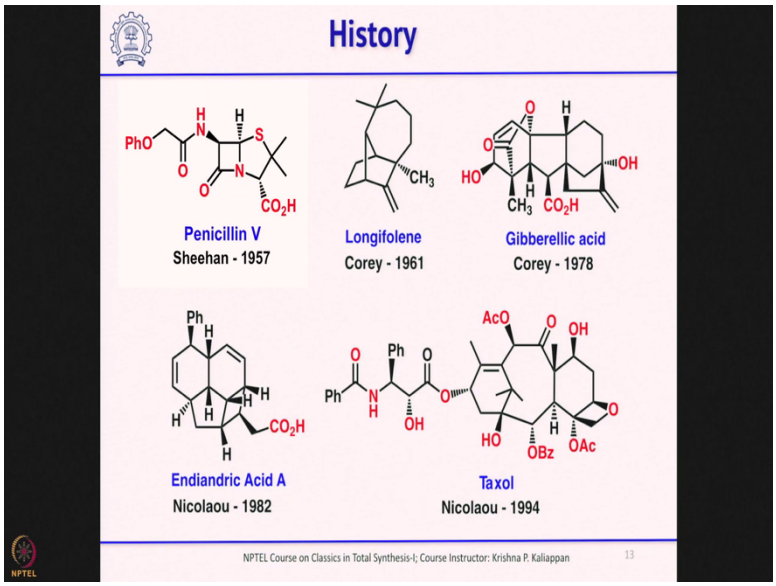

Then in 1957 though two decades before penicillin was isolated, but synthesis was very difficult that is particularly because of this highly labile four membered beta-lactam. There are many synthesis and in 1961 another don, another legend in total synthesis Corey started reporting synthesis of several complex natural products and one of them is longifolene and the longifolene is a classical synthesis followed by his synthesis of gibberellic acid ok.

It is also very very difficult synthesis, which deserves highest level of appreciation and considering the time in 1970s, such complex natural product was made. And around the same time Woodward also made another big complex molecule vitamin B12 and that time people never thought that molecules like vitamin B12 could be made, but Woodward made it. So, then in 1980s Nicolaou joined the top group of total synthesis chemistry and his synthesis of endiandric acid is one of the classical biomimetic type cyclization.

And he used that cyclization to make four five related endiandric acid using very simple strategy. And 10 or 12 years later another famous anti cancer agent, now it is a drug called taxol got major attention from many synthetic chemists Nicolaou and Holton were the first ones to make this natural product. Since then there are ten more total synthesis of taxol reported and all of them are very interesting and we will try to discuss few of them in this course.

Now, that is the history of our brief history of total synthesis. So, when you talk about history of total synthesis.

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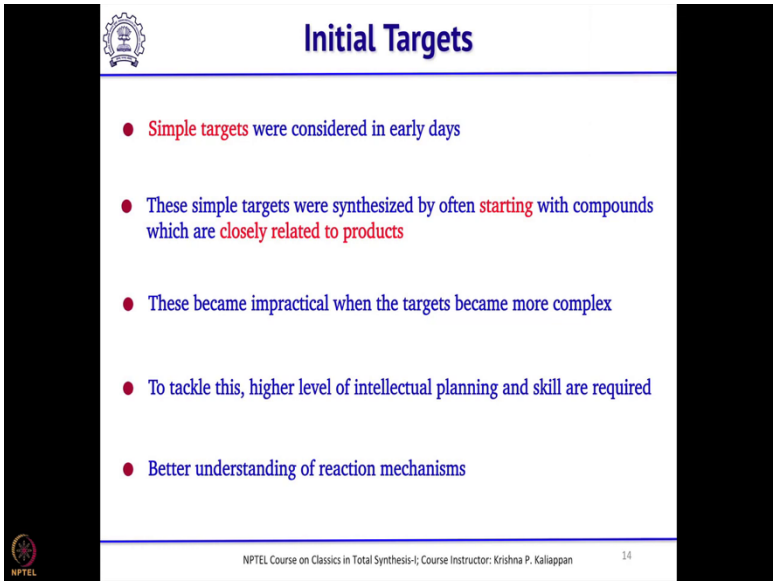

Initially how did they start? What were the targets? Did they start with bigger targets complex target? No. They all started with simple target because it was. See, one should remember that when they started there were no NMR, no IR, no UV, when they started. So, all these spectroscopy techniques came much later. So, it was not that easy to choose complex molecules. So, they always chose simple molecules, simple target molecules when they choose simple target molecules.

The target molecule will be very close to the starting materials which they use. So, that no it is easy ok it is easy for them to compare and then see whether they have made the compound. Then more and more complex natural products were isolated ok. So, when you isolate complex natural products, when synthetic chemists also will be very much interested in making these compounds. So, then you cannot start with equally complex natural product is not it?

See when you want to synthesize natural product and when we talk about total synthesis, the total synthesis means you should start from simple starting material is not it? You should start from simple starting material and accomplish the complete synthesis of the target molecule.

And if a target molecule is big then you cannot start with a similar similarly complex you know starting material. So, you have to start from very simple starting material then it becomes very very difficult. So, that was the time you know one need very high level of intellectual planning, skill, curiosity and that time lot of outstanding synthetic chemists join and they started working on total synthesis.

And try to address synthesis, the problems faced in synthesizing complex natural products. And physical chemists, inorganic chemists they all supported organic chemists and physical chemists you know they supported in terms of you know having spectroscopic techniques NMR, IR, UV, X-ray. All these helped organic chemists to solve structures.

And inorganic chemists, inorganic chemists were concentrating on developing new reagents ok and these reagents were used by organic chemists. Inorganic chemists all normally they are interested in unstable compounds ok, they are always interested in unstable compounds. For organic chemists it is blessing, you know why this unstable compounds are reagents for us.

So, organic chemists use this unstable compounds prepared by inorganic chemists as reagents. So, that way inorganic chemist and organic physical chemists played a very very important role in the development of organic synthesis. When we continue further, many times when reactions do not go that is the time one should try to understand the reaction mechanism.

Why reactions do not go? So, this is where physical organic chemistry comes into play. So, all started with synthesis and branched out and they were started working on physical organic chemistry. Physical organic chemistry played a very important role in addressing some of the complex problems associated with total synthesis.

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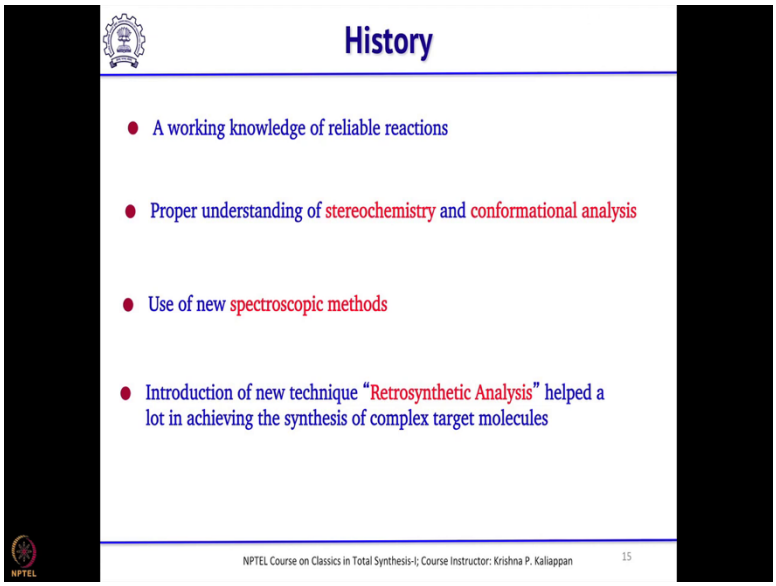

More and more new reactions were developed ok. So, synthetic chemist's job is to understand, remember, large number of reactions. And in the large number of reaction what is important is what are the reactions which are reliable and general because some reactions which will work specifically for particular transformation, but they cannot be general.

So, that is why the most reliable reactions one should consider when you talk about synthesis of complex molecule. Then important thing is when you talk about complex molecules, then some of the molecules have several stereo centers some of the molecules have several stereo centers. How do you incorporate or how do you install new stereo centers and some of them will give conformational problems ok.

So, in one particular conformation the reaction will work in the other conformation it will not work. And how do you make sure that your substrate is in that particular conformation, so that your reaction will work. So, the understanding of stereochemistry and conformational analysis also played a very important role in 60s onwards, ok.

Then I already mentioned spectroscopic methods played a very very important role for synthetic chemists to grow and in 70s a very famous technique called retrosynthetic analysis reported by Nobel laureate Elias Corey, actually helped all synthetic chemists to solve complex problems by dissecting the bonds into small, smaller and smaller and smaller molecules.

We can take complex molecule by using retrosynthetic analysis, you can cut and go to the next molecule cut go to the next molecule until you reach commercially available starting material. So, this retrosynthetic analysis were is one of the famous tools, used by synthetic chemist in addressing and solving many synthesis problems.

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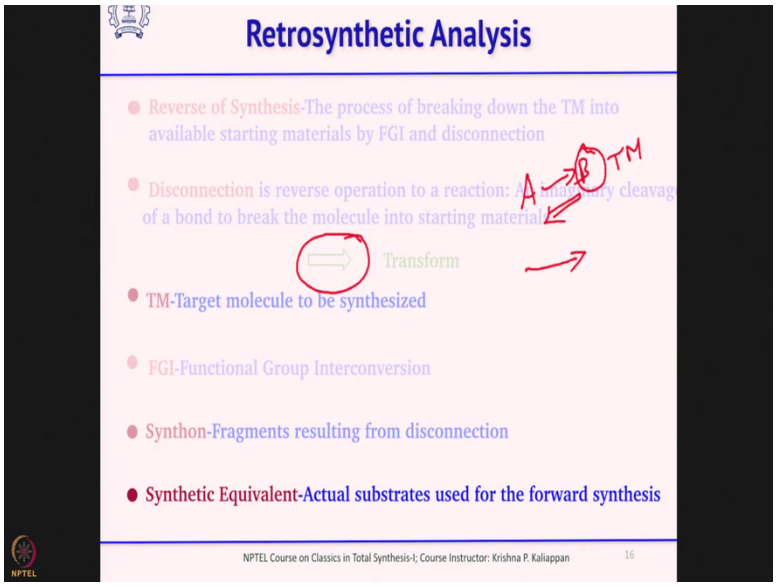

So, what is retrosynthesis? Retrosynthesis. So, that itself tells retro means reverse, reverse of synthesis ok. So, when you talk about synthesis if you want to make B you start with A. So, A to B is called synthesis is not it? A to B is called synthesis A to B is called synthesis. And B to A, B to A is called retrosynthesis you have B and how you can make B. If you identify A then that process is called retrosynthesis.

And that process is you if B is the target molecule ok and you break this B using some known reaction or using some functional group transformation and disconnection. If we can convert that into A then that process is called retro synthesis. And you also see another term called disconnection.

Again that disconnection is opposite to the forward reaction see normally you talk about A giving B, but in the disconnection you break your bond ok and when you break a bond you know you can identify. So, this will lead to another starting material ok. So, normally this retro synthesis, the disconnection is represented by this double related arrow and normal one you write like this ok. This is the major difference.

And TM again you will see in the literature TM is called Target Molecule to be synthesized and FGI is called Functional Group Interconversion or Functional Group Transformation. And synthon, what are synthons? When you break a particular bond when you break a particular bond and if it is if it is broken by hemolytic cleavage then you get diradical.

And if you break it by heterolytic cleavage one side you will get carbocation other side you will get carbanion ok charged species. So, the charged species are called synthons when you break you get two different two different fragments they are called synthons. And you also see another term called synthetic equivalent what is synthetic equivalent and what is the difference between synthon and synthetic equivalent.

Synthon is a fragment, it is a charged species ok it can be radical it can be carbocation it can be carbanion or the synthetic equivalent is the one is the actual compound actual substrate. For example, RBr when you cleave if you get R plus that is synthon RBr is synthetic equivalent. And sometimes you get R minus then also you can write RBr as synthetic equivalent, because if you do Grignard, then it becomes RMgBr becomes R minus is not it?

So, there is a difference between synthon and synthetic equivalent which you should know ok. So, I will not go into the details because this and all as I said in the beginning this course concentrates mainly on the total synthesis and we should have known about retrosynthetic analysis. And I am just doing a recap of what you know about retrosynthesis.

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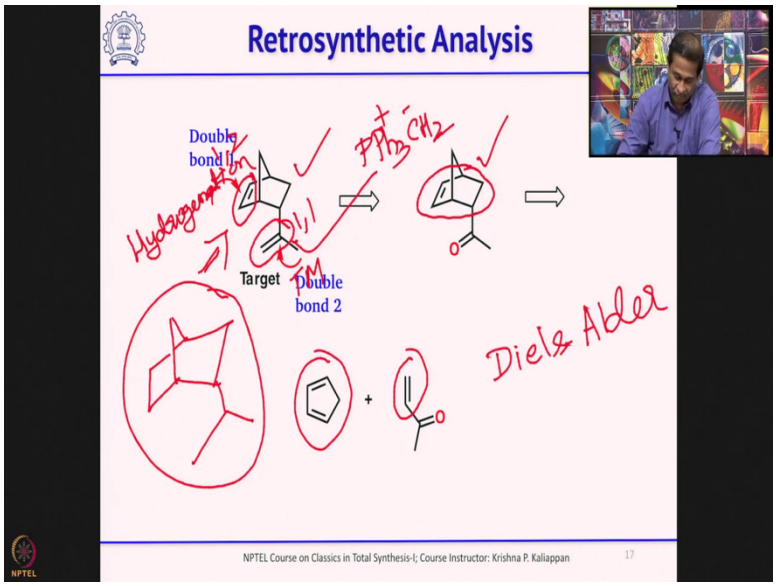

I just give one example of retrosynthetic analysis of a very small molecule before we move to the natural product synthesis. So, you look at this target molecule. So, when you look at this target molecule. So, you can write it as TM ok. Now there are two double bonds, isn't it? There are two double bonds one is a disubstituted double bond, the other one again it is a disubstituted double bond. The difference is here it is 1,1 disubstituted here it is 1,2 disubstituted ok.

So, now when you look at a molecule first thing you have to look at a molecule is whether the molecule has a functional group ok. So, now when you look at this it has two functional groups, two double bonds ok and next question is whether you want to make both the double bonds in one step or you want to make only one double bond.

If you are making only one double bond which double bond you will make ok. So, that way you have to think and simplify. So, now are you going to make this double bond or going to make this double bond. So, it's very easy from the look of this molecule if you want to make this double bond it can be made using Wittig reaction, is not it? If you want to make this double bond one can easily make using Wittig reaction.

Then what should be the precursor? The double bond b double bond do double double sorry, double bond 2 can be made by Wittig reaction; that means this is the precursor, is not it? This carbonyl group when you look at simple methyl Wittig will give your target

molecule simple methyl Wittig, is not it? If you take this Wittig will give you your double bond.

And now when you look at this precursor you can see a cyclohexene ok you can see here cyclohexene. Whenever and wherever you see cyclohexene one reaction which should come to your mind immediately is Diels-Alder reaction ok, one reaction which should come to your mind immediately is Diels-Alder reaction ok. So, now that tells how you can break this compound and make it as Diels-Alder starting material.

It's very simple if you do that you get cyclopentadiene which is the 4-pi component. And methyl vinyl ketone has the 2-pi component and this can undergo 4+2 Diels-Alder reaction. When it undergoes Diels-Alder reaction, as you know Diels-Alder reaction gives endo product as the major product and you get this compound.

So, basically this compound the target molecule can be made in two steps from commercially available starting material commercially available starting material that is cyclopentadiene and methyl vinyl ketone. So, now to make it complex ok, the same starting material I make it complex and then say instead of this compound TM, I write this compound, ok.

So, I revise the target molecule and the target molecule does not have any functional group, target molecule does not have any functional group ok. So, this is also very important when you look at a natural product when you look at a molecule and if you want to do retrosynthetic, retrosynthetic analysis normally what you look at is a strategic bond or if there is no strategic bond you look at a functional group.

If both are not there as in this case, then what you should do? You should introduce one or two functional groups, one or two functional groups. Because these functional groups will be the handle for you to carry forward the retrosynthesis, without functional group, without strategic bond you cannot do retrosynthesis ok.

So, that is what when you look at this hydrocarbon, it is a high simple hydrocarbon and it does not have functional group. So, first thing if your target molecule does not have a functional group or does not have a strategic bond, introduce, either introduce the functional group or introduce the strategic bond.

So, now it is very simple this target molecule can be made from the earlier target molecule, is not it? How do you do it? Very simple hydrogenation. This compound can be easily applied from this hydrogenation. So that means, the precursor is this you introduce two strategic bond, two double bonds you introduce. That will simplify the whole process.

So, in retrosynthesis analysis why I chose this particular example is, one you should know the strategic bond if you do not have introduce your strategic bond that will simplify the process ok.

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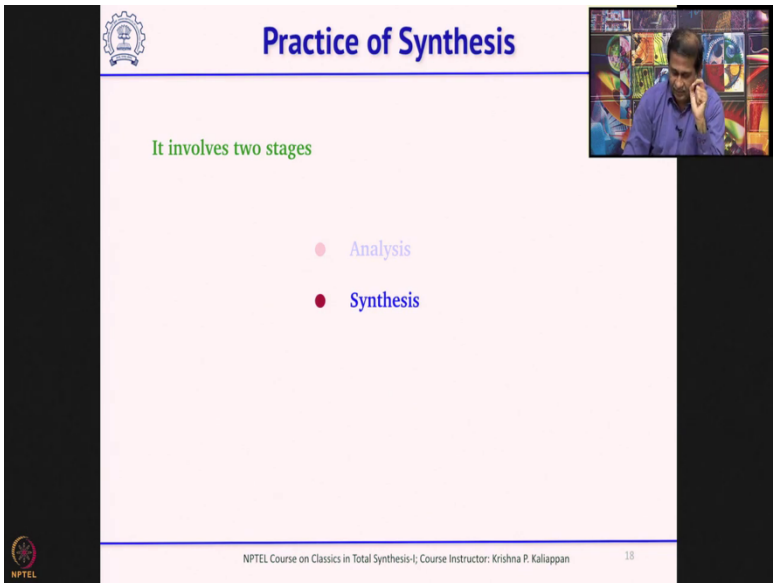

So, when you talk about any synthesis, synthesis generally involves two stages ok. These two stages are very important. Normally, nobody will teach, but you should know that synthesis involves two important stages one is analysis ok, I will come to that later second is the execution, but the synthesis part.

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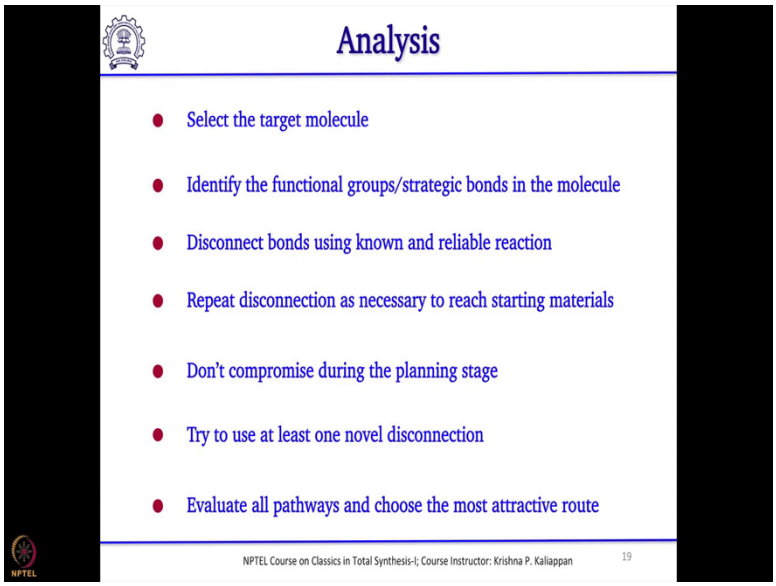

So, what is analysis? Very very important many times this is where people make mistake the first thing is select the target molecule? Why select the target molecule as I said there are 10000 natural products which are being isolated every year ok. So, you cannot synthesize all the molecule, is not it? So, you have to synthesize the target molecule you have to synthesize a target molecule, either the target molecule should show exceptional biological activity, very important or highly complex in nature.

Or you have some methodology or you have developed some new reagent or you have developed some new catalyst, that could be used to synthesize this target molecule ok. So, you cannot simply choose any target molecule, you have to choose target molecule based on this ok. See, that is the first and foremost step, many times people make this mistake. Simply re choose, randomly target molecule no choose a target molecule based on this.

Once you choose the target molecule then from retrosynthetic point of view, next thing you have to look at that molecule is whether it has any functional group or it has any strategic bond ok. These two are very important. Once you have that then you can use known reactions to break the bond or convert the functional group yeah. Once you see that functional group then you use the disconnection method ok disconnection method using the known reaction.

And of course, when you talk about known reaction reliable and general reaction to break them on ok. Then next step is you continuously do that continuously repeat the disconnection as much as possible to reach the starting material which is available commercially ok. So, that is very important ok, continuously do it is a starting material.

When you write a retrosynthesis never compromise this is very important ok, it may happen it may not happen no problem I will write no. You have to be very very strong, you should be 100 percent sure that when you do your retrosynthesis this can be obtained from this you have to be sure, then only that pathway you can proceed further. There is no compromise during the planning stage ok.

Then when you do a total synthesis it is very important it should not be a routine total synthesis. Your synthesis should have at least one interesting interesting, I do not use the word novel also people use novel one interesting disconnection ok. Where you can make 3 4 bonds or like you can use a multi component something unique, about that particular step one interesting disconnection you should have then only that synthesis will be attractive.

So, you are writing retrosynthesis when you do retrosynthesis you can see there will be several branches. So, many pathways for a same molecule you should be able to write ten different retrosynthesis. Then you write all the pathways, all the pathways separately all the pathways analyze; which one is better in terms of number of steps, in terms of commercial availability of starting material, cost all that you calculate.

And then see yes route c is the best route ok, choose that route. Now you have done the analysis part, the second part is synthesis that is the execution. But at the end of analysis what are the advantages you have one, that leads to readily available and inexpensive starting material ok. That is the first and foremost advantage of analysis, then you never compromised while doing the retrosynthetic analysis.

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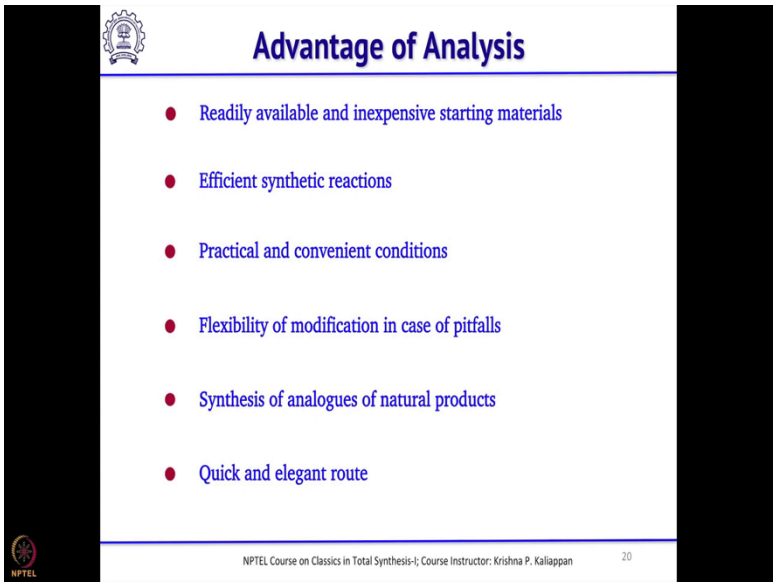

So, all the reactions you have planned are very efficient ok, you know that these reactions will work. The third one the conditions, so when you while doing the retrosynthesis itself you have seen whether these reactions can be carried out in our lab ok. Some reaction may not be able to be (Refer Time: 28:00) carry out in our lab. So, you should have thought about it.

So, it should be practical and it should be possible to do in our lab, so this is a third advantage when you do analysis. And while doing retrosynthesis also when you know one particular step does not work what are the other alternatives what one can do that you would planned. So, you know if there is a problem you can always fall back and then go to another side route and come back ok.

And last, but not the least is when you do these one can also synthesize several analogues of natural products using the strategy. And that will give you an opportunity to take care of structural activity relationship studies too. Of course, the route which you have finally, done is very quick and elegant.

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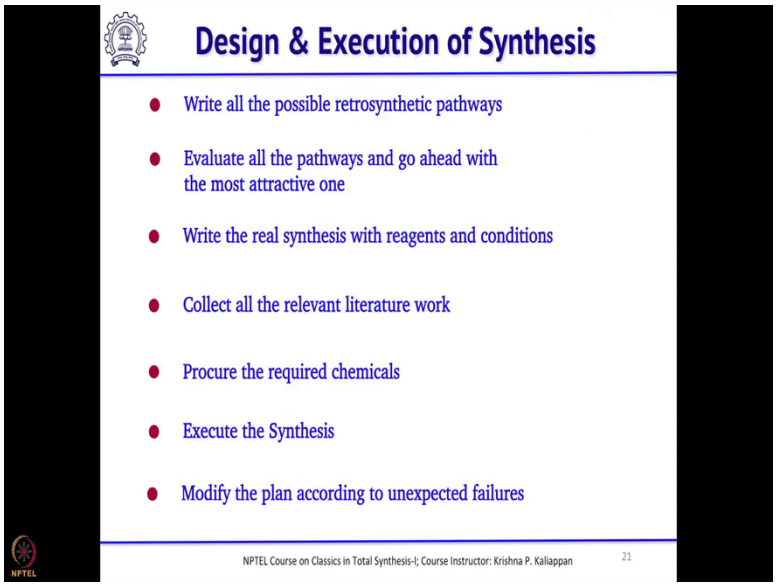

And now the second part is the execution part. As I said you write all the path pathways and choose the best one ok, that is the second step. Then the third step is forward synthesis what you have done during the analysis is the retrosynthesis, but in the during the synthesis you have to write the forward synthesis each and every step you write and with reagents and condition.

So, then only you know for moving ahead what are the chemicals you need ok and before that for each and every step go to the library collect all literature and experimental procedure for each step ok. Then what you do, order the chemicals, reagents required for all the steps then only you should go to lab ok, before doing all this you cannot go to lab and straight away start doing this. So, after doing all this then you go and then start the first step ok.

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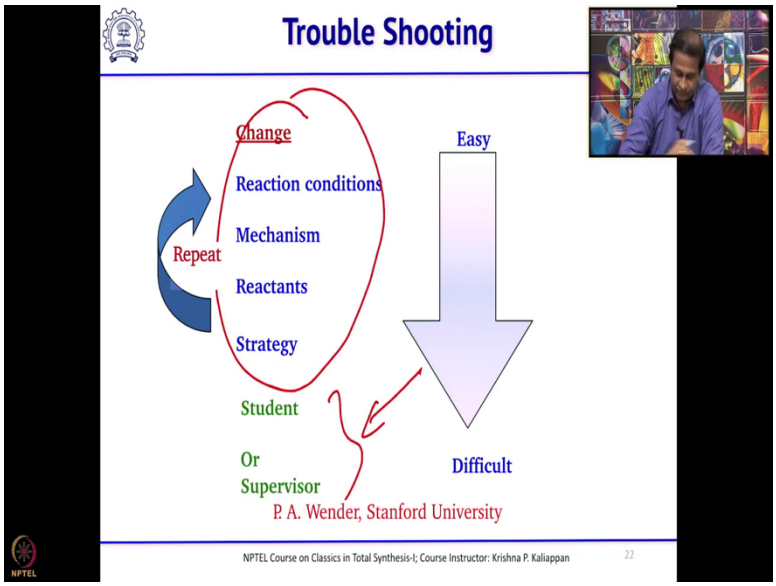

Now, you have done all this you go to lab, start the reaction. First step itself does not work it happens, sometimes second step will not work, sometimes in the last step it will last step last step will not work. So, what you do, then you should try to change the reaction conditions try to understand the mechanism change the reactants or if nothing works change the strategy ok, this is what you should do.

And if does not happen again go back try to change, again the reaction conditions, mechanism, reactant, strategy. So, according to Paul Wender from Stanford University this is what one should do ok, but as you know it is easier than and easier said that done. When if nothing works, you have to change the student because you do not know whether in the synthetic problems given it was because of student or because of the reaction conditions.

So, you supervisor think will think that after doing all this it is because of the student the scheme did not work, but the student will think that the supervisor is given you know unworkable problem. So, otherwise you know he or she would have thought easily that project would have been completed.

Well, I will not get into that, but one thing which is obvious is it is easy to do this, but difficult to do this ok changing student or supervisor is not easy. Once you join for PHD somehow you know should make sure that you successfully completed PHD and then go.

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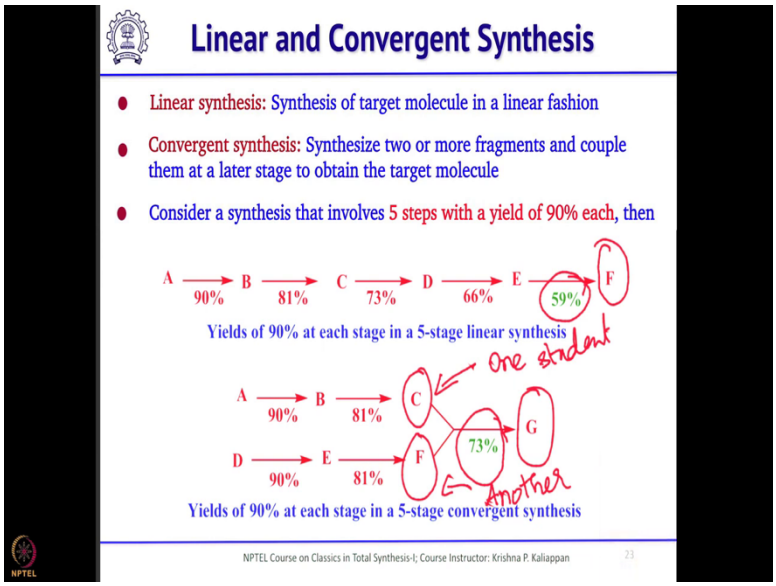

So, the last slide I just briefly talk about linear and convergent synthesis and what are the advantages of convergent synthesis. Linear as the name suggests; that means, you are synthesizing the target molecule in a linear fashion. Whereas convergent synthesis you are making two or more fragments and then converge it ok try to couple, so why convergent synthesis is better than linear synthesis.

Let us see a synthesis of the same target molecule using linear synthesis as well as by convergent synthesis. Assume that the linear synthesis as well as convergent synthesis is of 5 steps and in the case of linear synthesis you can say each step gives 90 percent. So, your target molecule at the end of 5 steps you get 59 percent ok.

The same thing you do by a convergent synthesis. Here you make two fragments C and F each by two steps, then try to come combine now the overall yield is 73 percent. So, you can see clearly there is a difference in yield, one. And the second important thing is when one does a complex total synthesis convergent synthesis is better for a simple reason. That the fragment C can be made by one student ok and fragment F can be made by another student.

So, more students can work on the same project, but the each student will work on different fragments. So, the speed in which you can assemble and then complete the synthesis is much faster. So, convergent synthesis always is advisable and sometimes it is not possible, but given a choice you should plan for convergent synthesis.

So, with this I will stop here. I have to summarize you know in this lecture, I talked about mainly retrosynthesis and also how you have to plan your synthesis start with analysis and then execution and also why convergent synthesis is better than linear synthesis. In the next class we will talk about total synthesis of three membered rings and we will start with synthesis of Illudins and we will go ahead with another natural product ok.

Thank you.