A Study Guide in Organic Retrosynthesis: Problem Solving Approach
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Lecture - 01
Introductory Remarks

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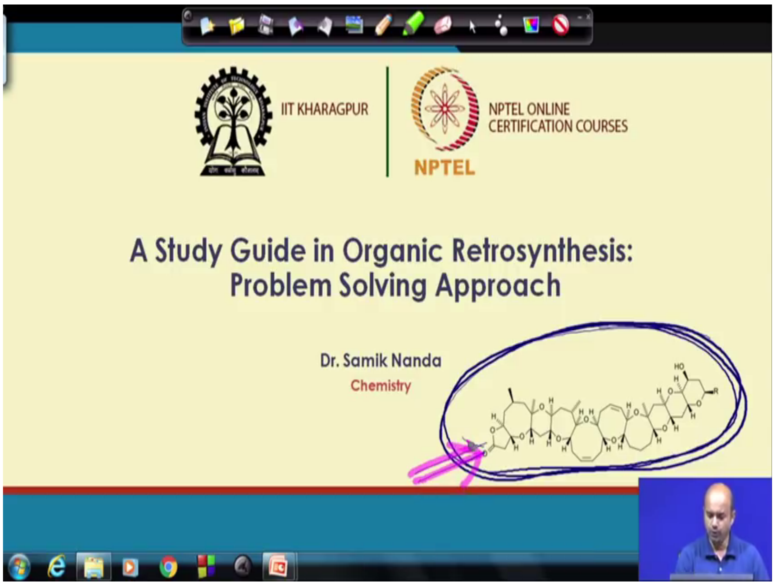

Welcome to all of you. So, myself DR. Samik Nanda from chemistry department IIT, Kharagpur. And I will be offering this course entitled as A Study Guide in Organic Retrosynthesis Problem Solving Approach. Now, we talk about retrosynthesis is basically a core area in organic synthesis and the name retro which have been used basically thinking the synthesis in a backward direction. This particular term will emphasize throughout our lecture, and I just see this particular these things problem solving approach throughout our entire discussion we will be guiding to you through different problems, and how to solve these problems in the context of organic synthesis.

Organic synthesis is really a very vast area. And essentially this is one of the core discipline in the area of organic synthesis where you can find this different scientist or different researchers have putting their continuous effort in this particular area. And eventually here you will see a huge molecule is a natural product, and is having important biological activity. Now, this natural product people are interested how you can make it and eventually if you study this particular course work which is named as organic retrosynthesis probably you have some guideline or some idea that this kind of big molecules also can be made. But eventually you have to be very focused and have to be quite sure that how this molecule can be made efficiently.

Throughout this work we will throughout this course work we will be talking about several such problems not such big molecules we will be taking the some small molecules where you can basically excel your ideas your thoughts in a piece of paper and then you can trying to solve those areas in a different way.

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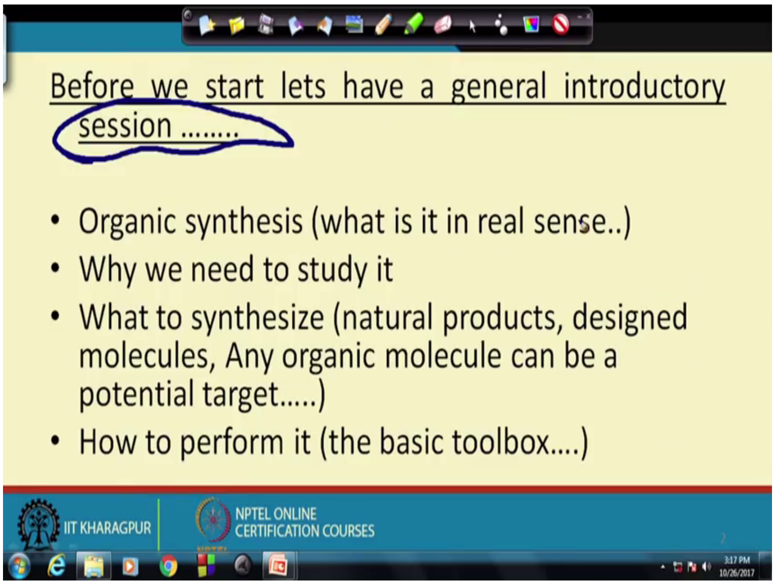

Coming to next slide to our next that. So, before we start we will just try to give you a very general introductory section, and what organic synthesis in reality. Now, this particularly session is basically belong to this particular following points. The points are organic synthesis what is it in real sense.

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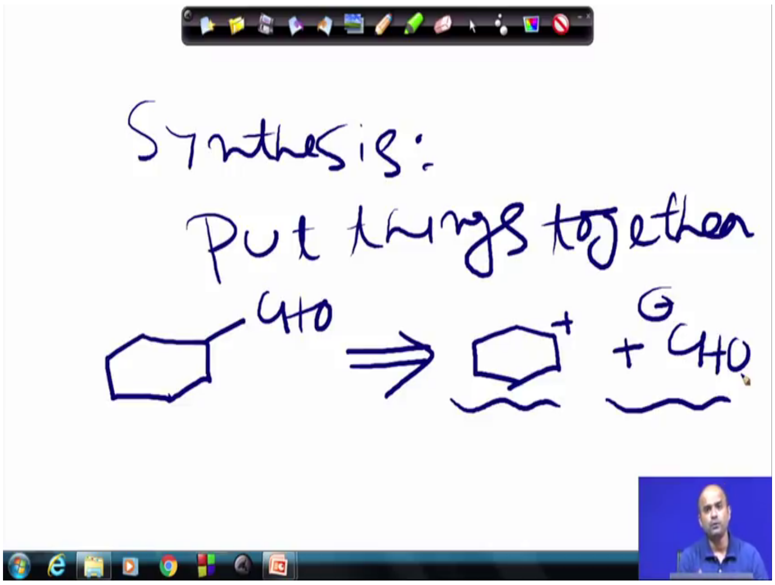

And if you think organic synthesis is basically nothing organic synthesis we will try to analyze this particular word synthesis. Synthesis literally means put things together and that basically give you a very good idea that when you are trying to make organic molecule let us say for instance is I am trying to write as very simple molecule that this molecule you want to make. It means that you have to make this molecule through different chemical component, and this chemical component could be say for instances this is one of the way you can make this molecule. Now, what is the way this is one thing this is one thing, you are basically assembling two units together to make this target molecule. So, in another what is basically nothing, but just making a big building kind of thing if you are thinking a mason who makes a huge building or a engineer who makes a or a architect who makes building what they need they basically need a large number of starting materials.

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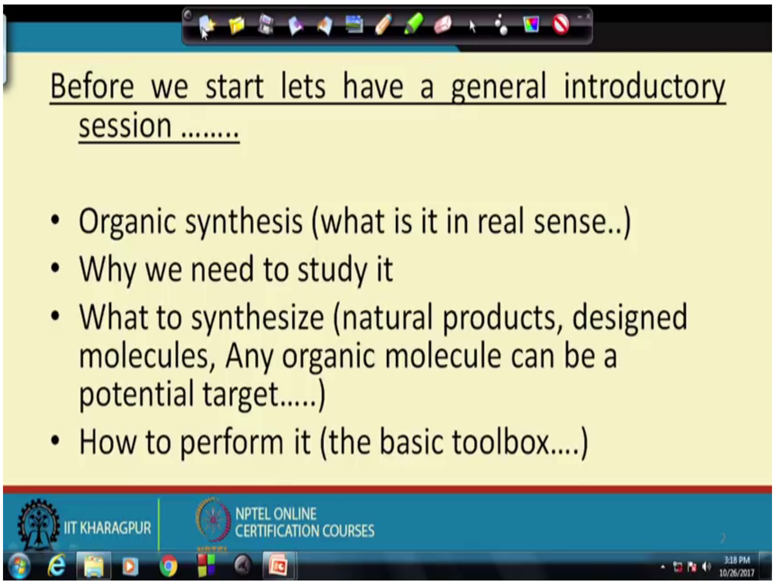

What are those they needs cements, sands, concrete etcetera to give a fine safe or architecturally safe, the same way we will be also trying to use organic synthesis in that area. Now, why we need to study organic synthesis, this is the prime question before you go to study in detail that why organic synthesis is require. And as I said organic synthesis one of the core discipline in the field of organic chemistry and medicinal chemistry. So, our society demands you should make organic molecules. Now, organic molecules are basically varied from any different kind of molecules, in your each and every day daily life we use several organic molecules.

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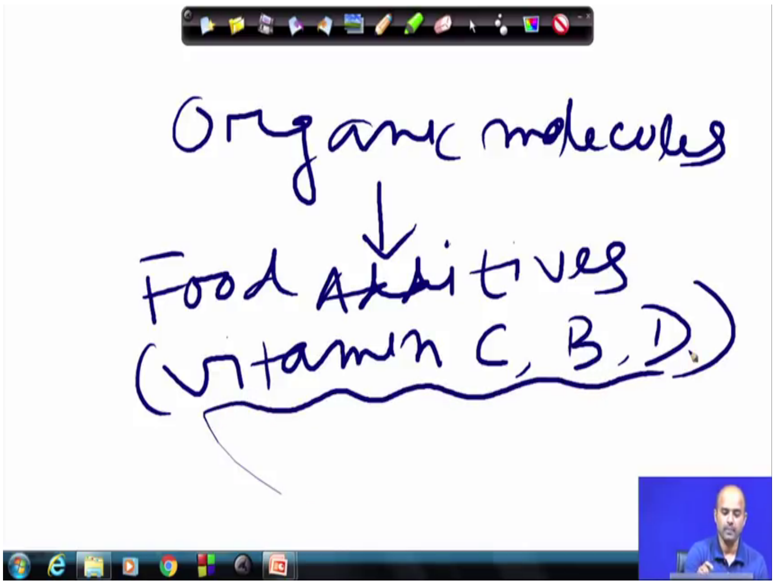

We use several organic molecules. As I said this is our main prime target organic molecules. Now, what are they organic molecules are basically consists of I will say food additives, you can use a new models organic compounds in your food additives, food supplement mainly vitamins those are all organic compounds let us say vitamin C, vitamin B, vitamin D, all cannot be synthesized inside the body. And they will need to as a dietary supplement. So, all these things you basically need.

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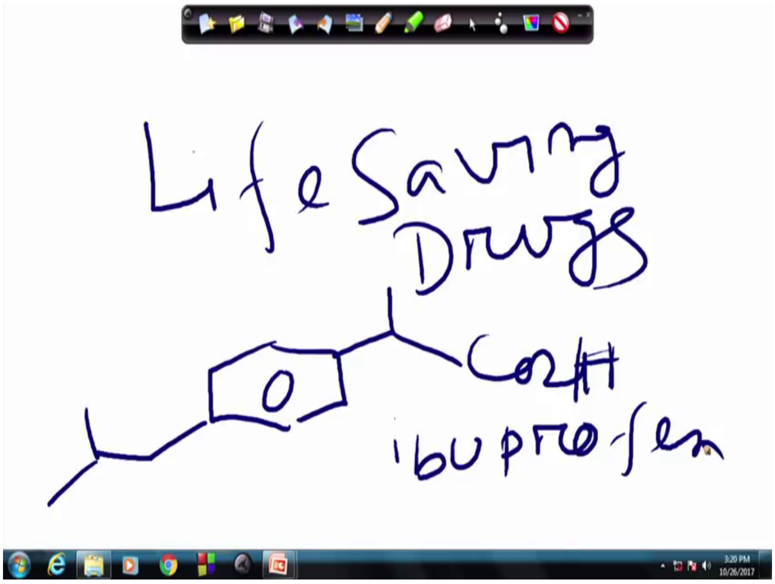

And then the main thing is coming your life saving drugs, all the life saving drugs are essentially organic molecules. Say for instance says I am trying to draw a graph whose structure is this and this compound is very well known painkiller its name is ibuprofen or ibuprofen and essentially ibuprofen is a organic molecule and being a chemist you probably need to know how this compound is made.

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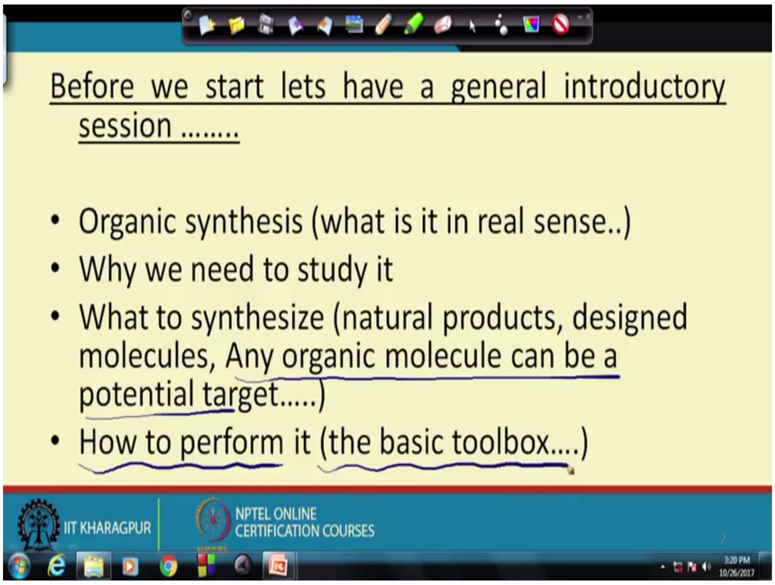

So, essentially our next thing will be how you can make organic molecules in a relatively easier way and efficient way. So, as I said any organic molecule can be a potential target any organic molecule can be a potential target. And the next question will be ask how you can make this molecule, basically you have to acquainted you have to familiar with the basic toolbox. Now, what are basic toolbox?

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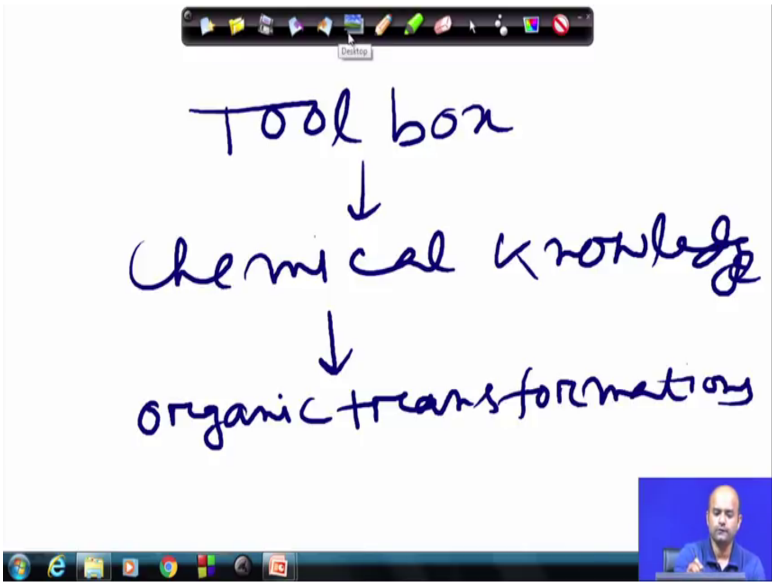

When you say a toolbox, toolbox basically means that your using your chemical knowledge this toolbox is nothing but your chemical knowledge or chemical logic which you have already acquired, chemical knowledge. It is basically a knowledge based approach. Now, from a synthetic organic perspective or synthetic organic chemistry view this knowledge is nothing, this knowledge is basically your ideas, your views about certain organic transformations, because organics synthesis is nothing but assembling organic transformations, organic transformations and how this transformations will lead you different organic molecules that is the only thing.

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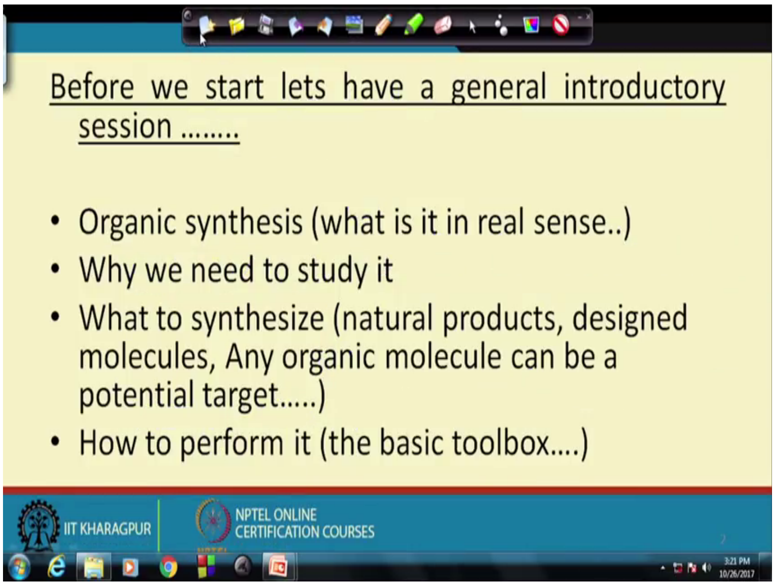

So, throughout this particular discussion we will try to give you a brief idea about how this things can be done.

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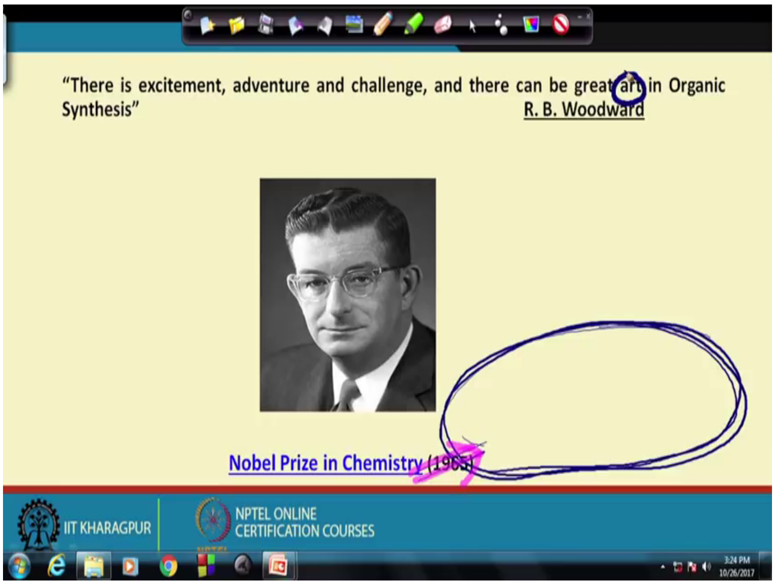

And initially before we start let us try to give a fitting tribute to all the great scientists or great chemist who make this field a (Refer Time: 08:27) exercise. At a very beginning, we will try to memorize this particular fellow, whose name is Robert B. Woodward. Now, Prof. Robert B. Woodward is one of the great scientists and great organic chemist who won the Nobel Prize in 1965 in chemistry. And he was one of the pioneer in this field of organic synthesis. So, Prof. Woodward once said there is excitement, adventure and challenge, and there can be great art in organic synthesis.

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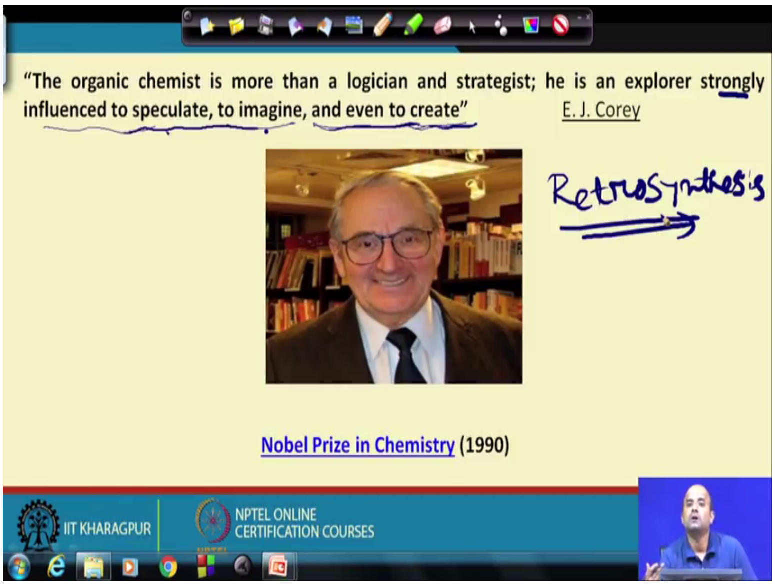

So, particularly we will try to emphasize this particular point which says the organic synthesis is basically nothing but so as I said Prof. Woodward once says there is a great art in this field of organic synthesis there particularly I will emphasize more on this particular terminology, which says art. An organic synthesis is basically trying to accumulate those different kind of artistic view point when a given when a organic molecule is given to you and that could be very (Refer Time: 09:38) exercise.

A Prof. E. J. Corey got his Nobel Prize in 1990 in organic chemistry. And Prof. Corey says that organic chemistry is more than a logician and strategist; he is an explorer strongly influenced to speculate, to imagine and even to create. So, basically the same word which have been echoed by Prof. Woodward this particular terms is create means it is nothing you have to be a great artist to create something and that is why organic synthesis basically believe in on this particular terminologies you have to speculate you have imagine and you have to then create.

And Prof. Corey was basically influential throughout this war throughout this course war we will talking about retrosynthesis, and Prof. Corey was the pioneer or who was the first who invented or to point this particular term retrosynthesis that is what Prof. Corey's work will be trying to figure it out in many times throughout our discussion.

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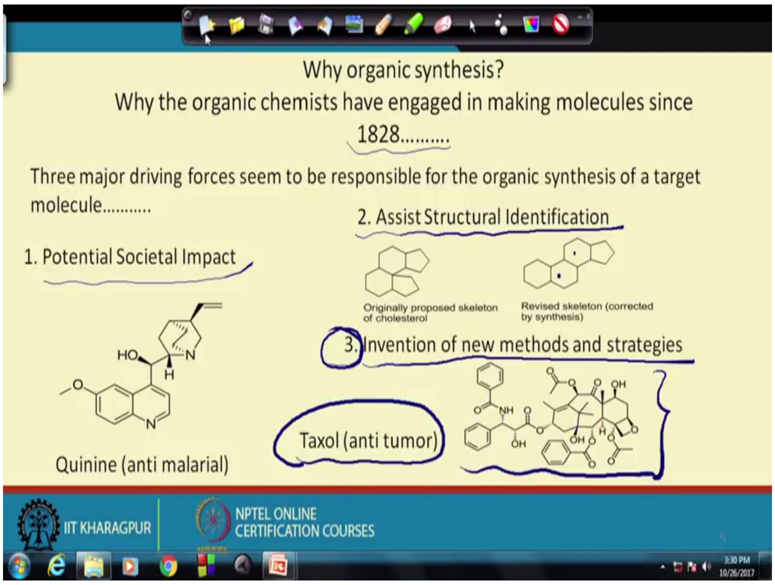

So, as I said initially why to study organic synthesis? So, the human being or synthetic organic chemist started to making this molecule since very earlier time since 1828. And there are three major driving forces seem to be responsible for the organic synthesis of a target given target molecule. The initial demand came from the society which is termed as potential societal impact. The society demands that you make some organic molecules.

Now, why society demands it, society says that you have to devise, you have to make some molecules which are essentially useful for human being. One of the greatest example from societal demand is quinine, the famous anti malarial compound which was used to treat malaria. And malaria is one of the lesser disease particularly in third world country like us. And eventually this kind of societal demands often forces us to make a huge number of target molecules, this quinine is one of the best example for this.

Number two point that why organic chemist will be trying to make this molecule, it is basically to do the exact structure of a natural product. Now, natural products are basically organic molecules which have been isolated from the mother nature. It could be a plant natural product which have been isolated from a plant source, it could be a marine natural product which has been isolated from a marine organism or marine sources, it could be a animal product which would been isolated from the animal body. Now, eventually when these products are isolated their structure needs to be clearly known and sometime synthetic chemist or organic synthesis helps to know the structure exactly.

Let us say for example, initially the cholesterol, which is very oil explode molecule; the initial structure was given a six member six member, five member five member. But in reality later on they are being found by organic synthesis the cholesterol structure was not like that the original structure is a linearly fused two cyclohexane ring with a cyclohexane and then a cyclopentane. So, this devices skeleton on cholesterol came into existence after the organic synthesis or the synthetic organic chemist coming to picture.

And finally, this number three point which is one of the most valuable point where we will be coming into the picture or the aspiring young organic synthetic chemist like you who wants to invent new methods and strategies, this is basically a purely academical interest as well as industrial interest that any target molecule of complexity can be made. The greatest example is taxol, taxol in an anti tumor agent; and it works wonder for ovarian cancer as well as breast cancer. Now, this compound taxol is a blockbuster drug; and it has been marketed by Bristol Myers Squibb in USA. Now, this molecule can efficiently be synthesized though the structure is pretty complex. So, this three points will basically give you a idea that why you would like to make organic synthesis as your core area of study or core area of discipline.

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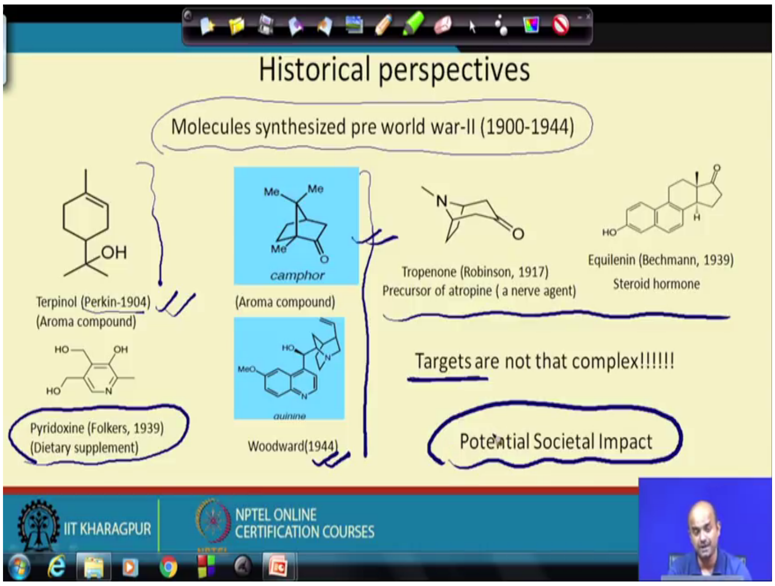

I try to give you a brief historical perspective from the very beginning of when human being or synthetic organic chemistry first started making molecules. The initially I will try to pick up few molecules which have been synthesized pre World War, you see the area 1900 to 1944, it is basically almost a century ago. The molecules at the time which were synthesized are not that complex, but eventually the molecules have useful biological synthesis. First molecule synthesized is terpinol, it is used as a aroma compound or giving a sweet perfume. It was first synthesized by Perkin the famous Perkin condensation if you remember in 1904 a century ago. The compound which was used as a dietary supplement or a vitamin B 3 is pyridoxine have been synthesized in 1939 by Folkers.

In the similar way compounds like camphor which all of us use in the different pujas and different rituals is camphor or kapur, this compound was synthesized long ago. This molecule quinine as I said in the earlier slide is a anti malarial compound and Prof. Woodward was the first one who synthesized in 1944. Now, if you see the entire structure of those molecules which have been enlisted in the slide, the targets target means the organic molecules which you want to synthesize are not that complex. Means that the target molecules have not that much complex architectural view point, but eventually all the molecules have great potential societal impact. If you see all the molecules are significantly biologically active and they contribute quite hugely in terms of society is concerned. So, initial view point that why you want to synthesize the molecule probably it will be quite clear, now coming to the historical perspective we have discussed few points and let us go back to a little bit further ahead.

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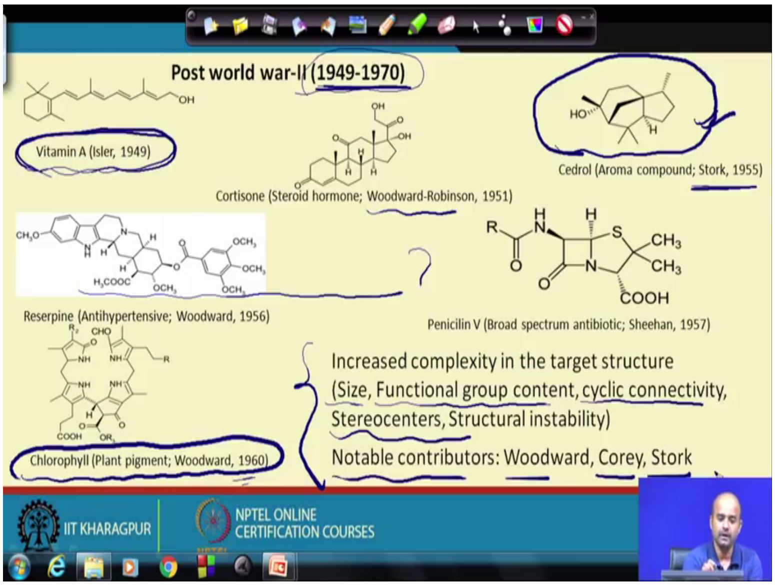

The molecules which have been synthesized after that decade we will try to focus in 1949 and 1947. 1949 and 1947 the molecule basically called post World Wars time an in during the time the first molecule vitamin A, which is often used to treatment or to treat people who are suffering from several eye related disease vitamin A Isler first synthesized in 1949. Molecules like cortisone which was used in the steroid hormone, it was synthesized in Woodward Robinson. Now, if you see the molecules which have been synthesized before the First World War or Second World War is during 1949, now this molecules which have been synthesized in 1949 and 1970, the structures have become complex means that with the advancement of time, your target has been more complexes.

Say for instances this molecule cedrol is using a aroma compound it was first made in 1955 by Prof. Gilbert Stork. And this molecule seed structure it is quite complex. A seven member ring having a five member ring fused insight with a linearly fused five member ring, and this molecule can be synthesized. Finally, one of the great achievement in our synthesis was synthesis sizing this particular molecule named chlorophyll which all of us know it is a green pigment responsible for the green color the plant leaves, and this was synthesized in 1960.

So, eventually the take home message is when complexity increased in the target structure still the organic synthesis synthetic chemist are able to make those molecules. These molecules which were enlisted in this slide, they are large in size, their functional groups are quite big enough, and they have some cyclic connectivity means rings have been quiet complex let us say for cedrol. And some molecules having stereocentres means the asymmetric synthesis parts comes into the picture. Aand in this area this 1949 to 1970, this 30 years plan or 20 years span you will find notable contributors such as Prof. Woodward Prof. Corey Prof. Stork who made significant contribution to make this field as a lovely and challenging.

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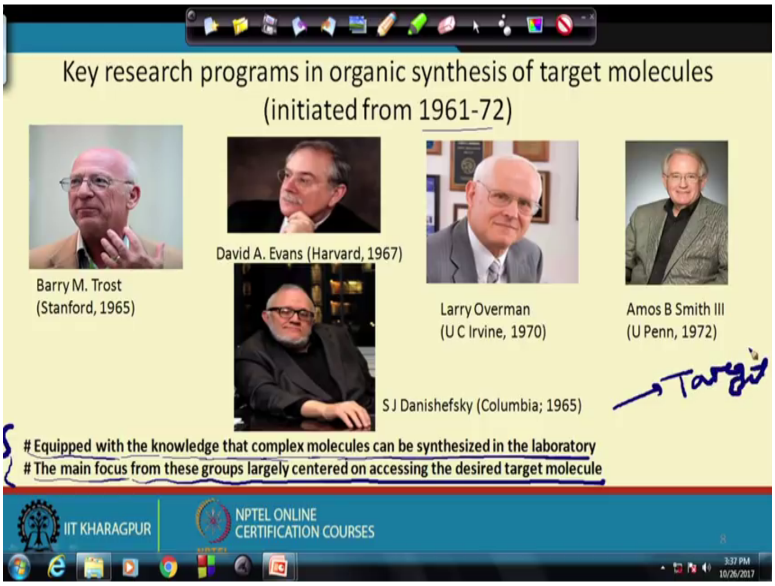

So, we will try to again a give a tribute to other synthetic organic chemist. We talked about Prof. Woodward, Prof. Corey, Prof. Stork, but definitely at the same time people like Barry M. Trost University of Stanford USA, Prof. David A Evans in Harvard, Prof. Samuel Danishefsky Columbia ,NewYork, Prof. Larry Overman University of California Irvine, Prof. Amos B Smith U Penn, USA 1972. So, this people made significant contribution, this people made significant contribution in the field of organic synthesis.

And eventually for their brilliant work, we can now think that any molecule with any complexity can be synthesized.

Now, see here we coined out two words, equipped with the knowledge that complex molecules can be synthesized in the laboratory. So, means that as I said if you are if you love to take the challenges, any complex molecular architecture can be synthesized provided that you are having enough resources. And main focus from this area we are talking about 1961 to 1972 the main focus is you have to access the target molecules by anyhow. So, eventually for synthesizing the target molecule no matter how close you are until and unless you achieve the target, you achieve the target that should be your final goal. The final target molecule should be achieved and that is the main take home message for any organic synthetic program.

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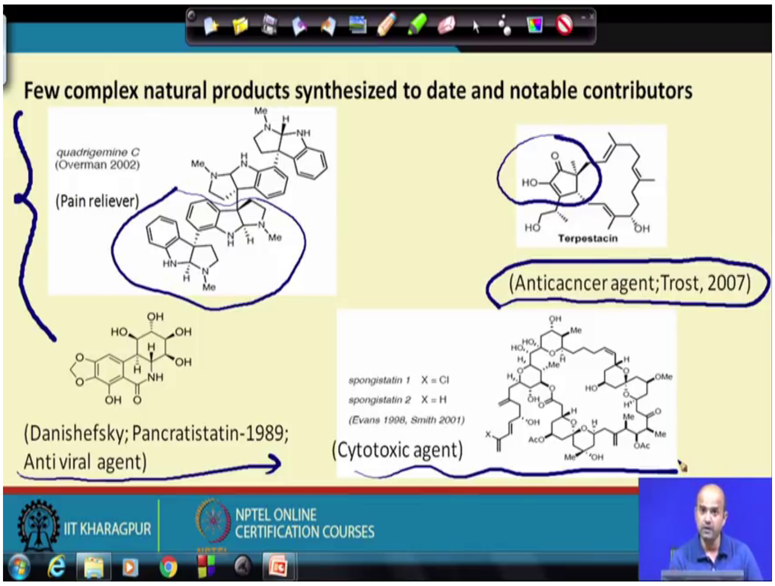

We will try to highlight couple of complex organic molecules, which have been synthesized till today. And if we see its structure, it is a basically I mean mind boggling. If you see some structure, let us say for instance is we are talking about the molecule, this molecule which was synthesized in 2002 quadrigernine c, it is used as a pain reliever, it relieves your pain. Now, see this molecules, this is basically a very complex molecule. It is a B sendal alcholide basically this part is having a B sendol moiety and be sendol moiety fused together make a tetrameric compound. It is the synthesized by Prof. Overman, the name we just saw in the last slide. The molecule like terpestacin is a anticancer agent and have been synthesized by Prof. Barry M Trost, 2007. Seed structure is a core cyclopentanone containing compound and then is functionalized at two position and three position with a again a large ring. Having couple of hydroxy group you have alpha beta unsaturated ketones. Molecules like pancratistatin in 1989 have been synthesized spongy state in habit synthesized. So, those molecules are quite big enough and you can have sufficient challenges to synthesize those molecules if you are equipped to with huge resources.

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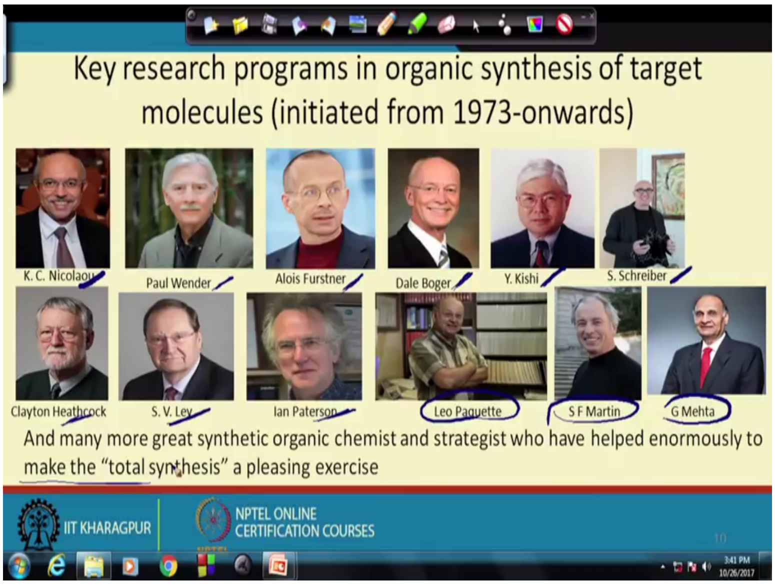

So, I will just try to squeeze it off I will try to give a again tribute to some other synthetic organic chemist who have notable contribution, but due to time and space constraint we cannot put everybody name Prof. KC Nicolaou one of the great organic chemist in our generation who did excellent work and who made significant contribution. Prof. Paul Wender University of Stanford, Alois Furstner in Germany, Dale Boger university of sorry it is (Refer Time: 23:43) USA.

Prof. Kishi in Harvard, Stuart Schreiber in Harvard, Clayton Heathcock University of California Berkeley, Steven V Ley University of Cambridge, UK, Ian Paterson UK, Leo Paquette Ohio State University, Stephen Martin Texas Austin and our Indian one of the notable contribution is Prof. Govardhan Mehta from University of Hyderabad. So, due to these fellows significant contribution, we now can say that total synthesis is a very pleasing exercise means that you can in theoretical in principle you can make any molecules with any size and that should be a regular exercise. So, based on the knowledge, which you are equipped to with and throughout this course work we will try to provide you that knowledge, which will be helpful to you to design certain pathways.

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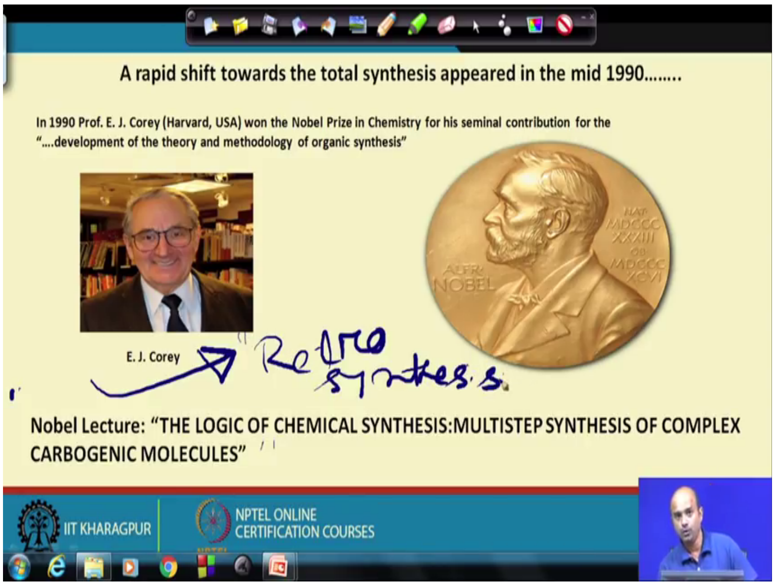

So once we reach to 1990, we started from 1921 or 1909 then we almost crossed 80 years and then we see that professor E. J. Corey who got the Nobel Prize in 1990, Prof. E. J. Corey who got the Nobel Prize in 1990. And Prof. Corey made a fantastic contribution in the field of organic synthesis Prof. Corey's Nobel lecture basically highlighted in the field of the logic of chemical synthesis multistep synthesis of complex carbogenic molecules. Carbbogenic means the organic molecules which have only carbons or hydrogens. Now, Prof. Corey was the first one to coin this term as I said retrosynthesis which will be our main discussion point throughout this lecture. Now, what are retrosynthesis and what is retrosynthesis and how we need to study those guidelines we will try to provide in our couple of next slides.

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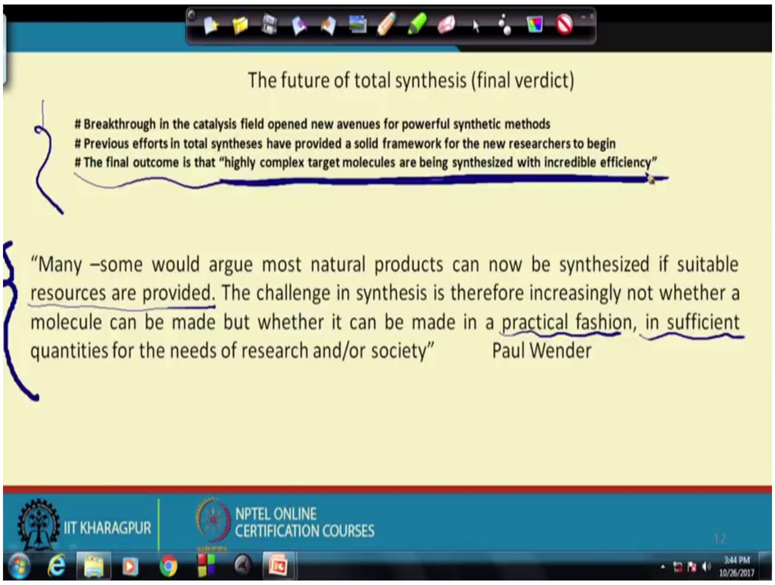

So, as I said that how you can start a organic synthesis program or what are the basic parameters we will be looking to it. And what is the future of the total synthesis this is also very important. So, the future I will try to take a quote from Prof. Paul Wender who says that many some would still argue most natural products or target molecule can now be synthesized it suitable resources are provided. I am trying to highlight these things if you are giving the suitable resources, you can make any target molecule, but the challenge in synthesis is therefore increasingly not whether a molecule can be made. But whether it can be made in a practical fashion because practical fashion what is more important it should be cost effective, it should be economically viable to a country like us and the point is in sufficient quantities. So, whether if you make the compound in sufficient quantities, so a society can be getting essentially benefitted from the entire things.

So, as I said the breakthrough in this different fields like catalysis, and other synthetic methods, we will have a very positive outcome. And the final outcome is that now this is our take home message highly compressed target molecule are can be made or are now being synthesized in the lab with incredible efficiency. You would not believe you give us a any complex target structure any complex natural products, there are reports, there are ways people are synthesizing the molecules as I said you have to give a suitable resources.

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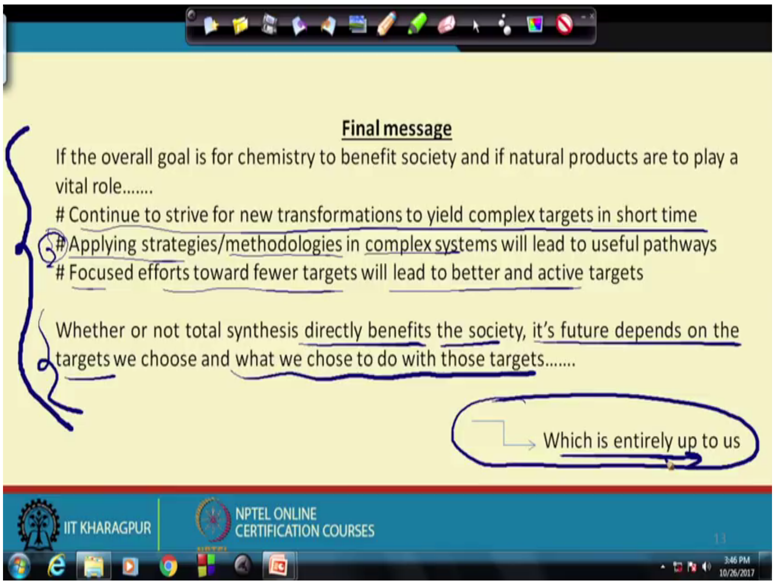

So, we coming to this final message. So, if the overall goal is for chemistry to benefit society definitely be a chemist, we cannot avoid the societal part that our research our work should benefit the society should benefit the human being human kind. So, we will try to we will being a synthetic organic chemist, we should play a vital role by making new molecules. How, we have to think about how new transformation or new organic reactions can give you complex target in a short time, applying different strategies, different methodologies in complex systems. Now, this particular point will be our guiding principle for retrosynthesis design and this effort should be focused, it should be a focused streamlined efforts to make target molecules.

And now the final message the target oriented synthesis definitely have a direct impact on the society definitely and its future always depends on the targets we choose. Now, what target to choose basically the targets which are biologically significant which have a direct impact on the society, we should choose those target. And then the point is what we choose to do with this targets, once you choose a target what you would want to do it? That I said which is entirely up to us because being a synthetic organic chemist you need to take those as a challenge. And if you are provided with resources you are taking up the challenge then let us make this molecule in a sufficient quantity in a cost effective manner economical viable manner, so the society can get a direct benefit out of that.

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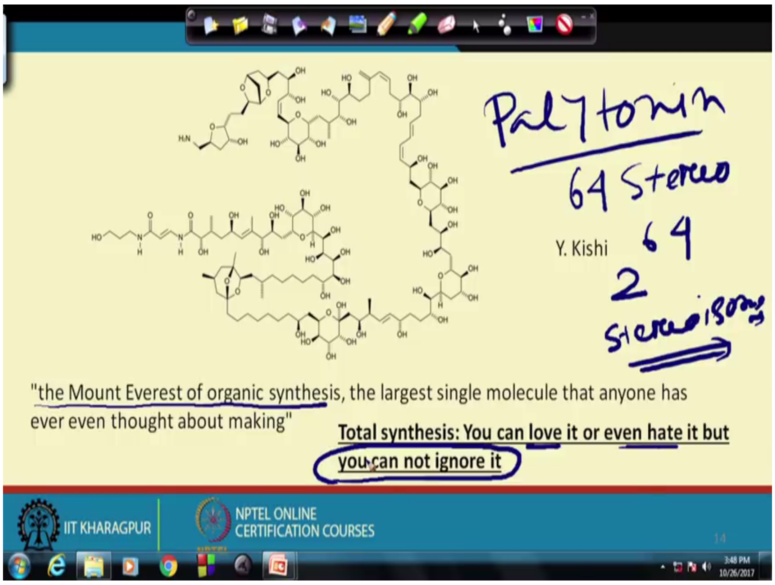

This particular molecule its name is palytoxin, this molecule name is palytoxin . If you say the molecule you would not believe how complex the molecule could be this molecule is a marine toxin. It have been isolated from a marine organism. This molecule does a base t four stereo centre. If I count we will start from one side to another side let us start from here 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23. So, basically you can count the entire things and it will give you 64 stereo centre and out of this 64 stereo centre means you are basically having 2 to the power 64 stereoisomers. Now, imagine how difficult is this that this molecule is a single enantiomers have been synthesized in the lab. And this challenge was one of the great challenge which is called Mount Everest organic synthesis.

This molecule took almost twenty years in Prof. Kishis lab number of graduate students number of post doctorals are involved to make this molecule to happen. So, starting from a design, starting from the execution starting from the final product the whole sequences took 20 years. So, the message is you basically can love it or even hate it, but product synthesis organic synthesis, you can ignore it. See it you can love it does not matter; if you are not liking it you can hate it, but you cannot ignore it because it is a fundamentally very important science and the logical reasoning is there, we have a sound chemical logic which basically drives you.