Classics in Total Synthesis-I
Prof. Krishna P Kaliappan
Department of Chemistry
Indian Institute of Technology, Bombay

Lecture - 01
Introduction Syllabus

So, good morning everyone and welcome to this NPTEL course on Classics in Total Synthesis Part I. First of all before I start my lecture I would like to thank NPTEL for giving me this opportunity to teach this course. So, I have been teaching at IIT Bombay, for the last 20 years or so. In that I taught this particular course basically on organic synthesis and focusing more on total synthesis for 10 semesters or so.

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The syllabus for this course starts with brief introduction to history of organic synthesis and then what we do is we will go with synthesis of natural products ring size wise. So, we will discuss total synthesis of few natural products having 3-membered ring as one of the rings. Then we will move to natural products having 4- membered ring then followed by 5- membered, 6-membered, then we will go to medium sized ring. And also we will try to discuss few natural products which have macrocycles. So, this is a overall syllabus of this particular course.

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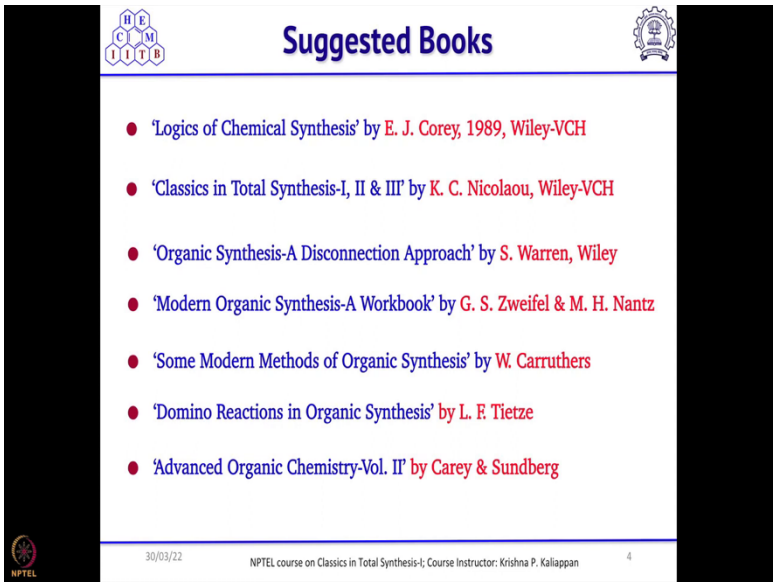

And if you want to read more books regarding this course, I will suggest at least the first four books. The first one written by the Nobel Laureate Professor Elias Corey and this came long back in 1989. Then there are three interesting books on total synthesis written by K. C. Nicolaou and co workers. So, they are considered as really you know excellent book for total synthesis. They called as Classics in Total Synthesis - Volume I, Volume II and Volume III.

And if you want to know more about disconnection how you can disconnect bonds, how you can functionalize then you can go through a book called Organic Synthesis - A Disconnection Approach by Stuart Warren then one can also go through Modern Organic Synthesis - A Workbook by Zweifel and Nantz. And particularly oxidation and reduction reaction if you want to know more you can go through Some Modern Methods of Organic Synthesis by Carruthers.

When we discuss some total synthesis you will find some domino reactions and for better understanding of domino reactions you can go through Domino Reactions in Organic Synthesis book by Lutz Tietze. And for various types of reactions in organic chemistry one should go through the Advanced Organic Chemistry Volume II by Carey and Sundberg, ok. Organic synthesis is you know very very important area in organic chemistry and not only in organic chemistry, organic synthesis play a crucial role and acts as a bridge between chemistry and biology.

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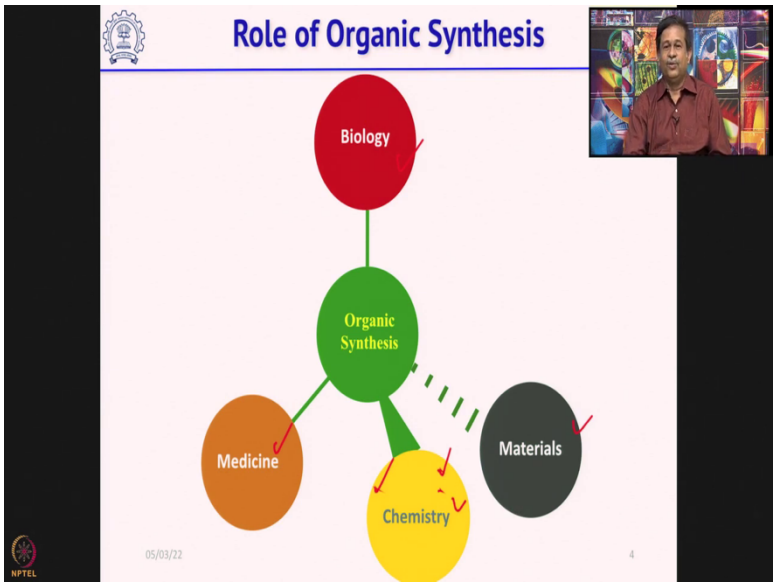

You can see it acts as a bridge between chemistry and biology, chemistry and materials and chemistry and medicine. So, without organic synthesis not much progress can be made in these three area. So, it is better if you understand organic synthesis very well then you can also enter into other four disciplines.

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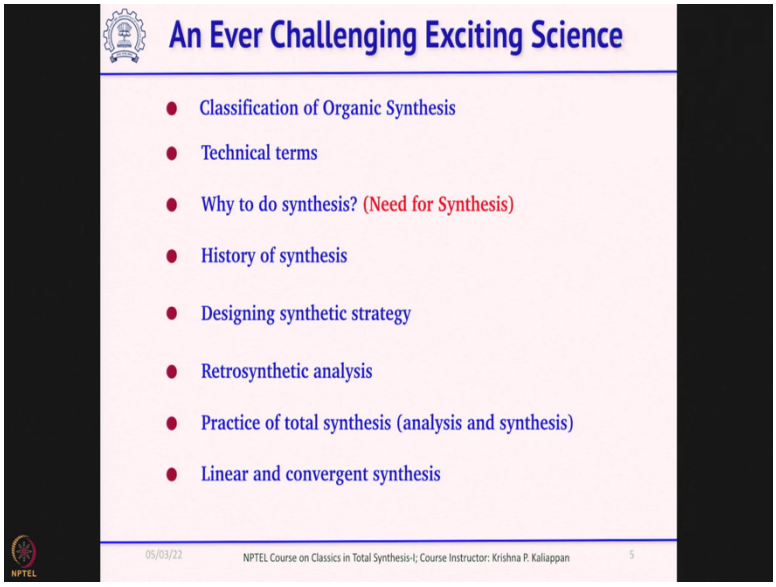

Organic synthesis has been you know always a great challenge because so, you have to have real skill to carry out you know organic synthesis. So, what we will do? First we will start with the classification of organic synthesis and there are many technical terms

which are used in organic synthesis as well as total synthesis. So, we will try to understand what are these technical terms.

Then like any area, the first question when you want to learn that area you ask is why should I do it, ok. So, if you want to do total synthesis you should ask a question, why do you want to do this, ok. So, need for synthesis need for total synthesis then I also will give you a brief history of synthesis may be in a couple of slides I will try to talk about brief history of synthesis in the last two centuries.

Then I will move to how one can design a synthetic strategy. So, when you have a molecule, how you can design a proper synthetic strategy for that molecule and I also will give or touch upon retrosynthetic analysis. I am sure all of you would have studied retrosynthetic analysis.

So, I will not go much through retrosynthetic analysis, but I will touch upon the practice of total synthesis. The practice of total synthesis is very important which involves two important components called analysis and synthesis, ok. So, these two are important before you start working on total synthesis. I will touch upon in the next hour. I also will introduce the concept of linear and convergent synthesis and then I will give lots of examples of total synthesis of complex natural products.

This particular course is mainly for second year master students and first year PhD students. So, why I am saying is you know by the time you come to this course you should have known or you should be aware of many organic reactions and should have got some idea about retrosynthetic analysis.

So, if you know this then it will be easy for you to understand this course and as some of you may be knowing total synthesis is the ultimate in synthesis. That means, if you want to make a molecule or in olden days when natural products were isolated, only way to confirm the structure of that natural product is to synthesize. You can you would have studied the elucidations of a natural products and the last line is finally, the structure of this natural product was confirmed by total synthesis.

Of late there are many techniques particularly X ray and NMR helps in assigning the correct structure of natural products or isolated natural products, but what happens? Even then there are quite a few natural products which were given wrong structure and finally,

the structures were corrected by total synthesis. So, total synthesis continue to play a very very important role in organic chemistry, pharmaceutical chemistry, medicinal chemistry, agrochemicals.

So, the experience in total synthesis helps a lot in all these areas. Now, let us start with classification of organic synthesis.

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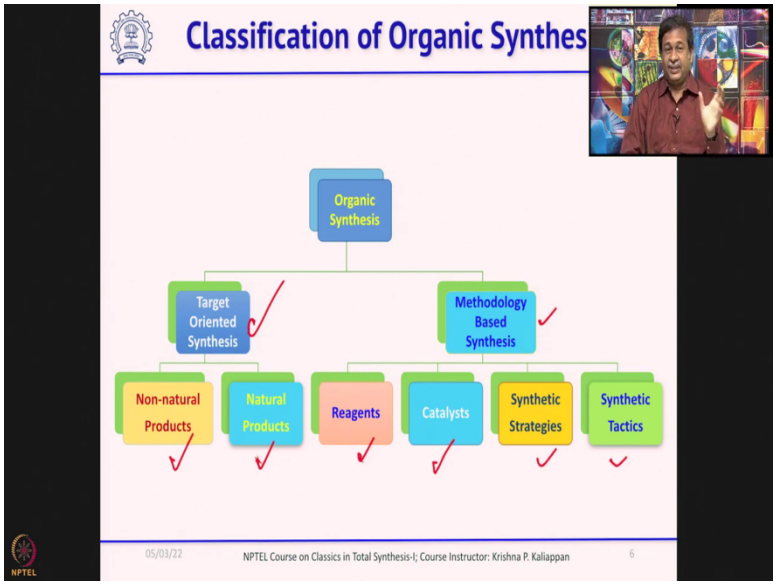

So, when you talk about organic synthesis, the organic synthesis can be broadly classified into two types. One is target oriented synthesis; that means, you have a target ok and your job is how to synthesize that target, ok. You have a target molecule, it could be natural product or non natural product does not matter, but it is target oriented. You have to make that particular target, ok. So, that is what I said. It could be non natural products or natural products.

The second type is methodology based synthesis, which means that you develop a methodology. That methodology could be you develop a new reagent ok, you can develop a new reagent and the best way to test the use of your reagent is to apply in total synthesis of a natural product. Then one can also develop new catalysts. So, when you develop new catalysts then you see how versatile your catalyst is. The best way is again apply in the total synthesis of natural products.

Then there are two more. One is synthetic strategies, another one is synthetic tactics. Here you develop your new strategy, ok. You have a natural product or natural product like molecule and then you develop a new strategy and see whether this strategy can be extended to synthesis of natural product or complex natural product.

Again you can develop new tactics ok to address certain problems which normally people face in synthesis and if you are successful then such synthetic tactics can also be applied in the synthesis of natural products, ok. So, broadly when you talk about organic synthesis, there are two types. One is target oriented synthesis, other one is methodology based synthesis. Both are interrelated and both depend on each other.

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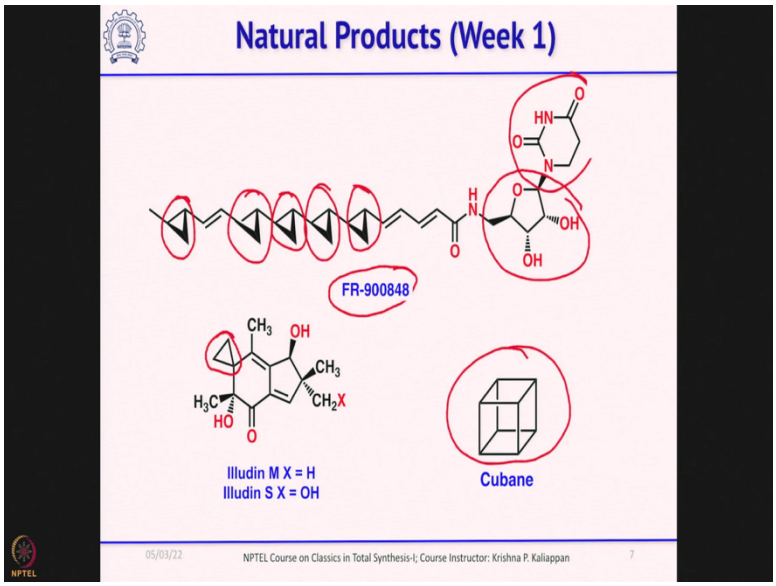

So, what I will do? This week, as I said we are going to talk about you know introduction. So, the first two lectures will be mainly on introduction and the third lecture onwards we will start talking about total synthesis of natural products. The first lecture on total synthesis will start with 3-membered ring.

So, when we talk about 3-membered ring there are two natural products which should come to your mind. One is illudin. So, there is a class of natural product having a cyclopropane you can see here. So, this is a natural product. We talk about total synthesis of two such natural product, illudin M and illudin C ok. Then we also talk about total synthesis of another natural product called FR-90848 having five cyclopropanes; 1, 2, 3,

4, 5, Five cyclopropanes and it is connected to a D-ribose sugar unit with a base ok. So, this also a very interesting natural product.

So, what we will do? In the whole course not only we discussed the total synthesis, the retrosynthesis and total synthesis of natural product, but also we discuss in details some of the key reactions which are used to make these natural products. For example, here key component in these two natural products is cyclopropane, ok. So, we will discuss how the cyclopropanes were made for each molecule, ok. And that particular reaction we will discuss in details.

Then we will move to 4-membered ring. So, when we talk about 4-membered ring first we will start with a non natural product that is cubane. We all know cubane is highly strained compound and the first synthesis of cubane was reported by Philip Eaton. So, that is a very interesting synthesis.

So, we will talk about the synthetic strategy developed by Philip Eaton to synthesize cubane. Later lot of derivatives of cubanes were synthesized, but nevertheless the first synthesis of cubane is very very important and milestone in total synthesis. So, we will discuss that. In the second week we will continue our discussion on the synthesis of 4-membered natural products and here we will start with interesting total synthesis of endiandric acids reported by Nicolaou's group.

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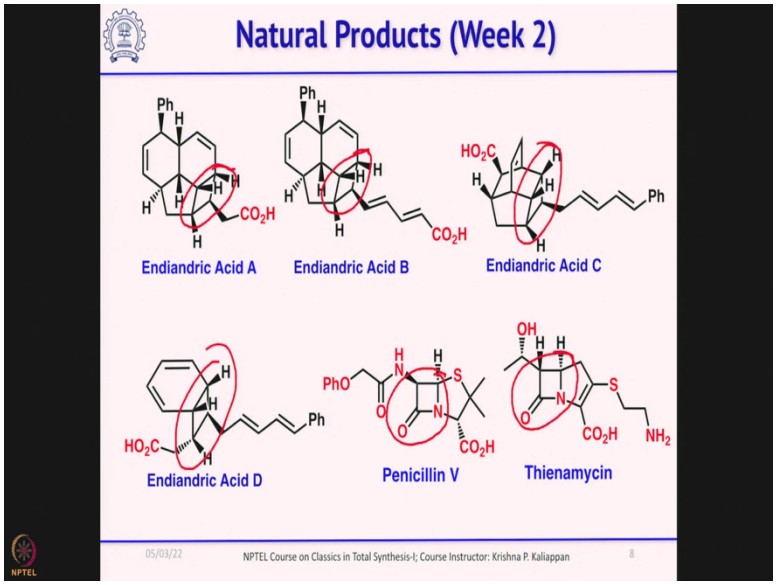

So, if you look at this molecule you can see it is a tetracyclic compound and the tetracyclic compound has a cyclobutane ok. So, there are four at least four natural products belonging to this. They are called endiandric acid A, B, C and D and all of them have you can see a cyclobutane ring and we will discuss the total synthesis of these four natural products as well as intermediate natural products which are converted into endiandric acid.

Then when we talk about 4-membered rings the next natural class of natural products which would come to your mind is penicillins, ok. So, we will discuss synthesis of penicillin as well as thienamycin. This is the first level of antibiotics nowadays. Is not it? So, in 1950s this was considered as you know the best discovery in antibiotic history. Now of late there are many more antibiotics have come, but still the first level of antibiotics given is penicillins, ok.

So, we will discuss the synthesis of penicillins as well as thienamycin. And here again you can see a 4-membered ring and the 4-membered ring is not a carbocycle, it is a heterocycle, it is a β lactam ok; β lactam present in both.

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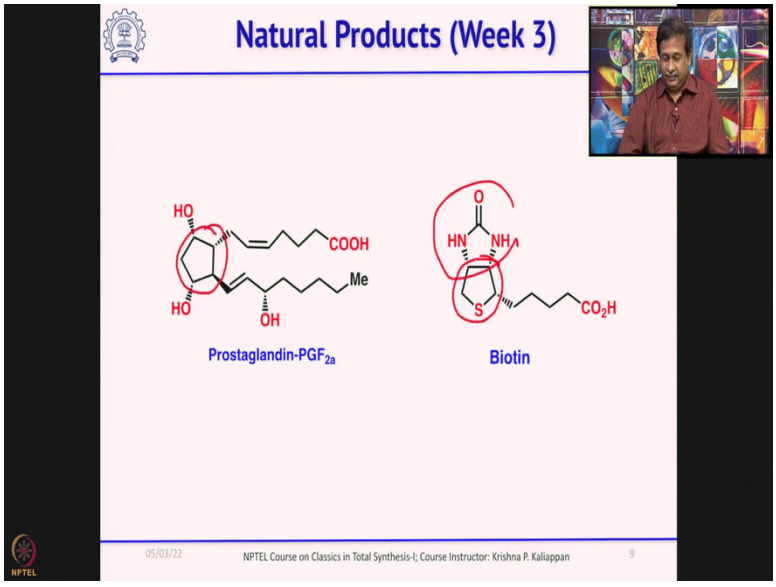

Then we will move to 5-membered ring. We will spend about 3 weeks on synthesis of natural products having 5-membered rings. When we talk about 5-membered ring, one class of natural products which would come to our mind is prostaglandins. So, prostaglandins you can see it is a 5-membered carbocycle having hydroxyl group, it can

be trihydroxy or it can be dihydroxy or it can be hydroxy ketone with two side chains ok at adjacent carbon.

And there are few prostaglandins. We will discuss at least synthesis of two prostaglandins by two different groups in our discussion in the week of 3. And then we also moved to a vitamin called biotin which has two 5-membered rings; one is you can see tetrahydrothiophene, the other one is cyclic urea ok. So, we will discuss these two class of natural products in week 3.

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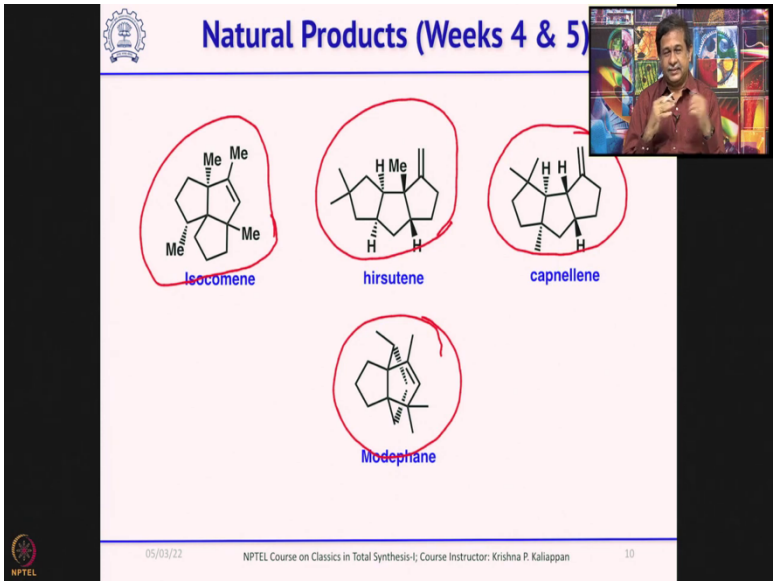

Weeks 4 and 5, we will move to another interesting class of sesquiterpenes called triquinanes, ok. So, that triquinanes can be linear. So, for example, if you take hirsutene three 5-membered rings quinane means quin 5. There are three 5-membered rings. So, it is called triquinane. Here all the three member rings are connected in a linear fashion. Same thing is true with capnellene.

But if you look at isocomene, it is angularly fused; three 5-membered rings are angularly fused. And we also have another type which is which we can call it as propalene and these three 5-membered rings are connected in a propalene like. So, we will discuss several synthesis of these class of natural products and some of them you know really outstanding total synthesis which involves domino reaction.

If you look at the history of organic synthesis 70s, 80s and 90s even many papers came on the total synthesis of this sesquiterpenes called triquinanes. So, we will discuss more about this in week 4 and week 5.

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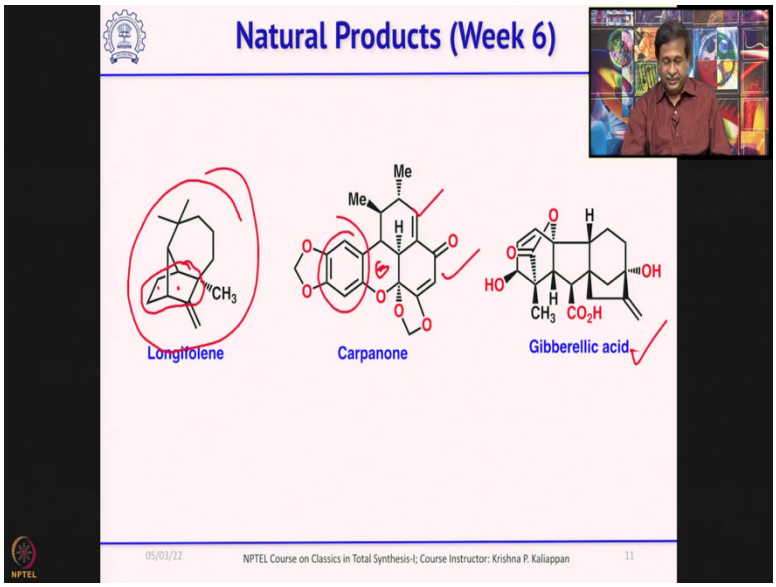

Then we will move to 6-membered ring and 6-membered ring one of the classical total synthesis reported and it is there in many textbook is longifolene. So, this was reported by E. J. Corey though you cannot see 6-membered ring properly, but this is a 6-membered ring you can see. So, this is a 6-membered ring and it has two 5-membered ring and one 7-membered ring. So, very interesting synthesis, one of the classical synthesis reported by E. J. Corey.

So, we will start with that for 6-membered ring then we will move to another natural product called carpanone. So, here again you can see two 6-membered ring, two 6-membered ring fused together and with another 6-membered ring which is a heterocycle ok, another 6-membered ring which is a heterocycle with an aromatic ring ok.

So, this also we will discuss followed by another famous total synthesis of gibberellic acid. This is one of the natural products you know which created lot of trouble for synthetic chemists who wanted to synthesize this molecule. And this was finally, you know the synthesis of this molecule was finally, successfully accomplished by E. J. Corey and this is when he got Nobel Prize synthesis of gibberellic acid also was mentioned in one of his accomplishments.

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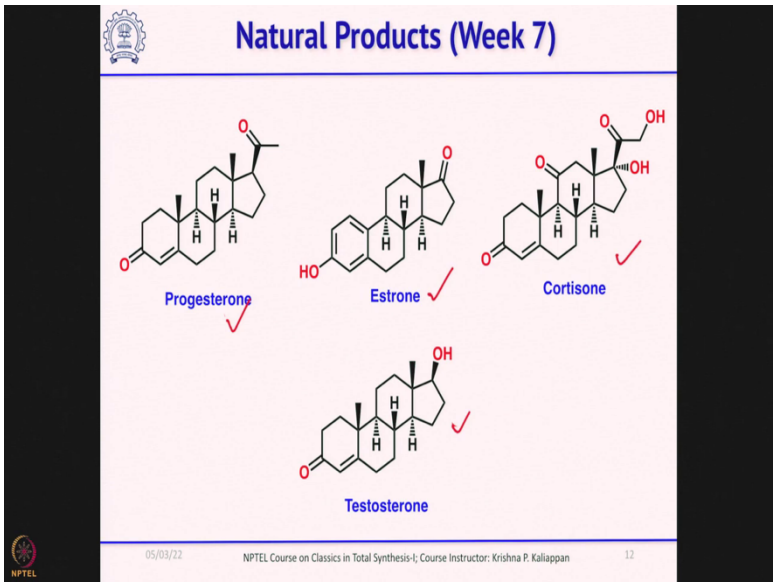

So, then we will move to synthesis of another important component of all of us that is steroids. So, we will start with total synthesis of progesterone, very famous biomimetic total synthesis of progesterone by William Johnson. Then we talk about Torgov's total synthesis of estrone the methodology even now many pharmaceutical companies use for making estrone.

And we also discuss about other methods other total synthesis of estrone then we continue our discussion on total synthesis of two more steroids; one is cortisone. We all know cortisone how important cortisone is. Particularly during the covid period we have seen how the cortisone, methyl cortisone were used for the treatment of covid and then we discuss about male sex hormone testosterone and its total synthesis.

So, these are the four steroid natural products we will discuss in the week 7. Then in week 8, we will move to from steroids to alkaloids.

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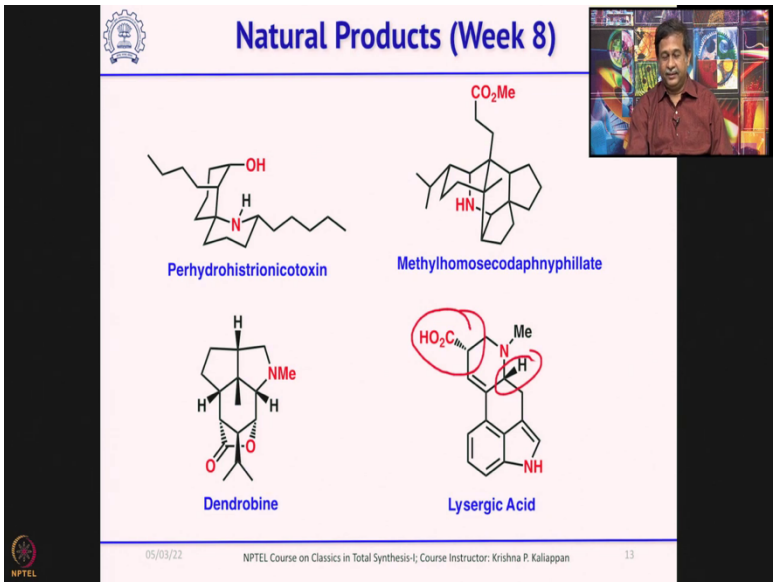

So, we will talk about a natural product called perhydrohistrionicotoxin is again another very very important total synthesis, it is a classical total synthesis reported by E. J. Corey. So, we will discuss not only the total synthesis, but two important reactions which Corey thought about making this molecule. Then we will talk about another alkaloid called methylhomosecodaphnyphillate. So, this total synthesis was reported by Clayton Heathcock.

This involves a multi component reaction followed by cyclization and many C-C bonds were formed in one step. Then we also talk about another natural product alkaline called dendrobine and here also a tandem reaction has been successfully used by Samir Zard in the synthesis of dendrobine. So, we will talk about Samir Zard's total synthesis of dendrobine and another natural product which is almost a bad substance LSD, so lysergic acid.

So, we will talk about the total synthesis of lysergic acid which has two chiral centers here as well as in the carboxylic acid.

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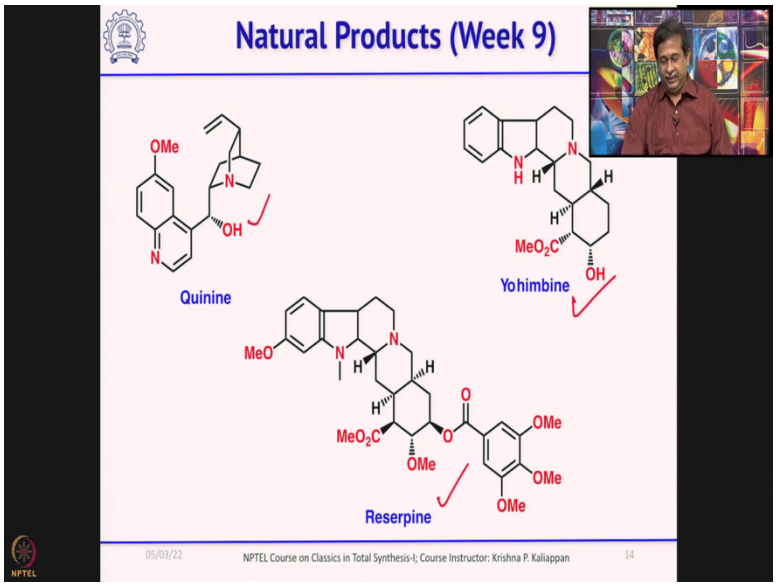

We will continue our discussion in Week 9 on alkaloids. So, we will start with quinine. Quinine was very famous in sixteenth century for the treatment of malaria and it continued to be very important. Even during the covid period many derivatives of quinine HCQ was initially given.

So, the idea of HCQ was started with quinine. So, then we will talk about total synthesis of two very complex alkaloids called yohimbine and these reserpine. So, now, there are many total synthesis, but we will stick to two important total synthesis of reserpine and yohimbine in Week 9.

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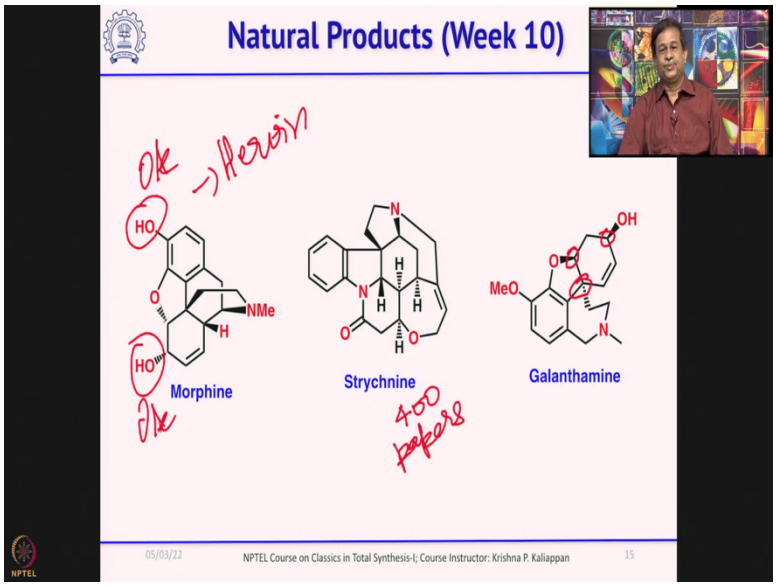

From there we will continue our discussion on some more alkaloids and the first alkaloid which we will talk about is morphine. So, morphine as you all know is a very good pain killer and if you acetylate these two hydroxyl group and it is called that you do not want to know, but it is called heroin.

So, then we will move to one of the most celebrated alkaloid called strychnine. The strychnine, there were 400 papers on the isolation and structural elucidations reported in 40s to 70s, ok. So, the first total synthesis of strychnine reported by Woodward and followed by two more really outstanding total synthesis of strychnine will be discussed in the Week 10.

Then we will move to another natural product called galanthamine. So, it has a quaternary chiral center here and followed by two more chiral centers. So, we will see how these chiral centers were installed and successfully synthesized galanthamine in Week 10.

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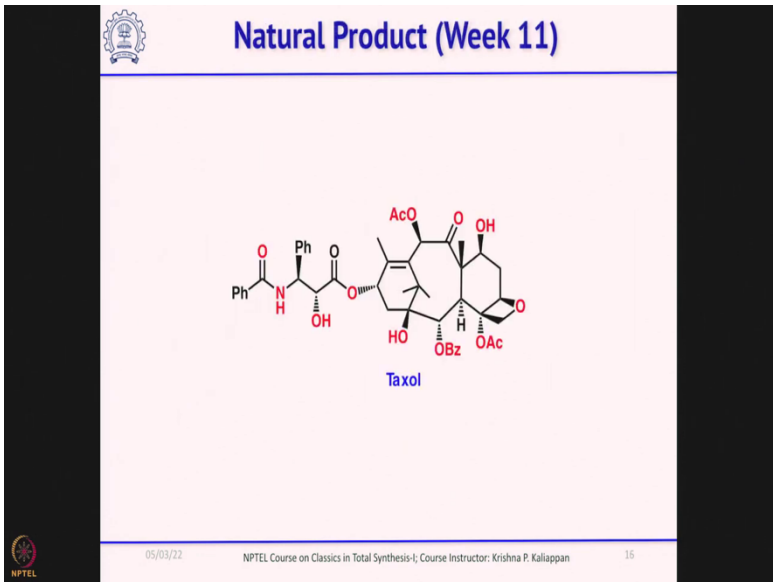

And Week 11, we will talk about a natural product which is also a drug called taxol and the first total synthesis of taxol was reported in 1994 by Robert Holton and K. C. Nicolaou. So, what we will do in Week 11? We talk about four total synthesis of taxol reported by Robert Holton, K. C. Nicolaou, Samuel Danishefsky and Paul Wender. So, we talk about four total synthesis of the same natural product by different groups.

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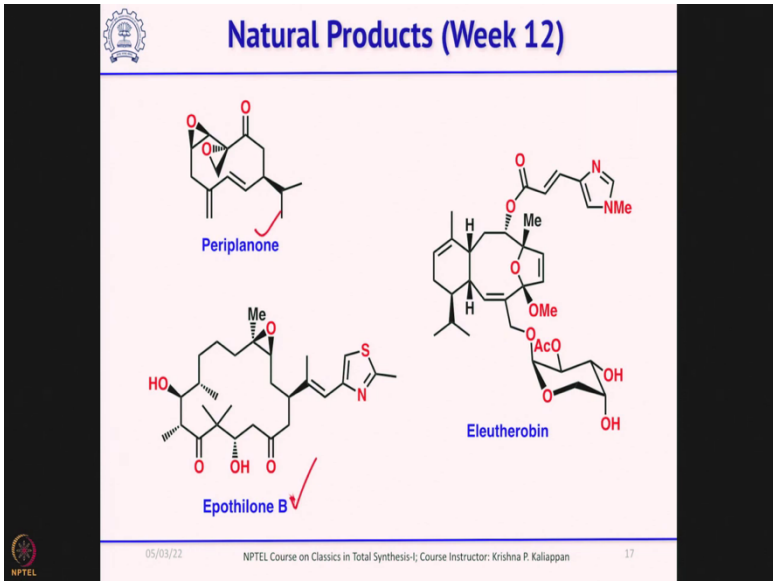

And the last week, so, we will talk about very interesting natural product, it is an anticancer agent eleutherobin. You can see it is a tricyclic compound with two side

chain. One is a sugar unit then we also talk about a simple natural product simple looking wise, but it is not that easy to make a periplanone and another anticancer compound it is a macrolide called epothilone.

There are many epothilone A, epothilone B and so on. And we try to discuss a couple of total synthesis of epothilones in Week 12. So, with this I will summarize. So, what we have talked about in this introduction lecture that this particular course is meant mainly for those who are in second year of MSc. as well as first year of their PhD.

And people who are in first year of MSc. also if they want they should have good knowledge about retrosynthesis and many organic reaction. Otherwise second year master students and first year PhD students can take this course. So, we will have periodical evaluation at the end of every week or alternate week.

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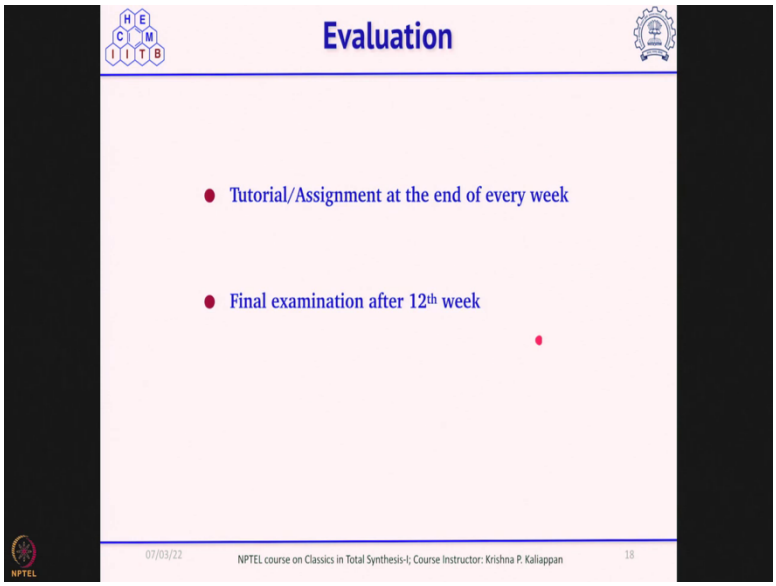

We will try to give some assignment as well as tutorial to solve and finally, at the end of 12th week in a week or two we will conduct the final examination, ok. So, then we will follow the standard NPTEL model for you know giving certificate based on your performance, ok. So, with this I complete the you know first class and I look forward to the second lecture where again I will continue our introduction to total synthesis and the third lecture I will start talking about total synthesis of 3-membered ring, ok.

Thank you.