Classics in Total Synthesis-I
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Lecture - 44
Steroids

So, good morning, welcome back to the NPTEL course on Classics in Total Synthesis Part 1. So, in the last lecture we talked about total synthesis of progesterone Steroid. So, we will continue our discussion today also on total synthesis of steroid particularly progesterone one more total synthesis as well as synthesis of cortisone and so on ok.

In the last lecture when I talked about total sense of progesterone by W. S. Johnson, there we talked about a domino cation triggered cyclization and that was like biomimetic total synthesis of progesterone that was a that was a classic one and it was of academic interest. If the same strategy has to be applied for industrial production of progesterone then it will be very very expensive.

So, for the industrial production of all these steroids you need much much better method and inexpensive method to synthesize ok. So, today we will talk about a method where progesterone, cortisone, testosterone all were synthesized on industrial scale and because of that it was inexpensive ok so, how?

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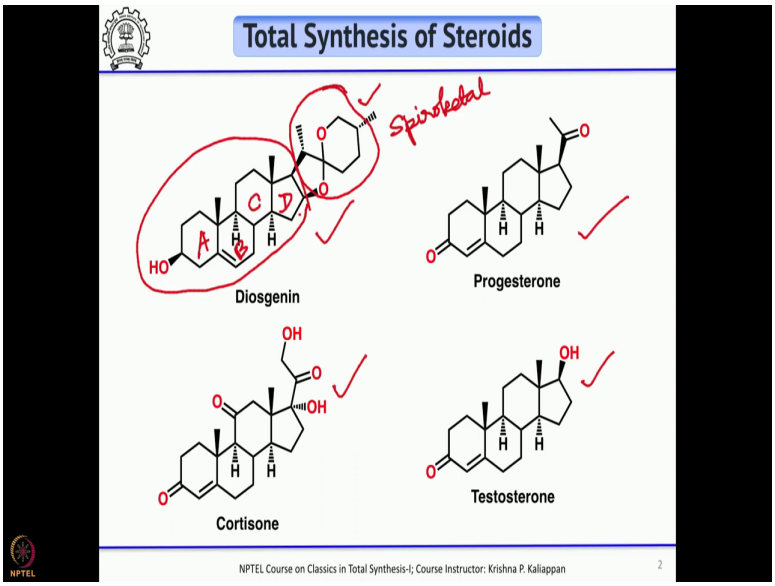

In today's lecture I talk about synthesis of three steroids starting from a compound called diosgenin ok this is called diosgenin, I will come back to that what is diosgenin and where from it was isolated and how it is used in its conversion to progesterone, then cortisone, then to testosterone.

As I mentioned during my introduction when you are starting with a natural product like compound or material obtained from a natural product, which has almost all the features of the target molecule then conversion of this natural product or natural product like molecule to the target molecule then the whole process is called semisynthesis, is not it.

So, here the synthesis which I am going to talk about starts with diosgenin ok. You can see that the diosgenin has the core structure of the three steroids which we are going to discuss today ok. Diosgenin as the core structure A B C D rings ok, all the 4 rings present in progesterone, cortisone and testosterone are there.

What is not required is the bicyclic system, the spiroketal ok the spiroketal is not required ok, how to get rid of the spiroketal and convert into the required side chain in progesterone, cortisone and testosterone ok. So, that is what we are going to discuss, but another interesting aspect about the synthesis which we are going to talk about is about industrial method ok, how one can prepare in large quantity, ok?

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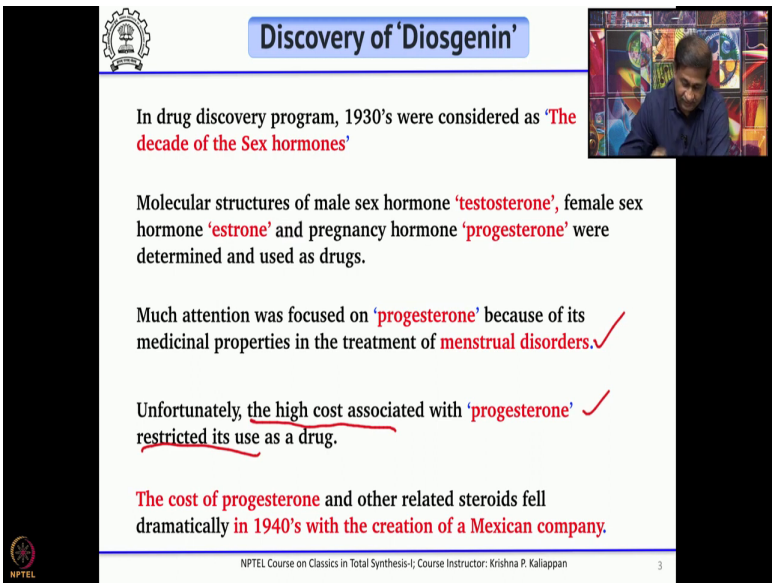

And we start with the discovery of diosgenin if you look at the history of steroids ok 1930's were the beginning of discovery of many major steroids in fact, 1929 was the discovery year of female sex hormone called 'estrone' ok. So, from 1930s to 1980s, steroids played a very very important role in pharmaceutical companies ok.

So, many drug discovery program of steroids were focused during these 6 decades and that is why we call this as you know the 1930's was called as 'decade of the Sex hormones', but subsequently the next 50 years lot of attention was given to synthesis of you know many many steroids.

Many structures of other steroids were discovered in the next few years particularly the male sex hormone 'testosterone', female sex hormone as I said was discovered in 1929 and little later the pregnancy hormone again related to females was 'progesterone' was discovered or elucidated and later these were used as drugs ok, but the isolation of this three steroids yielded very very you know minute quantity of the natural products.

So; obviously, if it has to be used as drugs then it has to be synthesized prepared in large quantity ok. So, how this can be done? Already we talked about the total synthesis progesterone by W. S. Johnson that came in 1950's ok, but among these three steroids particularly the steroid called 'progesterone' got much attention because these had very interesting medicinal properties in the treatment of menstrual disorders ok. So, this was a serious problem those days even now.

So, the progesterone used to be given as a track of choice those days. So, more synthetic efforts were on the synthesis of progesterone ok, but unfortunately as I said the high cost the high cost in the preparation or synthesis of this molecule restricted its use as a drug ok. However, in 1940's that the cost of progesterone fell dramatically in 1940's the cost of progesterone fell dramatically. And that is because of the formation of a Mexican company and how that Mexican company was formed and again how it was started from the academic laboratory, let us discuss in the next few slides.

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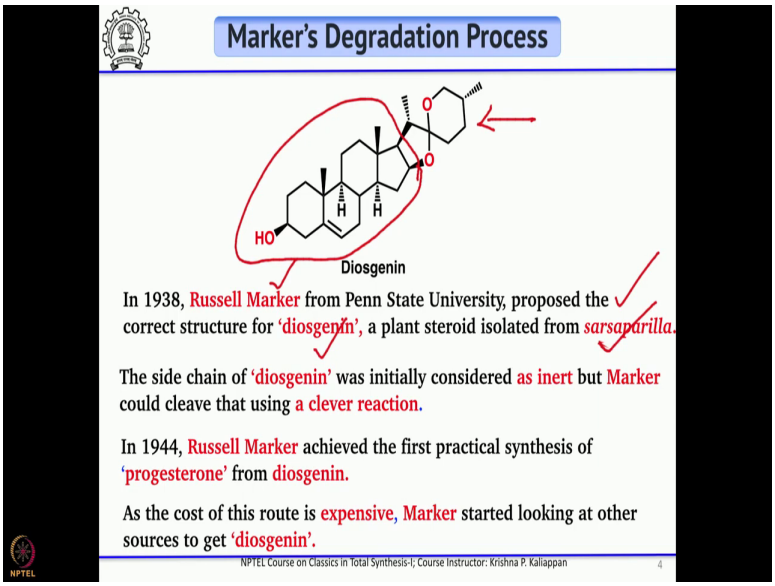

So, the person called Russell Marker was responsible for the synthesis of progesterone from diosgenin. So, diosgenin as I said is a naturally occurring compound it was isolated from the plant steroid called sarsaparilla ok. So, Russell Marker is a he was a Professor from Penn State University and he was the one who correctly proposed the structure of diosgenin and he did not stop there ok.

So, what was his aim? His aim was as I mentioned since diosgenin has the 4 rings present in all the steroids his idea was can we convert this diosgenin ok can we convert this diosgenin into other steroids that was his primary aim and how to do that? First, you have to remove this side chain ok the spiroketal because the spiroketal should be removed, initially the spiroketal was considered as inert to various reaction conditions ok it was considered as inert to various reaction conditions.

So, but Marker thought he can really cleave that and then he used a very clever reaction which I will come to that little later to cleave this spiroketal ok to cleave the spiroketal, once you cleave that then that opens the door for synthesis of several steroids ok. In 1944 I think after 6 years after establishing the structure of diosgenin he first reported the really practical synthesis of progesterone, practical means it is possible and it can be sold at affordable price from diosgenin ok that is very very important.

See, when we talk about academic work when we talk about industrial work ok these two are different extremes, I would say ok. One is for academic interest, other one you have

to keep it in mind the whole process should be affordable ok, it should be inexpensive and overall costing should be affordable ok. So, with that this practical synthesis of progesterone from diosgenin was one of the best synthesis reported for progesterone ok.

However, as I said he has to isolate diosgenin from the plant called sarsaparilla ok. So, that actually he could not get enough of this diosgenin from this plant steroid. So, that actually makes it makes the whole process little bit more expensive. So, he thought it is better to look for different sources ok different sources to get diosgenin, suppose if we can get another plant or any other plant which gives more of diosgenin then from diosgenin he can convert into progesterone ok.

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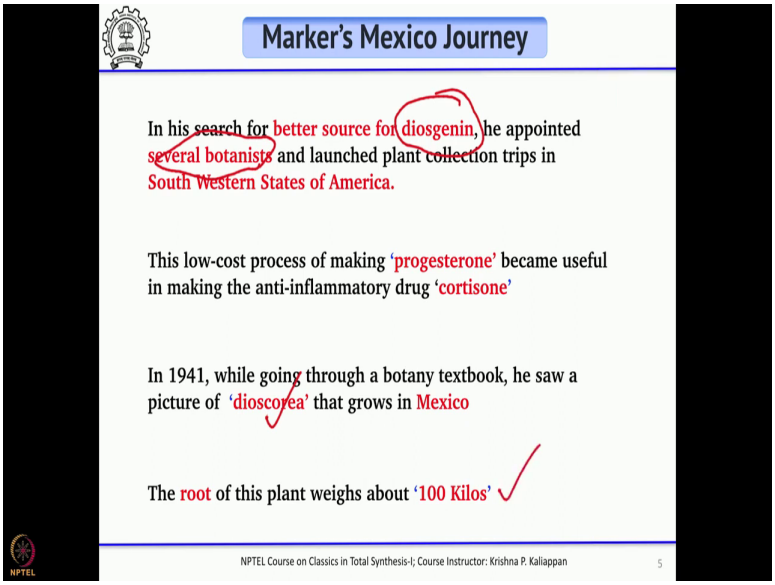

So, with that next what he did he sent few of his you know students most of them are botanists ok most of them are botanist. So, he asked them to search go around South America, America, Mexico and then search for different plant source, which will give more of diosgenin ok that was his first job. And second thing is his idea was once he makes 'progesterone' and if the process is you know inexpensive then he can make other famous drugs cortisone and testosterone ok. So, that was his idea.

So, idea is to develop a low cost process for progesterone and that depends on the isolation of diosgenin in large quantity ok. And meanwhile he was also searching and when he was going through a botany textbook he found a picture of dioscorea picture of a plant called 'dioscorea' and that was growing only in Mexico ok. So, he is a he is a big

professor in Penn State University he saw that easily he could have sent one of his students to go to Mexico.

And get this plant basically in that plant the root of the plant has diosgenin ok and the root weighs about 100 kgs, then you can imagine if we can get 100 kgs of this root of this plant how much he can extract diosgenin and from that how much he can make progesterone. So, with all this calculation his antenna went up and from academician he became an entrepreneur ok he thought ok it is better he himself start this process.

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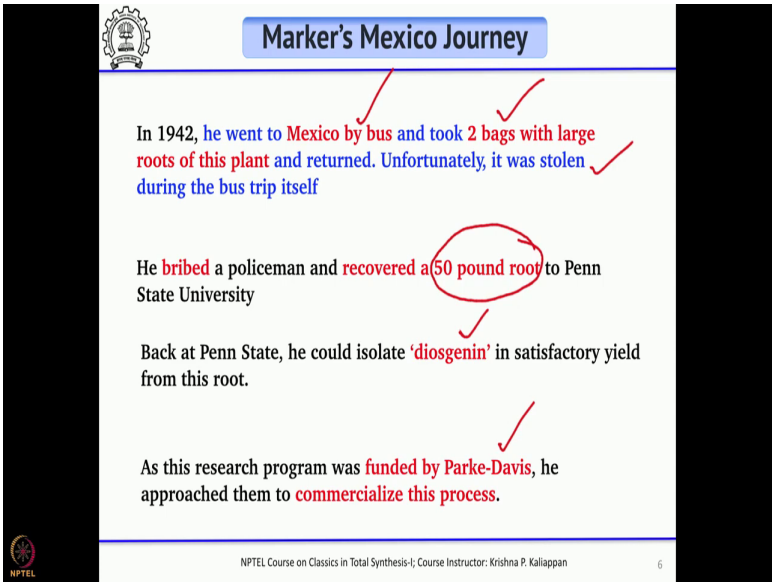

One day he went to Mexico ok. You can imagine, he went to Mexico by bus ok and he talked to few people and bought 2 big bags with large roots of this plant ok 2 large roots of this plant he returned by the same bus, but those days you know it was not like now. He put these 2 big bags on the top of the bus and after he crossed the US border when he got down already these 2 bags were stolen ok so, that used to be common those days.

However, what he did, he did another interesting thing he talked to a policeman and then somehow bribed and got 50 pound root ok so, 50 pound root and with that he returned to Penn State University ok. So, he could easily isolate the diosgenin in reasonably good yield ok, then he thought ok this is the best way to isolate diosgenin, once he isolates diosgenin in good quantities then he can go for the total synthesis of progesterone.

So, with this idea in mind he went to the company called Parke-Davis ok is a very famous company and his other research program was funded by this company. So, he went to them and then said he has developed a nice process for the synthesis of progesterone from diosgenin. Now, the diosgenin is available from this particular plant and this particular plant is available in Mexico. So, he wanted them to support financially so, that he can develop this process and then make this in large quantity.

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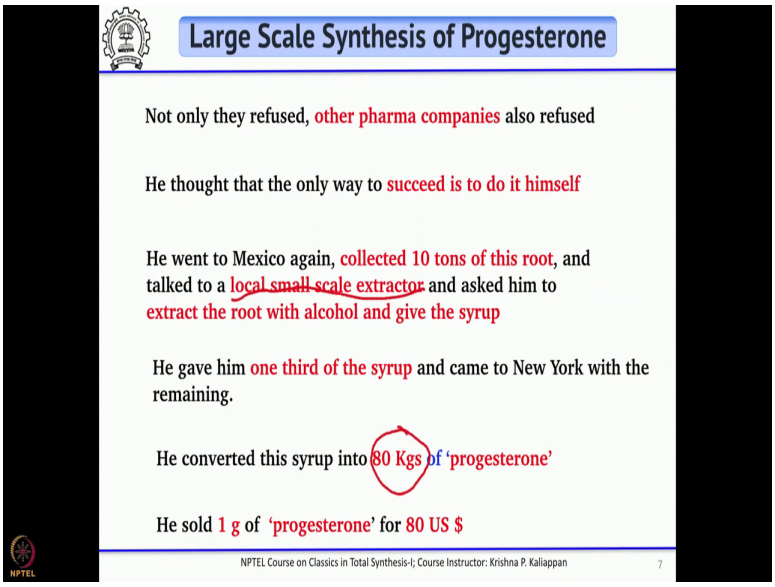

Unfortunately ok unfortunately not only that company he also approached other pharma companies all of them refused to fund this project. It was surprising those days because those days the requirement for progesterone and other steroids were really very high and it was a big surprise that pharma companies refused to fund this particular project. But as I said not only he was an academician he was also you know entrepreneur he thought why we have to talk to companies why not he himself can do it ok. So, he became entrepreneur as well as academician.

So, he thought he will do it himself this time he went to Mexico, but he was careful and what he did he talked to a small local small scale extractor ok. So, somebody who can do this job he talked to that person first then he collected 10 tons of that root 10 tons you can imagine ok, he gave this 10 tons to this local person and asked him you extract this root with alcohol ok. Then remove the alcohol and give only the syrup ok that person

agreed and it is like you know when you start a small industry what you do, you give certain percentage of share to that person, is not it.

So, what he did, when the alcohol was evaporated he got the syrup, one third of the syrup he gave it to that person who actually extracted, the remaining two third he brought it to New York ok, with this two third he got 80 kgs of progesterone with two third of you know whatever syrup he brought to New York he made 80 kgs of progesterone then he sold 1 gram of progesterone for 80 $ 1 gram of progesterone for 80 $.

Now, you imagine now you imagine how much money he made 1 gram cost 80 $ 80 kgs how much it is, that is the real you know entrepreneurship in him when he was an academician. So, this is very important not many academicians would like to become an entrepreneur, but at the same time this is a classical example when he realized that you know there is a possibility that he could be a successful entrepreneur. He moved ahead and then took the risk and then he became a successful entrepreneur ok.

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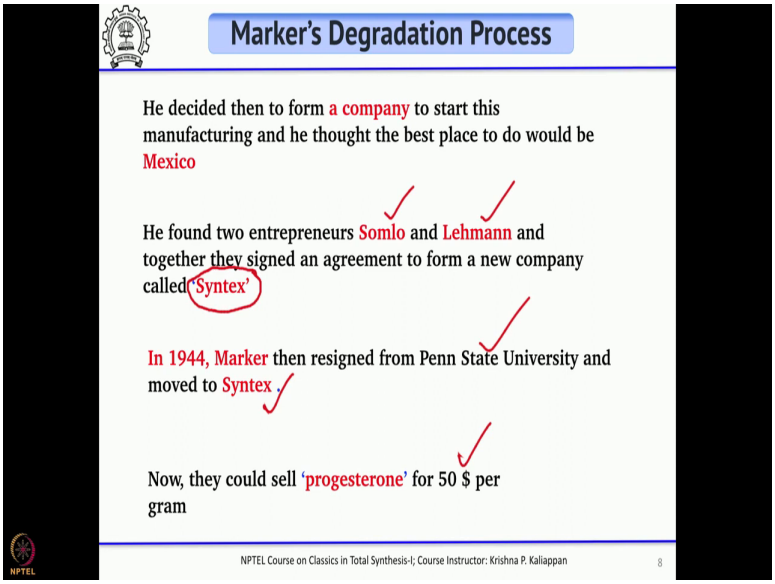

And he did not stop there. So, he thought ok we can he could make 80 kgs for the sustain development for the sustain development and sustained supply of progesterone, it is better to form a company is not it. Then while thinking about forming a company where to form the company, because this is also very important whether you want to form a company in US or you want to form the company in Mexico, always you know if you are

an entrepreneur you know very well it is better to form a company where your raw materials are available ok.

From a chemical companies point of view when logistics used to be a problem it is always better to start a company where raw materials are available. So, he decided immediately that he will form the company in Mexico. So, he talked to two more young dynamic entrepreneurs from Mexico called Somlo and Lehmann ok then as usual you know they have to sign an agreement for profit sharing. So, they signed an agreement then they formed a company called 'Syntex' they formed a company called 'Syntex.'

So, with this company they started producing progesterone ok, but in when you form a company with more people ok there is always a risk of you know getting into some trouble ok. So, in 1944 Marker did not get along well with these two entrepreneurs ok there was always you know profit sharing problem ok, then he had to come out of the company, but before that what he did, what Marker did? He saw that Syntex will take off very well. So, he resigned from Penn State University ok academic position he resigned academic position he resign and moved to Syntex.

He thought Syntex will be a good option he can sell and he can make a lot of profit ok and also in the process he can see he could sell progesterone for 50 $ earlier he was selling progesterone for 80 $ per gram. Now, since this company was formed in the place where the roots are available so, the raw material cost everything came down. So, he could sell the progesterone for 50 $ per gram.

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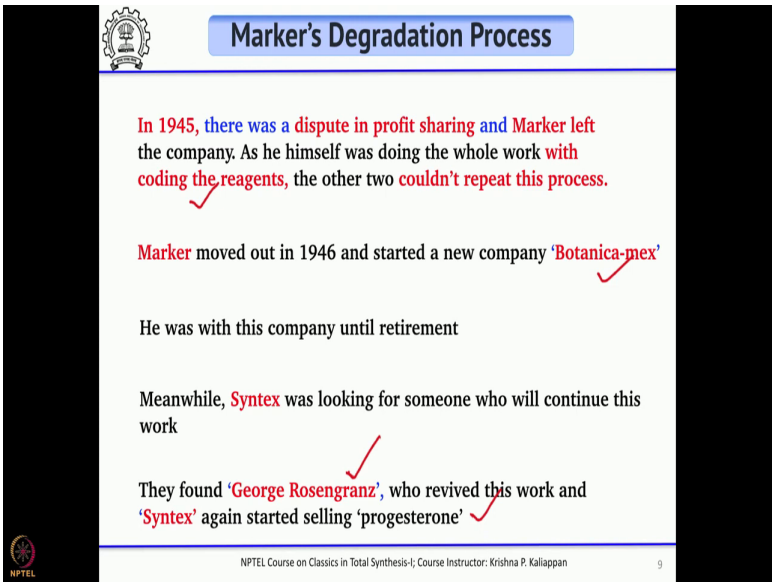

But as I said a year later there was a problem and profit sharing is you know as affected Marker and then he thought; ok why to stick with the company, but interestingly one should know this is very common at least this used to be very common until you know 10-15 years ago in process division.

Once you have the know how once you have the process of know how many people do not disclose many people do not disclose how to carry out the reactions Marker cleverly what he did, he used coding he used coding all the reagents. So, his partners did not know which reagent he was using, which reaction he was doing, they only know they only funded, they only know that he is responsible for the chemistry and they have funded and overall once they sell they will share the profit.

But they did not know the real chemistry ok, when as I said when there was a profit sharing Marker has to leave the company when he left the company; he just took the process because he himself did all the chemistry. So, others just could not repeat the process. So, what Marker did, he went out and started another company called 'Botanica Mex' ok. So, he also got supply of regular supply of the roots from others and with that he started a company Botanica Mex.

And that company was you know supplying progesterone and he remained in that company until retirement. Meanwhile, the other two entrepreneurs ok who started the company Syntex along with Marker. So, they saw the potential of this process, but they

did not have a person like Marker. So, what they did, they approached they approached many people many scientist who can think of this process. So, by now they know what is the starting material diosgenin.

So, they wanted to know somebody who can do the same process and then synthesize progesterone in large quantity. So, they appointed a person called 'George Rosengranz' ok and who did lot of you know optimization and revived the work and he could start making progesterone and that is how Syntex was really you know again back to business in making progesterone.

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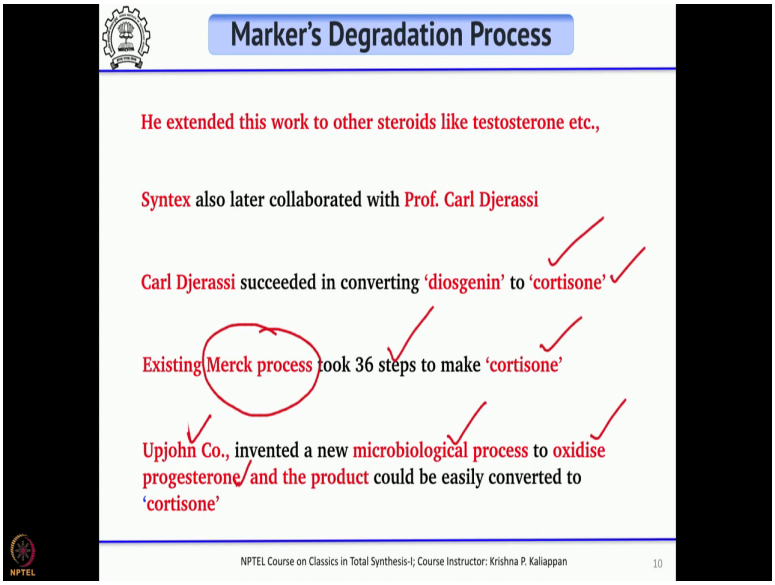

And not only that this person this chemist he extended this work ok, once he made the progesterone, the progesterone was converted into cortisone and testosterone ok. And Syntex later they also collaborated with a very famous chemist call called Carl Djerassi was well known for mass spectrometry and then his work on steroid particularly or on oral contraceptive. So, they collaborated with Carl Djerassi and Carl Djerassi was responsible for converting diosgenin to 'cortisone' and cortisone to testosterone and so on ok.

That time before Carl Djerassi used this method to make cortisone the Merck company was taking about 36 steps to synthesize cortisone ok, cortisone is one of the you know famous steroids being used now, but you can imagine if it has to take 36 steps to make cortisone then it will be very difficult for you know common people to buy this cortisone

ok. So, that is how this particular strategy was very very important to make cortisone in affordable.

Meanwhile, the Upjohn Company made a major breakthrough in oxidizing progesterone. See, if you look at the progesterone and if you look at cortisone you can see there is a hydroxyl group oxygenated at C ring ok this C ring hydroxylation was done by this microbiological process. So, because of that so you do not have to go through chemical process to introduce the hydroxyl group. So, this microbiological process reduced significantly the number of steps involved in the conversion of progesterone to cortisone ok.

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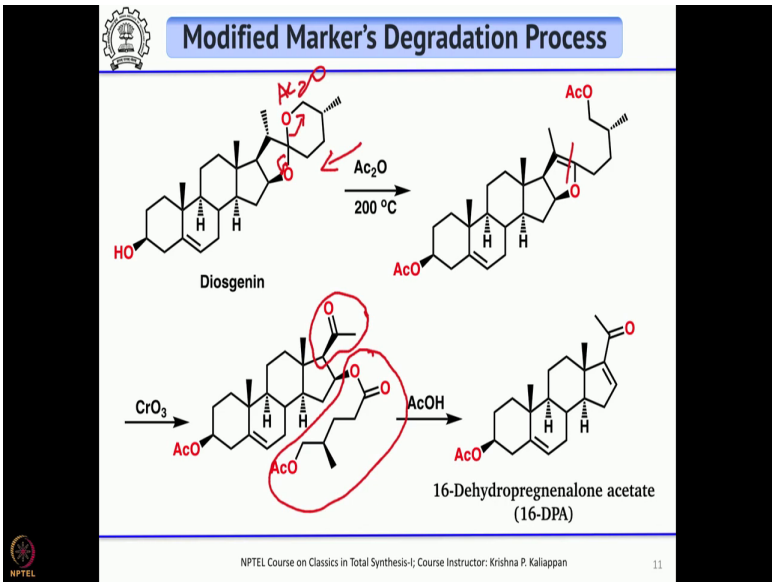

So, now let us go to the chemistry how Marker actually converted diosgenin to progesterone and later progesterone to cortisone and testosterone. So, this is diosgenin and as I said the first step is the removal of the spiroketal side chain. So, what he did he reflects this diosgenin in large quantity one can do it in tons also in acetic anhydride at 200° C ok at 200° C you reflex with acetic anhydride this cleaves and you get you can see this is a acetic anhydride and then this lone pair and this becomes -OAc and followed by loss of proton you get the corresponding enol ether ok.

Now, if you treat with chromium trioxide if you treat with chromium trioxide this cleaves ok, oxygenation followed by cleavage of this double bond one gets the acetyl group ok you can see this is what you need this is what you need in progesterone and

your free hydroxyl was also acetylated in the first step. Now, what you need is you need to remove this long chain ok remove this long chain. So, this can be done by treatment with acetic acid.

So, when you do acetic acid so, hydrolysis of this ester takes place followed by dehydration gives this compound gives this compound ok. Now this is a very important intermediate this is a very very important intermediate in steroids this is called 16 DPA what is 16 DPA it is called 16 dehydropregnenolone acetate. So, this is a very important intermediate for synthesis of several steroids that was obtained from diosgenin in three steps ok using simple reagents.

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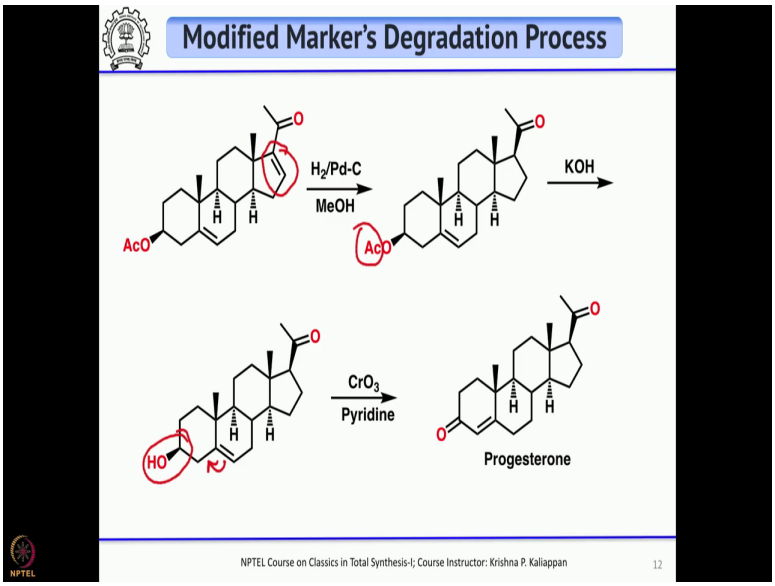

Once you have 16 DPA then one can selectively hydrogenate the C ring double bond ok. So, once you do that then you get the β acetyl group then hydrolysis the acetyl group is hydrolyzed with potassium hydroxide to get the corresponding OH. Now, if we oxidize now if we oxidize not only the hydroxyl group gets oxidized then the double bond also migrates that is nothing but progesterone.

So, if you look at the whole process basically in 6 steps in 6 steps one can convert diosgenin to progesterone all using very very simple reagents commercially available, inexpensive reagents to make progesterone, that is how Marker used this method to make you know tons of progesterone ok. Now, how 16 DPA, which is the intermediate ok,

which is the intermediate in the synthesis progesterone from diosgenin to convert into cortisone, ok.

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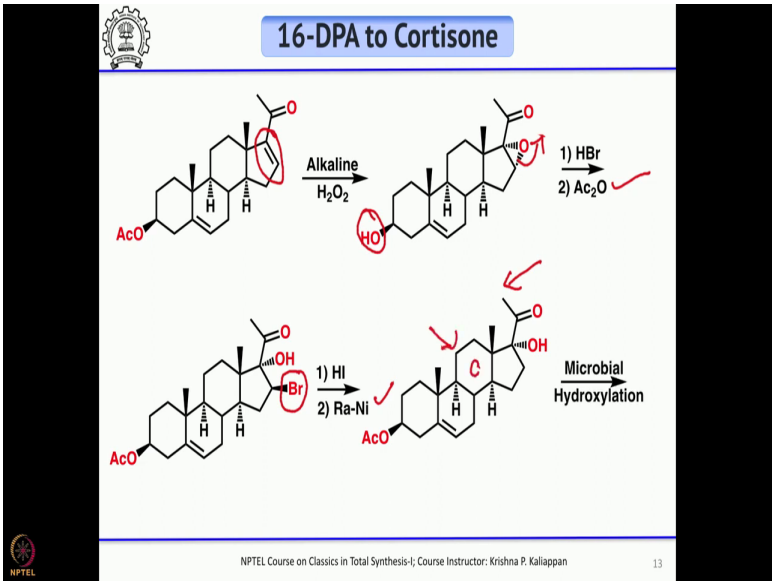

This is 16 DPA ok first you make epoxide of this double bond α–β and such a ketone. So, if you treat with alkaline hydrogen peroxide that will selectively epoxidized α–β unsaturated ketone. So, you make the epoxide, it is a stereo selective epoxidation the epoxide comes from the α side. Now, if you treat with HBr it opens up so, you get the tertiary alcohol and the β bromide, meanwhile when you treat with acetic anhydride the free hydroxyl group gets acetylated ok.

Having done that next you treat with HI. So, HI you know gives this bromide SN_2 like displacement to give corresponding iodide and then Ra-Ni nickel removes the iodide ok. So, what you have done basically the epoxide you open and then you have done the reductive removal of the halide ok. Now, as I said you need to introduce a hydroxyl group here and also a hydroxyl group in the C ring. So, this is where the Merck's process the microbial hydroxylation took place at this position very important transformation.

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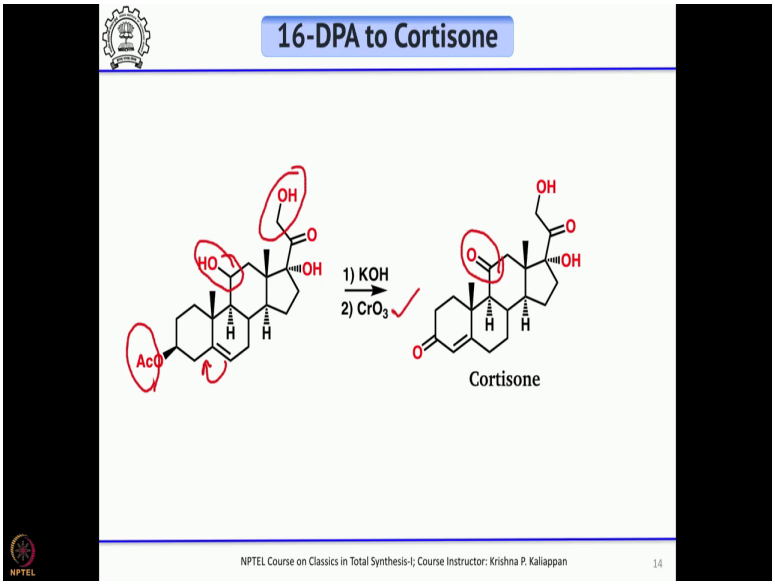

So, once you do that it does two things what are they, one the hydroxylation here and hydroxylation here two hydroxylation ok. The dihydroxylation actually helped ok reducing lot of chemical wastes, now potassium hydroxide will hydrolyze the acetate to alcohol then chromium trioxide will oxidize that alcohol as well as the secondary alcohol in C ring to give ketone.

And also the double bond will migrate. So, that is nothing but cortisone again you see from 16 DPA to cortisone in few steps and one of them is a microbial hydroxylation ok that is the key step in the conversion of 16 DPA to cortisone.

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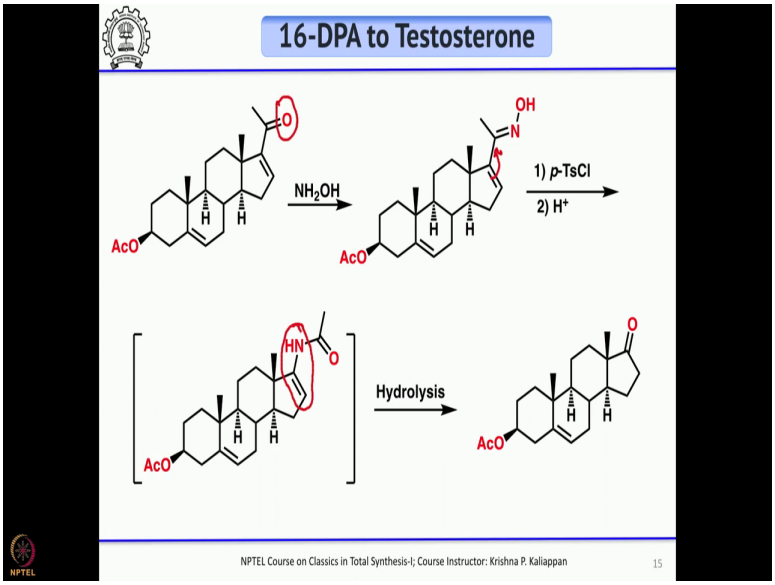

Then the same 16 DPA was successfully used to convert into testosterone male sex hormone, how? Same mean 16 DPA now you treat with hydroxylamine. So, when you treat with hydroxylamine you have a ketone and that will immediately form an oxide ok. When you have an oxide the next reaction, which should come to your mind is Beckmann rearrangement ok.

So, Beckmann rearrangement on treatment with *p*-toluenesulfonyl chloride and then acid so, you can see this will give you this corresponding amide ok corresponding amide. Once you have this amide now this is enamide is not it this is enamide that enamide can get hydrolyzed to give corresponding keton enamide gets hydrolyzed to the corresponding ketone.

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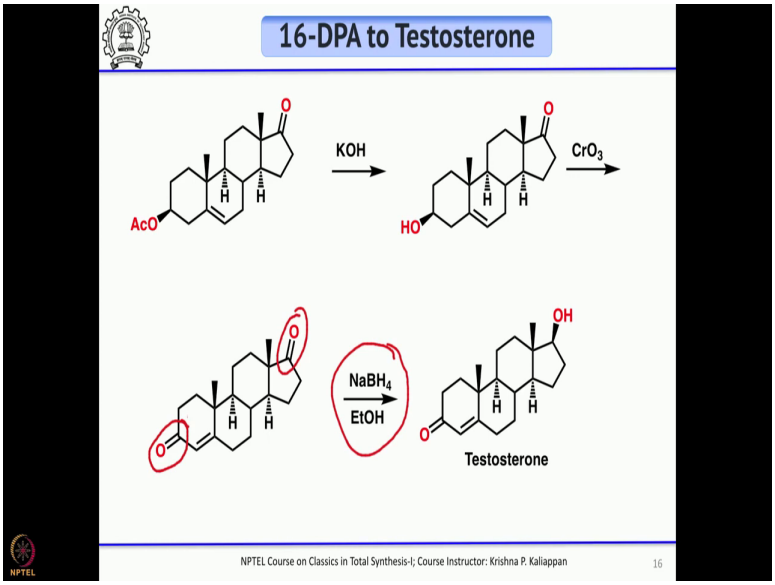

So, now from here testosterone was done in two steps first you hydrolyze acetate to alcohol then you oxidize you see you get the corresponding in diode, the 5- membered ketone reduced to alcohol ok. So, selectively one can reduce the 5 membered ketone with sodium borohydride to get testosterone. So, if you look at the whole process the whole process dependent on Marker's degradation step.

So, Marker cleverly used his 6 step process to convert diosgenin which is available from roots of you know Mexican plant to make 16 DPA in 3 steps and in 6 steps he converted that diosgenin into progesterone, from 16 DPA you can convert that into testosterone and cortisone ok. So, all this started with the clever use of oxidation of diosgenin to 16 DPA ok. So, I will stop here we will continue our discussion on synthesis of steroids in the next class.

Thank you.