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

Lecture – 45
Estrone

So, good morning welcome back to the NPTEL course on Classics in Total Synthesis. In the last lecture we talked about total synthesis of progesterone actually it is a semi synthesis of progesterone from diosgenin and we also discussed little bit about the history of diosgenone and how marker went to like Mexico.

And then got the roots which essentially gave tons of diosgenin and from diosgenin how we converted that into progesterone. So, later the formation of syntax company all that we discussed. So, today what we will do we will move to another steroid called Estrone, ok. This is a female sex hormone as you know.

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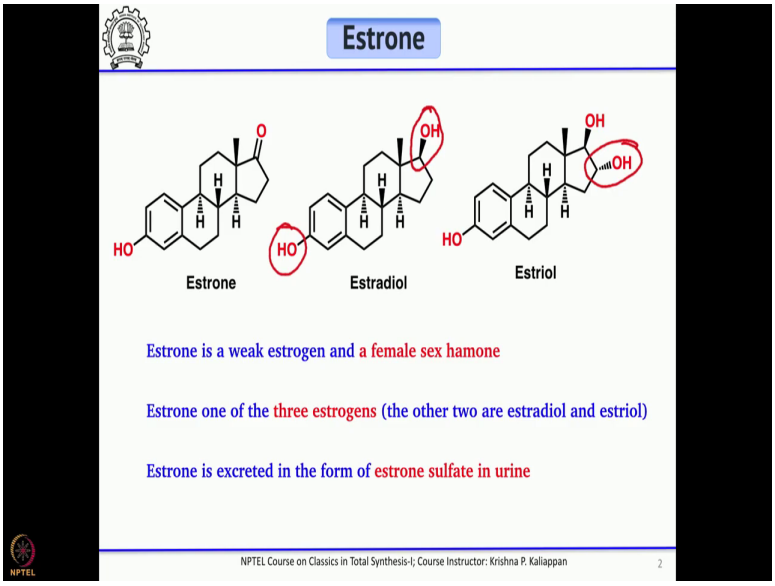

So, this one of the three female sex hormones estrone, estradiol and estriol, ok. See if you look at estrone and estradiol you can see the carbonyl group is reduced, ok. Already you have a hydroxyl group in the form of phenol in a ring and in addition we have another hydroxyl group in estradiol.

Whereas in estriol you have one more hydroxyl group, ok. So, these are the three you know estrogen molecules, but what we will do we will talk only about the total synthesis of estrone today. And estrone initially it was isolated ok, initially it was isolated in the form of estrone sulfate from urine, ok.

People have collected lot of cow's urine and from that they have done huge column huge column to get estrone sulfates, ok. And from synthetic point of view if you look at this molecule there are 4 contiguous chiral centers.

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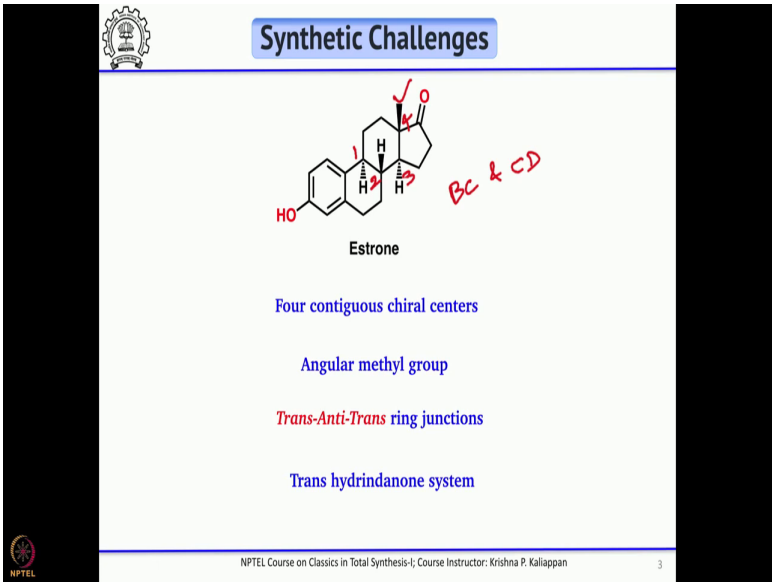

That is the first and four most challenge you see. So, 1, 2, 3, 4 there are 4 contiguous chiral centers. In addition, you have an angular methyl group and the ring junction ok, the ring junction if you look between BC and CD, they are trans anti relationship, ok. So, this is something which is quite difficult particularly when you talk about the hydrindanone skeleton.

Hydrindanone generally the cis relationship is more stable than the transform, ok. These are the challenging aspects when you talk about total synthesis of estrone.

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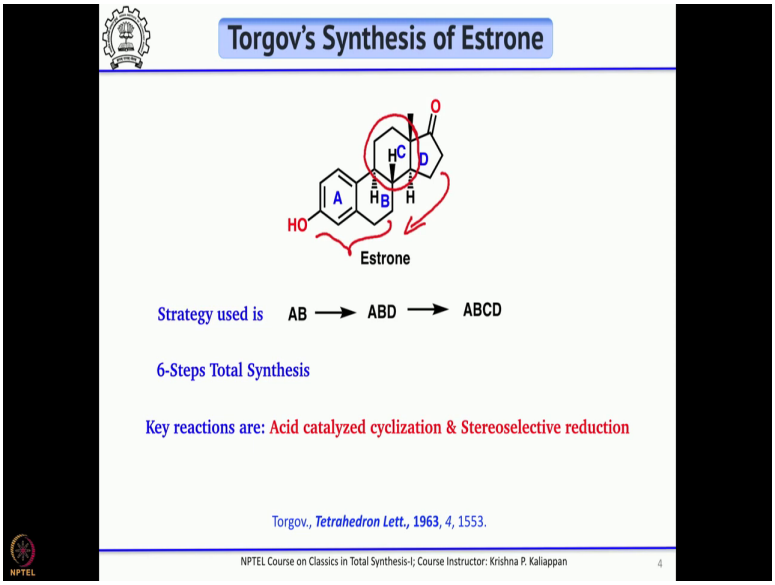

So, far the best synthesis of estrone was reported by Torgov in the early 60's in Tetrahedron Lett and the whole synthesis involved only six steps, the whole synthesis involved only six steps and their strategy is based on they will start with AB ring, ok.

They will start with the AB ring first then they will add this D ring AB and then they will add ABD ring then they will construct the C ring. So, they start with AB ring bring the D ring then form the middle ring that is C ring ok, and as I mentioned it was only six steps and that time it was considered one of the best synthesis.

And more importantly this route is still followed in industry, ok. This route is still followed in industry to make estrone and related steroids. The key reactions involved in the total synthesis estrone are one the acid catalyzed cyclization. Acid catalyzed cyclization to get the C ring. Second the stereo selective reduction of dienes there are two double bonds which are formed at the end of acid catalyzed cyclization.

I will discuss that when I go into the total synthesis. Then the reduction stereo selective reduction of this diene to get there the correct geometry of the ring junction, ok. So, let us see how he started this.

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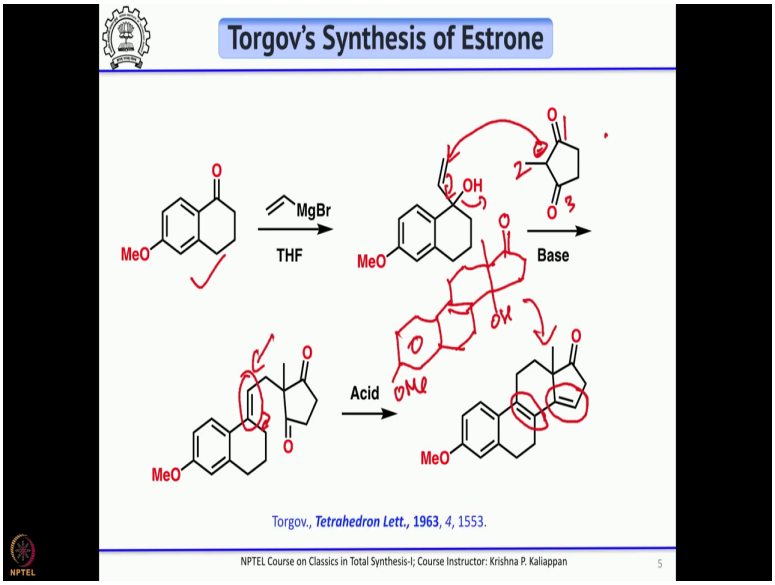

He started with readily preparable starting material called 6 methoxy 1 tetralone 6 methoxy 1 tetralone. And addition of vinyl Grignard ok, addition of vinyl Grignard gave this tertiary allylic alcohol, addition of vinyl Grignard gave this tertiary allylic alcohol. Now he treated this with 2 methyl 2 methyl cyclopentane 1,3 dione ok, 2 methyl cyclopentane 1,3 dione in the presence of these.

Even use titan B. Now this undergoes a substitution reaction like this, ok. So, what he got was this double bond. Next is one of the key reactions the acid catalyzed cyclization. So, when he treated with acids first the double bond migrates here then intra molecular Friedel crafts like reaction takes place to give this dione, ok.

The intermediate here is this compound, ok. This is the first step that is after the migration of this double bond then intramolecular Friedel crafts like reaction will give this intermediate then dehydration will take place to give this dienone, ok. Once you have this dienone you have to selectively reduce this double bond. Tri substituted double bond then you have to reduce the tetra substituted double bond. So, these two were done individually.

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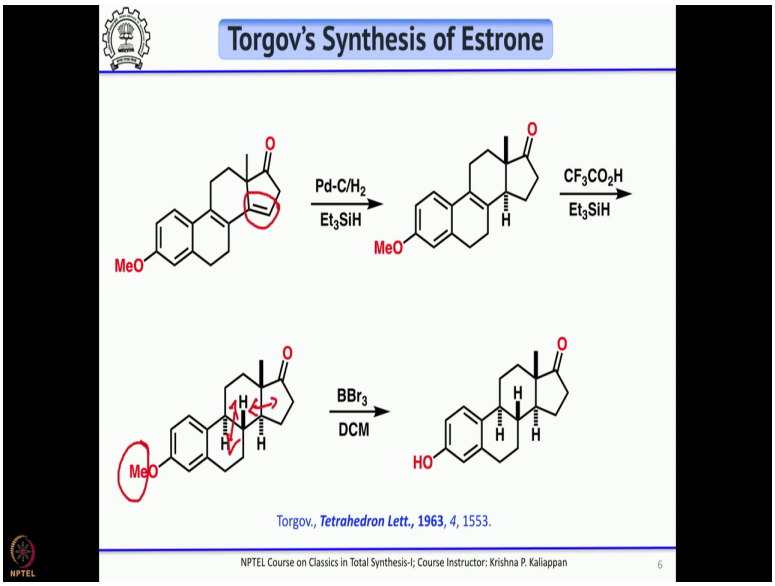

First that tri substituted double bond was reduced under hydrogenation condition in the presence of triethylsilane ok, triethylsilane also you can give hydrogen. First as I said this five membered ring the tri substituted double bond was reduced, ok. For the next one tetra substituted you need stronger condition. So, trifluoro acetic acid and triethylsilane was used to get the corresponding you can see *trans* and then *trans* ok, system.

So, once you have that what is left is to remove the methyl group or cleave the aryl methyl ether. So, that was easy by treating with BBr_3 to get St. So, overall if you look at the total synthesis of estrone reported by Torgov is only six steps, ok. And involves two key reactions one is cyclization acid catalyzed cyclization and then stereo selective reduction of the diene. However, the starting material six methoxy 1 tetralone, ok.

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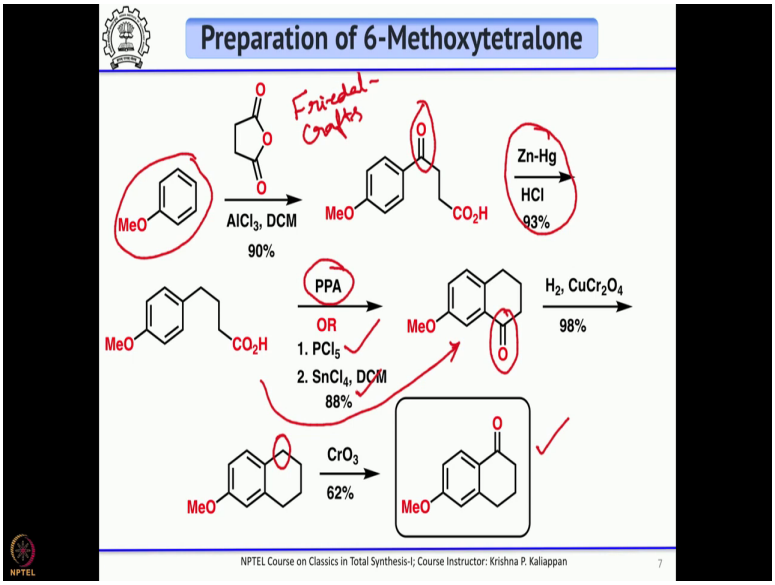

Six methoxy 1 tetralone was prepared in few steps, but all in good yield. The first step was the Friedel crafts acylation. Friedel crafts acylation of anisole with succinic anhydride, ok. So, that gave this keto carboxylic acid ok, that gave this keto carboxylic acid. So, now, if you do Clemmensen reduction, if you do Clemmensen reduction as you know Clemmensen reduction is known to reduce the keto group to corresponding alkene.

So, this ketone was reduced under Clemmensen reduction condition to get the CH 2. Now from here to here from here to here can be done in two steps or even in a single step. In single step means you have to use polyphosphoric acid ok, polyphosphoric acid is known to cyclize the polyphosphoric acid and our aromatic ring.

However, many times it gives poor yield. Instead, what one can do is one can convert the carboxylic acid to acid chloride, one can convert the carboxylic acid to acid chloride. So, once you have the acid chloride then intramolecular Friedel crafts acylation can be done with Lewis acid, ok. So, the second step is the intramolecular Friedel crafts alkylation.

Once you have that then the keto group is deoxygenated the carbonyl group is deoxygenated with hydrogen and copper chromate. And the last step is the regioselective regioselective benzylic oxidation with chromium trioxide.

So, we except the last step all other steps if you see all the remaining four steps give excellent yield, ok. So, this is one of the key starting materials 6 methoxy 1 tetralone is

one of the key starting materials in the synthesis of all the steroids almost all the steroids as well as you know many other natural products, ok.

That is why I thought its better to discuss how the 6 methoxy 1 tetralone was prepared, ok. So, the synthesis reported by Torgov was racemic synthesis. So, then people thought you one can use the same strategy, but somewhere if one can introduce chirality.

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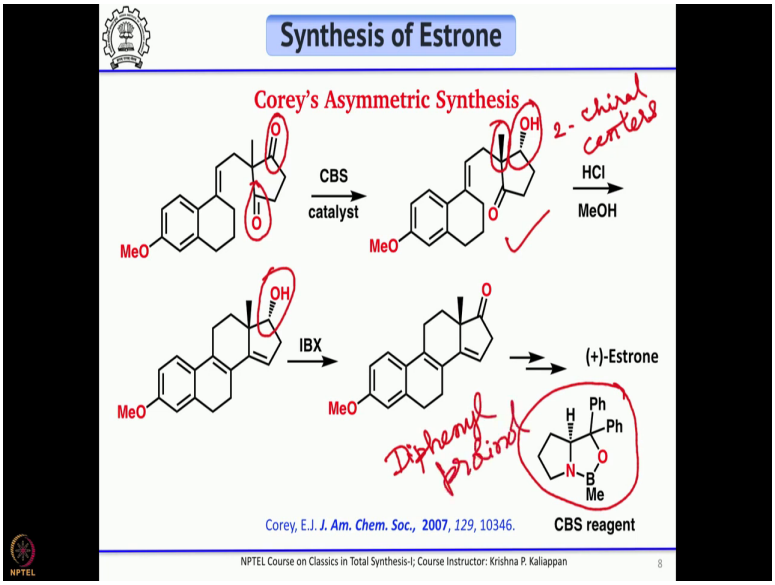

Then that will be asymmetric synthesis. So, E. J. Corey it took this compound. Now you have two ketones is not it? Two ketones one can call this is as symmetrical one this e reduced with is CBS catalysts ok, CBS catalyst Corey Bakshi Shibata catalyst with that catalyst he could get this compound, ok.

Now, you see it was racemic and he could get 2 chiral centers fixed ok, 2 chiral centers ok, using this CBS catalyst. Then what is there you have to do the acid catalyzed cyclization is not it? So, you did the acid catalyzed cyclization and then oxidize the alcohol ok, to ketone.

Afterwards in two steps that is using hydrogenation and trifluoro acidic acid and triethyl silane one can convert this into estrone followed by removal of the methoxy group, ok. So, in three steps this can be easily converted in estrone. But the difference is this is synthesis of estrone of one enantiomer ok, here it is (+) enantiomer has been synthesized

and for that the important reaction is the CBS catalyst mediated reduction of 1,3 diketone to get exclusively this size, ok.

This is the CBS catalyst. The CBS catalyst is prepared from diphenyl prolinol the CBS catalyst is prepared from diphenyl prolinol, ok.

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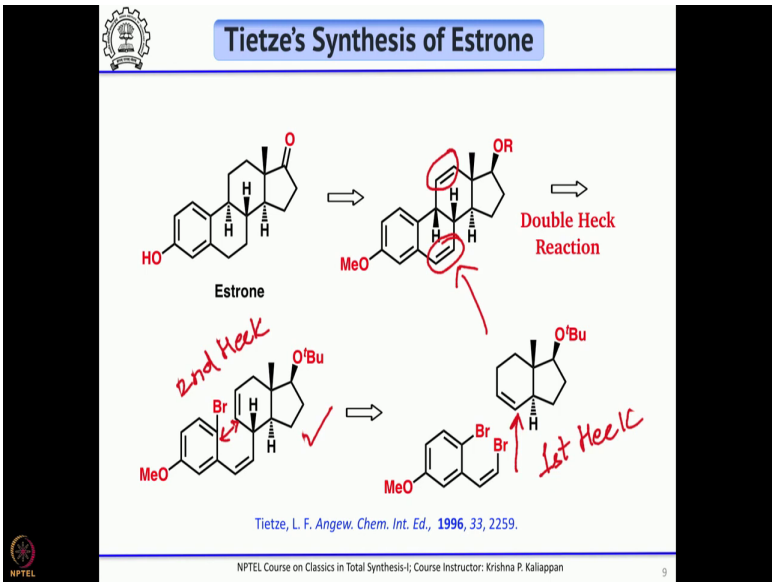

Then will move to two more very interesting total synthesis of estrone one was reported by Lutz Tietze. Here what he has cleverly used is a Double Heck reaction. Double Heck reaction to make the or connect the A ring with C ring, ok.

What did he do? So, his idea is if you want to make estrone then he thought if we can introduce these two double bonds um, if we can introduce these two double bonds. And these two double bonds, he felt can be can be introduced by Heck reaction, ok. His idea is like this, the Double Heck reaction can be done on this substrate, ok.

So, this is actually when you see this there is only one heck ok, that is only one heck, ok. The second heck is obtained from this. So, this will be the first heck ok, this will be the first Heck reaction and this will be the second Heck reaction. So, using a Double Heck reaction in the same part one can get from this compound directly this that was his original idea, ok. And how did he make the starting material particularly this one.

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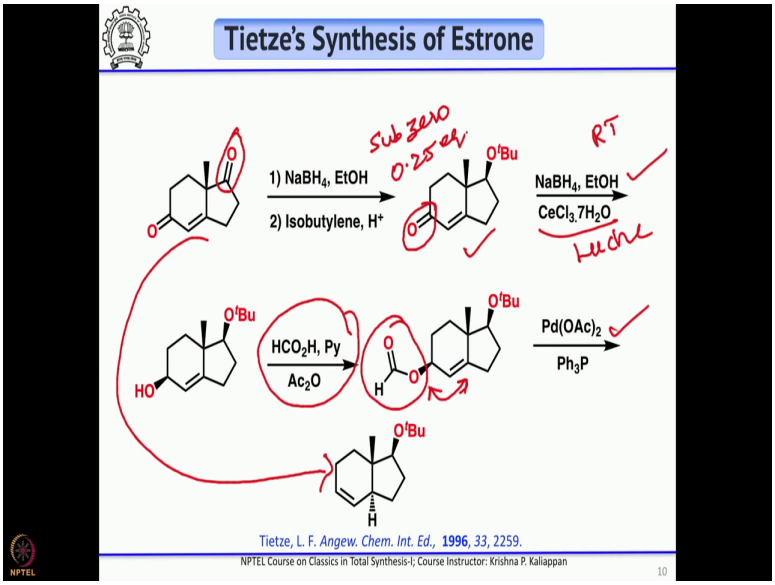

He made from the Hajos Parrish ketone, ok. He started from this and then select the reduction of the five membered ketone and protection of that alcohol as tert butyl ether we have this compound then one can reduce the enone, ok.

Here you have to do it at sub zero, ok. You have to do it at sub zero and 0.25 equivalent, ok. And this can be done at room temperature um. And of course, you have to use cerium chloride otherwise the double bond also will be reduced and this is called Luche reduction, is not it? Luche reduction is nothing, but reduction of α–β unsaturated ketone to corresponding allylic alcohol with sodium borohydride and cerium chloride, ok.

So, now you got this allylic alcohol and this and treatment with formic acid. Formic acid pyridine and acetic anhydride you get the corresponding formate. Now the double bond migration that is you know allylic ok, now you see this is allylic one, is not it?

So, you can use palladium catalysed the allylic transposition and you transfer the double bond at the same time this is being replaced the acetate the formate is replaced by hydrogen, ok. So, basically if you look at this in five steps Hajos Parrish ketone can be converted into one of the starting materials one of the starting materials required for estrone, ok.

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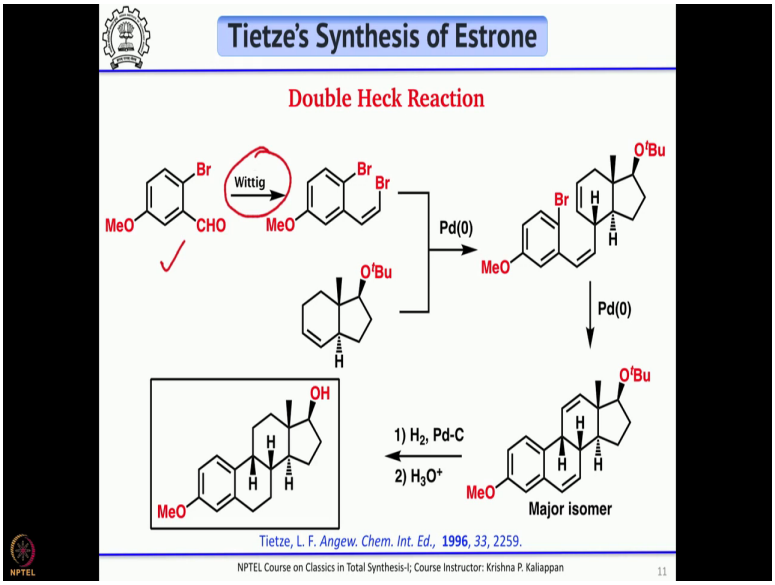

For the other starting material, you have to start from the corresponding aldehyde ok, this aldehyde. So, its a commercially available aldehyde you take the aldehyde then do a Wittig reaction, ok.

So, you have to do a Wittig reaction to get the corresponding cis vinyl bromide, ok. Take this and already you made this compound ok, do the double Heck reaction. So, when you do the double Heck reaction this is the first one first a product and the second Heck will give this compound as the major isomer, ok.

Now, you can do the hydrogenation followed by oxidation you will get corresponding estrone, ok. The third synthesis the third synthesis of estrone not you know order wise, but third synthesis which we are going to talk about involves a [2+2+2] cycloaddition ok, of 3 triple bonds, ok. We can call it as cyclotrimerization, ok. Cyclotrimerization also one can call. So, three triple bonds will trimerize to form an aromatic ring. So, that was the key reaction.

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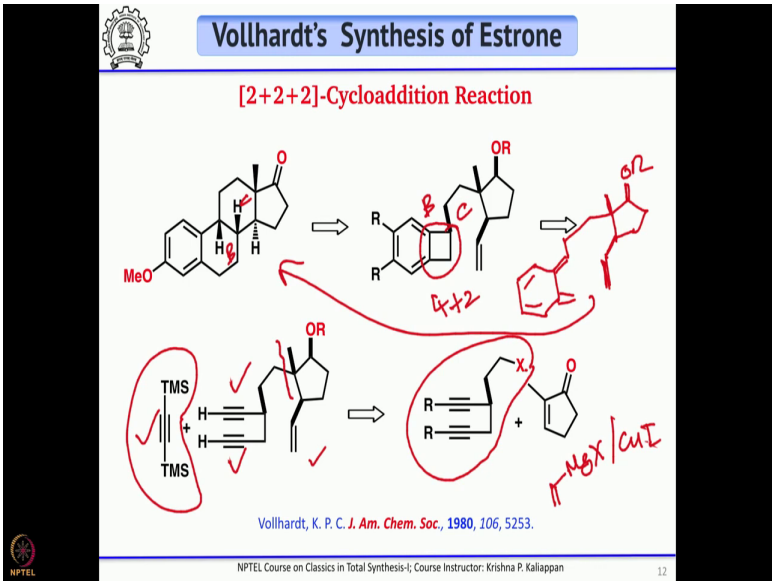

So, in the literature it is well known that if you use cobalt carbonate cyclopedia cobalt carbonyl or if you use Wilkinson catalyst this type of [2+2] cycloaddition can be easily achieved.

So, his idea is this first the B and C ring. B and C ring will be obtained by an intramolecular Diels Alder reaction intramolecular Diels Alder reaction. What is an intramolecular Diels Alder reaction? So, here if you heat it will undergo first an intra molecular electrocyclic ring opening.

So, this is nothing, but cyclobutane is not it? So, it can undergo intra molecular electrocyclic ring opening to give this intermediate, ok. So, now, this can undergo a [4+2] IMDA type I that is intramolecular Diels Alder reaction type I.

That will give you our compound ok, this come, ok. Now this can be obtained by the [2+2+2] cycloaddition reaction this is it this is a alkyne, this is an alkyne this is an alkyne. There are three alkynes that can undergo cyclotrimerization to give the precursor to electro cyclization followed by IMDA type I reaction.

And this can be obtained if you see this if you cleave this bond then this will be an electrophile. Now one can add vinyl copper, ok. If you add vinyl copper followed by quenching with this you will get this product, ok.

This is commercially available. So, once you have this then you can do the cyclotrimerization and then followed by heating should give the electrocyclic electrocyclic ring opening and [4+2] cycloaddition products.

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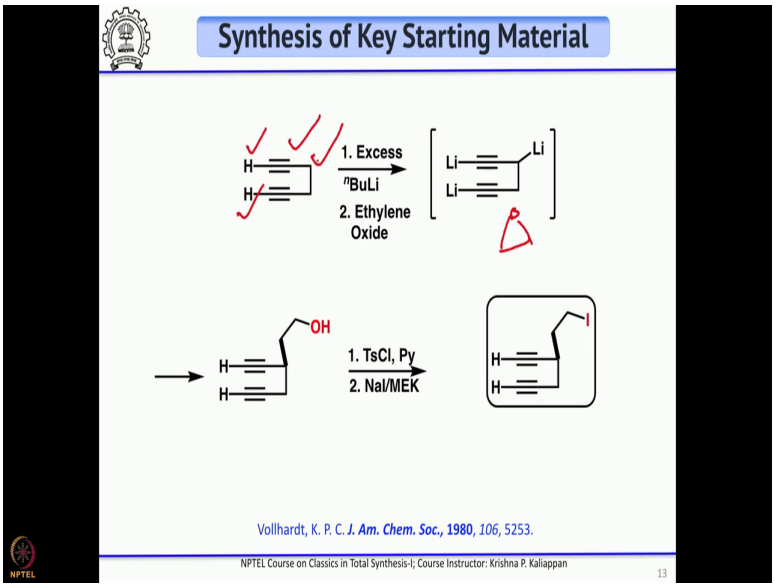

So, now let us see how the diene was prepared diene. So, he started with the known compound and then when you add excess n butyllithium at least three equivalents of n butyllithium is required. Three equivalents of n butyllithium is required. So, first these two acrylic protons will be lithiated followed by removal of the propargylic proton. So, you get a tri lithio species tri lithio species then you open with ethylene oxide you get the corresponding alcohol, ok.

If this can be converted into the iodide first by treating with tosyl chloride to get the tosyl tosylate then Finkelstein reaction with sodium iodide and methyl ethyl ketone you get corresponding iodine, ok.

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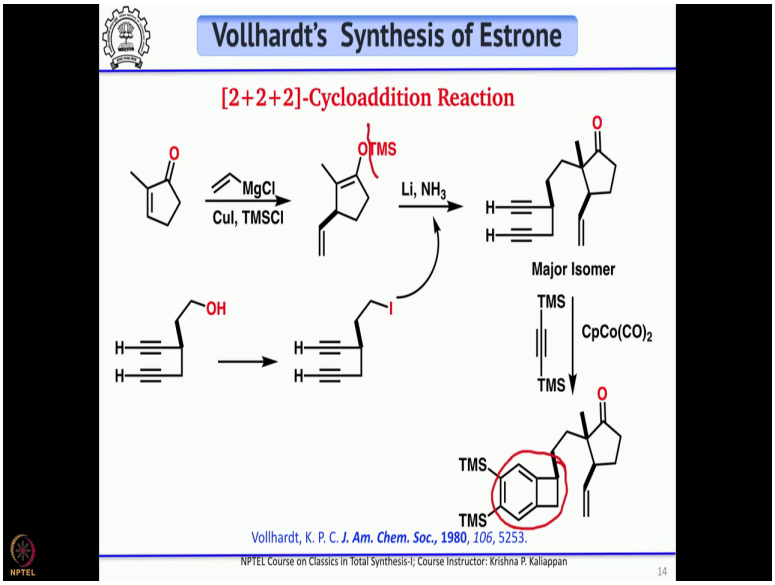

So, this is done and already as I told you the tri trimethylsilyl acetylene is a known compound. So, that can be directly used. So, for the other fragment you have to start from 2 methyl cyclopentanone. 2 methyl cyclopentanone then you carry out the vinyl 1,4 addition with vinyl magnesium bromide and cuprous iodide and quench the resultant enolate, ok.

Quench the resultant enolate with the TMS chloride, ok. So, now, what you have got is you have done the vinyl 1 4 addition, but the enolate is trapped the enolate is trapped as TMS ether, ok. So, the OTMS can be cleaved OTMS can be cleaved with either methyl lithium or lithium in ammonia.

So, that what will happen? You will generate the lithium enolate once you generate the lithium enolate you can quench with the iodide which we have already discussed. So, the iodide already as I said can be prepared from this alcohol. Now you treat with lithium ammonia you generate the enolate lithium enolate and quench with this iodide you get this as the major isomer, ok.

So, now you have this the next step is the cyclo trimerization that is [2+2+2] plus cycloaddition. So, this is normally achieved by either Wilkinson catalyst or cyclopentadiene cobalt dicarbonyl compound.

So, that reaction worked well. As you can see here that led to this benzo cyclo butane this is called benzo cyclo butane and this is one of the very good precursors for electrocyclic ring opening followed by intramolecular Diels Alder reaction. So, once you have that.

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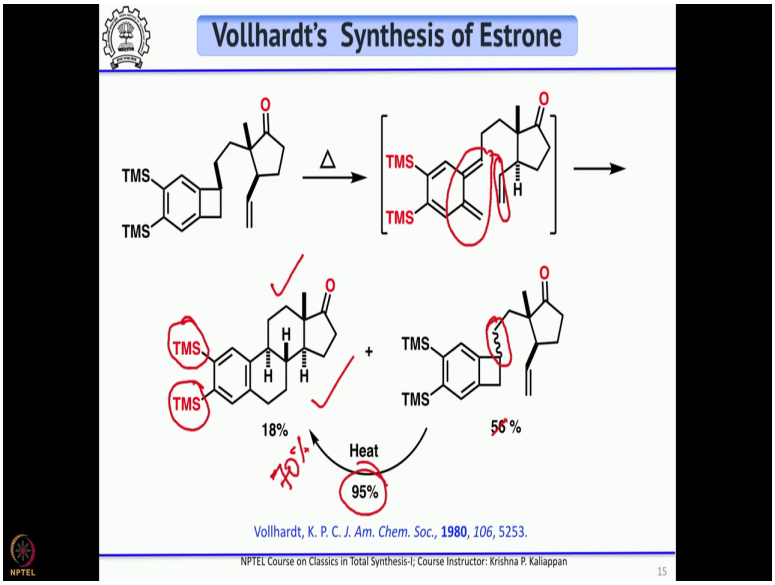

Next you have to heat it. So, heating gives the electrocyclic ring opening diene and that immediately undergoes intramolecular Diels Alder reaction to give these two products. One the intermolecular Diels Alder reaction product the other one the other one is the isomerized product this one.

You get back the starting material, but this is isomerized. Nevertheless, if you heat this further if you heat this further it gets converted into the expected product ok; that means, the 56% which you are getting is converted into the expected product in 95% yield so; that means, close to you know how much you get.

Close to 70% you get this as the product, ok. So, with this next step should be to remove this TMS group and exchange this TMS with hydroxyl group, ok. One of the TMS should be selectively removed or you can call that as proto desilylation. Whereas, the other TMS group should be converted into OH. So, before actually he tried to do this reaction, he thought it is better to use a model system and then study whether the silicon can be easily selectively removed. So, he took a model system that is a tetralin system.

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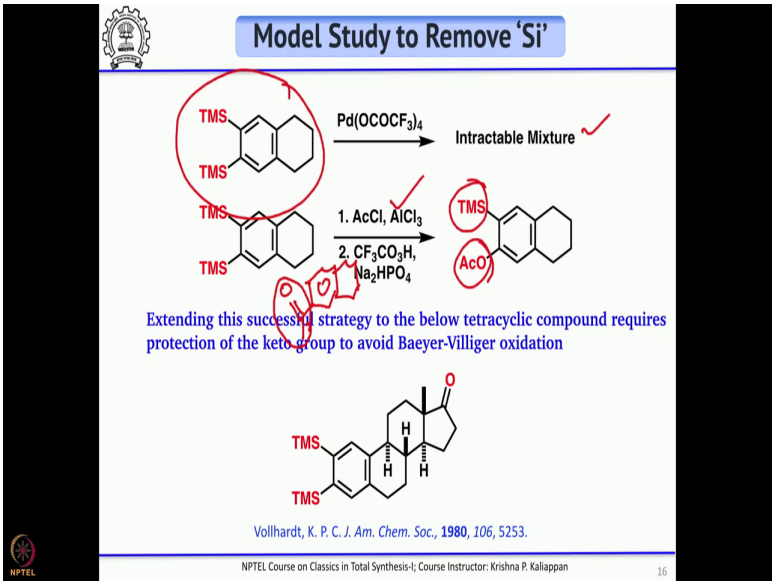

And then first he tried with the palladium trifluoroacetate ok, but what he got was a mixture. So, then he thought ok, this is not a good method. Then he used first acetylation its well known in the literature. If we have TMS group attached to aryl ring TMS group attached to aryl ring then if you treat with acetyl chloride aluminium chloride the TMS will be replaced by acetate group; that means, TMS will be replaced and then you are putting this acetyl group, ok.

So, that was the first step and the second step is the Baeyer Villiger oxidation. So, once you have the acetyl group acetate then O acetate it forms. Meanwhile the TMS is intact only one of them reacts, ok. So, with this he thought, ok. So, after he was successfully doing this, he thought he should extend this to real substrate and for that if he has to use this Baeyer Villiger oxidation.

The keto group which is present in D ring should be protected otherwise that keto group also can undergo Baeyer Villiger oxidation. So, his idea is now to get this keto group protected.

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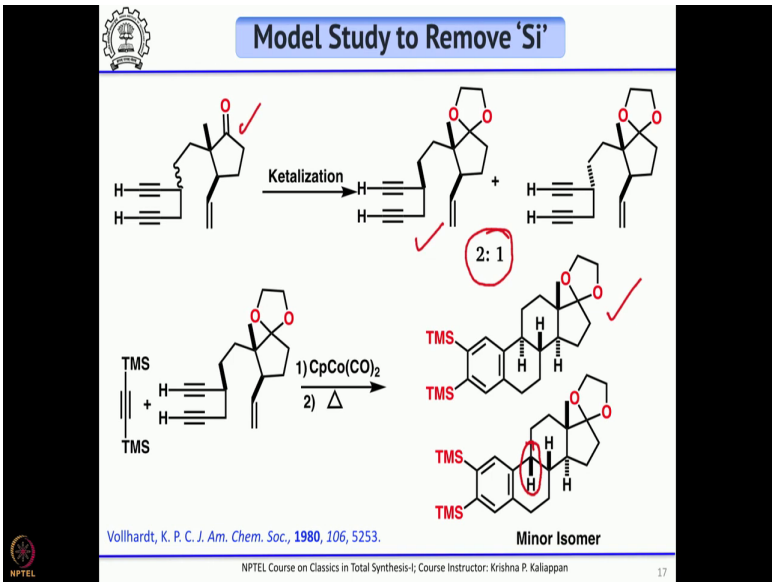

So, for that what he did? He started from the starting material before the cyclotrimerization then you protect the ketone as the ketal by treating with 1 2 ethane diol or ethylene glycol. So, now, you carry out the trimerization.

So, here what happen? When he did this, he could get 2:1 ratio of the required one then he did a cyclotrimerization and the cyclotrimerization gave this as the major product your required one as the major product and this where you can see unmounted series summers is the minor isomer, ok.

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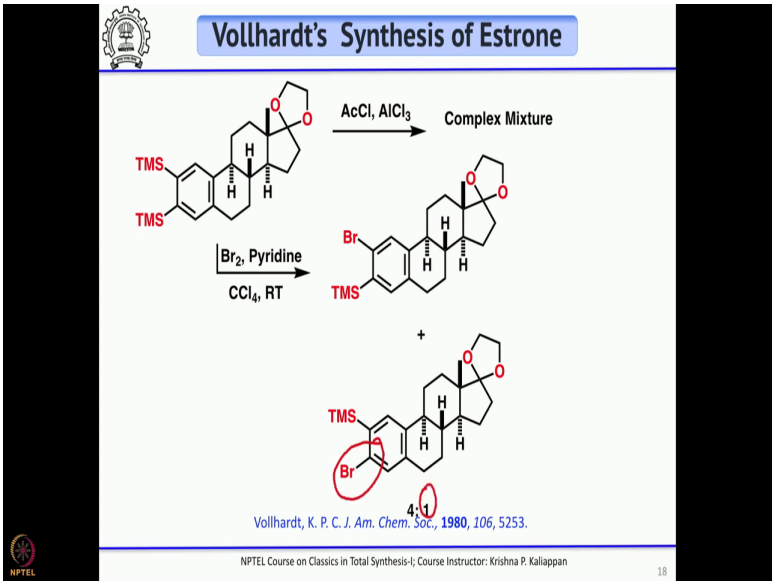

So, now the next step is to take the major isomer and treat with acetyl chloride and aluminum chloride ok, but contrary to the model system when he tried this reaction on this real system, he got complex mixture. So, again he has to revise.

So, what he did? He simply added bromine and pyridine. Bromine and pyridine because that is also known to replace the TMS group, ok. So, he wanted to know whether it can be selectively done. So, he we try to do this reaction with bromine and pyridine and here if you look at this, he got a mixture. Bromine which is at the required place because later this bromine should be replaced as OH that as the minor product 4:1 ok; that means, the required product is 1, ok.

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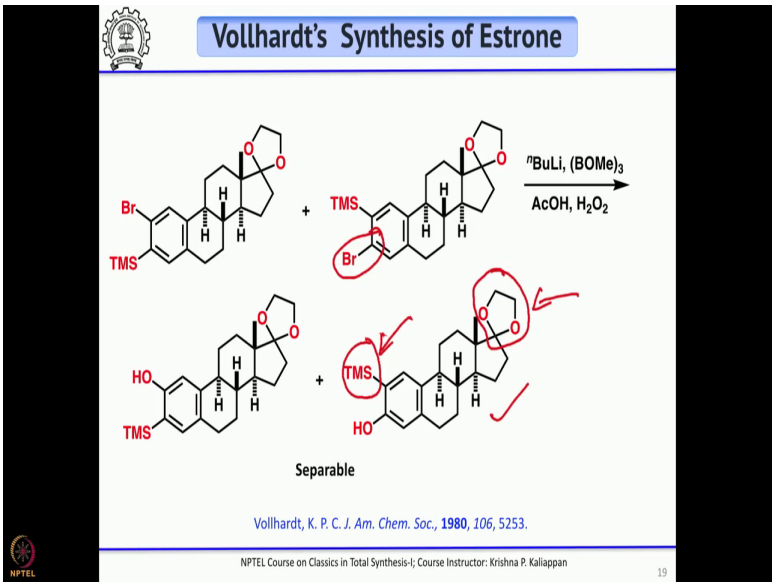

Nevertheless, he took the mixture and then tried to replace that ok, tried to replace it with OH. What you can do? You can treat with butyl lithium. So, once you treat with butyl lithium the C-Br bond will be exchanged and then you will get C-Li.

And then treat with trimethyl borate followed by treatment with acetic acid and hydrogen peroxide you can convert that into hydroxyl group ok, you can convert that into a hydroxyl group. So, now, he could separate at this stage. So, once you have polar group you know it is possible to separate.

So, he could separate this required compound and the next step is to remove the TMS as well as the ketal. If you can remove these two one is proto desilylation proto desilylation

other one is to remove the ketal. So, if you can do that then you achieve the total synthesis of estrone. So, that is very simple.

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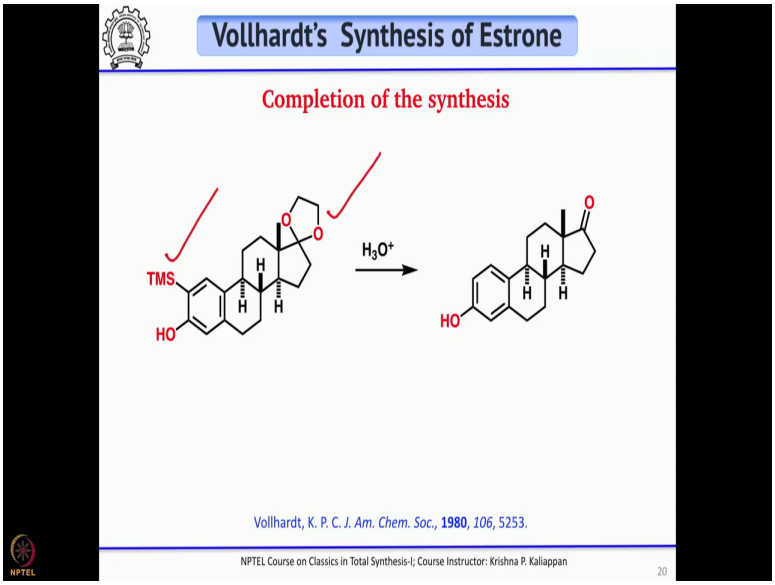

And after separating these two he took this compound that is required compound and then treated with mineral acid, ok. Once you treat with mineral acid dilute mineral acid. So, the ketal is removed and the TMS also is removed and that gives your estrone.

So, this is Vollhardt's completed the totals synthesis of estrone and here the key reactions which he used are cyclotrimerization then he also used electrocyclic ring opening of benzo cyclobutane followed by intramolecular Diels Alder reaction IMDA type I to construct the A B C ring, ok. So, with this I will stop here and then we will continue our discussion tomorrow, ok.

Thank you.