Classics in Total Synthesis-I

Prof. Krishna P Kaliappan

Department of Chemistry

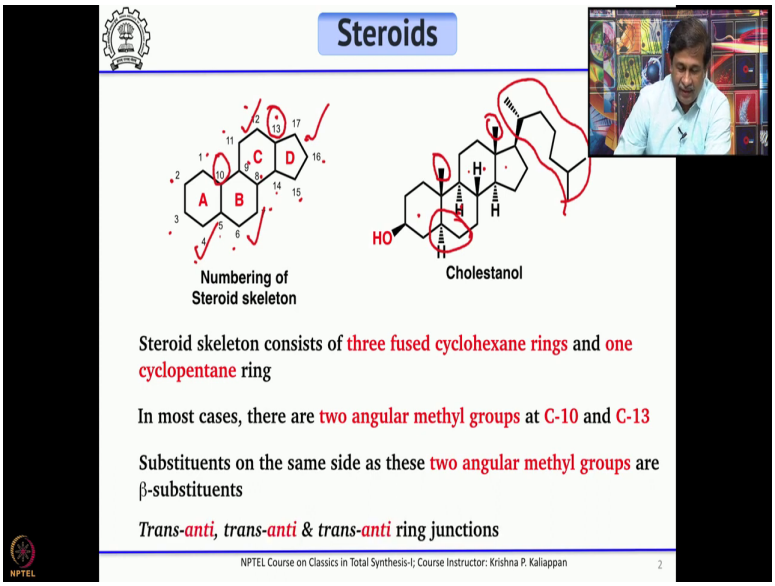
Indian Institute of Technology, Bombay

Lecture - 43

Progesterone

Good morning, this is Professor Krishna Kaliappan from Department of Chemistry IIT Bombay and welcome back to the NPTEL course on Classics in Total Synthesis. So, today what we will do we will talk about total synthesis of steroids, particularly one of the steroids called Progesterone. And, the next few days we will continue to discuss total synthesis of few more steroids.

(Refer Slide Time: 00:49)

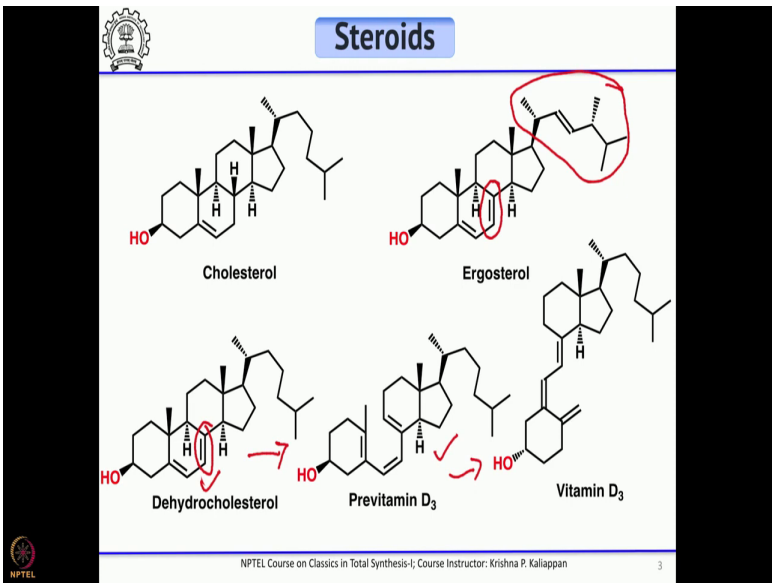


So, when we talk about steroids, you know the basic skeleton present in steroids has 4 rings 3 of them are 6 membered rings ok, you can see three A, B, C, they are all 6 membered rings and the D ring is 5 membered ok. The numbering of this steroid skeleton starts from the A ring, this is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10. First you number fully the A B ring, then go to C ring 11, 12, 13, 14, 15, 16, 17 ok. So, you can see there are 17 carbon atoms now.

Then, there are two angular methyl groups, one at carbon 13 and other at carbon 10 ok. Most of the steroids have these two angular methyl's at carbon number 10 and carbon number 13 ok. So, to give you an example so, this is a reduced version of cholesterol ok. Cholesterol has a double bond here, cholesterol has a double bond here. So, if you look at this you can see as I mentioned you have two angular methyl groups and the A B ring is transfused, likewise B, C also transfused and C, D also transfused and it has a long side chain ok.

So, this is the basic skeleton of most of the steroids ok. The A, B, C, D is common, but in some steroids you will see two angular methyl groups at C-10 and C-13 ok. And, usually these substituents that is the angular methyl groups are β, β means above the plane ok.

(Refer Slide Time: 02:47)



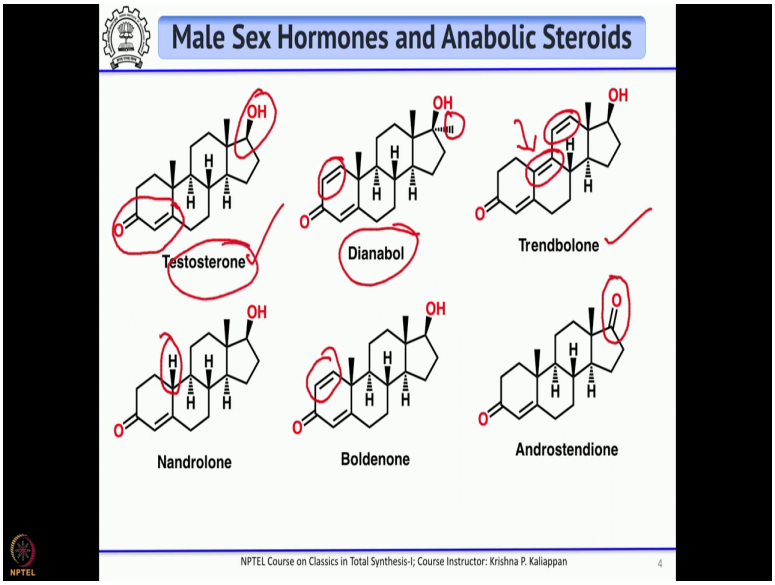
And, what are the well known steroids ok? So, this is cholesterol ok which we all have and if you introduce one more double bond ok. So, one more double bond and the side chain also ok. There is a change in the side chain, then this is called ergosterol ok. This is called ergosterol.

And, if you have only the extra double bond compared to cholesterol, this is called dehydrocholesterol dehydro; that means, you removed 1 hydrogen ok, dehydrocholesterol. From dehydrocholesterol ok, one can prepare vitamin D_3. This whole structure is called previtamin D_3. The previtamin D_3 is obtained from dehydrocholesterol ok, dehydrocholesterol by an electro cyclic ring opening reaction ok,

you can see. This is a cyclohexadiene and this is hexatriene ok. The electro cyclic ring opening of dehydrocholesterol you get previtamin D_3.

And, this previtamin D_3 becomes vitamin D_3 by [1,7] hydrogen shift by [1,7] hydrogen shift. Previtamin D_3 under photochemical condition gets converted into vitamin D_3. See all these are useful steroids.

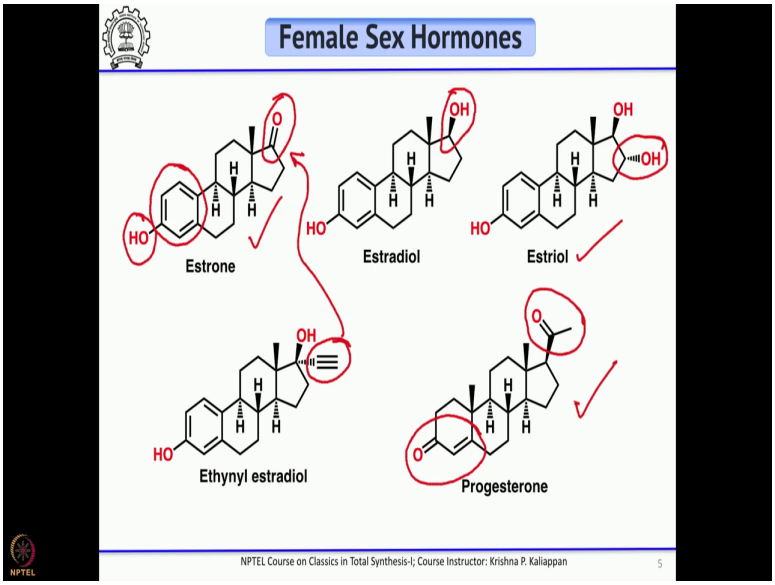
(Refer Slide Time: 04:13)



Then, we also have other sex hormones for example, male sex hormones, testosterone. So, the testosteron has enone in the A ring, enone in the A ring with the hydroxyl group in C,D ring. Then, there are some derivatives of that. So, the dianabol where you have extra double bond and extra methyl group in C D ring and trendbolone you can see you have two more additional double bonds and then angular methyl group is missing.

And, nandrolone is not having an angular methyl group at C 10 and boldenone has only one extra double bond and androstendione; that means, the hydroxyl group in D ring is oxidized. These are all derivatives of testosterone ok. These are all derivatives of testosterone which is the male sex hormone.

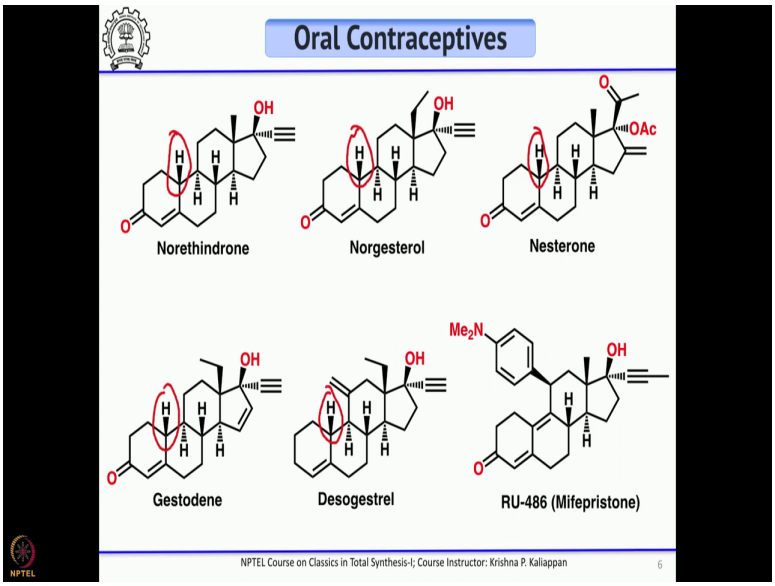
(Refer Slide Time: 05:17)



Then, coming to female sex hormone and its derivatives, estrone is the female sex hormone. Here, the A ring is aromatic, A ring is aromatic and you have a hydroxyl group at three position. Now, since the A ring is at of aromatic, the hydroxyl now is a phenolic hydroxyl ok and the D ring you have a ketone ok, that is called estrone. And, if you reduce the ketone, it is called estradiol. And, if you put one more hydroxyl group in D ring, this is called estriol.

Then, if you add a triple bond to the ketone here, if you add a triple bond to this ketone on estrone then you get ethynyl estradiol. So, these are all you know potential oral contraceptive. So, then we have progesterone ok, the progesterone again it is not aromatic. So, you have cyclohexanone and in the D ring instead of having a ketone or alcohol directly attached, you have acetyl group attached to the D ring ok. So, this is a major difference between progesterone and other female sex hormones.

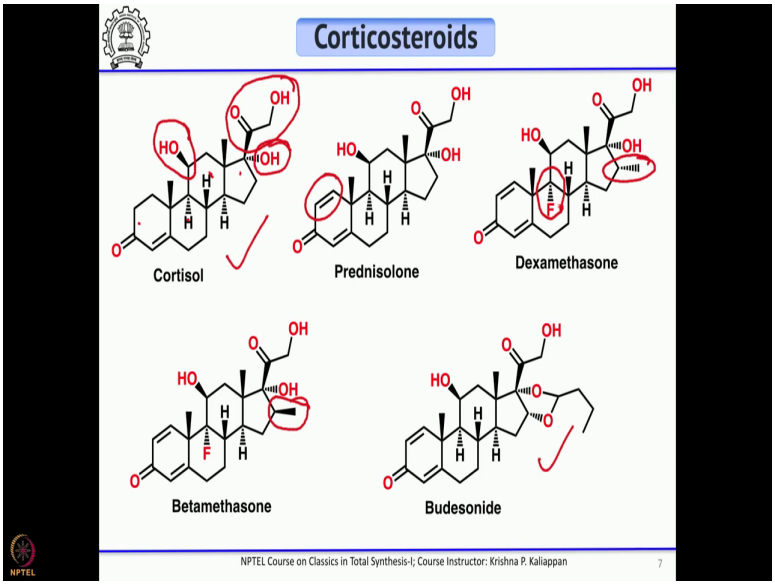
(Refer Slide Time: 06:39)



So, based on this several oral contraceptives were synthesized. These are all you know synthetic compounds ok, you can go through this leisurely. So, these are all well known, well known in the literature and most of them use birth reduction as the key reaction as you can see here.

There is no angular methyl group; that means, they all start from the aromatic compound and then do birth reduction followed by hydrolysis to get this compound ok. So, the starting material; obviously, has to be estrone, from estrone they make all these oral contraceptives.

(Refer Slide Time: 07:17)

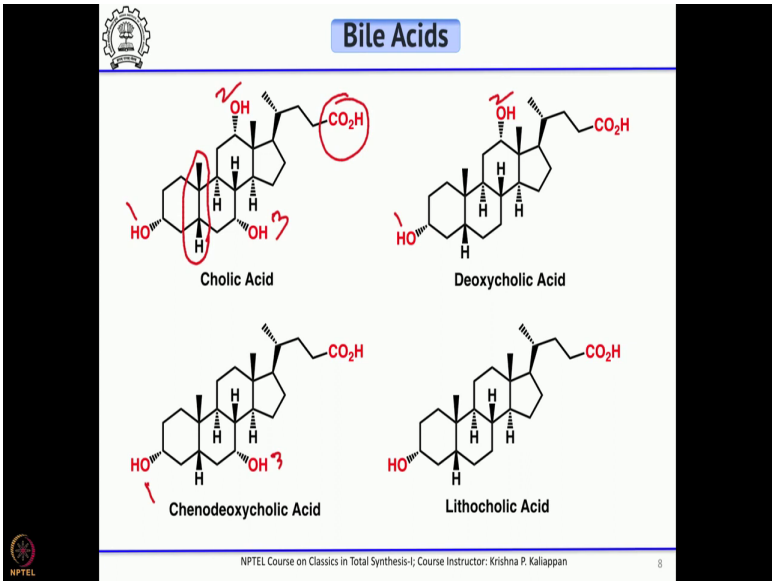


Then we have corticosteroids and the basic unit is cortisol ok. Again, you have the same A, B, C, D ring, but you have an additional hydroxyl group here, you have additional hydroxyl group in C ring. Normally, you in other steroids you do not see a functional group in C ring ok, only in corticosteroids you will see a functional group in C ring. And, in the progesterone you had -CO-CH_3, now it is -CO-CH_2-OH and also another -OH attached to the same carbon in D ring ok.

And, in prednisolone ok you have additional double bond in A ring and dexamethasone, you can see a very important group fluorine, fluorine in B ring and you also have additional methyl group ok, dexamethasone. During, the COVID treatment initially people were given dexamethasone. So, this is the structure and β methasone is an ointment normally given for skin treatment ok; generally if people have psoriasis or related diseases.

So, they give a β methasone which you can apply. So, that is also related to dexamethasone, only thing is you have β methyl group ok. Then budesonide, this is very interesting steroid, normally given for people with asthma. They can inhale taking this budesonide. So, all these are very very important steroids which are given for various treatments ok.

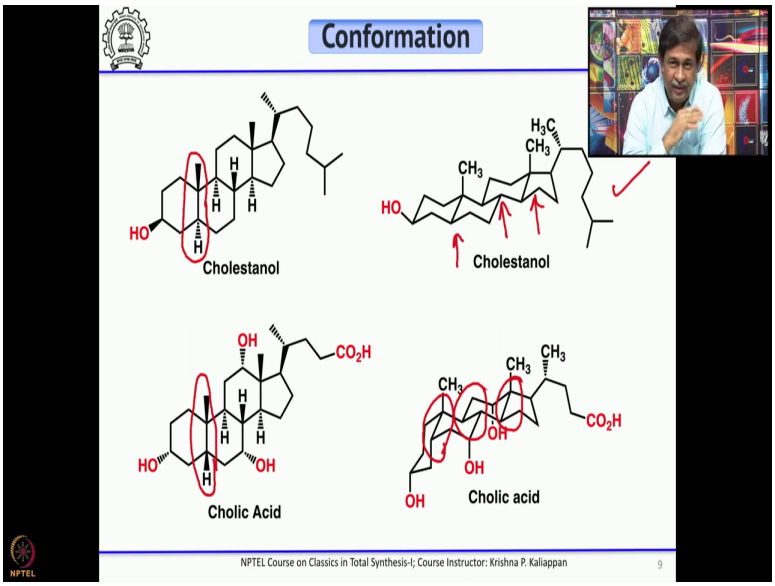
(Refer Slide Time: 09:07)



Then, we have bile acids. So, the bile acids the main difference is the A-B ring junction. If you look at all other steroids which we discussed, the A-B ring junction is trans whereas, in bile acids the A-B ring junction is cis. So, if we have 1, 2, 3 hydroxyl, 1 carboxylic acid, it is called cholic acid.

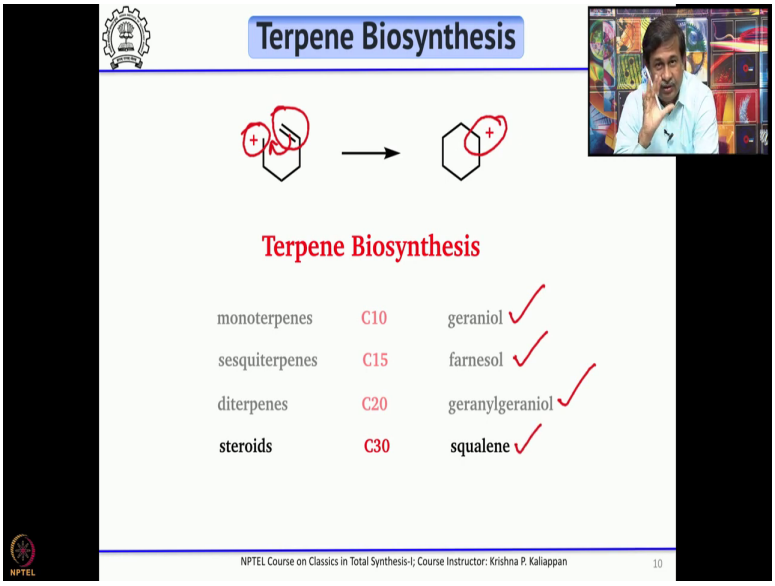
And, if we have 2 hydroxyl 1 and then 2, A and C ring then it is called deoxycholic acid. And, if we have same 2 hydroxyl, but in A and B ring, then this is called chenodeoxycholic acid. And, if you have only 1 hydroxyl that too in A ring, this is called lithocholic acid ok. There are 4 bile acids which you should remember.

(Refer Slide Time: 10:04)



And, when you talk about confirmation, cholestanol that is of reduced form of cholesterol have trans ring junction, isn't it? So, the most stable confirmation of cholestanol is this *trans* decalin, *trans* decalin and again *trans* hydrindane system. Whereas, in cholic acid as I said the A B ring is *cis*, the A B ring is cis so, you can see this is a cis decalin and this is a *trans* decalin and this is *trans* hydrindane ok. So, only A B ring is cis fused and all other 3 rings are trans fused ok.

(Refer Slide Time: 10:55)

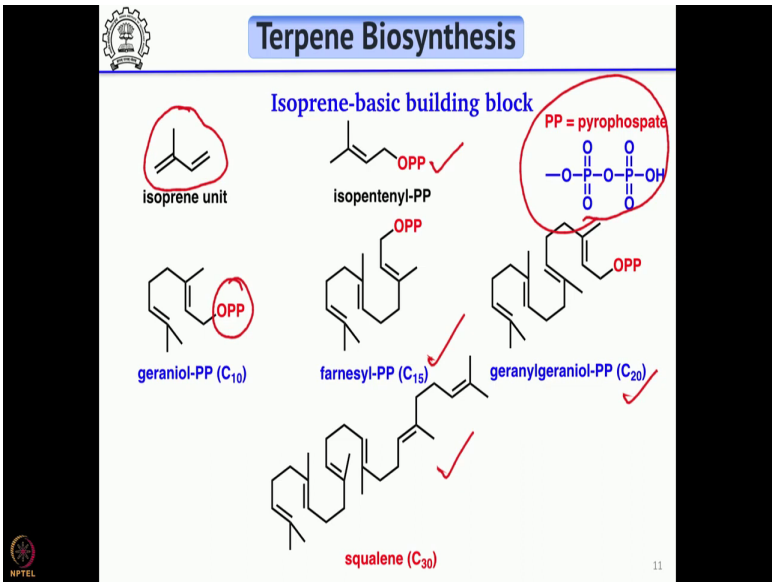


So, with this brief introduction so, now, let us see how steroids are synthesized in nature ok. Before that, before steroid let us start with biosynthesis of simple terpenes ok, mono terpenes, sesquiterpene, diterpene then go to steroids. So, normally if we have a double bond like this and a carbocation which is within the reachable limit, then the double bond can try to neutralize the positive charge and generating a ring as well as a carbocation. So, this is how in nature cyclization takes place to form a ring.

Somewhere carbocation is formed or you have a good leaving group, once the leaving group is ready to leave, the double bond can migrate and generate a carbocation. So, this is the basic principle in many terpenes and steroid biosynthesis. So, if you talk about C-10, then they are called monoterpenes. If you talk about C-15, that is 15 carbon atoms they are called sesquiterpene.

And, if you talk about C-20, they are called diterpenes and C-30 we can talk about steroids. For all this, there is a starting material in nature ok. So, geraniol if you start with geraniol, then that can lead to all monoterpenes and if you start with farnesol that can lead to all sesquiterpenes. And, if you use geranylgeraniol then that can lead to all diterpenes. Likewise, if you start with squalling that can lead to all steroids, that is how all the biosynthesis are you know working.

(Refer Slide Time: 12:49)

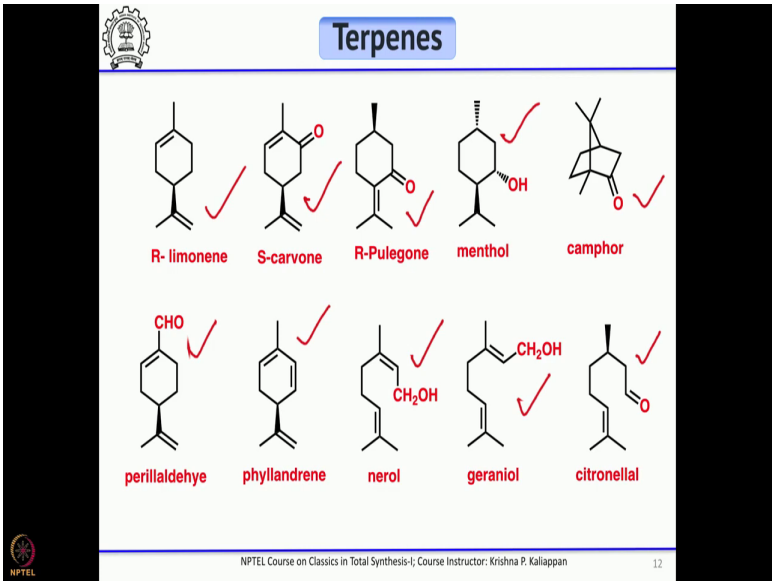


What is the basic building block? If you look at terpene or steroid, the basic building block is isoprene ok. The basic building block is a 5 carbon unit called isoprene, but in

nature isoprene is in the form of isopentenyl pyrophosphate, isopentenyl pyrophosphate. This is pyrophosphate. So, it is a good leaving group, basically it is a good leaving group. So, that you know if you have geraniol and then this is geraniol pyrophosphate.

So, this is the starting material in nature for making all mono terpenes and this is farnesyl pyrophosphate, you can see there are 15 carbon atoms. So, this is the starting material for sesquiterpenes, this is C-20 geranylgeraniol and that is a starting material in nature for diterpene. This is squalene which has 30 carbon unit ok. So, that is the starting material for all steroids ok. So, first let us see how these are all made in nature, then we will talk about synthetic approach to steroids ok.

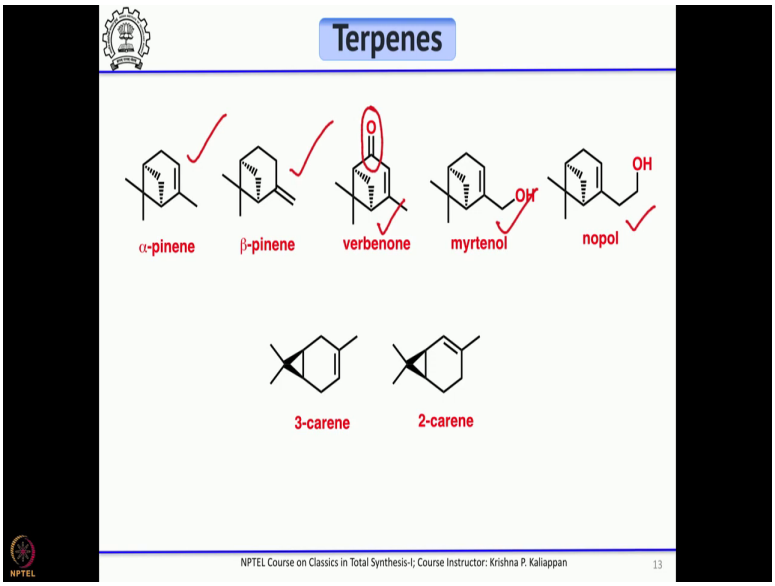
(Refer Slide Time: 14:10)



So, when you talk about monoterpenes, there are many monoterpenes just I am giving only few examples: a limonene, carvone, pulegone, menthol, camphor; I am sure all this you will know ok. You might have heard limonene, carvone, pulegone, menthol, camphor even citronellal you should know, geraniol you should know, nerol you know. These two phyllandrene and perillaldehye you may not know ok.

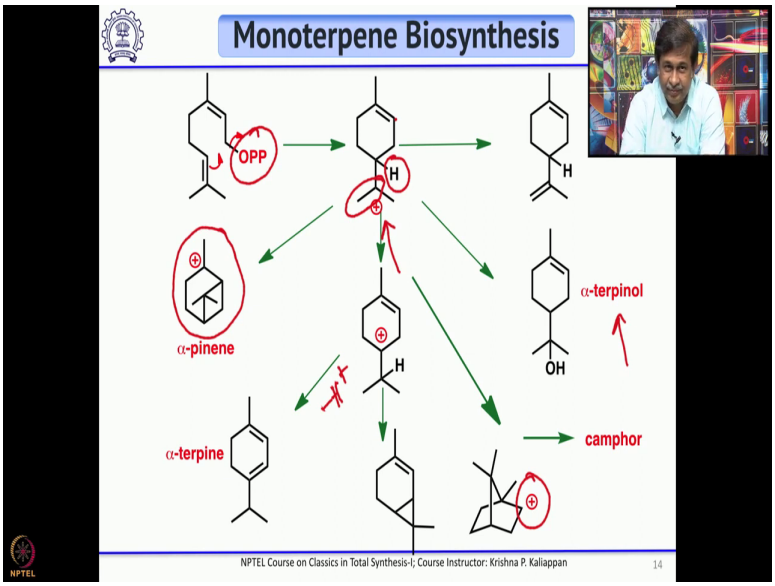
So, these are all you know reasonably well known monoterpenes. Why I am insisting these monoterpenes are important, because they are used as chiral starting material for synthesis of several natural products ok. Most of them most of them are chiral ok, except nerol and geraniol most of them are chiral and they are used as starting material for synthesis of many other natural products.

(Refer Slide Time: 15:08)



And, some more monoterpenes you know α pinene and β-pinene and if you do a do allylic oxidation of α-pinene, you get verbenone. And, then if the allylic oxidation takes place at the methyl group, this is called myrtenol. The nopol is a homologated hormone of α-pinene, then you also have 3-carene and 2-carenes. All this you see they are monoterpene ok.

(Refer Slide Time: 15:33)



How monoterpenes are synthesized in nature? What is the biosynthetic pathway? As I said the starting material in nature for monoterpene is geraniol pyrophosphate. So that

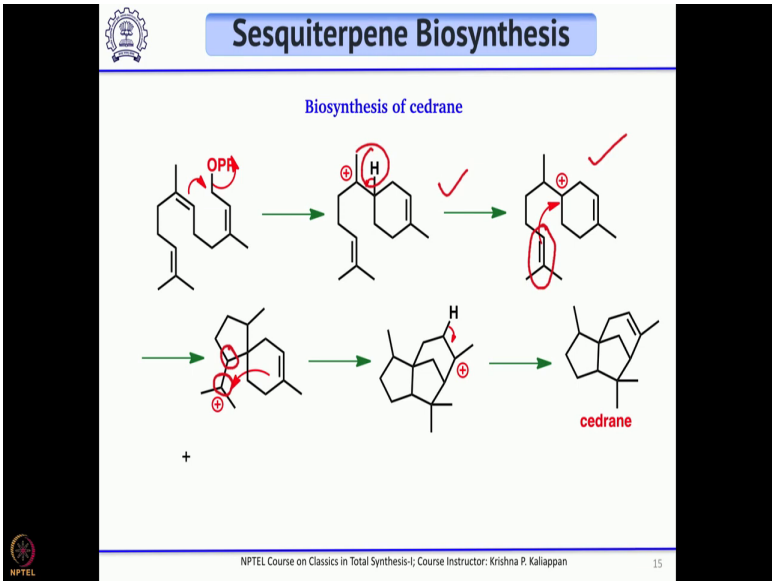
means, this is a good leaving group, this is a good leaving group which means that you can generate a carbocation line. So, this double bond which is very close to this can migrate and then pyrophosphate can move that will lead to this tertiary carbocation ok.

So, once this tertiary carbocation is formed, there are many further rearrangements possible ok. So, if your proton is lost then you get limonene. This is called limonene. And, here once the carbocation, if the double bond here the double bond here neutralizes a positive charge, then you get this intermediate. And, this intermediate one can convert later by loss of proton to give α-pinene or β-pinene. If exocyclic double bond is formed, that is β. If endo cyclic double bond is formed, then it is α-pinene ok.

Then, direct attack of water will give you α terpinol, direct attack of water to neutralize the positive charge you get α-terpinol. If the hydrogen migrates, if the hydrogen migrates then you get another tertiary carbocation ok. So, that will lead to the formation of 3-carenes and 2-carenes ok. And, here the double bond when it migrates there are two possibilities; one the formation of this pinene precursor, other one the formation of camphor precursor.

Once you have this carbocation water can attack followed by oxidation, it can give camphor ok. Then, simple loss of proton, simple loss of proton will give α-terpinol. So, basically if you look at all this biosynthesis, the starting material is geraniol pyro phosphate ok that is for monoterpene.

(Refer Slide Time: 17:52)



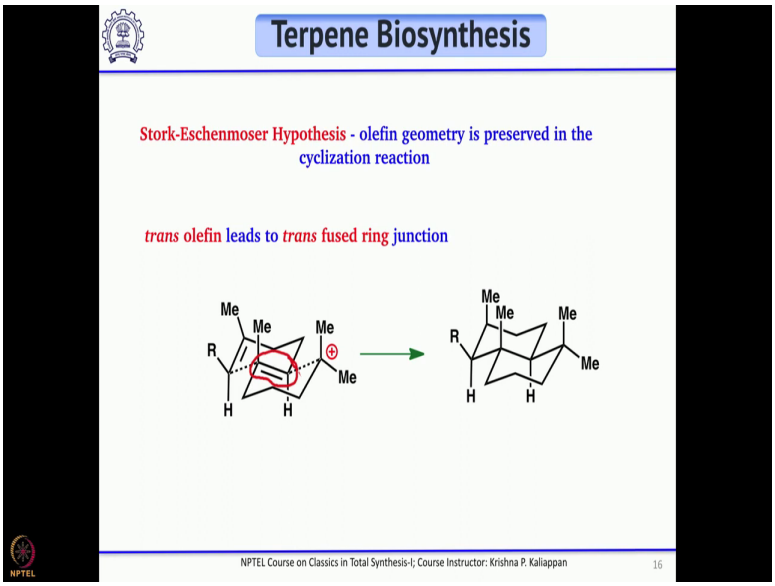
For sesquiterpene, as I said farnesyl pyrophosphate is the starting material ok. Again, the same way the pyrophosphate goes out and then you get a 6 membered ring with a carbocation ok. So, now what can happen? This hydrogen can migrate, if that migrates the carbocation comes to the 6 membered ring ok, carbocation comes to the 6 membered ring. Then, you have a double bond here ok, this double bond can neutralize the positive charge.

If that happens you get a spiro system, you get a spiro system and this will lead to a range of sesquiterpenes. They are called acorns ok and it depends on which double bond which side of the double bond neutralizes a positive charge. If this carbon neutralizes that will lead to at sesquiterpene type called acorns. And, if this carbon neutralises that will give another class of sesquiterpenes called chamigrene ok.

So, all these start from the same starting material. Now, you have another double bond, isn't it; that double bond can neutralize this, that double bond can neutralize the positive charge, that will give you this intermediate, now a loss of proton will give a sesquiterpene called cedrane ok. Please remember so, this is these two are the key intermediates ok, key intermediates that can lead to ok all mono sesquiterpenes. These two are the key intermediates that can lead to all sesquiterpenes ok.

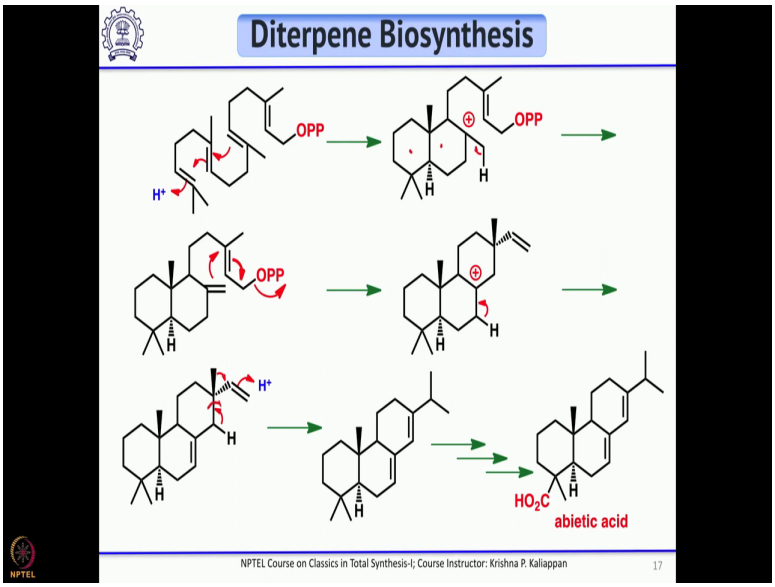
What is important is when you do cyclization, when you do cyclization whether the stereochemistry of the double bond will be preserved or not. According to Stork and Eschenmoser, whatever geometry your olefin has before the cyclization that will be preserved ok. If we have a *trans* olefin then after cyclization what you get is transfused ring and if you have cis olefin, you will get cis fused ring.

(Refer Slide Time: 20:20)



So, this is what they they write, you can see the center one is a *trans* double bond, can you see? It is a trans double bond. Now, after cyclization it forms a *trans* decalin system, basically the *trans* double bond geometry is preserved in the final product.

(Refer Slide Time: 20:46)

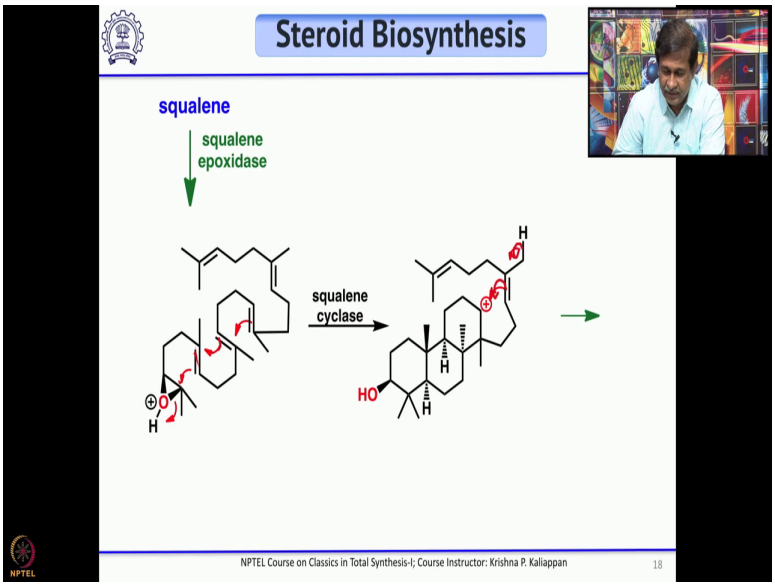


For, diterpene you have to go to geranyl, geraniol pyrophosphate and again the same way it can protonate and then you form the A-B ring. Now, the carbocation is here, then loss of proton will form a double bond. Then, what happens the double bond will attack and

this double bond will come and then pyrophosphate goes and you get this intermediates ok.

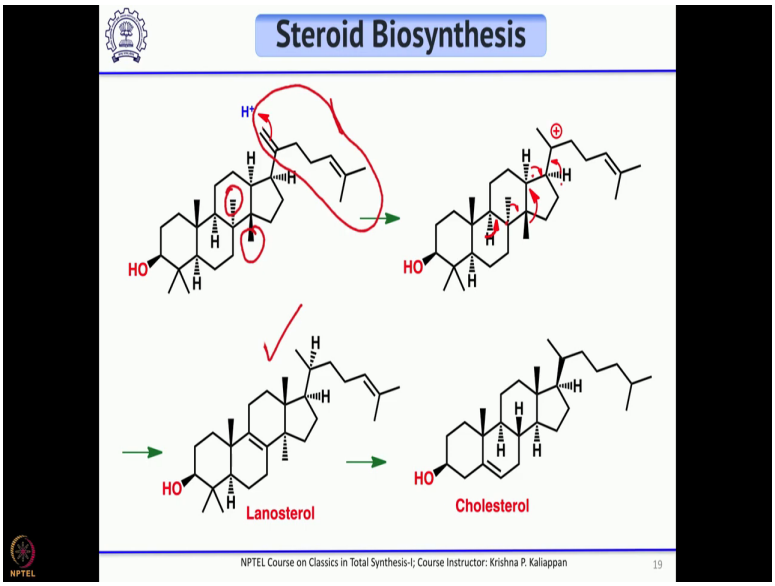
The next step is very interesting, the hydrogen from here is lost and you get a internal double bond ok, you get an internal double bond. Now, this internal double bond ok, another internal double bond is formed because of conjugation through this mechanism ok and that leads to a natural product called abietic acid, that leads to a natural product abietic acid. And, this is the key transformation and from here one can think of converting this abietic acid into many diterpenes. From diterpenes now we will move to steroid.

(Refer Slide Time: 22:02)



So, steroid it start with squalene and squalene epoxidaze enzyme epoxidases the terminal alkene ok. Now, a protonation takes place, once the protonation takes place the epoxide will open and then series of double bond migration will take place, that will lead to this carbocation. You can see the epoxide opens, then this double bond migrate, this double bond migrate, this double bond migrate and you get a carbocation. So, now what will happen? Again, ene type reaction will take place, ene type reaction will take place to neutralize the positive charge.

(Refer Slide Time: 22:44)



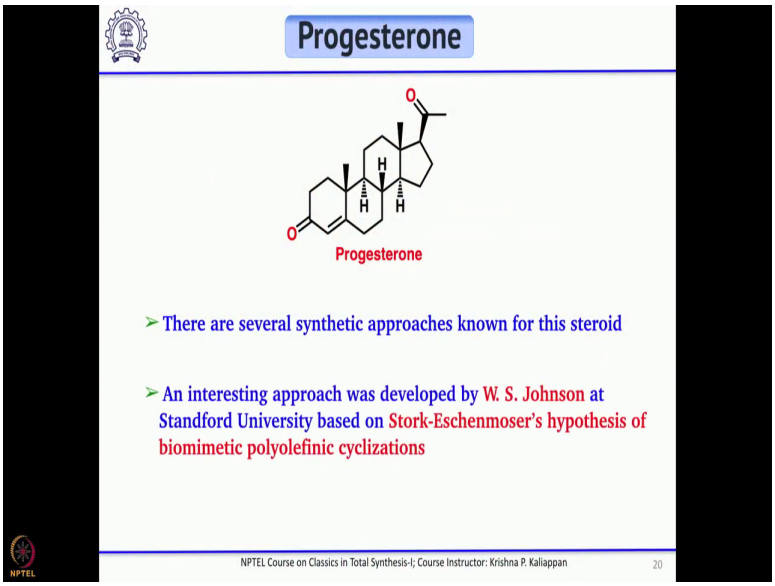
So, that will give you steroid skeleton with the double bond with the side chain, you can see a side chain. But, what you do not need is you have a methyl group here and this methyl group should go to this position. So, basically what you have to do again you have to protonate this carbon, you protonate this carbon ok, then you get a carbocation ok.

Then, what will happen? Series of migration takes place. First, this hydrogen will migrate, this hydrogen will migrate followed by migration of this hydrogen. Then, methyl group, this methyl group and loss of proton you get this compound and this is called lanosterol ok. Then, series of oxidation, decarboxylation takes place to give cholesterol ok. The key intermediate formed in the steroid biosynthesis is lanosterol, from lanosterol all other steroids are formed ok.

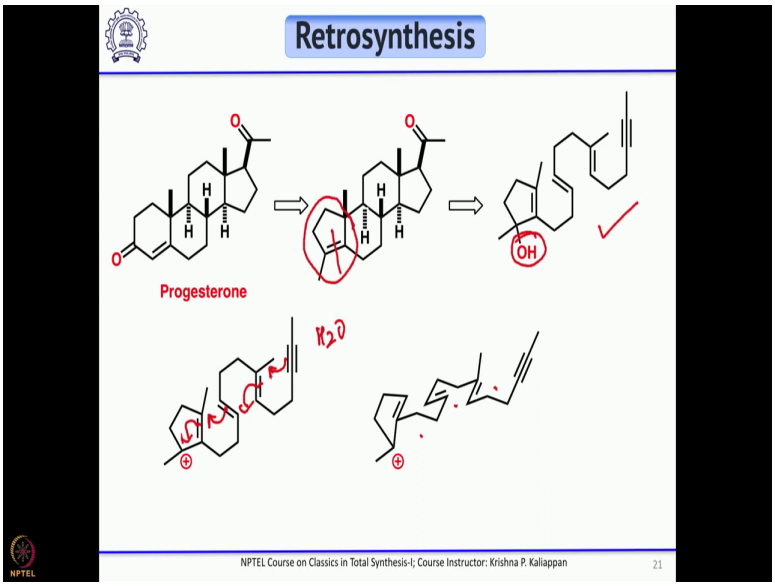
So, why I thought I should give a brief introduction to biosynthesis of steroids, before that biosynthesis of terpenes its important from the synthetic point of view whether can we follow what nature has been doing. So, that we can prepare the starting material and try to replicate what nature is doing ok. So, that we can call it as bio mimetic synthesis, you are just trying to mimic what nature is doing ok.

So, there was one synthesis of progesterone reported long time ago, more than 50 years ago by W S Johnson, where he exactly followed the principles adopted by nature to make progesterone ok. So, that is why we call it as biomimetic synthesis yeah.

(Refer Slide Time: 24:46)



(Refer Slide Time: 24:51)



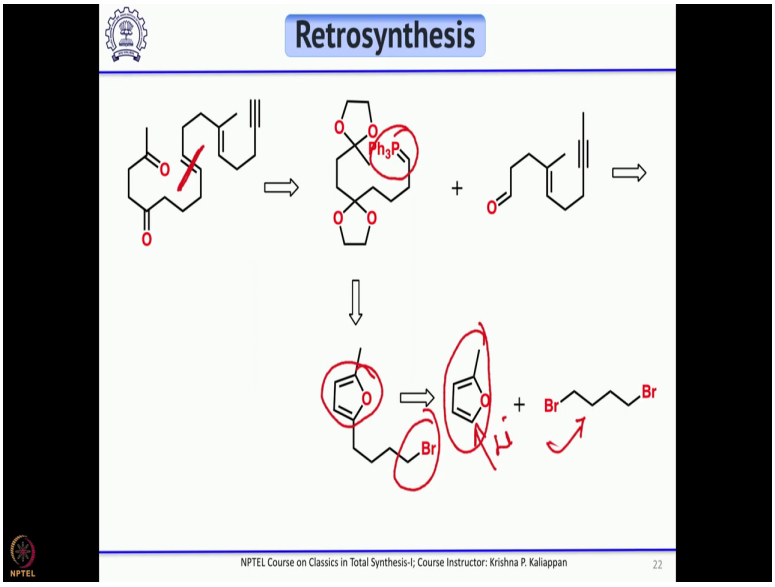
So, here the retrosynthesis is like this. So, when you have progesterone, this can be obtained from this 5 membered ring ok. How? If you cleave this double bond, you get a di ketone that is 1,5 diketone. This 1,5 diketone upon aldol reaction can give progesterone ok. Now, how you can get this 5 membered ring. So, this is where he wanted to use this bio mimetic reaction.

So, here if it forms a carbocation, the tertiary alcohol upon protonation you get a carbocation. Then, this bond will migrate, this bond will migrate, this bond will migrate,

this bond will migrate. Then, water will attack that will give you the corresponding ketone ok. And, this is how you know the chair like transition states, chair like transition state, chair like transition state ok.

So, basically what you need to do is you have to prepare this tertiary alcohol. How you can prepare this tertiary alcohol? Ok. This preparation of tertiary alcohol is quite easy ok and if you have a ketone, then you can prepare the Grignard addition will give the tertiary alcohol.

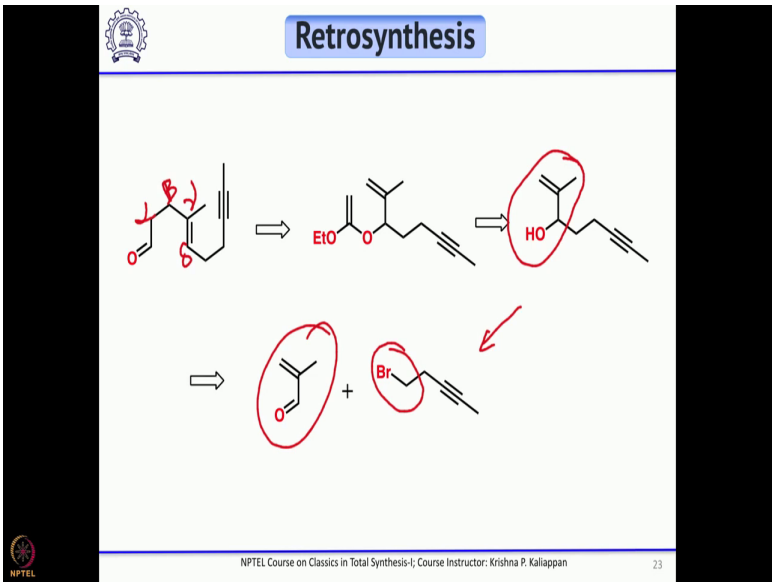
(Refer Slide Time: 26:09)



And, this 5 membered ring can be obtained from this diketone ok. This diketone just aldol reaction will give 5 membered ring, followed by Grignard addition you will get the tertiary alcohol. And, this can be obtained by a Wittig reaction ok, if you break this bond you can generate, you have the Wittig salt and this aldehyde ok and this Wittig salt can be made from this corresponding bromide.

So, the bromide is used for making the Wittig salt and this furan, furan normally as you know you can make it from 1,4 diketone. So, if you treat with acid, furan will open up and then you get corresponding 1,4 diketone, that in situ if you protect it with ethylene glycol, you get this compound. Then, the other aldehyde can be obtained by Claisen rearrangement. And, before that this can be easily obtained from 2 methyl furan and then you generate lithium species and quench with this 1 3, what is a 1 4 dibromo compound.

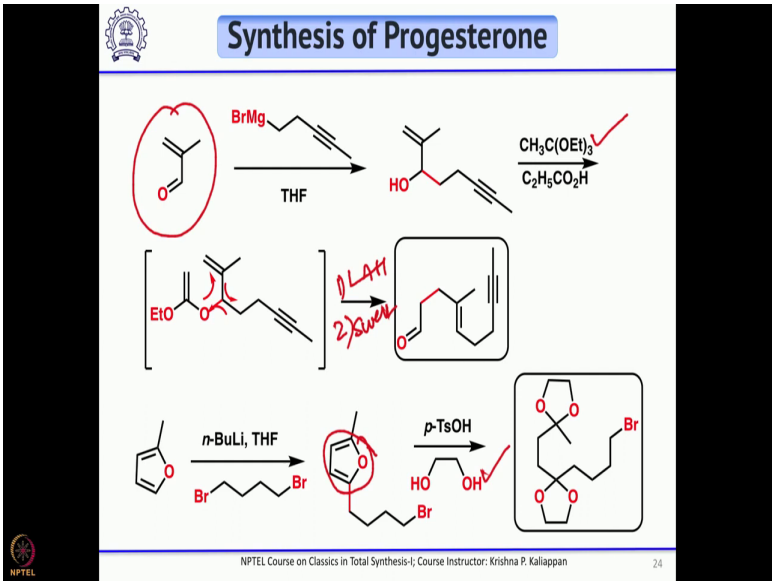
(Refer Slide Time: 27:21)



The other aldehyde can be easily prepared, if you look at this aldehyde it is α, β, γ, δ. So, γ-δ unsaturated aldehydes normally you know prepared from allelic alcohol *via* Claisen rearrangement ok. This is called Johnson ester Claisen rearrangement.

So, you can get this aldehyde from this, you will get an ester, that ester can be converted into aldehyde. So, now, that can be prepared from this allylic alcohol and that allylic alcohol can be prepared from this α- β unsaturated aldehyde and the Grignard reagent. So, it is a very very simple retrosynthesis.

(Refer Slide Time: 28:04)

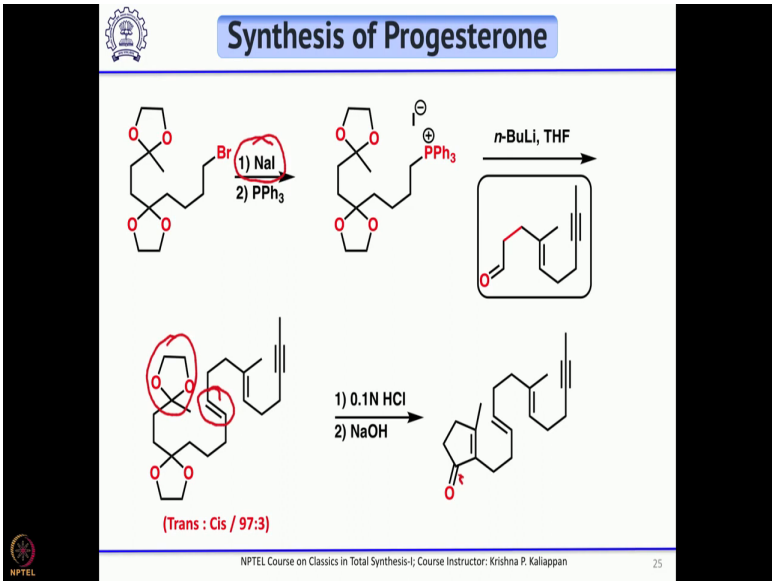


And, the synthesis started with this aldehyde and you do the Grignard reagent, in THF you get the allylic alcohol which is required for the Johnson Claisen rearrangement. So, for that you treat with triethyl orthoformate with catalytic amount of propionic acid, very important. You cannot use excess otherwise it will form corresponding ester ok, very very catalytic amount of propionic acid and it forms this intermediate ok.

Once you have this intermediate as you can see here this is a 1,5 diene, it can undergo the Claisen rearrangement to give the corresponding actually ester; that ester is reduced and oxidized to get the corresponding aldehyde ok. In two steps, after this you have to reduce with LAH one, then oxidize under Swern condition you get the aldehyde.

Once you have this aldehyde, then the other side can be easily prepared from 2 methyl furan, treat with butyl lithium and 1 4 dibromo butane and mono alkylation takes place. Now, if you treat with p-Ts para toluenesulfonic acid, it opens up the furan to give 1 4 di ketone and then 1,4 diketone is in situ protected by ethylene glycol, in situ protected by ethylene glycol.

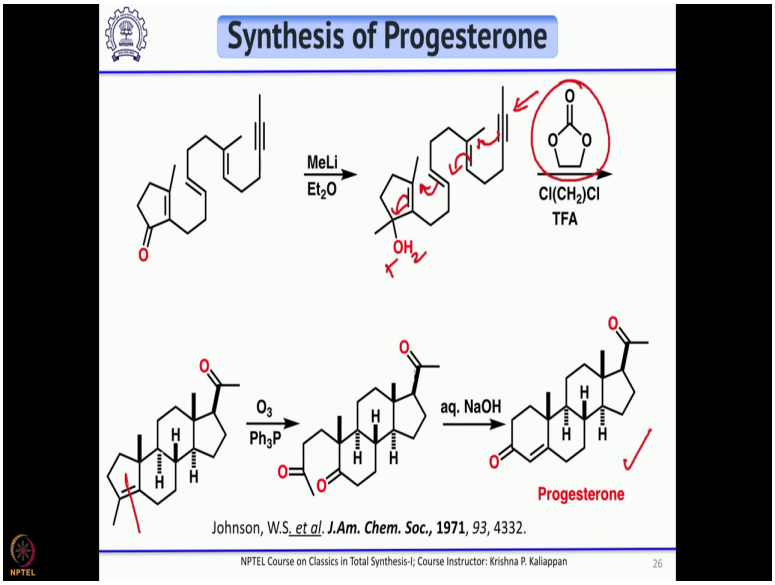
(Refer Slide Time: 29:36)



So, with this now you have the bromide and then using Finkelstein reaction you exchange that with sodium iodide and then tri phenyl phosphine, you make the Wittig salt. Now, treat with n butyl lithium, you generate the, elide then add this aldehyde and you get this alkene. So, you get a mixture of trans and cis and where *trans/cis* 97:3. So,

once you have that now remove the ketone, remove the ketone and then treat with sodium hydroxide you get the aldol product ok, the cyclopentanone.

(Refer Slide Time: 30:22)



So, what is left now? You have to add the Grignard reagent. So, you can add either Grignard or you can add methyl lithium to get the tertiary alcohol, now you treat with the acid ok, trifluoroacetic acid and quench with this compound ok. So, as I said here protonation will take place, this double bond will migrate, this double bond will migrate, this double bond will migrate, then triple bond will migrate, then water will attack; you get the corresponding ketone ok.

Now, from here to progesterone is very simple, ozonolysis will give the di ketone ok, ozonolysis will give the di ketone. Now aldol reaction ok, simple aldol reaction will give you the corresponding natural product that is progesterone. So, here the advantage of this method is just follow the nature, where you can carry out the polyene cyclization under acidic condition and followed by ozonolysis and aldol reaction one can get progesterone.

So, this is one of the classical synthesis of one of the steroid molecules called progesterone. In subsequent lectures, we will discuss about a more steroids and more total synthesis of steroids ok.

Thank you.