Classics in Total Synthesis - I
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Lecture - 35
Morphine (Parker and White)

So, good morning in the last lecture we talked about total synthesis of morphine by Gates and Larry E Overmans group. So, today we will continue our discussion on the total synthesis of morphine by two more groups.

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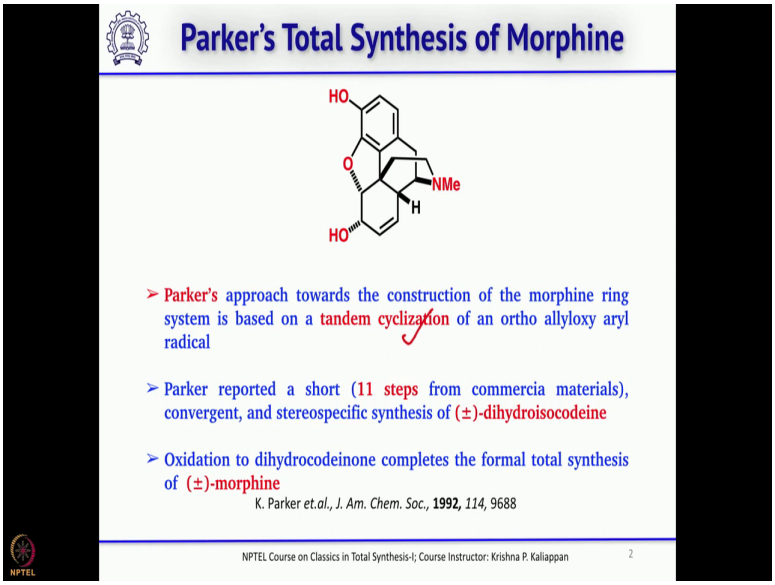

The first one is from Parkers group and the second one is from James White and in the case of Parkers total synthesis he has used a tandem cyclization where you generate a radical. So, that undergoes 6 endo and when it comes back it removes the phenylthiol radical and overall, he took about you know 11 steps to complete the total synthesis of morphine from commercially available Isovanillin. Let us see his retrosynthesis and how he has planned this synthesis using the key radical cyclization reaction.

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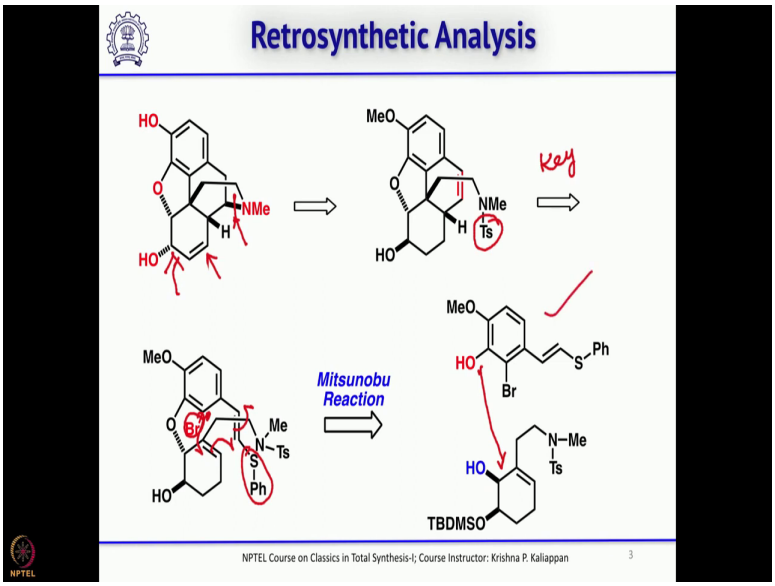

So, the first disconnection is this bond where this can be introduced using a hydroamination reaction. First you remove the tosyl group followed by intramolecular hydroamination, one should one should be able to introduce this particular bond. As well as you know later one has to introduce this double bond, for that you have a hydroxyl handle; so, that can be used to introduce the double bond.

Then this is the key reaction, the key reaction is 5 exo key radical cyclization reaction you have a bromine; so, it can generate a radical here. So, that radical can add first 5 exo then this can add a 6-endo ok, 6 endo and to form this radical that radical when it comes back this thio phenyl group will go out. So, that is how the tetracyclic core structure of morphine was planned. And this can be obtained by a simple Mitsunobu reaction on this alcohol the this corresponding phenol is the nucleophile ok.

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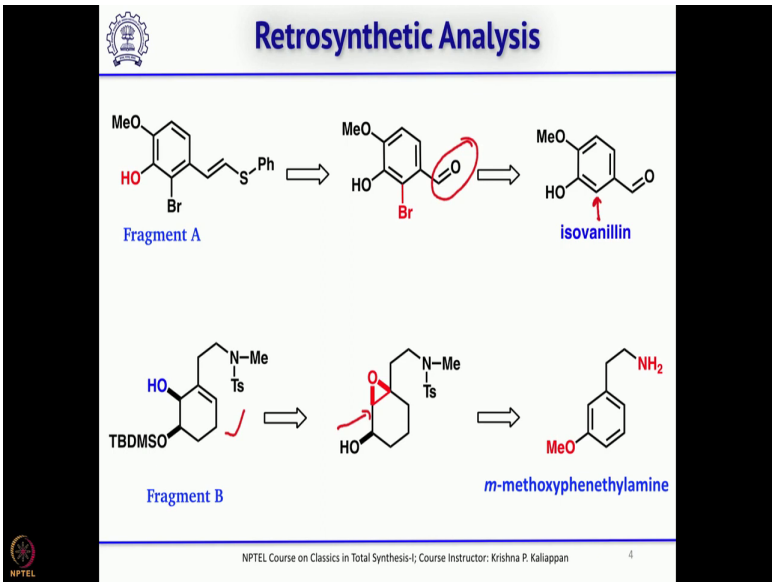

And further retrosynthesis the fragment A can be obtained from isovanillin in few steps where basically you have to introduce a phenyl group and then homologate the aldehyde. The other fragment that is fragment B can be obtained from this epoxide where you know you have to you know if you open this epoxide, you will get this allylic alcohol. And this can be obtained from meta methoxy phenethylamine using Birch reduction and hydrolysis as key steps ok.

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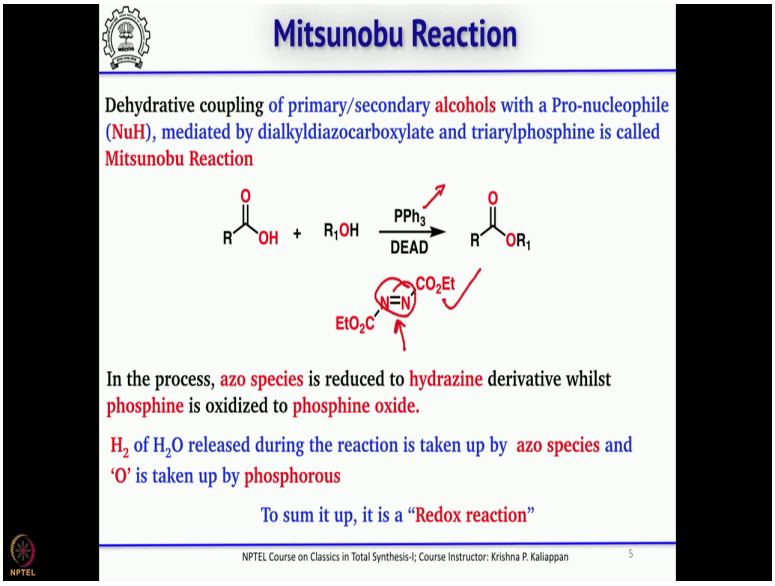

So, what are the key reactions? One is Birch reduction which we have already discussed, the other key reaction which is used is Mitsunobu reaction. So, Mitsunobu reaction is nothing but another method for making ester. You start with the carboxylic acid and then treat with alcohol in the presence of triphenylphosphine and diethyl azodicarboxylate you form the corresponding ester. This is the diethyl azodicarboxylate one can also use di isopropyl diazo carboxylate.

So, basically what happens in this reaction, this diazo will be reduced to get the corresponding hydrogen derivative and the triphenylphosphine will be oxidized to triphenylphosphine oxide. And the overall process of esterification from carboxylic acid and alcohol is after forming the ester you get a water molecule. From the water molecule hydrogen goes to this is the diethyl azodicarboxylate and then oxygen goes to triphenylphosphine oxide.

Basically, it is a dehydrating reaction and one can also call it as redox reaction, because the reagents which we use for this particular transformation is DEAD and triphenylphosphine, the triphenylphosphine gets oxidized and DEAD gets reduced. So, during this redox reaction your alcohol and carboxylic acids are coupled to form the corresponding ester.

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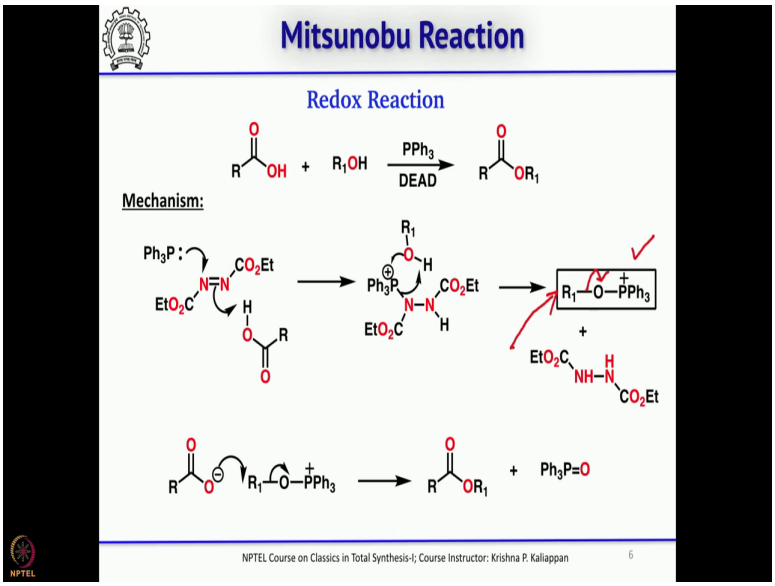

The mechanism is first the triphenylphosphine attacks the nitrogen of diethyl azodicarboxylate. Then the other nitrogen picks up hydrogen from carboxylic acid; so,

you get carboxylate anion and the positive charge is on the triphenylphosphine. So, now, the other substrate oxygen of the hydroxyl group attacks the triphenylphosphine; so, you get $ROPPh_3$ +.

So, this is the key intermediate in the mechanism for Mitsunobu reaction as well as many related reactions. So, this R_1 the nucleophile can attack the R_1 from the backside; so, that the R-O bond can easily break to form triphenylphosphine oxide. So, that is why this attack of RCO_2 minus is an S_N2 reaction ok. So, the carboxylate attacks the R 1 from the back side and that forms the ester and triphenylphosphine oxide ok.

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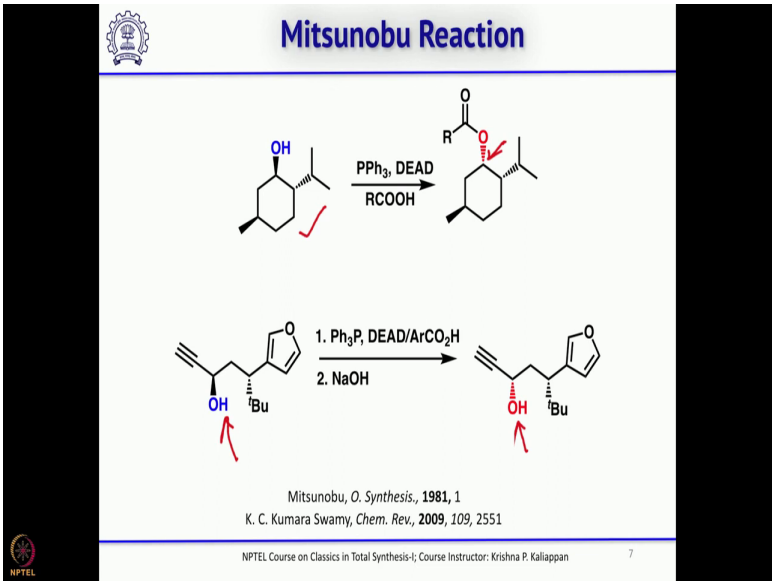

Here are some examples where you can see this is the menthol; so, one can do Mitsunobu reaction and look at the stereo center it is exactly opposite. Similarly; so, this is again that secondary alcohol and you do Mitsunobu reaction and followed by hydrolysis, if you hydrolyze then you get the completely inverted hydroxyl group ok.

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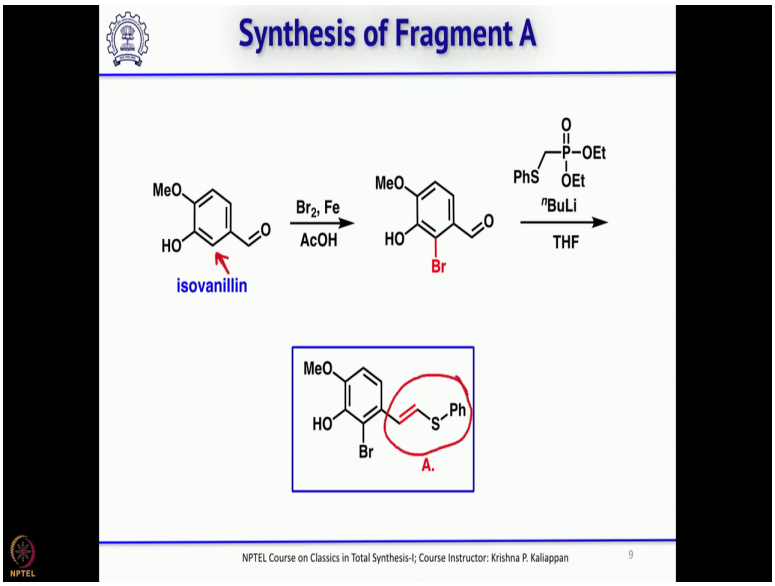

So, how the fragment A was synthesized by parker, he took isovanillin and then brominated at this carbon using bromine and ion. Then he did this stabilized Wittig to get the corresponding thio enol ether ok; so, that is the fragment A which is used for Mitsunobu reaction.

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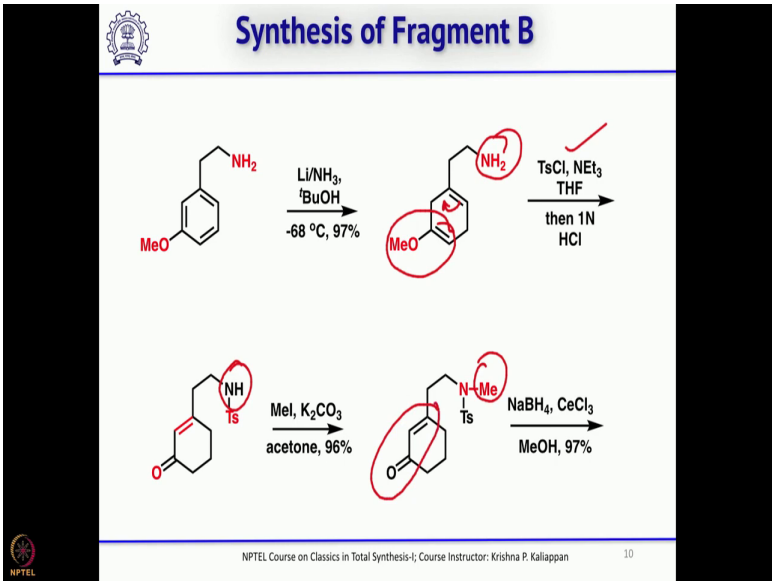

For fragment B, he started with meta methoxy phenyl ethyl amine and metal ammonia reduction that is birch reduction gave this diene. And if you hydrolyze this enol ether you will get the ketone and also the double bond will migrate to give the more it was

substituted and conjugated e none. So, you get this α–β unsaturated ketone, and during that process if you use TsCI chloride ok, you can protect this amine as -NH-Ts, then methylate this NH to get N methyl as you know in morphine you need this N methyl ok.

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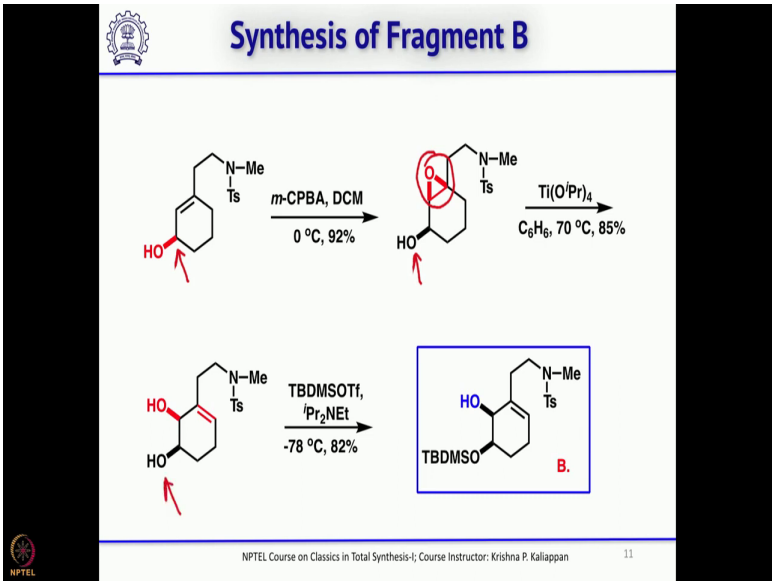

Then you have this enone, that enone can be reduced using luche condition that is sodium borohydride cerium chloride you get the allylic alcohol. And using the allylic alcohol stereo center ok of course, this is relative it is a racemic compound, you can direct the epoxidation using the alcohol.

So, you get the epoxide delivered from the same side of the hydroxyl group. Then you treat with Lewis acid titanium isopropoxide which opens the epoxide to get the corresponding allylic alcohol ok. So, then between these two this can be protected selectively using TBDMS triflet; so, that is fragment B.

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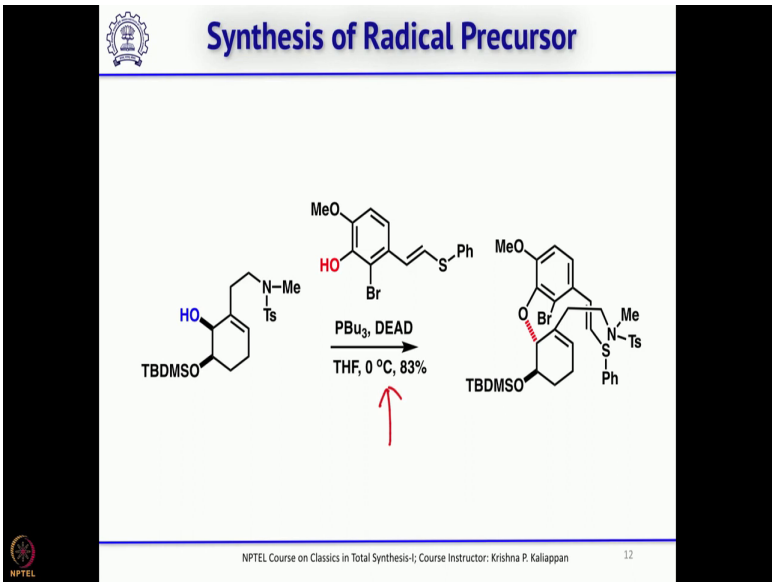

So, once we have fragment A and fragment B, then carry out the Mitsunobu reaction ok. So, first step is the Mitsunobu reaction for combining the fragment A and fragment B to get this bicyclic compound. So, this set the stage for the key 5 exo radical cyclization followed by 6 endo and elimination of the thiophenol.

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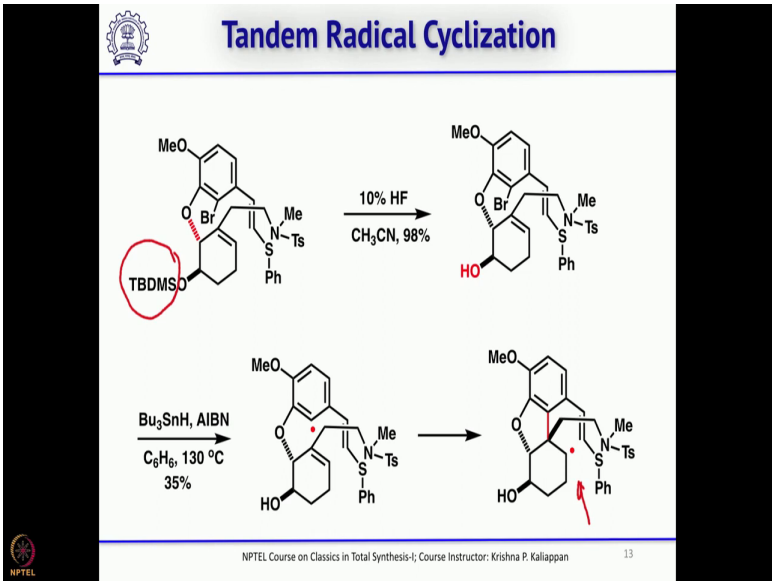

So, when you treat with a AIBN, TBTH this will happen, and before that this bulky TBDMS group can be cleaved using fluoride source to get the corresponding alcohol,

then you do the key reaction. So, that key reaction as I said first it forms the radical that radical undergoes 5 exo to give this intermediate.

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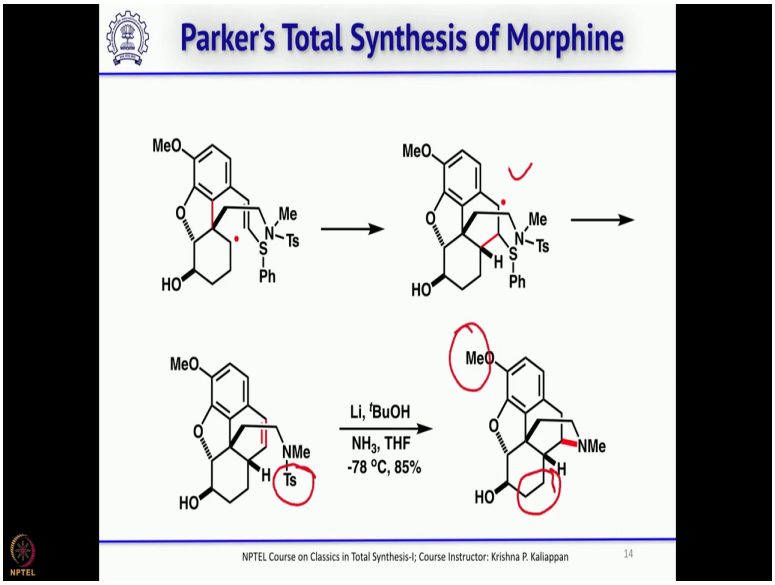

And again, this radical will further undergo 6 endo to give this radical; now, this will come back when it comes back you eliminate the phenyl thio radical ok. So, now, you have formed 4 rings the last ring is the 6 membered piperidine ring; so, that is formed by lithium and tertiary butanol in ammonia.

So, here what happens first the N-Ts group gets cleaved and then the hydroamination takes place to introduce the 5th ring. So, now you have all the 5 rings in correct place; so, what is to be done is you have to introduce a double bond here and also de methylate.

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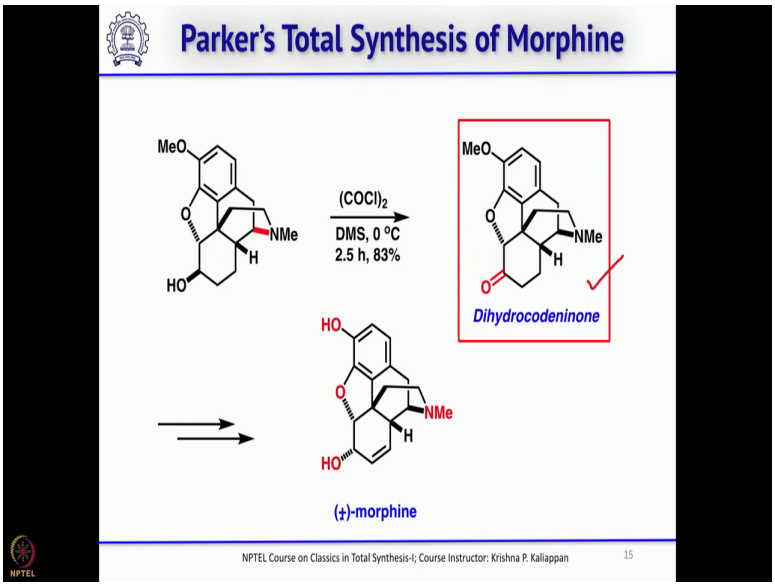

So, what is done you do Swern oxidation; so, that will give you dihydrocodeinone. So, the dihydrocodeinone has been already converted ok in the last lecture I talked about this dihydrocodeinone has been already converted into morphine. So, this completes the formal synthesis of morphine by Parkers group.

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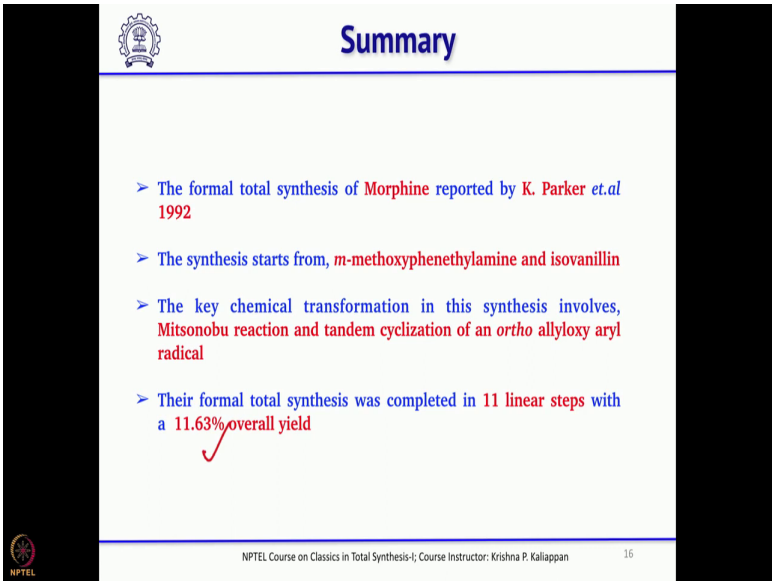

So, parker took about 11 steps to complete the total synthesis of morphine key steps are Mitsunobu reaction and tandem radical cyclization. And he also started with simple starting material isovanillin which is commercially available and meta methoxy

phenethylamine which also can be easily prepared. The overall yield of this is 11.63 % which is significantly higher than other methods reported as thus far ok.

That brings me to the fourth total synthesis of morphine which was reported by James White why I want to discuss this was the earlier synthesis. If I look at first one was racemic synthesis and then second and third were asymmetric synthesis. But they were they synthesize the naturally occurring morphine; whereas, James Whites group they wanted to synthesize the enantiomer of naturally occurring morphine that is (+) morphine ok.

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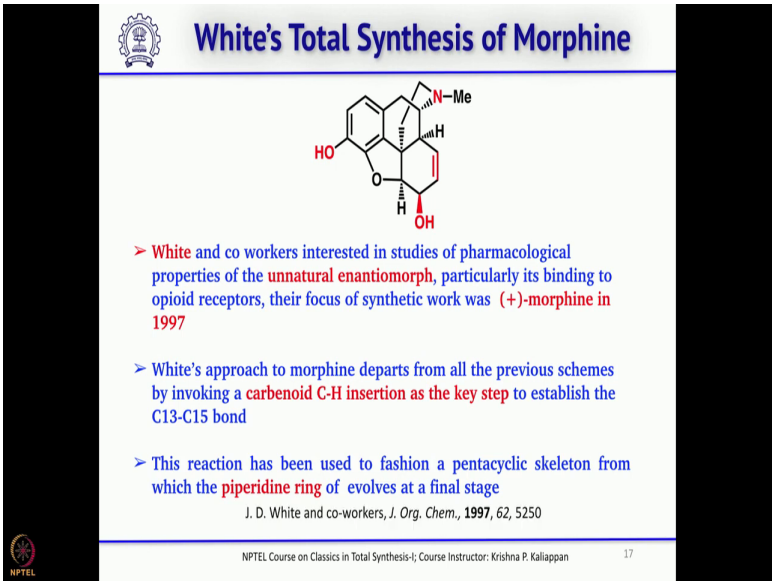

So, the key step in the total synthesis of James Whites group is carbenoid C-H insertion ok. So, that is another clever use of rhodium acetate catalyzed carbonate C-H insertion ok, I will come back when I talk about the total synthesis.

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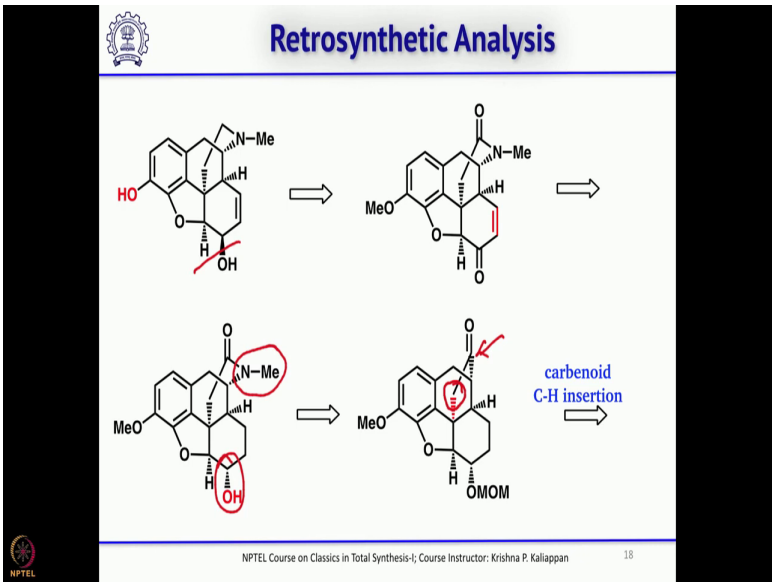

So, the retro synthetic analysis ok, the first step is the reduction of the ketone to allylic alcohol and that can be obtained from this particular alcohol as you know oxidation and then introduction of double bond you will get this. The second key step is the Beckmann rearrangement, if you have a ketone and the Beckmann rearrangement we can introduce this -NH, then we can methylate and the second key step is the C-H insertion.

So, the C-H insertion of that -CH_2 bond was done from this starting material; so, you can see this one gets inserted at this carbon ok.

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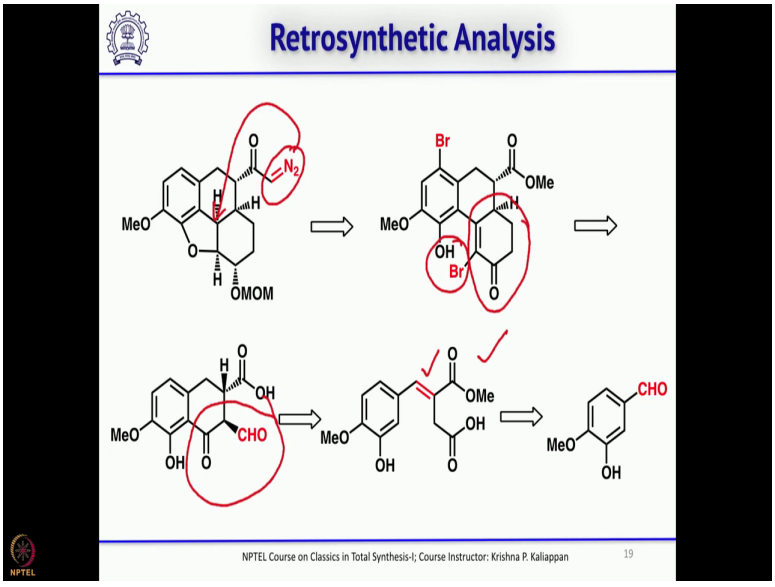

So, let us see how it was done when we talk about the total synthesis. And here this CO bond was done using intramolecular S_N2 like reaction and that can be obtained from this ketoaldehyde using a Robinson a relation sequence. So, if you look at this cyclohexanone as you know when you have cyclohexanone, one reaction which should come to your mind is Robinson annulation sequence.

So, the Robinson annulation sequence was used to introduce this cyclohexanone and that can be obtained from this particular compound using asymmetric hydrogenation ok Noyori as you know Noyori has developed several methods. So, yeah one modified version was used to highly stereo selectively reduce this double bond and this can be obtained from vanillin ok. This is the simple retrosynthesis put forward by James White and let us see how he has successfully accomplished the total synthesis of (+) morphine starting from vanillin.

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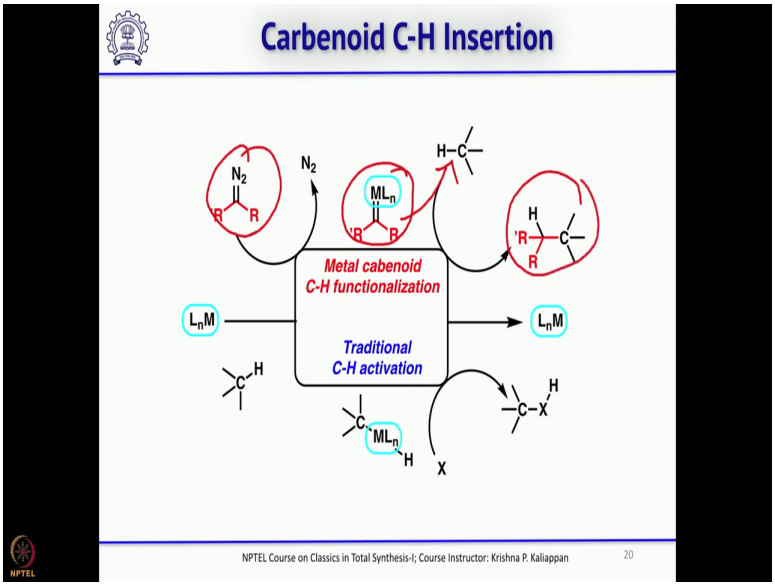

And this is the mechanism for carbenoid C-H insertion. So, if you have a diazo compound and then if you treat with either copper or di rhodium tetraacetate, you get this carbenoid and that inserts to any C-H bond and you will get like this ok.

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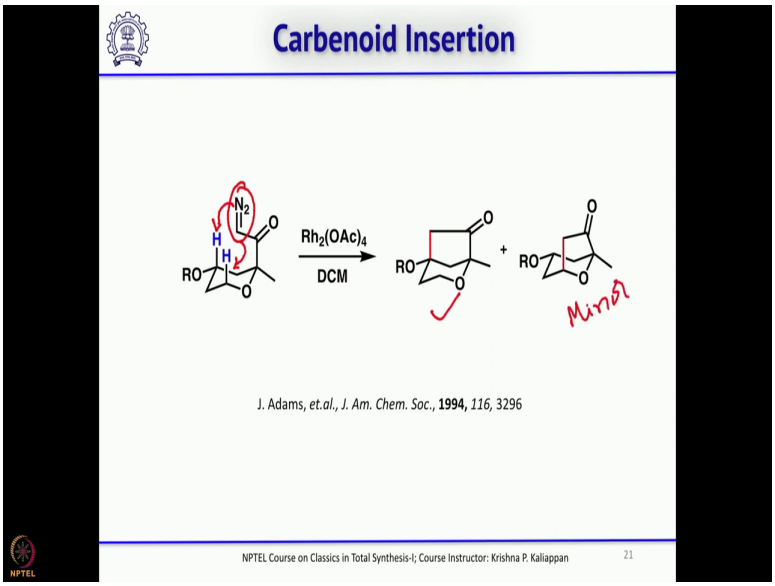

And there are many examples in the literature one of them is shown here. So, here you have a diazo compound either it can insert here or can or it can insert here and this is the major product and this is the minor product; so, both are possible ok.

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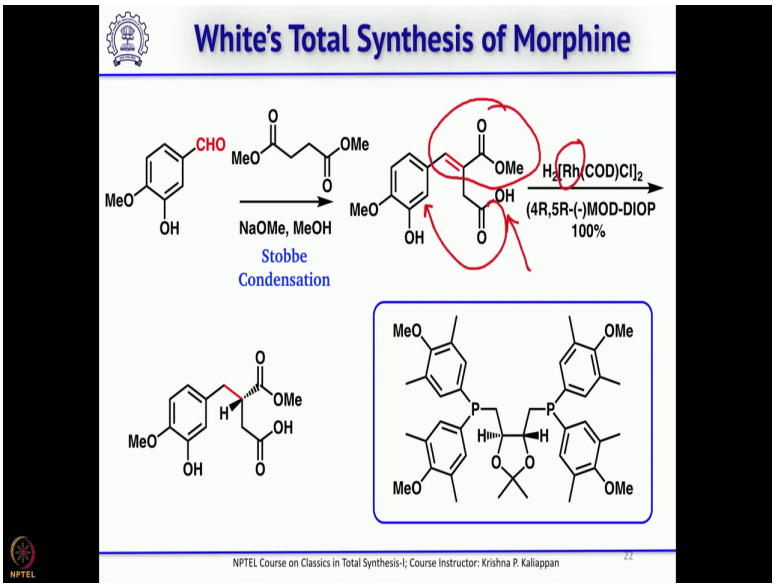

Now, let us see how whites group started the total synthesis and how they accomplished they started with isovanillin. And then you do a Stobbe condensation ok, this Stobbe condensation was done with dimethyl succinate sodium methoxide and dimethyl succinate. So, you get this particular α–β unsaturated ester which is required for

asymmetric hydrogenation at the same time you also have the CH_2-COOH which is required for cyclization either at this carbon ok.

So, the asymmetric hydrogenation was done using this catalyst that catalyst is little complex ok. So, this is what you know the ligand which is used with the chiral the rhodium species. So, that gives this isomer this is a high enantiomeric excess was obtained and then the next step is the fetal curve cyclization ok.

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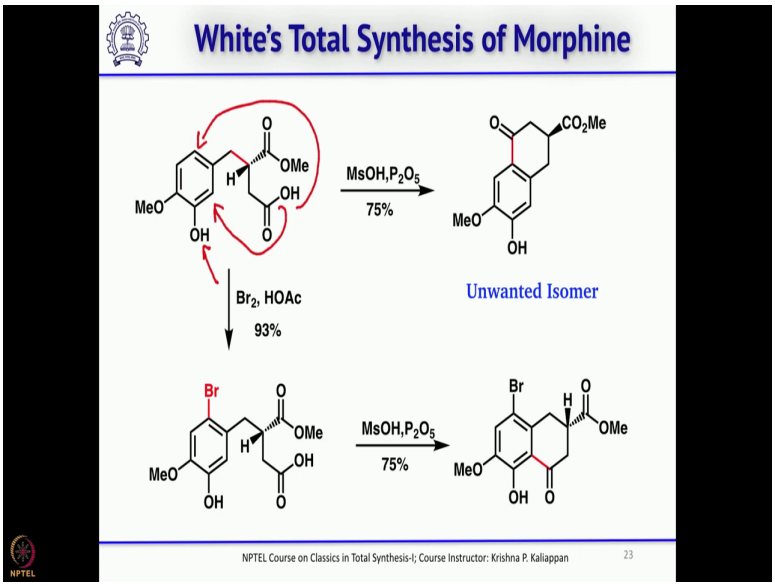

The expected one was, so, whether it can undergo cyclization here, but unfortunately what happened this cyclized at this carbon. So, not ortho to hydroxyl group, but it went to para; so, it says that the para is more reactive. So, in order to force this carboxylic acid to cyclize at ortho with respect to hydroxyl group you need to block the para position.

So, that was simply easily achieved by bromination. So, when you do the bromination, it goes to the para position then you do the product of oscillation intramolecular product of oscillation. Now, you can see it underwent it can undergo only at one place ok; so, that is how this substituted tetralone was prepared.

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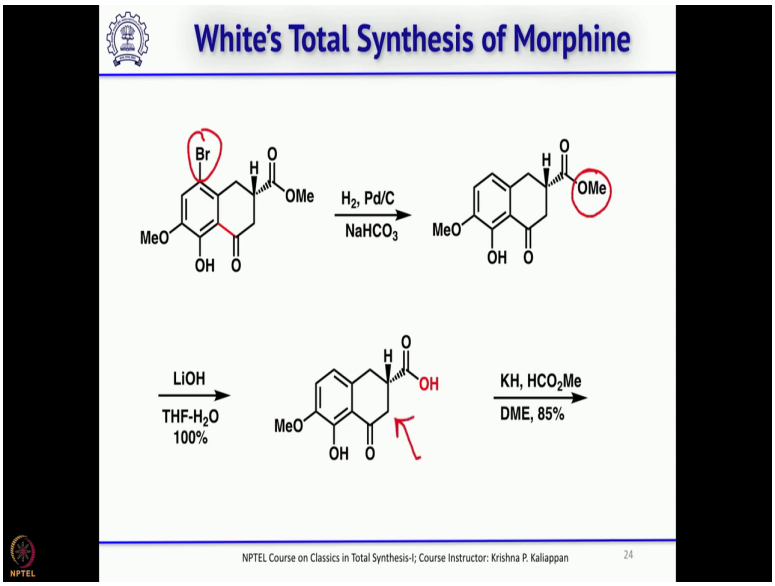

Then once we have this you do not it, the bromine is not it the bromine served its purpose of forcing the carboxylic acid to undergo product of oscillation ortho to the hydroxyl. So, reductive removal of bromine gave this tetralone, the next step is the Robinson annulation sequence. For doing the Robinson annulation sequence, first you have to hydrolyze this ester to carboxylic acid then you introduce an aldehyde here ok that was done by treatment with potassium hydride and methyl format; so, you introduce the aldehyde.

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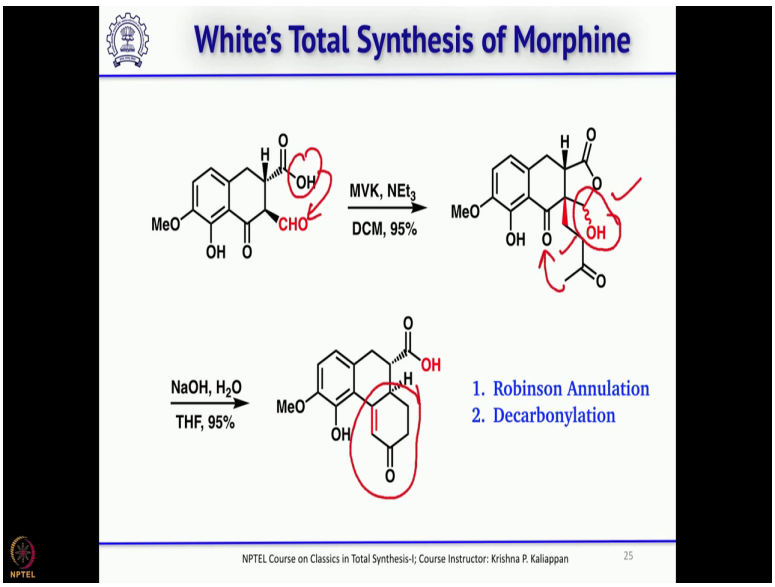

Then you do the Robinson annulation sequence, when you do the Robinson annulation sequence with methyl vinyl ketone. So, first the 1,4 addition takes place 1,4 addition takes place with methyl vinyl ketone and at the same time the carboxylic acid adds to the aldehyde to form this lactol type ok. Then sodium hydroxide will cyclase here to get the corresponding cyclohexanone at the same time the decarbonylation also takes place, the decarbonylation takes place to give this tricyclic compound.

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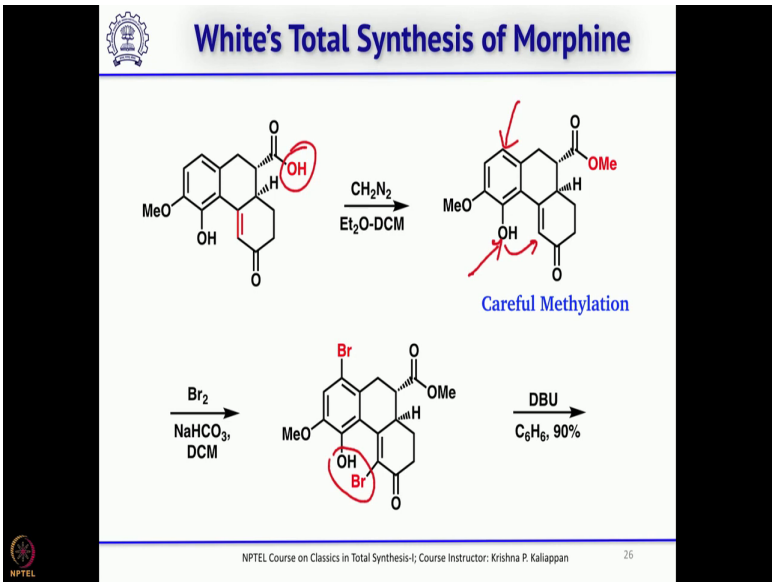

So, once we have this tricyclic compound; so, what is to be done you methylate this. So, esterification with diazomethane, you get the corresponding methyl ester and one has to be careful because you also have a phenolic hydroxyl group. So, both carboxylic acid and phenolic hydroxyl group can be methylated if you treat with diazomethane. But careful treatment with one equivalent of diazomethane one can selectively methylate the carboxylic acid and not the phenol.

So, once that is done then you have to cyclase this is not it. So, that is done by treating with bromine first, but as you know when you treat with bromine, bromine also we will go here is not it. Yeah, that is what happened because you brominated both this on treatment with DBU ok. You can imagine how on treatment with DBU; it will cyclase here, it is possible because DBU also can isomerize the double bond.

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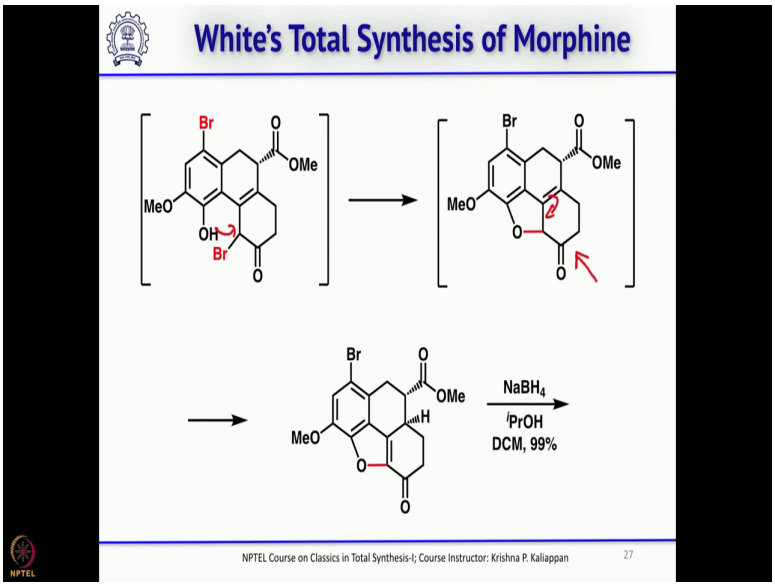

So, it goes through this deconjugation double bond was deconjugated, then the cyclization can take place you know it is an intramolecular S_N2 reaction, then followed by again migration of the double bond ok. Now, if the double bond migrates again. you get the tetra substitute compound, but it is in conjugation with carbonyl group; so, that is how it was done.

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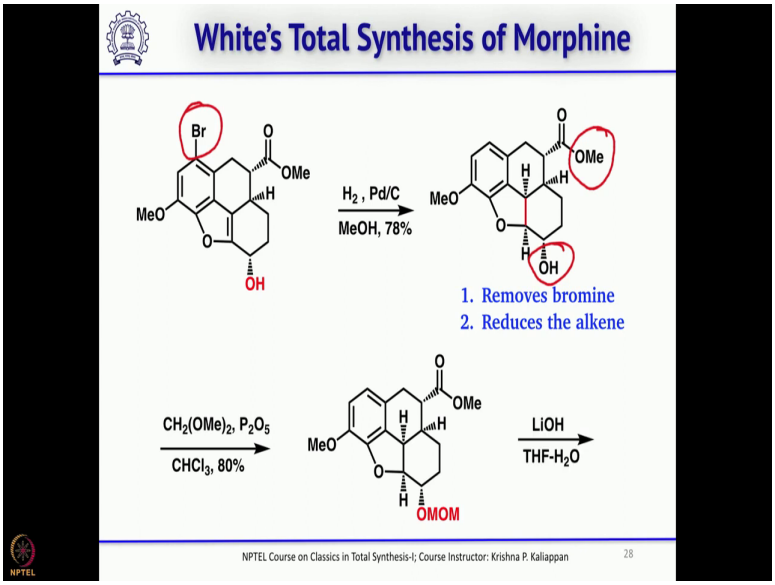

So, what is next you have to reduce the carbonyl group to corresponding alcohol ok; so, allylic alcohol was done then this bromine you do not need ok. So, reductively remove

the bromine under hydrogenolysis condition, your 4 rings are ready now ok. Then the fifth ring white as I mentioned has used an intramolecular carbenoid C-H insertion as the key reaction is not it. So; that means, you have to convert or you have to hydrolyze the ester to carboxylic acid convert that into diazoketone ok.

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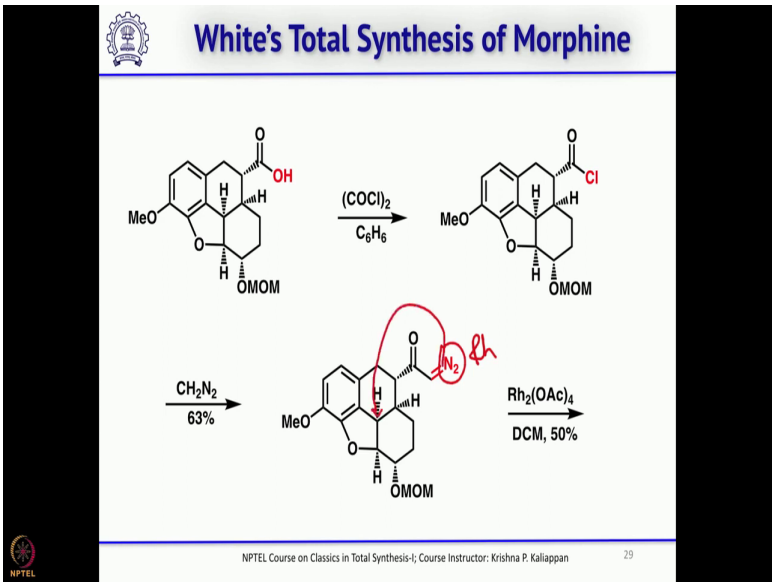

So, first you protect this 3 hydroxyl group ok as mom ether, then you hydrolyze the ester to carboxylic acid. You have the carboxylic acid it is easy to convert a carboxylic acid into diazoketone in two steps, convert this into acid chloride by treating with oxalyl chloride to form the acyl chloride; now, you treat with diazo methyl; so, you get the corresponding diazo ketone. So, once you have this diazo ketone next what you do is treat with dirhodium tetraacetate.

So, the dirhodium tetraacetate first it will form the corresponding rhodium carbonate and it will undergo insertion at this C-H.

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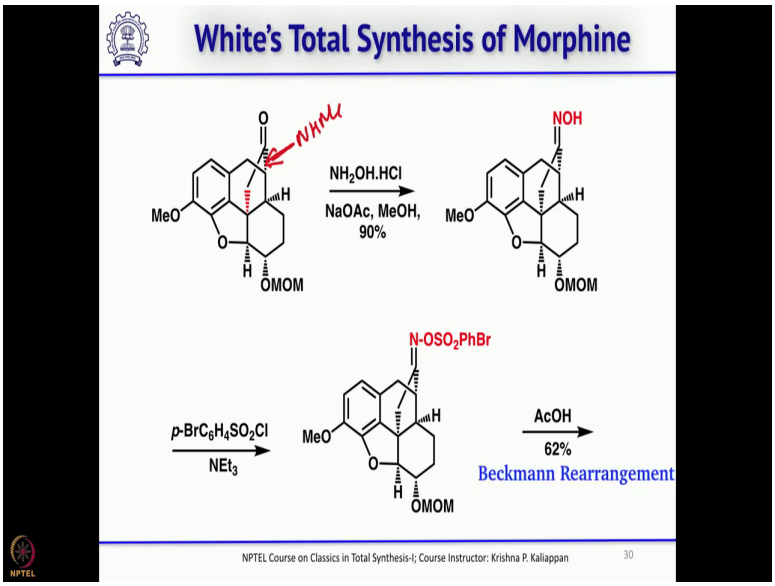

So, that will give you directly this compound ok, now you have the pentacyclic compound; so, what is missing is you have to insert a -NHMe is not it. So, that is normally done using a Beckmann rearrangement you have a ketone then once you have a ketone you can think of using Beckmann rearrangement to carry out the ring expansion.

So, for that what you should do you should convert the carbonyl into oxime. So, that was done by treating with hydroxylamine to get the oxime that oxime was made as a good leaving group ok by treating with p-bromobenzene sulfonyl chloride. So, N brosolate was formed then you do the Beckmann rearrangement by treating with acetic acid.

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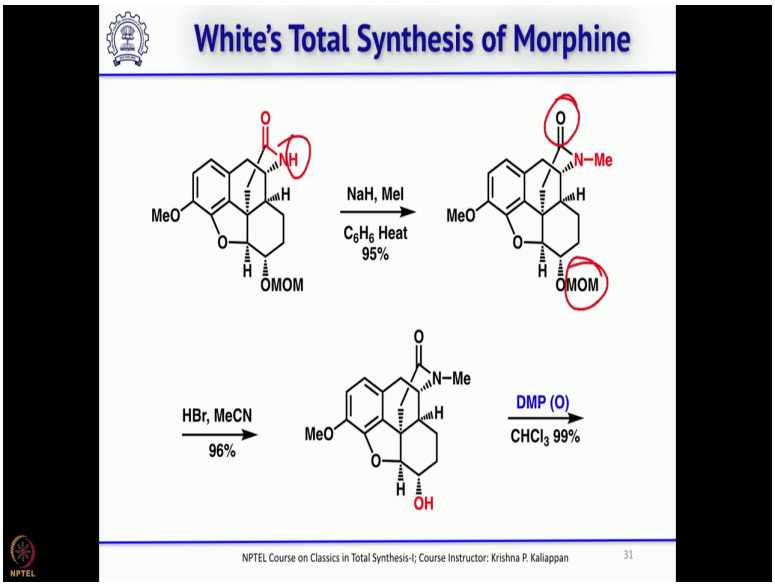

So, that will give the Beckmann rearrangement product that is the corresponding 6 membered lactam. The 6 membered lactam now one can easily methylate by treating with sodium hydride and methyl iodide you get the corresponding N methylated compound. And the carbonyl group also should be removed and the mom group also should be cleaved.

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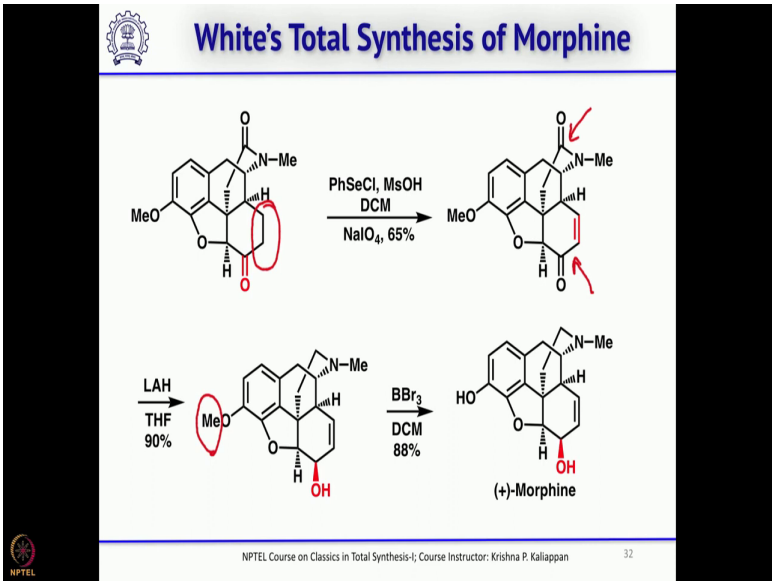

So, the mom group was cleaved using HBr in acetonitrile and the hydroxyl was oxidized under Dess Martin periodinane condition to get the ketone. And the double bond was

introduced ok in one part using phenyl silyl chloride and acetic acid and reduce the ketone that is this one as well as remove the carbonyl that is lactam to corresponding amine was done in one step with lithium aluminum hydride.

And now what is left is the removal of the methoxy methyl group. So, that will give the morphine that was easily achieved using Lewis acid BBr_3 at very low temperature one can do demethylation. So, that give the corresponding natural product that is (+) morphine which is the enantiomer of the naturally occurring morphine.

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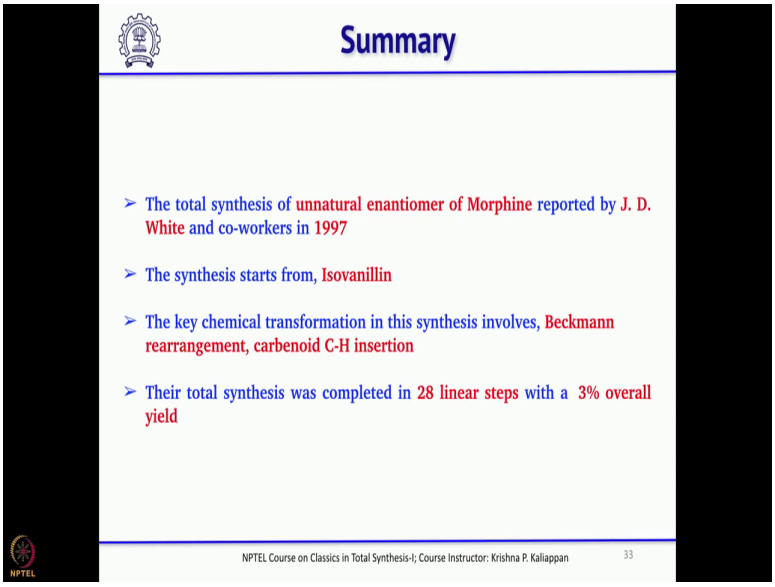

So, this is the first total synthesis of unnatural morphine ok. So, this was reported in 1997 in JOC. Again, the starting material like other synthesis of morphine was isovanillin and he used two key reactions, one is the carbenoid C-H insertion initially, then later he use Beckmann rearrangement to expand the 5 membered ketone to 6 membered lactam. So, overall, he took about 28 steps and yield was considering that it is 28 steps 3% overall its quite good ok.

So, with this I will stop and we have completed the four total synthesis of morphine and we will discuss some more synthesis of alkaloids ok.

Thank you.