Classics in Total Synthesis-I

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Lecture - 34
Morphine (Gates & Overman)

So, good morning, everyone, and welcome back to the lectures on Classics in Total Synthesis. We have been discussing total synthesis of many natural products. And in the last few lectures we are focusing on synthesis of quite a few alkaloids. So, today and tomorrow, we will talk about an alkaloid which is also very well known and famous alkaloid which is used as a pain killer, is none other than Morphine.

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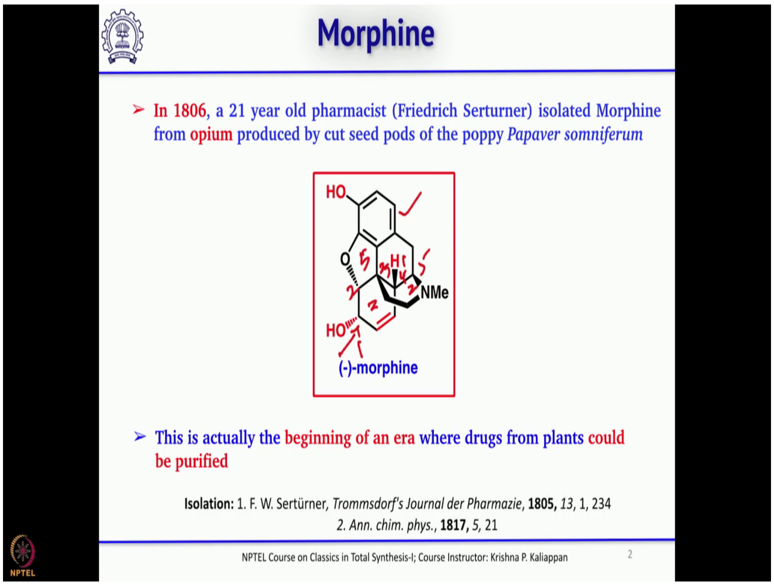

Morphine

- In 1806, a 21 year old pharmacist (Friedrich Serturner) isolated Morphine from opium produced by cut seed pods of the poppy *Papaver somniferum*

- This is actually the beginning of an era where drugs from plants could be purified

Isolation: 1. F. W. Sertürner, *Trommsdorf's Journal der Pharmazie*, **1805,** *13*, 1, 234
2. *Ann. chim. phys.*, **1817,** *5*, 21

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So, morphine is a interesting alkaloid. In fact, in 1806 that was the year where the morphine was isolated in pure form, ok, it was isolated in pure form from the poppy seeds. So, that was the beginning of isolation of pure natural products from the natural source. So, it was done by a young pharmacist called Friedrich Serturner. And this is the structure of morphine.

So, if you look at this molecule, it is a pentacyclic structure as an aromatic ring having a phenol and 3 six membered rings, 1, 2, 3 and a dihydrofuran ring, ok. And you can see one chiral center, 2, 3, 4, 5, there are 5 contiguous chiral centers in this molecule, ok.

And since, then there are many natural products which were isolated in pure form from the naturally occurring sources.

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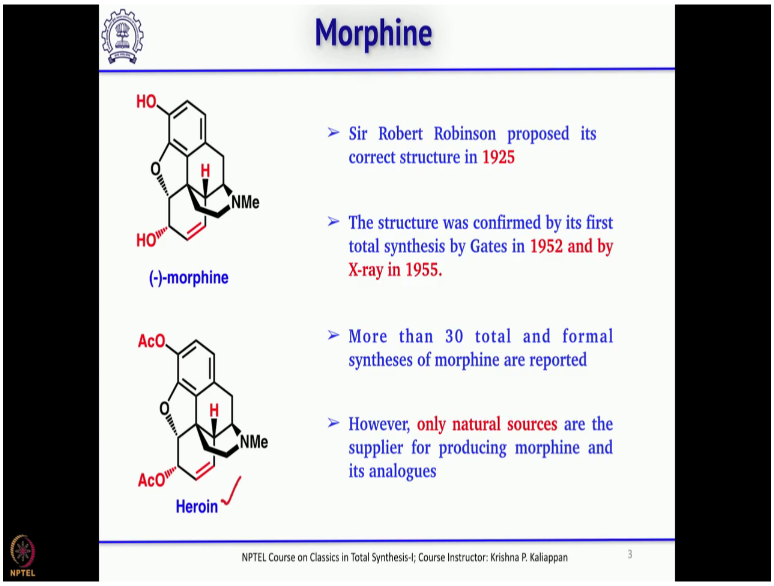

Morphine

(-)-morphine

Heroin

- Sir Robert Robinson proposed its correct structure in 1925
- The structure was confirmed by its first total synthesis by Gates in 1952 and by X-ray in 1955.
- More than 30 total and formal syntheses of morphine are reported
- However, only natural sources are the supplier for producing morphine and its analogues

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And as you can see the natural product is quite complicated structurally. So, it took quite some time to elucidate its correct structure. In fact, about 100 years ago, Sir Robert Robinson, a well-known synthetic organic chemist, he proposed the correct structure of morphine. And it took another 27 years to confirm the structure of morphine. As you know those days any new structure was isolated and then the correct structure was proposed by someone. But still the final proof came in the form of only total synthesis.

So, the first total synthesis of this molecule was reported by Gates in 1952, and 3 years later X-ray also confirmed its structure. So, there are several total synthesis of this molecule considering its complexity, it is understandable. Many synthetic groups jumped on the total synthesis of this molecule. More than 30 total and formal synthesis are there in the literature. However, this molecule, if it has to be used in you know treatment, particularly pain related treatment, still people use only the natural sources because it can be obtained in huge quantity from natural sources.

So, that is why that is a major supplier for morphine and its analogues. And since, morphine is well-known pain reliever, people started making several analogues. One of the infamous analogues is nothing, but diacetyl morphine which is which has a unique name called Heroin. Because of this particular infamous molecule which can be easily obtained by simple acetylation of morphine with acetic anhydride. Acetic anhydride is a controlled substance, ok.

So, we all know. So, when you have to use acetic anhydride, you have you have to follow certain guidelines, and then you cannot get more amount of acetic anhydride for academic purpose. And simple reason is the conversion of morphine to heroin can be done in single step using acetic anhydride.

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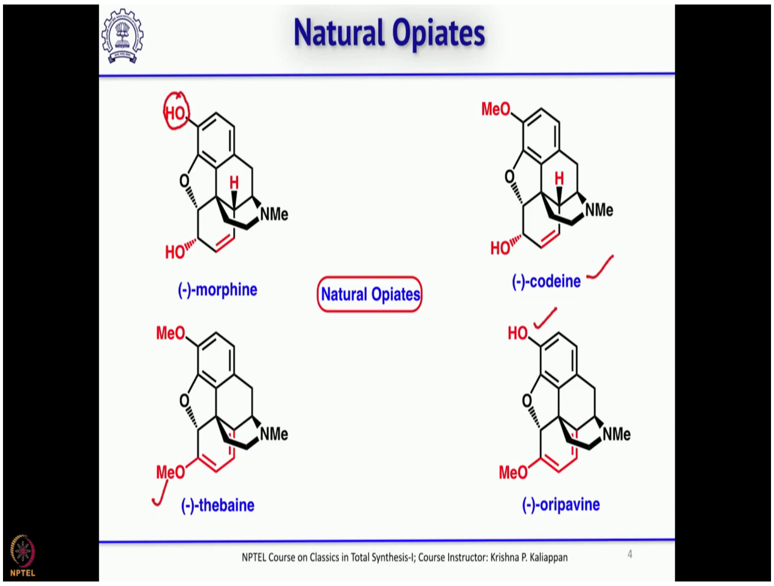

Natural Opiates

(-)-morphine

Natural Opiates

(-)-codeine

(-)-thebaine

(-)-oripavine

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There are several analogues, some are natural. See for example, if one of the hydroxyl, that is the phenolic hydroxyl group, if it is methylated then this is called codeine, so this also naturally occurring. And if both the hydroxyl groups are methylated then that natural product is called thebaine. And the phenolic hydroxyl group is free, and the other hydroxyl group, that is you have a diene. In fact, it is you oxidize this, the allylic alcohol to α–β unsaturated such as ketone, then you form the dienol ether. So, that is called oripavine, ok. So, these are all naturally occurring.

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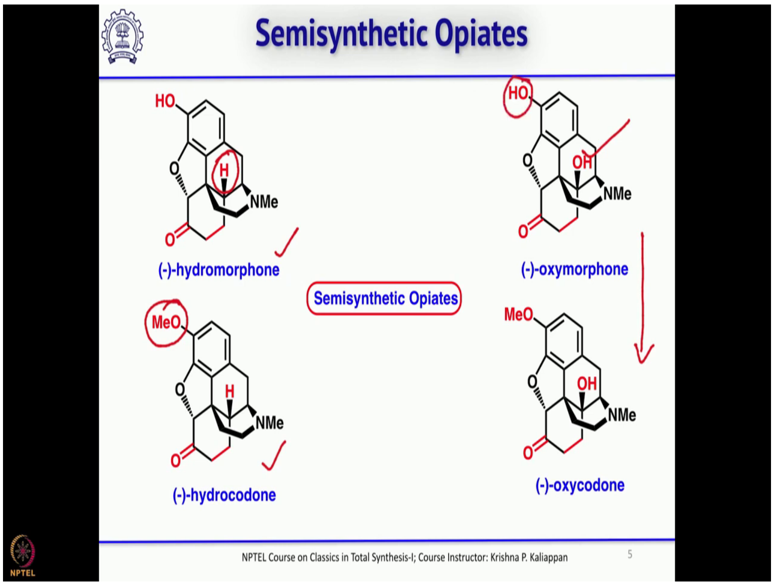

Semisynthetic Opiates

(-)-hydromorphone

(-)-oxymorphone

Semisynthetic Opiates

(-)-hydrocodone

(-)-oxycodone

But there was many semi, semi-synthetic molecules. So, one is hydromorphone; that means, you reduce the double bond and also oxidize the alcohol. So, that is called hydromorphone. And if this hydrogen is replaced by hydroxyl group, then it is called oxymorphone, ok. And this molecule is called hydrocodone, where the hydromorphone is just methylated. The phenolic hydroxyl group is methylated. And here too, the oxymorphone to oxycodone what you have done is the phenolic hydroxyl group is methylated. These are all semi-synthetic morphine derivative.

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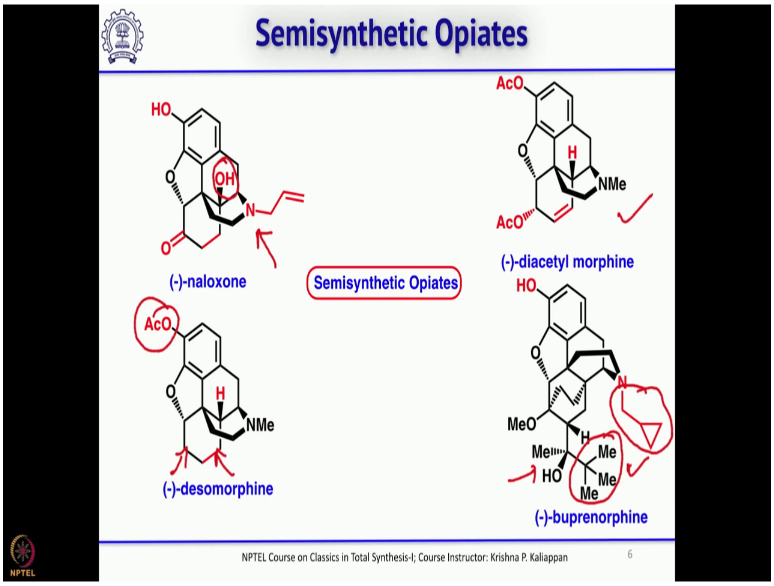

Semisynthetic Opiates

(-)-naloxone

(-)-diacetyl morphine

Semisynthetic Opiates

(-)-desomorphine

(-)-buprenorphine

And instead of N-Me group, ok. So, you morphine, N is methylated, and it is a methyl group if you have allyl group and here if you have a hydroxyl group, then this is called naloxone, ok. And this is diacetyl morphine, already I told you its common name that is heroin. And if you do not have carbonyl group, if you do not have that oxygen, if you do not have the double bond, and if the phenolic hydroxyl group is acetylated, so this is called desomorphine.

These are all for just information, you do not have to worry too much. So, why I am saying all this and then showing all these structures is because morphine derivatives are used as analgesic. So, there are still lot of work going on in making more one more analogues of morphine. So, this particular molecule, if you look at this is made from thebaine.

So, they take thebaine and then do a Diels-Alder reaction, ok, they do a Diels-Alder reaction with methyl vinyl ketone and followed by addition of tertiary butyl lithium. You introduce this. And here instead of methyl group you have cyclopropyl methyl group, ok. So, this is also a very interesting analogue of morphine.

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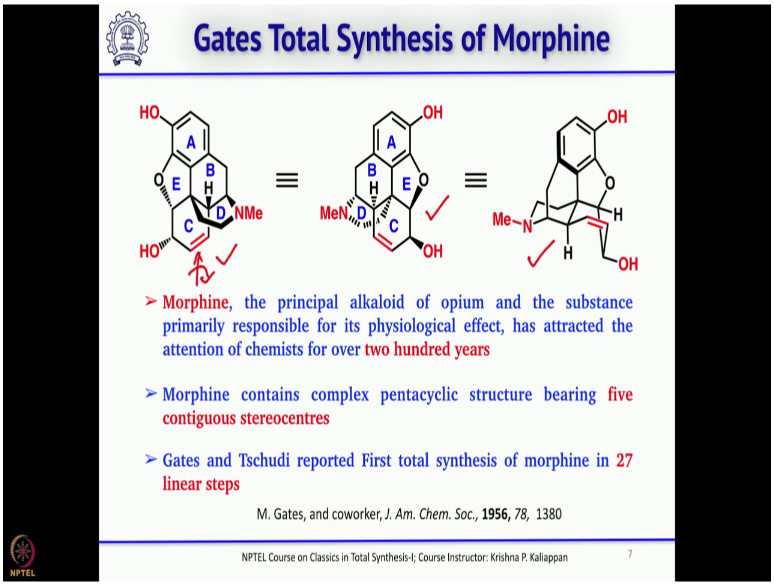

Gates Total Synthesis of Morphine

- Morphine, the principal alkaloid of opium and the substance primarily responsible for its physiological effect, has attracted the attention of chemists for over two hundred years
- Morphine contains complex pentacyclic structure bearing five contiguous stereocentres
- Gates and Tschudi reported First total synthesis of morphine in 27 linear steps

M. Gates, and coworker, *J. Am. Chem. Soc.*, **1956**, *78*, 1380

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So, now let us see how this molecule was synthesized and reported for the first time. As I mentioned, Gates was the first one to report the total synthesis of morphine and that was in 1952. So, you can imagine it took almost 150 years since its isolation and 27 years after its structure was you know proposed by Robert Robinson to complete the first total synthesis. So, this is the structure of morphine. So, if you do a 180° rotation, ok you get this structure, ok.

And that can be written like this because this is also important. When you think about any molecule in three-dimensional way, so the confirmation is very important. So, I leave it for few seconds, so that you know you can see how this molecule can be redrawn in this form, ok. And as I mentioned, morphine has 5 contiguous stereo centers, ok. And the first synthesis was reported by Gates, and they took about 27 steps to complete this total synthesis.

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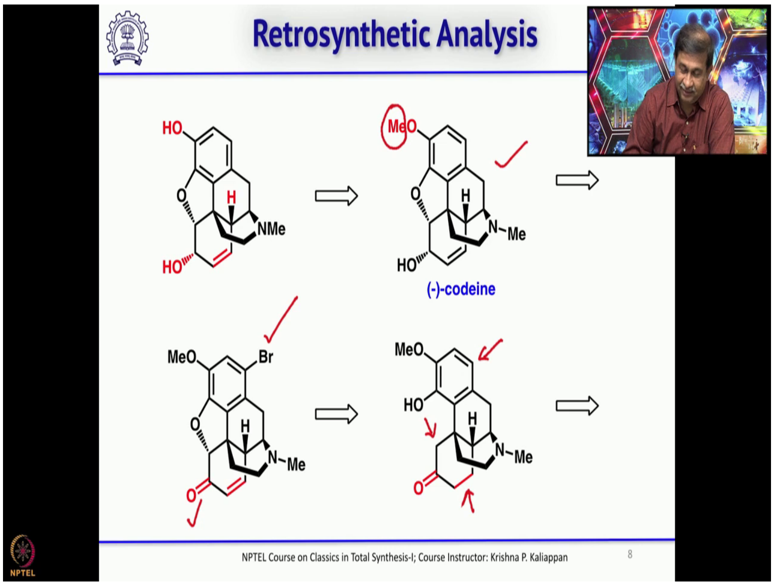

Retrosynthetic Analysis

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So, from the retrosynthetic point of view the first disconnection was the methyl group here. If you can demethylate then you will get the morphine. And this is also a natural product. As I mentioned it is codeine and this codeine can be obtained from this bromo codeinone. So, basically, you have to de brominate and then do the reduction of the ketone. So, both can be done in one step if you use LAH. So, debromination can be done and the keto-group can be reduced. And this can be obtained from this ketone, and if you look at this, this is one of the key steps in the synthesis of morphine.

What they have done? They have to introduce a double bond here, and they have to form a -CO bond, at the same time they also have to introduce a bromine, ok. All these were done in one step. I will come to that. It is a beautiful step. And how it was done I will discuss little later.

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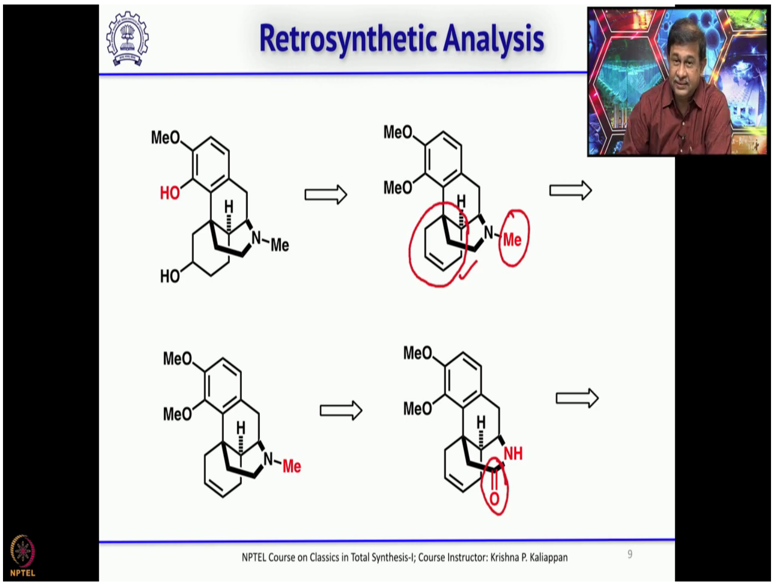

Retrosynthetic Analysis

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And this compound can be made from this alkyne, ok. So, you do either hydroboration oxidation, but that time hydroboration oxidation was not known. It is just addition of water, ok. It is just addition of water. We introduced the hydroxyl group. And when you see this molecule you can see a cyclohexene, is not it? And you all know the cyclohexene can be obtained by a Diels-Alder reaction.

So, the precursor for this compound should be the corresponding alkene and the diene, ok. Before that this methylation and reduction of this will lead to the required compound. Basically, what is important is the cyclohexene how you introduce.

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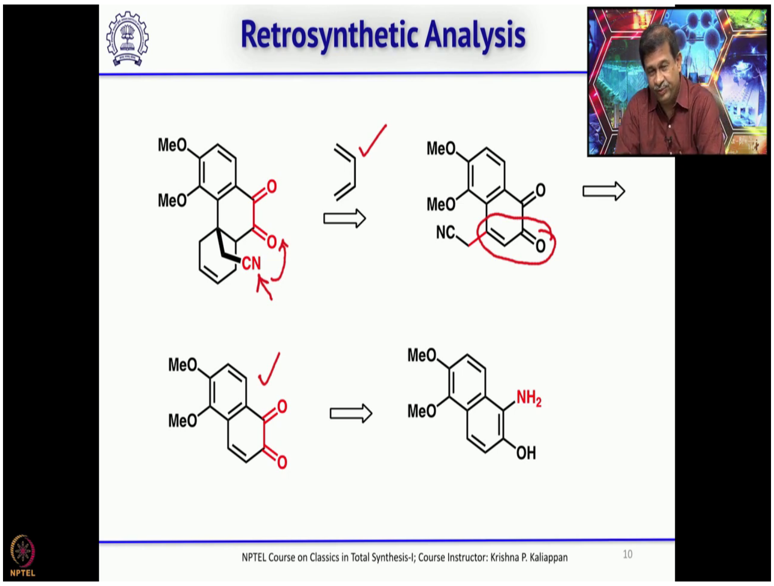

Retrosynthetic Analysis

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The cyclohexene is introduced using the Diels-Alder reaction between this dienophile, you can see this dienophile and simple butadiene, ok. Then the -CH_2-CN can be reductively cyclase with this ketone, ok. We will discuss more in details when we talk about the synthesis. So, that leads to this particular ortho-quinones, ok. That can be obtained from either the corresponding amino phenol or di-hydroxy compound.

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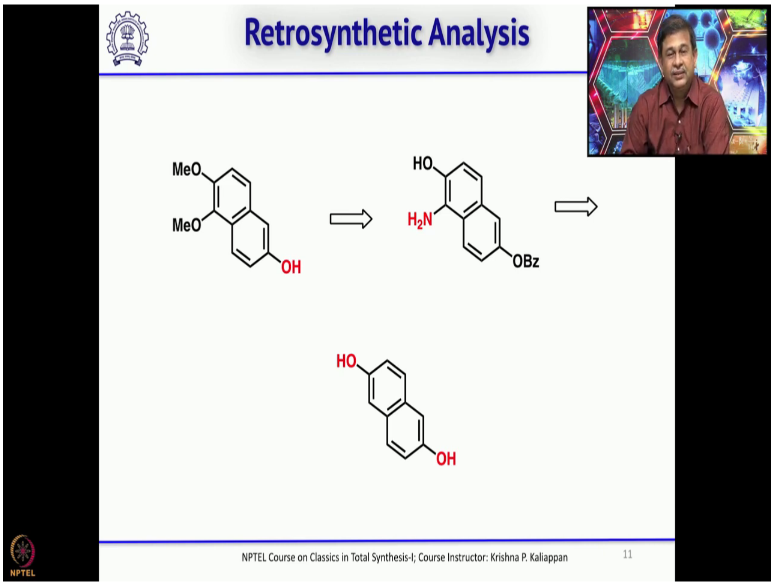

Retrosynthetic Analysis

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And which in turn can be obtained from the di-hydroxy naphthalene. So, this di-hydroxy naphthalene is the starting material, which is also, it is a symmetric compound, ok. Now, let us see how Gates has synthesized this morphine starting from di-hydroxy naphthalene.

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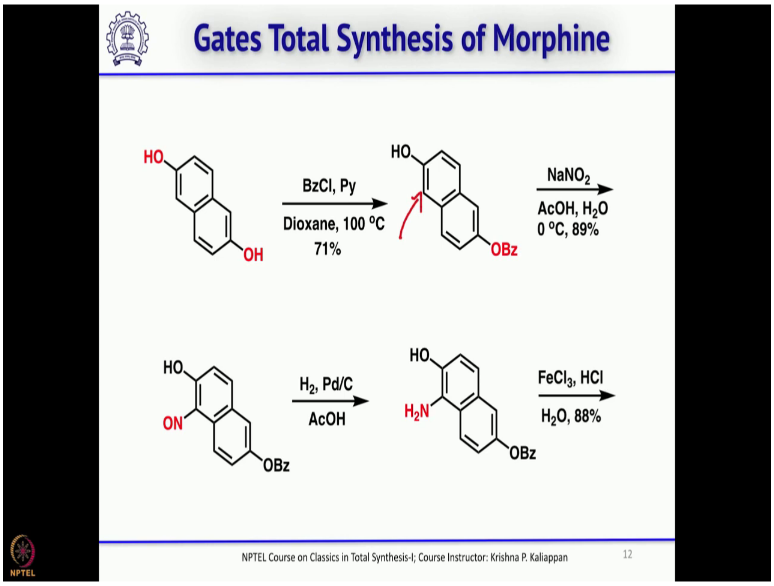

Gates Total Synthesis of Morphine

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So, he took this di-hydroxy compound. As I said this is symmetrical compound, so one can selectively protect one of the phenolic hydroxyl group as benzoate, then followed by you know nitration. So, treatment with sodium nitrite and acetic acid, one can introduce a NO group at this carbon, ok. So, that is what he did. And that NO group can be reduced to get the corresponding -NH_2.

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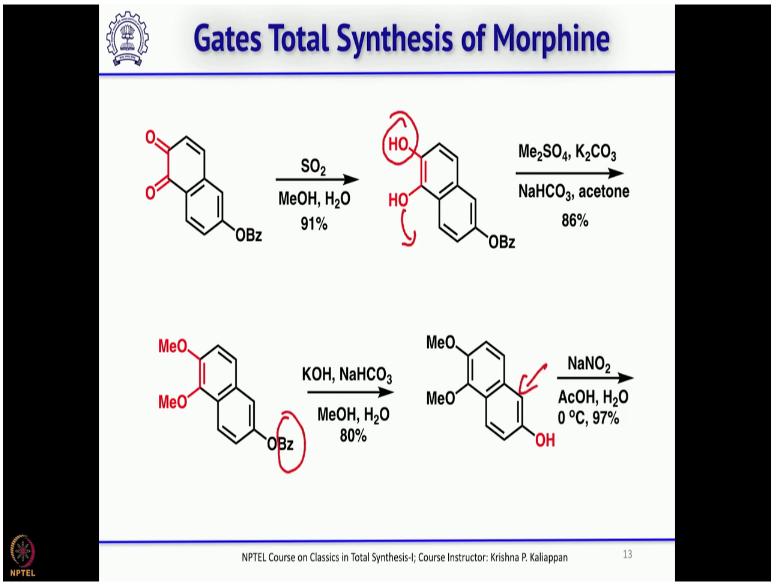

Gates Total Synthesis of Morphine

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So, once we have that, then you oxidize with ferric chloride. So, what you get is the ortho-quinone. And this ortho-quinone now can be reduced to get the corresponding di-hydroxy compound. So, this is how the di-hydroxy was introduced, which as you know one of them should be protect its methyl group, the other one should cyclase here, ok.

So, once we have this di-hydroxy compound methylate both of them, ok. The standard method is use a base mild base like potassium carbonate and dimethyl sulfate to introduce the methyl group. So, the next step, you have to remove this benzoate. So, you can remove it with potassium hydroxide and methanol, and introduce the -NO group here, ok.

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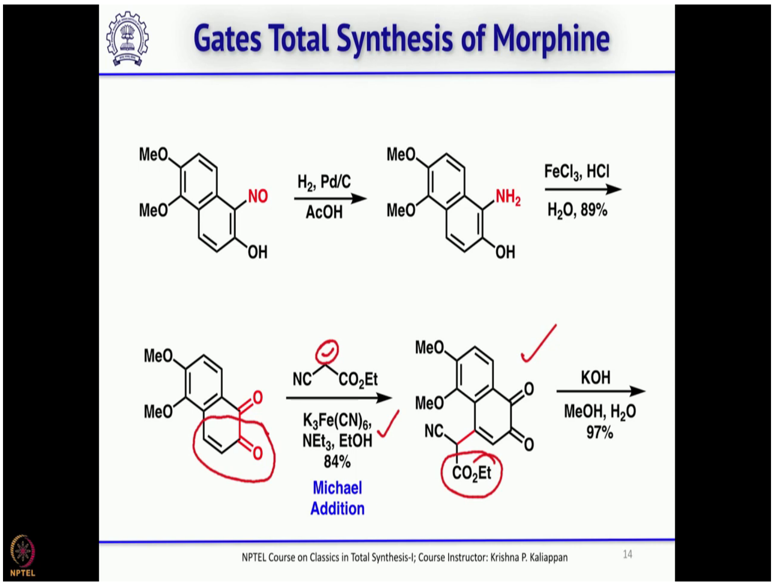

Gates Total Synthesis of Morphine

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So, the same thing sodium hydrate, acetic acid, you introduce the NO. And again reduce it to get the corresponding $-NH_2$ and oxidize this under the same condition which I had discussed where a ferric chloride you get the corresponding quinone. So, if you look at this, this is the Michael acceptor, ok this is the Michael acceptor. So, that means, it can undergo a 1, 4 addition. So, the next step has been the addition of anion generated from this cyanoethyl ester, ok.

So, that will undergo 1, 4 addition followed by introduction of the double bond. So, that can be done with potassium feri-cyanate. So, in this step, 1,4 addition takes place followed by introduction of the double bond, you get this compound, ok. Then you can do the decarboxylation. You do not need this ester. Once that it served its purpose you have to remove it. So, that ester could be removed by potassium hydroxide methanol. So, you get only the $-CH_2-CN$; the $-CH_2-CN$ only is intact, ok.

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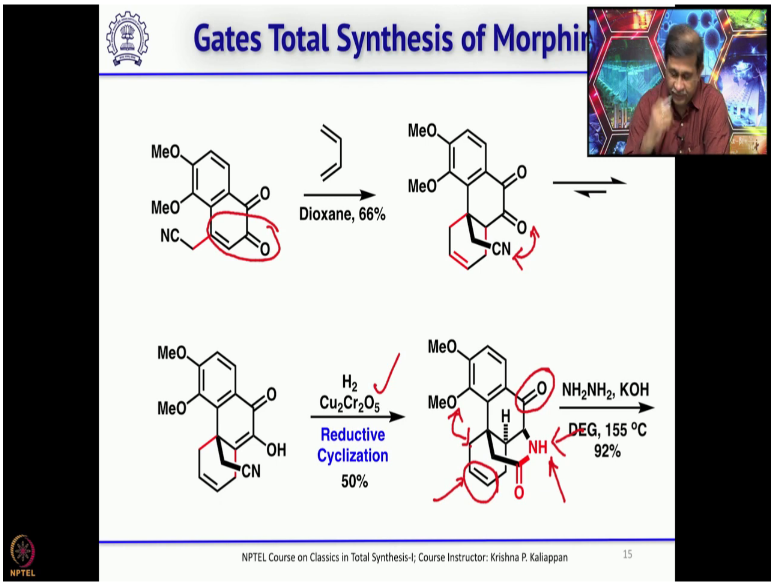

Gates Total Synthesis of Morphin

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So, what is the next step? You have the dienophile and now you should do the intermolecular Diels-Alder reaction with butadiene, ok. So, that work well. And the cyclohexene is nicely introduced, the next step should be to reductive coupling reaction or reductive cyclization. The cyanide should be hydrolyzed to -CO-NH$_2$ and that -CONH$_2$ to cyclase with one of the ketones of the ortho-quinone. So, that is you know safely done with hydrogen, and this copper chromium reagent. So, that reduce the cyanide to -CO-NH$_2$ and then cyclase and this was the final product.

So, now you have introduced 4 rings, 1 aromatic and 3 six-membered rings. So, what should be done to complete the total synthesis? One has to methylate here because n methyl is required for the synthesis of morphine. Then, you have to cyclase or the oxygen should form a bond with this. And also, the double bond should be isomerized, at the same time you also should introduce an oxygen at this carbon, ok. So, these are the few things to do, to complete the total synthesis of morphine.

So, the easiest one and obviously, the logically the first one to do is to methylate here, ok. But before doing methylation you do not need this ketone, is not it. If you look at the structure of morphine that carbonyl group is not required. So, you remove the carbonyl group using modified version of Wolff-Kishner reduction, ok.

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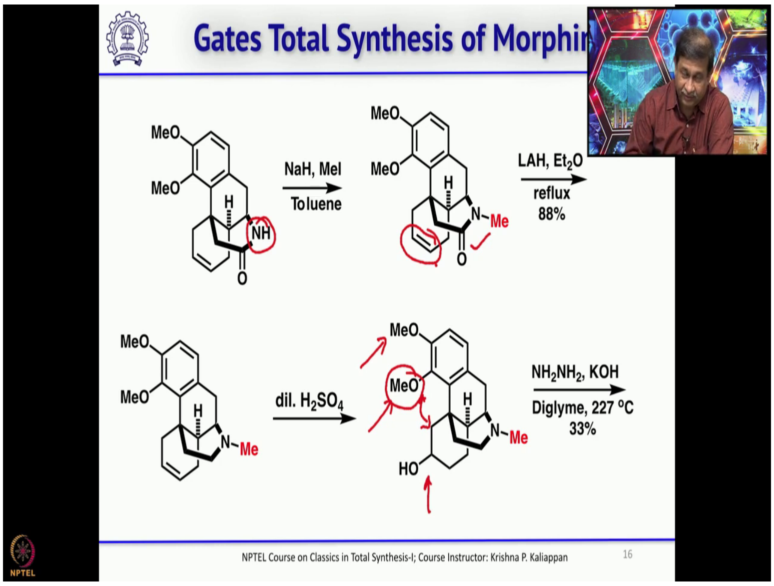

Gates Total Synthesis of Morphi

NaH, MeI
Toluene

LAH, Et_2O
reflux
88%

dil. H_2SO_4

NH_2NH_2, KOH
Diglyme, 227 °C
33%

So, now you remove the ketone, then obviously, the next step is the methylation of this lactam. So, methylation was done. So, the next step is the removal of the carbonyl group. So, that can be easily done by reducing with LAH, to get the corresponding amine, then dilute sulfuric acid treatment is nothing but addition of water. So, the addition of water takes place across the double bond and you get this regioisomer as a major product. So, once you have that now what you need to do? Between these two methoxy groups, this particular methoxy group should be demethylate.

So, that you can get the corresponding hydroxyl group, then you try to cyclase here. So, this was done almost under the same conditions as Wolff-Kishner reduction, ok. See, it when they carried out the Wolff-Kishner reduction you know as you can see in the earlier slide, they also I got some demethylated products. So, that is why they tried to repeat the same thing after other functional group transformations were done.

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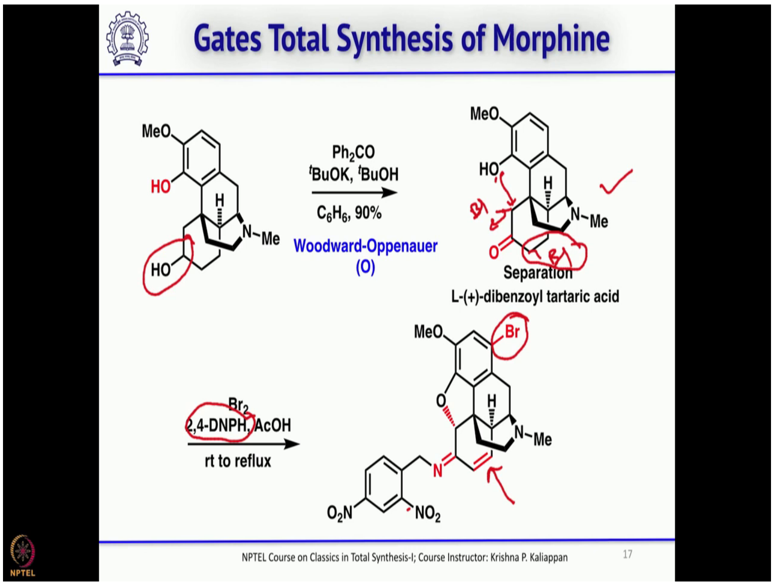

Gates Total Synthesis of Morphine

Ph_2CO
^tBuOK, ^tBuOH
C_6H_6, 90%
Woodward-Oppenauer
(O)

Separation
L-(+)-dibenzoyl tartaric acid

Br_2
2,4-DNPH, AcOH
rt to reflux

So, now they could get the corresponding phenol. Then, you oxidize the secondary alcohol. So, this was done using Woodward-Oppenauer oxidation condition to get this ketone. See, until here this was a racemic synthesis, ok. Until here it was a racemic synthesis. And at this point, they resolved with dibenzoyl tartaric acid to get that naturally occurring skeletal, ok. So, the dibenzoyl tartaric acid was used as a resolving agent.

Then, comes the key step. See, in this one step, many reactions were done. What is that? You add bromine and 2, 4 di-nitro phenyl hydrazine and acetic acid. Look at the product, how many reactions were done in one step? Ok. One this bromine was introduced, just obviously, if you have a phenol and if you treat with bromine, bromination will take place, fine. Then, what happen? You introduce a bromine here, you introduce a bromine here. So, basically 3 bromines were introduced, ok. That is the first step.

Second step this one cyclizes, this one cyclizes form of the dihydrofuran ring. And third one the elimination of HBr, elimination of HBr to introduce this double bond. And the fourth step, the ketone underwent 2, 4 di-nitro benzyl amine it form an imine, ok. So, 4 steps took place in this one step. 4 reactions took place in this one step.

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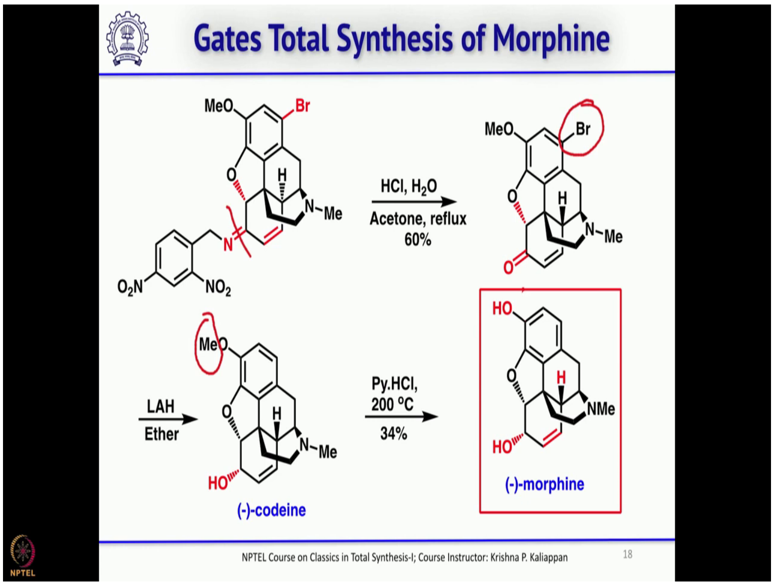

Gates Total Synthesis of Morphine

HCl, H_2O
Acetone, reflux
60%

LAH
Ether

(-)-codeine

Py.HCl,
200 °C
34%

(-)-morphine

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So, once we have that, next you have to hydrolyze this imine to get back your ketone. So, that was done with HCl and water. And the next step, just before completing the total synthesis is to remove or reduce the ketone, ok reduce the enone to corresponding allylic alcohol and remove the bromine. So, both were done in one step by doing, by treating with LAH.

And this is nothing but another natural product called codeine. And from codeine you what you need to do is just to do the demethylation. So, that was done with pyridine HCl at 200^o to get the corresponding demethylated compound which is nothing but morphine.

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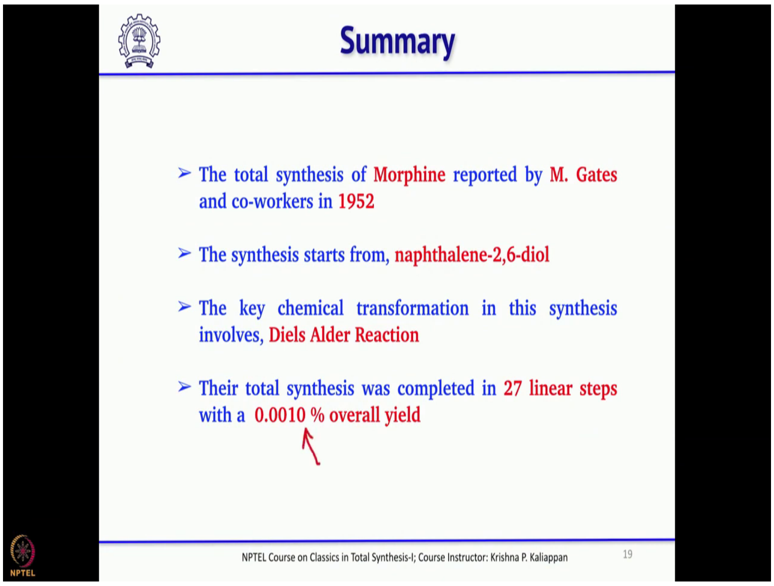

Summary

- The total synthesis of Morphine reported by M. Gates and co-workers in 1952
- The synthesis starts from, naphthalene-2,6-diol
- The key chemical transformation in this synthesis involves, Diels Alder Reaction
- Their total synthesis was completed in 27 linear steps with a 0.0010 % overall yield

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So, overall if you look at that synthesis, it was started from a naphthalene 2, 6 diol and the key reactions were Diels-Alder reaction and one part tri-bromination, elimination, cyclization and imine formation. So, this is the second key step. And it took about 27 longest linear steps, and the yield was poor, but considering the conditions on the year in which it was reported and that was the first total synthesis as well it was one of the classical synthesis of morphine reported until now, ok.

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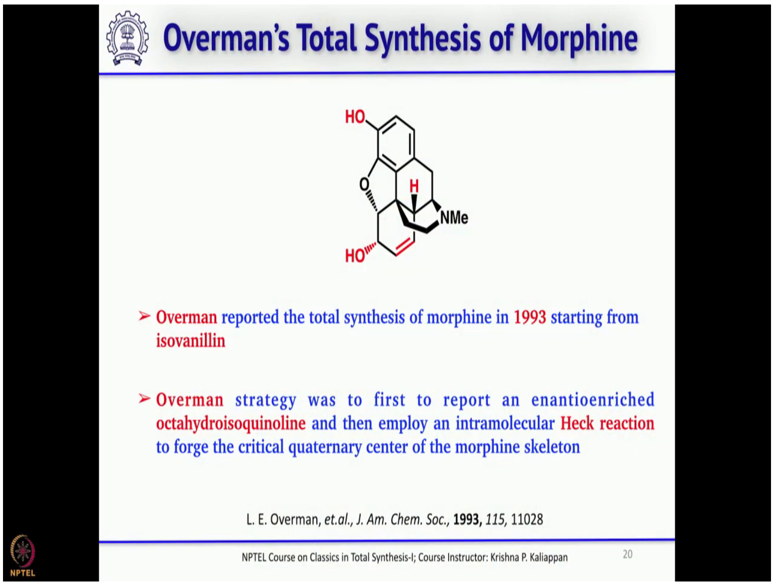

Overman's Total Synthesis of Morphine

- Overman reported the total synthesis of morphine in 1993 starting from isovanillin
- Overman strategy was to first to report an enantioenriched octahydroisoquinoline and then employ an intramolecular Heck reaction to forge the critical quaternary center of the morphine skeleton

L. E. Overman, *et.al.*, *J. Am. Chem. Soc.*, **1993**, *115*, 11028

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So, now we will move to the second total synthesis. Actually, this was the first I would say, asymmetric total synthesis, and was reported by Overman. And he has used an intramolecular Heck reaction; intramolecular Heck reaction as the key reaction to synthesize morphine.

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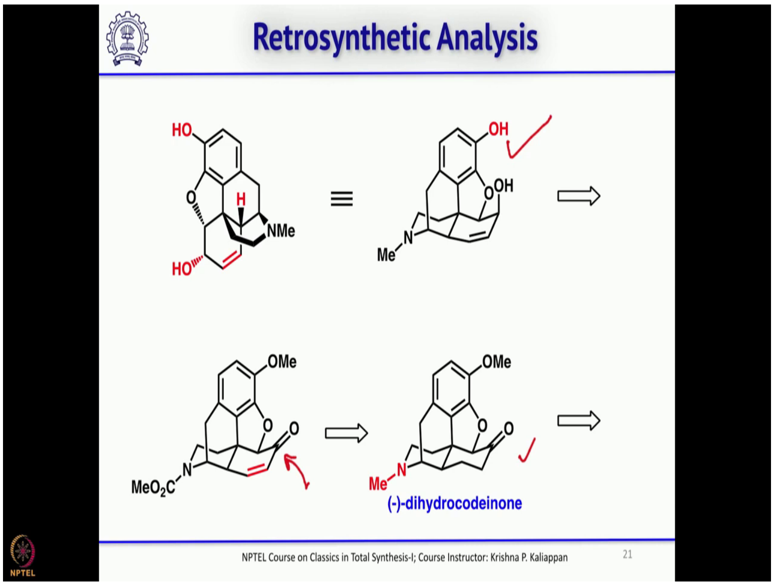

Retrosynthetic Analysis

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Let us see how he has done the retro synthesis because when you write conformational, it is easy to visualize, and this can be obtained from this enone, ok. Simple reduction of this enone you will get this axial alcohol. Now, you reduce the double bond, because the double bond can be reduced when we go for the forward reaction. So, this will lead to this compound called dihydrocodeinone, ok.

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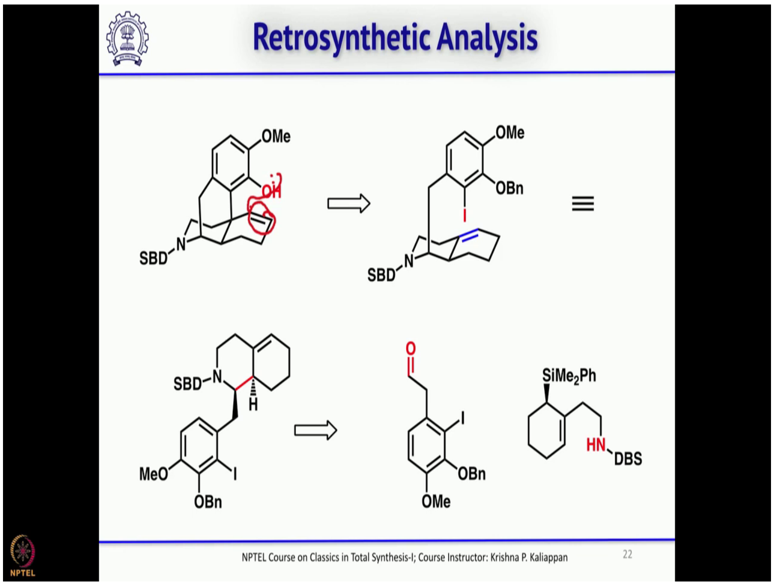

Retrosynthetic Analysis

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And that can be obtained from this alcohol. So, basically if you treat with m-CPBA, so it will form epoxide and then immediately this can cyclase, is not it. And this double bond can be obtained through intramolecular Heck cyclization and that can be obtained from these two compound, ok. So, you have aldehyde and this amine, and it can cyclase to give this compound.

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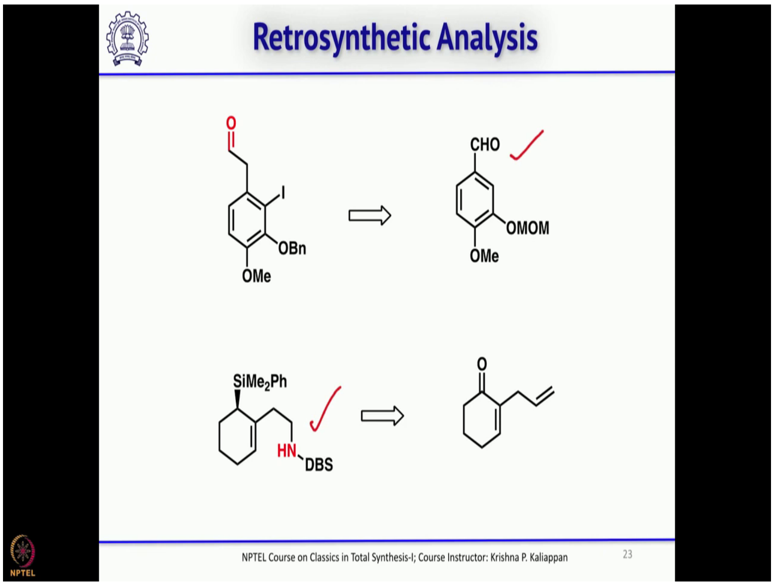

Retrosynthetic Analysis

And this particular compound that silyl one, can be obtained from this aldehyde. So, that aldehyde can be obtained from this di-protected aldehyde using a homologation and this particular allyl cyanine can be obtained from two allyl cyclohexane, ok.

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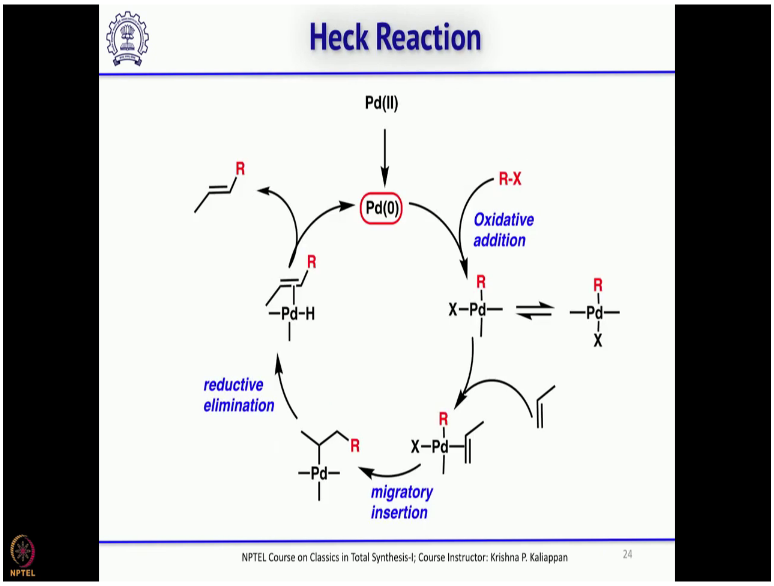

Heck Reaction

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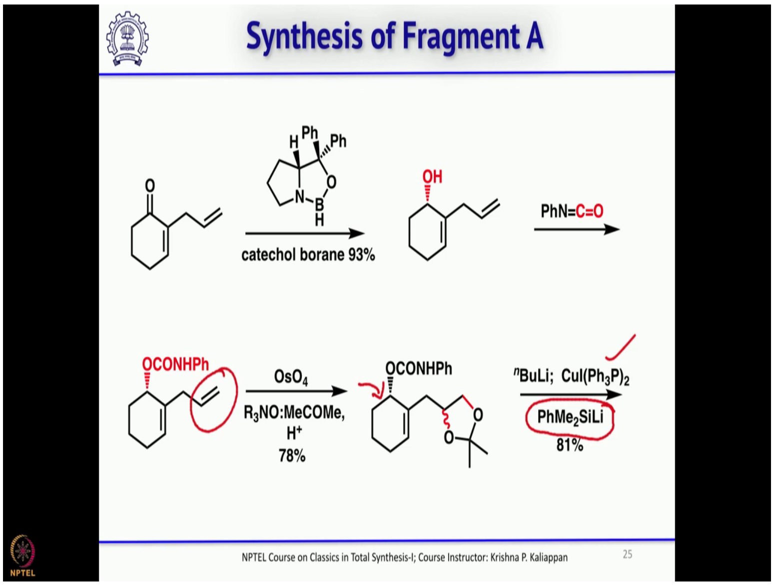

Synthesis of Fragment A

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Now, let us see how this synthesis was done. And this is the you know catalytic cycle for Heck reaction. So, I will not go into the details. So, Heck reaction is one of the well-known reaction and he has cleverly used this tetra molecular Heck reaction in the total synthesis of morphine. So, he started with two allyl cyclohexanone and used CBS reagent that is Corey-Bakshi-Shibata, borane reagent acts as a borane oxazaborolidine to get this allylic alcohol. And once you have this then treat with phenyl isocyanate to get the corresponding carbamate.

Now, the silyl group was introduced, and for that, before you do that this double bond should be protected. So, he did osmium tetroxide di-hydroxylation followed by protection. So, you get the corresponding acetonide, then you treat with this phenyl dimethyl silyl lithium in the presence of copper. So, it undergoes S_N2 reaction on this, SN 2 reaction on that particular carbon leaving this compound, ok.

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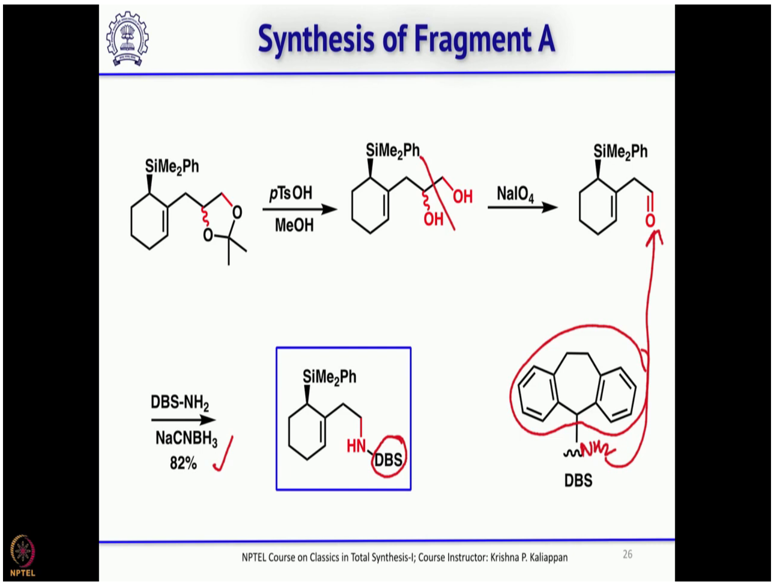

Synthesis of Fragment A

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So, once you have that you remove the acetonide and you get the diol and treat with sodium periodate, it cleaves the diol to get the corresponding aldehyde, ok. You have that aldehyde then you treat with dibenzo suberone amine, ok. And that along with sodium cyano borohydride, it undergoes a reductive amination, ok. So, so the DBS is nothing, but dibenzo suberone, ok. That -NH$_2$, ok this -NH$_2$, here if it is -NH$_2$, the -NH$_2$ will undergo imine formation followed by reduction you get this.

This is nothing but a protecting group. This DBS is a protecting group that can be cleaved under hydrogenation condition.

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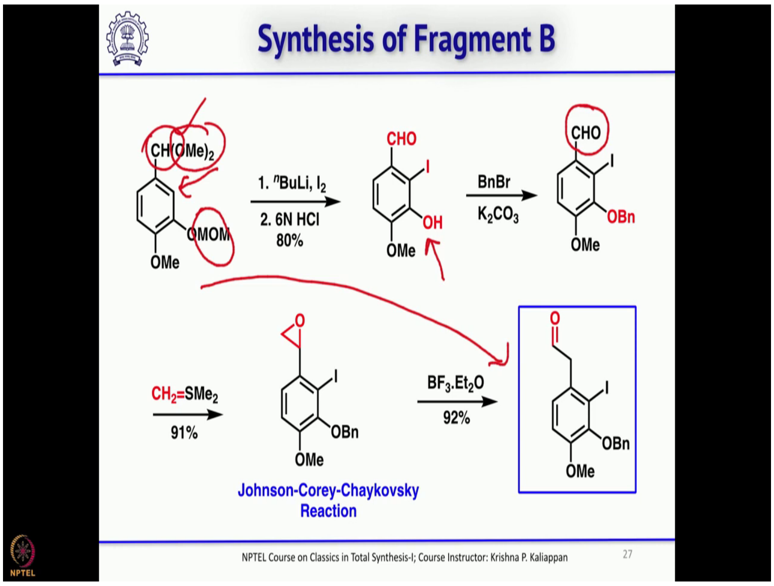

Synthesis of Fragment B

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So, you have this NH. So, now, this aldehyde, which is you know commercially available was protected as di-methoxy acetal, you treat with butyl lithium and quench with iodine followed by removal of the acetal, you introduce the iodine here as well as remove this. Not only the acetal will be removed, but also MOM group also will be removed, ok.

So, first you introduce the iodine, the MOM group helps to introduce at this carbon and then remove the MOM group as well as the acetal using HCl condition. Then, protect the hydroxyl group, protect the phenolic hydroxyl as the benzyl ether. Then, you homolog it the aldehyde to corresponding epoxide with dimethyl sulfonium ion. Then, that epoxide and treatment with BF_3 etherate, it rearranges to give the aldehyde which is now the homologated aldehyde. If you see this is the -CHO, protected -CHO and you have increased it by one carbon.

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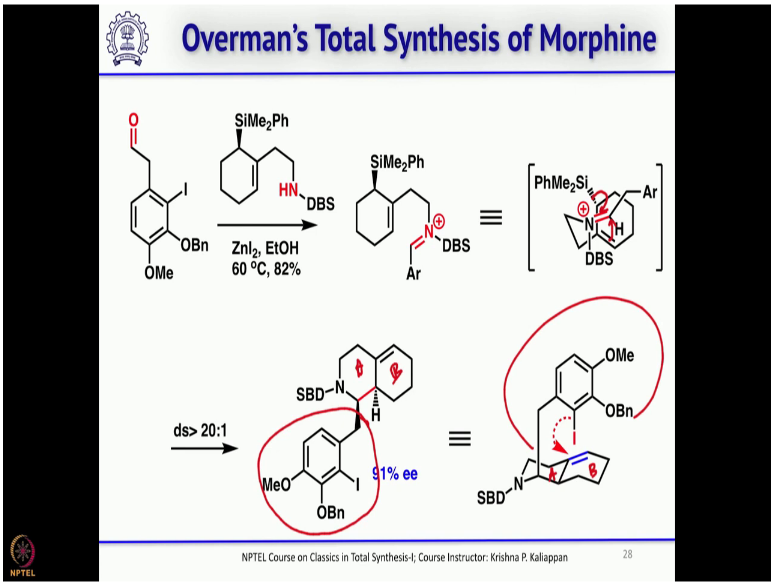

Overman's Total Synthesis of Morphine

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Take this aldehyde and then treat with this amine which we already discussed and do the reductive cyclization, ok. First, it forms the iminium ion and that iminium ion undergoes, this is a key cyclization. You can see this double bond will add and the silicon will come here. So, because whenever you generate a positive charge at β carbon with respect to silicon, the silicon will stabilize the positive charge, ok.

So, that is called β silicon effect and that gives you this particular compound in 91 percent ee. This also can be written like this, ok. So, I just leave it for few seconds, so that you can understand. So, this can be redrawn like this. So, this is the A ring, this is the B ring. So, you can see this is A, so this is B and the whole unit is here. So, now, this is set for the intramolecular Heck cyclization. So, when you do the Heck cyclization, the double bond also will migrate, is not it.

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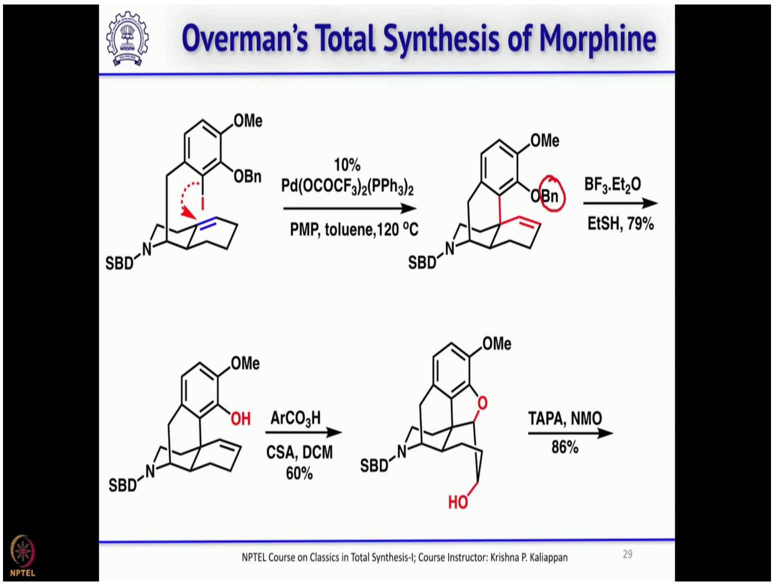

Overman's Total Synthesis of Morphine

10% $Pd(OCOCF_3)_2(PPh_3)_2$ → PMP, toluene, 120 °C

$BF_3.Et_2O$ → EtSH, 79%

$ArCO_3H$ → CSA, DCM 60%

TAPA, NMO → 86%

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So, that is how the double bond migrates and then C-C bond formation takes place. And now once you have the double bond, as I said you can treat with m-CPBA, ok you can treat with m-CPBA to get the epoxide, and that epoxide can be opened. But before that you need this benzyl group to be removed. So, then only as soon as the epoxide is formed the phenyl can open the epoxide.

So, benzyl group removal was selectively done with BF_3 etherate and ethanethiol, and you get the corresponding phenol, then you can treat with m-CPBA camphor sulfonic acid. So, the as soon as the epoxide is formed, intramolecularly the phenol will open the epoxide to give this alcohol, ok. So, now you can see all the 5 rings are ready, ok.

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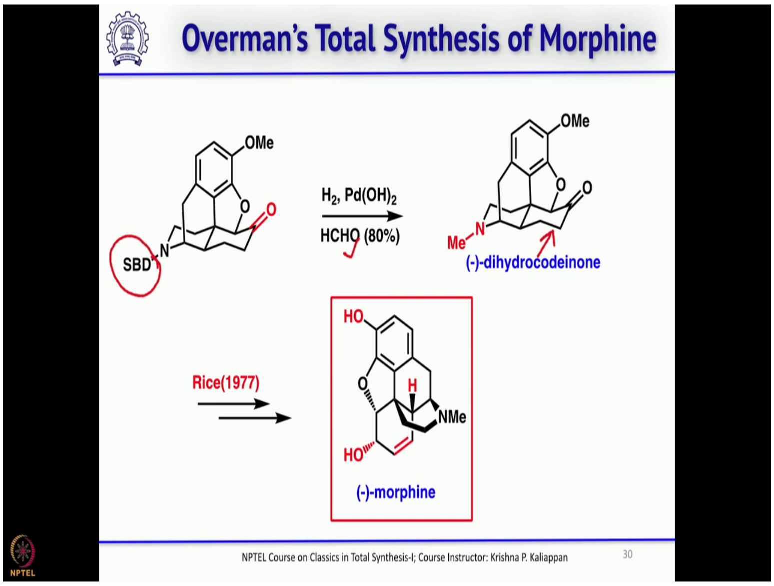

Overman's Total Synthesis of Morphine

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Oxidize the secondary alcohol, ok, to get the ketone, then remove that protecting group to get the corresponding secondary amine. And what you do, when you remove that; so, in the presence of formaldehyde what happens as soon as the -NH is formed, the -NH reacts with formaldehyde to form the iminium ion, ok. That iminium ion again is further reduced and you get the corresponding methyl group. So, if you look at this, this is dihydrocodeinone. What needs to be done is you have to introduce the double bond and reduce it. So, this is, this was already reported.

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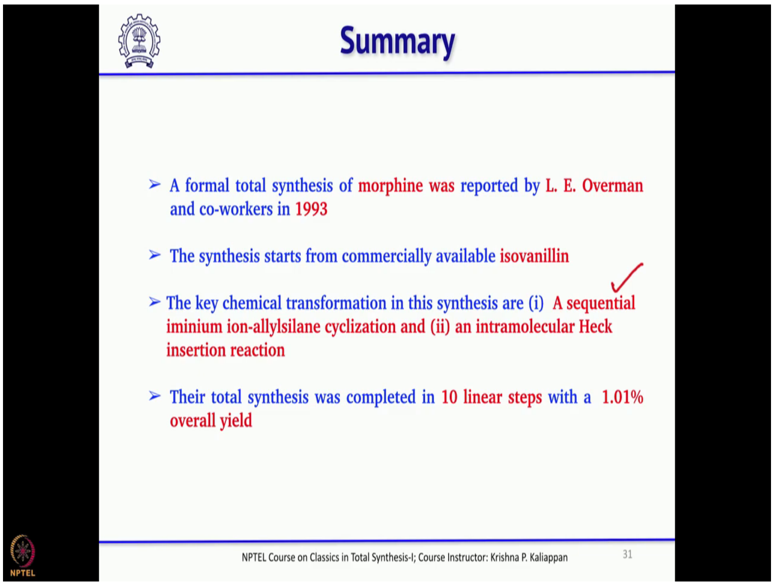

Summary

- A formal total synthesis of morphine was reported by L. E. Overman and co-workers in 1993
- The synthesis starts from commercially available isovanillin
- The key chemical transformation in this synthesis are (i) A sequential iminium ion-allylsilane cyclization and (ii) an intramolecular Heck insertion reaction
- Their total synthesis was completed in 10 linear steps with a 1.01% overall yield

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So, that is how Overman's, a formal synthesis of morphine was done, where intramolecular Heck reaction was the key step and he started from the commercially available isovanillin. And second important key step was sequential iminium ion allyl silane cyclization. Overall, he took about 10 steps and yield also was quite high compared to what Gates has reported, is about 1% overall yield. 10 steps, 1% overall yield is less.

But you have to see, this is a conceptually a new synthetic route to synthesize morphine in 1993, ok. So, I will stop here. And then, we will continue our discussion on total synthesis of morphine by two more groups in the next lecture, ok.

Thank you.