Classics in Total Synthesis-I
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Lecture - 22
Carpanone

Good morning. Welcome back to Classics in Total Synthesis lecture series. And, we have been talking about total synthesis of natural products having six-membered ring. So, we spoke about total synthesis of longifolene in the last lecture. So, today we will continue our discussion on total syntheses of few more natural products, particularly today we talk about total synthesis of one interesting natural product called Carpanone.

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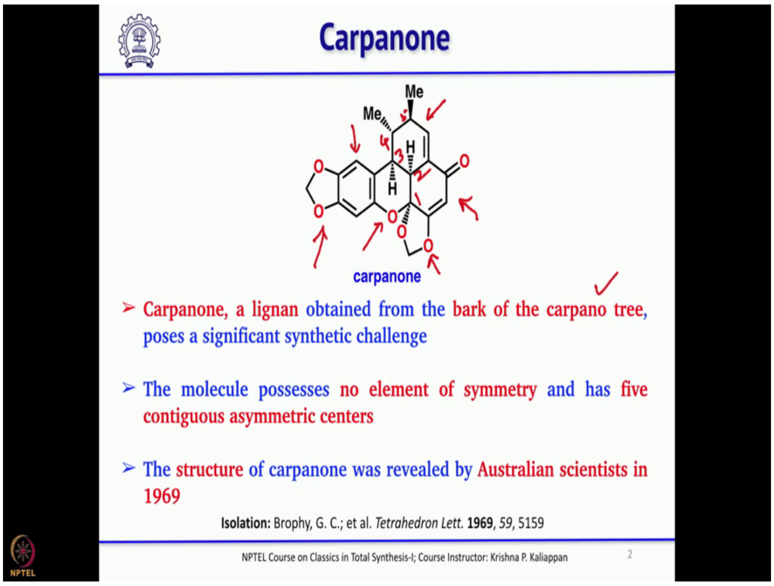

Carpanone

carpanone

- Carpanone, a lignan obtained from the bark of the carpano tree, poses a significant synthetic challenge
- The molecule possesses no element of symmetry and has five contiguous asymmetric centers
- The structure of carpanone was revealed by Australian scientists in 1969

Isolation: Brophy, G. C.; et al. *Tetrahedron Lett.* **1969**, *59*, 5159

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So, this carpanone was isolated from the bark of carpono tree. And, as you can see from the structure it has 3 six-membered rings 1, 2, 3 and 1 aromatic ring of course, you have 2 five-number rings, ok. So, it poses enough synthetic challenge. And, it also has 5 contiguous asymmetric centers, ok, 1, 2, 3, 4, 5. There are 5 contiguous asymmetric centers.

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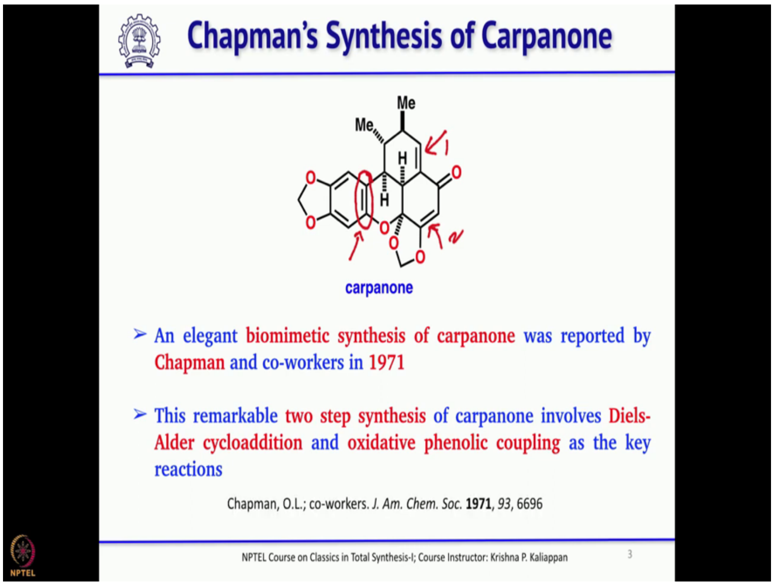

Chapman's Synthesis of Carpanone

carpanone

- An elegant biomimetic synthesis of carpanone was reported by Chapman and co-workers in 1971
- This remarkable two step synthesis of carpanone involves Diels-Alder cycloaddition and oxidative phenolic coupling as the key reactions

Chapman, O.L.; co-workers. *J. Am. Chem. Soc.* **1971**, *93*, 6696

But there was very interesting total synthesis reported by Chapman and this involved 2 key reactions one is intramolecular Diels-Alder reaction. So, other one is an oxidative coupling reaction. So, this was reported in 1971 and when you look at this molecule, you can see at least there are 2 double bonds in a cyclohexene ring, ok. So, whenever you have a six-membered ring with a double bond, then one reaction which should come to your mind is Diels-Alder reaction.

See for example, if you look at this molecule you can see there is 1 double bond here, that one can think of being constructed using a Diels-Alder reaction. There is another one here. So, 1, 2. This also in principle can be thought of being made through Diels-Alder reaction. There is one more double bond, ok, which you cannot see properly as a part of cyclohexene, but this is part of an aromatic ring, that also can be thought as a double bond which could be formed as a result of Diels-Alder reaction. But, here in this case it should be formed as a result of hetero Diels-Alder reaction.

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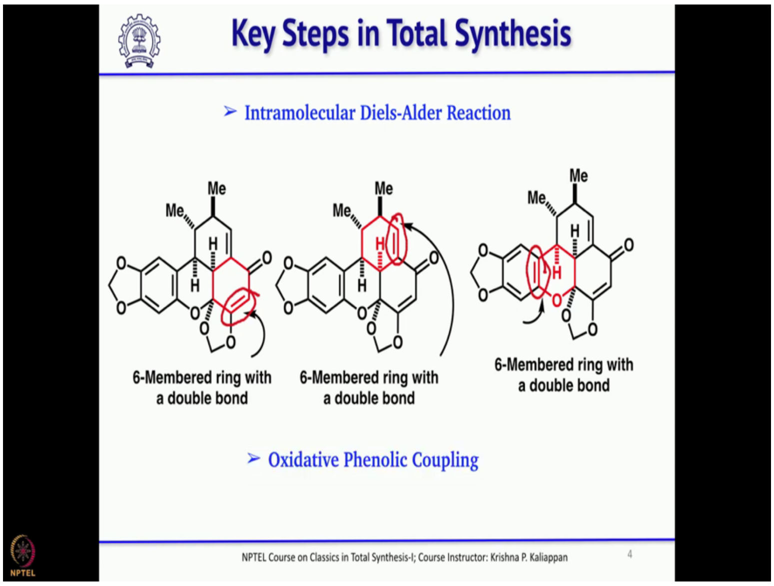

Key Steps in Total Synthesis

- ➢ Intramolecular Diels-Alder Reaction

6-Membered ring with a double bond

6-Membered ring with a double bond

6-Membered ring with a double bond

- ➢ Oxidative Phenolic Coupling

So, now let us see intramolecular Diels-Alder reaction could be successfully used in this total synthesis. For example, if you have to make this double bond, using intramolecular Diels-Alder reaction, ok, what should be the precursor? Likewise, if you have to make this double bond using intramolecular Diels-Alder reaction, what should be the precursor?

And the third option is this, ok. Now, let us see each double bond and how they can be made using the key intramolecular Diels-Alder reaction? Or, what should be the precursor for making these three? Then we will choose the right one. Of course, it should be followed by oxidative phenolic coupling. This is what Chapman has proposed.

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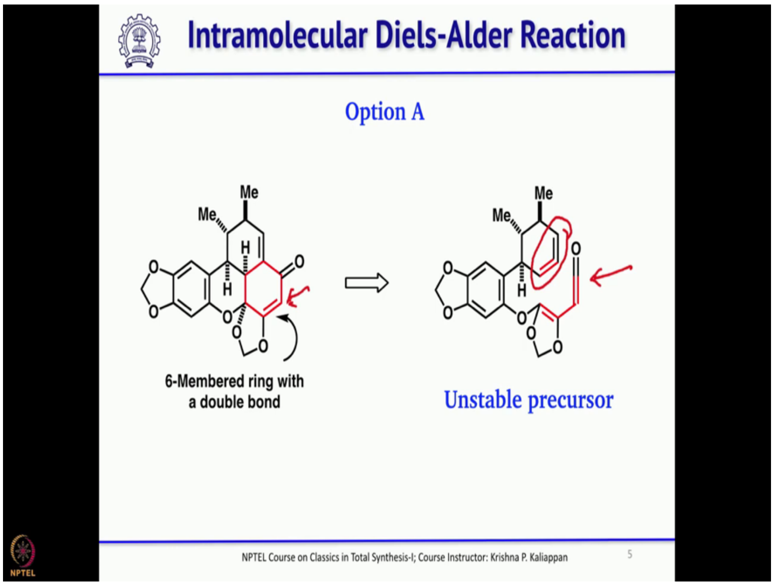

Intramolecular Diels-Alder Reaction

Option A

6-Membered ring with a double bond

Unstable precursor

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First, option A, if you want this double bond to be made using intramolecular Diels-Alder reaction, what should be the precursor? The precursor should be this one. And, what you can see here, you have a diene, in that diene one of the double bond is part of ketene. As you know ketene is unstable. And, second difficulty is you have a cyclic allene, a six-membered cyclic allene almost very difficult to make. So, this disconnection leads to highly unstable precursor, ok. So, option A could be ruled out.

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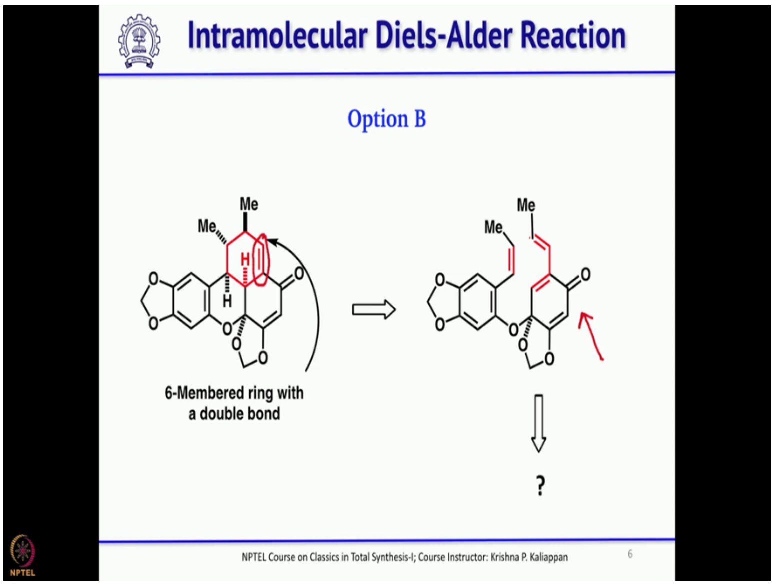

Intramolecular Diels-Alder Reaction

Option B

6-Membered ring with a double bond

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Now, let us see option B. So, option B you want to make this double bond, using intramolecular Diels-Alder reaction. So, then, what should be the precursor? Your precursor should be this, ok. It is still possible. But, maybe the precursor to this triene may not be that easy, ok. So, let us look at option C and then see whether that will be easy to make.

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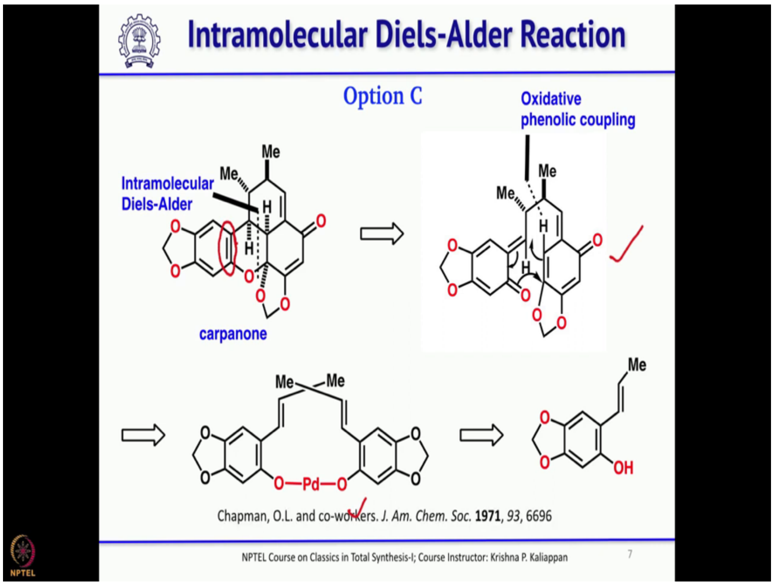

Intramolecular Diels-Alder Reaction

Option C

Oxidative phenolic coupling

Intramolecular Diels-Alder

carpanone

Chapman, O.L. and co-workers. *J. Am. Chem. Soc.* **1971**, *93*, 6696

So, for example, if you use or if you think about this double bond being made by intramolecular Diels-Alder reaction, then what you expect is this precursor. So, now if you look at this precursor, one can also further visualize, first of all it can undergo intramolecular Diels-Alder reaction and during that process this ring gets aromatised, ok. So, that is the driving force.

Second, as you have seen here if you break this one, that can lead to a symmetrical alcohol, symmetrical phenol, ok. This symmetrical phenol can undergo oxidative phenolic coupling, that will give you this intermediate which spontaneously can undergo an intra-molecular Diels-Alder reaction to form carpanone. So, what should be the starting material? The starting material is this compound, ok.

So, before we actually go into the details of the total synthesis of carpanone by Chapman, let us briefly discuss the 2 key reactions which are being used to synthesize carpanone. The first one is the intramolecular Diels-Alder reaction.

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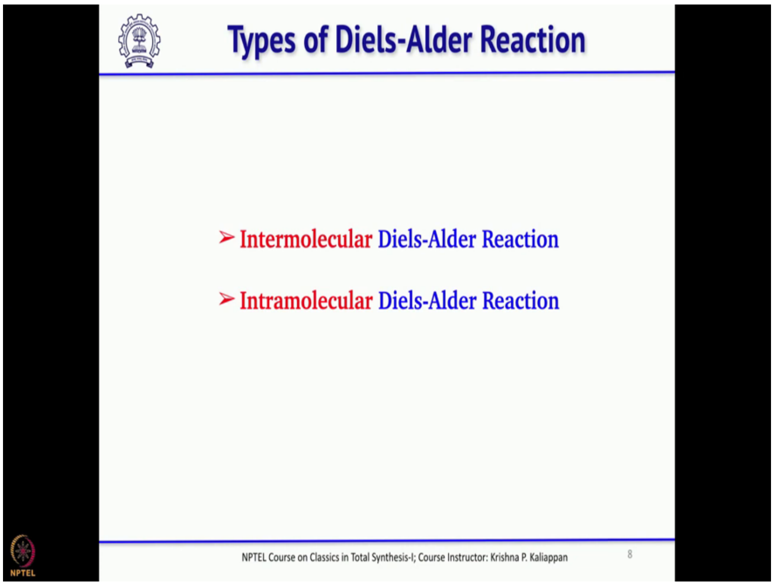

Types of Diels-Alder Reaction

- Intermolecular Diels-Alder Reaction
- Intramolecular Diels-Alder Reaction

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See, normally when you talk about Diels-Alder reaction, there are 2 types of Diels-Alder reaction; one is inter molecular Diels-Alder reaction. See, this intermolecular Diels-Alder reaction is the most common one you will see. And there are many intramolecular Diels-Alder reaction which can give more rings, ok.

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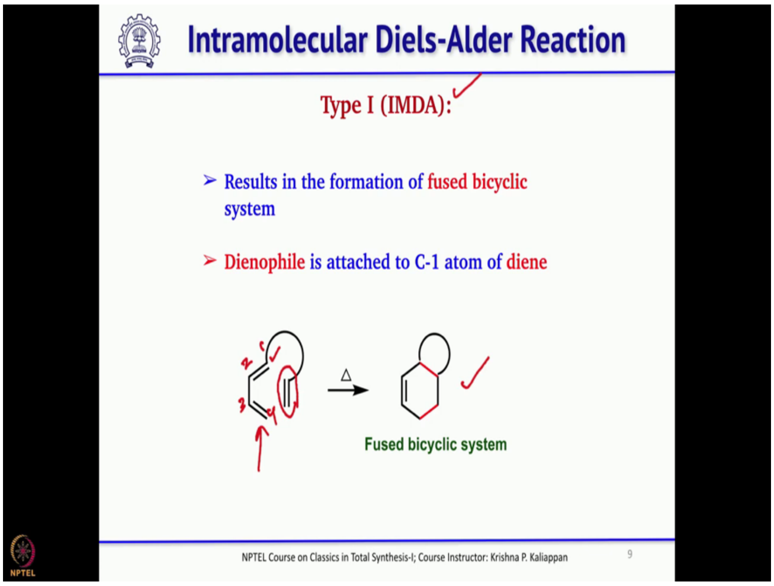

Intramolecular Diels-Alder Reaction

Type I (IMDA):

- Results in the formation of fused bicyclic system
- Dienophile is attached to C-1 atom of diene

Fused bicyclic system

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When you talk about intra molecular Diels-Alder reaction, they are mentioned as IMDA Intra Molecular Diels-Alder Reaction, say they write IMDA. And again, this IMDA is of two types; one is Type I, the other one is Type II. So, what is type I? Type I intramolecular Diels-Alder reaction means, you have the dienophile attached to carbon number 1 of the diene.

So, if you look at this diene; if you look at this diene, you start numbering from here 1, 2, 3, 4. Now, the dienophile if this is attached to carbon number 1 if this is attached to carbon number 1, then this intra molecular Diels-Alder reaction is called “IMDA type I”, ok because, it is attached to carbon number 1. So, that normally gives a fused bicyclic system, ok, that normally upon intramolecular Diels-Alder reaction gives fused bicyclic system.

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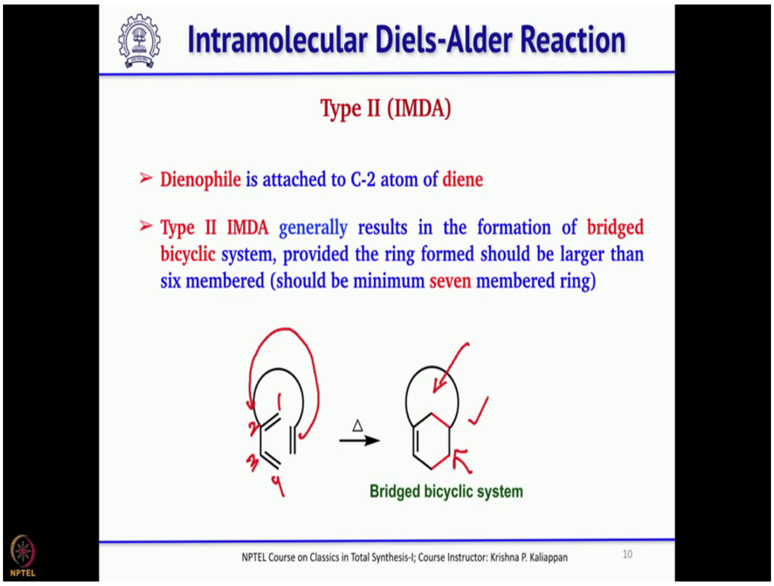

Intramolecular Diels-Alder Reaction

Type II (IMDA)

- Dienophile is attached to C-2 atom of diene
- Type II IMDA generally results in the formation of bridged bicyclic system, provided the ring formed should be larger than six membered (should be minimum seven membered ring)

Bridged bicyclic system

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Whereas, the type II where, your dienophile is attached to carbon number 2, ok, you can 1, 2, 3, 4. Now, your dienophile is attached to carbon number 2. This preferably and most likely gives bridged bicyclic system, ok. This gives bridged bicyclic system. And, if you look at this to form the bridged bicyclic system, you should have minimum seven-membered ring.

So, this will be always six-membered ring, is not it? 4 plus 2 cyclo addition will give six-membered ring. But, the ring size of the other ring which is going to be formed should be minimum seven-membered ring then only type II IMDA Diels-Alder reaction will work. Now, the reaction which we thought about or which Chapman used in the synthesis of carpanone is type I IMDA reaction; because that gives fused bicyclic system.

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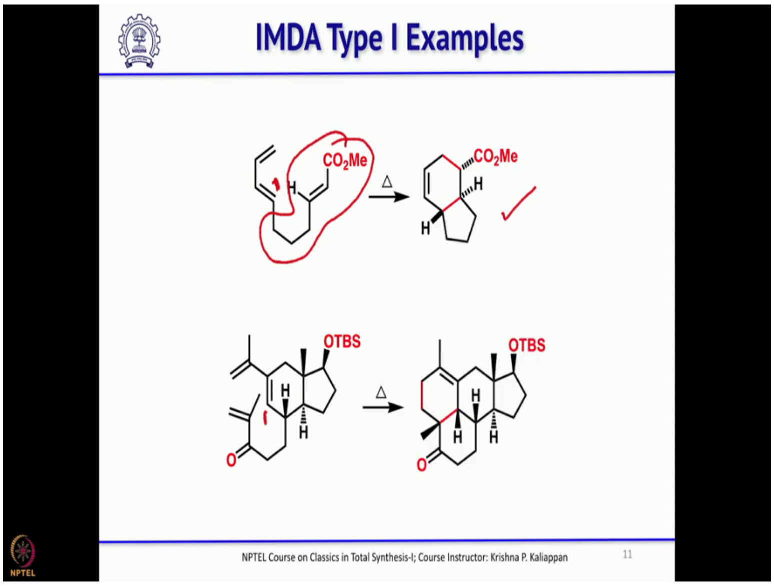

IMDA Type I Examples

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The other key reaction which we used is pinacol coupling, which I will come to the later. So, for IMDA type I, I am giving couple of examples. So, you can see it is type I because, the whole dienophile unit is attached to carbon number 1, that undergoes intramolecular Diels-Alder reaction to give this fused bicyclic system. And, this is another complicated system.

But, that also you can see the dienophile is attached to carbon number 1. So, this also should give the fused system.

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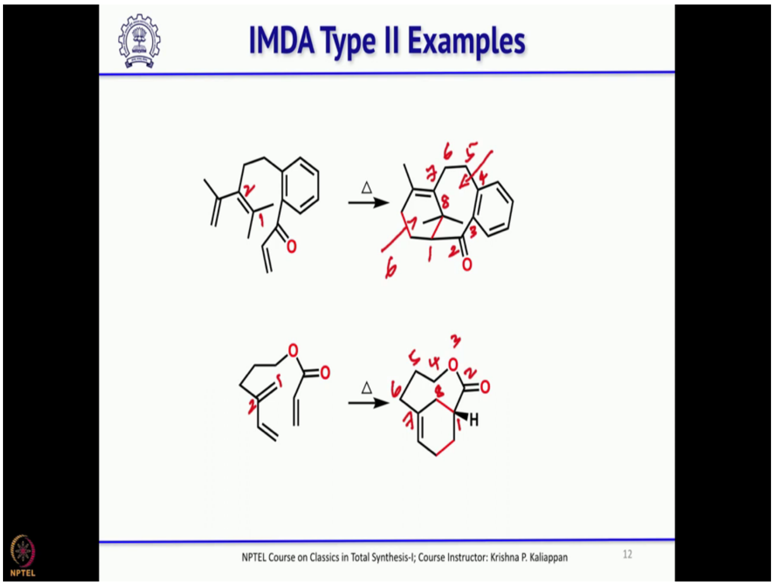

IMDA Type II Examples

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Whereas type II, is where you have the dienophile attached to carbon number 2. So, you can see here 1, 2. The dienophile is attached to carbon number 2. So, that will give you the bridged bicyclic system, ok. This is a classical example, where you form this tricyclic system using an intramolecular type II Diels-Alder reaction. Again, here in this example you see 1, 2. So, at carbon number 2 of the diene your dienophile is attached. So, that gives the bridged bicyclic system.

So, now, what you have to look at is the ring size being formed as a result of this IMDA type II reaction; obviously, 1 ring will be six-membered ring because this intramolecular Diels-Alder reaction 4 plus 2 should give six-membered ring, but you should calculate the ring size you should see the ring size of the other ring which is formed. So, now, if you look at this is 1, 2, 3, 4, 5, 6, 7, 8 as I said minimum seven-membered ring should be formed then only IMDA type II is possible.

So, here is eight-membered ring. And, in this example, you can see 1, 2, 3, 4, 5, 6, 7, 8. Again, this is eight-membered ring and this eight-membered ring could be successfully formed using IMDA type II reaction. Normally, eight-membered rings are little difficult to form, but using this IMDA type II one can easily make the eight-membered ring.

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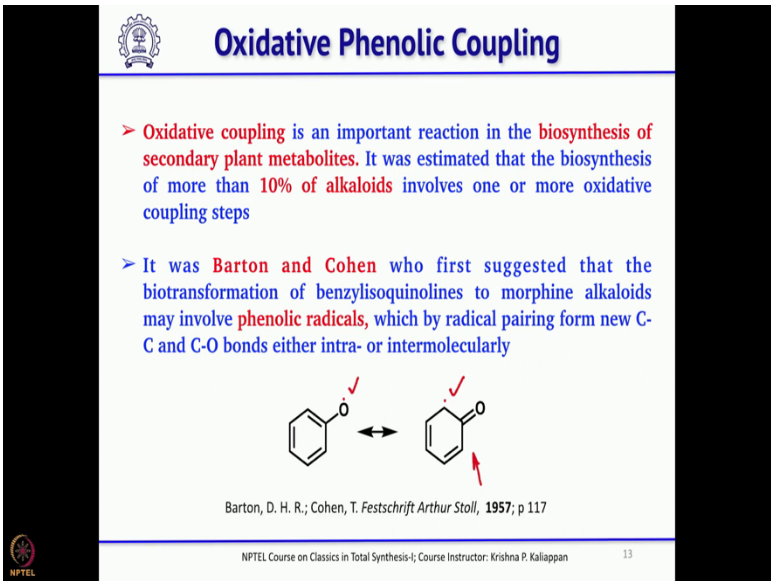

Oxidative Phenolic Coupling

- Oxidative coupling is an important reaction in the biosynthesis of secondary plant metabolites. It was estimated that the biosynthesis of more than 10% of alkaloids involves one or more oxidative coupling steps
- It was Barton and Cohen who first suggested that the biotransformation of benzylisoquinolines to morphine alkaloids may involve phenolic radicals, which by radical pairing form new C-C and C-O bonds either intra- or intermolecularly

Barton, D. H. R.; Cohen, T. *Festschrift Arthur Stoll*, **1957**; p 117

The second key reaction is the oxidative phenolic coupling. In fact, many biosynthesis involves this type of oxidative coupling reaction. And Derick Barton has proposed that many benzyl isoquinolines are converted into morphine alkaloids through this oxidative phenolic coupling reaction, ok. So, what happens? You take a phenol. So, under this condition, it forms this O radical.

The O radical, can tautomerize and then you can get this ketone and this allylic radical, ok. Now, these two can combine, ok, one possibility and other possibility is the same thing can combine, ok. So, like this coupling reaction leads to the formation of dimerization, ok.

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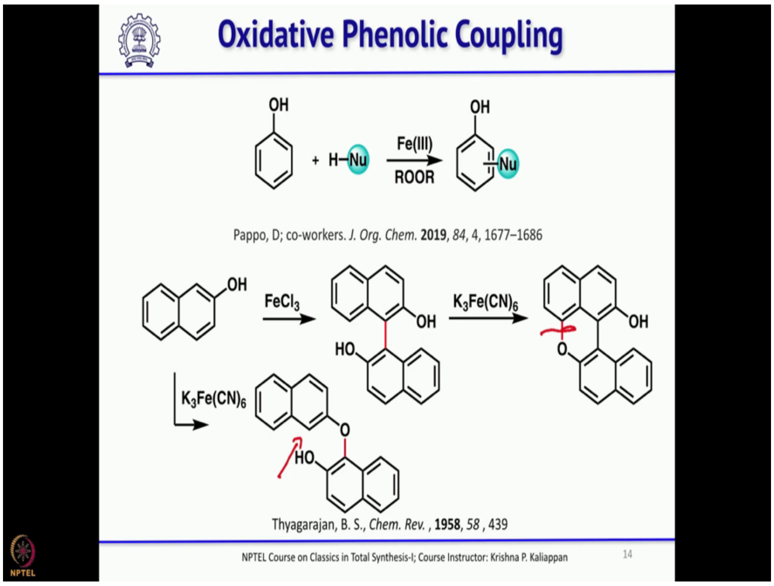

Oxidative Phenolic Coupling

Pappo, D; co-workers. *J. Org. Chem.* **2019**, *84*, 4, 1677–1686

Thyagarajan, B. S., *Chem. Rev.* , **1958**, *58* , 439

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So, I will give one example, where, how this oxidative phenolic coupling took place and what are the products possible; for example, if you take 2-naphthol and then treat with ferric chloride, as you know this is one of the key reactions which is done in tons scale to form binols, ok. And, if you use further oxidation with potassium ferricyanide, so then it can form this bond, ok. This is again through radical and then coupling reaction. And, it can also form to the other side, ok.

So, this type of oxidative phenolic coupling is known and Chapman has cleverly used a combination of oxidative phenolic coupling and intramolecular type I Diels-Alder reaction as key reactions to synthesize carpanone.

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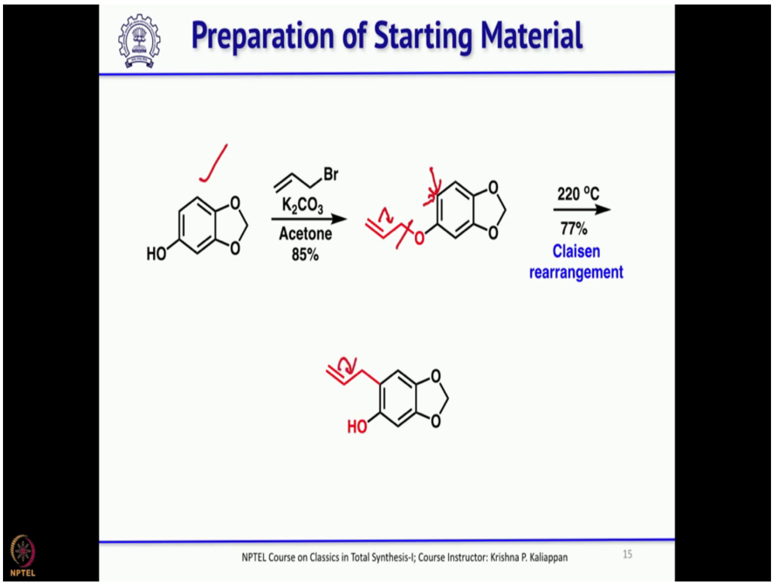

Preparation of Starting Material

Let us see. The starting material where you need the double bond trans double bond was made from this phenol. The first step was allylation, with potassium carbonate and allyl bromide. Introduce the allyl group. Now, what you need is the double bond should be isomerize. So, now, its a terminal double bond. The double bond should go inside, there should be internal double bond; as well as you know it should be at this carbon, ok.

Two things you have to do; one this double bond has to go inside and that should be at the adjacent carbon. So, the transfer of this allyl group to here can be easily done using Claisen rearrangement, ok. So, you just take it and heat it at very high temperature may be above 200. So, one can easily get this Claisen rearrangement product. Now, still the double bond is in the terminal position. So, what you need the double bond should go here.

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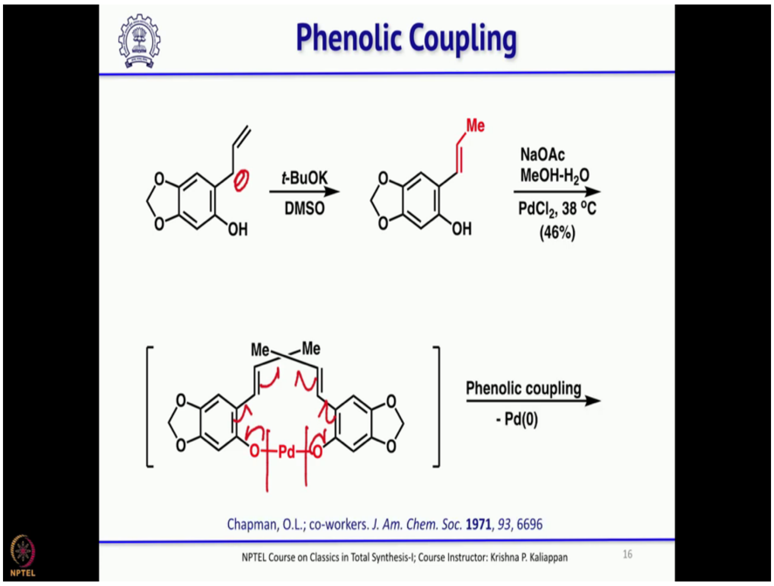

Phenolic Coupling

Chapman, O.L.; co-workers. *J. Am. Chem. Soc.* **1971**, *93*, 6696

So, that is done using potassium tertiary butoxide and DMSO. So, you treat with base strong base. So, like potassium tertiary butoxide, you can generate and isomerize the double bond. And, isomerization takes place to get the trans-alkene. So, the starting material is ready. Next key step is the phenolic coupling.

So, this phenolic coupling was best done with palladium chloride. So, the palladium chloride, it forms this dimer. And, once this dimer is formed, so, it can undergo you know the di-radical and then the di-radical will come and like this it will come. And, the same way it will come. And then it will dimerize. While dimerizing, these two methyl groups will be trans to each other, ok. These two methyl groups will be trans to each other, ok.

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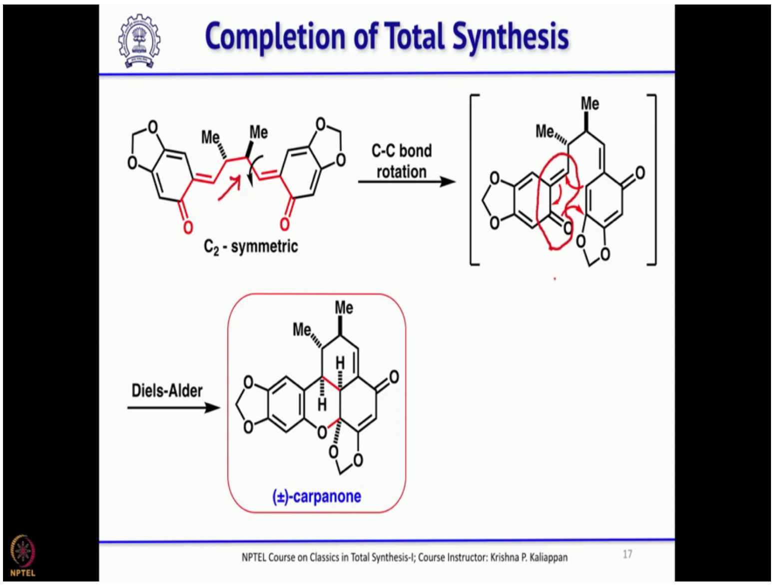

Completion of Total Synthesis

C-C bond rotation

C_2 - symmetric

Diels-Alder

(±)-carpanone

So, now, you can see that this is C2 symmetric compound. And, if you rotate this C-C, bond if you rotate this bond like this, ok, what will happen? You will get this particular intermediate. When you look at this particular intermediate, you can see as originally planned by Chapman, you can see here a diene. This is a hetero-diene, you have oxygen as one of the atoms, ok, you have oxygen as one of the atoms of the diene.

So, this is a hetero-Diels-Alder reaction where, hetero atom is present in the diene and that undergoes an intramolecular type I hetero-Diels-Alder reaction straight away to give carpanone, ok.

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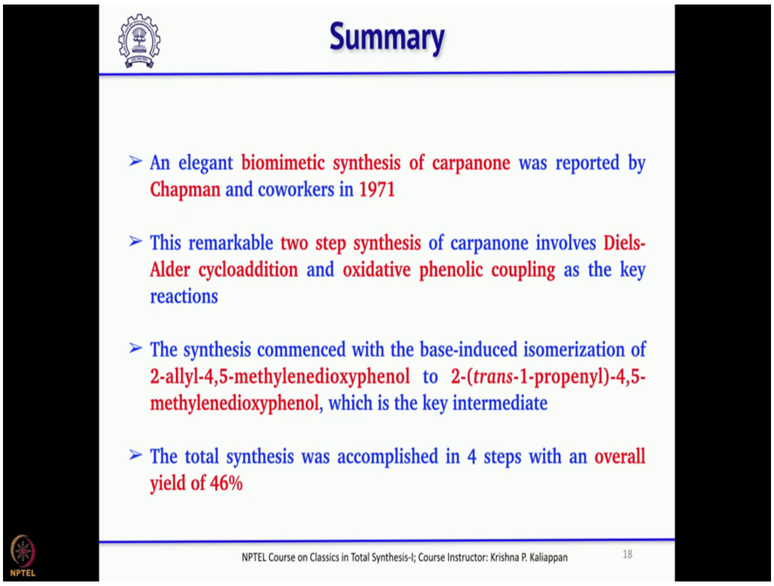

Summary

- An elegant biomimetic synthesis of carpanone was reported by Chapman and coworkers in 1971
- This remarkable two step synthesis of carpanone involves Diels-Alder cycloaddition and oxidative phenolic coupling as the key reactions
- The synthesis commenced with the base-induced isomerization of 2-allyl-4,5-methylenedioxyphenol to 2-(*trans*-1-propenyl)-4,5-methylenedioxyphenol, which is the key intermediate
- The total synthesis was accomplished in 4 steps with an overall yield of 46%

So, basically from commercially available starting material from commercially available starting material, carpanone was synthesized by Chapman in 1971, through what one can call it as bio-mimetic route. So, very elegant bio-mimetic synthesis of carpanone was reported. And his synthesis basically involve 4 steps starting from the corresponding phenol. And the key steps are oxidative phenolic coupling and intramolecular cycloaddition reaction.

And, the overall yield was close to 50 percent you know, you can imagine getting this compound natural product in 50 percent is really outstanding accomplishment, ok.

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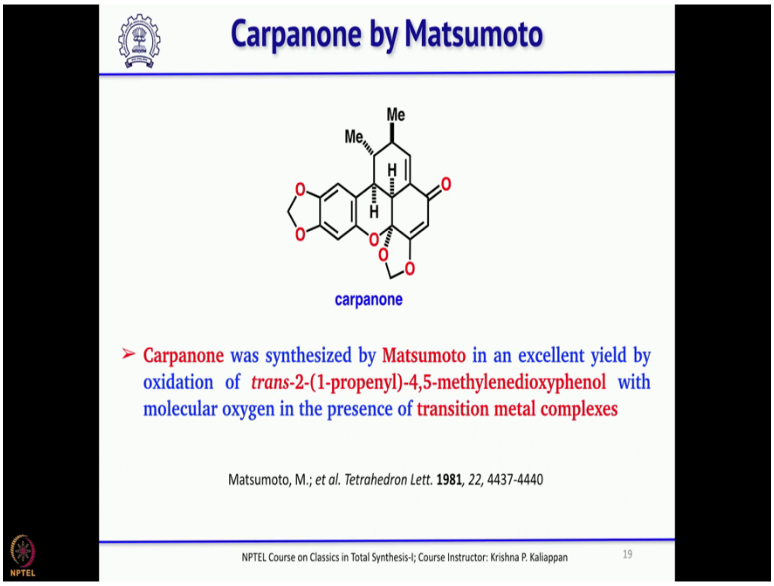

Carpanone by Matsumoto

carpanone

- Carpanone was synthesized by Matsumoto in an excellent yield by oxidation of *trans*-2-(1-propenyl)-4,5-methylenedioxyphenol with molecular oxygen in the presence of transition metal complexes

Matsumoto, M.; *et al. Tetrahedron Lett.* **1981**, *22*, 4437-4440

The second synthesis of carpanone, I will discuss is about Matsumoto synthesis. He also used the same intermediate, the only difference is in the case of Chapman he used palladium; here he used a saline complex, ok. So, the saline complex. And, this gave the directly the natural product not only the oxidative coupling took place, but also the Diels-Alder reaction.

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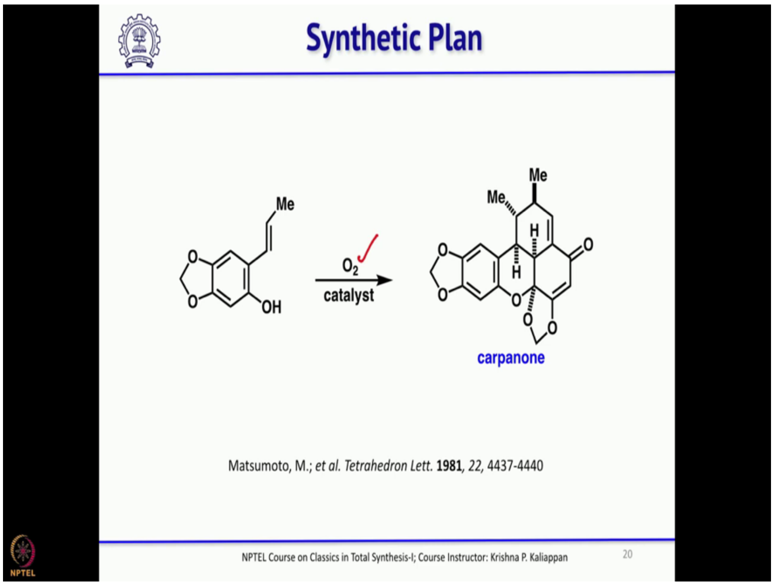

Synthetic Plan

carpanone

Matsumoto, M.; *et al. Tetrahedron Lett.* **1981**, *22*, 4437-4440

So, he started from this phenol which was already reported by Chapman. So, now, he used molecular oxygen in the presence of a catalyst, that gave directly carpanone in one step, ok.

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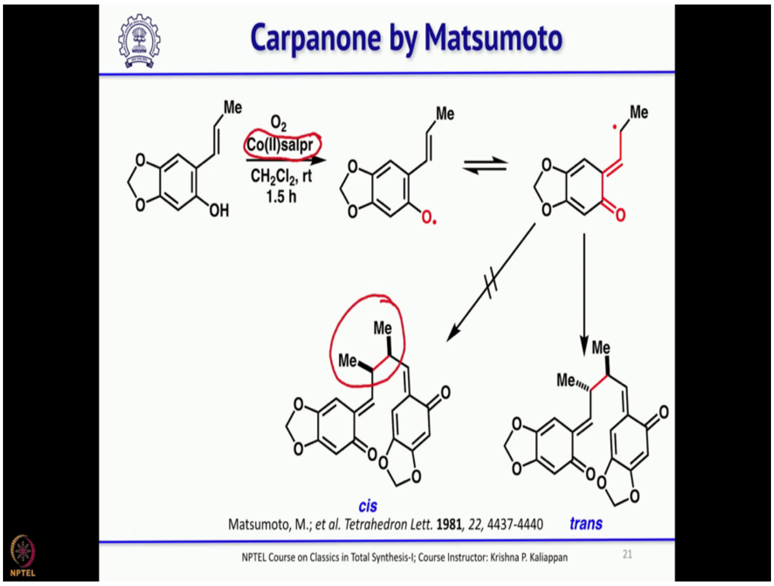

Carpanone by Matsumoto

O_2
Co(II)salpr
CH_2Cl_2, rt
1.5 h

cis

Matsumoto, M.; *et al. Tetrahedron Lett.* **1981**, *22*, 4437-4440

trans

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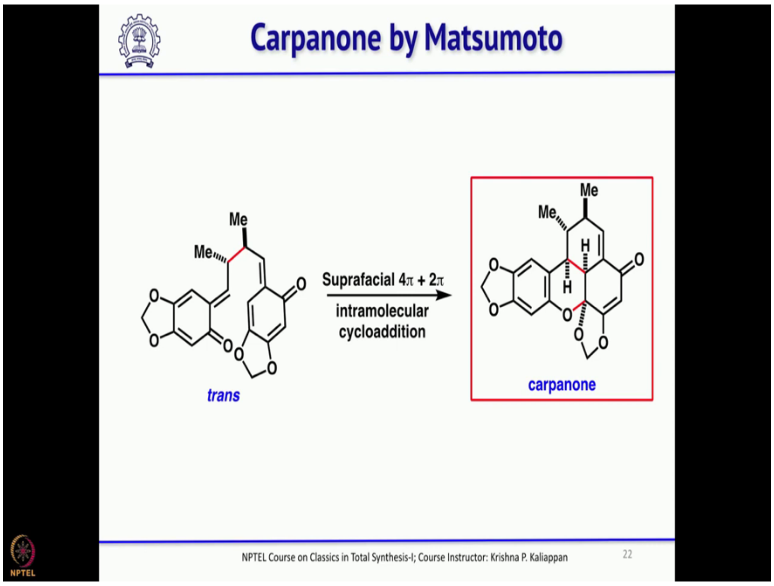

Carpanone by Matsumoto

trans

Suprafacial 4π + 2π
intramolecular
cycloaddition

carpanone

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So, what he did? He took oxygen and cobalt II saline complex and that gives the radical. So, that radical migrates and you get this allyl radical, that spontaneously undergoes dimerization. So, it does not give the cis isomer; it gives only the trans isomer. And, the trans isomer as soon as it is formed, it undergoes intramolecular suprafacial 4 pi plus 2 pi cycloaddition reaction to yield carpanone in one step, from the starting material which was already reported by Chapman, ok.

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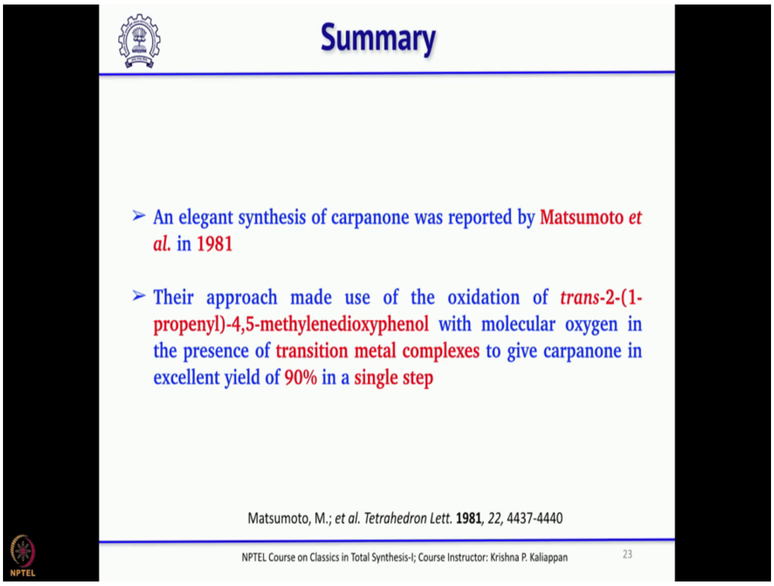

Summary

- An elegant synthesis of carpanone was reported by Matsumoto *et al.* in 1981
- Their approach made use of the oxidation of *trans*-2-(1-propenyl)-4,5-methylenedioxyphenol with molecular oxygen in the presence of transition metal complexes to give carpanone in excellent yield of 90% in a single step

Matsumoto, M.; *et al. Tetrahedron Lett.* **1981**, *22*, 4437-4440

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So, if you look at this synthesis, this is really a very elegant synthesis. And, this was obtained in 90 percent in a single step from the intermediate reported by Chapman, ok. So, I will stop here. And, then I will discuss about one more natural product called mevinolin, in the next class which is very very interesting and complex natural product. And, that was the key starting point for making several you know cholesterol lowering drugs. See you next week.

Thank you.