Pericyclic Reactions and Organic Photochemistry

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Module No. #04
Lecture No. #18
Pericyclic Reactions – Sigmatropic rearrangements continued…
Oxy-Cope and Claisen rearrangement.

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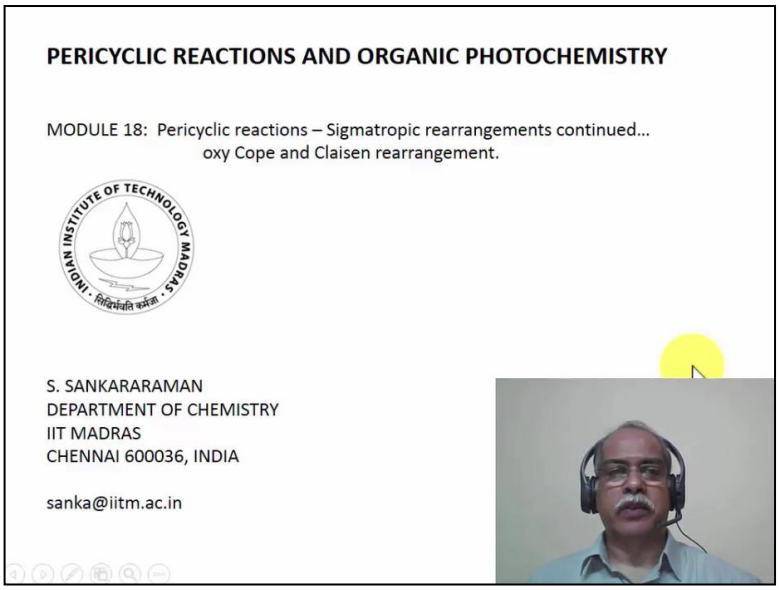

Hello, welcome to the online course on Pericyclic Reactions and Organic Photochemistry. We are in Module Number Eighteen, now. We will continue with Sigmatropic rearrangement. There are certain topics, still left in Sigmatropic rearrangement, such as Oxy-Cope rearrangement, Anionic Oxy-Cope rearrangement, and Claisen rearrangement, and so on. In this module, let us look at the Oxy-Cope, and Anionic Oxy-Cope rearrangement, and Claisen rearrangement.

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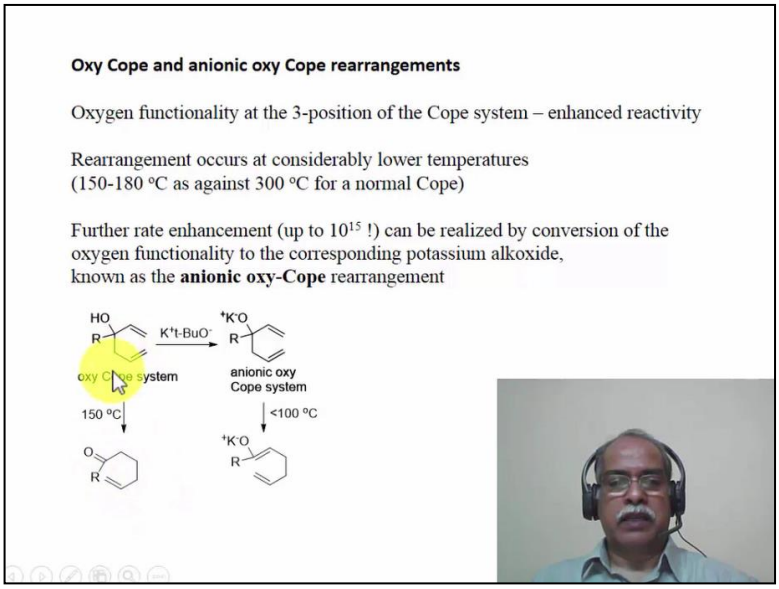

Now, if you introduce an Oxygen functionality, in the 3 position of Cope System, what i mean is, put a substituent with an Oxygen, which is a Hydroxy, or an Alkoxy, or a Phenoxy kind of a substituent, this remote functionalization of this Hexadiene unit, accelerates the Cope rearrangement. So much, so that, a factor of up to 10^{15} enhancement, in the rate has been observed, for such system.

So, this is an Oxy-Cope system, where the Oxygen functionality is introduced, in the third position of the Hexo-1,5-diene system. The rearrangement occurs, considerably at a lower temperature, around 150 to 180° Centigrade, as against the 250 to 300° Celsius, for the normal Cope rearrangement. This can be realized by conversion of the auction functionality to the corresponding Alkoxide, in the terms of the Anionic Oxy-Cope system.

The Anionic Oxy-Cope system is nothing, but the Anion of the Hydroxy functional group, generated by treatment of this alcohol, with the base. As you can see here, the Anionic Oxy-Cope systems can be synthesized by, taking the Allyl substituted Ketone. In other words, Allylic Ketone and addition of a Vinyl Grignard reagent, will give you the Tertiary alcohol. Such a Tertiary alcohol is known as, the Oxy-Cope system. And, the Anion generated by treatment of this Tertiary alcohol, in the presence of a base like Tertiary butoxide, constitutes the Anionic Oxy-Cope system.

It is in fact, the Anionic Oxy-Cope system, which shows a further rate enhancement of up to $10^{15,}$ because of the remote functionality, which is the Anion of the Oxygen, that is present in the system. So, this is what i meant, the Oxy-Cope system undergoes arrangement at around 150° Celsius, whereas the Anionic Oxy-Cope less than 100° Celsius, the rearrangement undergoes. You can see here, the rearrangement essentially give an Enol, in this particular case.

The Enol undergoes the tautomerization, to the Ketone. So, the final structure is essentially Delta-Omega kind of an unsaturated system, is what is obtained, in the case. Whereas, in the case of the Anionic Oxy-Cope, the Enolate is what is formed. It will stay in the Enolate form, until it is worked up, to give the corresponding Ketone. So, acid treatment of the product of the Anionic Oxy-Cope rearrangement, essentially produces the Ketone, same as the Oxy-Cope system.

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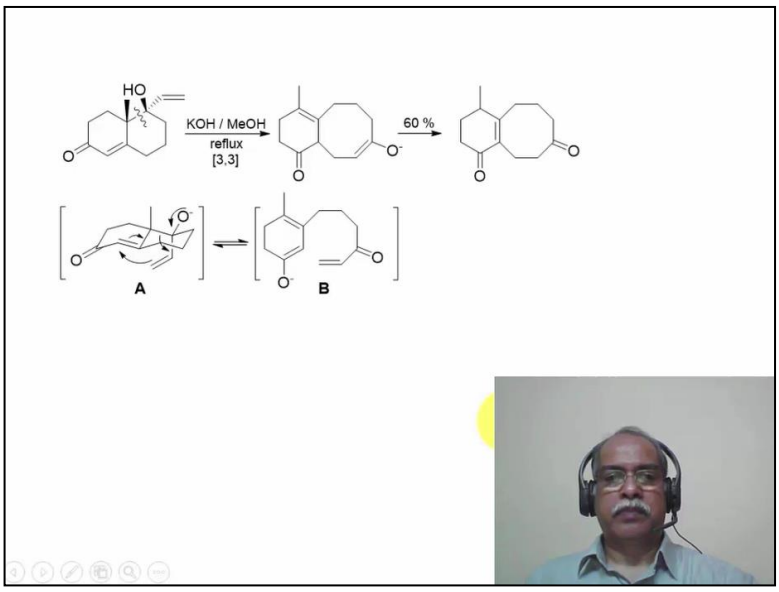

Now, this is an example of an Anionic Oxy-Cope system, where the Tertiary alcohol, which is a Vinyl substituted Tertiary alcohol, is treated with Potassium Hydroxide and Methanol. The Anionic Oxy-Cope rearranged product, is shown in this particular case. The bond that breaks, is this particular bond. So, starting from this sigma bond, if you count, it is Carbon number 1,2, and 3. On the other side, it is Carbon number 1,2, and 3.

So, the [3,3]-Sigmatropic shift essentially, would connect this particular Carbon, with the terminal Carbon of the Vinylic substituent, thereby constituting a [3,3]-System, in this particular case. Of course, this Ketone will not stay like this, in the presence of a base. This is a Enolizable Hydrogen. So, it will undergo the Enol formation, followed by protonation, to give a more conjugated system. This is a conjugated system, conjugated Ketone, which is more stable than an unconjugated Ketone of this type.

So, under the basic condition, the double bond isomerization will automatically take place, under this condition. Initially, this rearrangement was thought to be a stepwise process, involving the formation of an Enolate, and a Vinyl Ketone like this. For example, if you generate an Oxy Anion here, you can rearrange it to the corresponding Enolate structure,

which is this particular Vinyl Ketone structure. And, the Vinyl Ketone structure and the Enolate, is intramolecularly can undergo Michael addition reaction, to give the same product. But, later on, detailed studies essentially showed that, it is a concerted mechanism, which is operative. The Anionic Oxy-Cope rearrangement, through this particular type of a transition state, is what leads to the formation of this particular initial product, which undergoes double bond isomerization, to give the final product. So, although a surprise mechanism is possible to explain the formation of the product, in fact experimentally, it has been shown to be a non-stepwise concerted process of this kind, go into the final product of Anionic Oxy-Cope rearrangement in the system.

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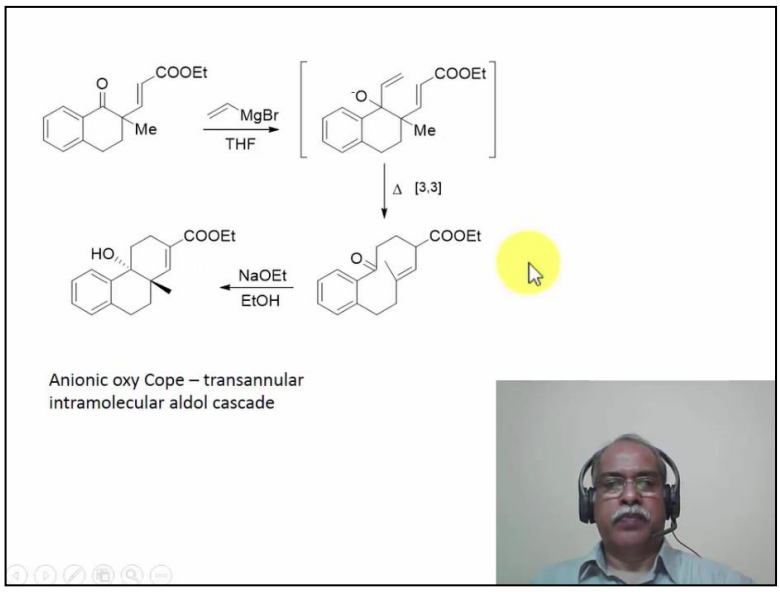

Here is another example. The Anionic Oxy-Cope system, is prepared by the addition of Vinyl Magnesium bromide, to this particular Ketone. This is an Alpha-Vinyl substituted Ketone. Addition of another Vinyl group, essentially constitutes the Anionic Oxy-Cope system. Under the reaction condition, the [3,3]-Sigmatropic rearrangement, essentially produces this medium-size Ketone.

In the medium-size Ketone, one of the prominent reaction, that one can expect is the, Transannular reaction. This particular Hydrogen in this position, is acidic. So, under the basic conditions of the reaction, the Enolate of this particular Alpha-Hydrogen is produced. And, the Enolate, of course is in conjugation with this Vinyl group, essentially producing the Vinylogues Carbanionic center, which undergoes the Intramolecular Aldol type of a condensation, to give this final product.

So, it is an Anionic Oxy-Cope, followed by a Transannular Intramolecular Aldol cascade, which will explain the formation of this particular system. So, essentially from a Decalone

system, we have synthesized a Hexahydro-Phenanthrene kind of a system, by means of the sequence of reaction, that takes place in this reaction.

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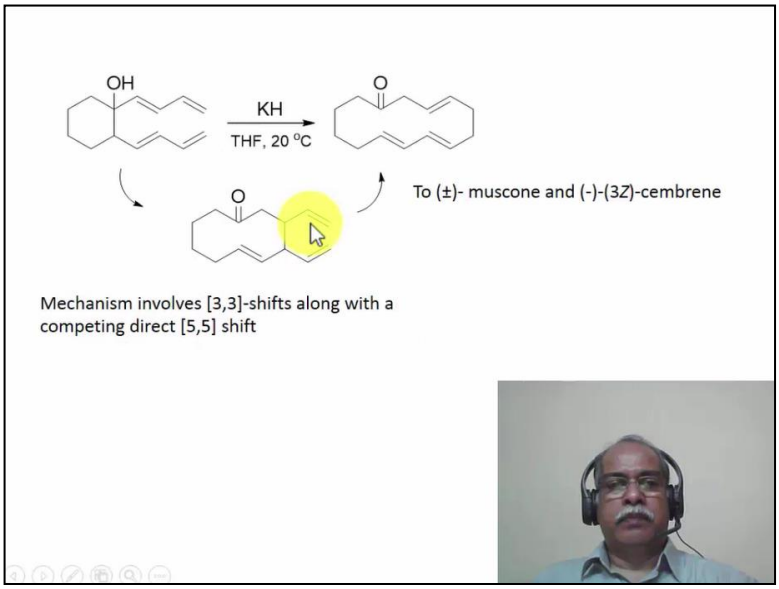

Another interesting facet of the [3,3]-Sigmatropic rearrangement, is the consecutive [3,3]-Sigmatropic rearrangement. In other words, a Domino [3,3]-Sigmatropic rearrangement, is what is taking place, in this particular instance. This is an Oxy-Cope system. So, under the basic condition, when treated with Potassium Hydroxide, the corresponding Anion would be generated, and the Potassium salt would be generated.

And, the Potassium salt is essentially, the Anionic Oxy-Cope system. So, it can undergo [3,3]-Sigmatropic rearrangement, to close this particular bond, and open this bond, by breaking of this Carbon-Carbon bond. So, this is 1-2-3-1-2-3, [3,3]-bond is what is formed, in this particular case. That in turn, sets up another [3,3]-Sigmatropic rearrangement, with the terminal Vinyl groups.

So, finally the terminal Vinyl groups, undergoes a ring closure reaction, to give the. This is an intermediate, that is formed in the first [3,3]-Sigmatropic rearrangement, which is an Anionic Oxy-Cope rearrangement. It is followed by the normal [3,3]-Sigmatropic rearrangement, essentially produces this product. One can also visualize this to be formed by a [5,5]-Sigmatropic rearrangement, which could be a competing reaction, in this particular system.

This is a medium-sized macrocyclic ring system. And, this macrocyclic ring system, is essentially used for preparing the racemic mixture of Muscone and the Cembrane, which is a terpenoid molecule, for example. So, these two molecules are essentially synthesized, starting from this macrocyclic ring system, that is synthesized by the consecutive, or the Domino

[3,3]-Sigmatropic shifts, starting from this particular compound, that is shown as a starting material.

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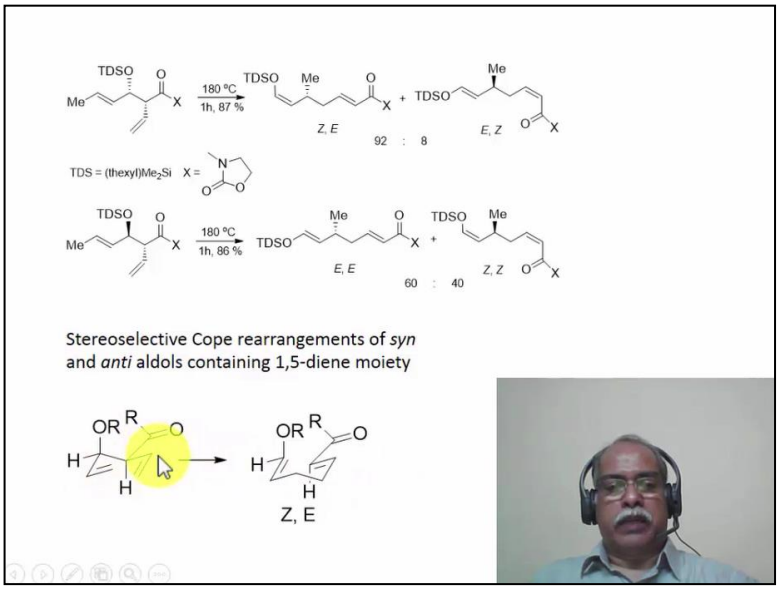

Here is an interesting example of a Stereoselective Cope rearrangement. If you consider this molecule, this is nothing but a Thexyl-Dimethyl-Silyloxy-Ketone. This is essentially an Aldol condensation product. If you look at, this is Alpha Beta Hydroxy Ketone, is what is formed. Beta-Hydroxyamide, in this particular case. The X-group is essentially, this Nitrogen unsubstituted heterocycle. So, this is an Amide derivative. And, this is a Beta-Hydroxyamide derivative.

So, essentially, it is an Aldol type of a condensation product. If you consider this, this is a Syn-Aldol. Because, the stereochemistry here is Syn. Whereas, this is Anti Aldol corresponding Diastereo isomer, is what is formed here, Anti Aldol. Both of them under go, [3,3]-Sigmatropic rearrangement. In other words, the Oxy-Cope [3,3]-Sigmatropic rearrangement. This is the Vinyl group, one Vinyl group. This is other Vinyl group.

So, the [3,3]-Sigmatropic rearrangement, essentially happens by the connectivity of the 3 position, with a subsequent breakage of this Carbon-Carbon bond, which is the 1-2-3-1-2-3. So, this bond will be broken. And, two terminal end of the Binalic groups, will be attached to each other, in a [3,3]-fashion. In doing so, the reaction is highly stereo selective, in the sense that, the Syn Aldol product essentially gives the, ZE isomer of the stereochemistry.

This is the Z-isomer, and this is the E isomer of the stereochemistry of the Olefins, that is formed, after the rearrangement takes place. The EZ isomer is a very minor product. On the other hand, if you take the Anti Aldol condensation product, which is this particular product.

The [3,3]-Sigmatropic rearrangement, which is the Oxy-Cope rearrangement, essentially produces the ZZ and EE isomer in the 60:40 ratio, as it is shown here.

So, the stereochemistry of this double bonds are fairly well-defined, which constitutes the stereoselective synthesis of this particular Cope rearrangement product, that is formed. If you are wondering, how the ZE is formed from the Syn Aldol condensation product, one has to write the chair form of the Syn Aldol. This is a Syn Aldol, where the two functional groups, or the two Hydrogens, are Syn with respect to each other. So, this Hydrogen, and this Hydrogen, are Syn with respect to each other. This is one particular confirmation, chair confirmation, of this molecule.

When the [3,3]-Sigmatropic rearrangement takes place, the Carbon-Carbon bond formation takes place, between these two Carbon centers, which produces for example, the Z isomer of this Olefin, and the E isomer of the other Olefin. So, this Alpha Beta Unsaturated Ketone is the E-isomer, whereas this Enol Ether is the Z-isomer, which is formed, as a result of the rearrangement, which can be explained, by forming the 6-Membered cyclic transition state, in the chair form, to give this.

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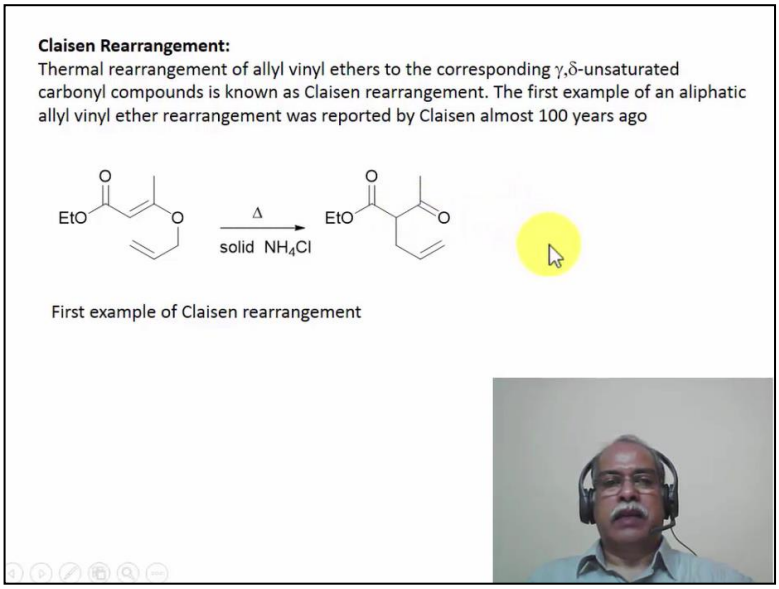

Now, the thermal rearrangement of Allyl Vinyl Ether, to the corresponding Gamma Delta Unsaturated Carbonyl compound, is known as Claisen rearrangement. This is the Vinyl-Allyl Ether. If you look at it carefully, this is a Vinyl group, and this is an Allyl group, connected to an Ether. And, this is a very first example, done by Claisen himself, on the rearrangement.

If you look at this molecule carefully, this is nothing but the Vinyl Ether of the Ethyl Acetoacetate. If we consider, this skeleton to be an Ethyl Acetoacetate skeleton, the Enolic form of the Ethyl Acetoacetate, has formed an Ether with the Allyl bromide, or some such

reagent. So, Allyl Vinyl Ether is essentially the Enol form of the, Allyl Ether of the Enol form of the Ethyl acetate, is what is being considered.

[3,3]-Sigmatropic rearrangement, closes this bond, opens the Carbon-Oxygen bond, resulting in the formation of the Gamma Delta Unsaturated Carbonyl functional group, in this particular case. This reaction is nearly 100 years old. Now, this is a very first example, that was done by Claisen himself.

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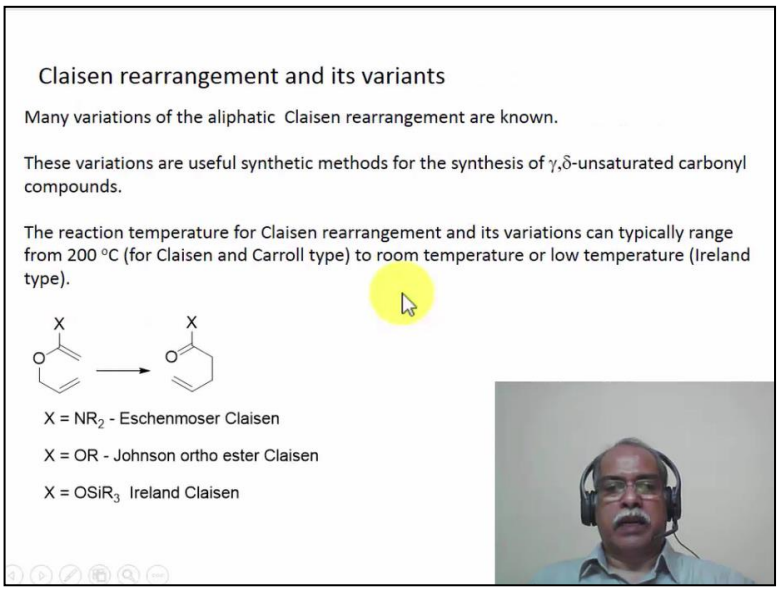

Apart from the Claisen rearrangement, there are many variations of the Claisen rearrangement are also known, in the Aliphatic Claisen rearrangement. These variations are very useful methods for the synthesis of, the various Carbonyl derivatives of the Alpha Beta Unsaturated Carbonyl compounds. It could be an Ester, it could be an Amide, it could be an Acid, and so on. The reaction temperature for the Claisen rearrangement, and its variation can typically range from 200° Celsius for the Claisen rearrangement, or the Carroll type of a rearrangement, to temperature as low as -78, for the Ireland type of Claisen rearrangement.

So, the substituent in the X, represented by X here, can have such a large influence on the activation barrier, thereby lowering the temperature, from all the way to the 200° Celsius to, nearly room temperature, or even low temperature, rearrangement can take place. Now, the various variations, that you see in the Claisen rearrangement, or the Eschenmoser Claisen rearrangement, where the substituent X on the vinylic position, is a Dimethyl Amino derivative. In other words, it is a NO-Aminol of the Ketene, is what is generated here.

On the other hand, if X-group is a OR group, then it will be a Johnson Ortho Ester Claisen condensation. If it is a Trimethylsilyl, or Trialkylsilyl derivative, then it is an Ireland-Claisen rearrangement. You can see here, the Eschenmoser rearrangement will give you an Amide.

The Johnson Ortho Ester Claisen condensation will give an Ester, which is a Gamma Delta Unsaturated Ester. The Trimethylsilyl derivative will give, the corresponding Trimethylsilyl Ester of the Gamma Delta Unsaturated Carbonyl compound, by these 3 types of variations, in the rearrangement process.

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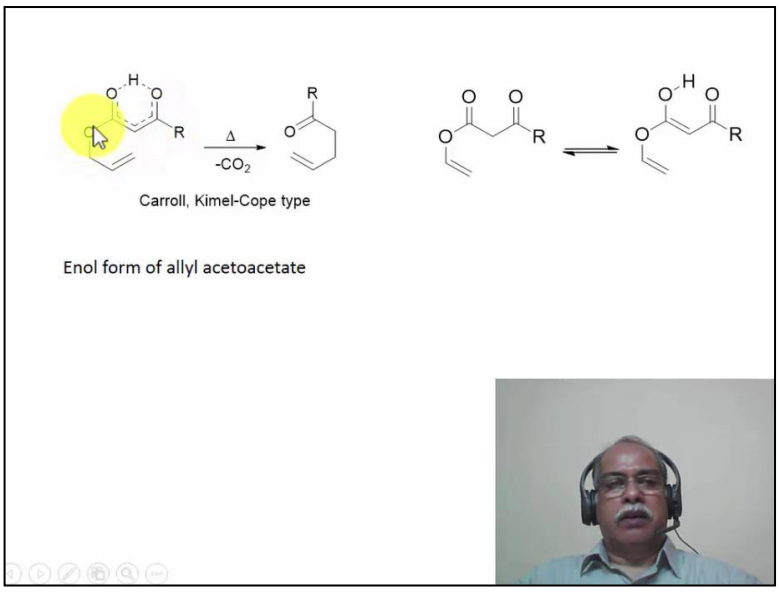

Now, if you look at the rearrangement of the Allyl Ester of the Ethyl Acetoacetate. Please recall here, this is an Allyl Ether of Ethyl Acetoacetate. Whereas, in the case of Carroll Kimel-Cope type of a rearrangement, this is an Allyl Ester of the Ethyl Acetoacetate. The Enol form of the Allyl Ester of Ethyl Acetoacetate, under the reaction condition, gives the product, which is this particular product.

This is an Ethyl Acetoacetate molecule. The Allyl, sorry, this is a Carbon missing here. This should be Allyl derivative. The Allyl Ethyl Acetoacetate, here is again one Carbon is missing. The CH2 Carbon should be there. This is an Allyl Ester of the Ethyl Acetoacetate in the Enol form. The Enol form, of course, will be in the Hydrogen bonded nature, in terms of the Carbonyl Hydrogen bonding, to the Enolic Hydrogen.

Under the reaction condition, it produces a Carboxylic acid, by a [3,3]-Sigmatropic rearrangement. The Carboxylic acid is a Beta-Keto acid. So, it readily undergoes Carbon dioxide elimination. Extrusion of Carbon dioxide takes place, to generate the Gamma Delta Unsaturated Ketone. This is called the Carroll Kimel-Cope type of a rearrangement, of the Enol form of Allyl Ethyl Acetoacetate.

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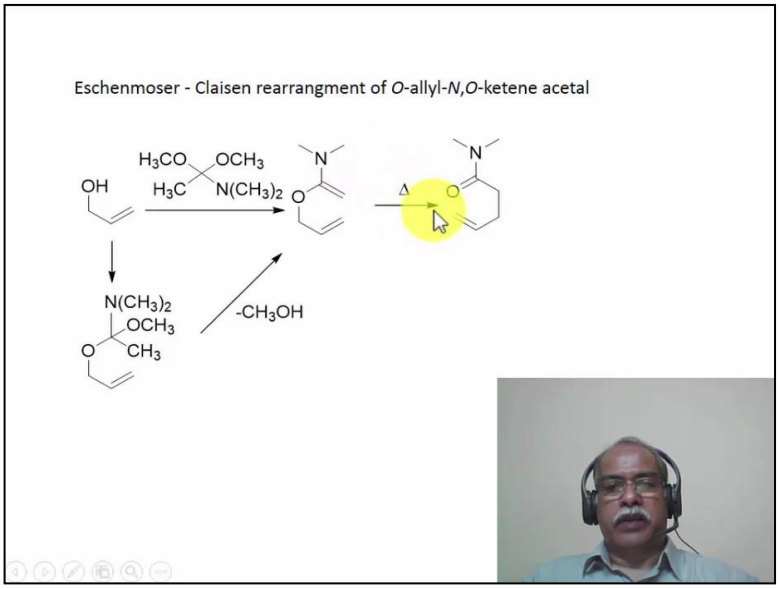

Now, in the Eschenmoser Claisen rearrangement, is essentially, converting an Alcohol to an Amide of this type. Sorry, not the amide. This is the Claisen system, which is Eschenmoser Claisen system, which is generated by treating this Acetal, which is nothing but the Acetal of N,N-Dimethylacetamide, by a Transetherification reaction, first. The Transetherification reaction between Allyl alcohol, and this Ketene as the N,N-Dimethylacetamide Acetal, is essentially generates this molecule.

Loss of Methanol, under acidic condition, would generate the elimination of the Methanol from this, forming a double bond here, to generate this particular derivative. This derivative, is what undergoes the Eschenmoser Claisen rearrangement, to produce the Gamma Delta Unsaturated amide. And, this takes place, typically around 150° Celsius or so, in terms of the temperature.

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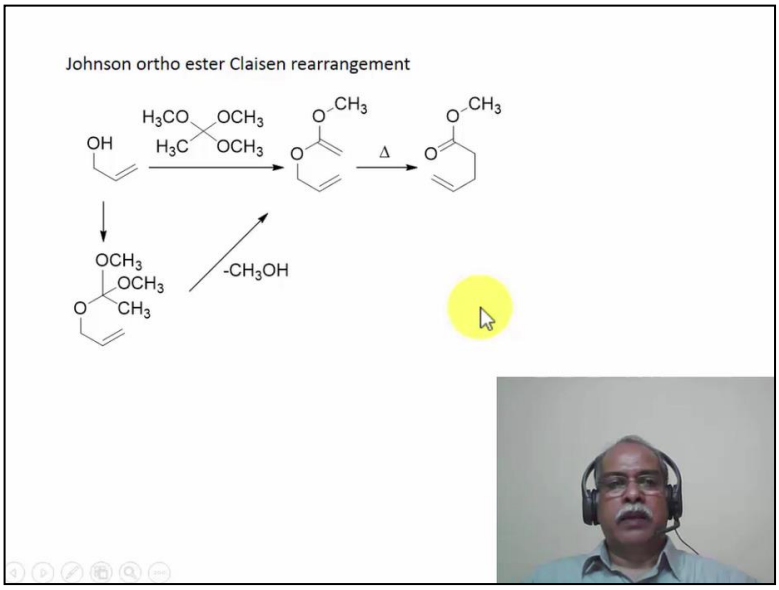

The Johnson Ortho Ester Claisen condensation, initially it is a Transetherification reaction, between the Ortho Acetate, of this kind. The Ortho Acetate, under acidic conditions, exchanges one of the methoxy group, for the Allyl alcohol, to produce the corresponding Allyl Dimethoxy Ortho Acetate. Loss of Methyl alcohol, essentially generates the Claisen condensation starting material.

This is the Ortho Ester Claisen condensation starting material, which undergoes the Claisen rearrangement, to produce the Gamma Delta Unsaturated Ester. So, the product of the Johnson Ortho Ester Claisen condensation, is essentially a Gamma Delta Unsaturated Ester, is what is formed.

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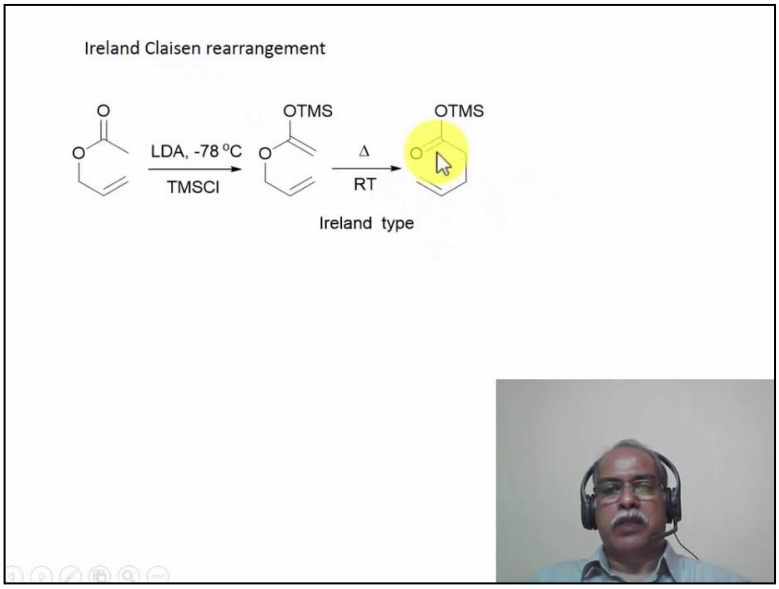

If you look at this molecule, this is nothing but, the acetate molecule. This is an Allyl acetate. If you enolize the Allyl Acetate, by treatment with Lithium Diisopropylamide, and then quench it with Trimethylsilyl chloride, you can generate the corresponding Ketene Silyl Acetal, of this kind. So, this Ketene Silyl Acetal, is essentially an Allyl Vinyl Ether, which will undergo the Claisen rearrangement, which is known as the Ireland-Claisen rearrangement, to produce the Gamma Delta Unsaturated Ester, in the form of a TMS Ester, is what is formed.

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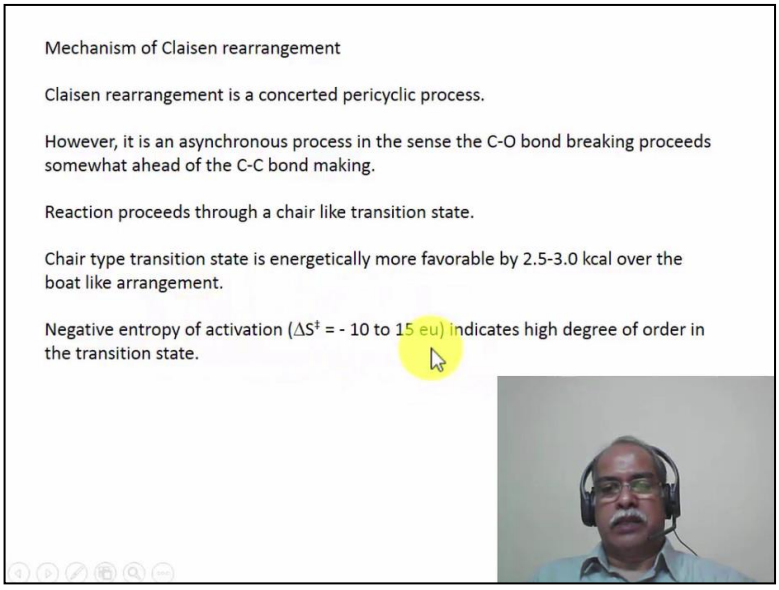

So, these are the variations of the various Claisen rearrangement products, that we have in the system. The mechanism of Claisen rearrangement, is fairly simple. Claisen rearrangement is a concerted pericyclic process. However, there is an asynchronous process, that is taking place, in the sense that, the Carbon-Oxygen bond breaking proceed, somewhat ahead of the

Carbon-Carbon bond making. In other words, this is a simultaneous reaction, but not a synchronous reaction, that is what it means.

The extent of the CO bond breaking, is much larger than the extent to which, the CC bond is formed, during the course of the rearrangement. The reaction proceeds through a chair like transition state. We will get to that, in a minute. The chair type of a transition state, is energetically slightly more favorable, in terms of 2 to 3 kilocalories, over the boat like transition state. The negative entropy of activation, essentially tells you that, there is a high degree of order in the transition state, during the course of this particular reaction.

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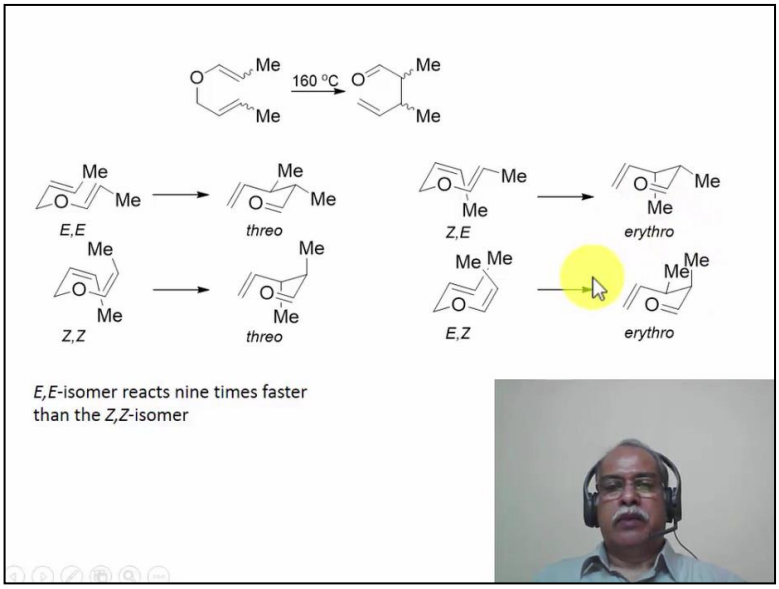

Now, if you consider the Dimethyl substituted Allyl Vinyl Ether, the stereochemistry of the product that is formed, is going to be highly dependent on the stereochemistry, of these two double bonds. Now, if you consider the various isomers, that are possible here, the Vinyl group, you can have the E-isomer, as well as the Z-isomer. Similarly, for the Allyl group also, you can have the Z-isomer, or the E-isomer, as in this represented, in this particular case.

So far, this Dimethyl Substituted Allyl Vinyl Ether, you can have 4 Diastereo isomer, EE, ZZ, ZE and EZ, depending upon, whether the Vinyl group has E-isomer, or the Allyl group have the E-isomer, or the Z-isomer, as the case may be. In each one of this rearrangement, the reaction is highly stereospecific, in the sense, the starting material geometry highly matters, in terms of, whether the Erythro product is formed, or the Threo product is formed, during the course of the migration.

You can see here; all the structures are, already written in the chair form. The starting material, chair form is written. If you form a Carbon-Carbon bond here, essentially the one of

the Methyl group, will be in this equatorial position, the other Methyl group will be in the adjacent equatorial position, which corresponds to the Threo isomer.

On the other hand, if one of the Methyl group is in the Axial position, the other Methyl group is in equatorial position, that would constitute the Erythro isomer. The two Hydrogens are Cis here. Here, the two Methyl groups are Anti with respect to each other. We can see here, Diaxial-1,2 is Anti. Diequatorial-1,2 is also Anti. So, this is a Threo isomer. Here, one of the Methyl group is axial. The other Methyl group is equatorial. So, this is Cis-1,2-Axial equatorial is Cis. So, the Erythro kind of a configuration, is what you have.

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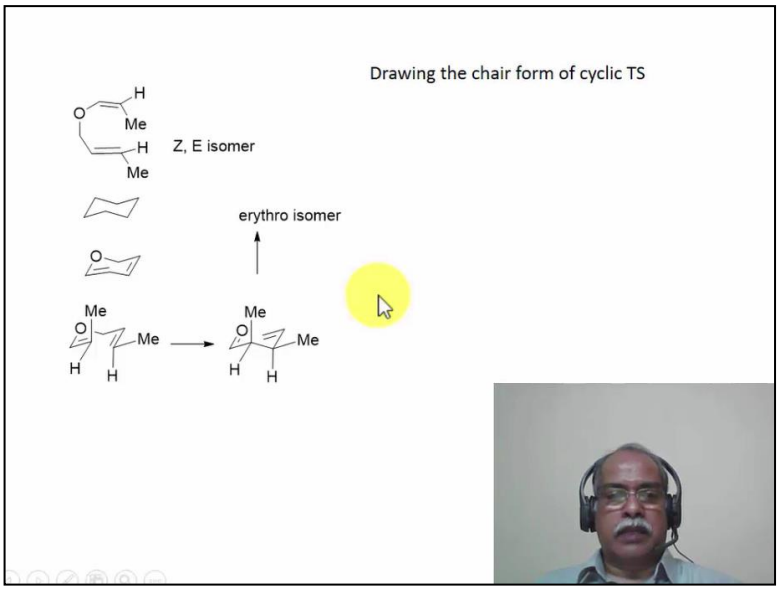

Now, how do we write the chair form of the molecule, is explained here. Let us take the example of the ZE isomer of the Allyl Vinyl Ether, with a Dimethyl Substituted Allyl Vinyl Ether. What you do is, first write a chair form of the Cyclohexane nicely. And then, substitute one of the Carbon with Oxygen. And then, generate the Vinyl group, adjacent to it, and an Allyl group, one Carbon away from the Oxygen atom.

So, this will be the Allyl part of the Ether, and this will be the Vinyl part of the Ether. So, this bond has to be broken, in the starting material. And, this bond has to be broken, during the course of the reaction. The CH2O bond has to be broken. So, initially, we get rid of this bond, and then put the substituents, such that, one of the double bond, which is this double bond. The Vinyl double bond is a Z isomer. And, the Allyl double bond is a E isomer. This is a Vinyl double bond.

So, the Methyl group and the Carbon-Oxygen bond functionality, should be Cis with respect to each other. That is possible only when, the Methyl group is in the Axial position, and the Hydrogen is in the equatorial position. In the chair type of a transition state, the substituents

will occupy, either the equatorial position, or the Axial position, depending on the stereochemistry of the double bonds, that are present here.

You can see clearly here, the Carbon-Hydrogen bond and the Carbon-Oxygen bond, are Trans with respect to each other, constituting the Z isomer. Because, the Methyl and the Carbon-Oxygen bonds, are Cis with respect to each other, constituting the Z isomer. The other substituent, which is the Allyl substituent, which is this particular substituent here, has to be Trans, because it is a E isomer.

So, unless, you put this in the equatorial position, and the Hydrogen in the Axial position, you cannot get the Trans isomer. Now, if you do the rearrangement, by connecting these two bonds, you clearly see that, the Erythro isomer is formed. Because, these two Hydrogens are Syn with respect to each other, and that Methyl groups are also Syn with respect to each other.

So, this is a convenient way to learn, to draw the chair form of cyclohexane, and convert it in the, either the Cope System, or the Claisen system. If you introduce an Oxygen in the ring, then it will be a Claisen system. If you do not introduce an Oxygen in the ring, then it will be a Cope System, which was considered in the earlier module, as we were discussing the Cope rearrangement, at that time.

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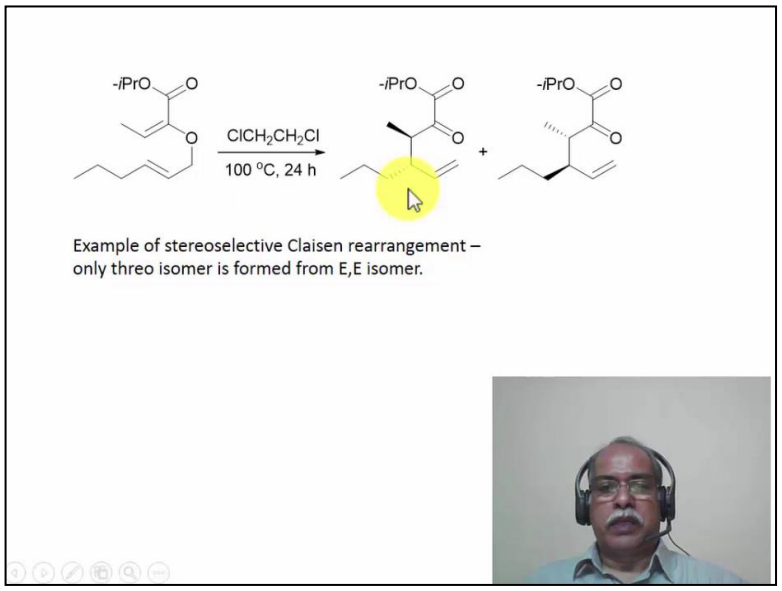

Now, a simple Diastereoselective Claisen rearrangement, is what is illustrated here. This is a EE isomer of the Allyl Vinyl Ether. The EE isomer of the Allyl Vinyl Ether, undergoes a rearrangement, to give only the Threo isomer of the product. You can see here, this Methyl and the substituent are Anti, with respect to each other.

So, this is a Threo isomer. Similarly, this is also a Threo isomer. Under this condition, the Erythro isomer is not at all formed. So, indicating the high stereoselectivity nature of this particular Claisen rearrangement, which can be explained by a chair type of a transition state, in this case also.

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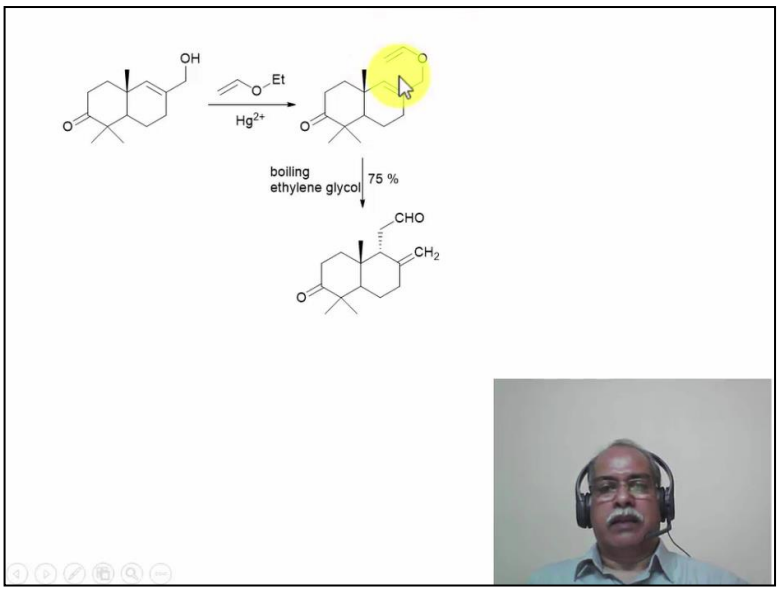

Now, here the Claisen system is synthesized, by a Transetherification reaction. What we need is an Allyl group, is already there. So, what you need, is a Vinyl group. So, the Vinyl Ether synthesis, is what is described in the first step. When you take Ethyl Vinyl Ether, and treat it with Mercuric salt like, Mercury chloride, or Mercury sulfate, in catalytic amount, the acidic nature of the Mercury sulfate, essentially catalyzes the reaction. And, instead of the Ethyl group, now you have the Allyl group, that is attached to the Vinyl derivative.

So, the Ethyl Vinyl Ether is essentially a vinylating agent, in terms of converting a simple alcohol into a Vinyl Ether derivative. Once you have the Vinyl Ether derivative, it undergoes the Claisen rearrangement, to give the corresponding product. So, you have started from the Allyl alcohol, you have gone to the Gamma Delta Unsaturated aldehyde, in this particular place, by a transformation, which is a Claisen Trans. First, the Transetherification to get the Vinyl Ether, followed by the Claisen rearrangement, to give the corresponding Allyl Vinyl Ether, in this particular case.

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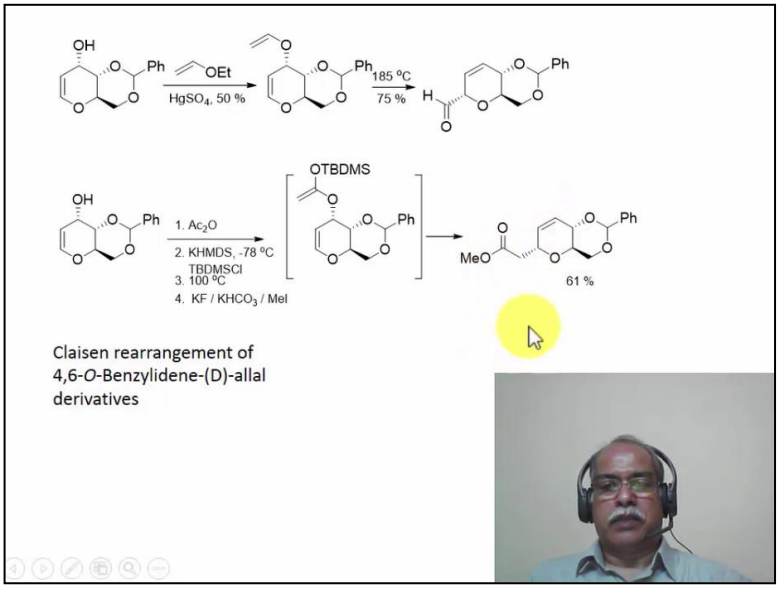

Now, several Carbohydrate derivatives, i have been shown, to undergo Stereoselective Claisen rearrangement, or the variations of the Claisen rearrangement. Here is an example of 4,6-O-Benzylidene-(D)-Allal, which is this particular skeleton, in the Pyranose ring form, is written. This is (D)-Allal. This derivative, essentially is made to undergo, several different types of the Claisen rearrangement.

The first instance, this is an Allyl alcohol, which is converted in to a Vinyl Ether, by treatment with Ethyl Vinyl Ether and Mercuric Sulfate, in this particular case. And, heating the Ethyl Vinyl Ether, essentially sets up the stereoselective rearrangement. You can see here, this is a [3,3]-Sigmatropic rearrangement, proceeding in a Suprafacial manner. So, this stereochemistry is essentially retained, in this product.

So, the final product is a Gamma Delta Unsaturated aldehyde, is what is formed, in this particular case. In the second instance, initially an Acetate is prepared of this Allyl alcohol. The Allyl acetate is Enolized, and it is quenched with Tertiary-Butyl Dimethylsilyl derivative, in the form of the Tertiary-Butyl Dimethylsilyl derivative, which is a bulky protecting group. And, this spontaneously undergoes, when treated with Potassium fluoride, D-Xylonation takes place, and the Enolate is generated.

Enolate is an accelerated system for the Claisen rearrangement, which undergoes [3,3]-Sigmatropic rearrangement, connected to this, with the retention of stereo chemistry at this place, same as the starting stereochemistry, resulting in the formation of a Gamma Delta Unsaturated Ester, in this particular case, and 61% yield.

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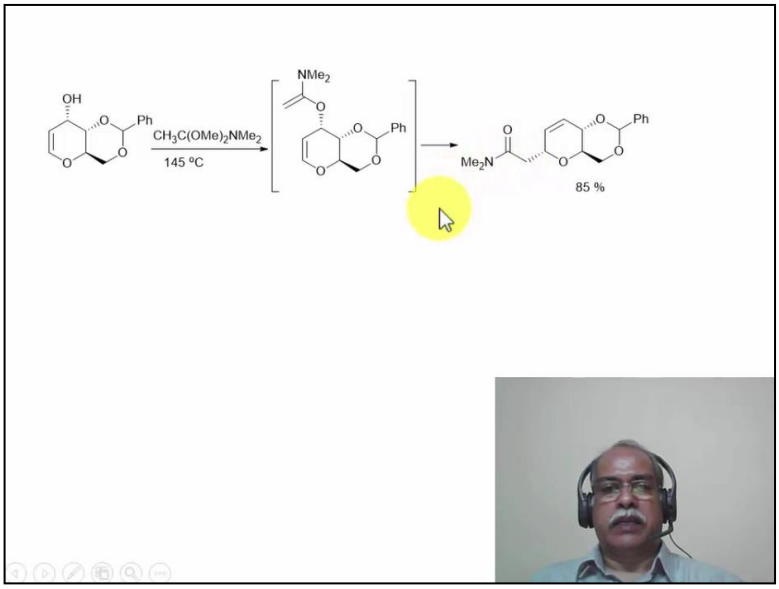

The same variation, in terms of the Eschenmoser variation, is what is depicted. The (D)-Allal derivative, is taken. It is converted in to the Ketene Silyl Acetamide kind of a, Ketene Silyl Acetal Amide of the system is generated, which undergoes the Eschenmoser Claisen rearrangement, to give the Gamma Delta Unsaturated Carboxamide, is what is generated, under these reaction condition.

So, the (D)-Allal derivative has been tested, to undergo the simple Claisen rearrangement, the Ireland-Claisen rearrangement. as well as the, Eschenmoser Claisen rearrangement, to give the corresponding acid derivatives, as the case may be.

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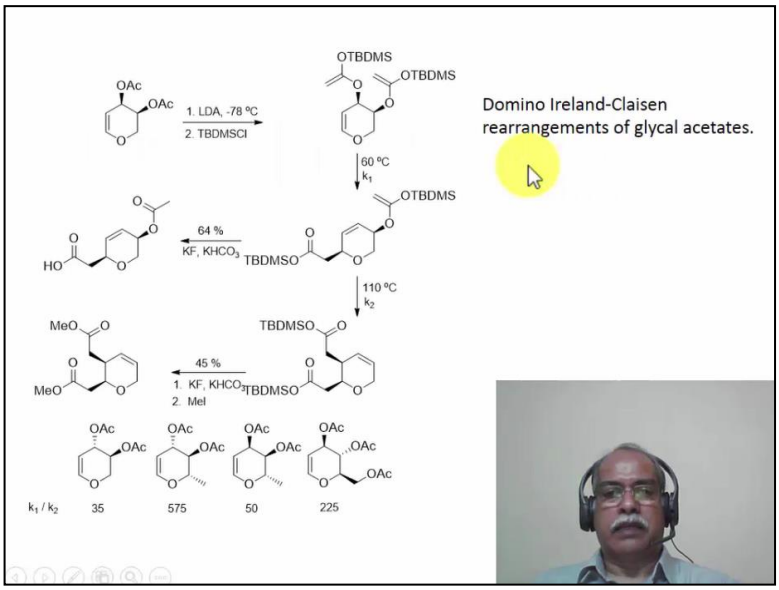

Here is a Diacetate. This is a Domino Ireland-Claisen rearrangement of Glycol Acetate. This is a Glycol Acetate. This is a Glycol. And, the Diacetate of the Glycol, is what is taken. When it is treated with the Lithium Diisopropylamide, and Tertiary-Butyl Dimethylsilyl chloride,

the corresponding Enol Tertiary-Butyl Dimethylsilyl Ketene Acetal are formed. And, this is set up for a [3,3]-Claisen rearrangement, now.

This is the bond, that is going to break. And, Stereoselective Syn Suprafacial migration to this position, essentially generates this particular system. This is now, a Vinyl-Allyl system again, so the domino process takes place. The first reaction, takes place around 60° or so. Whereas, the second domino reaction, essentially takes place at a higher temperature, indicating, that this is a much more facile rearrangement. And, the activation barrier for the second step, is much higher. That is reflected, in the relative K1 and K2.

K1 is the first Ireland-Claisen rearrangement. And, the second Ireland-Claisen rearrangement is a K2. The K1 by K2 is 35, in the case of this, Trans Acetate derivative. 575 in the Alpha Methyl substituted derivative. This 50, in the other derivative, which is a Cis derivative, here. 225, which is about the Trans derivative, with another Acetate, in this particular position.

So, the stereoselective nature of the retention of configuration, at this position, is what is illustrated, in all of this Allal derivative, in terms of the rearrangement, which is the Domino Ireland. Domino rearrangement is the first rearrangement, sets up the skeleton for the rearrangement. That is why, it is called a Domino effect, in terms of the Domino Claisen rearrangement, of the Glycol Acetates.

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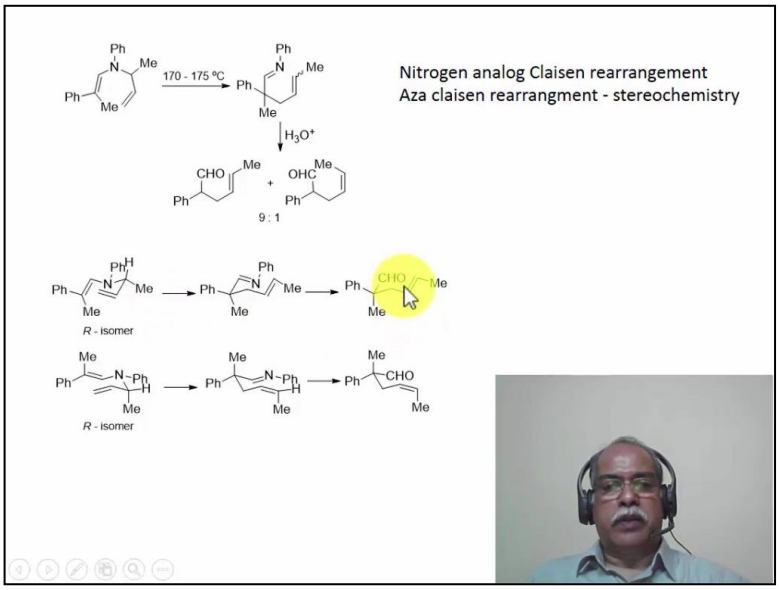

The Nitrogen Analog of Claisen rearrangement is called Aza-Claisen rearrangement. Instead of an Oxygen, which is the Claisen product, Claisen starting material, if you have a Nitrogen, then it is an Aza-Claisen rearrangement. Here is an example of an Aza-Claisen rearrangement, taking place of the Vinyl-Allyl Amine, which is a Tertiary Amine, in this

particular case, to get the corresponding Imine. The Imine is Hydrolyzed, in the presence of Aqueous acid, to generate the corresponding aldehyde, in this particular case.

This reaction can also be explained, on the basis of a chair type of a cyclic transition state, to yield this particular product, starting from a particular stereochemistry of the starting material, that is given here. So, the chair type of a transition state, is what is explained in this two pictures, for example. The R isomer of this particular derivative, as an optically pure R isomer, can exist in this two forms.

And, this two products, that are formed are essentially explained, on the basis of this. In this particular form, the Methyl group is in the equatorial position, which is a favorable situation. Here, the Methyl group is in the Axial position, which is an unfavorable system. The rearrangement, essentially produces these two types of products, in this particular case.

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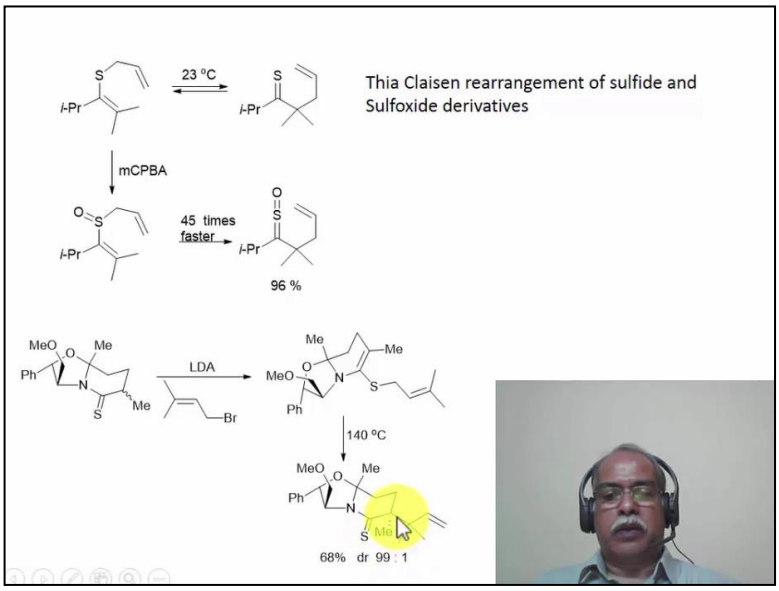

The Thia-Claisen rearrangement, is what is shown here. Instead of a Nitrogen or Oxygen, if you have a Sulfur here, then the Thia-Claisen rearrangement takes place. The corresponding Sulfoxide reacts 45 times faster than, the sulfide itself. So, this is probably taking place at a low temperature. This is a Vinyl-Allyl sulfide, is what rearranges to give the corresponding Thia-Claisen product. The Thia-Claisen system is synthesized, in this particular case, by initially allylating this position.

The S-Allyl derivative, is now set up for the Enolate of the Thiol. Thiolate, is what is generated by deprotonation of this position, and the corresponding Thiolate is produced. Thiolate is alkylated, because sulfur is a more nucleophilic center. S-Alkylation takes place, using the Allyl Bromide, in this particular case. So, now you have set up a Vinyl-Allyl derivative, which undergoes the Thia stereoselective rearrangement, through a cyclic chair

type of a transition state, to produce 99:1 ratio, of this particular Diastereo isomer, of the product.

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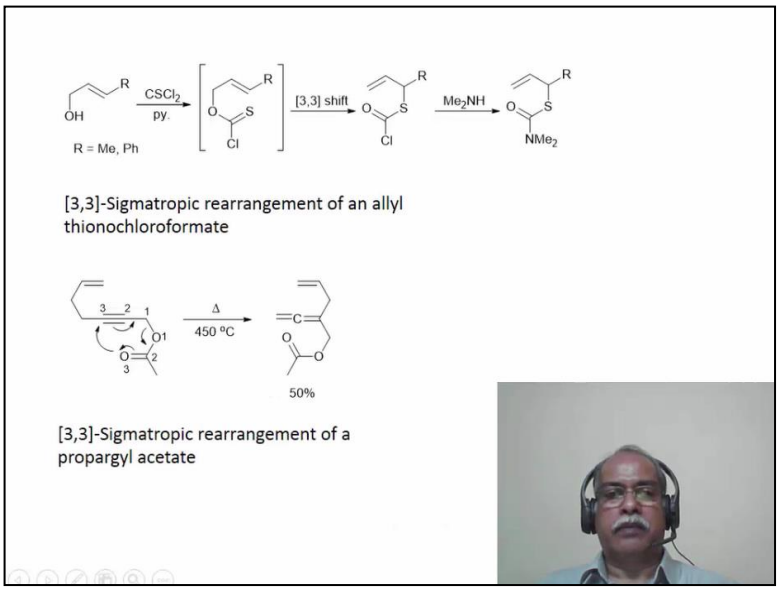

These are the other examples of [3,3]-Sigmatropic rearrangement, of an Allyl Thio Chloroformate. For example, if you take this Allyl alcohol, and treat it with, instead of a Carbonyl Chloride, the corresponding Thio-Carbonyl Chloride, the corresponding Thio-Chloroformate, is what is generated. Thio-Chloroformate is a [3,3]-Sigmatropic system. It undergoes the [3,3]-Sigmatropic shift, to give the corresponding product, which is this particular product. This is an Acid chloride.

The Acid chloride is quenched with an Amine, to give you the corresponding Thio-Carbonate, in this particular product. Now, [3,3]-Sigmatropic rearrangement of a Propargyl Acetate example, is given here. The numbering has clearly tells you that, this is a [3,3]-Sigmatropic rearrangement, to give this particular product, in about 50% yield. In this particular module, we have considered the Oxy-Cope rearrangement, the Anionic Oxy-Cope rearrangement, followed by the variations of Claisen rearrangement.

We have talked only about the, Aliphatic Claisen rearrangement. We still have not discussed, the Aromatic Claisen rearrangement, which we will discuss in the next module. This module, we have also shown the mechanism of the Claisen rearrangement, to proceed through a cyclic chair type of a transition state, highly stereoselective nature of the cyclic transition state, leading to a specific product formation, depending on the stereochemistry of the double bonds, that are originally present in the Allyl Vinyl Ether, has been illustrated with several examples. Thank you very much, for your attention.