Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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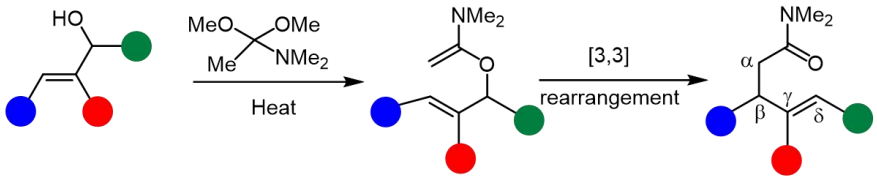
Lecture 09: Carbanion

Welcome you back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. I am talking about carbanion. So, in the last two classes I talk about carbanion synthesis stability and in the last class I talk about different type of rearrangement. I introduce this smiles rearrangement, neber rearrangement, I also talk about Claisen rearrangement, then Ireland Claisen rearrangement. In the today's class I am going to talk about several other variation of Claisen rearrangement. So, I am going to talk about the Eschenmoser-Claisen rearrangement, I am going to talk about the Johnson-Claisen rearrangement, then I will start with the Overmann-Claisen rearrangement and several different examples.

- Developed by Albert Eschenmoser in 1964.
  - Reagent: Allylic alcohol
  - Product: Gamma-delta unsaturated amides.

Example:

N,*N*-dimethylacetamide dimethyl acetal

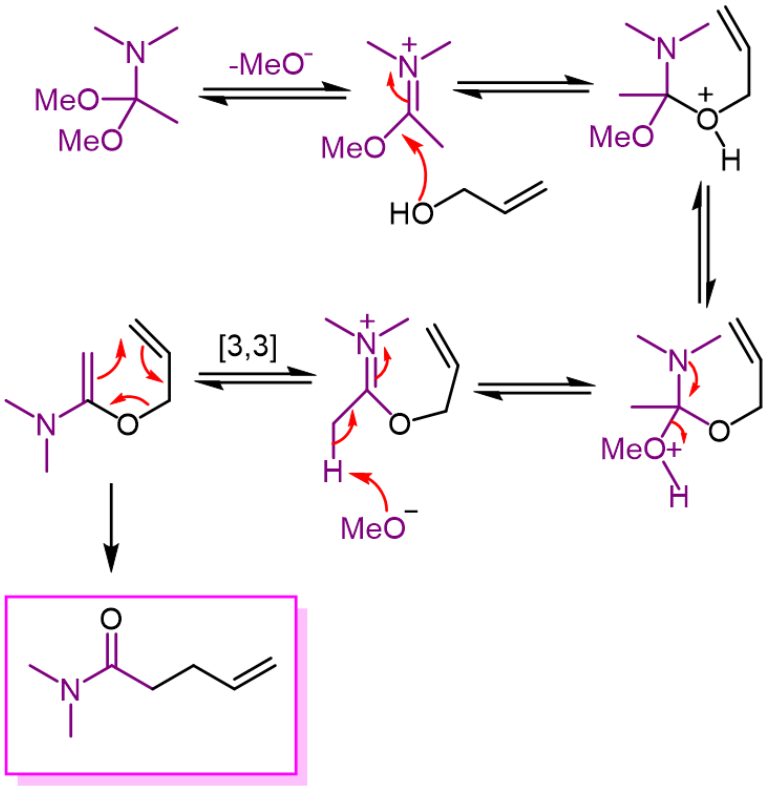


ketene aminal

And finally, I will end with the Cope rearrangement and Oxy Cope rearrangement. So, previously we have learned about the Claisen rearrangement and we have seen that in Claisen rearrangement the reaction you have seen there are two different class of substrate. One is the aryl allyl ether or the vinyl allyl ether. It actually getting converted to the corresponding gamma delta unsaturated carbonyl compound in case of Claisen and

then in case of Ireland Claisen we have seen that it is forming gamma delta unsaturated acid. But now we are going to learn about the Eschenmoser-Claisen which was developed by Albert Eschenmoser in 1964. So, here we are going to convert it to the corresponding the gamma delta unsaturated amide. So, that is the difference. Again I think the starting material will be the allylic alcohol here and now you are using this N,N-dimethyl acetamide dimethyl acetyl. So, this compound was treated in the presence of heat which is going to form the starting compound. which is a ketene aminal. Now, you can see there is this 1 2 3 and you can see this 1 2 3. So, now, this 3 and 3 3 position it will be participate in a [3,3] sigmatropic shift to get to this corresponding gamma delta unsaturated amide.

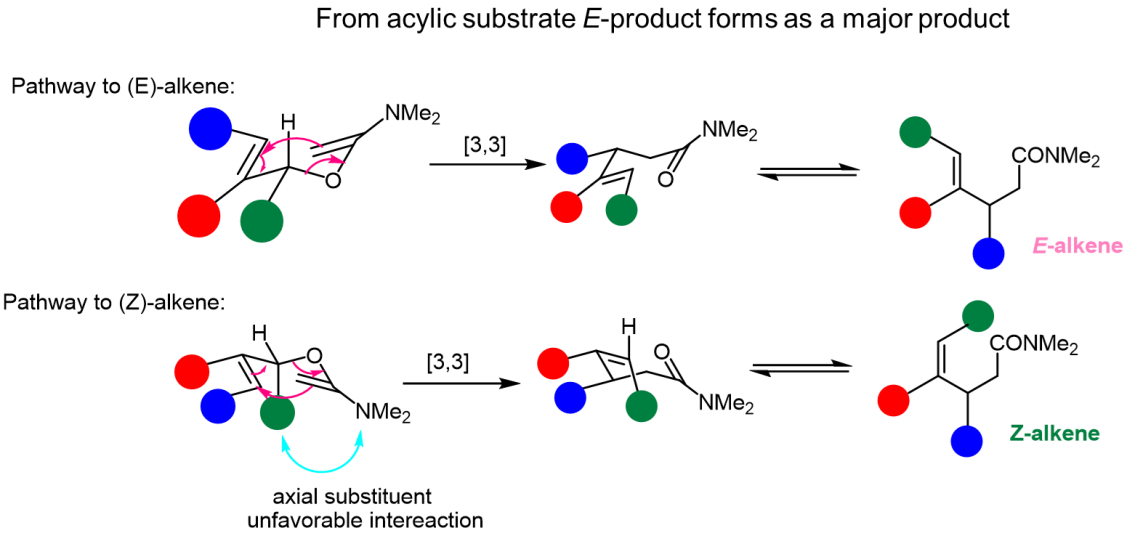
Mechanism:



So, the first thing is we try to understand how these things are synthesized. So, first thing is once you have this compound first thing this lone pair can push the electron density to get rid of this -OMe group to form this type of iminium species which is going to get attacked by the allylic alcohol from this compound after that release of the another methanol group here to form another iminium here.where this hydride is getting abstracted to form this particular compound which is now ready for the [3,3] Sigmatropic sift.

So, now we are trying to understand in the Eschenmoser-Claisen rearrangement what is going to happen form the the E-alkene or is going to form the Z-alkene. So, but for acyclic substrate the E-product is forms as a major product that means now we are

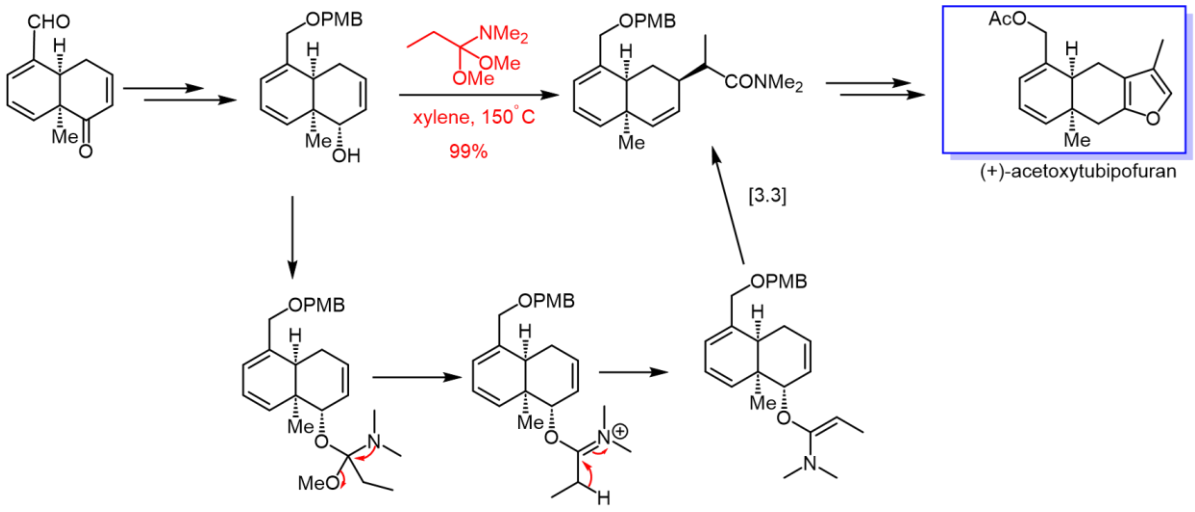
talking about in that I think I have already told the very similar thing that if you have a substitution in the terminal means you have a double bond to double bond in the terminal. Now if you have a double bond with a E or Z geometry Now, what is going to happen in the product ok. So, that is the first question we are asking here, again we have seen there if is going for this particular transition state versus this transition state what is the difference we are observing. Now, we can see for if you look for these green colored things here in this particular carbon we are talking about. So, it will be more preferable to keep this group which will be to a equatorial position and keeping the hydrogen in the axial position instead of keeping this group a bigger group in the axial position because once you keep this bigger group in the axial position it will have a possibility to generate some 1,3-diaxial interaction. That is why and also if you see this NMe_2 group can be interacted with this group there is another issue I was mentioning. So, those type of interaction can be avoided from this particular transition state. and that can able to give you the corresponding E alkene instead of the corresponding Z alkene.



So, now I am going to show you an example here again. So, there is a allylic alcohol in this particular compound in presence of this compound it is going to form this corresponding intermediate after the deprotonations is going to generate now this compound which is ready for the [3,3] sigmatropic rearrangement. So, you can see this is 1 2 3 and there is 1 2 3 ok. So, what is going to happen here that there will be a formation. So what is going to happen. So, there will be formation of a carbonyl group here. So, it is going to form this corresponding amide and then there will be double bond here ok. So, this position the allylic alcohol. So, this bond is going to get broken from here. and there will be a new bond going to form here and this terminal is going to reach to this position. So, at the end it is going to form this component the important part is there that if you see here this is going to form on the above phase instead of the bottom

phase to avoid some sort of a steric interactions and which can be finally converted to this natural products.

- Asymmetric synthesis by Eschenmoser- Claisen rearrangement:



There is another example here you can see in this molecule also we can see clearly there is allylic alcohol here. which can. So, this reaction can be done in place of microwave in instead of heating. Now, in presence of this type of ortho ester what is going to happen. So, this is going to first form the corresponding compound after formation of this compound once it can go for a [3,3]-sigmatropic rearrangement to get to this corresponding product where you can see wherever this bond was there. Now, how do you write the product. Now, you have to understand where the allylic carbon is there, this bond is going to get broken and there and there will be a new bond going to form here, we know from the arrangement that there will be new bond going to form here. So, this group is going to get migrated here. So, then we are going to find out that here this CH_2CONMe_2, this is going to come high here and there will be a double bond here which you have seen here ok. Again from this example, if you are trying to write the product for this, Eschenmoser rearrangement, what is happening? Again we can see there, the double bond is getting shifted here, and then we are seeing this particular group is moved here.

So now if you see that, this carbon oxygen bond is getting cleaving, so you have a double bond formation here, and this carbon you are seeing this CH_2, so this double bond is getting, coming to here. And, here we are seeing introducing of this CH_2CONMe_2 group. So, at the end of the day it is actually forming this gamma delta unsaturated amide.

Ex:

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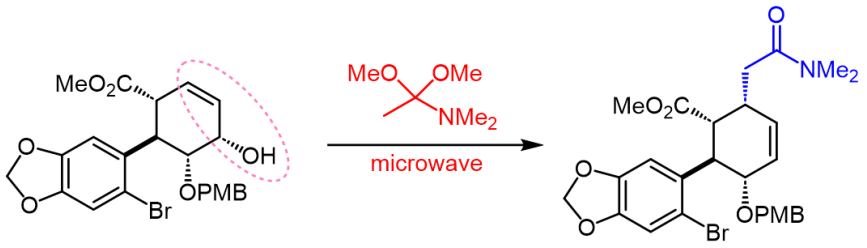

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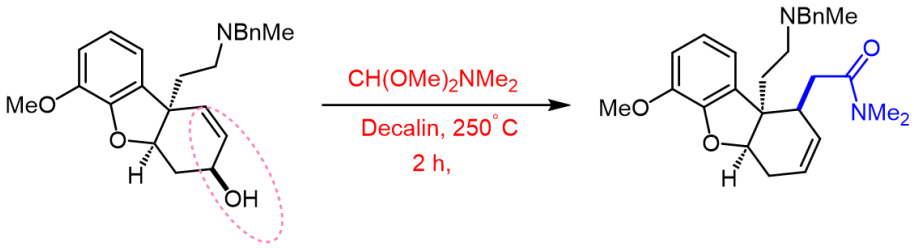


Now, we are going to move to talk about instead of the Eschenmoser we are going to talk about the Johnson-Claisen rearrangement. So the Johnson-Claisen rearrangement is an another class of Claisen rearrangement where it was, discovered at 1970 by Johnson et al. So here what is happening? This reaction need trimethyl orthoacetate or triethyl orthoacetate in place of organic acid. So once you take allylic alcohol in place of trialkyl orthoacetate, what is going to happen? It is going to form the gamma delta unsaturated ester. So, Claisen rearrangement is giving you the gamma delta unsaturated carbonyl group, then Ireland Claisen is giving you the corresponding acid, then in the previously the Eschenmoser-Claisen is giving you corresponding amide and now the Johnson Claisen is giving you corresponding esters ok. So, we are quickly try to understand how this what will be the starting material once you react this allylic alcohol with this trialkyl orthoacetate.

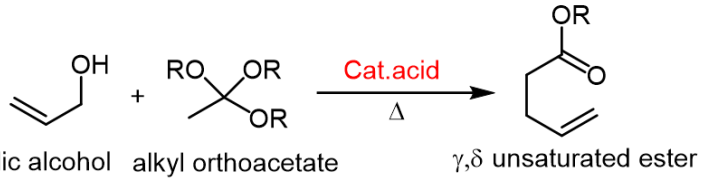
- This type of rearrangement is one of the varieties of Claisen rearrangement.
- In 1970 Johnson et al. useful modified this rearrangement.
- Known as orthoester Johnson- Claisen rearrangement.

Reagents: Trimethyl orthoacetate, Triethyl orthoacetate, Organic acids

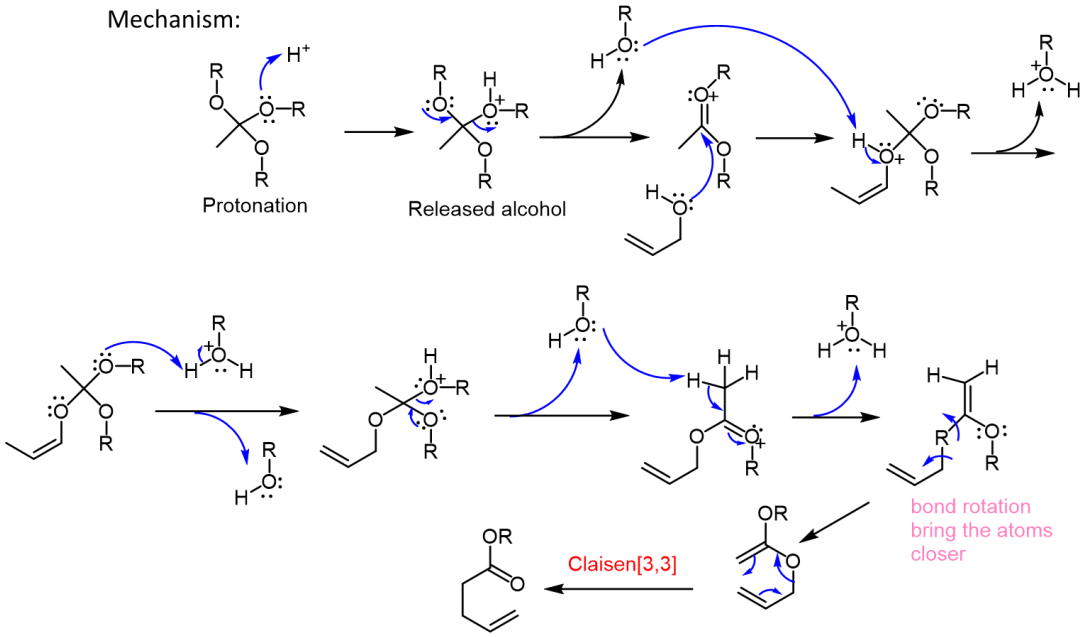
Reactants: Allyl alcohols

Products: Gamma-delta unsaturated esters

General scheme:



Again I think first thing is going to once you give the proton source here the H plus is going to protonate the oxygen and then there will be release of one ROH group from here form some sort of a oxonium intermediate again there will be a ROH going to take this proton then another protonation going to happen and there will be another ROH group going to come out after that finally, there will be a hydride. So, this hydride is getting abstract. So, this proton is getting abstracted from here and forming these type of starting materials ok. So, now, if you try to write them this compound in appropriate manner it is actually end up make making this one. So, here you can see you can write this 1 2 3, 1 2 3. So, the major difference is instead of -OR you have -NMe_2, here you have a OR group which is allowing to get to the corresponding ester after that [3,3]-Sigmatropic shift. So, the major difference is instead of -OR you have -NMe_2, here you have a OR group which is allowing to get to the corresponding ester after that [3,3]-Sigmatropic shift.

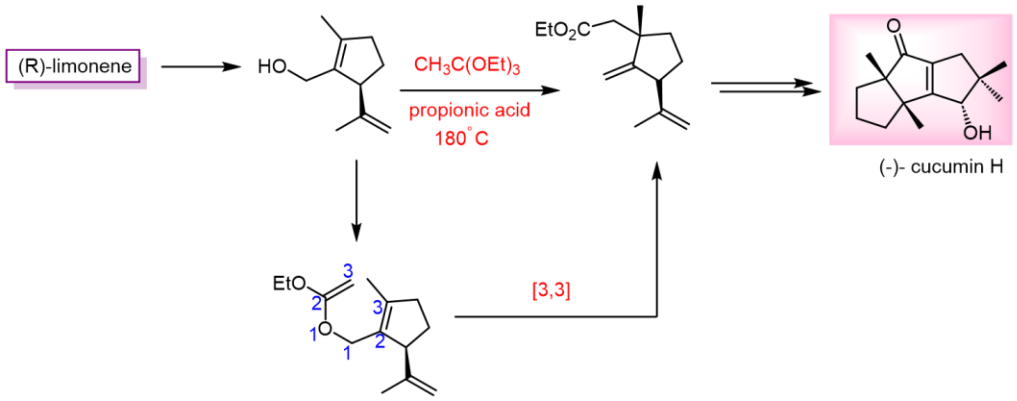


So, here there is a application of Johnson-Claisen rearrangement to the synthesis of an important compounds. So, here using propionic acid ok and with this compound what is going to happen is going to generate this type of intermediate species which is going to participate in the Johnson Claisen rearrangement to get to this corresponding again the gamma delta unsaturated esters ok, which is going to convert to the corresponding product. Again there is another example here, we are actually majorly focusing on the Johnson Claisen rearrangement, we are not focusing on the all the synthesis of the important compounds, we are mostly focusing on the rearrangement part only.

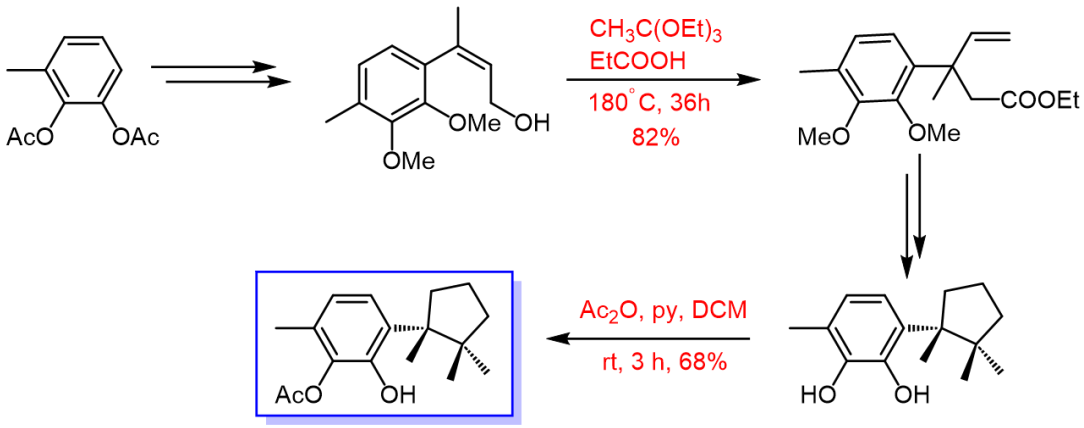
So, if you see from this particular compound again we can see this is allylic alcohol, We know that from allylic alcohol what is going to happen that once you react to this, it is this orthoformate and then this trialkyl orthoformate in place of acid, it is going to

generate the corresponding intermediate. Now, it is going to participate in [3,3] Claisen rearrangement to get to this corresponding compound. So, how do you write the product? As I told you, find out that this double bond going to move here and the rest of the CH_2 and CO, so this is the part CH_2. and then COOEt. So, this is going to come to this particular carbon ok. So, you end up making this particular product and then after some successive transformation it can able to convert to a important compounds.

- natural product synthesized from the (R)-limonene using Johnson-Claisen rearrangement .



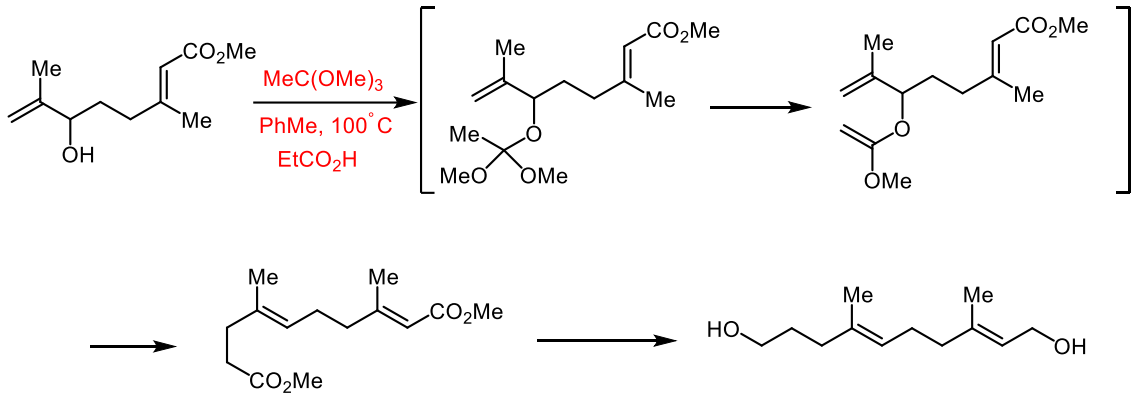
- Aromatic natural product synthesized by Johnson-Claisen rearrangement.



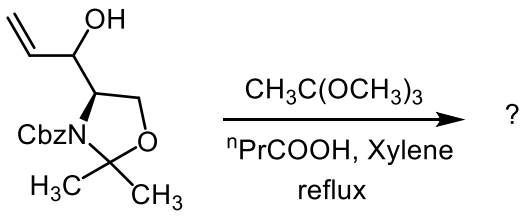
Helicobasidium mompa

There is another application which is given here again trimethyl orthoformate here. Here also you have this allylic alcohol. So, once this allylic alcohol you can able to form this type of intermediate. which can convert after this elimination of this -OMe which can able to make to this particular which can abstract a a proton from this methyl group to

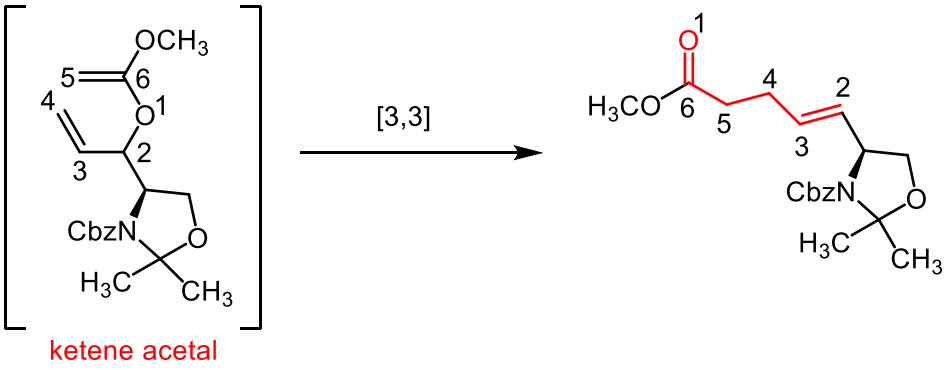
form this compound. Now, it is ready for this [3,3] sigmatropic rearrangement to to get to this corresponding product and which can further reduce to a important compound.



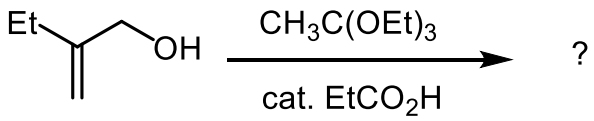
Another example here, I think these are the example which was collected from different type of net and gate exam. So, I think it is very good that you should practice these questions ok. So, what is happening here? We have also another allylic alcohol here and we are again using the conditions from the Johnson-Claisen rearrangagement. You can see this exactly the similar condition we have seen in the previous slide. So, it is going through this type of ketene acetyl as I told you at the beginning is forming this ketene acetyl. And now it is going for this [3,3]-Sigmatropic shift to get to this corresponding alpha beta gamma delta. So, it is going for this this the gamma delta unsaturated esters.



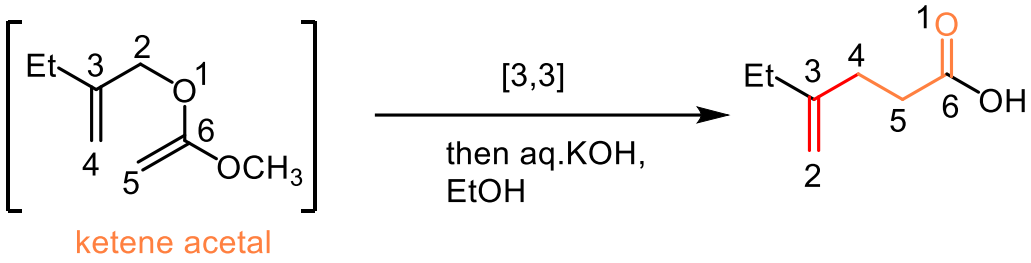
Hints:



Another example of Johnson-Claisen rearrangement here, again very similarly first thing is the formation of this corresponding ketene acetyl and then it is going for this [3,3] sigmatopic shift after the hydrolysis of this corresponding ester, it can form the corresponding acid. So, you should look for the reagent which is given in sometime they give both the first the Johnson-Claisen rearrangement condition and then they give you this KOH ethanol. So, that means it is going to hydrolyze the corresponding ester to corresponding acid.

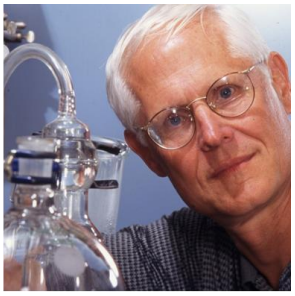


Hints:



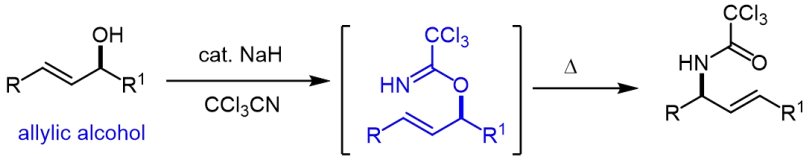
ketene acetal

- This rearrangement discovered by Larry Overman in 1974.
- Conversion of allylic alcohols to allylic trichloroacetamides.
- Formation an imidate intermediate.



Larry Overman

Ex:

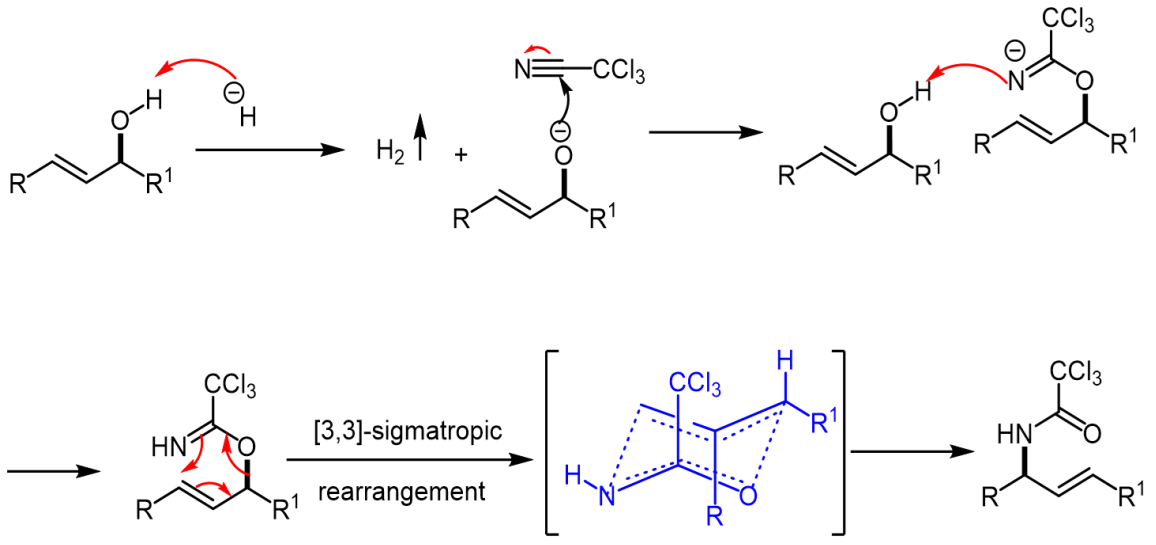


allylic alcohol

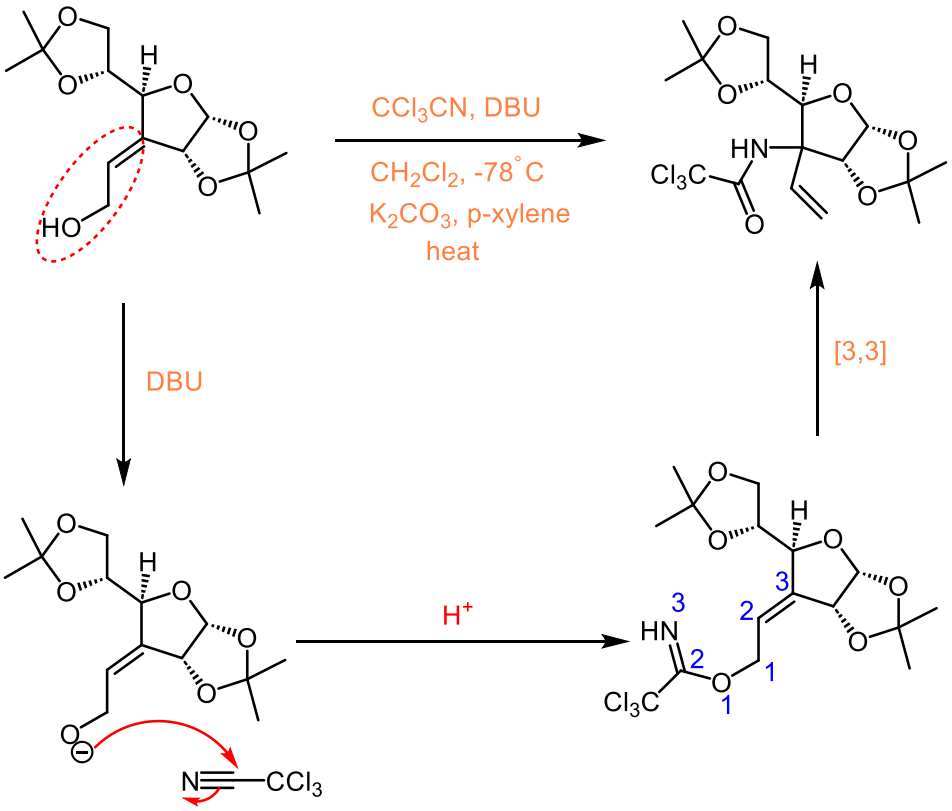
imidate intermediate

Now, I am going to introduce you to the Overman-Claisen rearrangement another very interesting rearrangement which was discovered by Larry Overman in 1974. He has done in a lot of contribution to this organic synthesis by using a lot of total synthesis and also discovered several reaction methodologies. So, in this reaction what is happening actually it is you are actually starting from this allylic alcohol ok. So, what is happening we are

going through a immediate. So, I am going to come back in a minute that using a sodium hydride and CCl_3CN we are making this type of immediate intermediate with a CCl_3 group which is actually making this $COCCl_3$ compounds that means again you have a carbonyl variation and again you have this double bond exactly in the gamma delta position. So, we will try to understand this reaction how this the formation of starting metal is happening. Once the sodium hydride comes it actually this hydride abstract this proton from this to form the H_2 and then this O minus can attack to this corresponding CN bond in a formation of this N minus which can take a proton and forms this intermediate which is now ready for the [3,3] sigmatropic rearrangement. So, now you can see you can give the numbering 1,2,3 we can give them 1,2,3. So, it is can go for some sort of a transition state like that to get to this product.



So, now we are going to talk about some example of this Overman Claisen rearrangement which was applied for synthesis of natural products. So, you can see here once you have this type of allylic alcohol, that if I have allylic alcohol then in the product one thing I have to look for that this bond going to move here the $NHCOCCl_3$. So, this is the part which going to attach with this particular carbon ok. So, that is something you should after you looking into the condition you should be prepare your mind how to write the product. Now, I think in place of debut first thing is what is happening it is actually abstracting this proton this OH proton it attacking on this compounds and then formation of this intermediate which is now ready for this [3,3] sigmatropic rearrangement to get to this corresponding product. Again there is another example of synthesis of alkaloid another important alkaloid here exactly first the abstraction of this O minus with the sodium hydride then going for very similar type of condition to get to this corresponding product. So you can understand the application of this type of Claisen rearrangement in organic synthesis.



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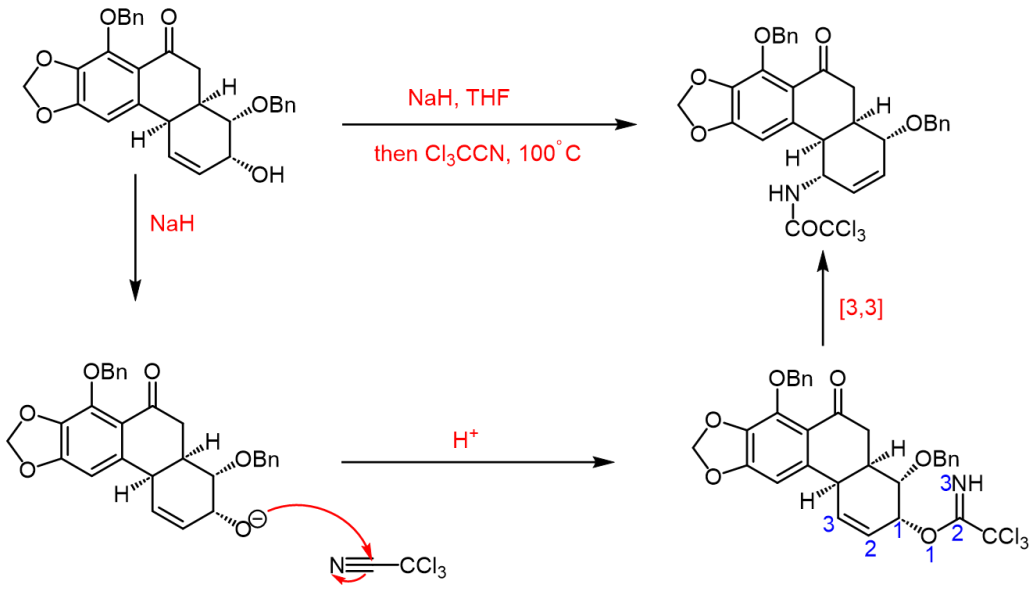
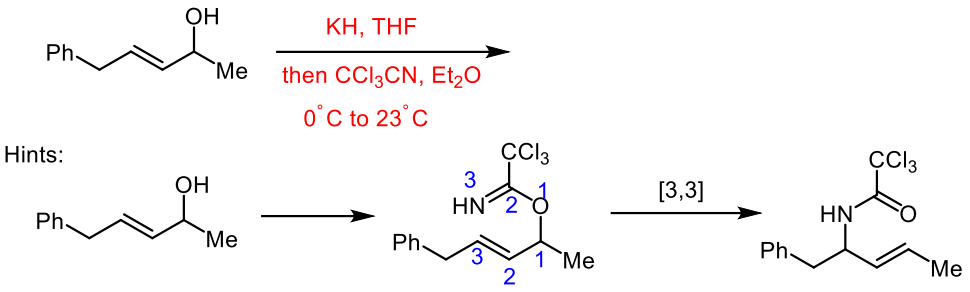


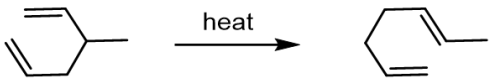
So there is another example here. I think you can also, practice this example for different type of exam. You have allylic alcohol here exactly under this similar condition.

After the [3,3]-sigmatropic shift, you can get to the corresponding product.

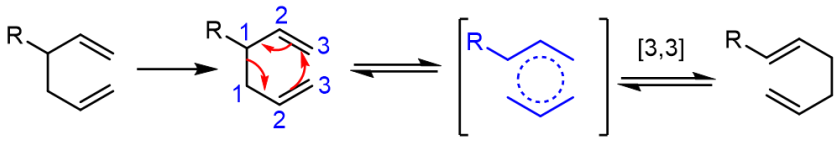


Cope rearrangement, another very important 3,3-sigmatopic rearrangement. So this is a 3,3-sigmatopic rearrangement of 1,5-diene. So instead of keeping oxygen at the middle, which is the Claisen rearrangement, now you do not have oxygen. So, it is actually in the pains of a heat it is actually going for a 3,3 sigmatropic shift I am showing here the corresponding the arrow pushing how you can push the arrow here. So, it is actually breaking the of this bond and then formation of this bond here and then after that it is actually going to this corresponding product through this type of intermediate.

- Cope-rearrangement is an extensively studied organic reaction.
- This is a type of [3,3]- sigmatropic rearrangement of 1,5- dienes.
- It was developed by Arthur C.Cope (1940).



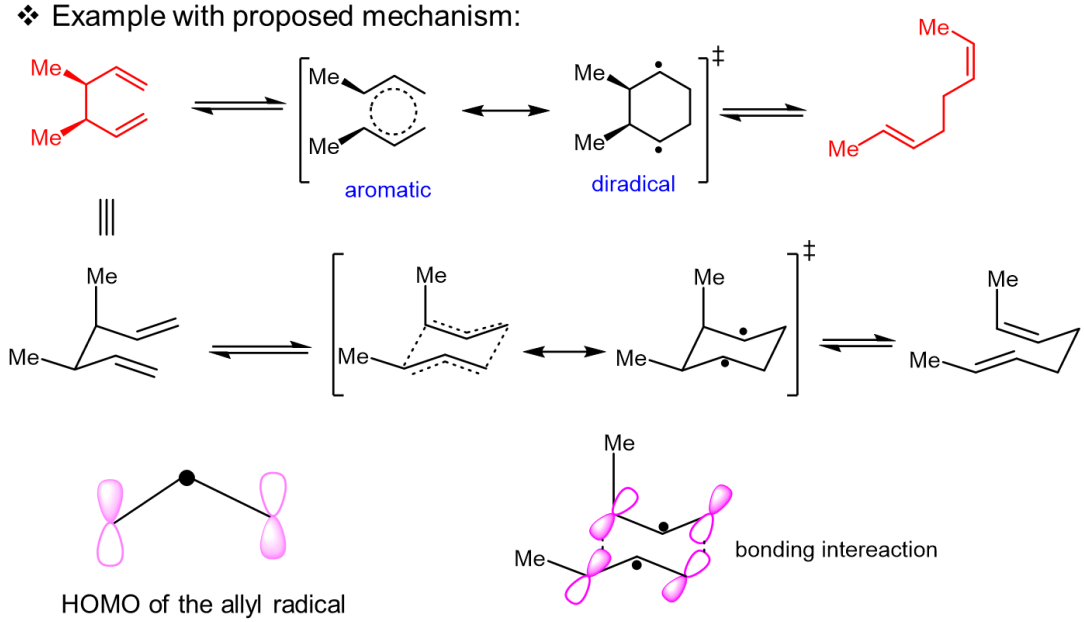
Mechanism:



So, again I think There is, some sort of a proposed mechanism for this, how this reaction happen. There is also a proposal that it can go through some sort of a transition state like this. We can also try to draw through a chair-like transition state to explain the product and, sometime we also write this type of transition state as a, di-radical species and which can finally go through the corresponding product. Again as you guys can see these reactions are reversible because at the end of the day you are breaking two of the

carbon carbon bond and you are forming two new carbon carbon bond only. Of course, here what is happening you are two terminal double bond means they are just mono substituted. that convert it to two disubstituted olefins ok. So, that might be the most stable compared to a terminal one ok. So, again we can able to clearly explain this type of bonding interaction which is that there is a possibility of formation of this type of di-radical species.

❖ Example with proposed mechanism:

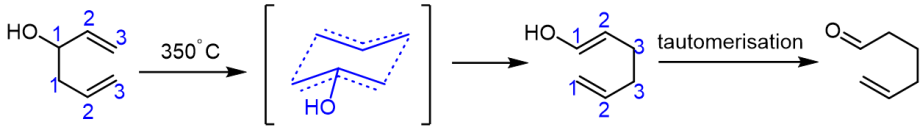


And now I am going to move to the oxy-cope rearrangement because we want to show some sort of a the rearrangement which are mostly focusing on anionic. So, in the oxy-cope what is happening in this position you have a OH group attached to it. So, oxy-cope rearrangement is involves reorganization of the certain unsaturated alcohols. So, what is happening here in the previous rearrangement I was talking about different this allyl vinyl ether, but here we are talking about some sort of a cope rearrangement where you have a OH group attached in the number one position here. So once you heat up, what is going to happen? There is a formation of this type of double bond with a, OH group. We know that after tautomarization, it is going to clearly going to convert to corresponding aldehyde. So now I think in this reaction, we can find a driving force that it is actually forming a stable compound starting from this. So forming a carbon-oxygen double bond. So now we are trying to understand what is happening. so this reaction can be done in case of heat. if you put a heat at 350 degree Celsius, but now think about it once you do a base treatment this reaction can be done at 0 degree Celsius. So, what is happening in place of base once you put a base here actually then base is actually bringing some negative charge density which actually giving electron density to this sigma star orbital of this corresponding sigma bond. So, that is allowing you to break the bond very easily. So, that is the key step of this reaction if you see The breakage of this particular bond is the

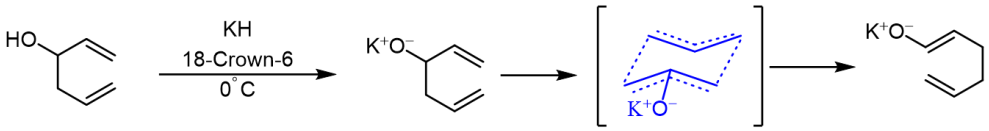
key step ok. So, once you try to write that in the mechanism. So, breakage of this bond is the important one. Now, if you give electron density to the sigmastar then it will be easy which goes to this transient state to the corresponding product and after the the protonation it can go to the corresponding aldehyde.

- ❖ Oxy-Cope rearrangement involves reorganization of the certain unsaturated alcohols.
- ❖ It is a variation of cope rearrangement.
- ❖ Formation of unsaturated carbonyl compounds.
- ❖ In the presence of base rate of reaction increases.

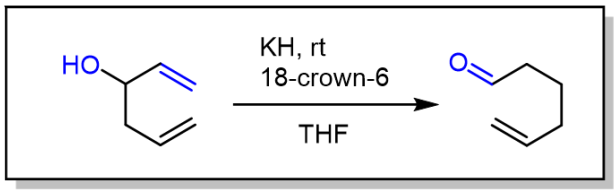
Example:



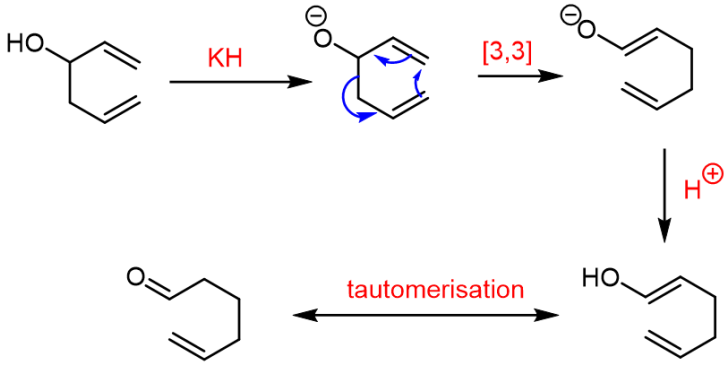
In presence of base



So, here are some example here in case of potassium hydride, it can abstract this proton, then it is go for the [3,3]-sigmatromic rearrangement here and then after protonation and the tautomerization goes to the corresponding aldehyde. So, now you can have this corresponding aldehyde from starting from this allylic alcohol.

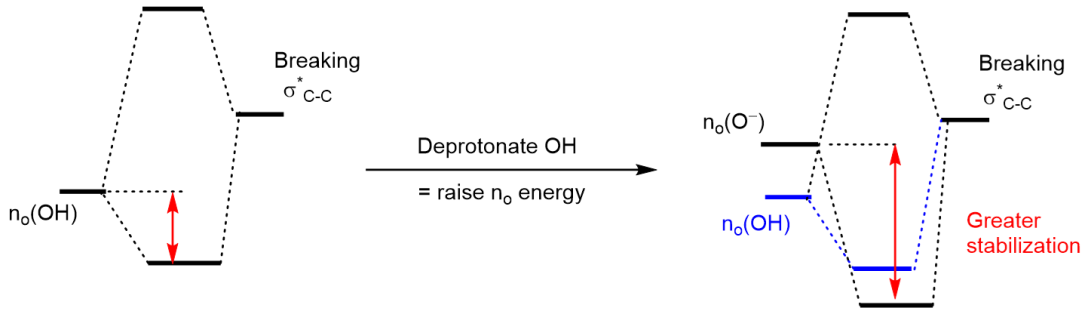


❖ Mechanism:



So, we can try to explain this through the molecular orbital that why if just making a deprotonation making the reaction faster again once you make a deprotonation you are getting a greater stabilization compared to if you do not deprotonate ok. So, that is actually raise the non-bonding orbital energy. So, which is giving the greater stabilization and actually the important is that actually it is giving this electron density to the sigma star orbital of this carbon carbon bond. So, that is the important thing. So, that is becoming very easy here once you becoming once it is actually becoming a O minus. Now, this the charge donation will be easier.

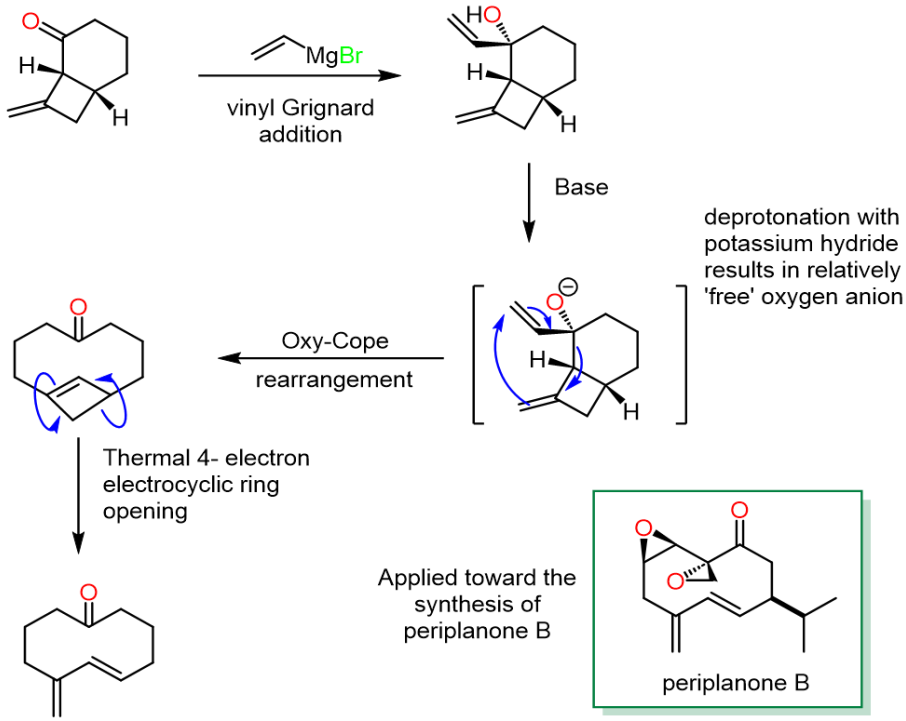
Molecular Diagram:



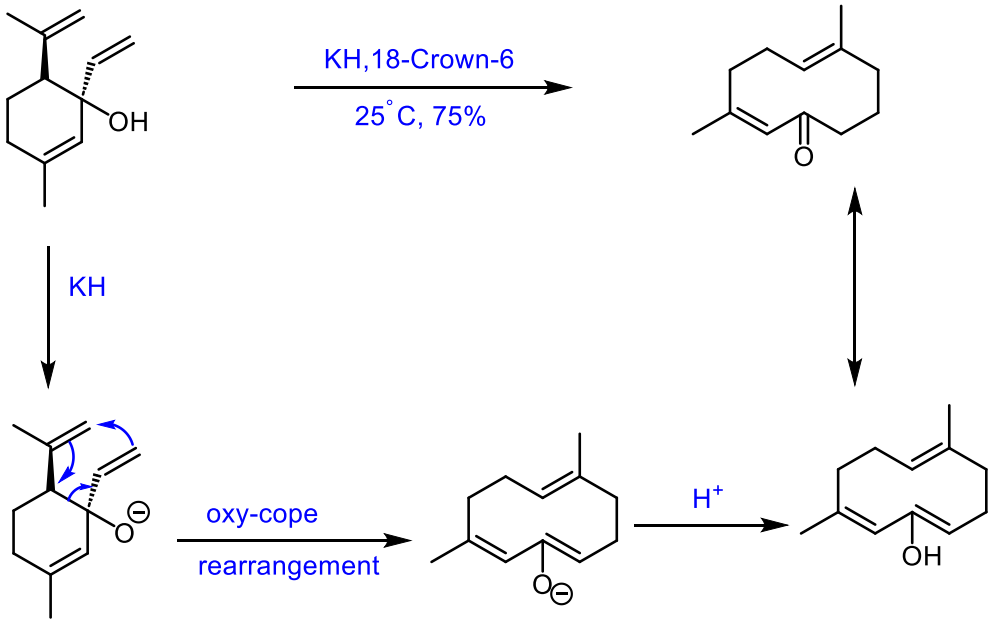
Here are some example of application of anionic oxy-cope rearrangement. So, in this particular substrate once you treat with Grignard I am going to discuss these things later on. using vinyl grignard you can able to make this corresponding allylic alcohol. Now, you have to look for it once do this type of transformation you have to look for this that once you see this compound have a allylic alcohol you should always look for there should be a chance of a sigmatropic rearrangement. Now, if you look for that then clearly going to be number 1 carbon, number 2, number 3, then number again we have a 1, 2, 3. So, this will go for a [3,3] sigmatropic shift which is shown here clearly and after that you will going to end up making this compound which will go for a thermal for electro cyclic ring opening you must have studied in the pericyclic reaction chapter to get to this corresponding compound.

now I am going to show you another important problem of oxy-cope rearrangement here so now you have this in this particular example you can see we already have allylic alcohol here now we can give them a numbering of one two three we can give them one two three now what is happening that in of course we once you give a potassium hydrate as and 18 crown six those are the two reagent you need for this oxy-cope rearrangement which actually now going to generate this O minus species here and now if you give them a numbering of 1 2 3. So, this will go for a [3,3] sigmatropic rearrangement. So, there will be a breakage of this particular bond 1 1 bond this is going to break 1 1 bond. So, it is going to break and now there will be a ring expansion going to

❖ Synthesis of the cockroach pheromone Periplanone B :

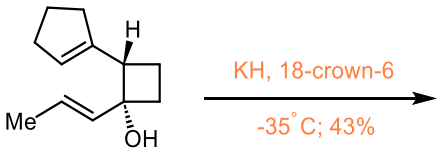


happen to form this particular compound after taking a proton is going to form this particular product ok. You can see if by doing this oxy-cope rearrangement from this

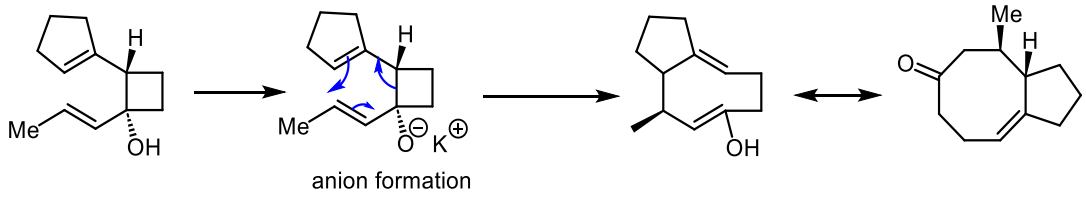


compound it is going through ring expansion and also going to form a corresponding ketone.

There is another example I think there are a lot of a lot of problem comes in the oxy-cope rearrangement in the in different exam like gate in a jam and net. So, I try to solve some of the question during the teaching and also I am planning to bring in a lot more questions at the end of all the chapter discussion because there are some problem where you have to use different things in that in the in the same that means you have to use the chemistry of carbanion you have to use the chemistry of carbocation radical in the same problem. So, that is why I am going to bring those problem towards the end of the all the lectures getting over. Here what is happening from this compound once you treat with KOH and 18 crown 6 it is going to the corresponding product first things starting from this corresponding alcohol there will be a deprotonation happening formation of this O minus potassium plus and then this is going to go for this is going to go for this corresponding 3,3-sigmatropic rearrangement and then it is going to form this particular compound here and then once it is getting a proton here, then it is going to form this particular compound. So, now you can see there we can able to form a bigger ring starting from this type of 5-member ring. So, this can get expanded to this type of compound.



Solution:



So, in this particular chapter what we have learned, about Eschenmoser-Claisen rearrangement, Johnson Claisen and Overmann Claisen. Now, if I summarize the Claisen rearrangement, you have started learning Claisen rearrangement from the previous class. So, we have seen that. So, this will be a [3,3] sigmatropic rearrangement and just by using Claisen rearrangement we can able to see the corresponding the gamma delta unsaturated ketones. By using Johnson Claisen rearrangement in the today's class we have found the synthesis of corresponding esters.Previously using the Ireland Claisen reagement we have seen synthesis of this the gamma delta unsaturated carboxylic acid. Then using the Eschenmoser-Claisen rearrangement, we are making the corresponding the gamma delta unsaturated amide. And I have shown you several example of this type of rearrangement. I talk about theanother important rearrangement is the Overmann Claisen rearrangement. I show you several example of it. And also I have tried to talk

about the mechanism and the different different transition state. I also talk about the cope rearrangement, I introduce you to the cope rearrangement, formation of the corresponding transition state, the formation of corresponding product. I also introduce you to the oxycope and I also try to differentiate you the what is the difference between cope and oxycope. The oxycope reaction rate is much faster compared to normal cope rearrangement. and I also told about the importance of oxycope it was used for the ring expansion to make a bigger ring from a smaller ring, thank you all thank you coming to the class and I am going to see you guys in the next class.