Introductory Organic Chemistry II
Professor Doctor Harinath Chakrapani
Indian Institute of Science Education and Research, Pune
Module 08
Lecture 60
Problem Set 8

So, I will now move on to solving some problems.

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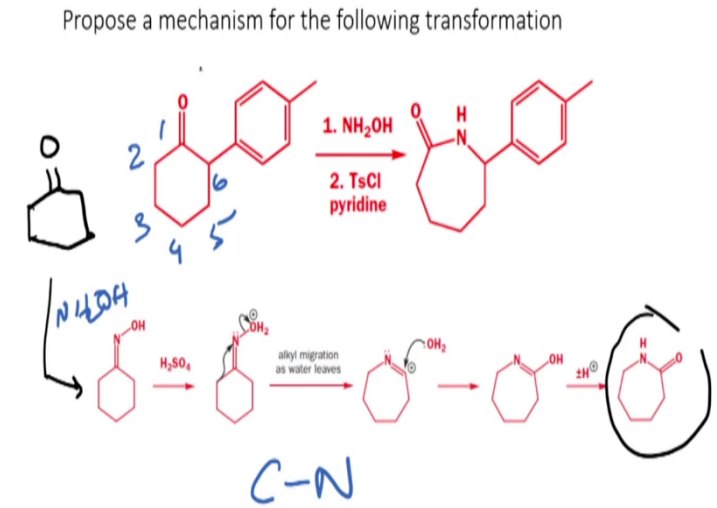

So, the first problem in this problem set it involves the Beckmann rearrangement. And so here the question is, when I start with this ketone, which I am just going to number here as 1, 2, 3, 4, 5 and 6, so it is a cyclohexanone with a substituent on it, and I react it with hydroxylamine and tosyl chloride and pyridine, I get this amide as the product and this is a 7-membered ring. And so, we have looked at the mechanism of this reaction, and we will get to it shortly.

So, when I react cyclohexanone with the hydroxylamine hydrochloride, the product that I get is oxime. But in the case of cyclohexanone, being a symmetrical compound there is no cis or trans isomerism that is possible. So, once it reacts with H_2SO_4, the hydroxyl group gets protonated. And then there is a carbon-nitrogen bond that is broken, which is the alkyl migration, this is a carbon to nitrogen migration.

And it produces the C double bond N and with a positive charge on it, which then subsequently reacts with water and tautomerism finally gives you this 7-membered amide

ring. So, as I mentioned, the cyclohexanone case, there is no question of cis and trans isomerism.

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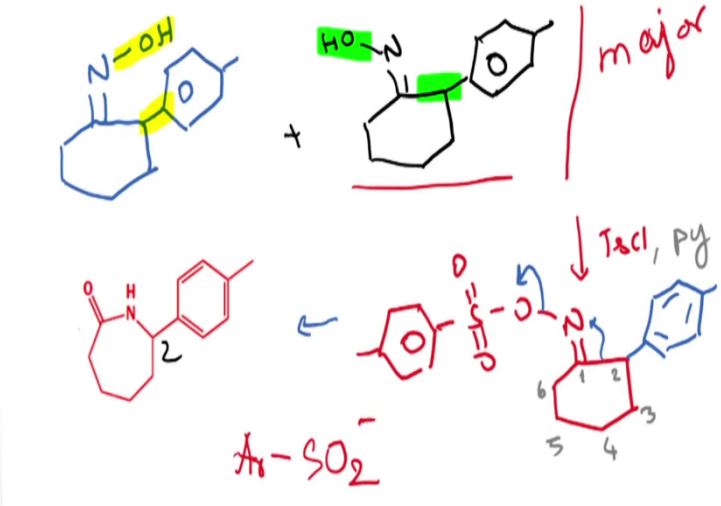

But in the case of the compound that we are looking at, there is a possibility of having cis or trans isomerism. So, the compound on the left which is colored in yellow is the cis isomer where the hydroxyl group and the phenyl group are close to each other and the one on the right is the trans isomer, where the hydroxyl group and the phenyl group are actually going to trans to one another.

So, we already know that the alkyl group that is trans to the leaving group is going to migrate. So, when you prepare these oximes, the oxime formation this is going to be the major if not the only product. So, if this is the major product, then the only availability for the oxime for the next reaction is this compound.

So, when you react this with tosyl chloride and pyridine, deprotonation of this hydroxyl group can occur, reaction with tosyl chloride gives you this product. And now if you observe this is the only product that is going to be available in solution for migration to occur. And so, the carbon 1-2 bond breaks and kicks out the Ts, basically SO_2^- and this para-tolyl group is here. And so subsequently, you are going to lose this proton.

And this gives you a 7-membered ring. And if I want to look at this numbering here, there is a new bond between carbon-2 and nitrogen that is formed and this is carbon-2 and the

carbon-2 still connected to the phenyl ring. So, the product formation is determined by the group that is anti to the leaving group. And since here the group that is oxygen formation is going to determine the fate of the reaction, we get only one product where the carbon 1-2 bond is being broken.

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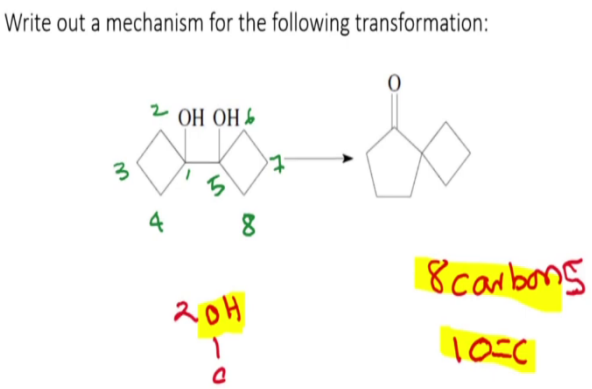

Now, moving on to the next question, this is an example of the Pinacol rearrangement. So, if I look here, on the left, there are 8 carbons there are two 4-membered rings and there are two hydroxyl groups here. On the right, there are 8 carbons again. So, if I see here, this is 5 carbons and then 5 plus 3, 8, but there is one C double bond O that is present. And so, you seem to have lost another oxygen in the rearrangement.

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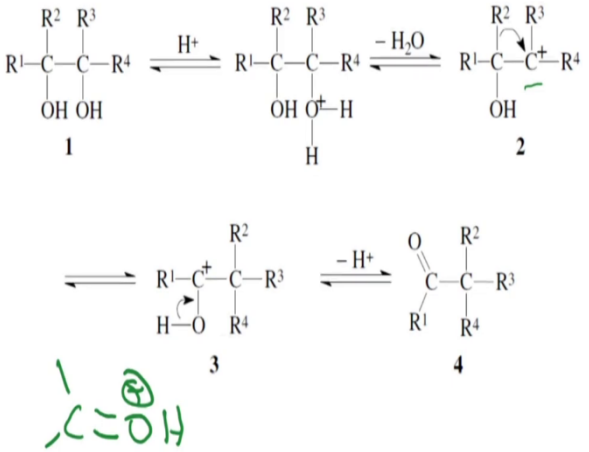

So, let us look through the mechanism. So, the mechanism is something that we already looked at, fairly straightforward. So, you have protonation of this OH and keep in mind both these OHs in the example that we are looking at are equivalent.

But here they are all, these two carbons are different. So subsequent loss of water is going to give you this carbocation and then there is a migration of this alkyl group which is going to produce a very stable carbonyl, C double bond O H with a positive charge, this is fairly stable and subsequently loss of water is going to give you this ketone.

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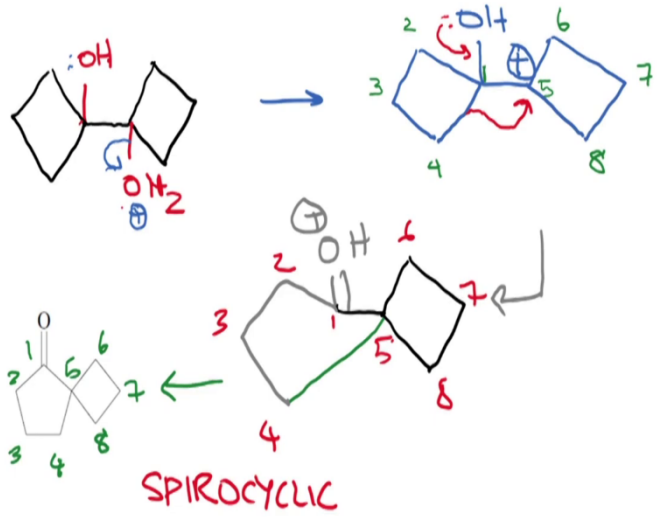

Now coming to the problem in hand, so you have two 4-membered rings and the 4-membered rings, one of the oxygens can get protonated and subsequent loss of water gives you this carbocation. And now if you look carefully, the migration occurs of this 1-4 bond and in conjunction with the carbonyl formation, C double bond O. And then there is a new bond between carbon-4 and carbon-5.

And so, you have a 5-membered ring attached to a 4-membered ring. And then loss of this proton is going to give you this product. And as I mentioned earlier, this is an example of a spirocyclic compound, where you have a quaternary carbon, which is flanked by 2 carbocycles or any other cyclic compound.

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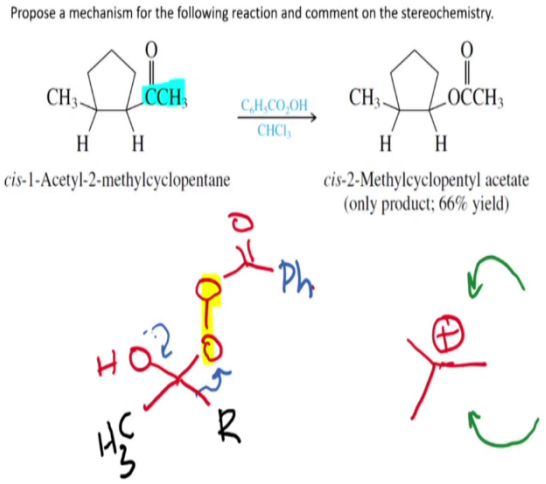

Moving on to the next problem, which is the Baeyer-Villiger oxidation. So, the question here is that, propose a mechanism and comment on the stereochemistry. So, in order to understand the stereochemistry here, what I am going to do is if you look at this carbon here, which has a chiral center, which is the carbon-carbon bond is going to break here, you see here that this is the highest priority group and then the other groups are essentially the same in the product

So, if you see that this carbon-carbon bond is broken, and that is now replaced by a carbon-oxygen bond. So, in this whatever stereochemistry is there in the starting material, it is retained in the product. So that is a first thing that we need to understand.

So, when you see that there is 100 percent retention, that means that it is the only product that is formed, immediately, we can start thinking that there is no intermediate in this reaction, because if you, for example, form a carbocation like intermediate, and the carbocation as you know is a planar, and so the attack can happen from the top side or the bottom side, and so it will lead to racemization.

But in this case, we do not see any evidence for racemization, and you see only 100 percent retention in stereochemistry, which likely suggests that it is going to be a concerted step when it is not a stepwise mechanism. So now coming to the key intermediate that is going to be formed here. The key intermediate here is as shown here, where you have, you know the peroxide bond here. And now when there is this OH, lone pair of electrons goes in, there is a

migration of this R group, and it is going to produce the, this is the key step that we are looking at.

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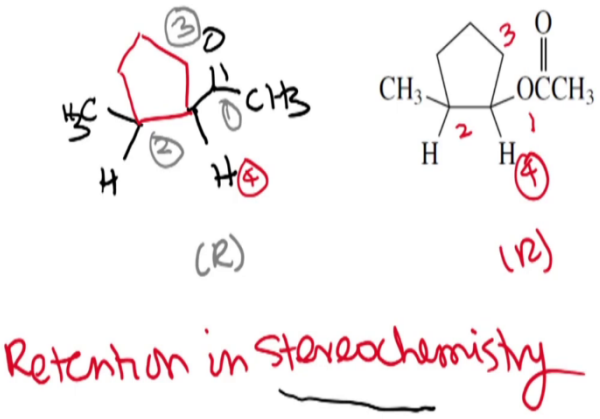

Now, after that migration, subsequently, loss of protons and so on, is going to give you the final product. So now what I will do is I will just assign the stereochemistry. So, it is easy for us to follow. So, for this carbon, this is priority number 1, this group is priority number 2, this group is priority number 3, and hydrogen is here.

So, now, if I look from the top, this is clockwise. And so, it is R and now looking at the product, the priority of the product is unchanged that is this group used to be priority number 1 continues to be priority number 1, the other two are the same. So, if I look again from the top, this is clockwise, so this would be R. So, there is clearly retention in stereochemistry.

What it means is that once there is retention in stereochemistry or 100 percent inversion in stereochemistry, one of the things that we will conclude is that there is no intermediate or there is no planar intermediate wherein there is scope for racemization.

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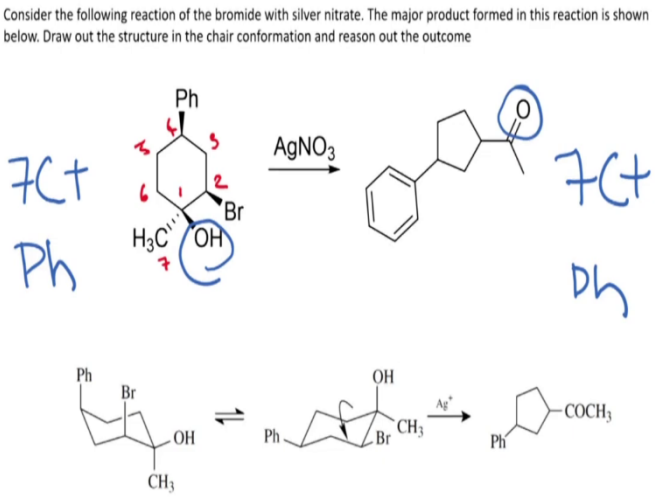

So let us move on to the next problem. So, this involves the rearrangement, which we have looked at when we were discussing the stereochemistry of rearrangement reactions. So, what we are going to see here is that when you start with a compound such as this and react it with $AgNO_3$, the product that you get is the ketone. So, if I number the carbons here, I have 6 carbons in the ring and one methyl group.

So, there are 7 carbons, plus a phenyl ring. On the right, if I see there are 5 carbons here, 6 and 7. So, there are 7 carbons, and there is a phenyl ring. So clearly the bromide is gone and the C-OH has now become a C double bond O of some sort. So, one of the ways to understand this reaction is maybe we can just look at the mechanism briefly and then come back to the stereochemistry.

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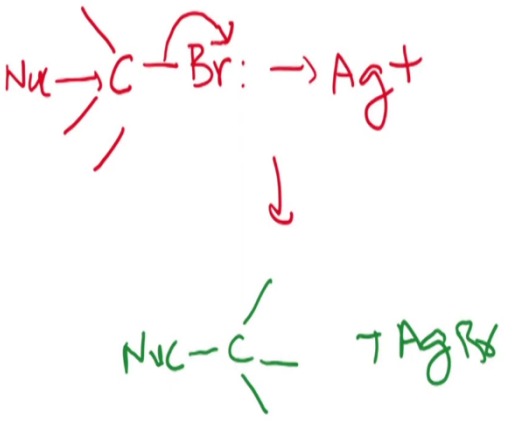

So, what happens is that when you have a carbon-bromine bond, and this can react with Ag^{+}, and so this is going to be lost and in the process. If there is a another, let us say nucleophile that attacks and you are going to get an inversion in stereochemistry plus AgBr. So, this is a good way to activate carbon-bromine bonds for the nucleophilic substitution reactions.

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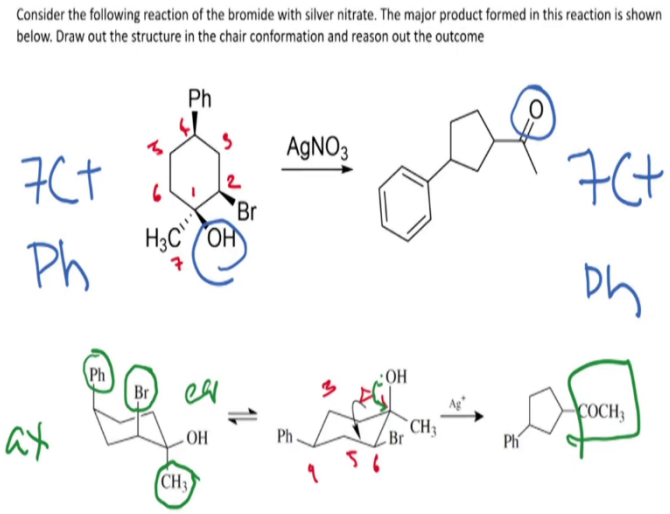

So therefore, moving here now what we need to understand here is the population of the conformation that is going to be important. So, the major conformer here would be the

reaction that is if you look at this conformer here, here this is in the axial position, this is in the axial position, this methyl group is in the axial position.

So, you have 3 groups in the axial position whereas the hydroxyl group which is relatively small compared to the other 3 groups is in the equatorial position. So, what we could suggest is that this conformation is not a significant conformation, that is the population of this conformation is extremely low. And it is not going to be present to a significant amount.

Whereas the other conformation which is wherein the 3 groups other than the hydroxyl group are actually in the equatorial position would be the most populous conformation even if not the greater than 99 percent or so conformation. So therefore, the reaction is dictated by this conformation here because the population of this other conformation is extremely low.

So, if I then push arrows, and then if I number the carbons, 1, 2, 3, 4, 5 and 6, so the carbon-bromine bond is going to be broken. And then subsequently, you have a new bond between carbon-2 and carbon-6, and then you have a hydroxyl group, the lone pair from here is going to come in here. And that is going to lead to the formation of this ketone.

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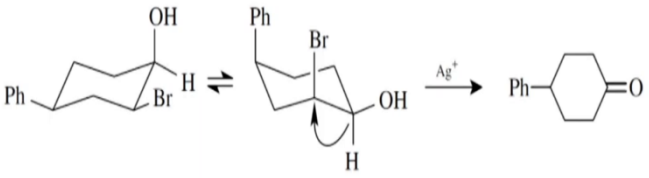

So now, I will leave you with a problem. Once you remove the methyl group from this compound and only put a hydrogen the product that you get is this ketone and not the one that

we saw earlier. So, I will let you go back and work out the mechanism for this although some clues are already given here.

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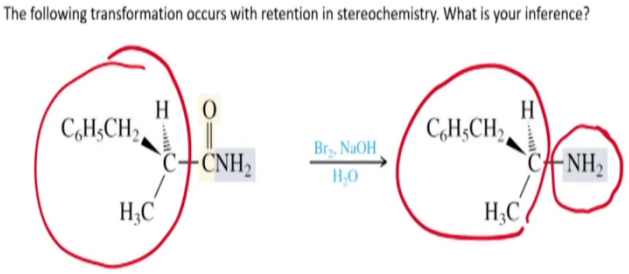

Moving to the next problem, which is the Hoffman bromamide synthesis. So, you start with this amide reacted with Br2 and NaOH, and you get this amine. So, the question here is that the following transformation occurs with retention in stereochemistry and what is your inference?

So again, it is important for us to understand that if there was a long lived intermediate, such as a carbocation or even to some extent, sometimes radicals to some extent, not always, then what happens is that there is going to be a racemization that is going to happen. So, therefore, what we can suggest is that the reaction is a concerted reaction. So, this group over here on the left essentially remains the same and the $CONH_2$ is replaced by an amine.

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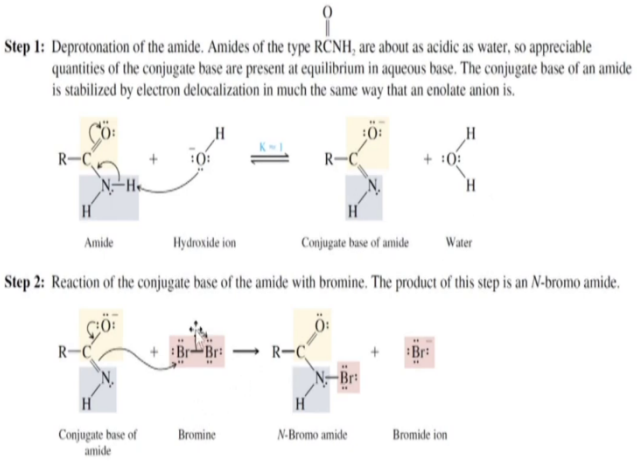

Now, let us look at the mechanism when you have an amide the pKa of the amide is low enough that it can be deprotonated by hydroxide ion. So, therefore, the hydroxide ion is going to be deprotonated and form this kind of conjugate base of the amide and form water. Now in the presence of bromine, this amide is going to react and give you this N-bromo amide. And now the N-bromo amide is also quite acidic.

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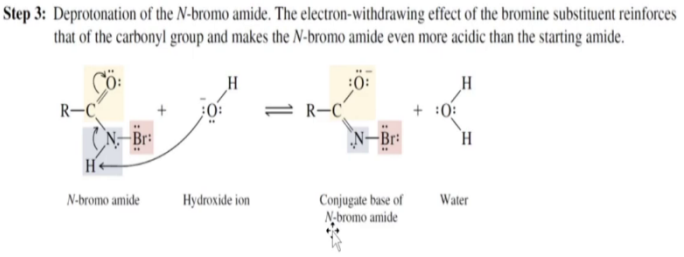

And the second deprotonation occurs to give you the conjugate base of the N-bromo amide.

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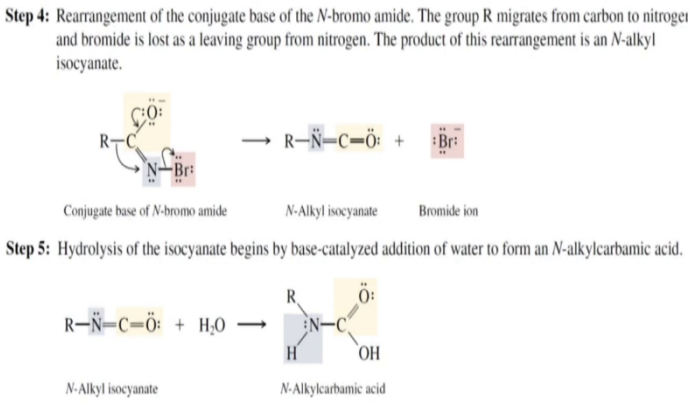

And after this the N-bromo amide is going to be in a position where in this migration can occur to produce this isocyanate. So here, this is the key step where this carbon-carbon bond is being broken and to generate an alkyl isocyanate. And now reaction with water gives you this N-Alkylcarbamic acids, as N-Alkyl carbamic acids are actually quite unstable and they may subsequently hydrolyze to give you the amine and carbonate ion and water, of course….

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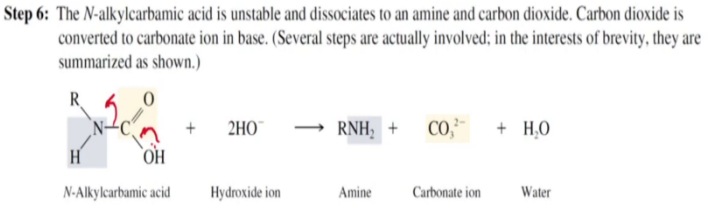

there are many steps involved in this one of them is of course, the loss of CO_2.

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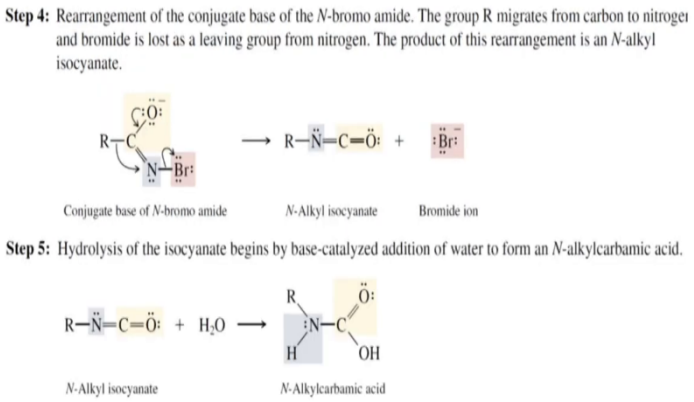

So, this is the mechanism and what we can understand from this mechanism is that this step 4, which is the most crucial step where the carbon to nitrogen migration occurs in a concerted manner. If not, you will have racemization but what we see here is clearly retention in stereochemistry.

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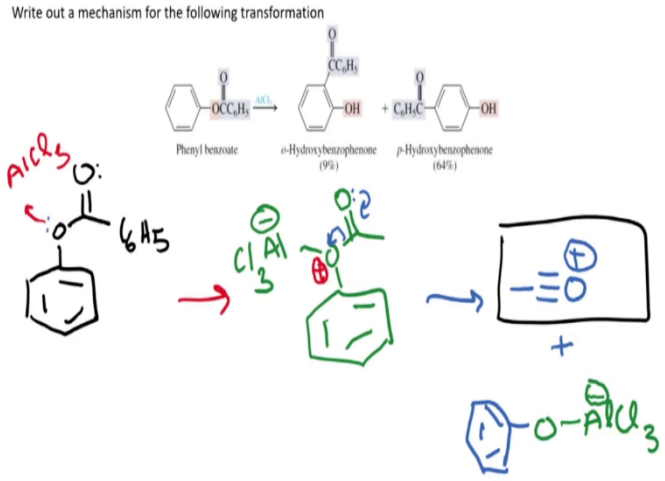

Let us move on to the next question here. When you start with phenyl benzoate and react it with aluminum chloride, the product that is formed is actually an ortho para mixture, which is ortho hydroxy benzophenone, which is 9 percent and para hydroxy benzophenone, which is

64 percent. Now, the general mechanism that we can propose is that when you have aluminum chloride, aluminum chloride is Lewis acid, it is going to start coordinating with oxygens.

So maybe it coordinates with this oxygen here and that results in the formation of a oxocarbenium ion, $C{\equiv}O^+$ and now this $C{\equiv}O^+$ can react with the benzene ring. I am not going to draw out the mechanism, I think that is something that you guys are already familiar with, and how the reaction can occur either at the ortho position or the para position and that gives you this mixture of products.

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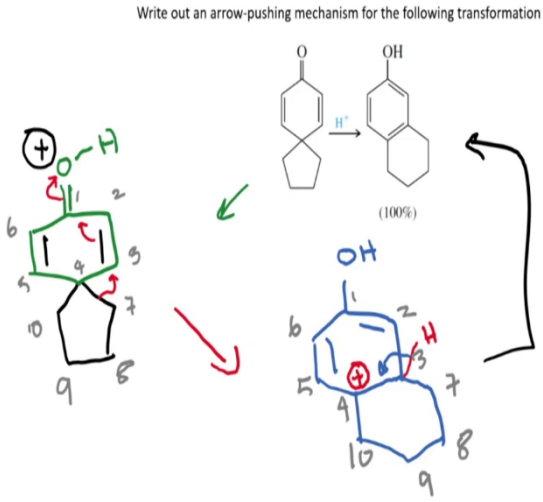

Now, moving to the next question here, which is the writing an arrow pushing mechanism for the following transformation. So, this we can reason out in the following manner. So, you have a 6-membered ring, which is spirocyclic with another 5-membered ring. And in the product, you continue to have the 6-membered ring, except that you have another 6-membered ring in the product, but there is no loss of carbon or oxygen here, carbonyl and two double bonds have now become an alcohol and 3 double bonds.

And the way we would understand this is that in the presence of H^+, this oxygen gets protonated. And then there is this bond between carbon-4 and carbon-7 that is broken and it is a conjugate addition which gives you this delocalized compound as the intermediate which

then subsequently can lose this proton as shown here to give you the final product, which is in 100 percent yield.

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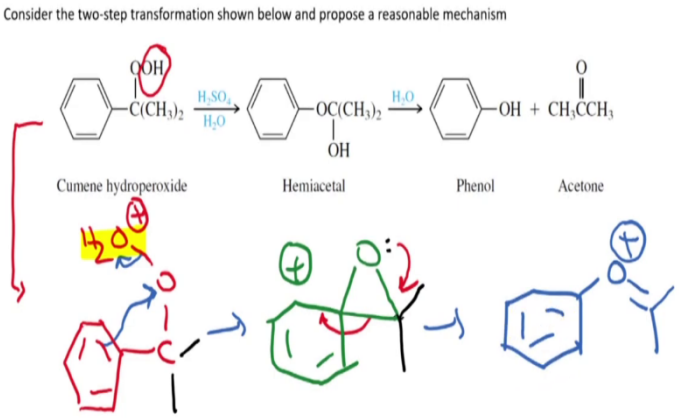

Now, moving on to the next problem, the question here is consider the two-step transformation which is shown below and propose a reasonable mechanism. So, we start with cumene hydro peroxide. So hydro peroxide is this group where you have this OOH and in the presence of acid it gives you this hemiacetal which then subsequently undergoes hydrolysis to give you acetone and phenol.

So, the question is what is the mechanism of this reaction. So, the first step wherein this hydro peroxide is present reminds you of this Baeyer villager oxidation. So, once you add H_2SO_4, this terminal oxygen can pick up a proton. And once this terminal oxygen picks up a proton, it is going to give you this $^{+}OH_2$ and now the rest of the mechanism is fairly straightforward as we have seen before this migration of this aromatic ring, kicking out water and it generates this kind of an epoxide and now this oxygen can donate its lone pair and form a carbonyl type intermediate and regenerating the benzene ring.

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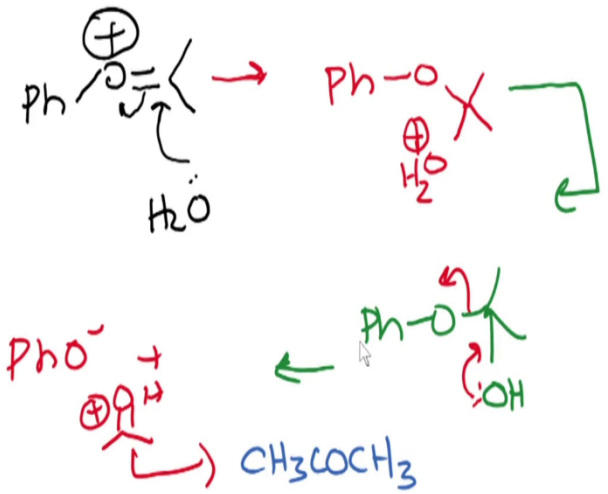

And now, this intermediate, I have redrawn it here is now susceptible to attack by water, it generates the hemiacetal as shown here and subsequently further breakdown of the hemiacetal gives you the acetone and phenol.

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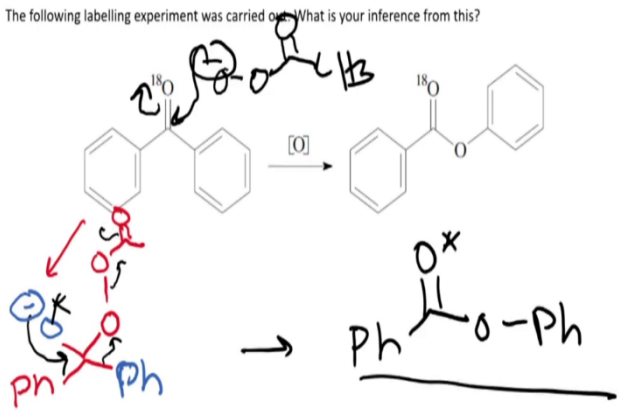

Moving on to the next problem, the question here is that if I start with this labeled benzophenone, I get under Baeyer Villager oxidation, I get the oxygen 18 labeled retained. So, what this means is that this is a very important piece of evidence that again that no major intermediate is actually formed wherein there is some possibility of scrambling.

So, the carbon-18 label which starts here, so, you have attack of the, let us say this type of a molecule which attacks here and generates, this type of tetrahedral intermediate and now collapse of the tetrahedral intermediate results in the migration of this phenyl bond to give you this as the final product. So, if there was any scrambling, then the label would not end up exclusively on the C double O but it could have been lost, but what this tells me is that this is a concerted step wherein there is no possibility of scrambling.

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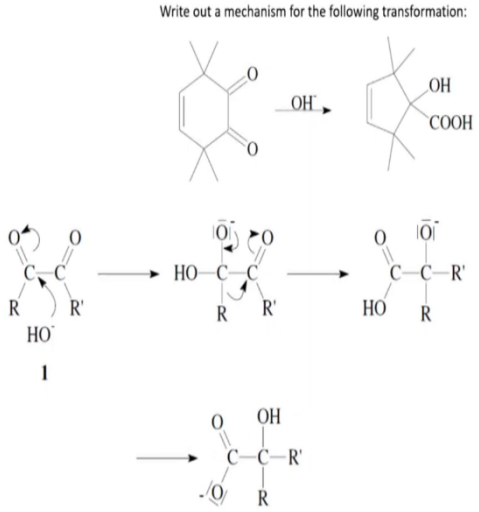

Now, moving on to the next problem, the question here is write out a mechanism for this reaction. So, this reaction as again, we are quite familiar with, I am just going to quickly go through the mechanism. So, hydroxide ion attacks, this carbonyl here and produces this tetrahedral intermediate and collapse of the tetrahedral intermediate results in the migration of this R group here and it produces an alcohol and a carboxylic acid which then transfer of a proton gives you carboxylate and this alcohol.

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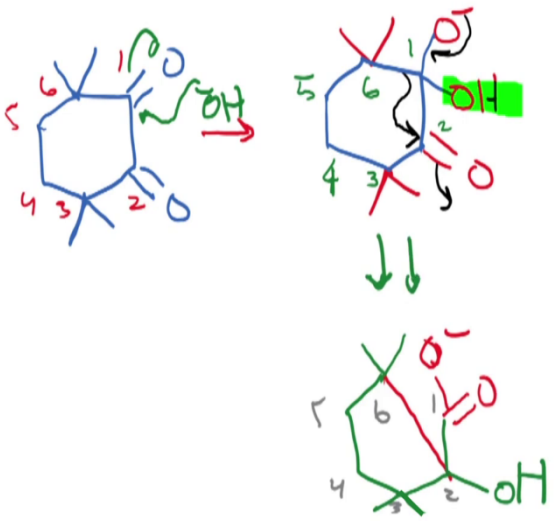

So, in this particular example, we will go through it in the following manner. So, let us number the carbons 1, 2, 3, 4, 5 and 6, carbon-3 and carbon-6 have dimethyl groups on it, carbon-1 and carbon-2 have ketones. So, the first step is attack of hydroxide. So, this is the hydroxide that attacks here and after hydroxide attacks you have this tetrahedral intermediate that is formed and then collapse of this tetrahedral intermediate.

So, keep in mind you have to, once you number the carbons you will get to know this clearly. So, carbon-1 and carbon-6 the bond is broken and the new bond between carbon-2 and carbon-6 is formed. And then this gives you this carboxylate ion or it gives you a protonated carboxylic acid and then it gives you the phenoxide, which then subsequently rearranges to give you a loss of a proton etcetera to give you the final product.

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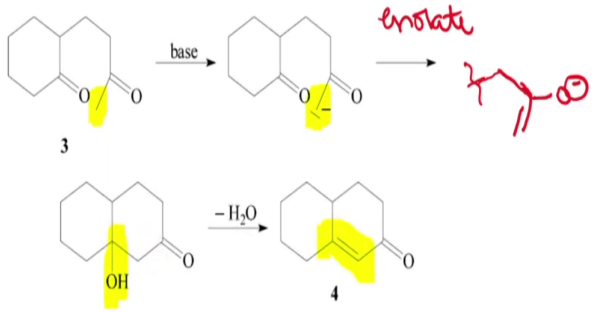

Now moving on to the next question here, write out the intermediate for the following reaction. So straight away, if you look at it, the first step here is the deprotonation of the cyclohexanone, which gives you this carbanion and the carbanion does conjugate addition to give you this compound 3 and compound 3 now is in a great position to form a cycle.

And so, the terminal carbon here undergoes deprotonation. And this deprotonation generates the corresponding enolate. And then the enolate can attack the carbonyl again, to give you this kind of an intermediate and then loss of water across this will produce a double bond, which is the product as shown here.

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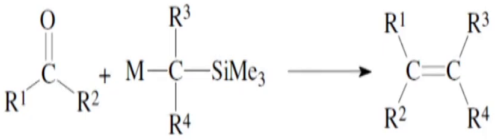
Write out a mechanism for the following transformation. M = Li or MgBr



Next, we will move on to the next question which is writing a mechanism for this transformation. So, here, we start with this metalated silyl compound, the metal can be lithium, or MgBr, which is the Grignard reaction and react it with a ketone and to form the olefin.

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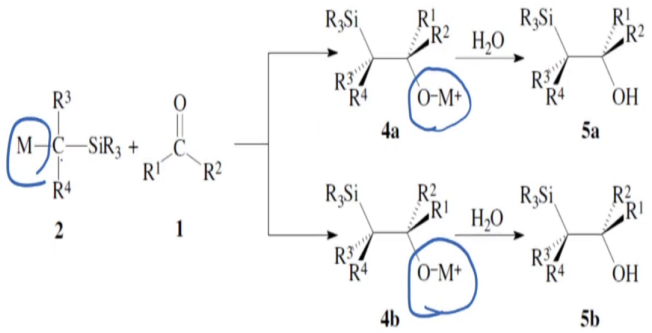

So, the first step here is the addition of this carbon-metal bond across the C double bond O. And it is going to produce two distinct set of conformations or products and we know that addition can happen along the C double bond O and produce this kind of product. And now, once it produces this product O-M this can undergo hydrolysis to give you this hydroxyl

compound and I will leave this presentation with you as a slide so that you can look through this at your own leisure.

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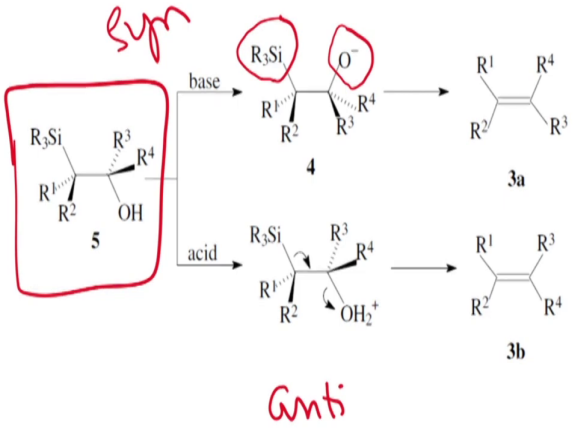

And now, you can have elimination happening in two different ways. If you add a base then the base can deprotonate here to give you O minus and then there is an attack of this oxygen on the silyl group and then subsequently there is a loss of this olefin which then gives you the product which is with this C double bond C. The alternative is for the deprotonation of this to give you migration of this carbon-silyl bond and give you this olefin over here.

Now, these two conditions will actually give you two different olefins. So here this olefin will undergo much like the Wittig reaction which will undergo a syn-elimination whereas here it would be an anti-elimination. So therefore, by making a compound such as this, we could selectively prove either the syn-elimination or the anti-elimination to give you the corresponding olefin.

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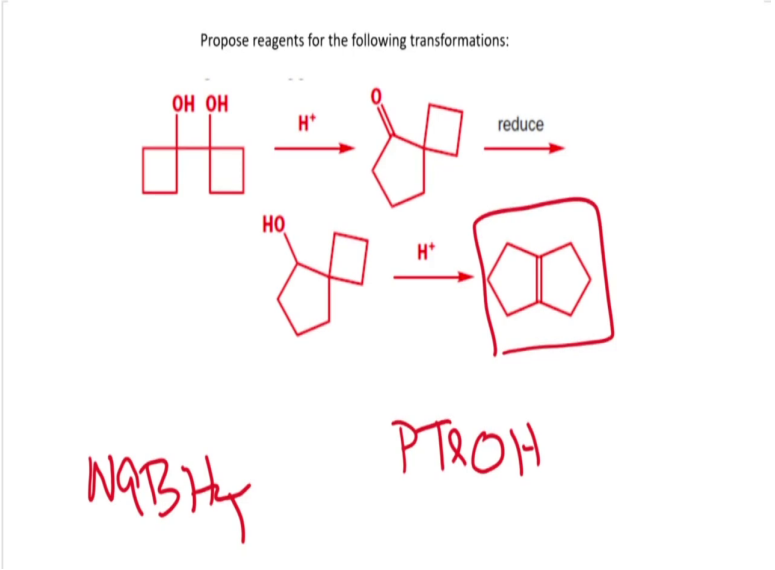

Now moving to the next problem, so we know that this kind of 4-membered ring with the diol gives you this intermediate, we have already seen, all you need to add is H_2SO_4, and then conversion of this ketone to the alcohol can occur with reduction.

So, you will use sodium borohydride and then subsequently, you can add para-Toluene sulphonic acid as the acid source, which will then do this rearrangement to give you this compound. So, I will let you guys work out the mechanism for this last rearrangement reaction.

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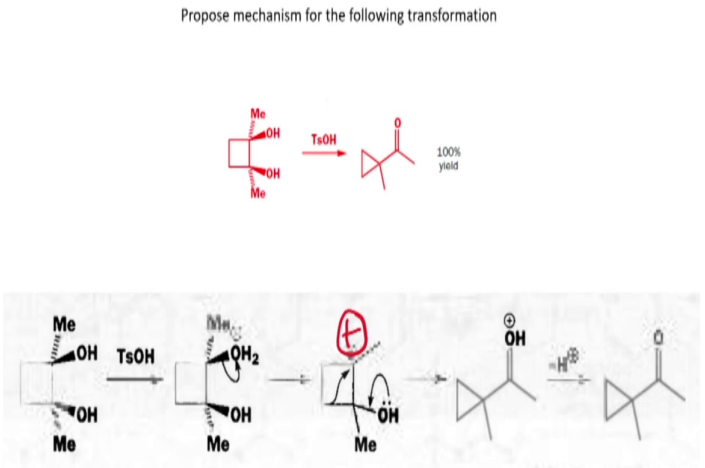

Now moving on to the next problem, which is again Pinacol type rearrangement. The question here is propose a mechanism for this reaction. So, what you do here is again, this is a source of proton, so one of the hydroxyl groups will get protonated and loss of this proton gives you a carbocation over here.

And then this migration of this group here gives you the corresponding product. So, I would like you all to number these carbons and write this in the correct way. And then it gives you this protonated carbonyl compound with a methyl cyclopropane ring, and finally you get this ketone as the product.

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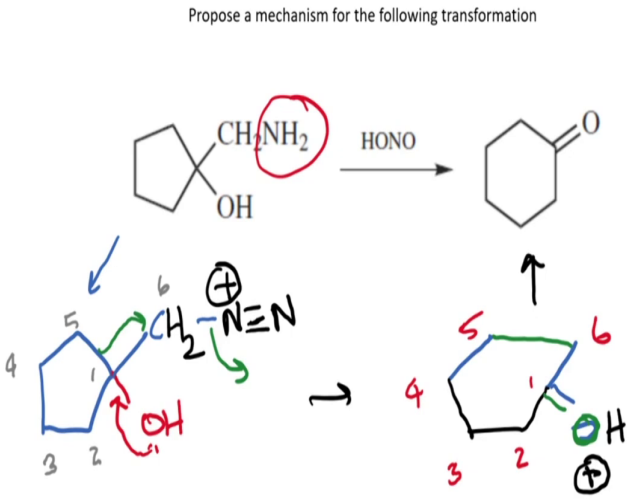

Now, let us move on to the next problem. So here this is a reaction of an amine with nitrous acid. So nitrous acid is generated with $NaNO_2$ and HCl. And this is a very good condition for diazotization. So, diazotization is the first step that can happen NH_2 gets converted to N≡N. Now, if I number the carbons 1, 2, 3, 4, 5.

And if this external carbon is on the sixth position, migration of this lone pair, or donation of this lone pair results in the making of this carbon-1 carbon-5 bond. And now there is a new bond formed between carbon-5 and carbon-6 and this actually ends up giving me a 6-membered ring with a ketone on it. So, the final product here is cyclohexanone.

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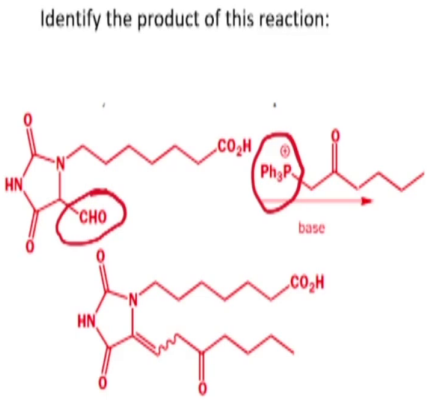

To next problem, identify the product. So here this is a Wittig reaction. So here, this aldehyde is going to react with this triphenyl phosphonium ion in the presence of this base. So, there is a carbanion that is produced and the carbanion attacks the aldehyde, and eventually generates an olefin. So, this is a mechanism that all of you must be quite familiar with by now.

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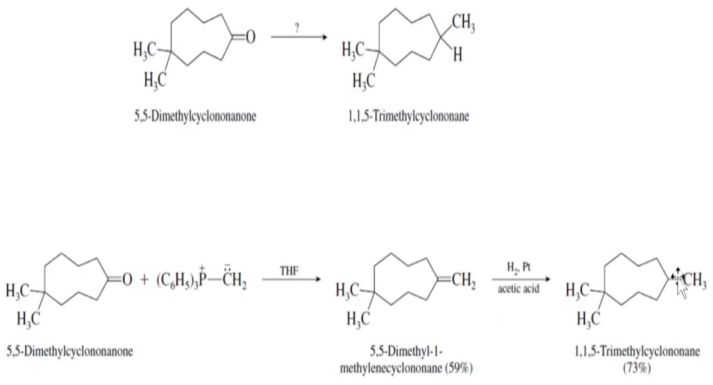

Moving to the next problem, so when you start with this ketone, what are the reagents that are going to give you this product? So, the first step here is there is a new carbon-carbon bond that is produced. And so, we could think about doing a Wittig reaction, with

triphenylphosphine ylide. And so, then this attack here, this is going to give you a C double bond C. And now you could do a hydrogenation, you can either use palladium or platinum and hydrogen and give you this final product.

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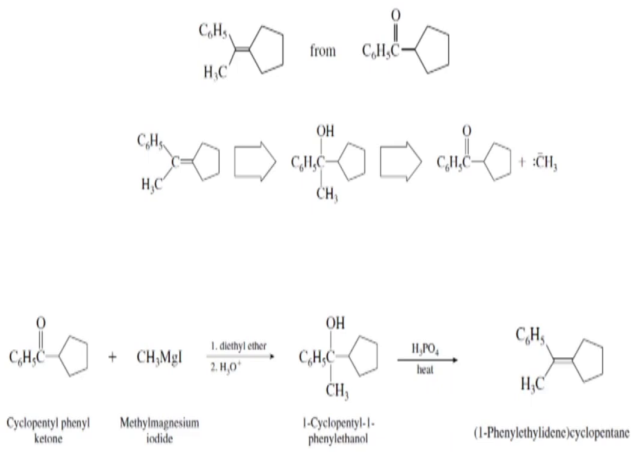

Next problem, you want to make this compound from this ketone. And so, if you see here there is another methyl group that has been added, and then there is an elimination that occurs. So, the first step here this is a retro synthetic analysis.

So, the first step here would be, if I start from this ketone, I would need to add a carbon so that carbon can be either a Grignard reagent or methyl lithium, it is going to give you this methylated compound, and then you need to do this elimination across this carbon-carbon, where this water elimination to give you the product.

So, what we will do is we will start with this ketone, add methyl magnesium bromide or methyl magnesium iodide in diethyl ether followed by hydrolysis, which will give you this alcohol. Subsequently, you can just add a proton source because the product that is formed is the more substituted product, and also the conjugated product. So, there is no competition here it will give you only, this as the final product.

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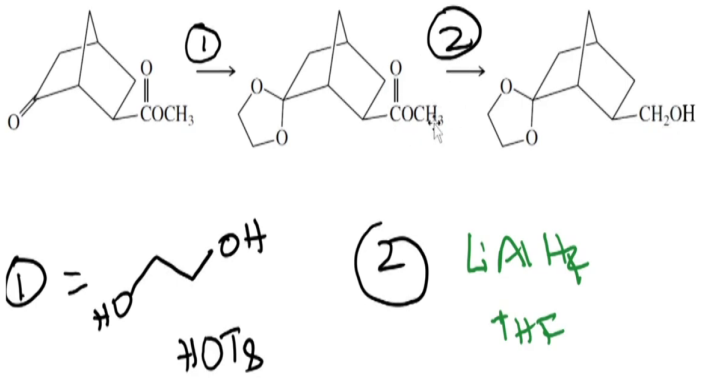

So, moving on to the next problem, what are the reagents that are needed for this reaction. So let us work this out. The first step would be basically it is a protection reaction, which is the formation of the acetal. So, we would start with ethylene glycol and para toluene sulphonic acid, and it would give you this product. The second step is actually reduction of this ester to the alcohol. So, the reduction of the Ester and the alcohol can happen using fairly strong reducing agents such as lithium aluminum hydride.

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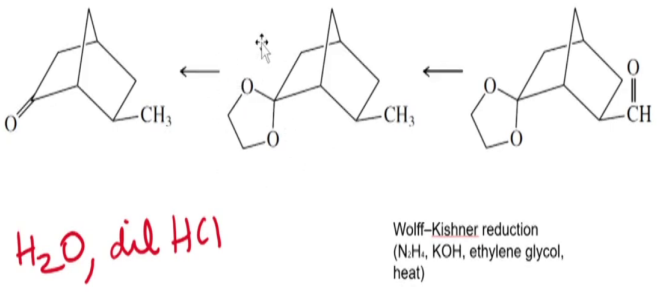

The next step here is an oxidation reaction. I think many of you may not be familiar with this. So, if you do not know the reagents, that is okay. But we can use reagents such as pyridinium chlorochromate, which will give you the aldehyde and penultimate step is the Wolff-Kishner reduction.

So, you want to convert this aldehyde to the methyl group. So, you can use hydrazine and potassium hydroxide, ethylene glycol, and then you heat. So, this is something that we have looked at previously. And so, it gives you this methylated product. And the last step is the deprotection of this which can be done in aqueous acid.

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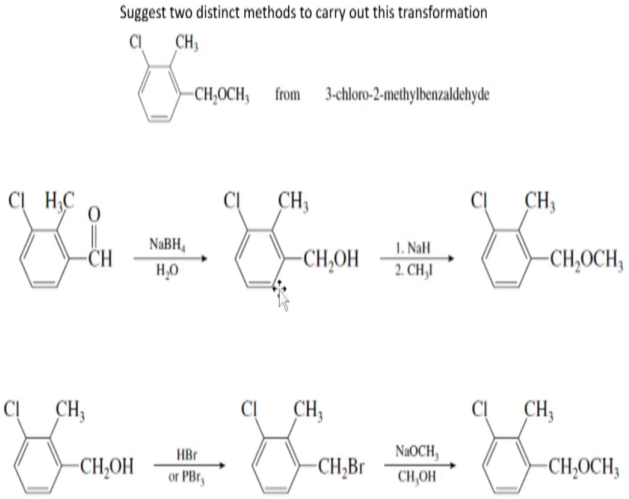

Moving on to the next problem, suggest two distinct methods to carry out this transformation starting from 3-chloro-2-methylbenzaldehyde to this ether. So, one way to do it would be this 3-chloro-2-methylbenzaldehyde. So, first step is you reduce this aldehyde to the alcohol, and then you deprotonate the alcohol and react with methyl iodide, you get this final product.

The second way to do this would be to reduce this alcohol but then you convert it to the bromide and then react it with sodium methoxide and methanol. So, this will be an S_N2 reaction to give you this final product. So, there are two distinct ways that one could do it starting from this aldehyde, but we would need to reduce it to the corresponding alcohol.

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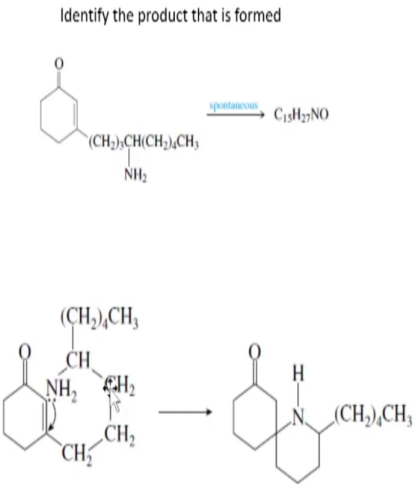

And now moving to the last question, what identify the product that is formed. So, if I turn this amine around and if you number these carbons, it actually forms a nice 6-membered ring by doing a conjugate addition. So, you would attack here and produce the spirocyclic compound as the product here. So, I would urge all of you to number these carbons so that you can keep track of what is going on.