Essentials of Oxidation, Reduction and C-C Bond Formation Application in Organic Synthesis

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Lecture-21
Beta-Cleavage in Barton and Related Reactions and Miscellaneous Oxidations Such as TEMPO Based Oxidations,
Pinnick Oxidation and
Pseudomonas Putida Mediated Oxidations

Hello to everyone, I would like to welcome you all to today's lecture. I am sure you would have had the opportunity to go through the last class. We will briefly have a recap of the last lecture the one that we looked at last time was oxidations at unfunctionalized carbons essentially Barton and related reactions.

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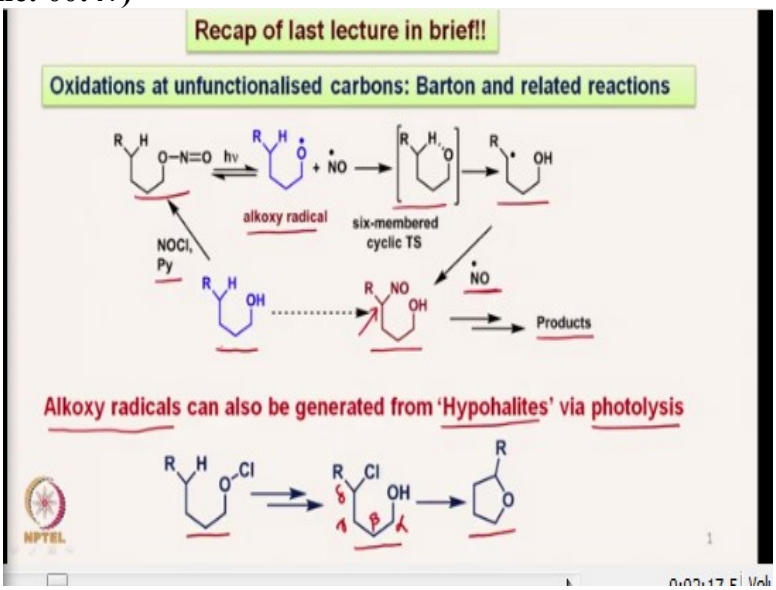

So, in the Barton reaction what we did was to convert an alcohol to a gamma functionalized product. Such as having a nitroso O group or an oxime group at the gamma carbon, and which was lead to different kinds of products by reacting the oxime and the hydroxy group. The way it went around was when we treated the alcohol with the nitrosyl chloride in the presence of pyridine, it gave the nitrite ester which upon photolysis gave the alkoxy radical.

And via 6 member transitions state gave the corresponding radical which was trapped by the nitrosyl radical. At the same time we also looked at the generation of alkoxy radicals via hypo halides by photolysis. So, if we have an appropriately substituted hypochlorite for example here that can go via the same alkoxy radical as we discussed above. And go to the corresponding chloro compound where the chlorine is at the delta position is alpha beta gamma and delta. And then that leads to the cyclization to form the corresponding tetrahydrofuran.

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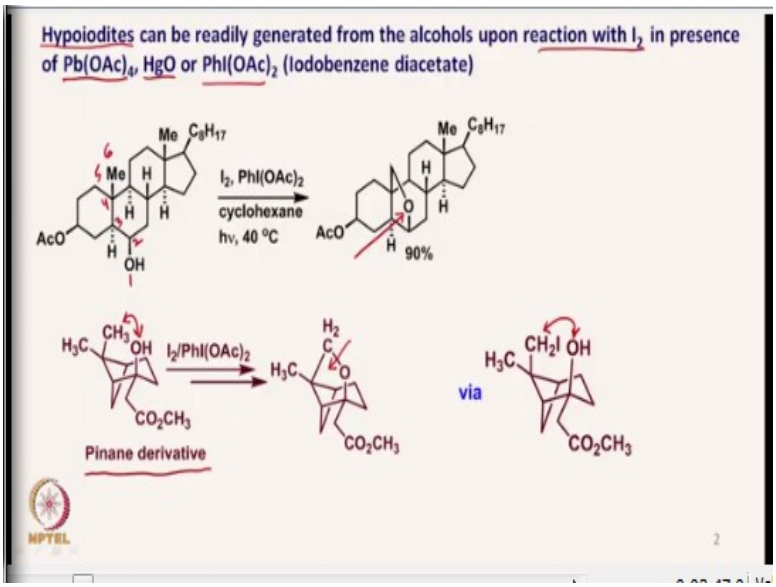

Now we can also generate a similar type of alkoxy radicals using hypo iodides which can be readily generated from the alcohols upon reaction with iodine in the presence of lead tetraacetate, mercuric oxide or iodobenzene diacetate. Eventually go via the corresponding similar type of alkoxy radicals and finally giving the iodo compound that can be cyclized to form the tetrahydrofuran unit like this.

So, basically you have 1, 2, 3, 4, 5th carbon and the 6th hydrogen and that is why we got the six member transition state which gave the corresponding iodo compound and that was cyclized to give this tetrahydrofuran. In a similar fashion if we take the pinane derivative, the pinane derivative there the methyl group and the hydroxy group are close to each other, and can form 6 member transition states they lead eventually to this tetrahydrofuran part via this hydroxy iodide.

So, such hypo halides can also be utilized not only nitrite esters but hypo iodides and hypo halide chlorides also.

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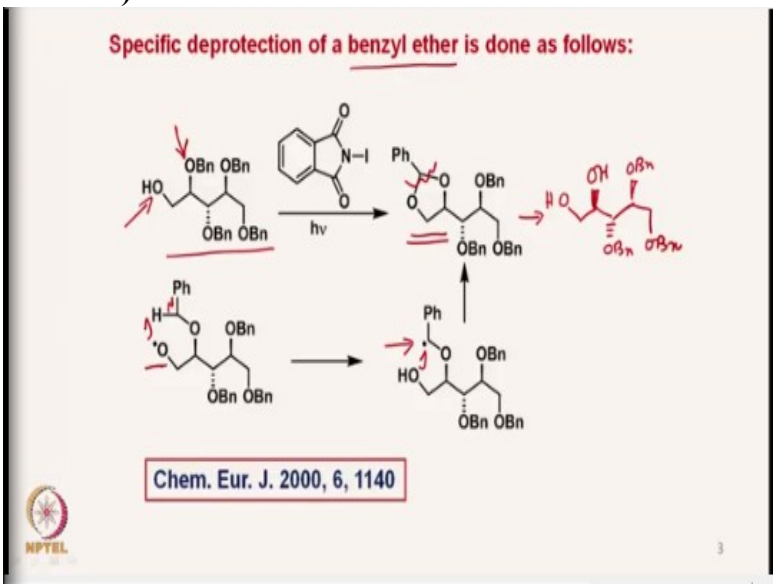

We also looked at the specific deprotection of a benzyl ether, an example we took was something like this, which has 4 different types of benzyl groups. And the one which was closest to the hydroxy group was debenzylated via the hypo iodide. So, if we take the

hydroxy group and react with N-iodophthalimide in the presence of photolytic condition. Then we generate via the hypo iodide the corresponding alkoxy radical which then picks up the hydrogen from here and forming this radical which is benzylic radical.

As well as it is next to the oxygen and then this cyclization here eventually leads to the corresponding acetal. Now this acetal can be hydrolyzed under acidic conditions and can lead to the corresponding diol which is basically nothing but the deprotected molecule in which one of the benzyl groups which is closest to the hydroxy group is deprotected. So, this is a very beautiful example of application of this hypo iodide based chemistry which is similar to the Barton reaction.

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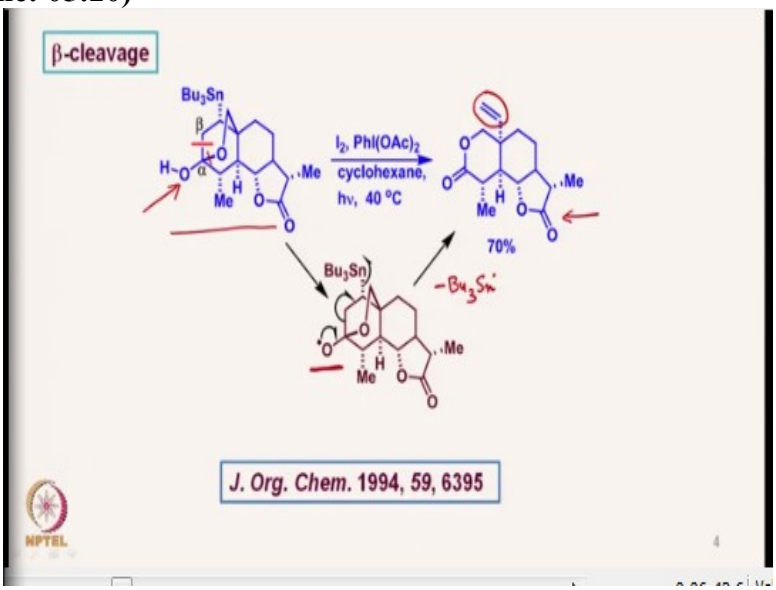

Beta cleavage is also now known under these conditions. For example if one takes a molecule like this which is essentially a hemi acetal because it would be a corresponding ketone and the hydroxy group will be coming from here. But then under it can also exist like a hemi acetal and when this is allowed to react in the presence of iodine and this benzene hydro diacetate in cyclohexene at 40 degrees under photolytic conditions.

What happens is this hypo iodide goes to the corresponding alkoxy radical which then cleaves the way it is shown here eventually leading to the formation of the corresponding lactone in which there is a loss of tributyltin radical. Now this tributyltin radical once it goes off we generate the corresponding double bond here, this double bond is coming from this part of the molecule, so this is an application of a beta cleavage.

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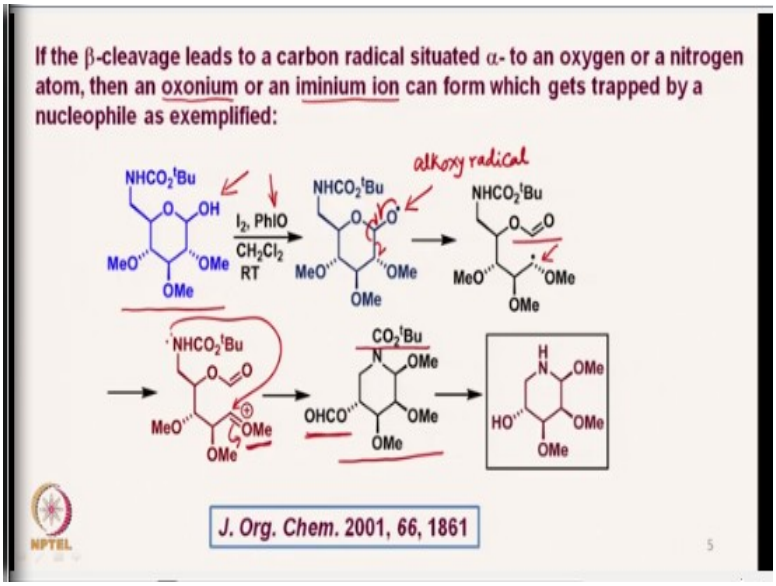

And if the beta cleavage leads to a carbon radical which is situated alpha to an oxygen or a nitrogen then an oxonium ion if it is next to an oxygen or an iminium ion if it is next to the nitrogen can form, and that can get trapped by a different nucleophiles. So, one example is here which is sugar based nitrogen containing molecule in which there is a hydroxy group at the anomeric carbon which is reacted with iodine in the presence of an oxidant in this case it is iodosobenzene.

And that allows to form the corresponding alkoxy radical, this is the alkoxy radical which can form via the corresponding hypo iodide. And then that undergoes cleavage from here like this where you generate a radical here and next to the oxygen. In the process you generate this formate that means this particular part has become aldehydic part and that has become a formate.

Now we have generated a radical which is alpha to the methoxy which then gets oxidized under the conditions and forms this oxonium ion. This oxonium ion then gets trapped by the nitrogen lone pair of electrons in this fashion and forms the corresponding six membered nitrogen containing molecule with the formate group being at this junction, this particular formate group which is here.

Now this can be hydrolyzed under basic conditions or under reductive conditions and we can release the corresponding this protection on the nitrogen and also this formate can be hydrolyzed or reduced to the corresponding hydroxy group. So, this is an example of a beta cleavage followed by the trapping of the generated oxonium ion to form a piperidine analog which is a basically glycosidase inhibitor.

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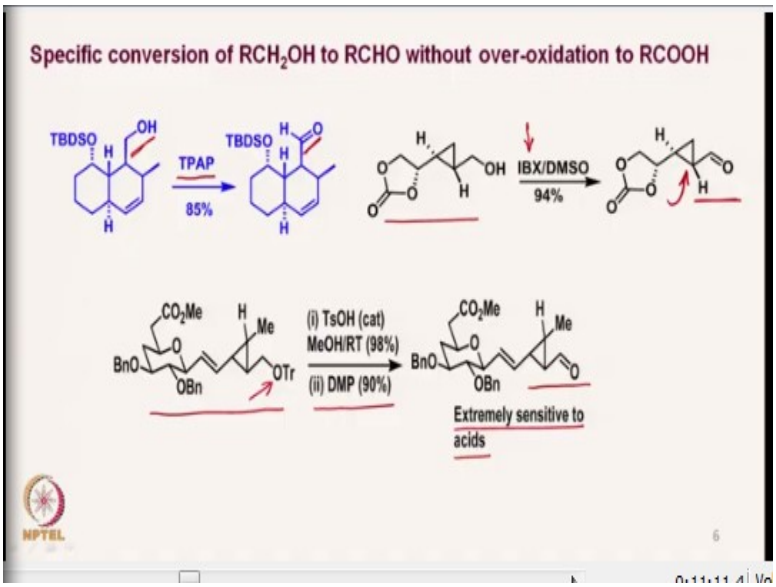

Now I would like to move on to something different which is something that we discussed earlier where specific conversion of alcohols to aldehydes was carried out without over oxidation to the corresponding carboxylic acid. I have an intention today to introduce another relatively cheaper and a good reagent which is useful at large scale. So, the first one that we did these are the examples that we already discussed is using this TPAP that is tetra-n-propylammonium perruthenate.

That led to the conversion of this primary hydroxy group to the corresponding aldehyde. We also did the reaction of primary alcohols as sensitive as this in which there is a cyclopropane ring with IBX which also led to the corresponding aldehyde without disturbing the stereochemistry or the cyclopropane ring. In a similar fashion when a molecule as sensitive as this which has a double bond, which has a sugar part, which has a cyclopropane and of course there is a trityl protection.

When this trityl protection is removed under acidic conditions using methanol and para toluene sulfonic acid. We generate the corresponding primary alcohol which was then oxidized using Dess-Martin periodinane oxidation which gave the extremely sensitive molecule to the acids, that mean this particular molecule is very sensitive to the acid. So, these are the 3 methods that we had introduced earlier.

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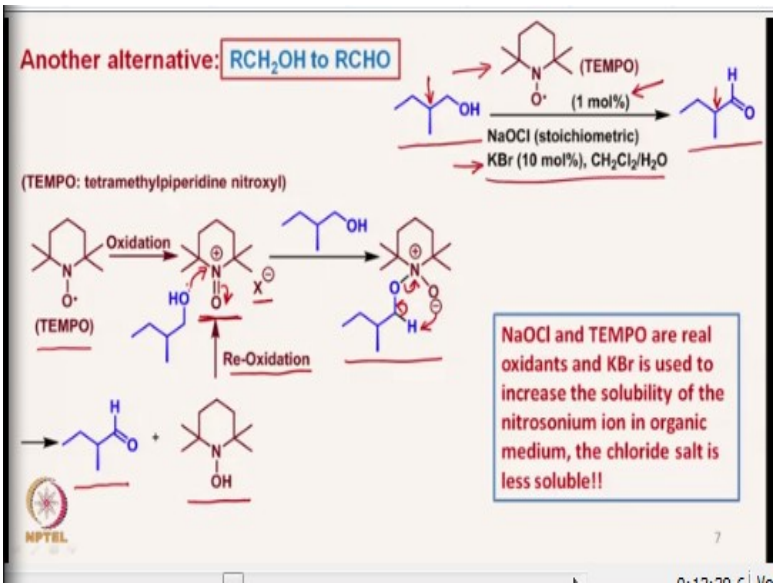

Now I would like to introduce another alternative which is using TEMPO. This is TEMPO which is basically tetramethylpiperidine nitroxyl in the presence of sodium hypochlorite and potassium bromide. Now the solvent that is used is dichloromethane and water. Say molecule like this in which there is an asymmetric center here which is prone to epimerization, that gets converted to the corresponding aldehyde where this proton is this particular center or this proton is highly susceptible for epimerization.

The way reaction occurs is the TEMPO gets oxidized with sodium hypochlorite to the corresponding this nitrosonium ion, where X is to start with is a chloride coming from sodium hypochlorite but then potassium bromide is used. So, that the corresponding salt, the bromide salt is soluble in organic solvent. Then this is reacted or this reacts with the alcohol essentially in this fashion that the lone pair of electrons from the oxygen attacks on the nitrogen and we get this particular intermediate.

This intermediate is now suited to undergo oxidation in this fashion to the corresponding aldehyde and the release of the corresponding anhydroxy piperidine and the corresponding aldehyde. This one here is reoxidized with sodium hypochlorite to go to the corresponding nitrosonium salt which is what is actually the oxidant that allows the alcohol to react and to form the aldehyde.

Now this was one of the alternatives which can be used on a large scale and is cheap because sodium hypochlorite is cheap. And the TEMPO that is used is only 1 mole percent, so it is a very nice method and does not allow any over oxidation to take place. Now when there is a need to convert aldehyde to the corresponding acid. There are many methods but then there should also be some simpler methods.

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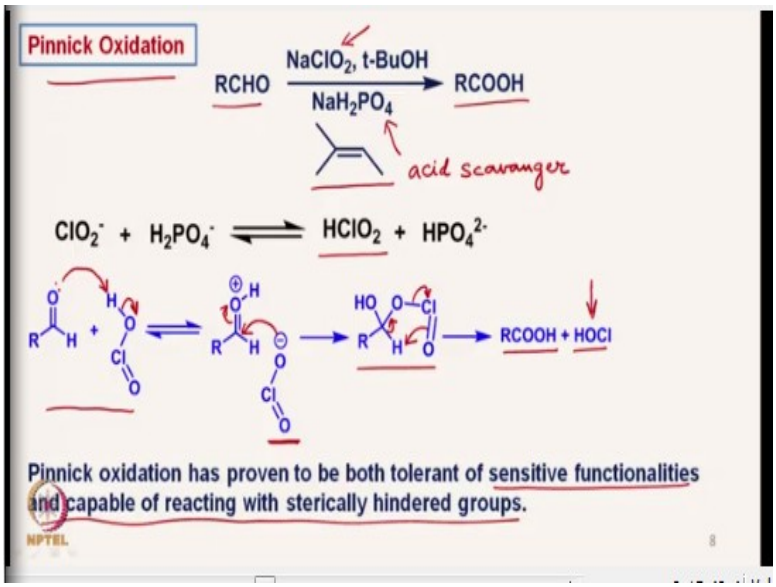

And in this regard the Pinnick oxidation is considered to be an interesting and useful oxidizing agent, where sodium chlorite is used in a buffer like this and in the solvent like tertiary butanol. So, aldehyde is converted the corresponding acid without any problem. In this particular 2 methyl, 2 butene is used as acid scavenger which is basically to take care of the hypochlorous acid that is formed in the reaction.

So, sodium chlorite reacts with this buffer to form this particular molecule $HClO_2$. And that reacts with the aldehyde in such a way that the protonation takes place by the release of this particular part of the oxidizing agent. That attacks on to the oxonium ion to form this intermediate which then undergoes the oxidation to basically form HOCl and corresponding carboxylic acid.

This is called Pinnick oxidation and has proved to be both tolerant of sensitive functionalities and also capable of reacting with sterically hindered groups. Because it is a very sterically unhindered reagent and therefore the oxidation occurs readily, now what happens to this particular part this hypochlorous acid.

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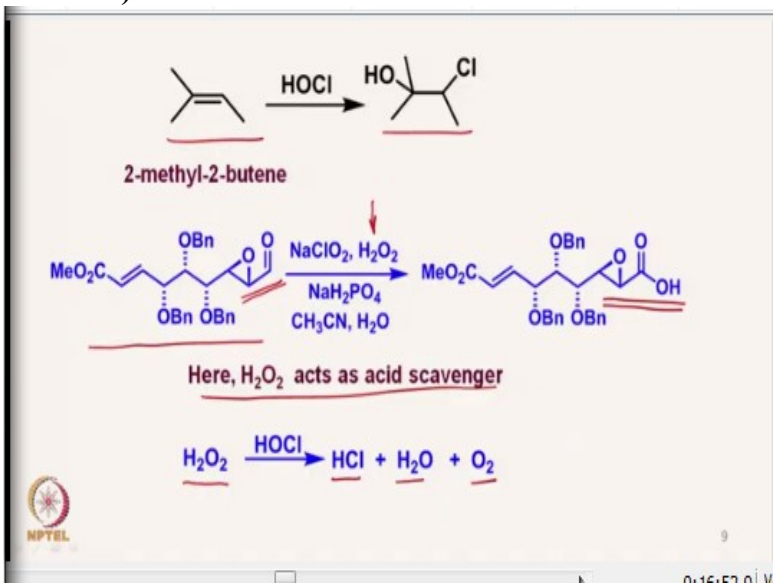

That reacts with the 2-methyl-2-butene where addition occurs and this is what the chlorohydrin is formed. Now we can see the application of it to an interesting and relatively

complicated molecule such as this, where the epoxy aldehyde is oxidized to the corresponding epoxy acid under these conditions. The difference that you can see from the top is the use of hydrogen peroxide as an acid scavenger.

Now what happens to the hypochlorous acid that is released, reacts it with hydrogen peroxide to liberate hydrochloric acid water and oxygen of course and that goes off the reaction medium. So, this is what the Pinnick oxidation is, and that allows the conversion of aldehyde to the acid. Now we will move on to another interesting oxidizing agent which is based on microorganism.

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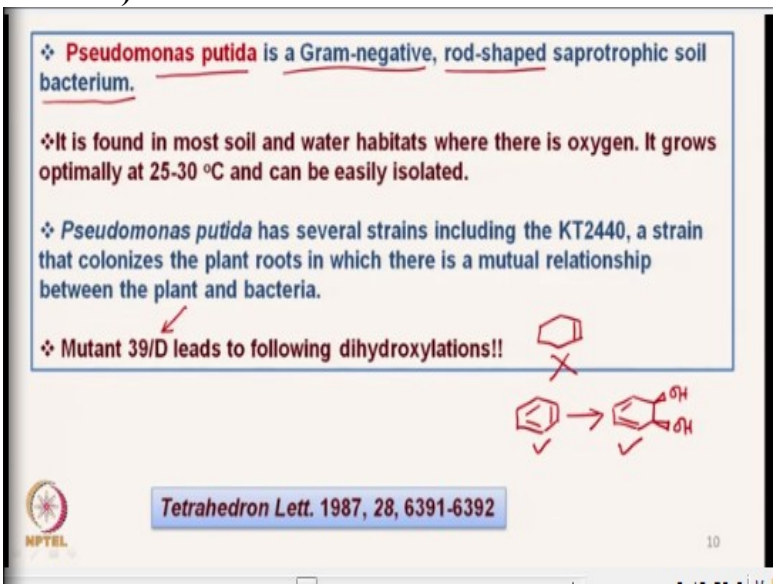

For example this Pseudomonas putida is a gram negative rod shaped saprotrophic soil bacterium. And it is found in most soil and water habitats where there is oxygen, it also grows optimally at 25 to 30 degrees and can be easily isolated. Now Pseudomonas putida has several strains including the KT2440, a strain that colonizes the plant roots in which there is a mutual relationship between the plant and bacteria.

However we are more concerned about this particular mutant, which is mutant 39/ D leads to dihydroxylations. And it is interesting to see that such do not happen on any olefin such as this, it does not happen, this does not react. But it reacts with aromatic molecules such as benzene for example, if the benzene is reacted it leads to the corresponding dihydroxy compound and that too it leads to cis dihydroxylation. This is an interesting method to basically convert benzene or substituted benzenes into the corresponding cis 1, 2 diol.

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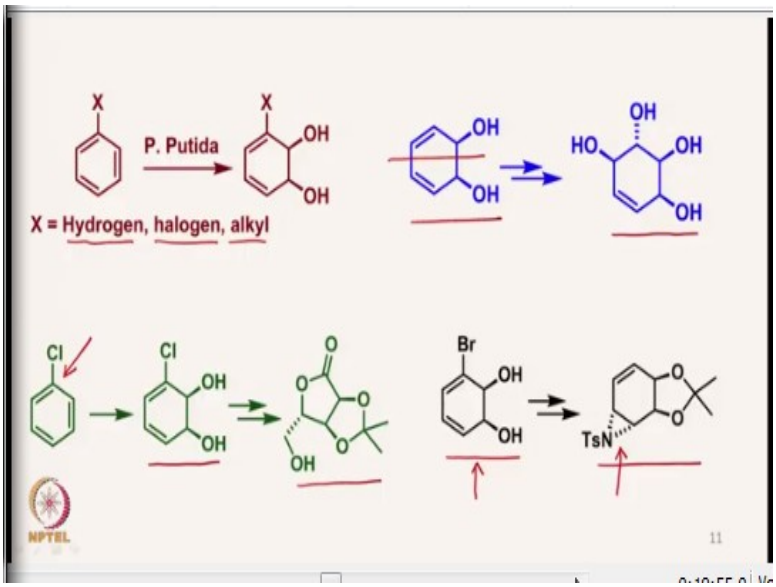

Now this is what it is. Now we can take X as hydrogen, we can take X as halogen, we can take X as alkyl also. Now if X is hydrogen as I showed you before is this is what is that formed. Now this obviously is having a symmetry therefore this is not a optically active molecule. But if we start with say chlorobenzene then the corresponding molecule the diol that is formed is optically active.

In a similar fashion we can start with the corresponding bromobenzene and get to this bromine substituted 1, 2 diol which is also optical atom. Now this particular molecule has been converted to this very interesting cyclohexane molecule, highly substituted cyclohexene molecule and chlorobenzene has eventually been converted to this optically active. Lactone and this bromobenzene have been converted to the corresponding six membered aziridine type of molecule which is also optically active. So, I would like to briefly discuss the synthesis how they have done it.

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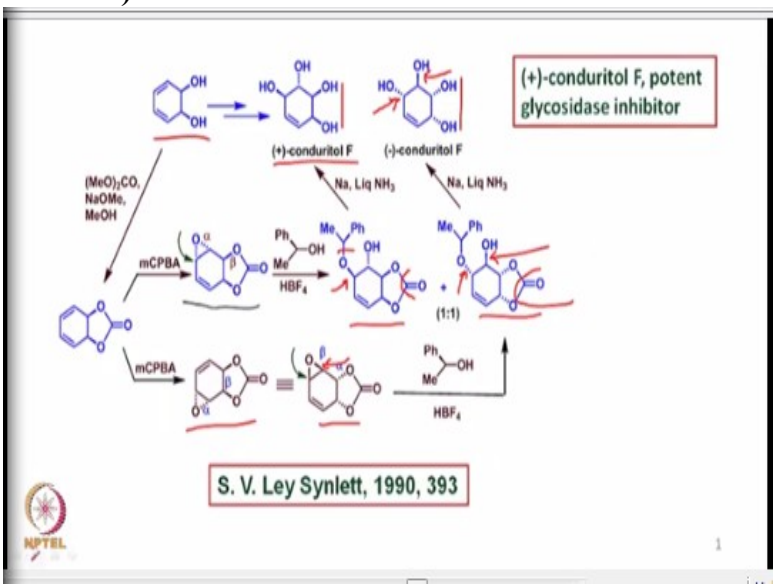

For example this particular type of molecule which has a plane of symmetry and has been procured from benzene by Pseudomonas putida based oxidation has been converted into +Conduritol F which is a naturally occurring potent glycosidase inhibitor. And it is mirror image which is -Conduritol F. What has been done is to protect these 2 hydroxy groups in the

form of the corresponding carbonate by reacting with dimethyl carbonate with sodium methoxide in methanol.

And once this carbonate is formed which also is having a plane of symmetry is then epoxidized with meta-chloroperoxybenzoic acid. Now both the double bonds are equally reactive and are indistinguishable because there is a plane of symmetry. So, if the above double bond undergoes epoxidation then one would expect to get a epoxide of this type here. Now this is because the carbon oxygen bond here is beta oriented and therefore the epoxidation would occur from the alpha side.

Now once this epoxide is formed which is a vinyl epoxide under acidic conditions like chloroboric acid we can protonate this epoxide first. And then that would make this particular carbon oxygen bond relatively weaker for the nucleophile such as this hydroxy molecule to attack onto this carbon atom preferentially over this particular carbon atom. Because this carbon atom would make upon protonation slightly delta positive here, because this is a allylic position.

And therefore the nucleophile attacks onto this carbon atom in an SN 2 fashion leading to this type of hydroxy molecule. Now this hydroxy molecule in which here the nucleophile has attacked from the beta side because the epoxide was alpha oriented. And thus the cleavage of this particular benzyl ether part with sodium liquid ammonia can release the hydroxy group in this beta oriented fashion.

And since this particular molecule here is optically pure, therefore this particular molecule is also optically pure. And when we carry out the basic hydrolysis of this carbonate then these 2 hydroxy groups are released having the beta orientation here. Now this translates to the formation of the stereochemistry of the 4 contiguous hydroxy groups similar to the naturally occurring +Conduritol F.

Now if we allow the epoxidation to take place on the lower double bond then we would expect to get this particular type of vinyl epoxide. Now since this carbon oxygen bond is beta oriented and therefore the stereochemistry of the epoxide is all now alpha oriented. We can write the same molecule in this particular fashion by lifting the molecule out of the plane and rotating it vertically at 180 degrees.

And such a fashion that the epoxide part goes on the top and the double bond part comes at the bottom. And in this fashion the alpha oriented epoxide now would be beta oriented and the carbon oxygen bonds which are here beta oriented would now become alpha oriented. Now this particular vinyl epoxide and this vinyl epoxide are now more or less comparable with each other in terms of the orientation of the functional groups on the molecule.

Except that the stereochemistry of the epoxide and this particular carbon oxygen bonds are exactly opposite to this particular stereochemistry of this vinyl epoxide. Now as we have opened this epoxide with this hydroxy compound under acidic conditions. In a similar fashion we can also open this vinyl epoxide in exactly same fashion and get to this particular molecule. And since this beta epoxide is beta oriented, so the nucleophile attacks from the alpha side here.

And the corresponding hydroxy compound is having the orientation in an alpha fashion here. And this epoxide is beta oriented and therefore the corresponding hydroxy group here is beta

oriented and the same way here it is also beta oriented. And now the carbonate part can be hydrolyzed under basic conditions and then release the corresponding diol which is now alpha oriented.

Now if one can see carefully then these 2 molecules are mirror images of each other. So, this is how Steve Ley reported the synthesis of these 2 molecules which are important glycosidase inhibitors starting from a molecule of this type which is having a plane of symmetry.

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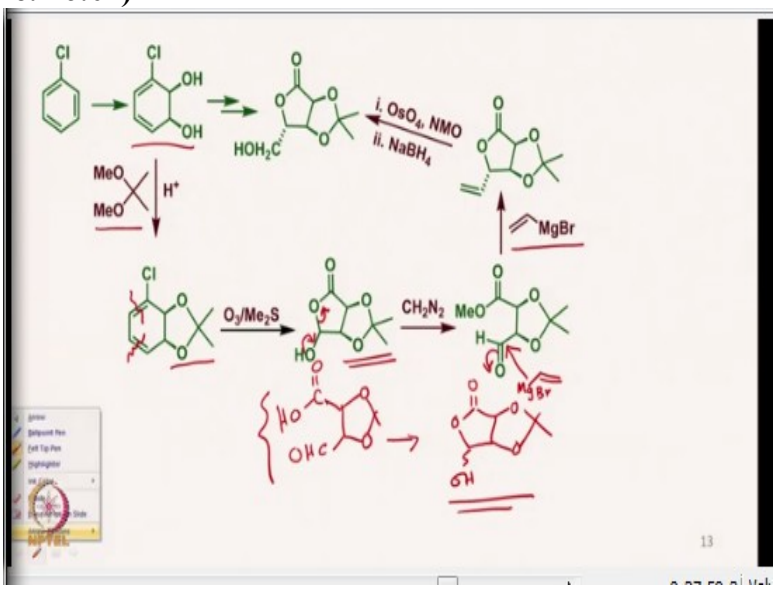

Now we can also have the conversion of the diol coming from the chlorobenzene which is optically active. Now we do not have now to worry about optical activity because it is not a symmetrical molecule. And this was protected as a corresponding acetonide by using this dimethoxypropane in the acidic conditions. Once it is formed, it was cleaved by ozonolysis as you can see and it can form the corresponding aldehydo acid.

This is how it is going to form, and that would exist as in equilibrium with the like this, which is what is shown here, so basically it is nothing but a aldehyde and acid in the same molecule. When this is treated with diazomethane, the diazomethane reacts with the acid part to form the corresponding methyl ester. And when this methyl ester is reacted with vinyl magnesium bromide the vinyl magnesium bromide attacks on to aldehyde.

And the negative charge which is generated here this will be magnesium bromide, when this reacts with the aldehyde, aldehyde will be more reactive than the ester for nucleophilic reactions.

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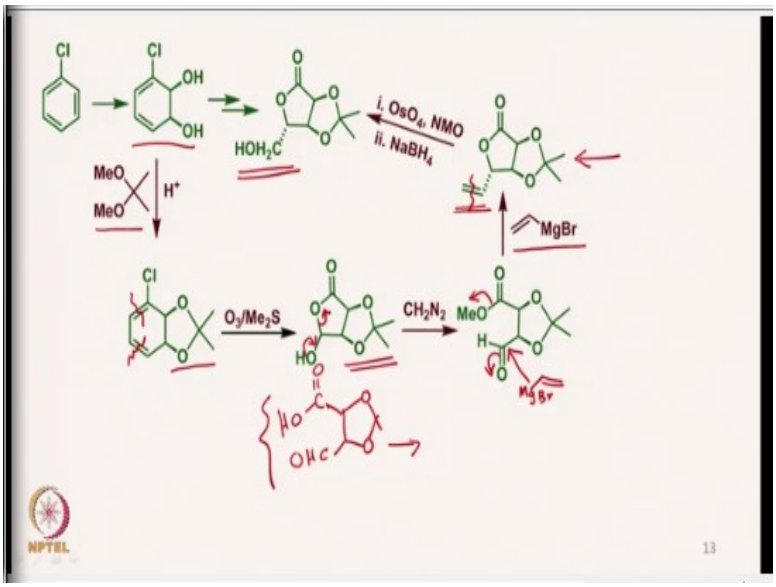

Therefore once the nucleophile reacts the anion which is generated reacts further with the corresponding ester, the anion which is formed here will go and react with the ester and this will go off to form the lactone in which the vinyl group comes here as a vinyl substituent. This can of course be cleaved to the corresponding aldehyde and reduce to form the corresponding primary alcohol. So, this is one another application of chlorobenzene based optically active diol to be converted to the corresponding lactone which is optically active.

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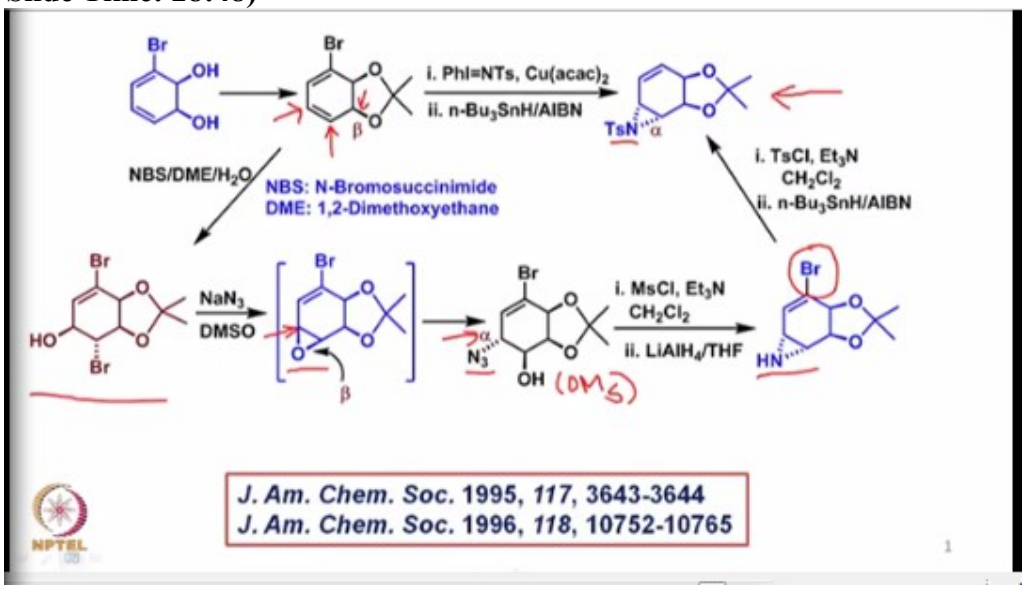

So, finally this type of chiral diol derived from bromobenzene was converted into a very interesting aziridine molecule of this type. Now what was done was first to protect this diol as an acetonide followed by it is reaction with this particular reagent which is PhI = NTs in the presence of copper acetylacetonate and followed by tributyltin hydride mediated debromination.

So, what happens first is this double bond gets converted into the corresponding as a aziridine, because this particular double bond is sterically more hindered because of the bromine. And therefore preferentially this double bond is converted to the corresponding as a redeem. And then under radical conditions this carbon bromine bond is cleaved to form this particular carbon hydrogen bond here, there is a hydrogen here.

So, this is a very straightforward synthesis involving 3 steps protection followed by aziridine formation, followed by debromination. But there is also a classical way of doing it, that is first you take this particular acetonide molecule and open it by using N- bromosuccinimide in dimethoxyethane and water. In such a way that the first the bromination would occur from the alpha side because this carbon oxygen bond is beta oriented.

And that particular bromonium ion will then open by water at this particular position here because that is the allylic position. And therefore what one would get is the corresponding bromohydrin of this kind where the water has attacked onto this carbon and bromine has come at this particular carbon atom. And the orientation of the bromine is dictated by the orientation of this carbon oxygen bond which is beta.

Now this bromohydrin under conditions in which sodium azide and DMSO is utilized. First forms an epoxide because under these conditions the hydroxy groups interacts with this particular carbon atom here, and bromine goes as a leaving group forming this particular type of beta epoxide here. And this beta epoxide then is opened by the nucleophile that is azide ion, at this particular carbon atom again.

Because this is the carbon atom which is the allylic carbon of the epoxide, and therefore preferentially this is attacked by the azide. And since this carbon oxygen bond of the epoxide is beta oriented therefore the azide attacks from the alpha side and one gets this azido-alcohol of this kind here. And now if we convert this hydroxyl group into a mesylate and then we reduce the azide into the corresponding amine, then this azide will get converted into corresponding amine.

And this of course would be in the form of O mesylate and this O mesylate is a leaving group. And therefore intramolecularly the amine will react with the corresponding carbon mesylate bond and forming the corresponding aziridine from the alpha side, that is because this is alpha oriented. Now once that has happened then of course we can do the N-tosylation using tosyl chloride triethylamine to convert this NH into the corresponding N-tosylate.

And of course under the radical conditions we can do the debromination or reaction of the carbon bromine bond to get to this debrominated molecule the same molecule which we had got this. Although this is a little bit a longer routes but this can also be achieved, both these routes have been published in these 2 papers. And they are very interesting conversions starting from bromobenzene to optically pure this particular aziridine which is an important synthon in organic synthesis.

So, we would stop it here and we will continue the next turn perhaps going to the reduction path of organic chemistry based reactions, take care and thank you, bye.