**A Study Guide in Organic Retrosynthesis: Problem Solving Approach.**

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**Lecture – 56**
**Stereochemical Strategies (Contd.)**

Welcome back students we are basically discussing Stereochemical strategies.

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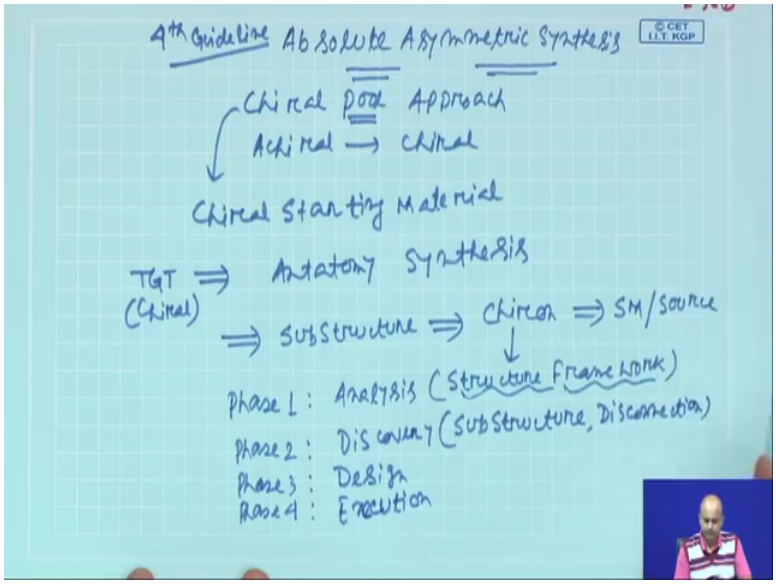


And today we will be talking about absolute asymmetric synthesis the fourth guideline which we said falls under the class of stereochemical strategies. And this particular absolute asymmetric synthesis which is the fourth guideline if you go the original pathway we said 4 guidelines are there and this is our final guideline.

And particularly this part will be trying to focusing on mainly chiral pool approach as well as if you have a starting material which are achiral you just need to create a chiral molecule.

Now, first you try to focus it more on the chiral pool approach. Now chiral pool approach is very old approach the approach says that you need to have some chiral starting material chiral starting material and why is called pool. Pool means this chiral starting materials are plentily available in the nature. They are very cheap starting material and they are basically easily available from the natural resources.

So, if I try to analyse the target molecule we will say that we will try to do a anatomy of the synthesis means how to execute the entire synthesis. So, you have a target which is essentially a chiral molecule. Now the target can be first classified to a substructure or a intermediate then as I will try to introduce a new terminology which is named on Chiron, then your starting material or source.

Now, Chiron's are basically chiral synthetic intermediate the intermediate which is having a chirality is called Chiron. Now this particular terminology was first invented by Professor Stephen harnessing. So, in principle this chiral pool approach follows 4 different phase or pathway phase1, phase 2, phase 3 and phase 4.

So, what exactly this individual phase the first one we do the analysis that how this target can be constructed through this different. So, this analysis means you have to think about the structural framework of the given target. So, you analyse the certain structural frameworks of the given target and what are the stereo centres edit to construct then you do the discovery part discovery means you know there are certain chiral pools, available in the nature and you know the absolute stereo centres of those starting materials.

So, now, try to correlate that how this target target structure can be correlated with this starting material. So, this is basically your this discovery part which will basically analyse you can close to it substructure or you can come to a substructure through a proper disconnection right.

And then the phase 3 which basically mainly based on the design that how do now design this entire pathway and the phase 4 is now the forward pathway where you can call about the execution the entire pathway how we will execute. So, as I said in nature there are many chiral starting materials or chiral pool materials are available.

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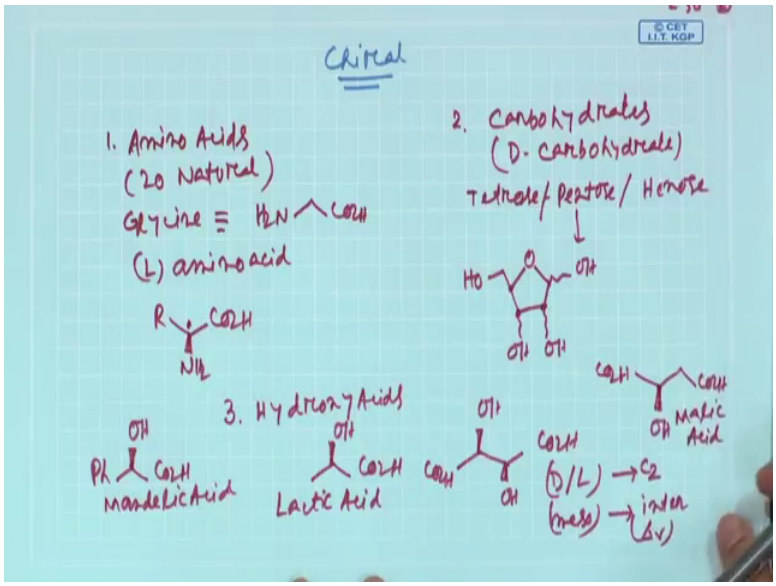


This can basically broadly classified into 5 or 6 different different categories you can let us say one is amino acids. Naturally occurring amino acids we are talking about naturally occurring amino acids there are 20 natural amino acids which are basically naturally occurring amino acids.

Now, except glycine except glycine all naturally occurring amino acids are chiral glycine is basically having this structure. Other amino acids which are L amino acids are all chiral and this amino acids are very available in enantio pure form very cheap starting materials. So, this particular stereo centre is fixed.

So, if you can use this stereochemical information for your synthesis design then basically you are using a chiral pool. The amino acid is one of the very good chiral pool the second is carbohydrates, carbohydrates are also naturally occurring starting material and find that there are mainly D carbohydrates in the D form are available in the nature so D sugars and L amino acids.

Now, out of this carbohydrates you can basically starting talking of this molecules like tetrose you can call about pentose, or hexose all the now say for instance is pentose is basically like a ribose so D ribose. So, the stereo centres I am now not putting here, but if it is a D ribose you will be or a pentose structure you basically having a this information you basically having this, this stereo centre is fixed, this is fixed.

So, 3 in built stereo centres you are getting in this molecule similarly hexose which is basically falls like glucose or manose they are having 4 in built stereo centres. Then other chirally occurring starting materials is hydroxy acid, hydroxy acids are also very important starting materials the first one probably is your lactic acid, lactic acid you can get both the enantiomers when the nature then the most important one is tartaric acid, tartaric acid.

Now, lactic acid having 1 stereo centre, tartaric acid having 2 stereo centre; tartaric acid is D or L which is c 2 symmetric and you also have a meso tartaric acid which is internally compensated or having sigma v. So, you have D L tartaric acid which is having c 2 symmetry and meso which is internally compensated having a sigma v.

So, this is the hydroxy acidic additionn you also have other hydroxy acid like that is a mandelic acid it is also a naturally occurring hydroxy acid. But do you have some other hydroxy acid I will just try to draw it structure the another hydroxy acid which is also very well known its named is malic acid. Now malic acid now normally you can isolate from apple fruit pyrus malus it gives you a rich source of malic acid so this 3 hydroxy acid.

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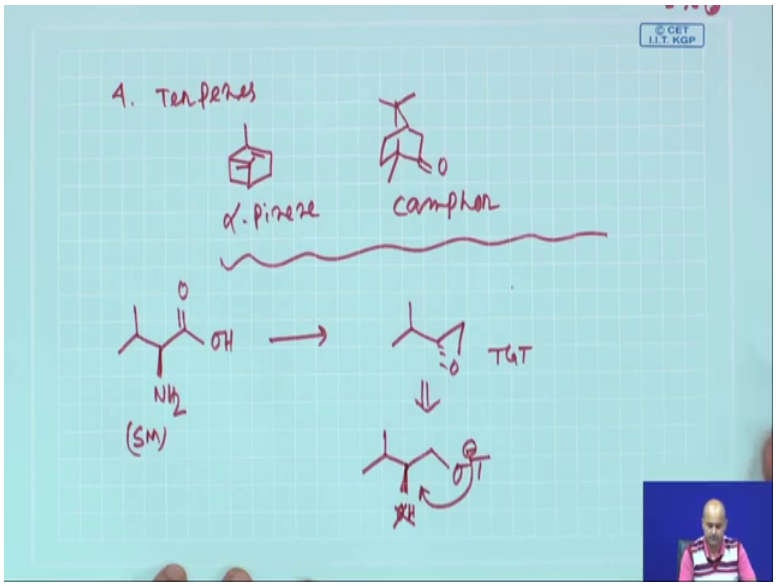


Then you are having compounds like terpenes, terpenes mainly mono terpenes are a are a good source of simple chiral building blocks compound like this alpha pinene is a alpha pinene is a mono terpene. Compound like this which is very well known is camphor

these are also you can get one single enantiomeric form in the nature these are very good starting material ah.

So, this you have a amino acids, carbohydrates, hydroxy acid terpenes and the list is basically basically many more, but we will try to try to figure it out how this chiral puts starting materials can be used in your synthetic pathway or your synthesis design

We first start with the amino acid and we see the how this amino acids can be synthetically useful for some FGI. initially I say we will have be giving you a amino acid whose structure is this compound is basically valid now I say I will be using this starting material and the my target structure which I am giving is this epoxide.

So, you have to design a pathway by using this chiral pool approach to achieve this target. Now simple retro synthetic pathway probably you can think about using this if you have some living group something like this or may be you can put a living group here and put something here o minus you can immediately close this ring with a inversion of configuration. Now for this amino acids they behave in a unique way they behave in a unique way for a particular reaction.

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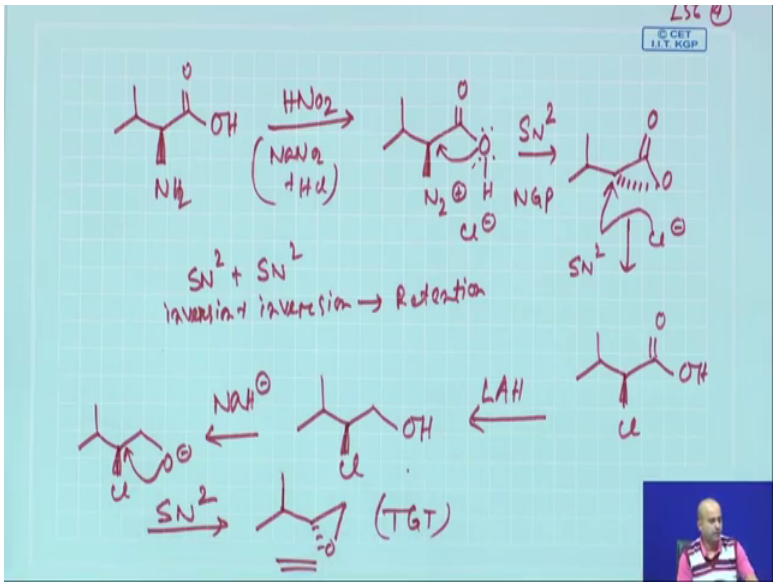


This reaction will be now a discussing if you having a alpha amino acids you react with nitrus acid which will basically dilutize the amino acids and will convert examine group to a diazonium thing.

Now this diazonium compounds having good living aptitude and then this O H this hydroxy O H it is basically seems to attack this diazonium carbon to give you a very strain intermediate through a S N 2 pathway; because S N one would not be operating here because they adjacent to your carbonyl group. So, S N 2 is very facile here.

Now if you are dilutizing with a H N O 2 which is basically means that if you have a N a N O 2 and H C L. So, the chloride minus is still there and this chloride minus can act as a nucleophile. Now this is basically a classic example of a nevering group participation a nevering carboxylic acid group first forms this lactone to give you a straint 3 member lactone ok.

In this C L minus acting as a nucleophile again to give react with this lactone again S N 2 fashion and then basically you will get this compound which is now the originals stereochemistry has basically retained retained. So, you say the retention is basically caused by 2 S N 2 means that two inversion together inversion plus inversion give you the retention and this is very common common phenomena for alpha amino acids alpha amino acid if you do dilutization and then treat with a nucleophile you can basically end up with this retention of configuration.

Now, if you just reduce this carboxylic acid with lithium aluminium hydride you will get this C H 2 O H. Now we are almost close to the synthesis primary alcohol you just treat with a base sodium hydride that will basically give you the alcocxite and this alcocxite.

Now react in a intra molecular the backside attack give you a S N 2 and then which now gives you the epoxide as it is. Now this epoxide is your target molecule and we have seen that starting from a simple amino acid the stereochemical information was retained here and then you get this target molecule as your main product. Similar kind of analysis with this amino acids will be trying to put in the assignments and you please basically try to solve it.

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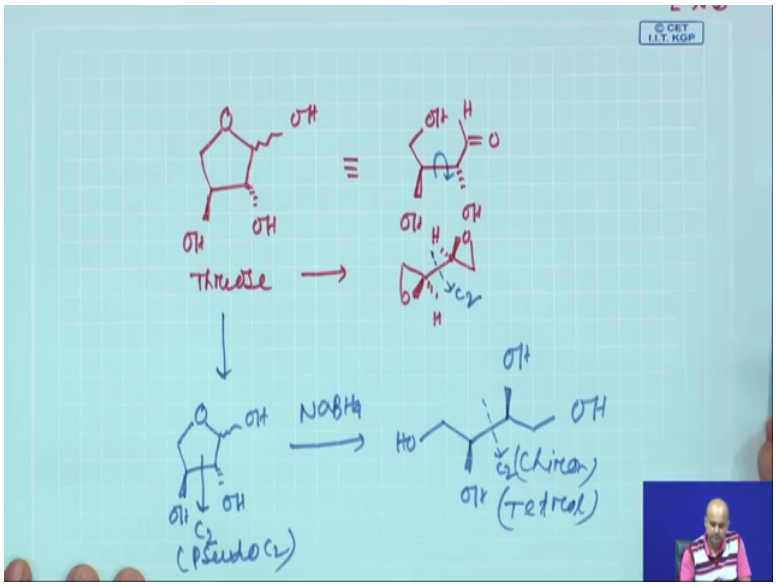


The next one will be giving you a another problem where will now switch it over to a carbohydrates switch it over to carbohydrates. Now this is the carbohydrates is a 4 member, or 4 carbon carbohydrate this carbohydrates basically threose. Threose if you write the linear structure is basically C H 2 O H is a O H here is a O H and having a C H O C H O.

So, this is the threose now I say you start with threose and I am asking you to make a or synthesize this b's epoxyte whose structure is this one. Now you see the structure this compound this b's epoxyte having a C 2 axis of symmetry. Now why it is important if you now analyse the threose structure threose if it does not have a O H here or if it is structure is something like I mean if it is a structure is like this it is a having a perfectly C 2 axis of symmetry. So, presence of this O H makes the C 2 symmetry is a pseudo C 2. Now, how it helps?

Now what you do you treat this threose with sodium borohydride sodium borohydride, now sodium borohydride basically reduce this aldehyde to give you a open chain compound. Now this open chain compound if you now draw it structure this O H C H 2 O H this bond rotation is free now write in there this particular way you basically get this compound this compound is nothing a tetreal. And this is basically the chiral starting material you come to a substructure or chiron this is your basically main chiron chiron intermediate. Now this compound is also having a perfect C 2 symmetry.

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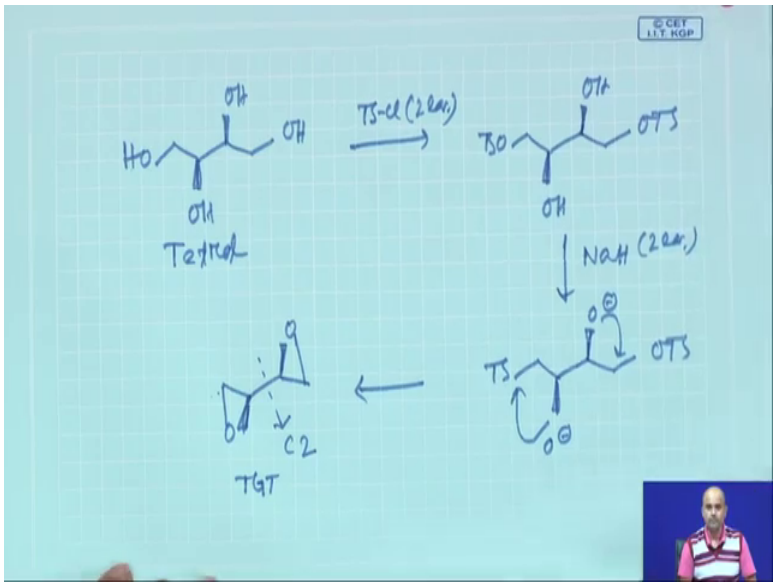


Now next as you can basically visualize that you need to have a you look it up initial after this sodium borohydride reduction you basically get this compound. Now what exactly you need to do? This is a tetreal having 2 primary hydroxyl, and 2 secondary hydroxy.

So, I said you react with 2 equivalent of tosyl chloride to get this ditosylate to get this di tosylate this is also C 2 symmetric fine. Now you react with two equivalent of sodium hydride sodium hydride what it does it will be making this corresponding alkoxide in this way and then this alkoxide will intra molecularly react to give you the structure which was your target molecule. So, stereochemistry of this tetrose was remain intact.

Now you can basically clip this epoxyte through either this way or this way does not matter because this ends are now homotopic anyway now I am going to discuss it say this is your target molecule which can be achieved. So, best thing is you basically try to take this starting material which is threose we convert it to a tetral by sodium borohydride reduction and you have 2 primary hydroxy to secondary hydroxy by simple functional group manipulation the 2 stereo centres of threose was kept intact to give you the target molecule. This is the very powerful o a to use the chiral pool starting materials for your synthetic exercises.

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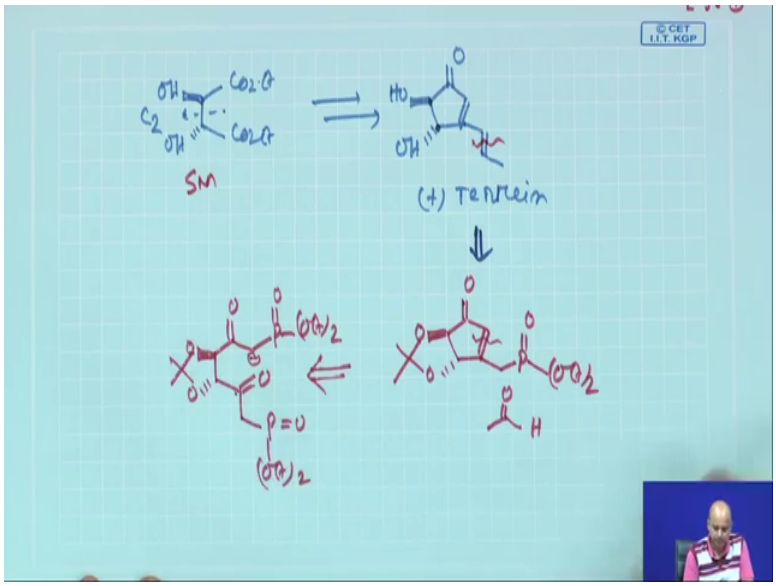


Next will be using little bit complex 1 and we will be using a hydroxy acid as our chiral pool. The hydroxy acid which I am basically using is basically tartaric acid and both the free carboxylic acid was a steady esterified as its ethyl ester. Now this compound is also having a C 2 symmetry means that this O H and this O H are homotopic this C O 2 to this C O 2 are homotopic.

Now target molecule which was needs to be constructed from here basically a natural product whose structure is the cyclopentenone based natural product is name is plus terrain that was serious structural analysis for terrain you will see that this two stereochemistry of this target molecules is coming from this tartaric acid.

Now you try to analyse through standard retro how you can convert this terrain and try to analyse how it can be construct from this starting material. We say that we will be trying to use some reaction initially we say you first make sure this free hydroxy group is properly protected.

So, best one is to do a acetonide kind of protection and if this case you will be having some phosphonate kind of thing you can do a intra inter molecular Horner Wadsworth Emmons reaction or witting reaction to make this particular bond. So, now we will be again disconnecting this part here and now we are saying that if we are having this keto phosphonate; this keto phosphonate say again a pseudo symmetrical.

Now, we say that first you do a intra molecular Horner wadsworth with one of this carbon ion to this carbonyl. Now no matter which carbonyl reacts because both this ends are homotopic both this ends are homotopic due to presence of pseudo symmetry.

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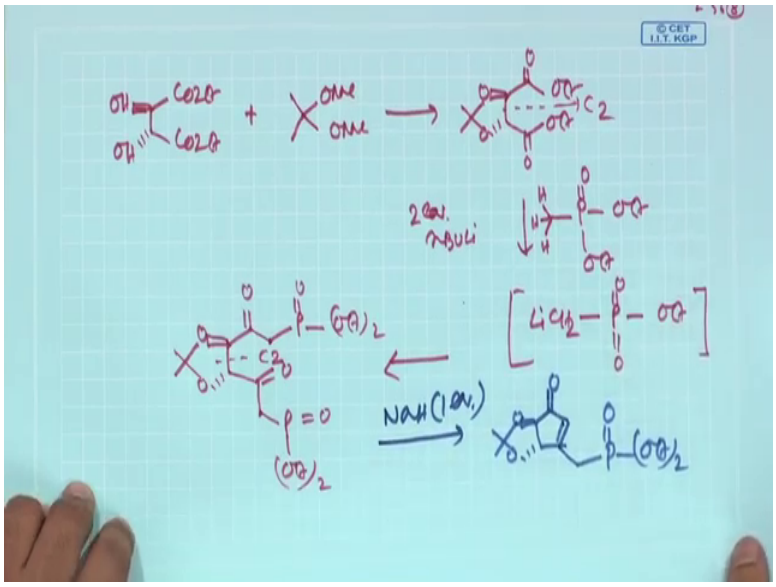


So, this is our chiron now we will try to do the forward synthesis and how this synthesis was done in reality. So, you have a tartaric acid ethyl ester react with 2 to d m p or acetone to first protect this tartar rate as its acetonide ok. So, you will get this acetonide protected diethyl tartar rate fine. Next I am saying that you react with a methyl phosphonate.

Now methyl phosphonates are commercially available you can easily make this hydrogen's are extremely acidic H; H; H; you can basically react with 2 equivalent of n butyl lithium to generate the corresponding phosphonate anion C H 2 L i as a nucleophile and react with this ester group of this tartar rate.

Now once you react it find that this tartar rate will now react to give you this keto phosphonate in this way now pseudo symmetry remains in unchanged C 2 this also C 2. Now this C 2 means that this half and this half is homotopic, or this C H 2 and this C H 2 is homotopic.

So, now, if we do a intra molecular Horner wads worth Emmons reaction, by just treating with one equivalent of sodium hydride you generate carbon and either here or here. Now

this carbon ion can react intra molecular with this carbonyl compound and then initially you get your this part is here, your acetonide is here. And you get this double bond here then your C H 2 p double bond O O e t whole twice was there. So, those are simple FG, but the visualization was that important.

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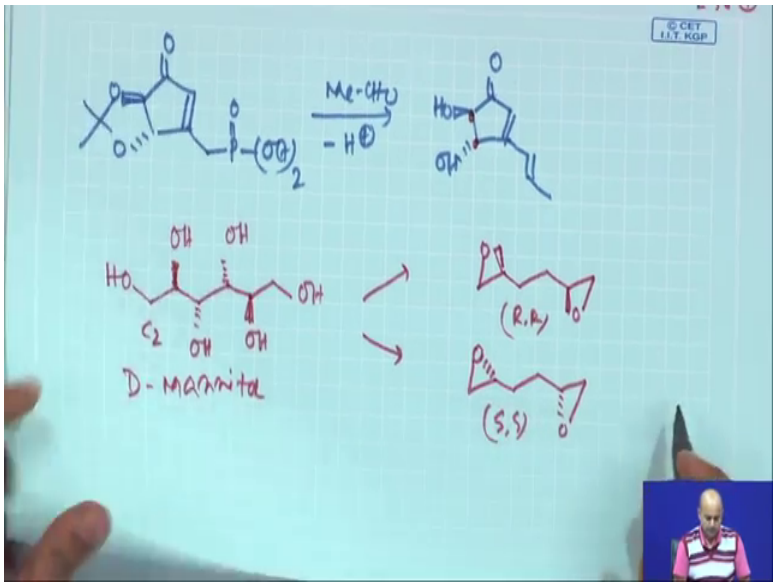


Now, we again draw the cyclopentene compound which we got by intra molecular Horner wads worth Emmons reaction and then you now can compete the synthesis. If you simply react with acetaldehyde followed by H plus treatment to remove this acetonide you can basically get your target natural product which is terrain.

So, eventually the synthesis was a very nice demonstration of using the 2 existing stereo centre of this particular tartaric acid and this stereo centre basically retained and in addition we take a take a demonstration of how pseudo symmetric molecule react as the pseudo symmetric molecules are having homotoipc ends this homotopics ends are chemically equivalent.

And similar context will now take up a carbohydrate derived compound which will now analyse the next a carbohydrate derived compound which is also a very good chiral pool agent is this compound is commercially available its name is D mannitol.

Now D mannitol is again a pseudo symmetric molecule now from D mannitol I say that you can prepare both of this epoxyte through a divergent pathway. So, this divergent was

pretty important you can so basic can basically get R R epoxyte or S S epoxyte. Now as a time is running out we will need to be little bit faster.

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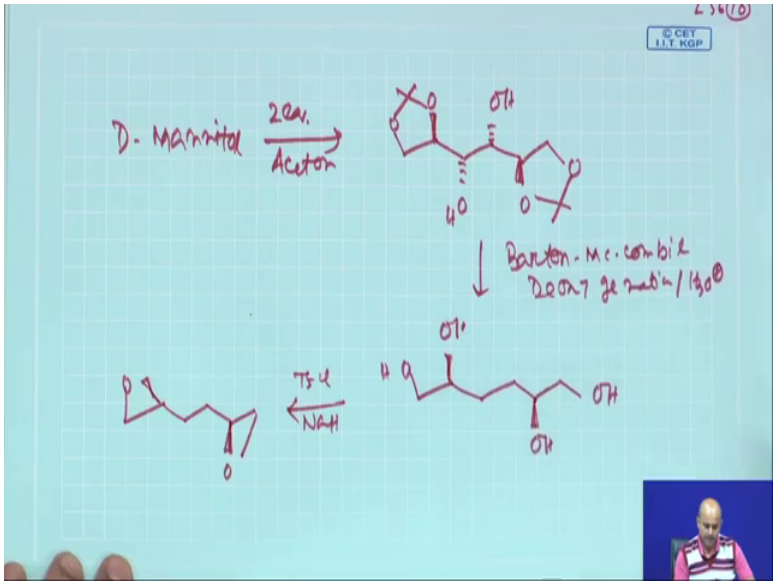


What I am saying you first take this D mannitol; D mannitol D mannitol if you react D mannitol with two equivalent of acetone you will initially get the acetonide protected thing and normally 1 2 diol will react by keeping the 3 4 diol free. So, initially you will get these compounds.

Now, next step was very similar or very simple because if you see its see your epoxyte the 3 4 position does not have a oxygen functionality. So, basically what you need to do you need to do a Barton deoxygenation which you already studied Barton McCombie deoxygenation deoxygenation and then you remove this acetonide by H 3 O plus treatment.

So, what will get you get this tetral, you get this tetrol. Now is absolutely simple what you do you first treat with tosyl chloride two equivalent to get the ditosylate then you react with sodium hydride you basically get one of this epoxyte which is desired by you this one. Now in other case you can you basically have to invert it.

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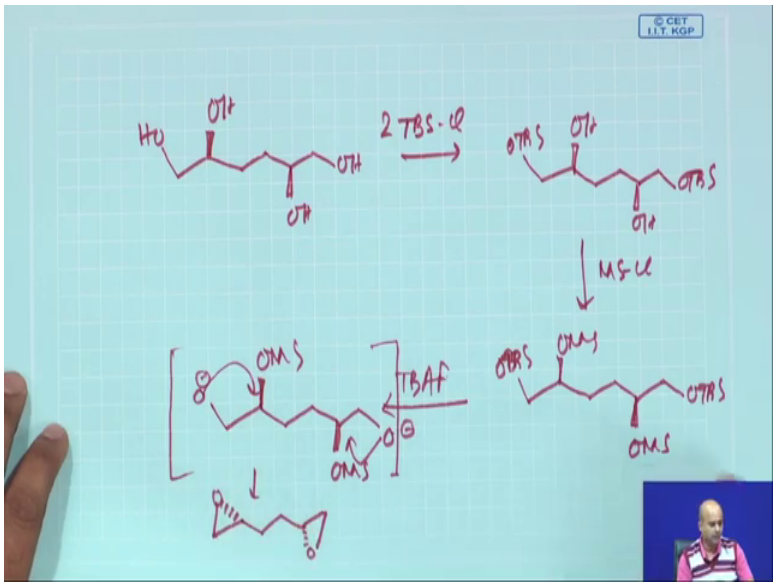


So, what you need to do you take it the pathway say you have this diol ok. So, first you do a protection with TBS chloride 2 equivalent. So, primary group will be protected O H, OTBS.

Now, here you can do a inversion to follow the same way otherwise you can do it other way also you put it the secondary group varies mesyl chloride. So, mesyl chloride will give basically give you OTBS at its mesyl. Now doing the mesylation basically helps you the secondary group now you are protect you are basically making the living group.

Now T BS group, deprotection can be done by T BAF. Now T BAF is basically basic in nature so one it is once it protect it basically gives you O minus. Now this o minus was there and then you this O minus this intermediate now intra molecularly react in S N 2 fashion to give you a backside attack to give you the epoxyte of the other enantiomer.

So, basically you have a divergence mainly the way you basically do the entire synthesis. So, divergence is quite possible if you can follow the earlier pathway that you carry the f g f g I and then do a stereo mutation at one step otherwise here also basically the same step because this centres are inverted to give you the compound they give you epoxide the divergence is very much possible.

So, chiral pool approach basically ends here and next we will try to figure it out some other topics which will probably give you a little bit more emphasis we will next focus

on pseudo symmetric molecules and strategic explosions of pseudo symmetric molecule. We will just try to give you 1 or 2 examples and then remaining lectures we will try to summarize how we came across through our entire course work.

So, just go through the entire topic and particularly try to put more emphasis on the stereo chemical strategies which is seems to be very much important. So, have a have a good time till then good bye.