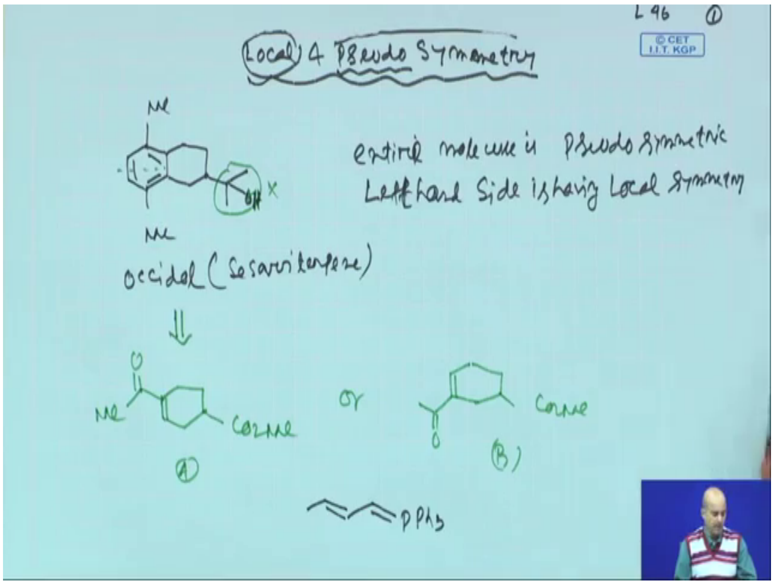
A Study Guide in Organic Retrosynthesis: Problem Solving Approach
Prof. Samik Nanda
Department of Chemistry
Indian Institute of Technology, Kharagpur

Lecture 46
Symmetry based Strategies (Contd.)

So, welcome back students, we were basically discussing Local symmetry and Pseudo symmetry.

(Refer Slide Time: 00:20)



L 46 ①

Local & Pseudo Symmetry

entire molecule is Pseudo Symmetric
Left hand Side is having Local Symmetry

occidol (Sesquiterpene)

And in last lecture we have talked about a natural product, whose structure contains local symmetry means one part of the molecular structure is having perfectly symmetrical structure and the remaining part. There is some functional group is present that makes the molecule or non symmetrical. So, then all together the molecules becomes pseudo symmetrical.

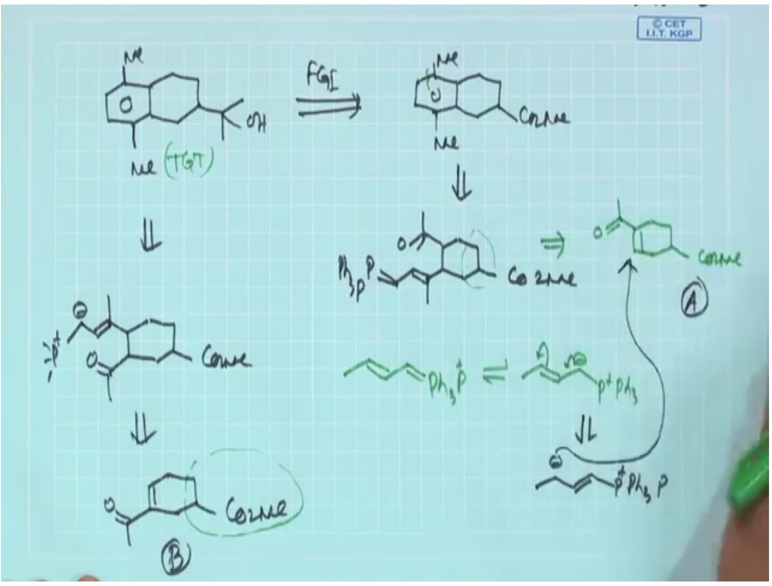
Now, we have explained that how a natural product by cyclamic acid can be synthesized by applying the concept of a local symmetry and pseudo symmetry. And you say that strict maintains of symmetry is a essential prerequisite, then next target or next problem will try to analyze this similar concept for again and natural product whose name is occidal this molecule is occidal is a terpene molecules basically a sesquiterpene .

So, which is having see 15 framework; now we see the structure of occidal part that the aromatic part is perfectly symmetrical ok. This part should be impossible symmetrical if this group was not there. So, the entire molecule is basically entire molecule is pseudo symmetrical entire molecule is pseudo symmetric, and the aromatic part is basically having local symmetry the left hand side the left hand side of the molecule is having left hand side is having local symmetry . So, this way basically you can see the structural features of a given molecule, then you can then you can predict that how

Now, occidal was reported to be synthesized by a unique Wittig type of cyclization from a two different region oisomeric compounds either A or B this was given in the literature now, but disconnection says that probably CO 2 Me and CO 2 Me will give you the this tertiary alcohol, because you need help in the alcohol here finally, you need a alcohol here is a basically alcohol functionality.

So, if a you reacts with excess Grignard range is methyl Grignard you get the alcohol. Now you see compound A and B which both are proposed at this in both the intermediates can lead you this compound. Now, A and B basically are a reguoisomers of a alpha beta unsaturated ketone. In addition, the other in which was given to you have to also use a, this Wittig elide this Wittig elide that. So, that was giving to you that is giving to you

(Refer Slide Time: 04:11)



Now, what I am trying to do? We will first trying to draw the occidal structure again occidal structure again as our target molecule and then, I say the initial F G I will be the Grignard reaction fine. Now, where from the pseudo symmetry and local symmetries coming I will be talking to you little bit later on I say I am having this particular compound ok. Now this compound is also similar is basically a, this part is local symmetry this part is pseudo symmetry entire molecule is pseudo symmetrical.

Now, what I am saying this particular intermediate will be can be constructed, let us follow a this path I am saying there I have this methyl you try to put a double bond here you try to put a this Wittig elide, which is basically you required and then you are having a methyl C double bond O I am saying that; probably one of this aromatic double bond can be constructed say intermolecular Wittig reaction.

Now, you need to make a c six unique. So, this is one this is two this is three four. So, basically you have you need to have a four carbon one two three four. So, you have this particular. So, I am saying that this disconnection probably you can do it and then you do a intramolecular Wittig reaction. And, then probably this one can be seen that how the starting material was related I am saying that this starting material can be connected and now the initial Wittig region which was giving to you having a structure Ph 3 P plus.

Now, exactly what is this Wittig regent? This basically nothing a Wittig regent where the things are just like this, eventually if you see allelic carbon ion which can also undergo resonance two put you, but to give you another regulating structure where you have this thing. Now, I am saying that if this initial compound is giving to you assume that, there might to be a this kind of regulating structure takes place and then this one is acting as a Michael Nucleophile to this Michael accepted this is a structure that structured both the methyl's are on this turbines .

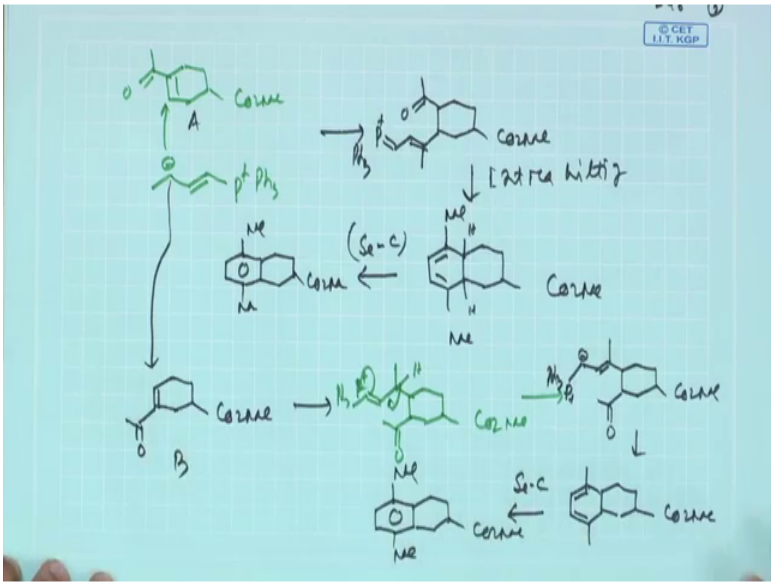
So, one methyl is coming from the ketone methyl and this methyl if it is initial Wittig solved undergoing this resonance charge transfer. Now, I this resonance thing and then gives you this things you basically can attach it here; then you basically get this elite you can close it. On the other hand the same molecule you can also cut into another way and here I am saying that you put the CO 2 Me here, that is fine and then the ketone methyl you put it in this way. Then also you can have a another as A minus and P plus triphenyl phosphine this also I said. So, this also can undergoes intermolecular Wittig 1, 2, 3, 4, 4 carbon.

Now, how this compound can be accessed this compound in reality can be access from this CO 2 Me and this CO 2 Me. Now this is intermediate B and this is intermediate A.

Now, I will do the for both the molecule I will try to do the forward pathway, if you see this retro for a same target molecule is only possible, because the molecule is having a local symmetry, that is; what two region isomeric compound. Either this or this will give you same target now reaction path ways almost similar, because you only touching this part this part remains un effected this part is remains un effected in the entire synthesis.

Now, let us talk about the forward synthesis and then then consider. So, initially I will say the take the intermediate one or intermediate A.

(Refer Slide Time: 10:05)



So, intermediate A is having this structure CO 2 Me Me CO Me your Wittig ylide as I said it is going to undergoing or have this resonating structure P plus Ph 3.

So, initially I said this goes in a Michael fashion and if it reacts in Michael fashion this compound A. So, what will get you will basically get CO 2 Me, this part is there your methyl ketone is there. Now your Michael attack of this Wittig ylide takes place and then you are basically having this P plus Ph 3 this is also a Wittig ylide.

Now, this Wittig ylide can easily undergo intra Wittig reaction intra Wittig it will essentially give you a cyclic product the structure of the cyclic product will be this methyl this compound. Now next what will to do? We just need to aromatize the molecule. So, this hydrogen need to basically remove normally this is done by standard selenium carbon, it is oxidative actually you need to remove this to hydrogen. So, you basically get the part this part.

Now, take with them, another intermediate or another starting material whose structure is B the structure of B is; now just the regio isomer of the compound A structure B.

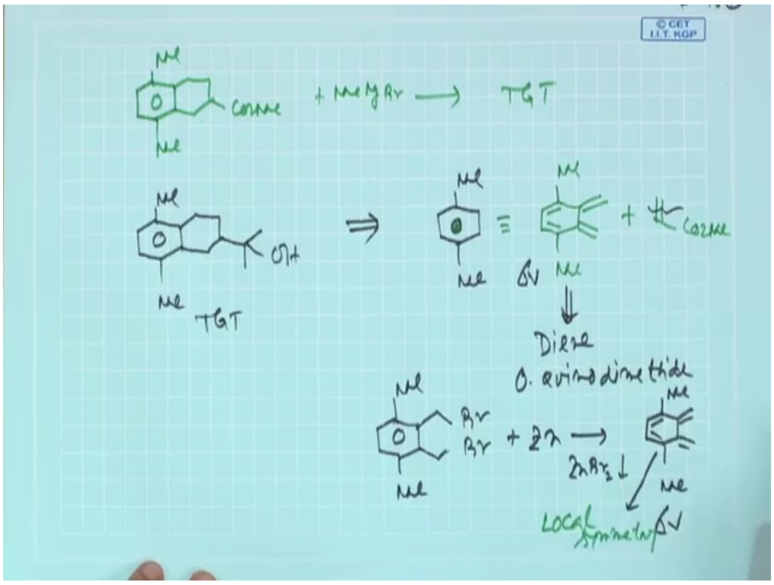
Now, here I am saying that this same intermediate attacks in the Michael fashion. So, this is now B. So, intermediate attacks in Michael fashion this CO 2 Me is here this CO Me C r. Now, if it attacks in Michael fashion you basically have this and then you are having this, your P plus and your P Ph 3 actually.

Now, here initially what happened this hydrogen it is since to be acidic have in this. So, this will put a negative charge. So, that Wittig reaction can effectively be taking place we will basically put a double bond here, and then now you formulate the Wittig things now this become ch 2 or you can basically get a negative charge, here I mean this things comes this gives a negative charge the first parts here. So, you get a P plus Ph 3 which is nothing a Wittig ylide. So, 1, 2, 3 this is 1, 4. So, now, if you do a intra Wittig you get the same compound as earlier CO 2 Me your this methyl is here this methyl is here this double bond is already there you make this new double bond here.

So, now this toward similar, again same selenium carbon you get the aromatized change. Now, if you see the entire entire forward pathway you starting from a both the regio isomers and reacting with a crotyl Wittig system you can basically come to a core structure. Now, this is only possible because the molecule is having a local symmetry.

The left part of the molecule is having the local symmetry; this is the main thing which basically gives you a entire symmetrical or the local symmetrical consideration. Now, synthesis can easily be easily be completed easily be completed once you have this intermediate which you have prepared just take this intermediate and react with excess methyl Grignard.

(Refer Slide Time: 15:22)



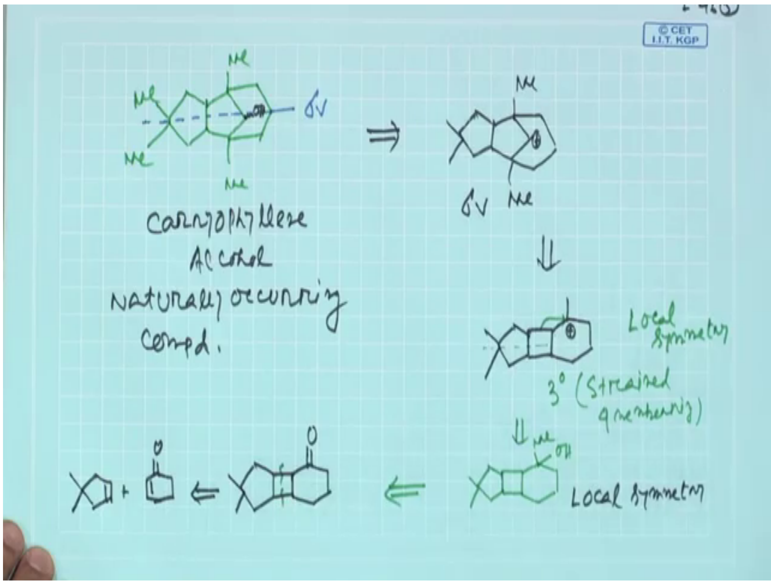
So, basically get the target molecule in actually occidal is a very nice target molecule from a consideration of local symmetry and pseudo symmetry. Eventually, other synthesis is reported for occidal also have a nice demonstration of how this part of done the probably, I have just try to give you angular synthetic pathway I will found that this occidal, how it has been constructed?

I am saying that now I will make occidal through a different way. Now, what is the different way as it is aromatic ring? If you have to considered the next stage do not keep this aromatic ring just these are aromatic ring ok, we will in draw the intermediate in different way I am saying you draw the intermediate in this way this methyl this methyl . So, put a double bond here put a double bond here and then you are saying if you do a 4 plus 2 gives under reactions that basically gives you a the same intermediate ok.

Now, what is this compound can be regarded as a effectively very good diene. Now this compound is having perfectly sigma v local symmetrical part and this part is your pseudo sigma v, because due to based on the CO 2 Me this is not perfectly symmetrical. Now, this diene is named as ortho quino di methide is ortho quinodimethide that is the very now how you can generate this kind of intermediate the usual way to generate is you take the corresponding dibezoilic bromide react with simple zinc metallic zinc you react with metallic zinc zinc B r 2 will precipitate and you basically get the ortho quino dimethide as a diene you react with this dinophile.

Now, this is sigma v perfectly sigma **v**. So, this is the this gives the local symmetry part in the target molecule this gives the local symmetry part in the target molecule . So, in this way you can basically basically consider now what I am trying to do I will give you a natural.

(Refer Slide Time: 18:22)



Product which is perfectly symmetrical perfectly symmetrical natural product same like semitone, but this structure is little bit little bit complicated.

Now, see the structure very carefully there are methyls here there are methyls here and in the central carbon you are having a O H. Now this molecule name is carriophillene alcohol carrio phillene alcohol is a naturally occurring sesquiterpene is a naturally occurring compound or you can isolate from nature if you see the molecule is it 3 ring, 1, 2, 3. In addition this 5 member and 6 member ring it forms a bridge actually is a bridge connection this molecule have a nice sigma v as you can formulate sigma v.

Now, synthesis of this molecule was done by following a very nice concept of exploration of local symmetry and pseudo symmetry. So, what I initially do? I will say the initial the this particular oh will be introduced at a later stage, I am say if you have this methyl this methyl if you have a carbocation which can be easily trap by this what are to give you this thing this carbonium ion is perfectly sigma v ok. Now, this carbonium ion is basically kind of a bridge carbonium ion bridge carbonium ion. Now, saying this bridge carbonium ion can be constructed by some classical carbocationic rearrangement which you probably seen in the pinacol pinacol rearrangement.

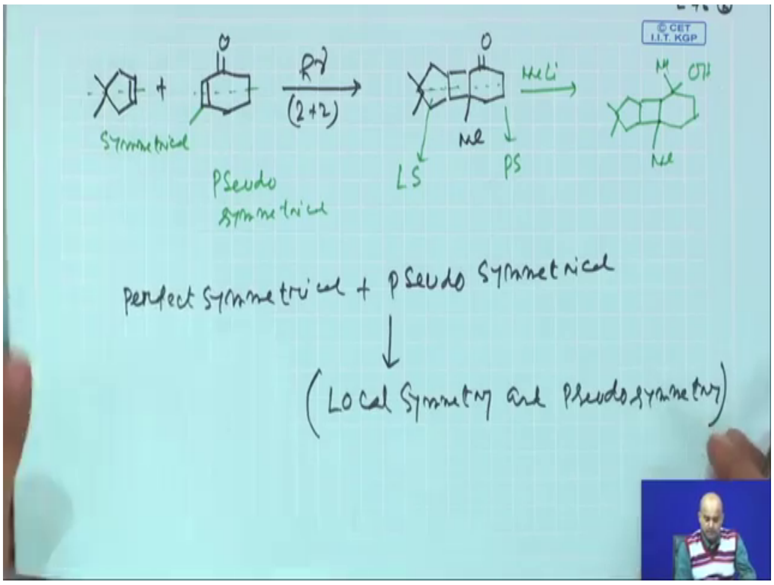
Now, I say if you have this carbonium ion which definitely 3 degree carbonium ion ok. When addition this carbonium ion is 3 degree tertiary, but this also const contains a strained four member ring four member ring this is very important point. The strained four member ring in this particular carbonium ion lead this carbonium ion to undergo one two migration.

Now, if this carbonium ion this bond basically migrates here the four member ring is expanded to a five member ring and putting a carbonium ion are electropositive thing at this central carbon. Now, where from this carbonium ion be generated, now the symmetry has been disturbed. Now the molecule is becoming basically local symmetrical this part is symmetrical this part is not.

Now, the molecule become local symmetrical now what is said this compound you can easily prepare starting from I say this methyl and this OH just by water removal just by water removal. So, this compound is again same local symmetry as well as pseudo symmetry this part is local symmetry this part is pseudo symmetry I say you need to have a tertiary alcohol center. So, I am trying to put the corresponding ketone

Now, we are coming that you basically have this olefin only and if you having a alphabet unsaturated cyclohexanone the best way to construct the cyclobutane is 2 plus 2 cyclo addition reaction now if you now do the forward synthesis you.

(Refer Slide Time: 23:29)



See that your synthesis starts from this particular compound you react with this things in a photochemical fashion as a 2 plus 2 ok.

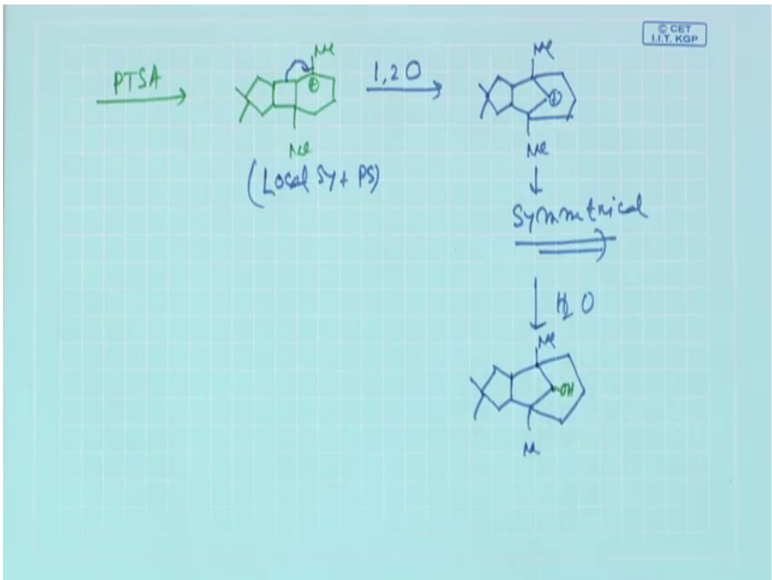
Now, after this 2 plus 2 you basically get this cyclobutane which is your photo adduct and here basically the ring is strained. Now initial starting material this starting material is symmetrical symmetrical ok. We as our synthesis was basically having extra methyl group. So, I have missed all the methyls here it will be methyl it will be methyl here it will be methyl here. So, a starting material is basically having methyls here.

Now, this part is symmetrical perfectly symmetrical and this part is not perfectly symmetrical this part is pseudo symmetrical pseudo symmetrical. So, what I am now trying to analyze a perfect symmetrical part perfect symmetrical part or perfect sigma v intermediate plus you react with a pseudo symmetrical intermediate. Pseudo symmetrical intermediate gives you a molecule which contains local symmetry in one part and pseudo symmetry at another part is obvious. So, this consideration I am basically trying to highlight it I have been normal text book you will not get it basically the the analysis through local symmetry and pseudo symmetry is very very crucial and is a nice demonstration. So, find initial you do this two plus two reaction ok.

Now, what next as situation demands you will has react with methyl lithium to get the another methyl part. So, now, you see this ini after initial 2 plus 2, this part is local symmetrical and this part is pseudo symmetrical this part I call l s local symmetry this part your pseudo symmetry ok. So, now, I do this methyl lithium addition you have this methyl o h.

Now, these compound this particular compound you basically treat with emilar isotopic paradonic sulphonic acid. So, initially what will be happening you basically get the corresponding carbocation as explained earlier.

(Refer Slide Time: 26:33)



Now, this carbocation will trying to migrate is a 1, 2 migration. Now migration takes place like this. So, this part is local symmetry now after this migration, there is a very beautiful observation. Once this migration takes place the four member ring, now become a 5 member ring the 4 member ring, now become a 5 member ring.

And as both the methyl groups are there the earlier methyl for this part makes it a local symmetrical molecule or pseudo symmetrical molecule. Now, here after this methyl migrates these two methyl was kind a perfectly symmetrical orientation this pseudo chemical part we did it considered. So, now if you see this molecule now becomes symmetrical. So, a local symmetrical molecule or a pseudo symmetrical molecule the molecule, initially having local symmetry as well as pseudo symmetry.

Now, converting to perfectly symmetrical intermediate, now this is only possible as the part of your molecule already having a symmetry local symmetry and by doing some transformation of a pseudo symmetrical part you are bringing or you are creating pseudo symmetry is very close to symmetry you basically need to rearrange or reconfigure the pseudo symmetrical part to convert it to a perfectly symmetrical part that is what we exactly did it here.

Now, if you see perfectly symmetrical you react with a water molecule and then you will find that your methyl will be there methyl will be there and you are basically having a OH here, because pseudo symmetry and local symmetry probably is a relatively new concept to you, but definitely you can have a nice way of thinking this particular problems in this angle and we I will talk about this motorization the remaining part in the symmetry based strategies in the next lecture. So, till then have a good time and goodbye.