A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture - 05
Transformation based Strategy for a Given Target

Welcome back. So, if you remember the last weeks our discussion we are trying to continue it and if you see.

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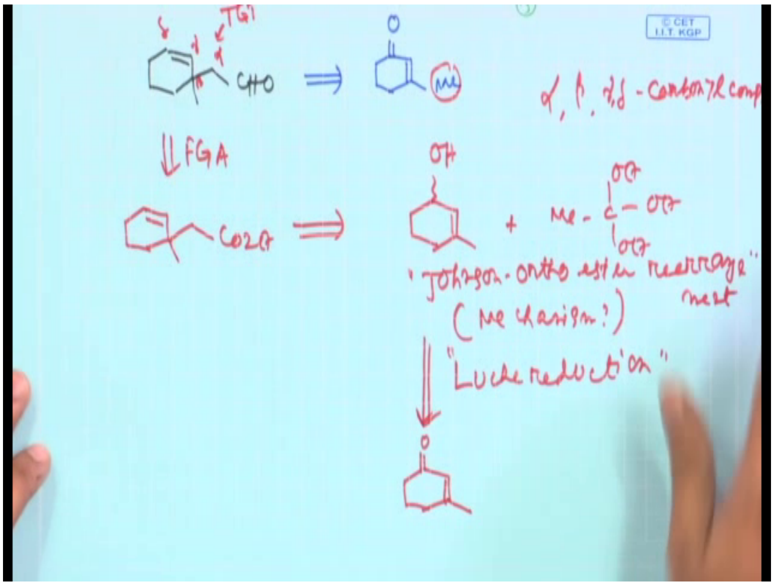

We are basically discussing a retro which was again you can see in the slide.

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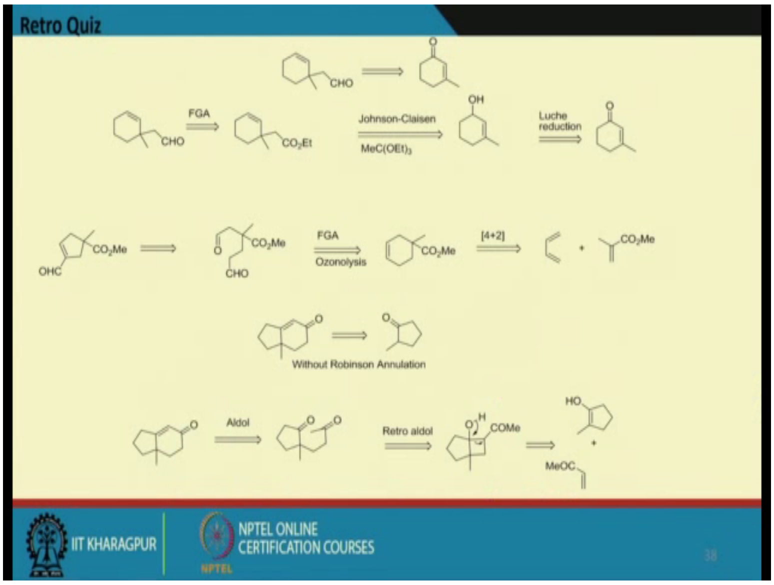
Retro Quiz

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And we said the compound which we will be trying to do a retro having a alpha beta gamma delta unsaturated carbonyl compound, it is a basically aldehyde functionality we said couple of important name reactions we said Johnson Orthoester Claisen rearrangement we said Luche reduction. So, what are those?

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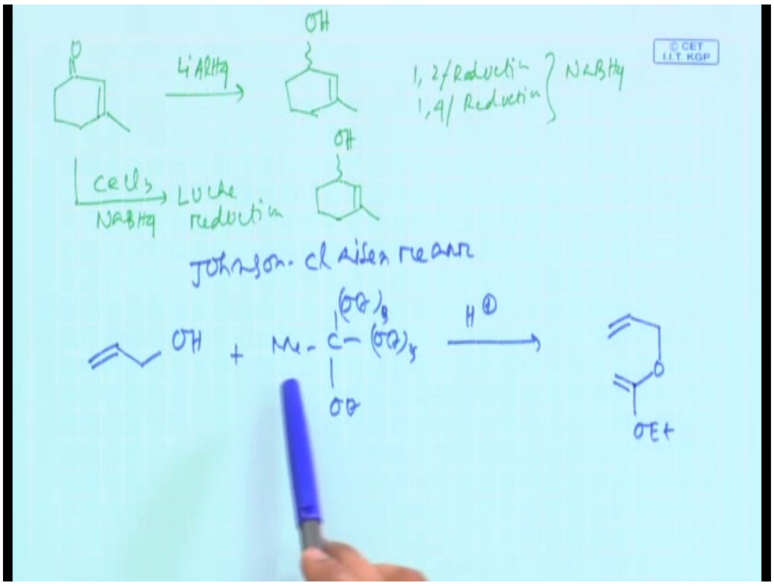

So, eventually let us first start with the starting material, the starting material which was given to you is basically 3 methyl cyclohexanone. Now the 3 methyl cyclohexanone if you want to do a reduction you want to do a conversion something like this, which is basically required for your next synthetic step for Johnson Orthoester Claisen rearrangement. Now for this carbonyl reduction if we use strong hydride reducing agent like lithium aluminum hydride you have a difficult scenario, you might have a 1 2 reduction as well as 1 4 reduction. So, both the product you will be getting and you do not want to do this.

Even sometimes sodium borohydride which is supposed to be a milder reagent that also does the same thing. So, in this case we are using a particular reagent condition which is named as cerium chloride and sodium borohydride it is called the Luche reduction condition and this Luche reduction condition will give you extensively 1 2 reduction in alpha beta unsaturated compounds. It is a very mild and chemoselective reduction. So, once this Luche reduction was done you can next follow that we need to do a Johnson Claisen rearrangement Johnson Claisen rearrangement which is given you.

Now, what is Johnson Claisen rearrangement we will now next try to focus on Johnson Claisen rearrangement it is a very important transformation Johnson Claisen rearrangement, it is basically a 3 sigmatropic rearrangement. Now what do we need you basically a allylic alcohol a starting material and you need to take this triethyl ortho acetate sorry this will be oet oet oet. So, mec oet oet oet. So, initially you makes those 2 compounds in presence of a acid acid catalyst you need a acid

Actually you will be getting a intermediate whose structure is this and this structure you can basically figure it out how it has been generated a very initially there will be trans acidic esterification kind of reaction. So, where one of the ethyl group will be replaced by this allyl group so you can pick it up this ethanol as a byproduct and put this O allyl here. The next step you are subjecting this compound with a high amount of heat an h plus then one of the ethyl oet and from this methyl one hydrogen with undergo 1 2 elimination to another round of ethanol elimination.

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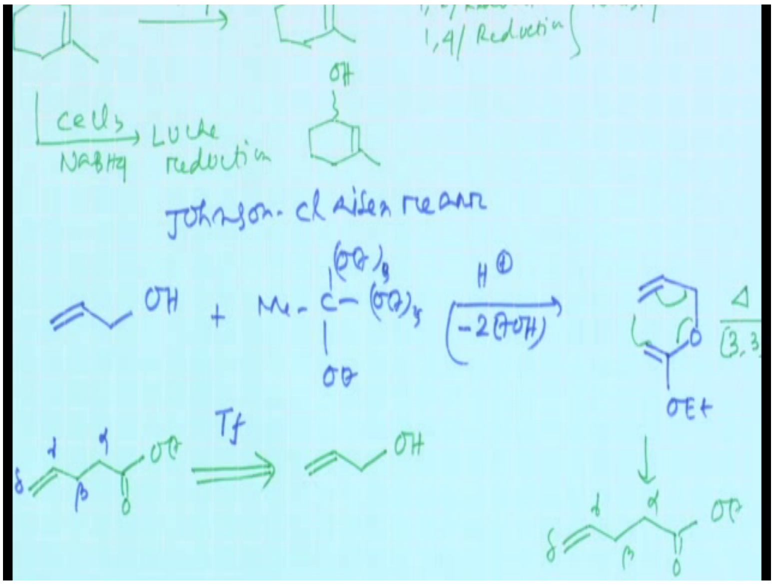

So, 2 equivalent of ethanol will be eliminated by this reaction and you will be getting this part is coming from this allyl part double bond C H 2 O C H 2 O then one of the oet remains here and this things coming from this methyl. Now is very nice an interesting reaction this probably all of you know subjected to heat a 3 3 sigmatropic rearrangement takes place this all of us probably know and then what will get we basically get a compound like this which is alpha, beta, gamma delta.

So, the general retro for this kind of compound whenever you are having a alpha beta gamma delta unsaturated compound this things you can straightforward do a retro based on Johnson orthoester rearrangement, Johnson orthoester claisen rearrangement and that was the basic transformation which you were looking for basic transformation, but this information you need to have it. So, it is a alpha alpha means alpha to carbonyl alpha to carbonyl then alpha beta is a gamma delta

Basically it is gamma delta unsaturated carbonyl compounds and eventually this is a very important transformations we will be trying to trying to figure it out this transformation throughout our courses and we will find that is a very important very interesting reaction fine. So, coming to another quiz another quiz it is a again a based on a a very simple transformations and let us see how it was designed the starting material was a simple starting material is basically having a cyclopentene, framework you see cyclopentene framework.

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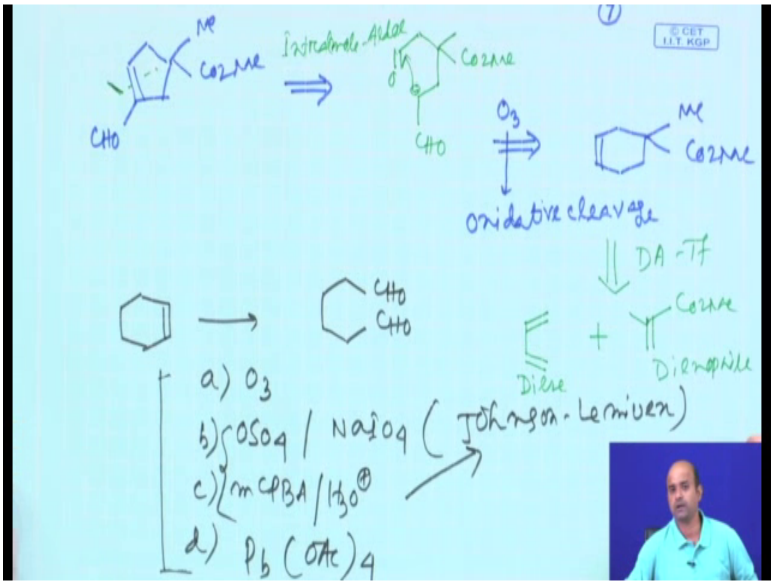

You are having a methyl here you are having a C O 2 Me here. So, it is gives a all substituted carbon substituted things at the one left half left hand you are having a alpha beta unsaturated aldehyde. So, it is a pretty small molecule the retro was very much simplified retro first retro was a intramolecular aldol type of reaction. So, how you basically cut this bond you cut this bond as I said this is a your retrosynthetic bond disconnection and what we will do you basically remaining part you keep similar and let us see. So, this is your initial retro which will be something like this.

So, you have a dialdehyde and this dialdehyde we assume that one of these aldehyde will abstract the alpha hydrogen and will attack to the another aldehyde now there is there must be regiochemical. So, definitely, but probably I said that this aldehyde having in between 2 C H 2 group or 2 methylene group while this aldehyde is having one methylene group. So, these groups are with pretty basically very close to this aldehyde, but this aldehyde having little bit far away from this group. So, this group does not exhibit or does not exert a steric crowding here. So, hydrogen from this aldehyde alpha hydrogen can easily be abstracted compared to this aldehyde that was the initial thought.

So, fine now you could I do a intramolecular aldol reaction which is pretty straightforward transformation, now this starting material how can it be the starting material the starting material as it is a dialdehyde you can straightforward go to a some compounds like these. Now what is this reaction it is a basically a oxidative cleavage or you can say ozonolysis. So, it is a oxidative cleavage oxidative cleavage now this kind of reactions you are basically very much fundamentally useful and you will find in many cases if you have a cyclic compounds you want to keep this kind of compounds to corresponding the aldehyde and what are the reagent of choice.

What kind of reagents you want to use it the best reagent is ozone you can do a ozonolysis there are other reagents the transformations first you do a hydroxylation then you do a sodium perborate which is named as Johnson Llemiuex, Johnson-Lemiuex reaction the spelling you have to check it Johnson Lemiuex reaction see you can do a MCPBA mediated epoxidation followed by water treatment that will give you the diol, then you do the same thing Johnson Lemiuex the other reactions you can first make the diol by making this reagent and then you treat with lead tetraacetate which is also cleave the corresponding diol to aldehyde.

So, these 4 conditions basically you can use for diol cleavage and that serves a very nice interesting pathway or is called oxidative cleavage to give you. So, now, you are here now what will be the next retro the further retro we have already shown in in the slide. The next retro is basically simplifying it by a 4 plus 2 dicellular cyclo addition or dicellular transformation. So, this is your Dien and this is your Dienophile methyl methapilate and basically if you can do a 4 pi plus 2 pi cyclo addition reaction you can get corresponding product which is one of the intermediate.

Do a oxidative cleavage by ozonolysis or any of this 4 method which was just discussed then you can do a intramolecular aldol reaction this is a transformation which is intra interam aldol intramolecular aldol reaction. So, this was the main key reaction or key synthetic transformation which we will be using to access this molecule and probably if it is not very difficult you have to see the molecule first and then you can eventually try to design the pathway which will be suitable for you. The next one is absolutely tricky next one is absolutely tricky.

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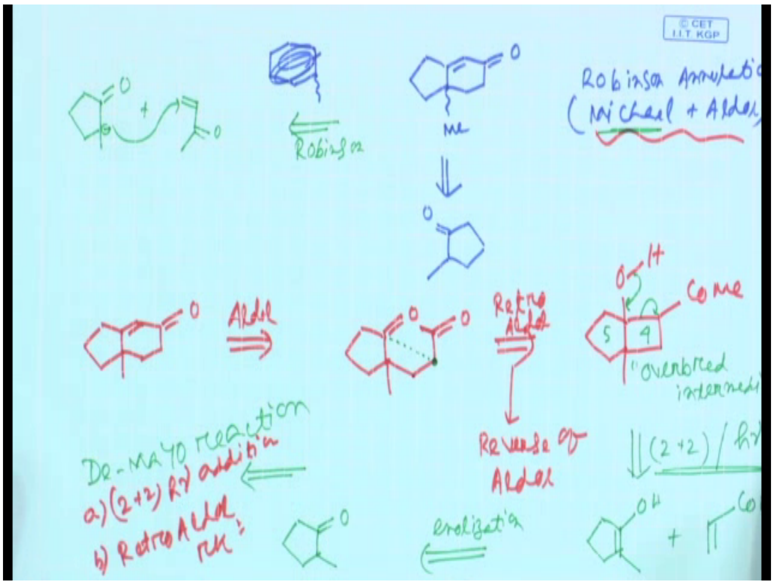

I said you have to make this kind of bicyclic compound sorry this structure is wrong. So, I said the you have to make a bicyclic compound which was drawn in the slide without using the Robinson annulation. Now remember last week we talked about Robinson annulation which is basically a combination of Michael and aldol reaction we talked about Robinson annulation Robinson annulation annulation means a ring formation reaction and we said Robinson annulation is nothing is a combination of Michael and aldol reaction.

Now here we are given the prerequisity the prerequisity is you cannot use Robinson annulation, I said without using Robinson annulation the starting material which was given to you similar kind of starting material which was used in the Robinson annulation that is absolutely tricky. So, you have to devise a other pathway which is not exactly similar as Robinson annulation pathway demands. Now let us try to analyze this pathway the initial retro was basically shown into the PowerPoint. So, I say if you have this target molecule you devise a pathway which looks this.

Now how you can this is basically the final pathway in Robinson annulation what you say Robinson annulation we do Michael and aldol that is the combination we said if you have this kind of carbonyl compounds you can basically do a aldol reaction that is fine that is the final pathway in the Robinson annulation. The next one next one you see is a absolutely tricky pathway we devise if you have a intermediate something like this something like this and we do a retro aldol kind of transformation.

Now, what is what is what is a retro aldol reaction is a reverse of a aldol reaction is reverse of a aldol reaction similar like a retrosynthesis it is a reverse of a synthetic steps this is a reverse of aldol reaction reverse of aldol reaction. Now see how this retro aldol takes place this is a 5 member ring this is a 4 member ring and we generally know that 4 member rings are strained. So, happen if you subject this molecule to a base it will try to open it up and will give a negative charge here because it is linked to a co me group which is electro withdrawing which can stabilizing.

So, then if you have a retro aldol kind of transformation that will basically give you A C double bond O here C H 2 C H 2 C H 2 this is the C H 2 where is going to be originated after the cleavage. So, in principal the cleavage is like this this is the 4 member ring 1 2 3 4 this is the cleavage. Now later on we will be seeing that this kind of strain intermediate or strain ring containing compounds are named as overbred intermediate we will be discussing it in detail in a subsequent section we said the intermediate which was strained are named as overbred intermediate and they have a very significant application in the field of organic synthesis as well as retrosynthesis fine.

So, now, whenever you have a choice to make a 4 member ring my suggestion is straight forward go to a 2 plus 2 photochemical reaction that is probably the one of the best reaction available in the literature or available to the synthetic organic chemistry community. So, now, you can easily find it out what is the 2 plus 2 retro. So, 2 plus 2 basically you will be requiring this vinylic alcohol and you require a methyl vinyl ketone fine where from you get this compound this is nothing this is the anole form of the corresponding ketone.

Now you see the starting material which was required in the Robinson pathway is of the similar see if I have to do a Robinson pathway which I say you cannot use it in this case the pathway for Robinson also similar I mean the starting method is exactly similar methyl vinyl ketone. So, initial Robinson pathway is basically this is undergoing a Michael thing and then you have a aldol if you rotate this molecule, but here the starting material is similar, but instead of the initial Michael reaction initial Michael we did not do initial Michael we replaced it with a 2 plus 2 photocyclo addition provided that the ketone is analyzable.

So, you make sure the ketone is analyzable. So, you can make the ketone with tautomerism analyzation and then this starting material is vinylic alcohol react into 2 plus 2 fashion now even eventually this reaction this reactions is now named as or it is known as de mayo reaction is named as de mayo reaction, what is de mayo reaction de mayo reaction is basically combination of 2 plus 2 photo cyclo addition photochemical addition addition I say and a Retro Aldol reaction retro aldol reaction. So, de mayo reaction is basically a combination of a 2 plus 2 H 2 O addition for photo cyclo addition and retro aldol itself and de mayo reaction is very significantly useful reaction significantly important reaction.

We will find in the couple of next slides when we talk about more transformation based approaches and find the de mayo reaction is absolutely brilliant to work with.

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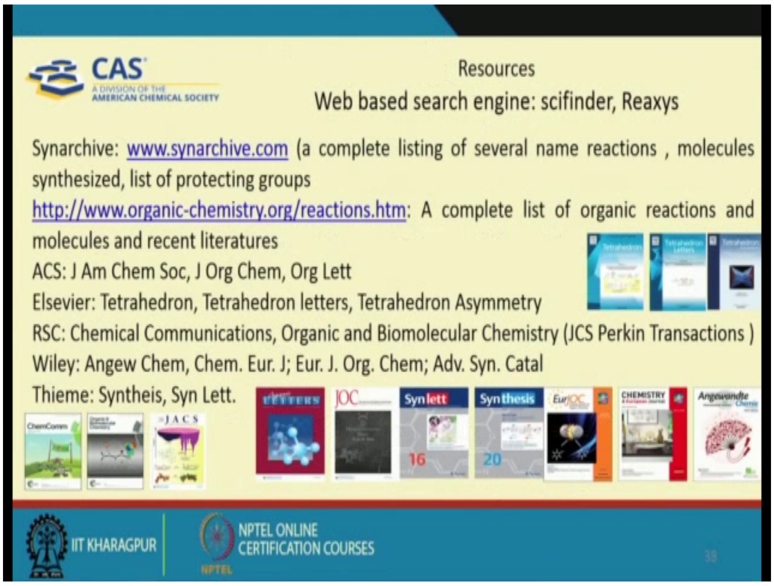

Resources

Web based search engine: scifinder, Reaxys

Synarchive: www.synarchive.com (a complete listing of several name reactions , molecules synthesized, list of protecting groups

http://www.organic-chemistry.org/reactions.htm: A complete list of organic reactions and molecules and recent literatures

ACS: J Am Chem Soc, J Org Chem, Org Lett

Elsevier: Tetrahedron, Tetrahedron letters, Tetrahedron Asymmetry

RSC: Chemical Communications, Organic and Biomolecular Chemistry (JCS Perkin Transactions)

Wiley: Angew Chem, Chem. Eur. J; Eur. J. Org. Chem; Adv. Syn. Catal

Thieme: Syntheis, Syn Lett.

So, next all groups talk about these things. So, this part is basically our quiz part ends here and finally, I will give you a list of a resources available in online, probably the best resources you can try is this one this synarchive dot com this synarchive dot com is a fantastic reaction is a fantastic website which basically gives you a you can try to search it from your from your things.

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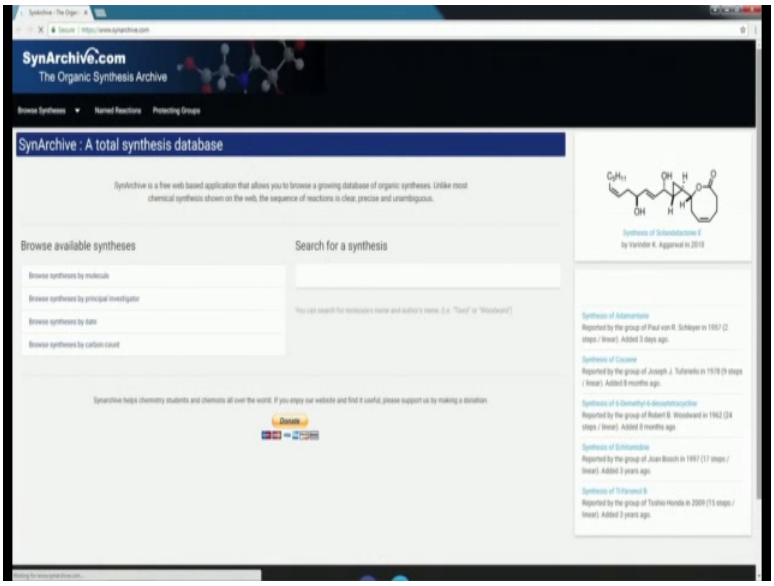

SynArchive : A total synthesis database

SynArchive is a free web based application that allows you to browse a growing database of organic syntheses. Unlike most chemical synthesis shown on the web, the sequence of reactions is clear, precise and unambiguous.

Browse available syntheses

- Browse syntheses by molecule
- Browse syntheses by principal investigator
- Browse syntheses by date
- Browse syntheses by carbon count

Search for a synthesis

You can search for molecule's name and author's name. (i.e. "Taxol" or "Woodward")

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Synthesis of Solandelactone E
by Varinder K. Aggarwal in 2015

Synthesis of Adamantane
Reported by the group of Paul von R. Schleyer in 1957 (2 steps / linear). Added 3 days ago.

Synthesis of Cocaine
Reported by the group of Joseph J. Tufariello in 1978 (9 steps / linear). Added 8 months ago.

Synthesis of 6-Demethyl-6-deoxytetracycline
Reported by the group of Robert B. Woodward in 1962 (24 steps / linear). Added 8 months ago.

Synthesis of Echitamidine
Reported by the group of Joan Bosch in 1997 (17 steps / linear). Added 3 years ago.

Synthesis of Trifarienol B
Reported by the group of Toshio Honda in 2009 (15 steps / linear). Added 3 years ago.

Now, we just have a look the synarchive the synarchive dot com basically gives you a complete idea, you can get the different name reaction you can get different name reaction just click it just click the different name reaction you will get a all name reaction which are basically potentially good transformation. So, all the transformation have been just now we said de mayo reaction now this is de mayo reaction.

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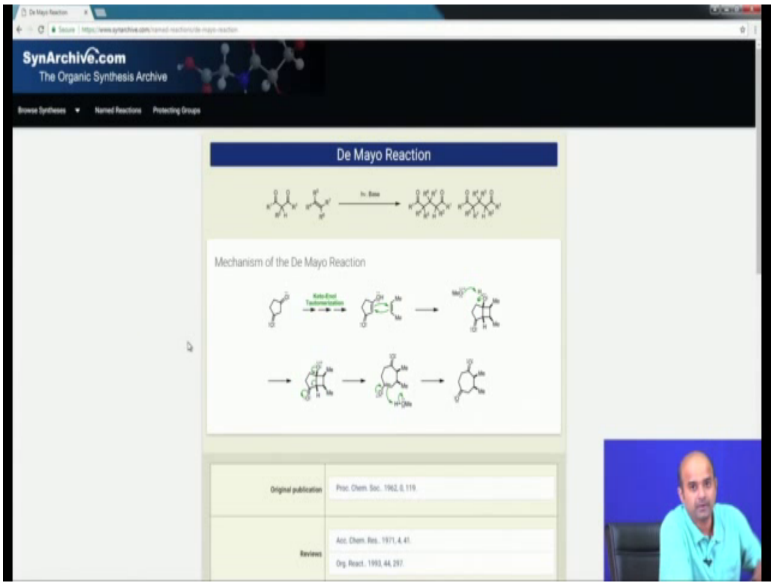

De Mayo Reaction

Mechanism of the De Mayo Reaction

Original publication	Proc. Chem. Soc. 1962, 0, 119.
Reviews	Acc. Chem. Res. 1971, 4, 41. Org. React. 1993, 44, 297.

So, click it click to the de mayo reaction and then we will find that de mayo reaction just now the similar kind of example we taught is a de mayo reaction as a ketonyl tautomerism then you have a 2 plus 2 cyclo addition followed by retro aldol cleavage.

So, this synarchive will give you essentially a huge resources for you is 3 it is a web based service and you can access from your smartphone if you have a internet connection you can do it and probably throughout this lecture will try to go through many of these transformation, which you will find useful now coming to other component of these things there are many other things which is basically available here. Let us say you are having several synthesis organ organic synthesis available like synthesis by molecule there are many natural products the target molecules have been listed here a stereo target molecules.

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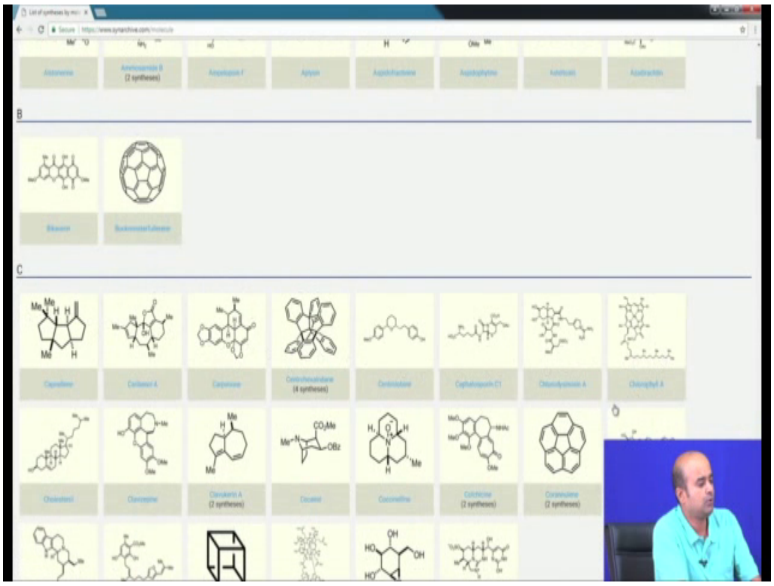

You can basically scroll them down alphabetically like see different molecules which have been listed here and many of the molecules if you just pick them they opens up and you can just go through it how the series has been reported in the literature by the scientist great scientist as we name them many of the scientist. In the last class and find quite interesting molecules probably some of the molecules will cover in this series as a potential target molecules and how those molecules can be synthesized you can have a initial hand on idea or you can just view it over this website you can design the pathway in your independent thinking and definitely then a the reactions if some reactions are not familiar with you can also can access the reaction throughout this portal.

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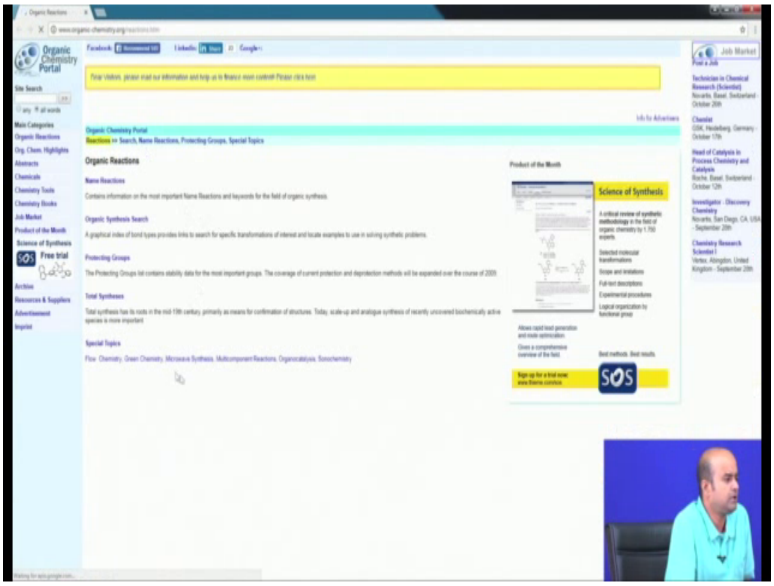

Organic Chemistry Portal
Reactions >> Search, Name Reactions, Protecting Groups, Special Topics

Organic Reactions

Name Reactions

Contains information on the most important Name Reactions and keywords for the field of organic synthesis.

Organic Synthesis Search

A graphical index of bond types provides links to search for specific transformations of interest and locate examples to use in solving synthetic problems.

Protecting Groups

The Protecting Groups list contains stability data for the most important groups. The coverage of current protection and deprotection methods will be expanded over the course of 2005.

Total Syntheses

Total synthesis has its roots in the mid-19th century, primarily as means for confirmation of structures. Today, scale-up and analogue synthesis of recently uncovered biochemically active species is more important.

Special Topics

Flow Chemistry, Green Chemistry, Microwave Synthesis, Multicomponent Reactions, Organocatalysis, Sonochemistry

Then this is a one good good resources which is available to you sometimes this is also helps is called organic chemistry or organic reactions, this portal is a good things which bacially give you a series of organic name reaction series of organic name reaction. And then similar kind of thing starting from alphabetically you can basically access a series of name reaction and let us say we talked about birch reduction at the birch reduction you can just click it out let us see this birch reduction is very interesting.

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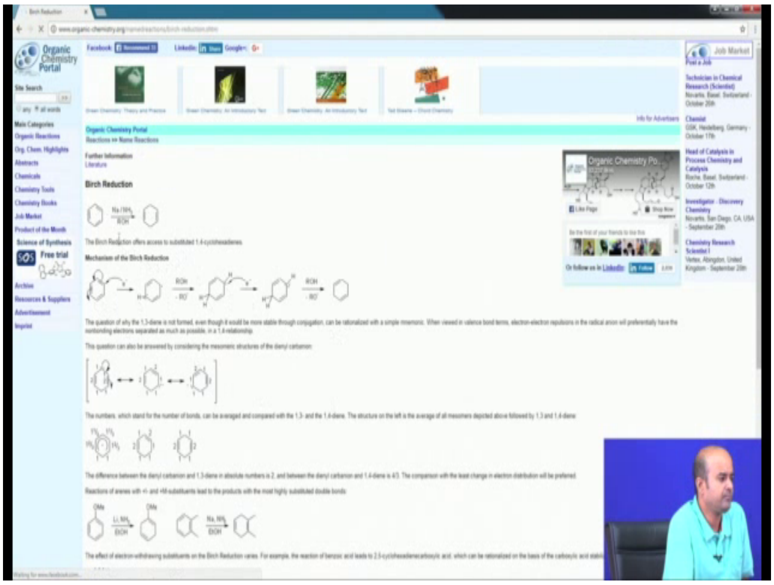

Birch Reduction

The Birch Reduction offers access to substituted 1,4-cyclohexadienes.

Mechanism of the Birch Reduction

And whatever mechanism I have shown it here you can get the instant access I said if you have electron releasing group like anisole you can basically think about the regio chemistry.

If I said electron withdrawing group like benzoic acid you basically get this kind of compound. So, this kind this this portal also is a very useful portal and that gives you a idea that what are the name reactions are available in the literature and what you might not know actually. And then you can just click them out and you find those the name reactions even this this rights this particular website gives you a lots of name reactions and then you can just go through it; obviously, our in our subsequent subsequent discussion we will try to cover some of the name reactions, but definitely due to time constraint due to space constraint we may not cover everything.

So, if those resources are available to you can easily access them and those are absolutely free those are free and. So, these 2 are basically the main resources we are talking about there are many research journals available here, but I would not recommend the journals to you at this moment because these are made for the specific researchers. So, you no need to access the journals currently. So, you can basically access these 2 websites and this websites will give you a a very good idea, that what you can think about based on a synthesis particularly synarchive; synarchive all the molecules a retrosynthetic pathway has been given and if you click for this this leads click the synarchive begin and then you browse synthesis by molecule. So, means that we will now target any molecule.

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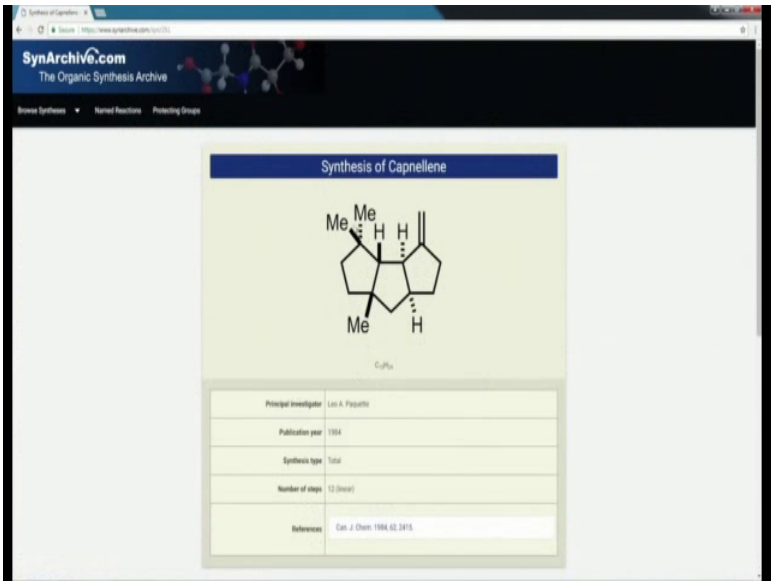

Synthesis of Capnellene

Principal investigator	Leo A. Paquette
Publication year	1984
Synthesis type	Total
Number of steps	12 (linear)
References	Can. J. Chem. 1984, 62, 2415.

Let us say molecule I will take this molecule now see this molecule they said that this molecule having this structure there are this molecule is reported in 1984 the investigator is Leo Paquiti is a great great organic chemist and see the entire forward pathway was given to you.

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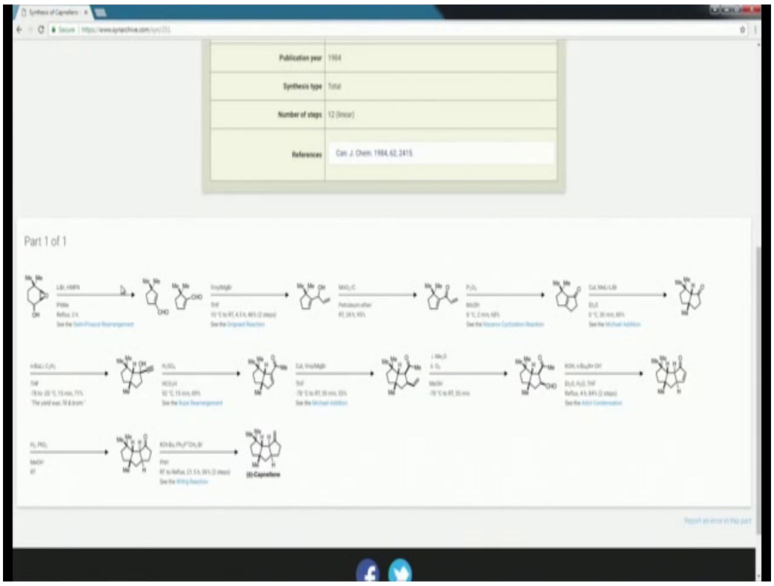

Publication year	1984
Synthesis type	Total
Number of steps	12 (linear)
References	Can. J. Chem. 1984, 62, 2415.

Part 1 of 1

So, if you want to get experience in the forward pathway and then you can think backward we will be first see the forward pathway and then you can devise independently a pathway that this route is known. So, by somehow can it be thought in a different way and that will give you a independent thinking that whether a new pathway all together a new pathway can be designed, but definitely that must be validated experimentally.

As I said organic synthesis is a a purely experimental science. So, you might have a 10 10 design pathways in a piece of paper, but until and unless all the pathways are validated those piece of paper are basically useless. So, out of 10 might be one pathway can validated in this lap setting. So, this these are the information you can basically work in out I mean you can work it out and this information would be really helpful and; obviously, you can you can contact me through this NPTEL platform regarding any clarification. So, we will see you in the next week. So, till today what we have discussed just go through it and if you have any clarification we can clarify your doubts in subsequent section.

So, have a good time.