Classics in Total Synthesis-I
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Lecture - 02
Introduction Technical Terms

So, good morning everyone and welcome back to the course on Classics in Total Synthesis, this is the 2nd lecture. So, in the last lecture you know we briefly talked about the syllabus which we will be covering in this particular course.

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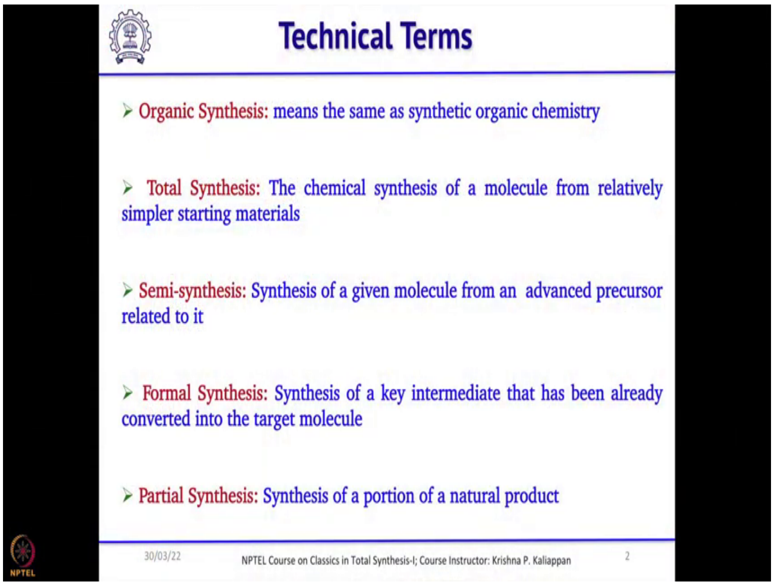

So, now we will move to the second part of our introduction. So, where you know we talk about many technical terms as well as some explanation on retro synthesis and so on. So, there are few technical terms which you should know and, in this slide, I will talk about some of the technical terms. Organic Synthesis; you know you often heard this term organic synthesis and in some places you know you people write synthetic organic chemistry.

But, please remember both are same ok, do not get confused organic synthesis and synthetic organic chemistry both are same. Then you also hear total synthesis, semi-synthesis, formal synthesis and partial synthesis. So, what are they? Total synthesis is nothing but complete synthesis; that means, synthesis of a molecule, it can be natural product or any other molecule, but starting from commercially available simple starting materials, ok.

You should start from whatever is commercially available and go all the way to the final target. So, that is called total synthesis. Then you also see semi-synthesis, semi-synthesis in literature and what does it mean? It means that you are making the target molecule, ok. You are also making the target molecule in this semi-synthesis route, but not from commercially available starting material. But from an advanced precursor which has almost all the elements, all the atoms present in the final molecule, ok.

I will give one example of semi-synthesis and I also will give an example of formal synthesis and partial synthesis. What is formal synthesis? Again, synthesis of a target molecule but, you do not synthesize a target molecule; but instead, what you do is you synthesize a key intermediate which many times advanced intermediate, but that has been already converted into the target molecule by somebody else, ok.

So, you are making only a advanced key intermediate and that advanced key intermediate has been converted into the natural product or the final target molecule by other people in few steps, ok. So, if you make that key intermediate then you can claim that it is a formal synthesis of that particular molecule. Then you also see in the literature partial synthesis.

So, what is partial synthesis? So, if you have a large molecule it has sometimes you know you do not want to report the whole synthesis, you do not want to wait complete the total synthesis and then report.

So, instead what you want to do is you want to make a fragment of that molecule or fragments of that molecule and then report. So, such synthesis of fragment, small fragment or fragments of a big target molecule is called partial synthesis.

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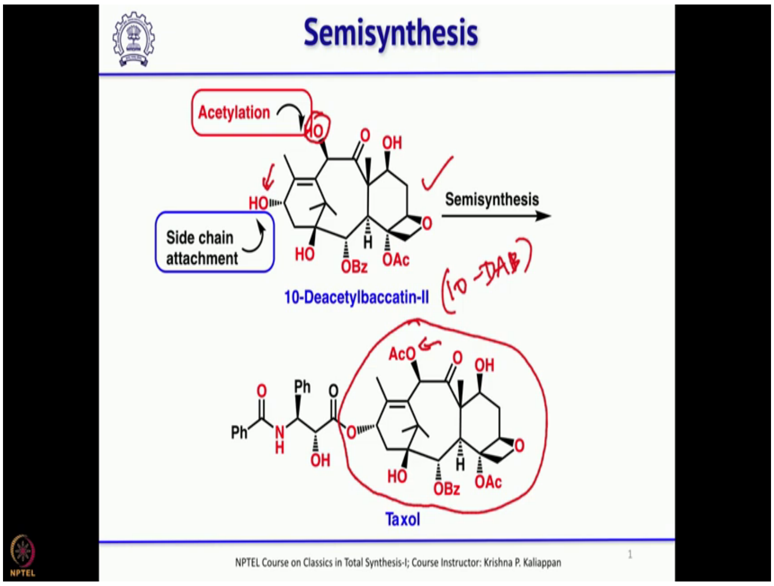

So, now we will move to what is semi-synthesis. Sometimes when you are trying to make a complex molecule, there is a possibility that from another natural source a molecule which is very close to the molecule which you are going to synthesize may be available. Then what you can do? You can take that molecule and then do only few functional group transformation and then synthesize the molecule which you want to make it.

I will give you one example. So, that will explain what is semisynthesis. So, this molecule is a diterpene called Taxol or paclitaxel. So, this is a drug used for the treatment of you know ovarian and other types of cancer, when this molecule was isolated in 1963, people did not think that this will become in a big blockbuster drug. In 1994 this was approved as a drug for the treatment of ovarian and breast cancer.

Afterwards lot of synthetic efforts went towards making this molecule. But the problem is when this molecule was isolated from the bark of Pacific yew tree. The Pacific yew tree was found to be very very slow growing tree. So, if you have to isolate more of this molecule then you have to cut almost all the trees, but still the amount of Taxol you can isolate from these trees will be very less to cure patients.

So, that time it was felt that there are only two ways one can make this Taxol to be available for the treatment of cancer, one is by synthesis other one is by biochemical methods, but fortunately what happened from the leaves of Pacific yew tree another molecule which is very close to Taxol.

If you look at these two molecules this is called 10-Deacetylbaccatin they call it as 10-DAB ok, which is almost close to what you have in Taxol. You can see in Taxol this is the core structure ok and 10-DAB has almost all of the core structure except that in taxol here you have acetate whereas, here you have hydroxyl group.

So, if we can isolate more of 10-DAB from the leaves of Pacific yew tree then what one needs to do is you have to carry out the acetylation selectively on that hydroxyl group, then you need to attach the side chain on this hydroxyl group. If you can do that then you complete the synthesis of Taxol from an advanced intermediate which is also isolated from a natural product.

So, this process is called semi-synthesis. See fortunately what happened in this particular case, this 10-DAB which was isolated from the leaves of Pacific yew trees could be used for making several analogs of Taxol. In fact, some of the analogs of Taxol were found to be more active than the parent compound Taxol that is one advantage.

The second advantage is the leaves of Pacific yew trees they grow faster, ok. So, you can remove leaves from the Pacific yew tree, isolate 10-DAB convert that into Taxol. After sometime immediately you know you see that leaves growing. So, this way you do not have to cut the Pacific yew tree to make Taxol what you need is you need to isolate 10-DAB from the leaves and then do some functional group transformation and you can complete the synthesis of Taxol, ok.

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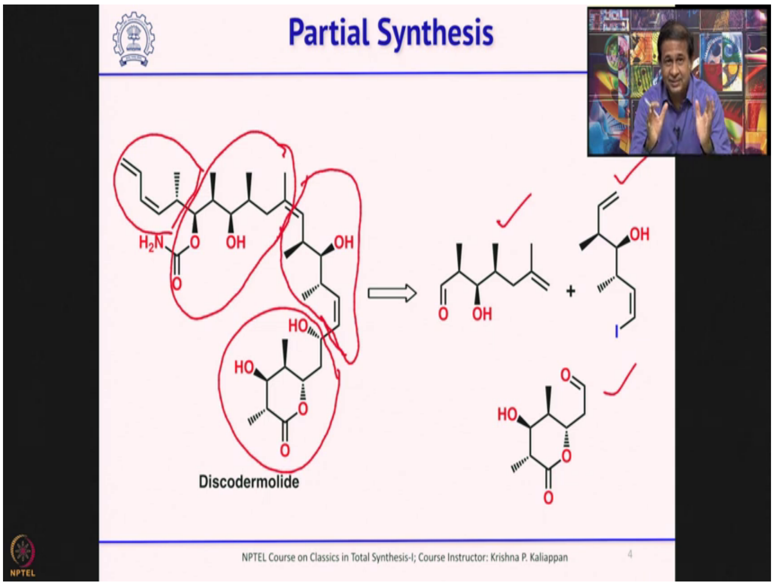

The partial synthesis: Again as I mentioned if you have large molecule ok. If you have large molecule and of course, when you want to synthesize such a large molecule it takes time and there will be always competition to report such synthesis. So, what you can do you can cut this molecule into several fragments fragment A, fragment B, fragment C, fragment D. Then try to make or try to synthesize these individual fragments and then report.

See here in this case an anti cancer agent called discodermolide there are 4 fragments; I have shown only 2 I have shown only 3. If you see if you can disconnect here, if you can disconnect here and if you can disconnect here, ok. So, this is one fragment this is one fragment and this is one fragment and you can see this is the third fragment and this is the fourth fragment, ok. So, there are 4 fragments.

So, if you report the synthesis of any of this 4, ok. Here I have written 3, the fourth one is on the left hand side ok. So, if you report the synthesis of any of these 4 then you can claim that it is a partial synthesis of discodermolide. Partial synthesis we also have to mention the fragment, C1 to C12, C12 to C14 whatever the number that you have to mention then you can claim that its a partial synthesis of that natural product.

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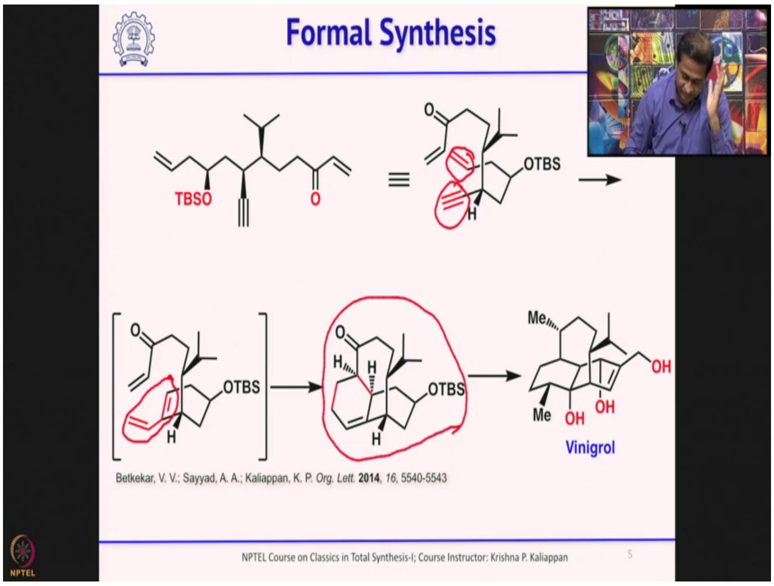

Then the third one is formal synthesis; the name itself suggest it is a formally done ok. You have not really done the whole total synthesis and you have done formally. Say for example, we will give our own example.

So, where we have taken this material which was prepared in few steps from commercial level of starting material and that can be redrawn like this. So, when you redraw you can see a double bond ok and a triple bond ideally situated for an intramolecular enyne metathesis ok this can undergo an enyne metathesis to generate this diene ok in situ.

Now, this diene can undergo an intramolecular diels alder reaction to give this tricyclic skeleton ok. So, this tricyclic skeleton is already converted into a natural product called vinigrol by two groups, ok. So, what we can claim is the formal synthesis of vinigrol where we have made this advanced intermediate, this intermediate has been already converted into natural product vinigrol.

So, we claim that this is a formal synthesis, ok. So, now you know what is total synthesis, what is partial synthesis, what is semi-synthesis and what is formal synthesis, ok.

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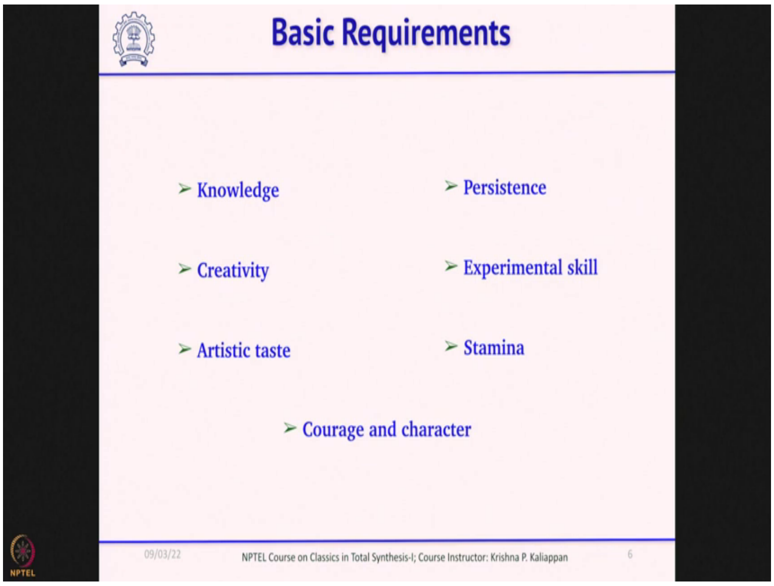

So, now before we go further into this topic what are the basic requirements one should have to carry out total synthesis, ok. First of all, as I mentioned yesterday the knowledge of most of the organic reactions in your fingertips is very important. The reason is when a particular reaction does not work then you should think about alternate reactions, so alternate pathways. So, that means, you should have knowledge of wide range of reactions. So, then only you should be able to face failures and then succeed.

So, knowledge of organic reactions and other related things in organic chemistry is very important. Then creativity; so, creativity is not only required for organic synthesis, but for every subject, but here creativity is more important for the simple reason that how you make the molecule, how you make the molecule is more important and that is directly related to the creativity.

See one can make a molecule it does not matter you know see, it may take 20 steps, it may take 50 steps no problem. One can work hard and then make that molecule, but if you are creative one can make the same molecule in 5 steps and compare that with the 15 steps 20 steps reported in the literature, then you feel your creativity really helped in reducing the number of steps ok.

So, creativity plays a very very important role when you talk about synthesis in this natural product or any pharmacologically important molecule. So, even industry creativity plays a very very important role. The third component this is you know it depends, but basically I prefer that artistic taste is also very important. So, its like a when you read a particular journal volume ok, you there may be several total synthesis reported in the in that particular issue.

Not all the synthesis you will remember ok after going through all the synthesis only few synthesis will linger in your mind. How did they do, how did they think it is so good fantastic you know. So, that is how you feel, that is because it is not about just synthesis how they thought about it, how they constructed the molecule, how they constructed a very important strategic bond.

So, these are all you know its like you have to have artistic taste then only you can really think about synthesis of a complex molecule in a simpler way. Then fourth component is also very important its persistence, patience and when you go to lab many times the known reaction will not work. So, you have to have patience you should know why the reaction did not go.

So, you have to analyze what did you do wrong. So, patience will really in the long run give you a long rope and then you can you should be able to achieve the total synthesis of molecule. So, persistence is one of the major ingredients, requirements for a successful total synthesis person.

And skill, see experimental skill varies when a first year PhD student does a reaction you know. A particular reaction you will come back and then tell either that reaction did not work or you will say the reaction worked with 50 percent yield though the reported yield will be 100 percent, ok.

So, the experimental skill over a period they you know they get it. So, it is important that you develop the experimental skill over a period by the time you finish PhD, we should have wonderful experimental skill. Why I am saying is at the end of PhD if you say I tried this reaction and that reaction did not work; that means, your supervisor should believe that so and so has tried that reaction and that reaction did not work; that means, nobody even if they try the recursion reaction it will not work.

Because he has such a fantastic experimental skill and still you could not do, still the reaction did not work ok. So, experimental skill play a very important role that can be acquired only over a period of time and it does not come naturally it takes time. And stamina, most of times in synthetic laboratory you have to stand and do the reaction and you can imagine synthetic chemist work very hard. So, its not like 8 hours laboratory work. So, they work much more.

So, they need both physical and mental stamina. Mental stamina also is very important because of the failures which they face. So, they should be very strong mentally and physically. And of course, one should be courageous and they should have character yes I can do it ok, whenever they fail they should get the confidence yes I will do it, I will make it work ok. So, these are the 7 basic requirements for a synthetic chemist to successfully carry out total synthesis, ok.

So, why I am insisting on this 7 important criteria because, unless you have all this or at least most of this it will be very difficult to carry out total synthesis ok, yeah.

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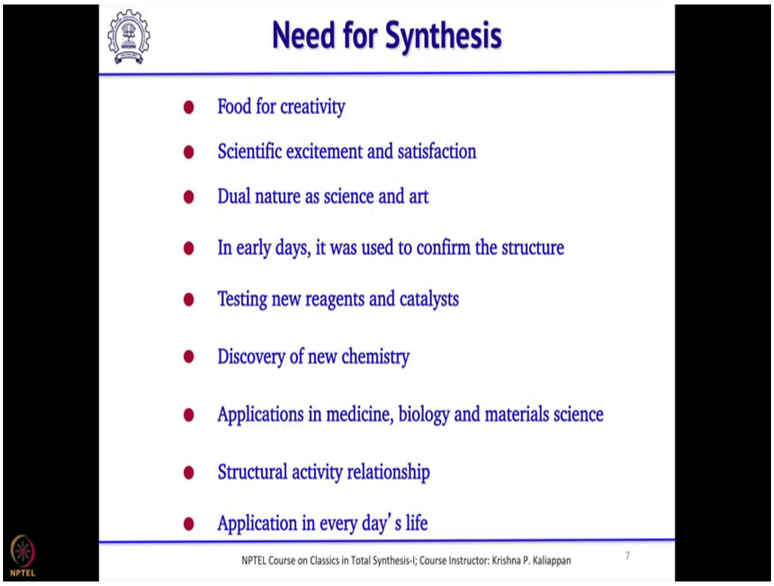

So, now we will move to why we need to do synthesis as for any subject the first question you should ask is why should you do, any branch any discipline any sub any subset. When you have to carry out something first question you should ask why should I do, ok. So, again when you ask why should you do synthesis? Already I told you it is a great place to use your creativity.

If you are highly creative yes in organic chemistry synthesis is the subject you have to work ok. It gives you know so much so many problems and using your creativity you can solve most of them ok. Creativity plays a very very important role. The second one is scientific excitement and satisfaction. See, imagine when you are working on a total synthesis of a natural product ok, what happens?

Nature makes this compound. So, that is why we call it as natural product and same thing you want to repeat that in the laboratory so; that means, you are trying to mimic what nature has done and trying to reproduce in the lab ok. The moment you make that natural product and see the spectra and which matches with the natural product, the amount of excitement and satisfaction you get is encumbered, nothing is you know closely nothing can come close, ok. So, that much excitement and satisfaction you will get.

So, this is very very important if somebody wants to do total synthesis. Then the third point is when you talk about science, when you talk about synthesis, the synthesis is not only science it is also an art. As I mentioned there may be so many synthesis of the same molecule, so many synthesis of same molecule, but still in your textbook only one synthesis will be discussed in details that is because it is not only synthesis.

It is beautifully constructed, the way in which the author thought about the synthesis, thought about the retro synthesis and assemble it. Art you know artistically you would have done it. So, that is why you know the science and art the combination synthesis is a combination of science and art, ok.

So, those who are interested in art those who are interested in science I think synthesis is the place and if you look at the history initially what happened? Earlier as I mentioned in the first in the first lecture the final step of elucidation of structure of any natural product is synthesis ok, they do all destruction, analysis all that degradation. Finally, the structure of the natural product was confirmed by its synthesis ok that is what it was used.

But, later many new reagents, many new catalysts, many new methodologies, many new tactics came into picture then how to test their reagents and catalysts, ok. The best way to test your reagents newly developed reagents, catalysts is to apply in total synthesis of natural product ok. I have made wonderful catalyst, but how do I know that is a wonderful catalyst?

Apply it in very difficult total synthesis, then you can claim yes my catalyst work and my catalyst was used by so and so in the total synthesis and it was the key reaction and it was highly successful ok. So, that is how the testing of reagents and catalysts should be done and even after having so many reactions, so many new reagents, so many new catalysts, some reactions will not work ok and it is very difficult to know why reactions do not work ok.

You can analyze we can you can still find a solution, but still sometimes you do not know, that is where there is a continuous need for development of new chemistry, ok. So, when something do not work you have to keep on thinking how to solve it, how to address it, how to make it work. So, the development of new chemistry parallelly goes along the synthesis of natural product, ok.

The same person can do or somebody else can do the same thing and try to help the synthetic chemist who are interested in the total synthesis of natural product. And needless to say synthesis plays a very very important role in medicinal chemistry, biology and material science and all these places all these areas synthesis contributed a lot to their growth.

Then the major advantage or I should say one of the major advantages of organic synthesis particularly total synthesis is when you make a natural product. Using the same strategy to make the natural product, one can make several simpler analogues or complex analogs of the same natural product and why that would be useful?

That would be useful mainly because when you make the analogs then using structural activity relationship studies you can also remove certain functional groups or you can add some functional groups to the natural product.

You can see whether the functional group x is required or a y is required ok. See if they are not required when you make so many compounds, so many analogs you can finally, you can using the structural activity relationship studies you can say x is not required y is not required, but z is required ok, that way you can simplify the natural product and study the biological properties ok.

And last starting from morning you start with brush and toothpaste and many things which we use in everyday's life is as a result of synthesis. Many times we do not realize, but it is as a result of synthesis.

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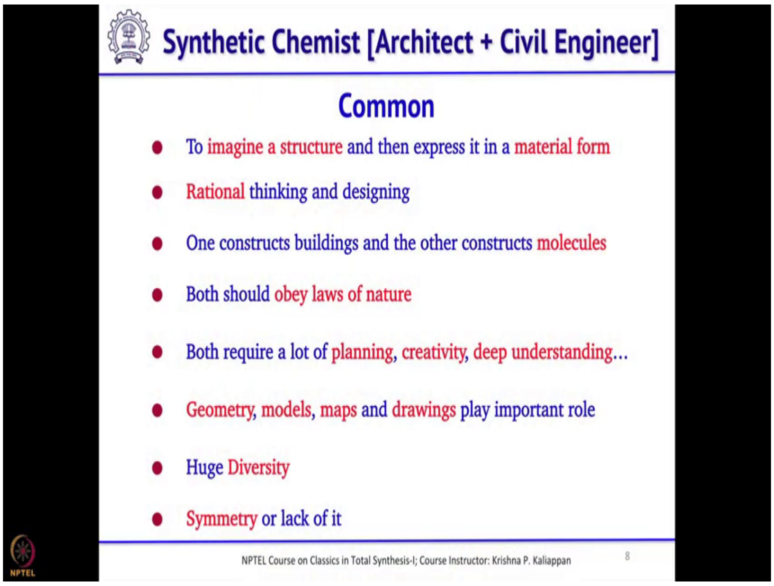

I always compare synthetic chemist it is a combination of architect and civil engineers ok. One can simply equate you know synthetic chemist is a hybrid of architect and civil engineer. There are many things which are common ok. For example, both of them, synthetic chemists as well as architect and civil engineer their job is to imagine a structure ok, this is a structure I want to build ok.

For architect and civil engineer buildings you know they have to imagine a huge building and how they design how they construct whereas, synthetic chemists they have to imagine a structure of a molecule ok, small molecule, big molecule, medium sized molecule, then how they make it, ok.

For both of them the goal is same. Then when you do that your thinking should be logical ok it should be logical while designing as well as executing because when it fails then you also should logically think why it failed and think about alternate strategies ok. So, rational thinking and designing is very important in both cases and civil engineer, architect together they construct buildings huge buildings whereas, poor synthetic chemists construct molecules.

But it is equally difficult. The reason is at least architects and civil engineers they can see the molecule see the building whereas, synthetic chemist they cannot see the building see the molecule real molecule, they can only see the structure you know assume this is the structure they have to make.

And of course, you have to obey law laws of nature otherwise nothing will move and needless to say both require lot of planning see planning is very very important before you start executing and when you plan lot of creativity goes in and understanding of the subject is very important.

And finally, execution, execution is very very important. You can have all three wonderful planning with high level of highest level of creativity and deep understanding of the subject, but those who execute those who execute your plan if they do not do it properly the whole thing will go back ok.

So, that is why it is very important all the 4 pillars of this are very very important and both synthetic chemist, architect, civil engineer they use geometry, models, maps, drawings etc. then only you know they can achieve whatever they want to achieve. From synthetic chemist point of view also the diversity is really huge because so many natural products around ten thousand natural products are being isolated every year, ok.

So, there when you talk about 10000 then obviously, you know the diverse natural products and similarly when you see the number of buildings even in Mumbai if you see so many types of building huge diversity, ok. So, diversity is there when you have so much diversity automatically the thinking, the designing everything is different, ok. The creativity you know you have to be very creative to have diverse thinking and execution, ok.

But there are few things which are not common and the last thing which is common is symmetry or lack of it. You see many buildings which are very symmetrical and you also see many buildings which are not symmetrical. Likewise, you see many natural products having some symmetry, but most of the natural products do not have any symmetry.

So, both give enough challenges for synthetic chemist as well as civil engineer and architect to construct. What are the major differences?

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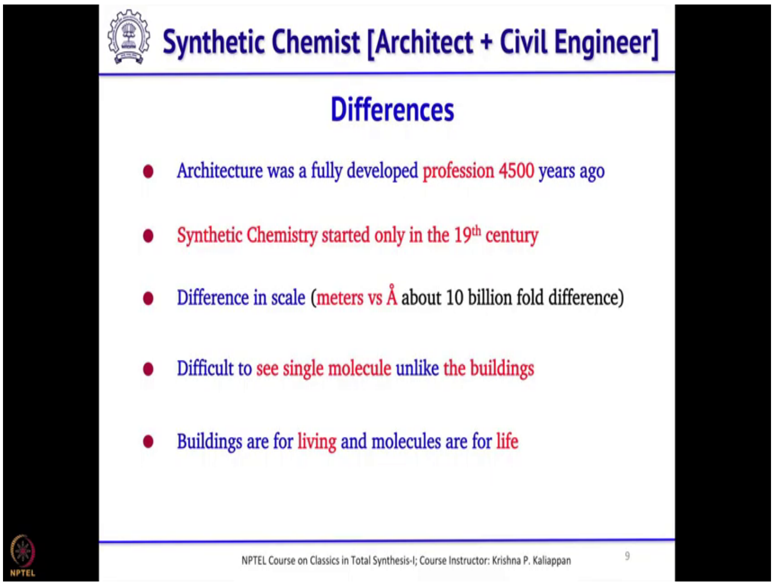

The major differences if you see the architecture was very nicely developed and fully developed profession about 4500 years ago, ok. But when you talk about synthetic chemistry or organic synthesis it started only in 19th century, it started only in 19th century.

As you know the first synthesis was reported by Wohler on urea and the second the third major difference is the scale, when you talk about building you talk about buildings in meters whereas, when you talk about molecule the scale is angstrom. The difference is about 10 billion fold that is a huge difference is not it meters versus angstrom 10 billion fold.

Then you can see buildings is not it, even model one can see the buildings whereas, for a synthetic chemists it is very difficult to see single molecule with his naked eye. Though there are now spectroscopic techniques one can try to see a single molecule lot of efforts have gone in the last 2 to 3 decades to see a single molecule, but for most of us it is still you know far away subject to see a single molecule unlike architect and civil engineer who can see the buildings and accordingly they can visualize.

So; that means, that much difficult for synthetic chemist to see and then make the molecule and last, but not least the major difference is when you construct building the buildings are meant for living is not it. When you construct a building all the buildings are for living whereas, when you make molecule when you make molecules, molecules are for life. So, these are the major differences between synthetic chemist and combination of architect and civil engineer.

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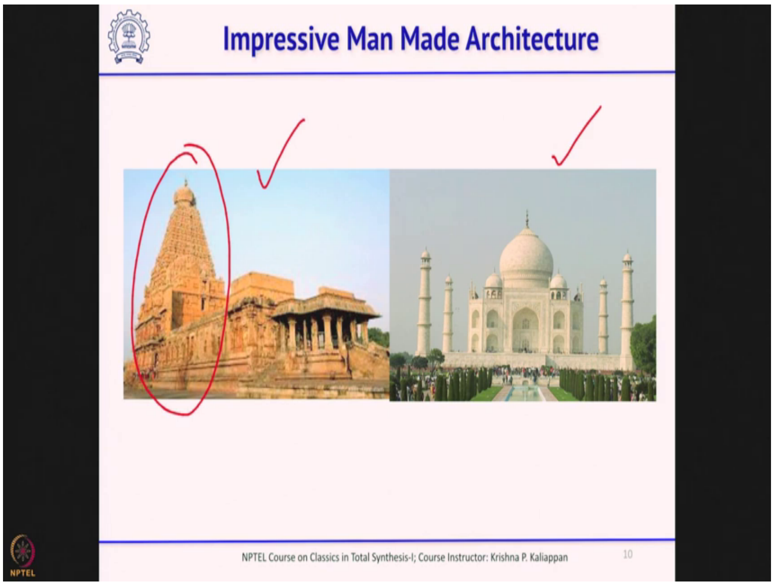

So, here I show two important man-made architecture. I had an opportunity to visit both the places a few years ago hm. So, this is a place called Thanjavur or Tanjore, it is more than a 1000 years old still maintain its a UNESCO certified place and the other one I am sure all of you know it is Taj Mahal, these are all very very impressive man-made structure. There are many such man-made structures in India just I am showing only two places where I have gone and took these two pictures its wonderful ok.

See this tells the creativity man's creativity, how one can be creative and construct buildings ok. So, when you talk about symmetry you can see Taj Mahal, you can see a clear symmetry ok and similarly you can see symmetry in the tower of Tanjore, Tanjore temple, ok. Huge accomplishment huge accomplishment several centuries ago ok, several centuries ago we are much ahead of others in terms of architecture and construction ok.

So, I will stop here for today's lecture and I will continue this introduction in the next lecture. So, here in to summarize in this lecture what we discussed is what are the basic requirements to become a synthetic chemist and why we need to do synthesis and how a synthetic chemist can be compared with an architect and civil engineer, ok.

So, now we will we may need one more lecture on introduction, ok. So, we will continue our discussion in the next class and complete the introduction and we will move to natural products having three-membered ring ok.

Thank you.