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Student-Faculty Research in Organic Chemistry

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Honors and Awards Assembly 2011
April 27, 2011
Remarks by Timo Ovaska, Hans and Ella McCollum '21 Vahlteich Professor of Chemistry

Good evening everyone and thank you, Dean Brooks, for the nice introduction. I would like to begin by thanking professor Stan Ching and the chemistry department for nominating me for the 2010 Nancy Batson Nisbet Rash Research faculty award. I feel honored and humbled for having received this award and it really means a great deal to me.

Well, I know that this award ceremony isn't about me; it is about all of you who have won various honors and awards for your academic achievements. However, I simply can't resist the temptation to spend a few minutes telling you about science and my research, and I *will* do my part to try and demystify the subject of organic chemistry, which, especially as far as college courses are concerned, has a reputation of being somewhat, should I say, challenging ... At least if one is to believe a certain article that recently appeared in The College Voice! I'm also going to show you a few slides throughout this presentation, so if you get bored at least you have something to look at and you can keep yourselves entertained that way.

I think it goes without saying -- and I might be a just a bit biased about this -- that organic chemistry is an extremely important field, and if you really stop and think about it, organic chemistry and organic molecules really are all around us. The clothes we wear, the colors we see, the foods we eat, the fuels that power our cars, the medicines that make us heal and feel better, even the biochemical reactions that happen in our bodies at this very moment are all manifestations of the importance of organic chemistry in our daily lives.

Just like most students who start their college careers today, I had no idea that I would ever become an organic chemist until I took my first organic chemistry course in college. I found the subject utterly fascinating and I couldn't wait to learn more. I was definitely hooked. However, most of my classmates, for reasons I still don't understand, did not share my enthusiasm for the topic and wondered what was wrong with me! But for me, this started a journey that led me to pursue a career in organic chemistry both in research and teaching - a journey that has continued up until this very day.

Now, let's turn our attention to the screen to my left. [slide] When a biologist looks at this scenery, he or she would not only see a nice tropical vacation spot but also an environment that is teeming with life, animals, plants, microbes and so on. When an organic chemist looks at this picture, he or she might go a bit further and marvel at all the wonderful organic molecules that the various organisms are capable of producing.

I have always been intrigued by natural products, which are simply organic molecules produced by different organisms in various environments. The question is, who cares, what is the big deal? Why are they important?

It turns out that medicine and natural products have a very long history that dates back to the dawn of civilization and far beyond. In fact, herbal medicine is the oldest form of healthcare known to mankind. Centuries ago, tribal healers and medicine men knew how to use certain plants and herbal extracts to help cure infections, aches, and other diseases. Many of these extracts have now been analyzed and the organic molecules responsible for their healing properties have been isolated and identified.

It is true that even today, most medicines have their origins in natural products. A recent study published in the *Journal of Natural Products* reveals that around 70 percent of all new drugs introduced in the past 25 years in the U.S. have been derived from natural products.

Of course there are many natural product-derived compounds that became drugs long before the 1980s. For example, we all know about Sir Alexander Fleming's accidental discovery that a certain fungus growing on a petri dish inhibited the growth of bacteria.

This ultimately led to the isolation and identification of penicillin, which, at the time, was hailed as a miracle drug that saved thousands of human lives. Of course there are numerous other examples I could talk about if I had more time.

So where else do natural products come from?

I already mentioned medicinal plants, which can be found just about anywhere on earth. Some 120 prescription drugs sold worldwide today are derived directly from rainforest plants alone. Then there are animal sources, and of course the microbial world - bacteria and fungi which have yielded a great variety of medicinally important compounds over the years.

Perhaps the least known of the four sources listed here is last one; the marine world. The marine environment is probably not the first thing that comes to mind when you think about where drugs come from. And there is a good reason for that. Historically, it has been - and still is - a lot easier to collect plant species and microbial samples from dry land than it is to collect samples of marine organisms, many of which reside in very inhospitable places - often a thousand feet or more below the ocean's surface, so it has been very difficult to get to them. However, with advancements in technology and engineering, more and more of this type of exploration is taking place now and it is fair to say that the marine environment represents a new frontier in natural product-based drug discovery. As new species from the deep oceans are discovered, scientists are also able to identify new chemical entities and study their medicinal properties. In fact, a whole host of novel marine-derived natural products are currently in clinical trials and a few have already made it to market.

Where does organic chemistry fit into all of this? It turns out that the supply of bioactive compounds from natural sources is very often a big problem. It certainly was a problem for this recently approved anticancer drug, Yondelis, which comes from a sea squirt [slide] whose picture you can see on this slide. A whole metric ton of the sea squirt is needed to extract just one gram of the bioactive compound, and some five grams of the material were needed for the initial clinical trials. It goes without saying that harvesting that amount of the organism simply isn't feasible without practically wiping out the species.

Clearly, help from organic chemists was needed, so a group of chemists from Harvard University took on the task of designing and carrying out a lab synthesis of the compound. Of course performing a lab synthesis of something this complicated from scratch is certainly not easy, there is a lot of trial and error involved, and in this case the process took several years to complete. But at least through chemical synthesis there is a chance to scale up the process and ultimately produce large amounts of the required material without having to harm the organism that makes it in nature. In addition, laboratory synthesis offers possibilities for the preparation of close analogs of the natural product which may have even better biological properties than the actual natural product itself. That is very often the case.

While I'm interested in all kinds of natural products, let me tell you a bit about our own efforts in the area of marine natural product synthesis. In recent years, we have spent quite a bit of time and effort trying to devise viable synthetic routes to a class of marine natural products which are derived from sea sponges. Sea sponges are very interesting creatures that come in all kinds of shapes, colors, forms and sizes. Some grow very large; the one in this picture [slide] is big enough for the diver to easily fit inside of it.

My guess is that all of you have probably seen and even used sea sponges at some point in your lives, like the one I have brought with me here this evening. This one is obviously quite dead and all dried up, but it is great for all kinds of washing purposes.

Turns out some 5,000 different sea sponges are currently known, and while many of them are great for bathing and cleaning purposes due to their unique texture and water absorbing ability, many of them also produce extremely interesting biologically active compounds, most of which the organisms synthesize to fend off their natural predators.

The class of marine derived products I'd like to tell you about is called frondosins, which were initially isolated from the Micronesian sponge Dysidea frondosa. Their chemical structures are shown here, in case you're interested. [slide] These compounds exhibit interesting biological properties ranging from anti-inflammatory to anti-HIV and even potential anti-tumor activity. As such, they represent attractive targets for chemical synthesis.

In order to put together the necessary ring structures, we had to first develop some new chemistry that allowed us to construct the seven-membered ring systems which are central to all of the compounds in this class and, in fact, to many other classes of natural products as well.

Unfortunately this type of ring size is difficult to access synthetically in the lab using existing methodologies. Without going into a lot of technical detail, suffice it to say that we were, in fact, able to develop a highly efficient cascade strategy that allowed us to arrive at these types of ring structures using readily accessible starting materials and microwave irradiation. We do this in what we call a one-pot sequence, which enables us to get to the desired reaction products without having to isolate any of the intermediates. So one might liken this type of strategy to a cascading waterfall where each pool is like a reaction intermediate that serves as a new starting point for the next fall or reaction.

Anyway, using this type of strategy in combination with other chemical transformations has allowed us to prepare three of these natural products in our laboratory so far. We are also making good progress toward the synthesis of the Frondosin D, which possesses promising anti-HIV activity, as well as Guanacastepene A, which is a novel antibacterial agent that comes from a different class of compounds. It has taken us about seven years and lots of external funding to get where we are, so I am obviously not telling you the whole story. I could go on for hours telling you about all the work that we have done, but don't worry; I decided not to do that this evening!

Suffice it to say that along the way, we have been able to prepare a large number of previously unknown compounds, even close analogues of these natural products. Some of these compounds may turn out to have more therapeutic potential than the actual natural products themselves. Also, by being involved in this work we have been able to advance the science of organic chemistry, which is important in its own right, certainly from an academic perspective.

I am the first one to admit that the work that I just briefly described for you would not have been possible without the contributions of all the students who over the years made the commitment to take on independent research under my direction. I am deeply indebted to them. On the slide shown here, I have collected pictures of a small fraction of my students from the past and present; these are certainly faces that I will always remember. [slides] As the saying goes, it is easy to sit up and take notice. What is difficult is to stand up and take action. My students did exactly that; they stood up and took action by voluntarily choosing to get involved in organic chemistry research. Imagine that!

It is true. There is no mandatory research component for the chemistry major at Connecticut College. They chose to get involved not because it was going to be easy but because they were genuinely interested, they had the to desire to learn more than they would simply by going to class, and although they knew it would be a lot of work, they were up for the challenge.

Indeed, anybody who has worked in my lab, or any other organic chemistry lab for that matter, knows that synthetic organic chemistry is very labor intensive, hard work. It takes considerable effort to get good at it; the learning curve is very steep. The nature of this work is such that most of the new reactions we try typically fail. And while it can be discouraging at times, there ARE those occasional moments of success, and it is the unexpected results that we often learn the most from.

So, the path to success in the field of synthetic organic chemistry is not easy, it’s an uphill battle, it requires well-defined goals, commitment, the right approach, a solid foundation, and one simply can’t quit. The work involves a lot of failures, but we learn from them, and it is just plain tiring sometimes. BUT there are those occasional moments of triumph that make it all worthwhile.

For me personally, teaching and research is one unified activity where the concepts learned in the classroom are reinforced and taken to a completely new level where we always discover something new. I think that’s what makes being involved in active research so exciting; it’s contagious and students quickly become part of it. What starts out as a typical teacher-student relationship usually progresses to a stage where I regard my students more like my co-workers who share a common goal and very often I learn from them just as they learn from me.

Many of my former students have themselves become successful chemists after graduating from Connecticut College. I’d like to point a few of them for you now. People like Jamie Tuttle, who first worked at Pfizer as a research scientist but then decided to go back to school to earn his Ph.D. Pfizer quickly hired him back and he is now in charge of developing new medications to treat schizophrenia and Alzheimer’s disease.

Another person I would like to mention here is Sarah Reisman, who after graduating from Connecticut College in 2001, went to Yale for her Ph.D., then continued on to Harvard University for her post-doctoral work and recently landed a job as an assistant professor of organic chemistry at California Institute of Technology. In the short time of less than three years, she has built a dynamic research program there, focusing on the synthesis of complex bioactive natural products. I am very proud to report that she is doing extremely well.

Obviously, there have been many other successful individuals from my lab who ultimately decided to pursue areas other than chemistry. Like Jon Roses, who, after working as a chemist for several years, decided to pursue a law degree. He is now a patent lawyer in the Boston area. Jessica Lee and Kerrin DePeter are medical doctors, and Cait Macintosh became a veterinarian. Needless to say, I am very proud of all of them.

I am personally convinced that working in a research environment offers benefits that go beyond the obvious, such as gaining further insight into the discipline, perhaps getting your name in a publication as a co-author and providing better chances to get into the very best graduate programs in the country. Although all of the above are important, there is much more to it. Being involved in research builds character. It teaches patience and persistence. It teaches one to be an independent thinker, to have a positive and optimistic attitude (next time it will work!) When reactions don't work as anticipated, there always needs to be a Plan B, a back-up plan. Isn't that true in everyday life as well!?

Conducting research also encourages one to be adventurous and bold, to try something new that may open up new avenues. It teaches that one must be well-informed in order to make good decisions; one must know the facts. It also teaches that the results, whatever they are, must be carefully analyzed, and the loose ends need to be tied up. Whatever happens, positive or negative, something can always be learned from what was done. Working in a lab setting with other people also promotes teamwork and individual responsibility within a team environment. It is important to able to get along with others, and most importantly, to clean up your mess and do your own dishes! These clearly are principles that apply to nearly all aspects of life.

The fact that you are being honored this evening means that you didn't just sit up and take notice either; you stood up and you took action. You are here because you didn't want the easy way out; you didn't choose the easiest courses from the course catalog.

Instead, you wanted to challenge yourselves, you put in the extra effort and you went the extra mile. That's why you have succeeded and that's why you are being honored here tonight. For me personally, nothing is more rewarding than to see my students succeed, and I am 100 percent certain that this sentiment is shared by our entire faculty here at Connecticut College and we are so very proud of your achievements.

Finally, my advice to you would be to keep doing what you do and make the most of your remaining time here at Connecticut College. Continue to stand up and take action, get involved in research, if you are not already, or other academic pursuits that go beyond the classroom setting. Take a chance and you never know where you will end up.

But tonight, enjoy the moment, give yourself a pat on the back, and think of this award as one of the many awards and successes that will come your way in the years ahead.

Again, congratulations!