Young Career Focus: Professor Jeremy Wulff (University of Victoria, Canada)

Background and Purpose. From time to time SYNFORM meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Professor Jeremy Wulff (University of Victoria, Canada).

Biographical Sketch

Prof. J. Wulff

Jeremy Wulff is originally from Vancouver Island (Canada), and completed his BSc at the University of Victoria (UVic, Canada) in 1999. He then undertook PhD studies at the University of Calgary (Canada) with Professor Thomas Back, and postdoctoral work at Harvard University (USA) with Professor Andrew Myers before returning to UVic as an independent investigator in 2007. He was promoted to Associate Professor with tenure in 2013.

Dr. Jeremy Wulff holds a Michael Smith Foundation for Health Research Career Investigator Award, as well as the Tier II Canada Research Chair in Bioactive Small Molecule Synthesis. His research program revolves around organic synthesis and medicinal chemistry.

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Prof. J. Wulff My group is most excited about making interesting organic compounds that have useful biological functions. I'm fortunate that my laboratory space at the University of Victoria includes both a well-equipped synthetic lab for making complex molecules, and a class II biosafety lab for studying the biological effects of our final compounds.

SYNFORM *When did you get interested in synthesis?*

Prof. J. Wulff I've always enjoyed making things. When I'm not doing science, I build new decks and sheds around our house, and also spent a few years' worth of 'free' time making a 17-foot cedar strip kayak with a friend. The joy that comes with creating new things has always been a driving force for me.

I didn't set out to be a chemist. But in the 2nd year of my undergraduate studies, I suddenly realized that a person could ***make molecules*** and I was hooked for life. For the next several years, I devoted all of my energy to learning how to be a better molecule maker – participating in several undergraduate research projects in both academia and industry before finally doing a total synthesis PhD with Thomas Back at the University of Calgary.

Eventually I became just as interested in what those molecules could do. In my postdoctoral work with Andrew Myers (Harvard University) I took on a chemical biology project that required me to learn an entirely new field. I'd never done so much as a high-school biology course, but before I knew it I was culturing cancer cells, running Western blots, expressing proteins, spending days camped out in front of a flow cytometer, and even designing my own biological assays. When it was time to set up my own lab, this experience was invaluable in allowing me to craft a unique research program.

SYNFORM *What do you think about the modern role and prospects of organic synthesis?*

Prof. J. Wulff Organic synthesis has so much to offer the world! Every aspect of biology and medicine requires new molecules and synthetic techniques in order to move forward. Just think of the tremendous impact that automated peptide and polynucleotide synthesis has had upon the practice of biological science. Not to mention the impact of the polymerase chain reaction (PCR), which is really just a fancy implementation of supramolecular chemistry (annealing) and enzymatic synthesis (chain extension).

Much has been said about how the trend in the pharmaceutical industry toward the use of therapeutic antibodies or RNAi to control protein function will lead to a decrease in the importance of the traditional practice of small-molecule-

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based medicinal chemistry. But this ignores the fact that such agents are prohibitively expensive and (for technical reasons) don't become 'generic' as easily as small-molecule drugs. For a number of reasons, small molecules will always be better drugs than antibodies. And someone will always have to know how to make them.

Having said that, it's worth acknowledging that organic synthesis has not experienced the kind of 'quantum leaps' that have occurred in other fields. People doing biochemistry or high-energy physics right now are carrying out experiments that would have been unimaginable a couple of decades ago. And that's simply not the case for us synthetic chemists (despite what one might believe from the bombastic titles of our papers). To really unlock the potential of organic synthesis will require a paradigm shift in transform predictability and synthetic efficiency.

SYNFORM *Your research group is active in the areas of total synthesis and bioorganic chemistry. Could you tell us more about your research and its aims?*

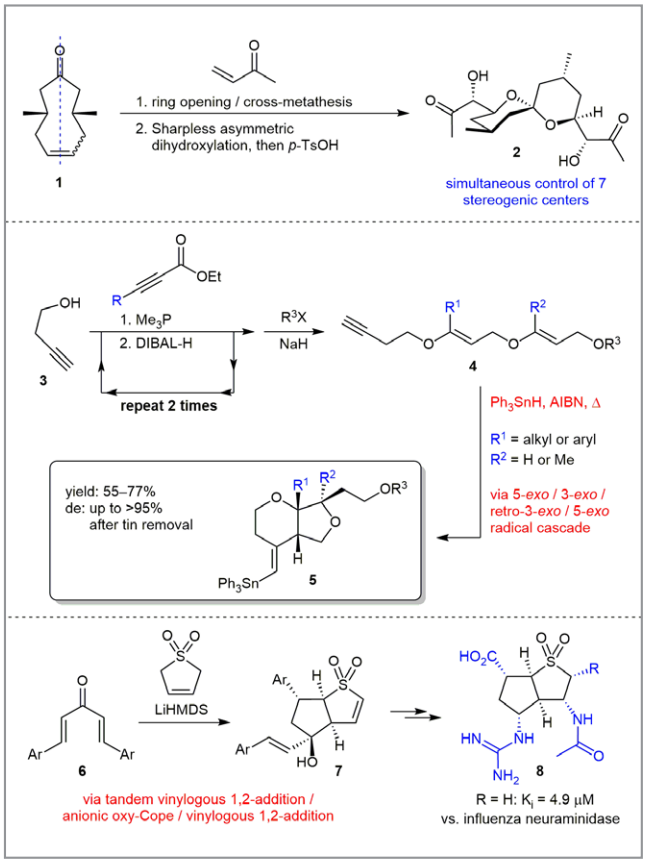
Prof. J. Wulff One of the things that architecturally complex molecules have going for them is their intrinsic molecular rigidity. I'm fascinated by the idea of exploiting this rigidity as a way to precisely control biology. We therefore look for targets where we can (1) create an efficient tandem or cascade synthesis of a complex, functionalized core of some defined molecular geometry; (2) decorate the core with functional groups necessary for engagement with a biological system; and then (3) use the resulting molecule in a medically relevant problem of biological control.

Some of our targets are natural products. For example, we recently developed a cascade to transform *meso*-cyclononenone **1** (possessing no absolute stereochemistry) into the functionalized, rigid core of didemnaketal A, a molecule thought to function as a dissociative inhibitor of HIV-1 protease.[1]

Other times our targets are non-natural structures that we design for specific purposes. For example, we described an iterative synthesis of oligovinyl ethers (**4**)[2] that we could subsequently use as substrates in a radical cascade reaction to access functionalized bicycles **5**.[3] We envision that related transformations will lead to oxasteroidal molecules with a range of interesting biological properties.

SYNFORM *What is your most important scientific achievement to date and why?*

Prof. J. Wulff Probably the clearest example of what we're trying to do has been our sulfone-based neuraminidase inhibitors. These came about through our discovery of a novel tandem reaction that couples bis-vinyl ketones (**6**) and simple cyclic sulfones to provide rigid, orthogonally functionalized sulfone bicycles.[4] These can be further decorated to achieve, among other things, molecules like **8** that mimic the enzyme-bound state of the potent antiviral agent peramivir.[5,6]



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