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University of Zürich Hosts Symposium in Honor of Dr. Albert Hofmann: Scientist and Scientific Inspiration

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From left to right: Prof. Jiali Gao, Prof. Jonathan Spencer, Prof. Ted Molinski, Dr. Albert Hofmann, Prof. Jay Siegel, Prof. Kim Baldridge, PD Nathaniel Finney, Prof. John Robinson, Simon Duttwyler (grandson of Dr. Hofmann, a doctoral student in the OCI). Photo by Dr. Osmialowski.

On Friday, 27 January, the Organic Chemistry Institute of the University of Zurich hosted a ***symposium in honor of Dr. Albert Hofman's 100th birthday***. Dr. Hofmann received his PhD from the University of Zurich in 1929 for his pioneering work with Karrer on the determination of the chemical composition of chitin and chitosan. He obtained the enzymes required to degrade these biopolymers from snails he collected by hand from a neighbor's vineyard – an early example of what would become his lifelong passion for the chemistry of the living world. This beginning led to more than 40 years of natural product isolation, characterization, and synthesis at Sandoz AG (now Novartis), during which time he discovered LSD and numerous other important biologically active substances. He retired in 1971 as the head of the natural products department. As the discussion at the Symposium clearly illustrated, Dr. Hofmann retains a keen interest in natural product chemistry. Equally clear, however, was the range of his other interests: a computational talk was included in the Symposium at his request – "to make sure he learned something new" – and he noted with pleasure that Friday was also the 250th anniversary of Mozart's birth.

The Symposium covered the entire span of modern natural products chemistry, with lectures on computational modeling of rhodopsin and steroid cyclases (Prof. Jiali Gao,

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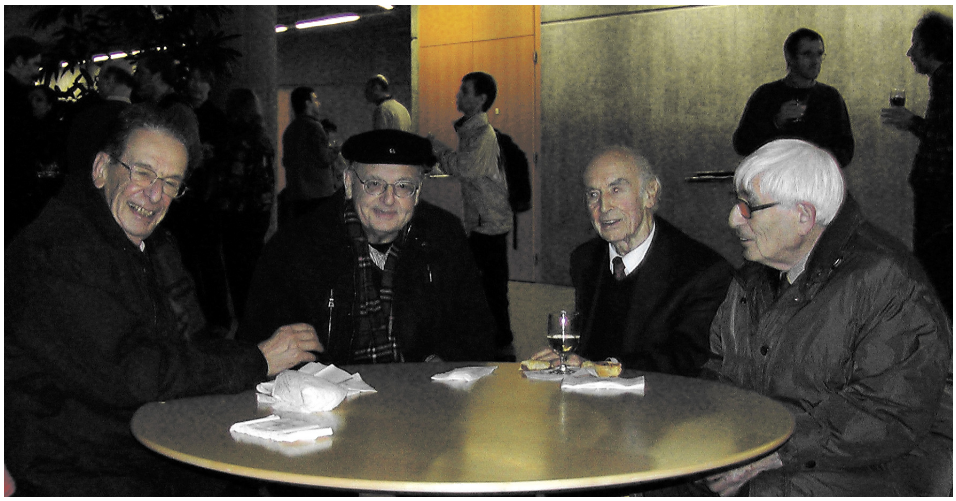

Dr. Hofmann with Prof. em. D. Arigoni, Prof. em. A. Eschenmoser, Prof. em. J. Dunitz. Photo by Herr Hofmann

University of Minnesota), the dissection of metabolic pathways for polyketide synthesis (Prof. Jonathan Spencer, University of Cambridge) and the integrated use of circular dichroism, NMR and partial synthesis in natural product structure determination (Prof. Ted Molinski, University of California, San Diego).

Prof. ***J. Gao*** provided a detailed description of computational efforts in his group to address aspects of protein structure and function that cannot be studied by direct spectroscopic methods. Proteins are too large to treat entirely with current *ab initio* methods, and Gao and coworkers have instead developed a hybrid quantum mechanical/molecular mechanics (QM/MM) approach to handle such systems. The QM/MM approach treats most of the protein using computationally inexpensive MM methods while focusing the computationally-intensive QM treatment on the portion of the protein that is of greatest interest. The power of this approach was illustrated by recent results that explain how small changes in the structure bacteriorhodopsin proteins lead to dramatic changes in the absorption maxima of the bound chromophore, and how surprisingly subtle factors can influence the balance between thermodynamic and kinetic control in sterol cyclases.

Prof. ***J. Spencer*** provided an overview of how the tools of molecular biology can be used to study the chemical mechanism of polyketide biosynthesis and the subsequent oxidation and cyclization of polyketides to complex natural products. As a specific embodiment, Spencer described a recent collaborative effort that has revealed the order of events in the biosynthesis of monensin, an ionophore antibiotic of great practical and academic interest. Following the stepwise assembly of a densely functionalized linear 'prepolyether' containing three trisubstituted alkenes, a series of enzymes enantioselectively epoxidize the polyene and chaperone an electrophile-induced cyclization cascade to form the polycyclic product. Selective stepwise deletion of the genes for the enzymes both established the individual role for each enzyme and revealed for the first time the stereochemical configuration of the polyene intermediate. This molecular-level understanding of the biosynthetic pathway opens the door for metabolic engineering to produce novel 'monensin-like' antibiotics that may have improved activity against drug-resistant bacterial strains.

Bringing the Symposium full circle, Prof. ***T. Molinski*** described efforts in his laboratory to harness the combined power of modern spectroscopy and 'partial' synthesis for the determination of natural product structure. With the newest generation NMR instruments allowing analysis of nanomoles of material, and mass spectrometry methods more sensitive still, it is easier than ever to map out the basic connectivity of newly isolated natural products. However, assigning the relative and absolute configuration of a compound of interest is often still a significant challenge, especially as the amounts of material in question are so miniscule that X-ray crystallographic analysis is not an option. NMR coupled with computational modeling can often provide a partial assignment of relative configuration. However, definitive assignment can only be made by the synthesis of all of the possible diastereomers and direct comparison of the spectroscopic properties. This daunting synthetic challenge is simplified by the fact that total synthesis of the natural product is not required, but rather just partial synthesis of the portion of the molecule containing the unresolved stereochemistry. This partial synthesis approach, when combined with the remarkable sensitivity of circular dichroism, also allows the assignment of absolute configuration.

The Symposium was followed by animated discussion and an apéro. The OCI would like to express its appreciation to the speakers for their outstanding presentations, the KGF for generous financial support, and the chemistry community of Zürich for enthusiastic participation in paying tribute to Dr. Hofmann.

The OCI will host three additional symposia in 2006: the Dorothy Crowfoot Hodgkin Symposium (May); a Symposium in Honor of Prof. Heinz Heimgartner (June); and the Siegfried Medal Symposium (September) (see *http://www.oci.unizh.ch/group.pages/baldridge* for details).

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