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Chemical Biology and Synthesis

The Spring Meeting of the Swiss Chemical Society, March 10th, 2005, Department of Chemistry and Biochemistry, University of Bern

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Abstract: The 2005 Spring Meeting of the Swiss Chemical Society was held at the University of Bern on March 10th, 2005. The one-day symposium was dedicated to recent advances in chemical biology and synthesis. The four speakers, Dennis P. Curran, Johann Mulzer, Scott Miller, and Samuel Danishefsky covered a wide range of modern organic chemistry emphasizing "the formidable power of chemical synthesis" (Danishefsky) to investigate biologically relevant problems.

Keywords: Chemical biology · Drug discovery · Fluorous chemistry · Organocatalysis · Total synthesis

The Spring Meeting of the Swiss Chemical Society took place in Bern on March 10th, 2005. The organizing committee, composed of *Robert Häner*, *Christian Leumann*, *Philippe Renaud*, and *Jean-Louis Reymond*, chose the general title of 'Chemical Biology and Synthesis' for this one day meeting. This orientation corresponds to one of the main research topics ('Molecular Foundation of Biological Processes') at the Department of Chemistry and Biochemistry of the University of Bern.

The first lecture of the 2005 Spring Meeting, entitled 'Making Natural Product Libraries by Fluorous Mixture Synthesis' was given by ***Dennis P. Curran*** (University of Pittsburg). One of the major focuses of his group concerns fluorous organic chemistry and more particularly fluorous mixture synthesis. Dennis Curran began by presenting the potential uses of fluorous reverse phase silica gel in a solid-phase extraction mode to separate fluorous-tagged compounds from non-fluorous organic compounds, and in a chromatographic mode to purify and separate mixtures of organic compounds tagged with different fluorous tags. With this new tool at hand, they developed the technique of 'fluorous mixture synthesis'. The synthesis of both enantiomers of mappicine and pyridovericin using the 'quasiracemic synthesis' was presented. A very efficient synthesis of a 560 mappicine library using a tagging strategy was used to highlight the potential of the method. Interestingly, the fluorous mixture synthesis allows a rigorous characterization and analysis of target products from a mixture and is highly suitable for elaborating high quality libraries for structure–activity relationship studies in medicinal chemistry, natural product synthesis, or other chemical discovery settings.

Johann Mulzer (University of Vienna) followed with his presentation on 'Success and Failure in the Synthesis of Polycyclic Natural Products'. His group is interested in asymmetric synthesis of natural products to prepare material for biological testing and to develop novel synthetic methodologies and to elucidate reaction mechanisms. In the first part of this talk, he focused on the total synthesis of epothilone B discussing the stereochemistry control of the (*Z*)-

Dennis Curran describing the efficacy of fluorous mixture synthesis

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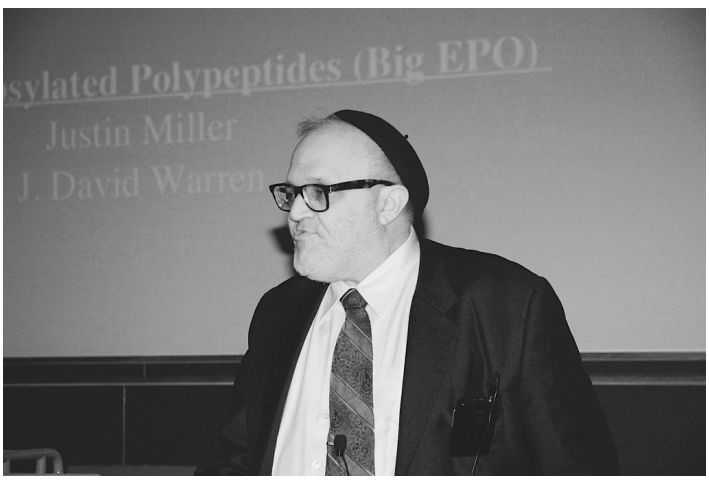
An enthusiastic audience

12,13 double bond. In the second part of his talk, he presented the total synthesis of laulimalide by proposing a strategy that takes into account the high instability of laulimalide under basic and acidic conditions. A superb use of the Sharpless asymmetric epoxidation taking advantage of the presence of two allylic alcohols with opposite topicity allowed him to prepare the natural product with very high regio and stereocontrol. The preparation of isoprostanes and kendomycin were described in the last part of the lecture. Mulzer's presentation was particularly instructive since the difficulties encountered during the synthesis of these complex natural products were clearly described and proved to be a motivation of the development of original solutions.

Scott Miller (Boston College) spoke about 'A Biomimetic Approach to Asymmetric Synthesis'. He and his group seek to discover new reactions and to apply new principles to the selective synthesis of complex molecules by utilizing the architecture and design principles presented by biologically relevant structures and processes. Miller's talk was focused on peptide-based catalysts like histidine-derived peptides, which offer intriguing analogies to enzymatic systems. He studied their efficiency as asymmetric acylation catalysts for the kinetic resolution of a variety of racemic secondary alcohols. Asymmetric syntheses of phosphatidylinositol-3-phosphates with saturated and unsaturated side chains through catalytic asymmetric phosphorylation were presented. Another application concerns the synthesis of chiral sulfinates by sulfinyl transfer using a unique dynamic resolution process. Finally, demonstration was made that such peptide catalysts are suitable for the catalysis of an enantioselective Stetter reaction. All together, Miller's examples suggest that the field of organic synthesis and enzymology has curious intersections.

The last lecture entitled 'Total Synthesis in Drug and Vaccine Discovery: The Quiet Revolution' belonged to ***Samuel Danishefsky*** (Columbia University and Sloan-Kettering Institute), who began his talk by answering the question "Why chemical synthesis of complex molecules?" It's not only to share challenges but also to find new methodologies and to develop creativity. It is a medium for the discovery and development of new drug possibilities as well. During his lecture, he attempted to suggest the implications of creative interfacing of the unsurpassable 'wisdom' of natural products with the formidable power of chemical synthesis. This was illustrated by taking epothilone macrolides, potential agents in cancer, as an example, and notably 12,13-desoxyEpo B which has already been advanced to late phase I and phase II clinical trials. During his talk, he showed us the way they designed a second-generation epothilone which will have more pharmacostability in human than dEpoB and will exhibit a clinically and readily exploitable therapeutic index. Emphasis was put on the fact that all the different candidates were obtained through total synthesis and therefore demonstrated the interactivity between chemical synthesis and drug discovery. Danishefsky's talk underscored the potential applicability of directed total synthesis, even in a multistep setting, in the quest for new substances of material clinical benefit.



Samuel Danishefsky explaining the formidable power of chemical synthesis

In the closing remarks, *Philippe Renaud* emphasized the high quality of the four lectures as well as the excellent attendance of the meeting by academic and industrial researchers. The success of this meeting is closely related to the generous financial support obtained from industrial partners as well as the organization support from the Division Chemical Research of the Swiss Chemical Society.

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