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Highlights from the 37th ESF/EUCHEM Conference on Stereochemistry, Bürgenstock, Switzerland, April 2002

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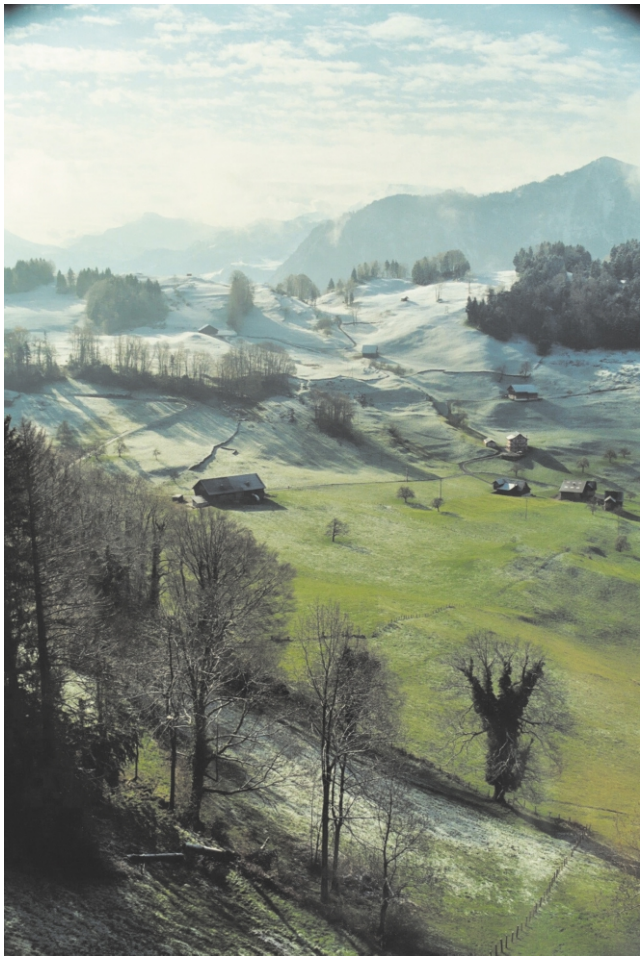
Fog of proverbial British quality surrounded the Bürgenstock, a peak on the fringe of Vierwaldstättersee facing Lucerne – fitting natural conditions for a conference, where the invited participants know neither who else is coming nor what the exact programme will be. Only the broad (and hence wisely chosen) title, 'Stereochemistry' stands clear for now over 40 years. Every year it is redefined, by some 20 speakers who shed light on what they see integral to the theme allowing the conference to evolve steadily to encompass aspects of 'stereochemistry' beyond its original organic home turf in biology, materials science and polymer chemistry. This year the President, Lia Addadi, and the Organising Committee year put together an excellent programme and this article highlights the key features of the scientific programme all the way from synthesis to the interface of chemistry with biology and materials.



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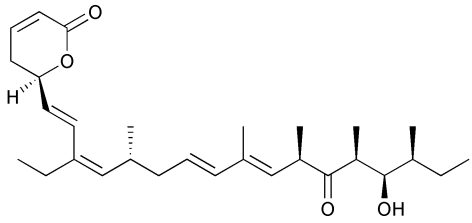

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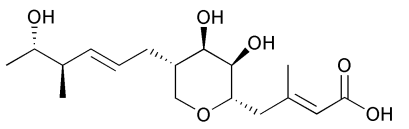
The synthetic chemistry element started with a tour de force lecture by **Mark Lautens** (University of Toronto) on new metal-promoted reactions and their utility in organic synthesis. He presented a new synthesis of callystatin A (**1**), a natural product used in the treatment of human epidermoid carcinoma. The main feature of his approach was the exploitation of the metal-mediated ring opening of [3.2.1]oxazabicycles to prepare the polypropionate section of the target molecule. Related rhodium-catalysed asymmetric ring-openings of oxa- and azabenzonorbornadienes were presented as the key step in the preparation of a range of anti-depressants and analgesics. A detailed study highlighted the importance of using rhodium iodide rather than rhodium chloride-based catalysts for improved enantioselectivities. More recent work on the addition of arylboronic acids to unactivated alkenes in an aqueous medium was presented as an alternative aqueous Heck reaction. The addition of arylboronic acids to 2-pyridinyl disubstituted alkynes was shown as a new method of forming trisubstituted alkenes in a regio- and stereospecific manner.

A second total synthesis of callystatin A (**1**) was presented by **Dieter Enders** (University of Aachen) and the feature of his approach was the use of SAMP/RAMP-mediated asymmetric alkylation chemistry. Indeed the SAMP/RAMP chiral auxiliaries formed the focus of this lecture which presented their use in a variety of asymmetric processes as the key step in the preparation of a range of biologically interesting molecules. Further highlights of the presentation included the first Brehme reaction (nucleophilic acylation of azaenamines) and a carbene-catalysed enantioselective benzoin condensation.

The development of novel methodologies for the efficient synthesis of complex natural products was the cornerstone of the lecture presented by **István Marko** (Louvain-la-Neuve). A serendipitous discovery of novel chemistry of a silane-containing silylenol ether was explored in an elegant fashion in the synthesis of monic acid A (**2**) in which the longest linear sequence was seven steps in an overall yield of 17%. Further elegant examples of the art of total synthesis were given by Marko and included the development of diastereoselective cyclopropylboronate formation and reactivity as a key intermediate in the preparation of ambruticin (**3**).



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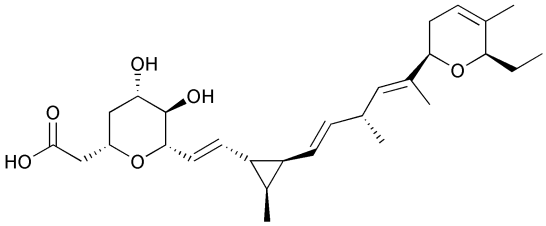

3

There is little doubt within the synthetic community that olefin metathesis has developed into a reaction of extraordinary synthetic utility and it was of little surprise that it formed the basis of two lectures. The first by **Siegfried Blechert** (Technical University of Berlin) focused on the application of Grubbs-type catalysts for metathesis in combination with domino processes. Examples given included cross metathesis followed by reduction, double reductive amination and Diels–Alder reactions. He also detailed elegant examples of ring opening-ring closing metathesis as a synthetic strategy for the preparation of challenging target molecules. He also described recent attempts by his group to circumvent one of the practical problems with olefin metathesis, namely the relatively high (5 mol%) catalyst loading. His approach was to heterogenise the catalyst by linking the carbene ligand to a polymer support to give a recyclable and reusable catalyst albeit with lower reactivity after multiple reuses. He presented recent work on the application of an axially chiral BINOL-derived alkylidene which demonstrates superior catalyst reactivity compared to the Grubb's carbene ligand in the formation of pyrrolidine rings by ring closing metathesis.

Amir Hoveyda (Boston College) described his groups research on the development of new Mo- and Ru-based catalysts for olefin metathesis. His work on Schrock-type Mo–carbene complexes derived from chiral BINOL and related ligands emphasised the importance of working with a universal ligand class that can easily be changed in a modular fashion. Many examples of the matching of ligands and substrates in a range of ring closing metathesis reactions for small and medium rings drove this point home. He outlined the recent successes in his group in improving the practicality of Mo-based catalysts by developing systems which do not require the use of dry boxes, thus overcoming one of its normal limitations. A further issue of practicality, the recycling of Mo-based catalysts was also solved by linking the ligand to a polymer support. Evidence was also given of Mo-catalysed ring openings of norbornenes, substrates which are unreactive towards Ru-catalysts. He outlined his recyclable isopropyl-alkylidene 'garage' to which the Ru-catalyst returned after reacting. Exciting new developments were presented on glass-supported Ru-catalysts which could be recycled up to thirty times with little loss of reactivity. Hoveyda's lecture closed with some important developments on asymmetric ring opening of epoxides, the asymmetric Strecker reaction and conjugate addition reactions with peptides inducing the asymmetry obtained.

Dave Tirrell (Caltech) reported new *in vivo* methods to incorporate unnatural amino acid into proteins – globally (*i.e.* by substituting all amino acids by a given analogue) or specifically in only one place. The degrees of freedom won by engineering the protein synthesis are then used to generate new materials based on known elements of secondary structure that are functionalised, broken or changed by strategically placed non-natural amino acids. *In vitro* methods for making proteins containing new amino acids have traditionally been inefficient due to the limited availability of tRNA loaded with the new amino acid that has to be there in stoichiometric amounts. **S. Pitcher** (ETH Lausanne) introduced an efficient convergent chemo-enzymatic synthesis of tRNA loaded with any new amino acid on a mg scale. The availability of mg amounts of (mis-) charged tRNA building blocks may bring proteins bearing alternative amino acids closer to everyday lab practise, for example, in *in vitro* protein expression systems.

Crystals are traditionally seen as a static entity and an 'abiological' state, incompatible with the flexible solution chemistry characteristic for the cellular cocktail. This view was revised by **Abraham Minsky** (Weizmann Institute) who has discovered a bacterial defence strategy that involves formation of DNA crystals by and with a stress induced protein, Dps. Bacterial thus protect DNA by limiting its accessibility in the solid state. Regular lamellar structures are formed *in vitro*, but, as shown by electron microscopy, also exist *in vivo*, where their appearance correlates directly to expression of the inducer protein Dps. **Dorit Hanein** (Burnham Institute, La Jolla) contributed other examples of biological relevance that highlighted the renaissance of electron microscopy as a tool that, combined with modelling based on existing X-ray structures, can give insight into larger biological machines.

Tom O'Halloran (Northeastern University) highlighted that in the cellular context even processes that had been thought to work automatically (*i.e.* by diffusion) require enzyme catalysis. Intracellular copper trafficking for example is facilitated by metallochaperone proteins (*e.g.* Atx1) that accelerate transfer and make it specific. A similar issue can be addressed by a technique that specifically labels any protein with a suitable small molecule – for visualisation or for any other purpose. **Kai Johnsson** (ETH Lausanne) has developed a technology to transfer small molecule labels onto any chosen protein using a methyltransferase that accepts a label rather than its natural cargo.

T. Aida introduced biomimetic materials science. Taking a cue from molecular chaperones like GroEL the Aida group can grow defined fibres with a molecular weight over 6 million and 30–50 nm diameter using mesoporous zeolith catalyst template made by assembly around micelles. The zeolith then acts as a template for Ziegler–Natta polymerisations that 'push' the extending chain out of the zeolith tunnels. **Ruth Duncan** (Cardiff) connected polymer science to medicinal applications and showed how polymeric materials for drug delivery by controlled release have advanced from the bench to clinical trials. **Sam Stupp** (Illinois) can build up complex polymer structures after spontaneous self-assembly of monomer building blocks. A healthy debate ensued which type of polymer – 'classical' or self assembled (and, *in vivo*, **dis**assembled after use) – is the way forward.

At the end of the conference we find that the fog is gone and before us stands a clear panorama of modern chemistry as well as the Swiss Alps. Which of the two is more beautiful we cannot tell, but it is close …