CONFERENCE REPORT

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Highlights from the 39th ESF/EUCHEM Conference on Stereochemistry, Bürgenstock, Switzerland, April 2004

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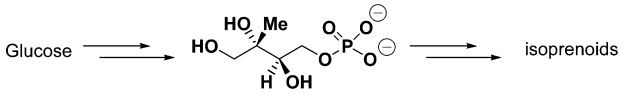
Over 130 chemists attended the Bürgenstock resort for the 39th ESF/EUCHEM Conference on Stereochemistry between 17th–23rd April 2004. This year's president, **Herbert Waldmann** (MPI Dortmund), and the Organizing Committee of **Hans-Beat Bürgi** (University of Bern), **François Diederich** (ETH Zürich), **E. Peter Kündig** (University of Geneva) and **Klaus Müller** (F. Hoffmann-La Roche, Basel) prepared a spectacular line-up of science. Also, the vice president, **Alain Krief** (University of Namur), and the Guest of Honor, **Ekkehard Winterfeldt** (University of Hannover), each played their special responsibilities. The highlights of the conference are described below.

Roger S. Goody (MPI Dortmund) started off the scientific talks after celebrating his 60th birthday on the first evening of the conference. The talk took us on a journey of the structural and mechanistic aspects of vesicular transport and its regulation by Rab/Ypt proteins. These GTPases characterize a family of key membrane traffic regulators in eukaryotic cells whose function is managed by the GDP dissociation inhibitor (RabGDI). The audience was challenged with the problems of structurally characterizing the protein–protein interactions involved. The key feature of the voyage described a blend of chemical synthesis and protein engineering to generate the high resolution crystal structure of the Ypt1:RabGDI complex. This not only provided a structural basis for the ability of RabGDI to inhibit the release of nucleotide by Rab proteins, but also provided a molecular basis for understanding human diseases such as familial mental retardation and choroideremia.

The focus of the next presentation by **Ilme Schlichting** (MPI Heidelberg) was on the structural biology of proteins that use heme cofactors such as the ubiquitous cytochrome P450 enzymes and nitric oxide synthases (NOS). There are many human P450 enzymes involved in metabolism of endobiotics (biosynthesised molecules) and xenobiotics (drugs) with a wide range of specificities. Specificities of individual enzymes are determined by six substrate recognition sites in P450s on the way to the reactive heme located in a deep cleft within the enzyme. Changing tack, the dimeric multidomain nitric oxide synthases were discussed in depth. Again the substrate binding sites explain isoform specificity, for example inducible NOS and neuronal NOS differ in amino acid residues lining the substrate binding channel so that the drug AR-R17477 can bind selectively.

Michel Rohmer (Université Louis Pasteur, Strasbourg) brought an excellent first day of lectures to a close with a fascinating presentation regarding terpenoid biosynthesis. Until recently it was believed that all isoprenoids were biosynthesised *via* the mevalonate pathway, and in most cases this could be shown unambiguously *via* isotope labelling experiments using ^{13}C-acetate as the carbon source. In some cases however, "unusual" labelling patterns and low incorporation levels were observed in bacteria and this was difficult to explain. During work on the hopane family of natural products it was noticed that terpene-derived and sugar-derived fragments were linked in a number of structures and a series of labelling experiments were performed using ^{13}C-glucose as the carbon source. High incorporation levels were achieved and this meant that an altenative non-mevalonate pathway was being used by the bacteria. Following some very elegant and extensive work a completely new isoprenoid biosynthetic pathway was uncovered which uses methyl erythritol phosphate (MEP) as the key 5-carbon building block. This MEP pathway has now been identified in chloroplasts, green algae and eubacteria and this will almost certainly require a number of textbooks to be rewritten!



Methyl Erythritol Phosphate

The second day of lectures began with a stunning presentation by **Jonathan Ellman** (University of California, Berkeley). The first part of his talk detailed the development of a new method for the asymmetric synthesis of amines by the addition of nucleophiles to *tert*-butyl sulfinyl imines. The sulfinyl group acts both as a chiral auxiliary and a protecting group, with removal from the amine products being readily achieved by treatment with HCl–MeOH. A large number of illustrative examples were presented and the versatility of this new methodology was very clearly demonstrated. Imines derived from ketones could be deprotonated (LDA, $MgBr_2$) and used in a nucleophilic sense in reactions with suitable electrophiles. In addition to the asymmetric synthesis of "simple" amines, this chemistry was applied to the synthesis of more complex targets such as α,α-dialkyl-α-amino acids and to the solid-phase synthesis of the natural products pavine and isopavine. The second part of the presentation concerned the development and use of novel C–H bond activation methods. In particular the rhodium-catalysed activation of aromatic C–H bonds was described and this was used to synthesise benzofuran-containing targets. The activation of C–H bonds on aromatic heterocycles such as imidazoles was also described and some mechanistic detail was provided.

The morning session was continued by **Matthias Beller** (Leibniz-Institut für Organische Katalyse, Rostock, Germany), with catalytic processes being the main focus of attention. The lecture began with the use of transition metal catalysis in multi-component

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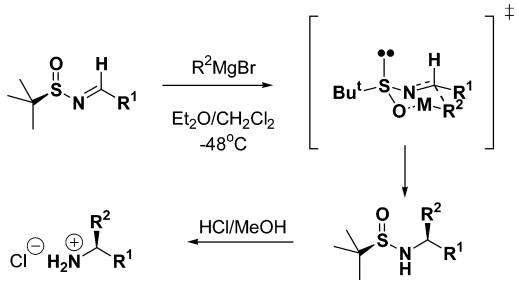
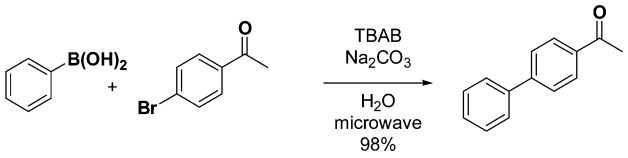


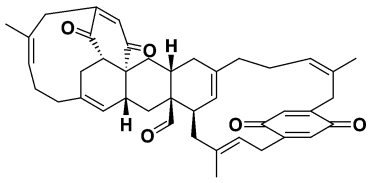
coupling reactions (MCRs) with amido-carbonylation being an excellent example. This MCR involved the condensation of an aldehyde with an amide, followed by a transition metal-catalysed carbonylation reaction to provide amino acid products. In a related MCR, condensation of α,β-unsaturated aldehydes with alkyne-containing amides produced dienes, which were utilised in a subsequent Diels–Alder cycloaddition. The resulting cyclohexene was used as a substrate for a Pauson–Khand reaction to afford the core structure of dendrobine. A wide range of other catalytic processes were described and these included activation and carbonylation of aromatic and heteroaromatic chlorides using a range of palladium-based catalyst systems. The catalytic conversion of aromatic halides to aromatic nitriles was a particularly fascinating reaction, with non-toxic $K_4[Fe(CN)_6]$ acting as the source of cyanide. The use of this reagent overcomes the problem of cyanide anion deactivation of the palladium-based catalyst system. The lecture ended with an extremely efficient synthesis of 1-octene. This catalytic process proceeded with turn over numbers of 1 500 000 and this example was a fitting way to demonstrate the power of modern catalytic processes.

Nicholas E. Leadbeater (University of Connecticut) gave a very entertaining overview of a range of transition metal-mediated processes that were accelerated by the use of microwave irradiation. The nickel-catalysed Finkelstein reaction for aromatic halides and palladium-catalysed Suzuki reactions were notable highlights. He then went on to describe the discovery of a number of transition metal-catalysed processes that could be performed in the *absence* of the transition metal! The story behind these unusual and intriguing observations was described and some preliminary ideas about possible mechanisms for these transformations were presented.



In the second lecture of the Monday afternoon session, **Milton R. Smith III** (Michigan State University) presented his work on the development of an iridium-based catalytic borylation reaction. This remarkable process involves selective C–H activation of the *meta*-position of aromatic substrates and results in the production of arylboronates that are suitable substrates for use in subsequent Suzuki coupling reactions. A wide range of functional groups were tolerated and hence this chemistry will provide an excellent way to access functionalised aromatic core structures that are difficult to obtain by other methods.

Matthew D. Shair (Harvard University) concluded the second day of lectures with a blend of natural product target synthesis and novel synthetic methodology. The first part of the lecture described an elegant total synthesis of the heptacyclic natural product (−)-longithorone A using a strategy that was based around its proposed biosynthesis. The synthesis relied upon the enantioselective construction of two fragments that could then be united in an intermolecular-Diels–Alder reaction. Following the intermolecular cycloaddition, an oxidation and a transannular Diels–Alder reaction afforded the heptacyclic core. This synthesis provided an excellent example of how stereochemistry can be relayed from existing chiral centres to new chiral centres *via* the intermediacy of atropisomeric intermediates. The second half of the lecture regarded the development of novel methodology for the synthesis of polyketide derived targets. Taking inspiration from polyketide biosynthesis, a new catalytic decarbonylative aldol reaction was developed using malonic acid half-thioesters as the nascent nucleophiles. The copper (II)-catalysed process could be run under ambient conditions and was tolerant of exposure to both water and air.



(-)-Longithorone A

Atsushiro Osuka (Kyoto University) delivered the first lecture on the "materials day" of the conference and he treated the audience to a truly magnificent display of modern porphyrin chemistry. The lecture began in relatively modest style by describing how two porphyrin units could be linked with the use of $AgPF_6$ to generate novel dimeric structures. The stakes were raised considerably, however, when it was demonstrated that these dimeric structures could then be linked to generate tetrameric porphyrin, and the resulting tetramers could be linked to generate novel linear octameric porphyrin-based structures. This iterative chain growth could be repeated time and time again and it was possible to generate *single oligomeric molecules* comprised of 1024 *meso–meso* linked porphyrins of between 0.1 and 0.8 μm in length! These materials could then be oxidised with DDQ to afford extended flat, linear arrays that possessed electronic excitation in the IR region of the electromagnetic spectrum! The synthesis of a range of other porphyrin-based materials was described, but perhaps the most fascinating were the *meso*-aryl expanded porphyrins. In one case a macrocyclic octaphrin structure displayed "molecular mitosis" and divided to produce two daughter porphyrins as products.

The materials theme was continued by **Harry Anderson** (Oxford University) with a very impressive display of how self assembly processes can be used to protect molecular wires and encapsulate dyes. In particular, rotaxanes and polyrotaxanes were used to produce "insulated" materials with the thread being shielded from degradation by the presence of a macrocyclic sheath. Dye-containing threads were protected from chemical and photochemical bleaching thus enhancing the useful lifetime of these materials. In a related study, Suzuki couplings were also used to construct rotaxanes with stilbene-based threads and these materials showed enhanced fluorescence yields. *E*/*Z* isomerisation of the stilbene thread was also possible and this resulted in unidirectional shuttling of the cyclodextrin macrocycle along the thread. Conjugated polyrotaxanes could also be synthesised using phosphine-free Suzuki couplings and these materials showed significant fluorescence enhancement. Preliminary experiments exploring the behavior of these new materials for use in electroluminescent light-emitting diodes were also described.

The penultimate day was a rich display of state-of-the-art chemical biology starting off with **Kazunari Taira** (University of Tokyo). The talk began with a enlightening discussion of ribozyme technology and the problems with designing intracellularly active ribozymes. Fundamental studies were described of oxygen replacement by sulfur to identify catalytically critical positions in the hammerhead ribozyme. The use of ribozymes in exploring gene function was convincingly conveyed. Since mRNA secondary structure is difficult to predict, because it does not take account of RNA binding proteins, ribozyme activity could be dramatically increased by attaching a RNA helicase to the ribozyme. Gene discovery by these hybrid ribozymes was illustrated by the identification of target genes with a pro-apototic function. Combinatorial synthesis of ribozyme sequences generated randomized ribozymes that were screened in a chemotaxis assay. These

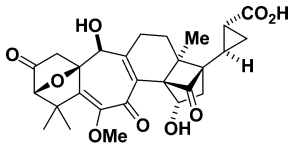
assays revealed that small RNA sequences originating from the so called "junk" (non-coding) DNA regions were important in gene regulation. siRNA technology could be used to induce gene specific silencing in mammalian cells, and the presentation included a portrayal of advanced vector-based shRNAi (small hairpin RNA interference) that have a markedly reduced interferon response. The audience was left convinced of the importance of small RNA technology in many areas of cell biology, such as neurons, tumour genesis, apoptosis, immunity and aging.

After gaining our collective breath again **Michael Famulok** (University of Bonn) continued the RNA theme by describing the use of ribozymes for drug screening. Loss of function phenotypic analysis using transgenic knockouts, antisense oligonucleotides, intracellular ribozymes or siRNA can only tell us so much about the function of gene products. Even with these important techniques questions such as "Is the protein gene product druggable?" are still difficult to answer. For example what functional roles do sub-domains and post-translational modification play? A process to rapidly identify ligands to target proteins could be obtained by *in vitro* selection and delivered into cells with a transgenic virus or lipofectin. The intracellular aptamers (intramers) were illustrated in exploring guanidine exchange factors. Just as the pharmaceutical chemists in the audience were starting to be concerned about their future, the exploitation of intramers as potential drugs was dismissed. Nevertheless the use of intramers in the discovery of protein function was memorably exhibited.

The climax of the day heralded **Kevan Shokat** (University of California, San Fransisco) to parade his chemical approach to explore the function of kinases, phosphorylating enzymes that require ATP. Kinases are implicated in pathways and disease states as diverse as tumours, memory, apoptosis, cell differentiation, immune response, and hypertension. Rather than using genetics or RNAi technology, the use of small molecules allowed immediate-early effects, rather than steady-state effects, of a kinase to be identified. The major problem with a small molecule approach is that there are not enough specific small molecule kinase inhibitors known. No problem; by changing the highly conserved "gatekeeper" threonine residue in the ATP binding site of a chosen kinase a potent kinase inhibitor can be made specific. The kinase inhibitor was modified to incorporate a bulky group that could only inhibit a kinase without the gatekeeper residue, thereby introducing an analog sensitive allele of any chosen kinase. Over 100 alleles of kinases have been generated and single to multiplex inhibition experiments have been performed, transcriptional profiling was used to make sense of the effects. Pathway mapping with orthogonal, labelled ATP analogues, and post-translational modification mapping was magnificently demonstrated. The *piste-de-resistance* came with an innovative approach to identifying the kinase of a given substrate by cross-linking.

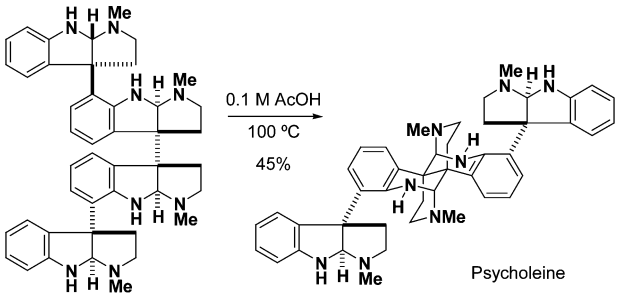
With the dawn of a new day came the final series of lectures with the theme being synthesis. Studies toward the synthesis of solanoeclepin A, a hatching agent of potato cyst nematodes, were presented by **Henk Hiemstra** (University of Amsterdam). Potato cyst nematodes are parasites that feed solely on the roots of potato plants. By spraying an empty field with the natural chemical signal the nematodes will hatch and die of starvation, thereby riding the field of the parasite in an environmentally friendly manner. Sounds simple, but unfortunately the compound needs to be synthesised, and that is not a trivial task. Solanoeclepin A contains 3-, 4-, 5-, 6- and 7- membered rings and is not stable to acid or basic conditions. A beautifully elegant allene photocyclisation approach was illustrated leading to a structurally complex tetracyclic fragment. Rewardingly, simpler analogues of solanoeclepin A showed significant biological activity. Potatoes are back on the menu.

Continuing the excellence in synthesis tour, **Larry Overman** (University of California, Irvine) presented solutions to the special challenges in constructing "all-carbon" quaternary stereocentres. In particular, the chiral centre must be made *via* a C–C bond-forming



Solanoeclepin A

reaction and be compatible with the inherent steric congestion. The polypyrrolidinoindoline (cyclotryptamine) and cyclotryptophan diketopiperazine alkaloids are ideal families of natural products to explore the challenges of any new methodology since they have diverse biological activities, the absolute configuration of many members of the family is unknown, and they incorporate challenging architectures of vicinal and diaryl quaternary centres. The catalytic asymmetric Heck cyclization was spectacularly developed to meet all the challenges required for efficient synthesis. The highlights of the presentation included elegant total syntheses of higher order polypyrrolidinoindoline alkaloids, such as Hodgkinsine, Hodgkinsine B, Idiospermuline, by a dissymmetric dienolate dialkylation followed by an asymmetric Heck cyclization. The crescendo was the breath-taking total synthesis of the dodecacyclic alkaloids Quadrigemine C and Psycholeine.



Quadrigemine C

Psycholeine

The last lecture of the conference was given by **Karl Wieghardt** (MPI Mülheim) on the fascinating co-ordination chemistry of life. There are many transition metals essential for life, and they are usually incorporated as metalloprotein enzymes, in fact approximately 40% of all enzymes are metalloproteins. Two enzymes were focussed upon; galactose oxidase and photosystem II (PSII). Galactose oxidase uses a square-based pyramidal Cu(II) ion that is co-ordinated by a modified tyrosyl radical to oxidise galactose with O_2. Model phenoxyl radical complexes of Cu(II) mimicking the enzyme have been made in the lab and analysed leading to greater understanding of the enzyme itself. PSII is responsible for the oxidation of water with light into protons (required for ATP synthesis), electrons (required to reduce CO_2) and, the by-product of the reaction, O_2. A large tree uses photosynthesis to supply enough O_2 for five people. The enzyme is remarkable since it catalyses the reaction with charge separation, that is to say it does not produce H_2, which is what happens in the lab using electrochemistry. PSII is a metalloenzyme with a tetranuclear Mn complex at the heart of the catalytic machinery. By synthesising model Mn complexes the proposed mechanisms of the reaction were explored. One model catalyst was used as an additive in washing powder as it allowed effective washing at lower temperatures. Unfortunately, it was withdrawn since the catalyst also produced a small amount of H_2O_2 that eventually destroyed clothes. Nevertheless, a brilliant functional model for PSII was designed with Ru(II) oxidising centres and phenoxyl radicals.

The last surprise was given in customary fashion by **Klaus Müller**, who supplied a hilarious, epigrammatic summary of the week's proceedings. The highly anticipated 40th Bürgenstock meeting was confirmed for the 16th–22nd April 2005 with the president being **Alain Krief** (University of Namur) and the vice-president revealed as **Bernard Kräutler** (University of Innsbruck).