Highlights from the 40th EUCHEM Conference on Stereochemistry, Bürgenstock, Switzerland, April 2005

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'Where most see a wall, some see a door and a few go through to discover a rich, new world.....open sesame!'

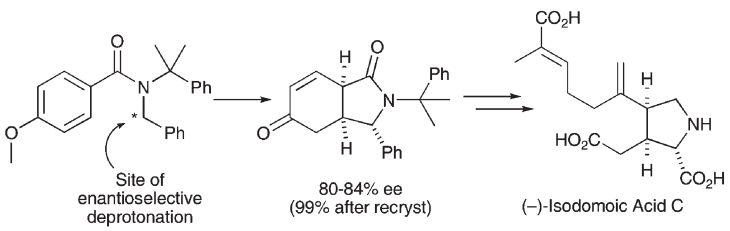
Such was the opening of this 40th EUCHEM Conference on Stereochemistry, in a mist-shrouded Bürgenstock, Switzerland. The coincidence of this 40th anniversary with the bicentenary of Hans Christian Andersen's birth was too tempting for the organising committee to resist and indeed, the President **Alain Krief** (University of Namur, Belgium) and organising committee of **Hans-Beat Bürgi** (University of Bern, Switzerland), **François Diederich** (ETH, Switzerland), **Peter Kündig** (University of Geneva, Switzerland) and **Klaus Müller** (Hoffmann-La Roche AG, Switzerland) put together a magical programme of talks, in keeping with the fairytale theme. The highlights are described below.

Jonathan Clayden (University of Manchester, UK) kicked off scientific proceedings with an inspiring talk on lithiated amide mediated synthesis and stereocontrol. Chiral lithium bases facilitate enantioselective deprotonation of *N*-benzyl benzamides and this initiates an asymmetric de-aromatising cyclisation to enantiomerically enriched isoindolinones, a ring structure which has led them into synthesis of members of the kainoid family of natural products, *e.g.* isodomoic acid C. A discussion of conformational memory and remote stereocontrol then followed. The latter can be achieved with rigid compoundsz containing amide functionality: diamides may be tethered together and the conformation of the amide groups controlled by a terminal chiral centre. The amide groups line up in an ordered fashion (minimizing the overall dipole of the molecule) and in turn, influence stereoselective reactions at the distal terminus from the original chiral centre: Clayden has now demonstrated stereocontrol over a reaction taking place more than 20 bond lengths from the controlling centre, corresponding to a linear distance of over 2.5 nm! This impressive transmission of information may one day be of real practical importance: a molecular mechanism for the communication and processing of information.

In the following talk, **Charles Mioskowski** (Université Louis Pasteur, France) presented the development of a high-throughput immunoassay to screen for optimal conditions in the asymmetric reduction of oxophenyl acetic acid to mandelic acid (MA). Three monoclonal antibodies were used in the assay: one which recognises both enantiomers of MA and the other two each specific for recognition of one enantiomer of MA. Using this system, a library of bidentate ligands, different hydrogen sources and different solvents were investigated. Optimal conditions with respect to yield and enantiomeric excess could be found using this method. The second part of this talk dealt with the screening for antioxidants. Norbadione A and other pulvinic acid derivatives were identified as protective agents against oxidative stress caused by γ-radiation, UV radiation or Fenton conditions and, in conclusion, a total synthesis of norbadione A was also presented.

Uncovering biosynthesis pathways is the key interest of **David Cane** (Brown University, USA) and his lecture focused on two polyketide macrolides, erythromycin A and picromycin. In the case of erythromycin, 6-deoxyerythronolid B synthase (DEBS) is the molecular machinery that performs most of its biosynthesis. The enzyme can be subdivided into six modules, each consisting of a set of domains that are responsible for either C–C bond formation, ketone reduction, dehydration or double bond reduction. Details of how the polyketide chain is moved along this path, particularly the intermolecular substrate transfer between modules, were discussed. Similarly to DEBS, picromycin synthase (PICS) is responsible for the biosynthesis of picromycin. The product formation of a modified module 2 of PICS containing a thioesterase was used to determine the configuration of those alcohols that serve as precursors for double bonds.

The second day of lectures saw a general shift in focus to methodology and began with an interesting talk by **Guy Lloyd-Jones** (University of Bristol, UK) on isotopic desymmetrisation in the study of metal-mediated processes. The ligand induced regio- and stereochemical outcome in the reaction of a variety of allylic substrates was discussed. Cyclohexenyl and π-allyl systems were used to investigate whether



Chiral deprotonation and application to natural product synthesis

Pd-phosphine complexes exist as monomeric bis-coordinated discrete Pd species or oligomeric structures (which provide inferior enantioselectivities). Ligand–substrate match or mismatch provides stereoinduction, which was evaluated through nucleophilic attack on the system. Alkene–alkyne metathesis was also discussed and experimental evidence shown which supports the less proposed yne then ene mechanism. In addition, during an investigation of ring closing Pd-mediated reactions, the question of *syn* or *anti* β-hydride elimination had been thoroughly investigated. Although initially an *anti* elimination pathway seemed to be operating, it was found that reaction rate was not base dependent and, through the formation of stereochemically pure labelled substrates, it was found that the *syn* elimination pathway was indeed the mechanism of elimination.

Keiji Maruoka (University of Kyoto, Japan) was next to speak and switched our attention to C_2-symmetric chiral quaternary ammonium salt phase transfer catalysts and their indisputable efficiency as organocatalysts in asymmetric synthesis. Around 20% of the top 500 drugs contain amino acids and their derivatives and the first part of the talk concerned rational catalyst design and application to the synthesis of these natural and unnatural amino acids (some with a quaternary chiral centre). The direct asymmetric aldol reaction of glycine Schiff base with aldehyde acceptors was shown to proceed under mild, biphasic conditions with excellent stereocontrol, offering a powerful chemical method for the synthesis of β-hydroxy-α-amino acids. Furthermore, new polyamine based chiral catalysts have been most recently developed, the turnover of which is remarkable: it is possible to use them at a level of just 0.01 mol% and obtain a 92% yield and 98% ee in only 9 hours. Their large scale utility has now been verified in a 10 kg scale unnatural amino acid synthesis.

To close the day, **Paul Knochel** (LM-University of Munich, Germany) provided a very entertaining lecture on the practical synthesis and use of organometallics in his laboratory. He contradicted commonly held beliefs and assumptions on the compatibility of aryl Grignard reagents with, for example, esters and nitro groups on the same aromatic ring! A new reagent, *i*PrMgCl·LiCl, was shown to be particularly efficient for the simple, high yielding preparation of a broad range of functionalised aryl- and heteroarylmagnesium reagents and the reactions may be performed on a large scale. In addition, iron-catalysed cross-coupling reactions were also touched upon, presenting a new and economical way to perform aryl–aryl cross-couplings, a topic which is currently under further investigation within the Knochel labs: watch this space.

Ian Wilson (Scripps, USA) got day three underway, with a structural rationale for the neutralisation of HIV-1 by human monoclonal antibodies. Antibody 447-52D recognises the hypervariable gp120 V3 loop of HIV-1, and the X-ray structure of its Fab fragment complexed with a 16-mer V3 peptide has been resolved. A second antibody called b12, recognising the CD4 binding site of HIV-1 was also presented. Understanding the structural features of these antibody interactions will hopefully provide the foundation for the development of HIV vaccines. Next, the 1918 influenza virus took the audience back to the future: the reconstruction and X-ray structure of the major surface antigen revealed structural features primarily found in avian viruses, providing a possible explanation of the high infection and mortality rates in this epidemic.

The biochemical day of the conference continued with **Thomas Carell** (LM-University of Munich, Germany) and his fascinating story of DNA repair at an atomic level. FaPydG is one of two major guanine-derived oxidative DNA lesions. It was mimicked by a cyclopentyl analogue, cFaPydG, which was synthesised and incorporated into DNA. Contrary to literature assumptions evidence was presented that this lesion forms a base-pair with dT and not with dA. The talk continued, explaining how oxidative lesions are recognised and cause mutagenesis. The question as to how those lesions are repaired was then addressed in more detail. In order to do this, the crystal structure of a photolyase bound to a cyclobutane pyrimidine dimer (CPD)-like lesion, after *in situ* repair, was used most effectively: the structural information obtained made a thorough analysis of the recognition mode of lesions of this type possible.

Following an evening of chamber music by the Aura String Quartet, the participants were refreshed and ready for the next morning's session, on material science, begun by **Klaus Müllen** (MPI, Germany). His talk started with the synthesis and properties of 2-dimensional π-conjugated systems (graphite disks) that could lead to new semiconductor materials for transistors, LEDs and photovoltaic devices. These well-defined systems were synthesised by oxidative cyclodehydrogenation of propeller-like precursor molecules. Advancing into the 3D world, benzene derived dendrimers were shown to form films with gold nanoparticles. Dependent on the nature of the dendrimer used, the film properties

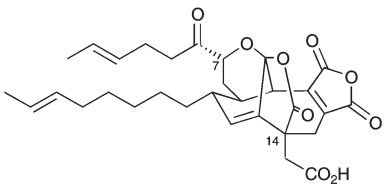
varied considerably, and some of these films are promising new candidates for sensor technology. Finally, he presented a new type of carbon nanotube, formed by pyrolysis of well-defined graphitic precursors within a preorganised porous template, and with potential for use in many microscale applications.

Masahiro Irie (Kyushu University, Japan) then provided a most amusing and magical photochromatic show. Using liquids, photochromic compound coated filter papers and crystals, he demonstrated the phenomenon of compounds (such as diarylethenes) which can make a rapid geometry change given light of the right wavelength: red colour to colourless and back again in two flashes of the UV light – and the repeatable cycle number can be extremely high at $\sim 10^5$. Though lighthearted, the more serious aim of the work was certainly not overlooked: these compounds have vast potential for use in 3D memory storage, spanning DVDs and switching or display devices, among others. In an extension to this idea, the fluorescence of single molecules was shown under the confocal microscope: single molecules can be photoswitched. Can it be possible, therefore, to store memory in a single molecule?

Snapshots of two metalloproteins in action were presented by **Catherine Drennan** (MIT, USA). Her talk started with the X-ray structure of biotin synthase (BioB), the enzyme which catalyses conversion of dethiobiotin to biotin. In this remarkable radical transformation, a sulfur atom is inserted between two nonactivated carbon atoms. The enzyme is a member of the *S*-adenosyl-methionine (SAM) radical superfamily and is further characterised by its dependence on an Fe_4S_4 as well as an Fe_2S_2 cluster. The highly controversial issue as to the origin of the sulfur in biotin could be addressed: the crystal structure shows the Fe_2S_2 cluster occupies an ideal position for sulfur insertion, a result that is in line with ^{34}S labeling experiments. The evening ended with the discussion of the bifunctional enzyme CO dehydrogenase/acetyl-CoA synthase. The X-ray structure showed that a Fe_4S_4 cubane, bridged to a Cu/Ni binuclear site, serves as the cofactor in the AcCoA forming event. Most interestingly, a channel of 138 Å in length was identified that acts as a duct for CO between the two active sites of the enzyme, thus preventing the release of this toxic molecule into solution.

It was on the last day of the conference that the mist and clouds of the week finally lifted and **Mikiko Sodeoka** (Tohoku University, Japan) gave her lecture on the development of intracellular transduction modulators. Inhibition of the protein serine/threonine phosphatase PP2B (calcineurin) is usually effected by compounds like FK506 or cyclosporin A, after they have formed complexes with FK binding protein (FKBP). To find a direct inhibitor molecule, the simple natural product cantharidin, a PP2A inhibitor, was explored as a lead candidate. Using a computational binding model and a ''core pharmacophore'', several derivatives were synthesised and tested. Among these compounds, a selective PP2B inhibitor (IC_{50} = 7 μM) was identified.

John Wood (University of Yale, USA) opened his lecture on a more philosophical note and reminded us all that the point of synthesis is not a means to an end but a journey. His focus was phomoidride D, a bridged polycyclic natural product and an inspirational target for total synthesis.



Phomoidride D

The synthetic challenges the molecule poses are manifold: the highly complex [4.3.1]-decadiene skeleton, bridgehead olefin and maleic anhydride moiety together with a quaternary centre, bridged spiroacetal and an epimerisable centre at C7. Several strategies towards the synthesis of this challenging architecture were discussed, among which radical cascade reactions have proven themselves to be the most promising. These were discussed in some detail and interspersed with philosophical notes throughout. Through the challenge of this complex architecture, a new xanthate deoxygenation method was developed and a study showed this to provide reliable deuterium incorporation when D_2O was used in the experiment, proving the original theme of the talk: it's not the end but what we learn along the way...

Following a superb magic show by **Koji Nakanishi**, the closing lecture of the conference came from **David Evans** (Harvard University, USA). The bis oxazoline box and pybox ligands were discussed and used to exemplify the importance of both metal selection and counterion choice when applying ligands in synthesis. A chemical journey from copper to tin and from nickel to scandium then ensued, most effectively illustrating these principles. For example, nickel box derivatives provide excellent *syn* : *anti* ratios (98 : 2 to 92 : 8) and enantioselectivities (90–96%) in the aldol reaction whilst copper box performs extremely well (though obviously not exclusively) in the glyoxalate ene reaction, now run on a forty gram scale. Further to this, application in total synthesis was also illustrated in the copper pybox mediated vinylogous aldol reaction, used to set up a key stereocentre in his elegant callipeltoside A synthesis. Truly a spectacular finish to the scientific part of the conference.

However, no Bürgenstock would be complete without the final whistle-stop tour from **Klaus Müller**, reminding us all of both the amusing and scientific highlights of the conference!! During this, in reference to a picture shown of him shaking hands with the Queen, Guest of Honour **Sir Jack Baldwin** amused us all with an anecdote of the meeting which followed: himself and Prince Philip! You'll have to ask Sir Jack about that one. On a more serious note, the President of the 41st Bürgenstock was confirmed to be **Bernhard Kräutler** (University of Innsbruck, Austria) and the Vice President and President Elect for the Conference 2007, **Samir Zard** (École Polytechnique, Palaiseau, France): Aladdin's cave will open again.

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