Chemistry Unprotected**

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What makes the Bürgenstock Conference unique is its multidisciplinary spirit created by little more than 100 participants. The program of the conference is not revealed to the participants—even the speakers—until the conference starts. There is no book of abstracts and, of course, it is not allowed to take photographs of the presentations (a questionable habit that has become common in many other meetings). The 42nd Bürgenstock Conference (April 14–20, 2007) honored Rolf Huisgen (LMU München, Germany),[1] who served as president in 1982. Huisgen's outstanding contributions to organic chemistry were evident in many of the 14 lectures. 1,3-Dipolar cycloadditions are indeed fundamental. Samir Zard (École Polytechnique, Palaiseau, France) was this year's conference president, and, yes, there was a lot of radical chemistry going on. A particular focus of this year's conference was natural products synthesis, radical reactions, and catalysis. Two days were reserved for materials sciences and chemical biology.

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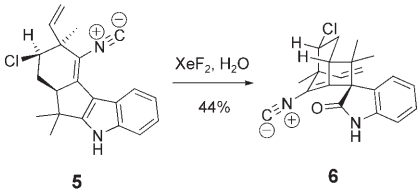
[**] 42nd EUCHEM Conference on Stereochemistry in Bürgenstock (Switzerland) April 14–20, 2007.

Natural Products Synthesis

The ideal total synthesis of a natural product would proceed in one step and in 100% yield from a commercially available starting material. This dream is increasingly driving natural products synthesis as a science. The synthetic works discussed at the Bürgenstock Conference point to reaction sequences free of protecting groups as one step towards that ambitious goal. To use natural products in chemical biology, however, would require gram rather than milligram quantities.

Barry B. Snider (Brandeis University, Waltham, MA, USA) presented the total syntheses of symbioimine, platensimycin, thallusin, (+)-Sch642305, jenamidine A (revised structure), NP25302, descurainin, cartorimine, and berkelic acid. The terpene alkaloid thallusin from the epiphytic marine bacterium *Cytophaga* YM2-23 was isolated from the green alga *Monostroma sp.* and caused considerable interest because of its ability to induce cell differentiation in *Monostroma oxyspermum* in concentrations of less than 1 fg mL^{-1}. Unfortunately, the synthesized product turned out to be *ent*-thallusin, which was biologically inactive.[2] A presumably biomimetic [5+2] cycloaddition of bisacetoxypyranone **1** and methylenebutyrolactone **2** paved the way to a formal total synthesis of polygalolides A and B (Scheme 1), almost racemic phenolic lactones with an unusual skeleton. Synthetic intermediate **4** was available in only two steps (19% yield) from fructose-derived **1**.[3]

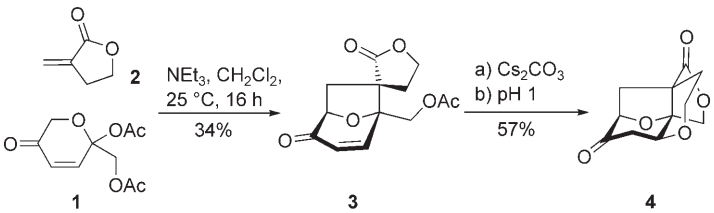
"The catalytic cycle of discovery in total synthesis" was highlighted by Phil S. Baran (The Scripps Research Institute, La Jolla, CA, USA), who focused on the biomimetic synthesis of structurally complex indole alkaloids: chartelline C, welwitindolinone A (and related compounds: hapalindoles, fischerindoles, ambiguines), stephacidin B, and haouamine A. Welwitindolinone A (**6**, originally isolated from the blue-green algae *Hapalosiphon welwitschii*) was enantioselectively synthesized starting from carvone oxide on a gram scale and without the use of protecting groups (Scheme 2).[4] Baran pointed out the number of days within which his total syntheses, once developed, could be accomplished (e.g., ten days for **6**).



Scheme 2. Biomimetic conversion of (−)-fischerindole I (**5**) to (+)-welwitindolinone A (**6**).

This speed of synthesis could encourage the chemical industry to use natural products as templates more frequently. Baran proposed that total syntheses be analyzed with respect to the number of steps versus the oxidation state (Figure 1) as well as their complexity.

Pierre Vogel (EPFL, Lausanne, Switzerland) demonstrated the versatility of SO_2 in organic synthesis, especially for hetero-Diels–Alder and ene reactions, which he employed, for example, in the formal total synthesis of the natural product apoptolidine A.[5] It was also interesting that methallyl, prenyl, and methylprenyl ethers can be cleaved in the presence of allyl ethers by heating with diphenyldisulfone or solid poly-



Scheme 1. Biomimetic [5+2] cycloaddition towards polygalolides A and B.

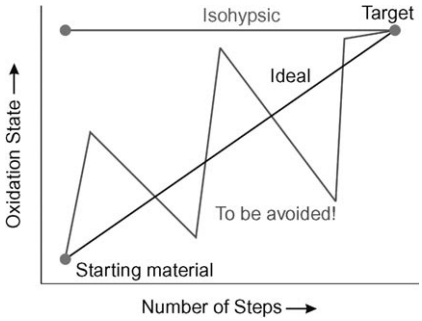
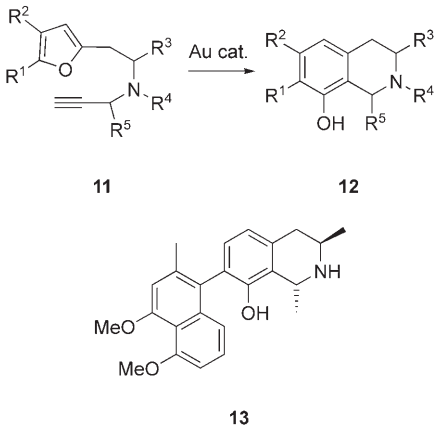


Figure 1. The change in oxidation state as a function of the number of steps in a total synthesis (Phil S. Baran).

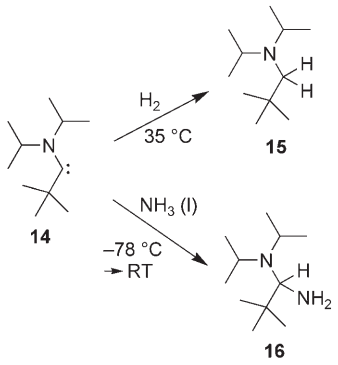
sulfone (**10**), generated by copolymerization of SO_2 with methylidenecyclopentane (Scheme 3). Initially, a sulfonyl radical is added to the alkene. The slightly lower ionization energies of the alkyl substituted with respect to unsubstituted allyl ethers seems to be the main factor enabling the preceding alkene isomerization.[6] Vogel also presented total syntheses of the natural products baconipyrone A/B, rifamycin, apoptolidine A, and (−)-dolabriferol.

Stephen K. Hashmi (University of Heidelberg, Germany) is helping to drive the current "gold rush".[7] Around 70 research groups around the world are now working on homogenous gold-catalyzed reactions. A very interesting and useful reaction is the gold-catalyzed phenol synthesis starting from furan and acetylene (Scheme 4). It was good to notice Hashmi's accuracy in the elucidation of reaction mechanisms in gold chemistry. Furthermore, the total syntheses of three natural products (jungianol, ajudazol A, and dioncophyllin A) were presented. Jungianol was synthesized in six steps without the use of protecting groups. The synthesis of a substructure of the isoquinoline alkaloid dioncophyllin A (**13**) is an example of Hashmi's gold-catalyzed phenol synthesis (Scheme 4).



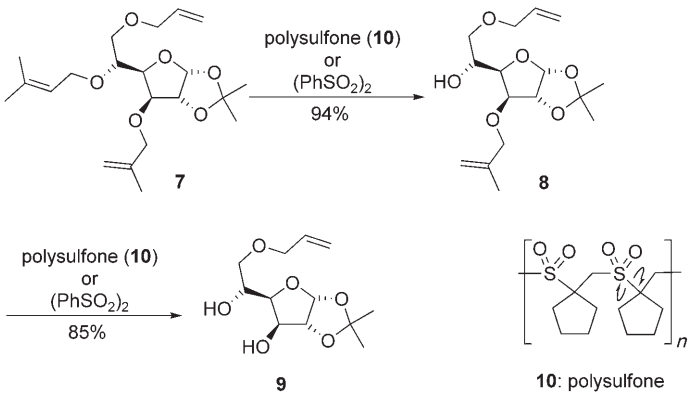
Scheme 4. Gold-catalyzed phenol synthesis of dioncophyllin A (**13**), a 8-hydroxytetrahydroisoquinoline alkaloid.

Guy Bertrand (University of California, Riverside, CA, USA) presented his latest results on the activation of dihydrogen and ammonia by singlet (alkyl)(amino)carbenes. This reaction was known for transition metals, which act as electrophiles. In contrast, (alkyl)(amino)carbenes primarily behave as nucleophiles, generating a hydride-like hydrogen atom.[8] In particular, activation of ammonia is difficult with transition metals, because Lewis acid–base adducts are formed instead. While diaminocarbenes do not insert into H–H or H_2N–H bonds, Bertrand was successful when employing the monoaminocarbene iPr_2NCtBu (**14**; Scheme 5). The concept of considering singlet carbenes as resembling transition-metal centers is intriguing.

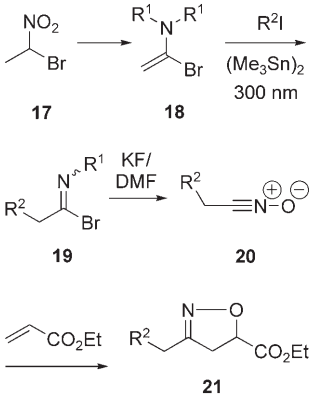


Scheme 5. Insertion of monoaminocarbene (**14**) into H–H and H_2N–H.

Sunggak Kim (Korea Advanced Institute of Science and Technology, Daejeon, South Korea) compared radical and ionic approaches for several reactions (e.g., alkylation of carbonyl compounds and organic nitro compounds, γ-alkylation of α,β-unsaturated carbonyls, and carbonylation of alkyl lithium). An example for the radical alkylation of organic nitro compounds is shown in Scheme 6.[9] The alkylation of **17** is followed by 1,3-dipolar cycloaddition to form the 1,2-oxazoline **21**. Kim also described a tin-free variation of this reaction, as well as several syntheses of sesquiterpenes (e.g., zizaene, hirsutene) employing radical chemistry.



Scheme 3. Chemoselective cleavage of alkyl-substituted allyl ethers (**7** and **8**) under neutral conditions.



Scheme 6. Radical alkylation of an organic nitro compound followed by 1,3-dipolar cycloaddition (R^1 = OTBS, $R^2 = CH_2SO_2Ph$; TBS = *tert*-butyldimethylsilyl).

After William B. Motherwell (University College London, UK) reported recent results on the direct amidocyclopropanation of alkenes using organozinc carbenoids,[10] he turned to the question of noncovalent interactions between arenes and functional groups. Motherwell chose as "molecular instrument" 9,10-propylene-bridged dihydroanthracenes, the conformation of which is dependant on the nature of the substituents located at the center of the bridge.

Materials Sciences

Eiji Yashima (Nagoya University, Japan) introduced his interesting contribution on helical oligomers and polymers with a survey of helical structures in nature. Mimicking the concept of DNA, Yashima's research focuses on helical structures without metal ions. Amidiniumcarboxylate salt bridges were used as the supramolecular junctions between the strands. The complexity of the synthetic helices is enhanced when going to triple helices, quadruple helices, or chiral cylinders.[11] Formation of enantiomerically enriched or pure helices can be induced by chiral bases. If this chiral base is replaced by an achiral base the induced helical structure is maintained. This memory effect is not yet understood. It is also still unclear why the helical sense switches when the solvent is changed, for example, from toluene to chloroform.

The lecture by Gero Decher (University Louis Pasteur, Strasbourg, France) on multilayer films had its roots at the Bürgenstock Conference of 1991.[12] A more recent review in *Science* by Decher has been cited more than 2000 times.[13] Decher presented his view on how molecular self-assembly may lead to new materials in the future. In particular, multistep assembly procedures, of which the layer-by-layer (LbL) deposition technique is a key example in which polyanions and polycations are consecutively adsorbed on solid interfaces, have enormous potential for the preparation of complex multilayer materials in both hard and life sciences. Today, LbL assembly has developed into an emerging technology for the preparation of hybrid films with nanoscale precision. The fact that functional surface layers or even thin-film devices can be easily constructed by dipping or even more rapidly by spraying of aqueous solutions has already kindled commercial interest. Coated kitchen fleece that can slow down ripening of fruits and vegetables, as well as contact lenses constructed with LbL coating, have already appeared on the market. The latest development in the field is the inclusion of living cells in multilayer films.

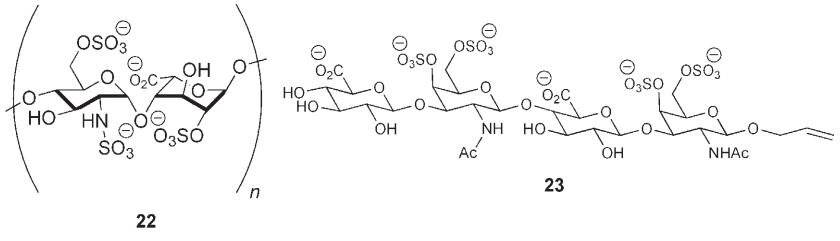
Chemical Biology

Not much is known about the chemical basis of biological adhesion phenomena. Deborah E. Leckband (University of Illinois, Urbana, IL, USA) is particularly interested in an atomic-level understanding of the interaction between the transmembrane protein CD2, expressed on the surface of T lymphocytes, and the lymphocyte-associated function antigen CD58. For this it is necessary to quantify the influence of single charge mutations on equilibrium binding, kinetics, and the adhesion strength of the CD2–CD58 interaction.[14] Force–distance profiles are determined with His_6-tagged proteins immobilized on supported lipid membranes.

Linda C. Hsieh-Wilson (California Institute of Technology, Pasadena, CA, USA) gave an overview of recent progress on chemical neurobiology in her group. Her key hypothesis is that sulfation patterns of glycosaminoglycans may encode molecular recognition and activity.[15] Tetrasaccharides, which are subunits of chondroitin sulfate (CS) glycosaminoglycans, were synthesized and tested for activity (Scheme 7). It was found that specific sulfation motifs indeed function as molecular recognition elements for growth factors and modulate neuronal growth, pointing to the existence of a "sulfation code".

Benjamin F. Cravatt (The Scripps Research Institute, La Jolla, CA, USA) gave an overview of his work on proteomic[16] and metabolomic techniques. Activity-based protein profiling (ABPP), also known as activity-based proteomics, was co-developed by Cravatt.[17] He demonstrated the discovery of several novel cancer targets by ABPP. The role of proteomics in target and drug discovery will depend on the balancing between breadth and depth. In the ABPP-MudPIT (multidimensional protein identification technology) approach, probe-labeled proteins are enriched by binding to avidin-conjugated beads, subjected to onbead trypsin digestion, and identified by multidimensional LC separation and MS–MS analysis. ABPP-MudPIT exhibits superior resolution and sensitivity to gel-based methods, facilitating the identification of lower-abundance targets of chemical probes in proteomes.[18] As metabolites have no direct link to the genome, Cravatt developed a technology to begin to deconvolute this link, discovery metabolite profiling (DMP). This approach is an LC–MS-based analytical method to evaluate the global metabolic effects of enzyme inactivation in vivo.

The nematode *Caenorhabditis elegans* prefers oxygen levels between 5 and 12%. Michael A. Marletta (University of California, Berkeley, CA, USA) and collaborators discovered that this is due to specialized oxygen-sensing cells in the nervous system expressing a soluble guanylate cyclase (GCY-35) sensitive to oxygen. GCY-35 contains the domain H-NOX (heme-nitric oxide binding domain), which is able to bind both NO and oxygen. Further investigations revealed that H-NOX forms Fe^{II}–NO complexes, which are primarily six-coordinate at low temperatures and five-coordinate at high temperatures. It was shown by mutagenesis that H-NOX



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Scheme 7. The glycosaminoglycan heparin (**22**) and the tetrasulfated tetrasaccharide CS-E (**23**).

requires the presence of a tyrosine residue to bind oxygen. Upon its replacement with phenylalanine by mutagenesis (Y140F) in the crystallized H-NOX domain from the thermophile *Thermoanaerobacter tengcongensis*, the enzyme remains sensitive only to NO and, as a potential application, may be used as NO sensor.[19] Enzyme mechanisms were an important topic of this year's Bürgenstock Conference.

Perry A. Frey (University of Madison, Madison, WI, USA) and colleagues crystallized two mechanistically different bacterial lysine aminomutases (LAMs) that catalyze similar reactions and act on similar substrates. Whereas 2,3-LAM is an adenosylmethionine-dependent iron–sulfur enzyme,[20] 5,6-LAM is adenosylcobalamin (coenzyme B_{12}) dependent.[21] Overall, the topic of chemical biology was dominated by speakers from the USA.

The experienced organizing committee (this year François Diederich, E. Peter Kündig, Klaus Müller, Philippe Renaud, and Jay Siegel) promises a fruitful conference in 2008 under the presidency of Don Hilvert (ETH Zürich, Switzerland). The president of Bürgenstock 2009 (vice-president 2008) will be Ben L. Feringa (University of Groningen, Netherlands). If you have the opportunity to join the Bürgenstock conference in the future you should definitely take the chance.

[1] In his concluding remarks of the conference, Klaus Müller noted that Rolf Huisgen was the most active guest of honor in the scientific discussions of the Bürgenstock Conference (despite having been emeritus for 19 years).

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