ESF-COST High-Level Research Conference Natural Products Chemistry, Biology and Medicine III

Hotel Villa del Mare, Aquafredda di Maratea, Italy, 5–10 September 2010

Natural Products Chemistry, Biology and Medicine III was the third conference in a series of events sponsored by the European Science Foundation (ESF) and the European Cooperation in the field of Scientific and Technical Research (COST). Scientists came together from within and outside the EU to present cutting-edge developments in chemical synthesis. Research areas included the synthesis of natural products, methods development, isolation/structural elucidation and chemical biology. As our capacity to produce new chemotherapeutic agents relies on chemical synthesis, this year's conference has never been so timely. This report highlights several of the scientific contributions presented during the meeting.

General comments

Natural Products Chemistry, Biology and Medicine III brought together leading scientists and young researchers for informal and open discussion on the most recent developments in natural product chemistry. The conference was Chaired by Jef De Brabander (University of Texas Southwestern Medical Center, TX, USA) and Vice-Chaired by Dieter Schinzer (University of Magdeburg, Germany). The organizing committee was comprised of Trond Hansen (University of Oslo, Norway) and Mathias Christmann (Dortmund University of Technology, Germany).

The core activity of the conference comprised invited lectures, which were divided into seven sessions. Each session ranged from 3 to 4 h to give sufficient time for discussion and informal interaction between participants. There were 20 lectures (45 min) and 11 short lectures (20 min). Because there were no parallel sessions, everyone could participate. In addition, there were 43 poster presentations, equally important for active discussion and the exchange of ideas. Poster prizes were given to Nadine Bluhm (Leibniz University of Hanover, Germany) and Dmitry Ushakov (University of Tübingen, Germany) for their outstanding research efforts.

A total of 23 countries were represented including several European countries (Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Norway, Poland, Portugal, Spain, Switzerland, the Czech Republic and the UK), Canada, India, Israel, Republic of Korea, South

Africa, Taiwan and the USA. A total of 82 scientists, including speakers, program committee members and participants were in attendance.

Because it would be beyond the scope of this report to discuss all of the research presented during this conference, two scientific contributions have been selected from each of the seven sessions and will be discussed. It is anticipated that this format, rather than an exhaustive listing of research, will give the reader a better insight into the science and an appreciation for the conference theme.

Session I (Monday 6 September)

■ Chair: Mathias Christmann (Dortmund University of Technology, Germany)

The conference commenced with the total synthesis of complestatin (I, also known as Chloropeptin II) reported by Jieping Zhu (Ecole Polytechnique Fédérale de Lausanne, Switzerland) (FIGURE 1) [1]. Complestatin is a linear nonribosomal peptide that has undergone oxidative phenolic-coupling. Although it resembles vancomycin, it is inactive against Gram-positive bacteria but displays potent activity against HIV-1-induced cytopathicity, syncytium formation in CD-4 lymphocytes and inhibits HIV replication by inhibition of gp-120–CD-4 binding at a low-micromolar level. The total synthesis was accomplished using a 3 + 3 segment coupling to assemble the hexapeptide backbone. This was followed by an intramolecular Suzuki–Miyaura reaction to form the macrocyclic aryl–aryl bond and an intramolecular S_NAr reaction to form the macrocyclic aryl–aryl ether.

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Phenols are ubiquitous in medicinal and natural product chemistry, but classical methods for their preparation often require harsh reaction conditions, which are often incompatible with sensitive functionality. To overcome this problem, Edward Anderson (University of Oxford, UK) developed a silicon-based phenolation methodology for the synthesis of hydroxylated aromatic compounds (**FIGURE 2**) [2]. Silicon, which is nontoxic and inexpensive, is readily introduced into an aromatic compound via metal-halogen exchange or deprotonation with an organolithium. The trick was to use diethylaminochlorodimethylsilane ($\text{ClSiMe}_2[\text{NEt}_2]$) as a trapping agent for the aryl-lithium to give aryl silane (**2**). The phenol was then obtained by treatment with isopropanol and sub-stoichiometric amounts of fluoride at room temperature. Anderson believes that the phenolation occurs through a pentavalent silicate intermediate similar to those in classic Tamao oxidation reactions of non-aromatic silanes.

Session 2 (Monday 6 September)

■ Chair: Arthur Catino (Harvard University, MA, USA)

Krishna Kaliappan (Indian Institute of Technology Bombay, India) reported the synthesis of palmerolide A (**FIGURE 3; 3**) [3]. Isolated from

Figure 1. Complestatin (chloropeptin II).

Figure 2 . Phenols via aryl silanes.

Figure 3. Palmerolide A.

Antarctic tunicate *Synoicum adareanum*, palmerolide is a 20-membered macrolide with a total of five stereocenters and an enamide side chain. It exhibits cytotoxic activity against melanoma cell line UACC-62 and modest activity against colon cancer cell lines. For its synthesis, Kaliappan elected to use a non-aldol based approach, which he argued was higher yielding and more efficient than traditional aldol-based approaches. For example, the syn C19–C20 stereocenters were introduced via Sharpless asymmetric epoxidation followed by a stereoselective Pd-catalyzed epoxide hydrogenolysis with inversion of stereochemistry. Sharpless asymmetric dihydroxylation and kinetic resolution were used to install the syn C10–C11 and C7 stereocenters, respectively. A Yamaguchi esterification and ring closing metathesis were used to assemble the 20-membered ring.

The first enantioselective total synthesis of clavirolide C (**6**) was reported by Michael Brown (Harvard University, MA, USA) [4]. Clavirolide C is a member of the dolabellane family of diterpenes isolated from Pacific soft coral *Clavularia viridis*. It contains a strained *trans*-bicyclo[9.3.0]tetradecane core structure with an angular methyl group at C1. The entire clavirolide family (A–F) possesses an array of biological activities including cytotoxicity toward carcinoma cells, blocking of calcium channels and negative inotropic activity. Brown's synthesis featured two catalytic asymmetric conjugate addition (ACA) reactions to generate fragments **4** and **5** (**FIGURE 4**). Brown noted that ACA reactions of β -substituted cyclopentenones are notoriously difficult, spawning a fruitful methodological initiative with *N*-heterocyclic carbene (NHC)-copper catalysis. The total synthesis required 17 steps (longest linear sequence) and afforded the target molecule in 3.5% overall yield.

Session 3 (Tuesday 6 September)

■ Chair: Jef De Brabander (University of Texas Southwestern Medical Center, TX, USA)

John Wood (Colorado State University, CO, USA) discussed his research in the field of oxindole natural products. Special emphasis was placed on the important lessons that he and his group learned during the total synthesis of welwitindolinone A isonitrile (**FIGURE 5; 7**) [5]. Isolated from marine blue-green algae, it is one of several related oxindole-containing alkaloids showing antifungal activity. Welwitindolinone contains a dense array of complex functionality, for example, there are three all-carbon quaternary centers, a neopental chlorine and a spiro-fused cyclobutane. For its synthesis he used a regio- and diastereo-selective ketone cycloaddition to establish the bicycle[4.2.0] octane core. A very clever Cl^+ -mediated semipinacol reaction was used to install the chlorine and C12-quaternary center simultaneously with excellent stereocontrol. To construct the C3-quaternary center of the oxindole, his group developed a new anionic cyclization methodology using SmI_2 . The target was obtained in 2.5% overall yield with an average yield per step of 81%.

Karl Hansen (formerly Merck Research Laboratories, NJ, USA; presently Amgen, MA, USA) discussed a few of the challenges faced by process chemists at Merck, namely the desymmetrization of diphenyl methane *bis*(phenol) (**FIGURE 6; 8**) [6]. This reaction was particularly challenging because the reactive centers in **8** are substantially removed from the pro-stereogenic center (molecular mechanics calculations suggested it is greater than 5.7 Å). Typically, one would use so-called substrate control to relay stereochemistry (stoichiometrically) or an enzymatic resolution (catalytically). Hansen and his team at Merck, in collaboration with Scott Miller (Yale University, CT, USA), developed a peptide-based asymmetric acylation catalyst to mimic an enzyme. The desymmetrized product **9** was obtained in high yield and enantiomeric excess using only 2.5 mol% (100 mol% = 1 stoichiometric equivalent) of catalyst. Mechanistic studies indicated that hydrogen bonding between the catalyst and *bis*(phenol) starting material are responsible for the desymmetrization.

Session 4 (Tuesday 7 September)

■ Chair: Bruno Botta (University "La Sapienza," IT)

Jérôme Waser (Ecole Polytechnique Fédérale de Lausanne, Switzerland) discussed the total synthesis of goniomitine (**13**) and indole

alkaloid from the tree *Gonioma Malagasy*, using a donor–acceptor cyclopropane strategy (**FIGURE 7**) [7]. A donor–acceptor cyclopropane is one that contains an electron-donating substituent and an electron-withdrawing substituent. Under certain conditions these types of cyclopropanes can undergo ring opening and nucleophilic capture. Waser reported that cyclopropane (**10**)

Figure 4. Catalytic asymmetric conjugate addition for the synthesis of clavirolide C.

ACA: asymmetric conjugate addition.

Figure 5. Welwitindolinone A isonitrile.

Figure 6. Peptide-catalyzed desymmetrization of a bis(phenol).

could be readily prepared and treated with dilute acid to give polycycle (**12**). The reaction likely occurs via the intermediacy of *N*-acyliminium ion **11**, which is captured by indole. Goniomitine was finally obtained by deoxygenation and

silicon deprotection. Biological studies showed promising antiproliferative effects in several tumor-cell lines.

Several total syntheses were discussed by Dirk Trauner (Ludwig-Maximilians-Universität München, Germany). A particularly notable example was a three-step, protecting group-free synthesis of pycnanthuquinone **C** (**14**) using a vinyl quinone Diels-Alder (VQDA) reaction (**FIGURE 8**) [8]. Pycnanthuquinone **C** is part of a family of natural products isolated from a variety of biological sources. Related compounds (**A** and **B**) have antihyperglycemic activity. Trauner explained that unlike the classical Diels-Alder reaction involving quinines and electron-rich dienes, the VQDA reaction involves an inverse-electron demand cycloaddition of a dienophile to a vinylquinone. The initial product of the VQDA reaction is an isoquinone methide, which can undergo subsequent reactions (either tautomerization or nucleophilic capture) to give functionalized tetraline quinones.

Figure 7. Synthesis of goniomitine using a donor-acceptor cyclopropane strategy.

Figure 8. Vinyl quinone Diels-Alder (VQDA) for the synthesis of pycnanthuquinone **C**.

Figure 9. Construction of the B-ring of taxol using ring closing metathesis (RCM).

Session 5 (Wednesday 8 September)

■ Chair: Dieter Schinzer (University of Magdeburg, Germany)

Taxol (**15**) remains one of the most effective chemotherapeutic agents for the treatment of breast and ovarian cancer whose synthesis remains a considerable challenge. In particular, formation of the B-ring using ring closing metathesis (RCM) is particularly difficult due to the formation of an unfavorable eight-membered ring and α -gem-dimethyl-substitution on an olefinic partner. Joelle Prunet (University of Glasgow, UK) and her group have carefully examined this reaction and discovered that the C1,C2-diol moiety plays a key role in dictating the course of the RCM (**FIGURE 9**) [9]. After a detailed examination of relative stereochemistry and various protecting groups, she discovered that diol **16** undergoes quantitative RCM with Grubbs second-generation catalyst in refluxing dichloromethane to give **17**. It is believed that diol-protecting groups such as carbonate or acetonide induce a conformation that is unfavorable for cyclization.

Nicolai Cramer (Eidgenössische Technische Hochschule Zürich, Switzerland) discussed the activation of strained C–C σ -bonds for generating alkylmetal species, which in turn can undergo further reactions (**FIGURE 10**) [10]. In one study, he reported the preparation of acyclic quaternary stereocenters from achiral cyclobutanol derivatives using rhodium(I) catalysis. Treatment of readily prepared

cyclobutanol (**18**) with catalytic rhodium(I) and a chiral phosphine ligand (L^*) gave the acyclic methyl-substituted compound **21** bearing a quaternary stereogenic center. The mechanism likely occurs through the intermediacy of a rhodium cyclobutanoxide (**19**) obtained via ligand exchange. Enantioselective β -carbon cleavage then generates a rhodium(I) alkyl species **20**, which is protonated to give product **21**. The driving force for the β -carbon cleavage reaction is the release of ring strain and the formation of a strong C=O. His group has already begun to develop several other useful transformations based on this theme.

Session 6 (Thursday 9 September)

■ Chair: Trond Vidar Hansen (University of Oslo, Norway)

The power of aminocatalytic cascade reactions to prepare daunting synthetic targets was illustrated by Paolo Melchiorre (Institut Català d'Investigació Química, TGN, Spain). For example, his group found that a primary-amine catalyst derived from a natural-cinchona alkaloid efficiently activates acyclic enones to react with nitroolefins (**FIGURE 11**) [11]. The result was a stepwise double-Michael addition reaction to give cyclohexanone products with 3 to 4 contiguous stereogenic centers. Melchiorre discussed several other cascade methodologies that his group developed using this chiral-amine catalysts and related compounds. He stressed that these reactions are particularly relevant today because they are both atom-economical and environmentally friendly/sustainable. Melchiorre's long term hope is that these cascade reactions will be the starting point for assembling libraries of enantiopure compounds for drug candidate testing.

There is no doubt that aromatic and heteroaromatic compounds are important structural elements in several biologically active compounds. Toward this end, Timothy Donohoe (University of Oxford, UK) reported a programmed approach for the preparation of highly substituted furans via cross-metathesis using Grubbs second generation catalyst (**FIGURE 12**) [12]. The chemistry relies on the generation of *trans*- γ -hydroxyenones (**22**), which can be treated with acid or undergo Heck arylation to give *di*- and *tri*-substituted furans, respectively. To demonstrate the generality of this method, Donohoe's group prepared a substituted furan within a 13-membered macrocycle, the key structural element

in cembranolide natural products. Recently, he was able to extend this methodology to the synthesis of *di*- and *tri*-substituted pyrroles using *trans*- γ -aminoenones [13].

Figure 10. Rhodium-catalyzed C–C Bond Cleavage for the construction of quaternary stereogenic centers.

Figure 11. Organocascade reactions of enones catalyzed by a chiral primary amine.

Figure 12. Rapid access to furans using Olefin cross-metathesis.

Figure 13. Haouamine A.

Figure 14. *N,N*-Diethyl *O*-Carbamates for directed metalation and Suzuki-Miyaura cross-coupling partners.

Session 7 (Thursday 9 September)

■ Chair: Evgeny Prusov (Helmholtz Centre for Infection Research, Germany)

The first total synthesis of haouamine A (**23**) was reported by Noah Burns (Harvard University, MA, USA) (**FIGURE 13**) [14,15]. Isolated in 2003 from a marine tunicate *Aplidium haouari-anum* off the coast of Spain, haouamine A was reported to have high activity against HT-29 human colon-cancer cells ($IC_{50} = 0.1 \mu\text{g/ml}$). This unprecedented polyphenolic alkaloid contains a 3-aza-[7]-paracyclophane macrocycle that is so strained that the cyclophane arene is bent out of planarity and exists in a boat-like conformation. Burns synthesized this challenging target in only eight steps from a readily available indanone precursor. The key feature of his synthesis was the transfer of point-chirality to

planar-chirality. He also described a second-generation total synthesis of haouamine A, which allowed for the production of greater than 0.5 g of material. Biological testing of this compound as well as a number of analogs was performed in PC3 human prostate cancer cells.

Victor Snieckus (Queen's University, Canada) capped off the conference by reporting a useful extension of the directed *ortho* metalation reaction [16]. His group found that *O*-carbamates, such as **26**, undergo Suzuki-Miyaura cross-coupling to give biaryls and heterobiaryls (**FIGURE 14; 27**). Snieckus explained that the *O*-carbamate group is one of the best groups for directed metalation reactions due to its ability to stabilize organolithium intermediates (as shown in **25**) and to undergo high-yielding reaction with electrophiles (E^+). He argued that any reaction that can transform these resultant *O*-carbamates would be highly useful. After extensive optimization, he determined that cross-coupling reactions with aryl *O*-carbonates can be achieved with a boronic acid and a catalytic amount of inexpensive and bench stable $NiCl_2(PCy_2)_2$ to give **27**.

Conclusion

Natural Products Chemistry, Biology and Medicine III continued its tradition of bringing together leading scientists to discuss recent developments in chemical synthesis across a wide range of disciplines. The meeting was appropriately high level as chemical synthesis plays a decisive role in the production of chemotherapeutic agents, which is the foundation of modern medicine. This year's meeting took place in southern Italy and was comprised of 31 lectures and 43 poster presentations delivered by scientists and students from 23 different countries. In addition to an outstanding scientific venue, the meeting was highly interactive, culturally rewarding and most certainly enjoyable.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter of materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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