

SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2007 / 02

THE INSIDE STORY ▶▶▶▶

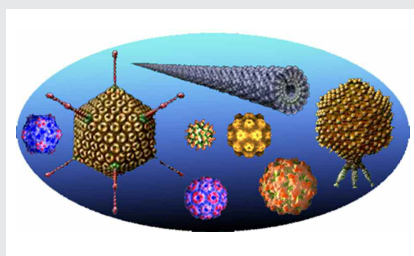
The Role of Chemistry in the European Seventh Research Framework Programme – FP7

SYNSTORIES ■ ■ ■ ■

■ Total Synthesis of
(±)-Vigulariol

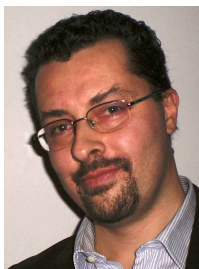
■ Polyprenoids from an Enantioselective Halocyclization Induced by Nucleophilic Phosphoramidites

■ Young Career Focus:
Professor Qian Wang



CONTACT ++++

Your opinion about SYNFORM is welcome, please correspond if you like: marketing@thieme-chemistry.com



Dear readers,

The quest for funding is certainly one of the principal activities for researchers worldwide.

European researchers, regardless of their area of research, know very well that it is time for undertaking a new

campaign of “money-hunting”. Why? Well, the answer is easy: the European Commission has very recently launched the Seventh Framework Research Programme (FP7), which is the tool of the executive body of the European Union (EU) to fund research until 2013. In this huge “melting pot” of opportunities, schemes, research areas, topics, and projects, European researchers will try to find a way to obtain the often desperately needed money to both experimentally test and put into practice projects and ideas. This represents a daunting competition with success rates often lower than 5%. The situation is even more complicated if you are an organic chemist. In fact, at first sight, organic chemistry as such seems to have almost disappeared from the funding priorities of the EU. Is this true? **SYNFORM** decided to learn more about the role of chemistry in FP7 by interviewing an EU officer who accepted the invitation to answer some basic questions on the importance of (organic) chemistry in FP7 – what a chemist should do in order to get funded in FP7, what the opportunities are for extra-European chemical scientists, and much more – for our **INSIDE STORY** in this issue of **SYNFORM**.

One of the **SYNSTORIES** this month introduces an up-and-coming young researcher, Professor Qian Wang, the first in the series **Young Career Focus**. One of the latest articles that was chosen as Synfact of the Month in **SYNFACTS**, namely Professor Kazuaki Ishihara’s fantastic work on the enantioselective halocyclization of polyprenoids, is the focus of another **SYNSTORY**. The third **SYNSTORY** is dedicated to an article dealing with an aspect of copper catalysis in natural product synthesis. Recently, **SYNTHESIS** devoted a Special Topic to “[Copper in Organic Synthesis](#)”, where you can find more in the way of interesting, current research results in this specific area of chemistry.

Let me conclude by inviting all of you, kind readers, to get in touch with us for ideas, comments, and (why not!) criticism, through our e-mail Synform@chem.polimi.it.

Matteo Zanda

Editor of **SYNFORM**

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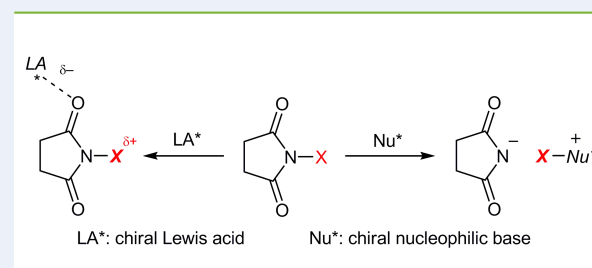
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If you have any questions or wish to send feedback, please write to Matteo Zanda at: Synform@chem.polimi.it

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The Role of Chemistry in the European Seventh Research Framework Programme – FP7

ABSTRACT

■ **Topic description.** In granting the Seventh Framework Research Programme (FP7) with more than € 50 billion for the period 2007–2013, the Council has acknowledged the importance of research as a means to meet the Lisbon objectives.

FP7 is designed to respond to Europe's employment needs, competitiveness and quality of life. The broad objectives of FP7 have been grouped into four categories: **Cooperation, Ideas, People** and **Capacities**. For each type of objective, there is a 'Specific Programme' corresponding to the main areas of EU research policy. The core of FP7 and its largest component by far, the *Cooperation Specific Programme*, fosters collaborative research across Europe and other partner countries, according to several key thematic areas. These themes are: health; food, agriculture, fisheries, and biotechnology; information and communication technologies; nanosciences, nanotechnologies, materials and new production technologies; energy; environment (including climate change); transport (including aeronautics); socio-economic sciences and the humanities; space and security. For more information, see: <http://cordis.europa.eu>.

INTERVIEW

(Questions by M. Zanda, answers by F. Gouardères)

Question 1 | *What are the funding opportunities for a chemist, particularly for an organic chemist, in FP7?*

Answer 1 | It is not only a matter of getting grants for a lab. Chemistry is everywhere in FP7. I will return your question by saying: How can chemists best contribute to achieve the FP7 objectives? Certainly in providing new knowledge and transforming it into innovations. Organic chemistry is an asset for designing innovative medicines or better drug delivery based on nanosystems, for manufacturing performance and 'intelligent' special materials. Combined with research on catalysis, it also contributes to pave the way for reducing greenhouse gases from industrial processes and transports. From frontier research to applied research, the spectrum of opportunities for chemists is broad. FP7 is a flexible programme; there are many opportunities to grab, as long as excellence and innovation are addressed, of course...

Question 2 | *Is it possible for non-EU chemists, and their institutions, to be funded within the frame of FP7? If this is the case, how?*

Answer 2 | Yes, it is possible and not only for chemists. FP7 goes beyond the 27 EU member states, and some cooperation at the international level may be the solution. Of course, certain funding rules apply to non-EU organisations, but indeed, a non-EU organisation can participate and bring added value to a collaborative project. In fact, international cooperation between the EU and other regions of the world could be vital in the Health or Environment (in particular climate change) programmes – I mean, when the problem is global. As far as individuals are concerned, the **People** programme provides significant support for research mobility and career development, both for researchers inside the European Union and externally. The famous 'Marie

Curie actions' are designed to help researchers to build their skills and competences throughout their careers. The programme includes activities such as initial researcher training, support for lifelong training and development via trans-national European fellowships and other actions, as well as industry-academia partnerships. An international dimension with partners outside the EU helps to further develop the careers of EU researchers by creating international outgoing and incoming fellowships to foster collaboration with research groups outside Europe. While celebrating 50 years of 'living together' in the EU, the **People** programme is a great tool for strengthening the European research area and opening it to third-country participants.

Question 3 | *Chemistry is definitely not, as such, one of the FP7 priorities. Many chemists, including myself, have the feeling their discipline is somewhat neglected by the European Commission. Indeed, in order to be funded, chemists often need to provide a service to groups working in other fields, such as biology, physics, etc. Do you share this view? If so, what are the reasons for this situation?*

Answer 3 | Not true, chemistry is a priority. Being by definition a scientific discipline that studies the transformation of matter and its behavior, chemistry has a strong cross-sectoral character. Within FP7 it is embedded in most of the themes: in Health, in Transport, in Energy, in Environment, and it is of course a priority for the theme Nanotechnologies, Materials and New Production (NMP) that is focusing on the transformation of industry and the creation of new business models. As provider of goods, the chemical industry already cooperates with a wide range of downstream users. It is an essential 'component' of the manufacturing chain. Cooperation is the key for achieving success stories. The technology platform 'Sustainable Chemistry' has been fully encouraged by the Commission; it aims at developing further the concept of catalyst for growth and innovation. Understanding better the phenomena that occur at the nano-level, exploiting the potential offered by renewable raw resources, and redesigning production facilities could provide a new impetus. Therefore it is vital to get new knowledge. To achieve this, a measure of 'decompartmentalization,' that is, the breaking down of traditional academic disciplines, at both horizontal and vertical levels (with all actors of the value chain) is needed for solving complex problems and addressing society demands. Chemistry should not be perceived as an isolated area of research.

BIOGRAPHICAL SKETCHES

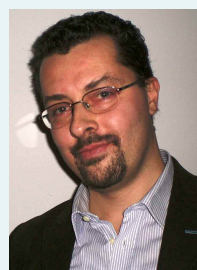


INTERVIEWEE

Frédéric Gouardères, PhD

European Commission
Research Directorate-General
Directorate G "Industrial Technologies" Unit: New Generation of Products.

Frédéric Gouardères has studied science in France and in the UK. He followed the full French Academia course leading to a DEA in physical chemistry (University of Pau), and completed a PhD in polymer chemistry in the UK (Aston University Birmingham, under the supervision of Prof. Allan Amass). He worked in the USA as a researcher in the chemical industry (Elf-Atochem North America) improving, in particular, the synthesis of nanoparticles as performance additives for plastics compounds. In 1997, he returned to Europe and joined the European Commission as Scientific Officer in DG Research. He contributed to the scientific and socio-economic orientation of European Research Programmes (Brite-Euram III, Growth, NMP) as well as their implementation. He is also active in the development of policies in the field of research for new products and their production, with an emphasis on sustainability issues. He is currently Programme Officer in the Directorate 'Industrial Technologies', managing the implementation of the thematic priority 'Nanotechnologies, Nanosciences, Materials, Production Processes' of the Seventh Framework Programme.



INTERVIEWER

Matteo Zanda, PhD

Matteo Zanda was born in 1966 in Alzano Lombardo (Bergamo, Italy). He received the 'Laurea' degree in chemistry at the Università degli Studi di Milano under the supervision of Professors C. Scolastico and G. Poli in 1991. After civil service, he joined the group

of Professor P. Bravo at the chemistry department of Politecnico di Milano and obtained a PhD in industrial chemistry in 1998. He then spent one year as a postdoctoral fellow at ULP Strasbourg (France) under the supervision of Dr. C. Mioskowski. After three years as a junior researcher at Politecnico, he was appointed senior researcher of the National Research Council (CNR) in December 2001. He currently works at the Institute of Chemistry of Molecular Recognition (ICRM) and leads a group of 15 researchers working at the interface of organic chemistry and biomedicine. Matteo Zanda is involved in several projects funded by the European Commission, serves as evaluator of EU projects, and is co-founder of (1) Pyramos (<http://www.pyramos.eu>), an agency that provides international and national project evaluation, monitoring and management and (2) KemoTech s.r.l., a start-up company operating in the field of organic synthesis and bioorganic/medicinal chemistry. He is coauthor of about 120 papers and editor of Thieme Chemistry's **SYNFORM**.

Question 4 | You have mentioned industry–academia partnerships. What are the opportunities offered by the FP7 to a company, particularly a Small or Medium Enterprise (SME) operating in the arena of organic chemistry? Do you foresee more collaboration or more competition between academia and industry for the conquest of the strongly desired FP7 grants?

Answer 4 | SMEs (with less than 250 employees) represent 99% of all enterprises in Europe, and they contribute more than two thirds of the European GDP and provide 75 million jobs in the private sector. They are essential for economic growth and employment in Europe. One can distinguish two kinds of small and medium-sized companies, the ones with R&D capabilities, with highly qualified personnel within an R&D department, and

the ‘more traditional’ companies focusing on the manufacturing of compounds, with less research intensity. FP7 is accessible to both of these types of companies through simplified procedures. The **Capacity** programme offers a scheme in which a group of SMEs outsources its research to a technical center or a university; in return they can improve their products or processes, it is a win–win situation. Under the **Cooperation** programme, an ‘innovative’ SME can participate as partner in a collaborative flagship project. These types of projects are built on added value brought by each of the participants. The calls for proposals detail the specific features and expected impacts of each project and SMEs are sometimes specifically targeted. It is recommended that partners prepare a consortium agreement for securing intellectual property. ■

Matteo Zanda

INFORMATION ++++

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Total Synthesis of (±)-Vigulariol

Angew. Chem. Int. Ed. **2007**, *46*, 437–440

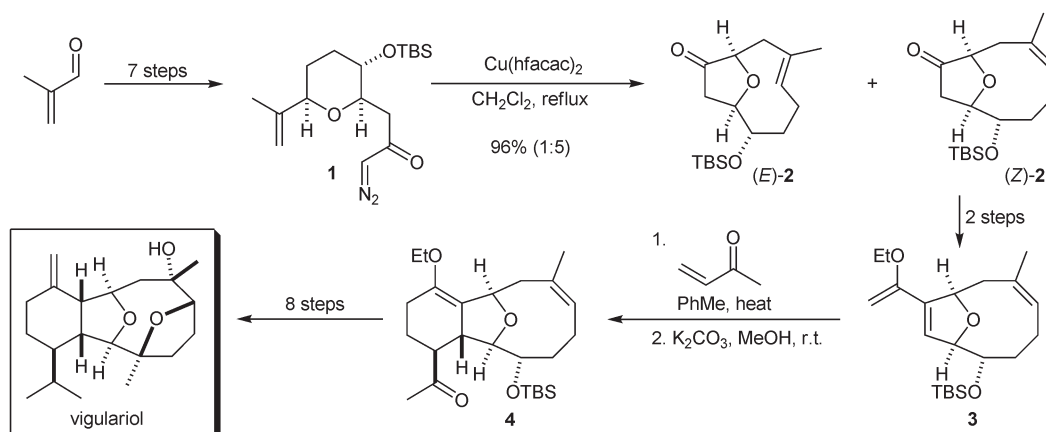
■ The cladiellin (eunicellin) family of natural products comprises over 60 members which have been isolated from marine invertebrates. The cladiellins possess substantial and varied biological activities and several of them display potent cytotoxicity against tumor cell lines (e.g., scleropytin A, which displays activity against L1210 cells at concentrations of 1 ng/mL). The cladiellins are highly alluring synthetic targets as a consequence of the synthetic challenges they present and the significant biological activities that some of them display. In recent years, intensive efforts to synthesize the cladiellins have resulted in impressive total syntheses of several members of the family (see the original article for a bibliography).

Now, Professor J. Stephen Clark and co-workers at the WestCHEM – University of Glasgow (UK) have developed a highly efficient and diastereoselective total synthesis of the cladiellin natural product vigulariol in racemic form, starting from cheap and commercially available achiral starting materials. The synthesis is very short (20 steps) for a target of such complexity (four rings, eight stereogenic centers) and is highly efficient, giving the natural product in 4.0% overall yield (i.e., >85% yield per step). The key feature of Clark's synthesis is the use of a catalytically generated copper carbenoid, prepared from the diazo ketone **1**, to deliver a putative bicyclic oxonium ylide which undergoes [2,3]-sigmatropic

rearrangement with ring expansion to afford the oxabicyclo[6.2.1]undecenone system **2** in exceptionally high yield (96%), with the (*Z*)-**2** isomer predominating. Tandem oxonium ylide generation and rearrangement has not been used to prepare this system previously and the yield is one of the highest (if not the highest) ever recorded for this catalytic sequence. Other notable transformations in the synthesis include the preparation of the tetrahydropyranyl precursor to the diazo ketone **1** using a samarium-mediated cyclization reaction, and the use of a regioselective and stereoselective Diels–Alder reaction (**3**→**4**) to construct the third (cyclohexyl) ring.

“We are interested in developing new methods for the efficient synthesis of ether-bridged polycyclic systems using metal-mediated reactions,” Professor Clark says. “As part of this general program of research, we chose to design a general strategy for the total synthesis of cladiellin natural products that would be applicable to any member of the family and could be applied to the construction of structurally related bioactive marine natural products such as the briarellins and asbestinins.”

“Many of the other cladiellin natural products should be readily accessible from late-stage intermediates generated from the oxabicyclo[6.2.1]undecene system **2**,” Professor Clark continues, “and so, our synthesis constitutes a novel, general and widely applicable strategy for the construction of



this entire class of natural products. Our synthesis of (\pm)-vigulariol also has the highest overall yield of any synthesis of a cladiellin natural product and is also one of the shortest in terms of total steps and longest linear sequence.”

Although Clark and co-workers have prepared vigulariol in racemic form in this study, the synthesis is highly diastereoselective and stereogenic centers are introduced relative to the first-formed stereocenter using substrate control without recourse to reagent control. “A very early acyclic intermediate in our synthesis has been prepared reported as a single enantiomer in the literature, and so both the (+)- and (-)-enantiomers should be readily accessible using the route described in our paper,” Professor Clark notes.

“We are in the process of completing enantioselective total syntheses of several other cladiellin natural products using the same general strategy that was used to synthesise vigulariol,” he concludes. “As part of this program, we are also attempting to identify the biological mode of action of cytotoxic members of the cladiellin family in the hope of discovering new compounds with potential anti-cancer activity”.

“The most efficient and stereocontrolled total synthesis of cytotoxic vigulariol was achieved by J. S. Clark and co-workers,” comments Masahiro Hirama, professor of chemistry at the Tohoku University, Japan and expert in the synthesis of complex polycyclic ethers. “Vigulariol belongs to the cladiellin family of ether-bridged 2,11-cyclized cembranoid marine natural products and possesses the most complex structure



Prof. J. S. Clark



S. T. Hayes

among the family; that is, tetracyclic ring systems including two ether bridges, with eight stereocenters,” Professor Hirama continues. “Their synthesis was very well designed in terms of both ring construction and stereocontrol, and also luck seemed to be with them. The final eight stereocenters were all induced from the initially existing C6-stereocenter that was generated by the Grignard reaction of the first step and disappeared at the key tandem oxygen-ylide formation and [2,3]-sigmatropic rearrangement. This tandem sequence provided the first application to the synthesis of the oxabicyclo[6.2.1]undecane (nine-membered cyclic ether) system.” ■

Matteo Zanda

NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■

Polyprenoids from an Enantioselective Halocyclization Induced by Nucleophilic Phosphoramidites

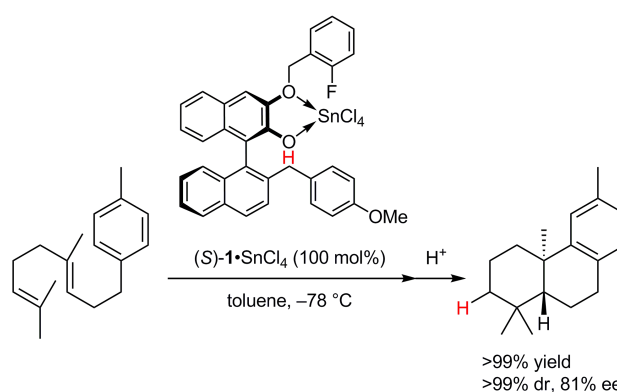
Nature **2007**, *445*, 900–903

■ Polycyclic bioactive natural products that contain halogen atoms have been isolated from a number of different marine organisms. The biosynthesis of these natural products appears to be initiated by an electrophilic halogenation reaction at a carbon–carbon double bond via a mechanism that is similar to a proton-induced olefin polycyclization. Enzymes such as haloperoxidases generate an electrophilic halonium ion (or its equivalent), which reacts with the terminal carbon–carbon double bond of the polyprenoid enantioselectively, inducing a cyclization reaction that produces a halogenated polycyclic terpenoid. Use of an enantioselective halocyclization reaction is one possible way to chemically synthesize these halogenated cyclic terpenoids. Now Kazuaki Ishihara, chemistry professor at the Nagoya University, Japan, and co-workers have developed the first enantioselective halocyclization of simple polyprenoids using a nucleophilic promoter. Achiral nucleophilic phosphorus compounds catalytically promote the diastereoselective halocyclization reaction in dichloromethane to give a halogenated cyclic product in excellent yield. Moreover, chiral phosphoramidites stoichiometrically promote the enantioselective halocyclization of simple polyprenoids with N-iodosuccinimide in toluene to give iodinated cyclic products in up to 99% ee and 99% ds.

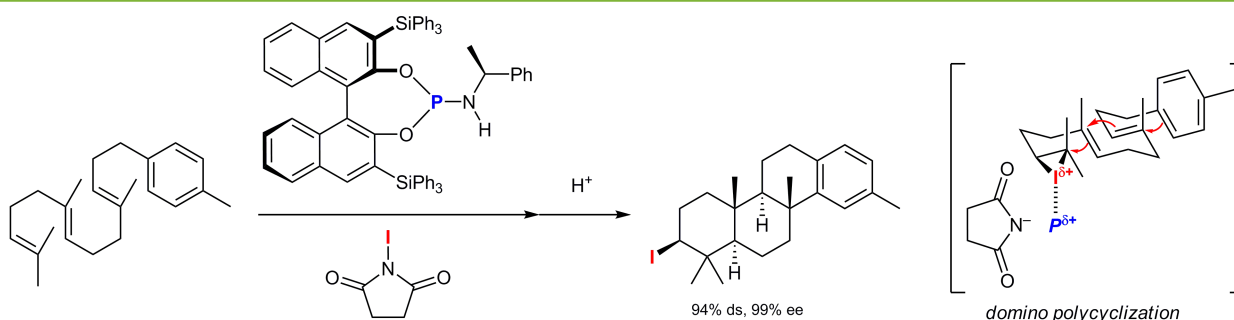
“In principle, the iodopolycyclization of *p*-(homofarnesyl)toluene may provide 32 (= 2⁵) diastereomers and enantiomers of tetracyclic 3-iodoterpenoids,” explains Professor Ishihara. “Surprisingly, the present method gave the desired

tetracyclic 3-iodoterpenoid with 99% ee and 94% ds.”

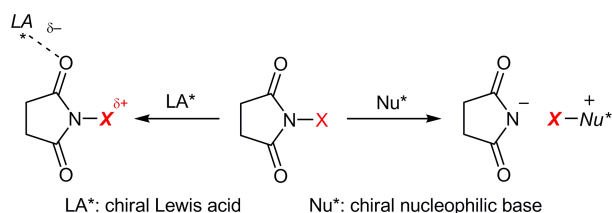
This work has its origins in the year 2004, when Ishihara’s group and Professor Hisashi Yamamoto at the University of Chicago demonstrated the proton-induced enantioselective cyclization of polyprenoids (*J. Am. Chem. Soc.* **2004**, *126*, 11122–11123). The enantioselectivity was induced by a tin(IV) chloride chelated chiral binaphthol derivative, which is called a Lewis acid assisted chiral Brønsted acid (LBA).



“To achieve high enantioselectivity in electrophilic halocyclization,” continues Professor Ishihara, “we focused on the method used to activate the halogenating reagents by chiral nucleophilic promoters (Nu*). In the chiral Lewis acid (LA*) approach, the activated halogen atom (X) would be

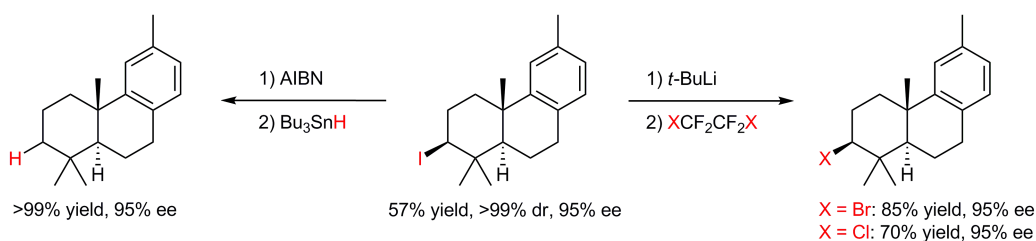


placed far from the chiral environment of the LA* in the active species. In contrast, if Nu* can activate the halogenating reagents, X could be placed close to the chiral environment of the Nu* in the active species, and the halogenated products would be obtained with high enantioselectivities.”



enantioselective halocyclization of polyprenoids induced by catalytic amounts of nucleophilic chiral promoters. “Conventional multi-step synthesis of natural products reduces the overall yield of target molecules,” concludes Professor Ishihara, “whereas biomimetic enantioselective domino reactions induced by small-molecule, artificial enzymes would be more useful for the practical synthesis of natural products and related compounds.”

According to David O’Hagan, professor of chemistry at the EastCHEM – St. Andrews University, UK, “the chiral phosphoramidite-mediated halogenation extends the repertoire of asymmetric halogenation reactions in an impressive manner. This particular reaction has biomimetic connotations with iodination mediated in very high %ee. The reaction is

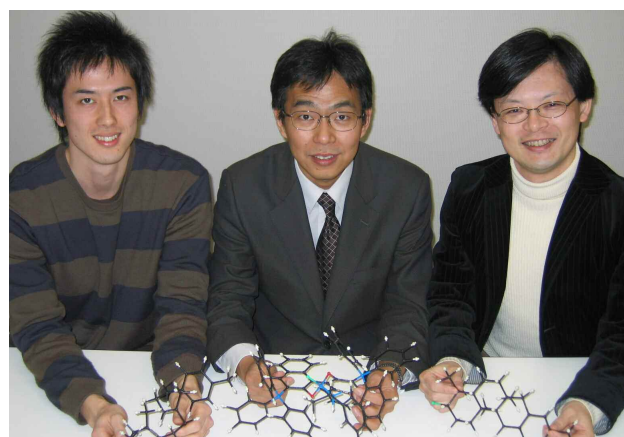


The present methodology provides low enantioselectivity and low reactivity for enantioselective bromo- and chlorocyclizations. However, polycyclic 3-iodoterpenoids can be converted into other halogenated derivatives by stereospecific transhalogenation. Furthermore, polycyclic 3-iodoterpenoids can be converted into dehalogenated products, which are enantioselectively synthesized through LBA-induced polycyclization. “The enantioselective introduction of functional groups into the 3-position of polycyclic terpenoids is useful not only for the synthesis of halogenated bioactive compounds but also for the derivation to a variety of chiral building blocks,” Professor Ishihara adds.

It is extremely interesting to compare the new synthetic methodology with biosynthesis. “FeHeme- and vanadium-haloperoxidases have been discovered in many marine organisms,” explains Professor Ishihara. “The molecular weight of these enzymes is more than 10,000 Da. In contrast, the molecular weight of these enzymes is more than 10,000 Da. In contrast, the molecular weight of the chiral phosphoramidite that we developed is 951. Although the chiral phosphoramidite is required in a stoichiometric amount for the enantioselective iodopolycyclization, it should be noted that the molecular weight of the chiral promoter is less than 1 wt% of that of the natural haloperoxidases.”

In perspective, the next stage is the development of the

exciting as a novel strategy is developed for transfer iodination and it offers new prospects for asymmetric halogenation reactions in a much wider range of substrates. I fully expect that the chiral phosphoramidite/NIS or NBS combination will be explored widely over the next few years in many different laboratories with important new results emerging which move the field forward.”



Prof. K. Ishihara (center, with model of chiral phosphoramidite) developed the new reaction with co-workers A. Ukai (left, with substrate) and Dr. A. Sakakura (right, with polycyclic product)

Matteo Zanda

NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■

Young Career Focus: Professor Qian Wang (University of South Carolina, USA)

■ **Background and Purpose.** From this issue on, **SYNFORM** will regularly meet young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. In this first **SYNSTORY** with a **Young Career Focus**, we learn about Dr. Qian Wang, Assistant Professor at the University of South Carolina, Department of Chemistry and Biochemistry and NanoCenter, Columbia (USA) (wang@mail.chem.sc.edu).

BIOGRAPHICAL SKETCHES



INTERVIEWEE

Dr. Q. Wang

Qian Wang received a BS (1992) and PhD (1997) in organic chemistry from the Tsinghua University, P. R. of China. After a postdoctoral study with Professor Manfred Schlosser at the University of Lausanne, Switzerland,

he joined the group of Professor M. G. Finn as a postdoctoral fellow at the Scripps Research Institute, La Jolla, USA, in 1999, and was promoted to Senior Research Associate in 2001. He started his independent career as an Assistant Professor at the University of South Carolina in 2003. His research interest focuses on novel biomaterial development at the nanometer level based on the combination of organic synthesis, molecular biology, bioconjugation chemistry and materials science. He is also interested in the development of fluorescent protein markers by combinatorial synthesis. Currently, he is an editorial board member of *Experimental Biology and Medicine* for Bionanoscience (the leader of nano-biotechnology at Nanocenter of USC), a member of the American Chemical Society, the Materials Research Society, and the American Association of the Advancement of Science. He has authored or coauthored more than 60 peer-reviewed publications, with about 30 of these stemming from his independent research.

See also: <http://www.chem.sc.edu/people/facultyStaffDetails.asp?SID=245>

INTERVIEW

(Questions by SYNFORM, answers by Prof. Q. Wang)

SYNFORM | Prof. Wang, what is the focus of your current research activity?

Prof. Q. Wang | Currently my research is focusing on exploring the complexity of cellular interactions. However, I am addicted to synthesis, which is always the cornerstone of our research.

SYNFORM | When did you get interested in synthesis?

Prof. Q. Wang | When I was 11 years old, I started working in the lab of my Mom, who was then a chemistry teacher in high school. It was just the most wonderful feeling that you could change the color and smelling of a “thing” just by some simple operation such as adding another solution to it; and you could indeed make a “thing” that never existed in the world before! That was the driving force to let me go further and further in chemistry, particularly in organic chemistry and synthesis.

SYNFORM | What do you think about the modern role and perspectives of synthesis?

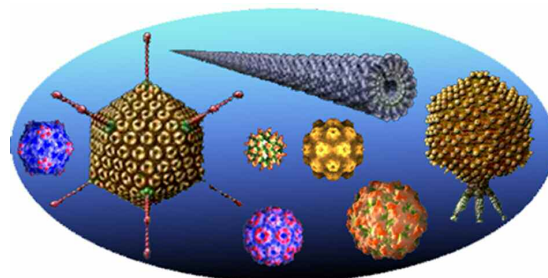
Prof. Q. Wang | Synthesis (organic or inorganic) is the art of manipulating atoms. In the past century, organic synthesis has developed at a dramatic, fast pace. Thousands of new reactions, new reagents, and new reaction conditions have been discovered and invented. Nowadays, synthetic chemists can precisely construct natural products with multiple stereocenters and super-complicated molecular architectures; can build up beautiful organometallic complexes; can synthesize all kinds of polymers or dendrimers with defined structures and properties; and can synthesize colloidal and nanoparticles with controlled size and shape. Certainly it is still desirable to develop new synthetic methodologies for

further improving all of those syntheses for various applications in pharmaceuticals, functional materials, fine chemicals and biotechnologies. On the other hand is the question I keep asking myself – can we develop methodologies to perform synthesis beyond the current length scale but still maintain the precision at atomic level? In my opinion, it will be one of the most important directions for modern chemical synthesis.

SYNFORM | Your research group is active at a fascinating frontier, combining chemistry, biology, and materials science. Could you tell us more about it?

Prof. Q. Wang | As an organic chemist, two major features of biological systems always surprise me: the properties of the assembly of simple molecules are amazingly different from the simple accumulation of the properties of the individual molecules and usually much more advanced, and the signals (information) can be stored and transported in an unbelievably efficient and accurate manner over different length scales. A mammalian cell is one of the smallest units to represent these complexities. For example, life processes between cells and their fluidic and surface environments are complex. Studies have demonstrated that the density and defined spatial arrangements (orientation, distance and geometry) of various ligands account for the complexities of cell response and behavior. Although much attention has been focused on the involvement of such factors, increasing evidence also points to the importance of additional parameters such as rigidity, tensile forces, and topography of the cells' surrounding microenvironment. ***In order to address many of these factors, our approach is to synthesize three-dimensional programmable scaffolds to mimic the native extracellular matrices (ECM).*** Our synthesis aims to control the organization of cell-interactive ligands not only at sub-nanometer precision, but also extending to multi-micrometer scale (or even beyond it). Moreover, the physical properties, including rigidity, tensile forces, electric properties, and topography should also be taken into consideration. Many research groups, including those of George Whitesides, Milan Mrksich, Samuel Stupp, Laura Kiesling, Jeffery Hubbell, and many others, have made fundamental contributions in related directions. In our research, we focus on developing hierarchical assemblies of biological nanoparticles (BNPs) with defined patterns at the nano- and micrometer levels, and using such organized assemblies to study and to manipulate cellular responses and behaviors. The ultimate goal is to model these assemblies as natural ECM, and thereby gain greater understanding of the complexity and dynam-

ics of the interactions between cells and their surrounding environment.



SYNFORM | BNPs are the object of an extremely strong and ever-increasing interest for their potential applications in a number of fields. Could you add something about them?

Prof. Q. Wang | BNPs, including viruses, ferritins, and other protein cages, as self-assembled supramolecules, are amenable to both genetic and chemical modifications – an unparalleled feature in supramolecular chemistry. Using BNPs as starting materials for organic and inorganic synthesis, we are able to control the functionalization precisely to near-atomic level. Using BNPs for chemistry and materials development was pioneered by Stephen Mann, Trevor Douglas, Mark Young, M. G. Finn, John Johnson and Angela Belcher.^{1,2} With our collaborators, we aim to construct hierarchical structures with 1D, 2D and 3D assemblies of BNPs, taking advantage of the uniform size and shape of BNPs.³⁻⁶ Furthermore, we initiated the cell-response study using BNP-assembly based artificial scaffolds.

There are two important differences between BNP assemblies and conventional culture surfaces. First of all, while ECM molecules in conventional cultures are presumably tightly immobilized on the surface, BNPs are more likely to be mobile in response to the forces exerted by the cells during growth and expansion. Secondly, the lattices on BNPs are set with defined distance in nanometer range and the cell-binding ligands can be readily displayed on the surface of BNPs at defined locations. Therefore, with BNP assemblies, it is possible to dissect and control the effects of chemical and non-chemical factors (physical property and nanometer ligand spacing) in cell adhesion and cell behaviors, including growth, differentiation, migration, regeneration, and apoptosis. Our efforts in synthesizing such hierarchical BNP assemblies will offer exceptional model systems to answer many fundamental questions in cell biology, such as relationship between ligand distance spacing and cellular behaviors. The results from these studies can lead to pro-

found benefits in tissue engineering applications by having a flexible, dynamic, nanoscale scaffold that can be programmed with precise spacing to direct cell behaviors such as differentiation, regeneration, proliferation, and maintaining stemness.

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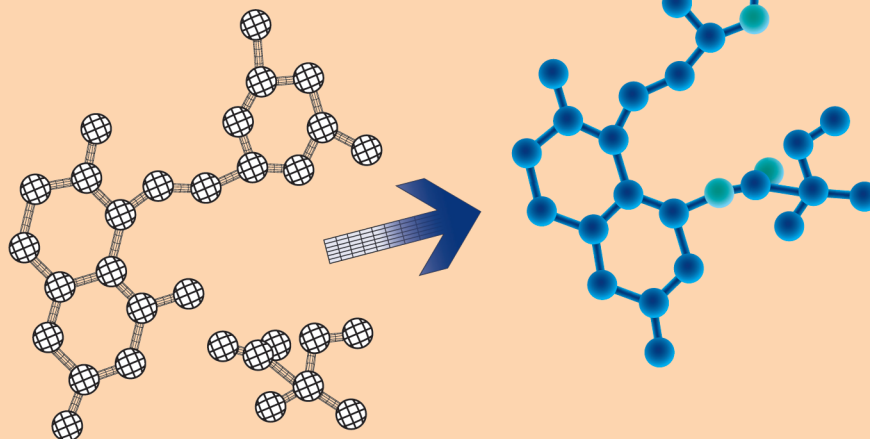
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