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
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 ‘decompartimentalization,’ 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.
**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
Total Synthesis of (±)-Vigulariol


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 (+)-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 diaste-reoselective 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 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
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 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 iodonated cyclic products in up to 99% ee and 99% ds.

“In principle, the iodopolycyclization of p-(homofarnesyl)toluene may provide 32 (= 2^5) 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 Bronsted 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...
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 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.”

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
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).

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 pharmaceutics, 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 subnanometer 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 dynamics 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.

REFERENCES


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► The Impact of REACH (Registration, Evaluation and Authorization of Chemicals) on the Chemical Enterprise

Interviewee: Mr. Geert Dancet, Head of Unit “Reach” at DG ENTERPRISE and INDUSTRY of the European Commission

SYNSTORIES ► ► ►

► Functionalized Cyclopentenes through a Novel Gold(I)-Catalyzed Cyclization of Enynes

(Focus on SYNLETT Cluster on Gold in Organic Synthesis)

► Stereoselective Approach to Natural Products by Intramolecular Cyclobutadiene Cycloaddition/Cyclopropanation/Thermal Rearrangement

(Focus on Synfact of the Month)

► The Gallium(III) Triflate Catalyzed Strecker Reaction of Ketones and their Fluorinated Analogs

FURTHER HIGHLIGHTS ► ► ►

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Review on: Sialic Acid and Structural Analogues: Stereoselective Syntheses
(by A. J. Bennet)

SYNLETT
Account on: New Strategies for the Construction of Molecular Complexity: Enantioselective Cascade Catalysis
(by D. M. C. MacMillan, Thieme-IUPAC Prize winner 2006)

SYNFACS
Synfact of the Month in category „Metal-Mediated Synthesis“: Low-Temperature Cross-Coupling of Functionalized Grignard Reagents

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