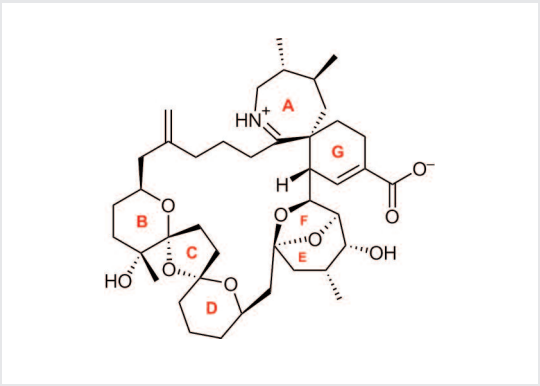
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2008 / 08

SYNSTORIES

- Efficient, Selective, and Green: Catalyst Tuning for Highly Enantioselective Reactions of Ethylene
- FOCUS on the Second European Workshop in Drug Synthesis (II EWDSy), May 25–30, 2008, Siena (Italy)
- Total Synthesis of (+)-Pinnatoxin A
- Thieme-Chemistry Journals Editorial Board Meetings 2008



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Thieme Chemistry

Dear readers,

August is holiday time for many colleagues, particularly in the south of Europe, but ***SYNFORM*** is still fully operative and eager to inform you about the latest trends and the most exciting achievements in organic chemistry. Certainly exciting is the total synthesis of the complex natural structure pinnatoxin A that was elegantly synthesized by the group of Professor A. Zakarian (USA). Another important work covered in this issue of ***SYNFORM*** is the use of an abundantly available building block like ethylene for catalytic enantioselective synthesis, as described by Professor T. V. RajanBabu (USA). For the first time, ***SYNFORM*** presents a report on a symposium, specifically the Second European Workshop in Drug Synthesis, recently held in Siena (Italy). The organizers of conferences who are interested in having their event covered by ***SYNFORM*** are invited to get in touch (*synform@chem.polimi.it*) well in advance. The issue closes with a brief report on the 2008 Thieme Chemistry journals editorial board meetings recently held in Thessaloniki (Greece).

Enjoy your reading!

Matteo Zanda

Editor of ***SYNFORM***

CONTACT

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

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FOCUS on the Second European Workshop in Drug Synthesis (II EWDSy), May 25–30, 2008, Siena (Italy)

From May 25th to 30th 2008, Siena (Italy) hosted the Second European Workshop in Drug Synthesis (II EWDSy). The venue was the prestigious "Certosa di Pontignano", with its beautiful and charming cloisters, the Congress Center of the University of Siena. The site has a rich and ancient history, dating back to 1314 when the order of Carthusian monks was expanding throughout Italy.

In such a culturally stimulating environment, the organizer Professor Maurizio Botta (University of Siena) and the International Scientific Committee, formed by Professor Botta, Professor Maurizio Taddei (Italy), Professor Stephen Hanessian (Canada and USA), Professor Gerhard F. Ecker (Austria), Dr. Hugo Kubinyi (Germany), and Dr. Chiara Ghiron (Italy), put together an impressive list of international speakers. The medieval atmosphere of the Certosa, together with the additional help of fantastic food and wine, combined to produce a magic blend of science and relaxation, to the great advantage of the about 40 "students" attending the Workshop, who were selected on the basis of their curriculum vitae. Not to mention the benefits for the "teaching body"... Some of the lectures that were presented at the II EWDSy are highlighted here.

The first lecture was held by Professor Trevor M. Jones, who gave a conceptually very stimulating and informative talk on the opportunities and challenges for medicinal chemistry in the search for better medicines. Professor Stephen Hanessian, affiliated both to the University of Montreal (Canada) and to the University of California, Irvine (USA), described the recent achievements of his group with proximity-assisted cycloaddition reactions, and provided as usual an inspiring and passionate lesson of organic chemistry. Professor Oliver Kappe from the University of Graz (Austria) explained how to fully exploit the potential of microwaves in organic synthesis. His lecture was followed by Dr. Jieping Zhu from the Institut de Chimie des Substances Naturelles of the CNRS (France), who reported on the potential of multicomponent reactions.

Professor Peter Wipf from the University of Pittsburgh (USA) reported on recent research by his group on the synthesis and medicinal chemistry of highly cytotoxic natural molecules that target the vinca-domain of tubulin, such as disorazoles and tubulysins, which represent very promising potential drugs for cancer chemotherapy. Professor Wipf's talk was the first of a long series dedicated to the topic of cancer. Epothi-

Group picture of the II EWDSy attendees

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lones and their synthetic derivatives are another class of extremely important natural molecules acting at the level of microtubules, interrupting cell mitosis and causing apoptosis; this was discussed by an expert in the field: Professor Karl-Heinz Altmann from the ETH Zürich (Switzerland). The targeting of cancer was the topic presented by Professor Lutz Tietze from the Georg-August-Universität of Göttingen (Germany), who described synthesis and bioactivity of the immunoconjugates recently synthesized by his research group. Professor Jürgen Borlak from the Medical School of Hannover (Germany) gave a highly appreciated and stimulating talk on cancer stem cells, and their possible role in cancer re-growth and metastasis, while Professor Alan P. Kozikowski from the University of Illinois at Chicago (USA) gave a lecture about new findings on histone deacetylase inhibitors, which are also of interest in the field of CNS disorders and malaria. Professor Stephen Neidle from the London School of Pharmacy (UK) covered the use of G-Quadruplex DNAs as therapeutic targets in human cancer, and Professor Carlo Melchiorre from the University of Bologna (Italy) gave a talk on new strategies for identifying high-affinity ligands for the therapy of the Alzheimer disease.

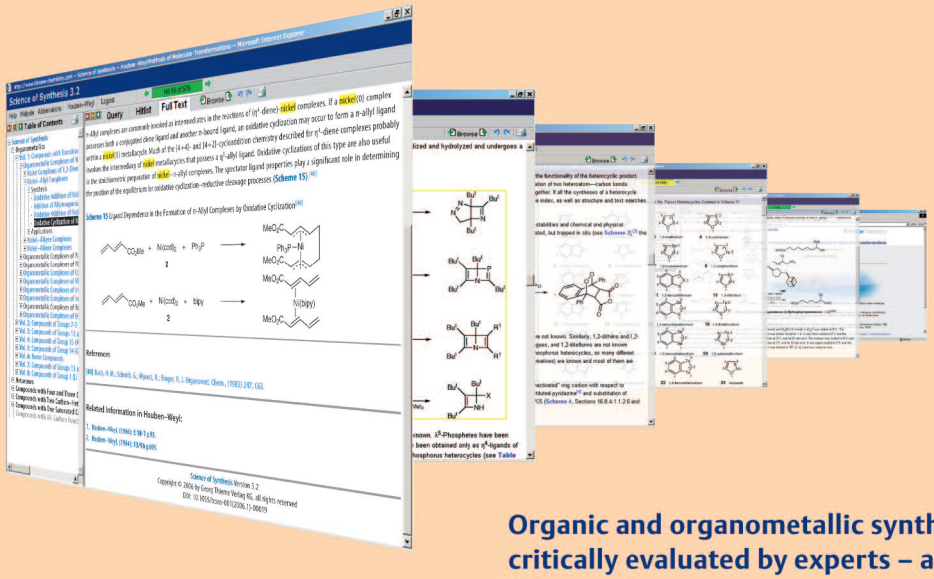
Last but not least, a round-table chaired by Professor Antonio Giordano (University of Siena) addressed the increasingly important topic of "stem cells", with the participation of international experts from academia and industry. The rich program was completed by at least 10 further multidisciplinary lectures, and by a practical training program involving organic synthesis problems, chiral HPLC purifications and microwave-promoted reactions. A small poster session, from which a few communications were selected for an after-dinner oral presentation (with beer and wine served) was also included.

Overall, the II EWDSy was a very useful and extremely well organized event that certainly can be considered as a small gem in the crowded agenda of courses and workshops dedicated to organic chemistry.

Matteo Zanda

INFORMATION ++++

Science of Synthesis



Organic and organometallic synthetic methods critically evaluated by experts – an authoritative information resource

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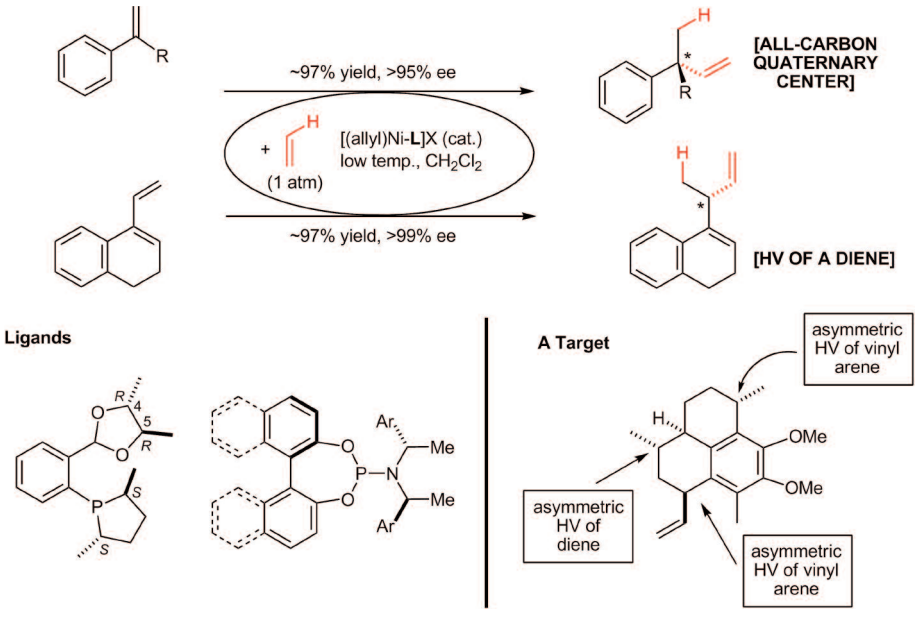
Efficient, Selective, and Green: Catalyst Tuning for Highly Enantioselective Reactions of Ethylene

Org. Lett. **2008**, *10*, 1657–1659

According to Professor T. V. RajanBabu from the Chemistry Department of the Ohio State University in Columbus (USA) the "discovery of efficient catalytic processes for *activation* and *selective incorporation* of abundantly available feedstocks such as ethylene, butadiene, styrene, HCN, CO, and H_2 could have an enormous impact on how chemical intermediates are synthesized in the lab, and eventually manufactured on an industrial scale. Among these," he continued, "processes that yield *practical* levels of asymmetric induction will be especially attractive to synthetic chemists. Seldom has chemistry seen an area where the scientific goals are so challenging, the economic and environmental benefits so obvious, and the intellectual and ethical reasons for doing the research so compelling. Through an approach that relies primarily on mechanistic insights and a systematic examination of ligand effects, our group has been looking for highly efficient and selective protocols for the use of feedstock materials for asymmetric synthesis."

Recently, the RajanBabu group described an improved methodology for the asymmetric hydrovinylation (HV) of styrene derivatives using ethylene as the vinyl group source.

"This paper is an important milestone in our work on the nickel-catalyzed asymmetric hydrovinylation," said Professor RajanBabu, "a reaction that was initially discovered by the Wilke group at Mülheim almost 36 years ago (Review: T. V. RajanBabu *Chem. Rev.* **2003**, *103*, 2845). This reaction received only scant attention until Nobu Nomura in our group discovered a new protocol (*J. Am. Chem. Soc.* **1998**, *120*, 459). Our group also discovered stringent demands with respect to ligands and counter ions (*J. Am. Chem. Soc.* **1999**, *121*, 9899) for this exacting reaction." Since then, a number of successful ligands, among them phospholanes (*Org. Lett.* **2004**, *6*, 1515; *J. Am. Chem. Soc.* **2006**, *128*, 54), phosphinites (*J. Am. Chem. Soc.* **2002**, *124*, 734) and phosphoramidites (the title paper and others cited under reference 6) have been successfully used for asymmetric hydrovinylation reactions of vinyl arenes, 1,3-dienes and strained bicyclic molecules. "The Feringa phosphoramidite, first used by Leitner's group (*J. Am. Chem. Soc.* **2002**, *124*, 736) under our protocols," continued Professor RajanBabu, "are especially valuable for the reaction of vinyl arenes. As this communication illustrates, this highly *tunable* ligand can be easily modified to



New approaches to the control of exocyclic stereochemistry

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achieve the best selectivities observed to date for all classes of substrates, including vinylarenes that produce all-carbon quaternary centers (*J. Am. Chem. Soc.* **2006**, *128*, 5620)." Especially noteworthy is the synthesis of 3-arylbutenes, which are precursors for widely used 2-arylpropionic acids such as ibuprofen, naproxen and ketoprofen. "Enantiomeric excesses over 96% can be achieved for these valuable intermediates," explained Professor RajanBabu. "In more recent work, Craig Smith has since achieved substrate-to-catalyst ratios of over 7000 for some of these transformations, making this one of the most selective and efficient carbon–carbon bond-forming reactions known."

Dan Mans, a recent graduate from the RajanBabu group, completed the total syntheses of various pseudopterosins using back-to-back hydrovinylations of vinylarenes and dienes, demonstrating the excellent functional group compatibility of these reactions. "The intermediates he prepared are potentially useful for other highly sought after molecules such as elisabethin and colombiasin," confirmed Professor RajaBabu. "The hydrovinylation reaction has also been used to construct side chains of steroid D-rings carrying either 20(*S*)- or 20(*R*)- substituents (*J. Am. Chem. Soc.* **2008**, *130*, 9000). These discoveries provide a new approach to the control of exocyclic stereochemistry in several biologically relevant molecules like arylpropionic acids, pseudopterosins and steroids," he added. "Detailed procedures for the syntheses of ligands described in this paper and the hydrovinylation reactions have recently appeared in the literature (*Org. Synth.* **2008**, *85*, 235; 245)."

"Our ongoing research encompasses reactions of bicyclic and acyclic dienes (best to date: 80% ee), use of other metals (Ru, Co) and ligands to expand the scope of the reaction, and further applications in natural product synthesis," concluded Professor RajanBabu. "Exciting leads on ruthenium- and cobalt-catalyzed reactions have been reported by Yi and Vogt. A recent modification of the ruthenium-catalyzed HV reaction (*J. Org. Chem.* **2003**, *68*, 8431) should provide further impetus for work in this area."

Matteo Zanda

From left: Prof. T. V. RajanBabu, Craig R. Smith

About the corresponding authors

T. V. (Babu) RajanBabu received his undergraduate education in India (Kerala University and IIT, Madras). He obtained his PhD degree from The Ohio State University (USA) under the direction of Professor Harold Shechter, and was a postdoctoral fellow at Harvard University with the late Professor R. B. Woodward. He then joined the Research Staff of Dupont Central Research. He returned to Ohio State as a Professor of Chemistry in 1995. His research interests are in new practical methods for stereoselective synthesis focusing on enantioselective catalysis, free-radical chemistry, applications in natural product synthesis, and organic reactions in water.

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Thieme-Chemistry Journals Editorial Board Meetings 2008

The White Tower of Thessaloniki

The 2008 Editorial Board Meetings of the Thieme-Chemistry journals **SYNTHESIS**, ***SYNLETT***, and ***SYNFACTS***, including the supplement ***SYNFORM***, were held on June 20th and 21st 2008, in the vibrant city of Thessaloniki (Greece). The Editorial Boards of the three journals and the staff of the Thieme-Chemistry editorial office met at the Mediterranean Palace Hotel as shown in the group picture. Many topics were addressed in the general meeting session, as well as in the single journals meetings, including a brand new joint Editorial Advisory Board that will be fully operative from 2009 onwards, and a stimulating discussion on the strategies that will be pursued to further increase the quality of the journals. The program was completed by a highly appreciated cultural event – a guided tour of the archaeological site of Vergina, about 80 km from Thessaloniki, that hosts the magnificent palaces and tombs of ancient Macedonian kings, including Philip II, and queens, with perfectly preserved works of miniature art and original paintings. The appointment for the next Editorial Board Meetings is in 2009 in Granada (Spain).

Matteo Zanda

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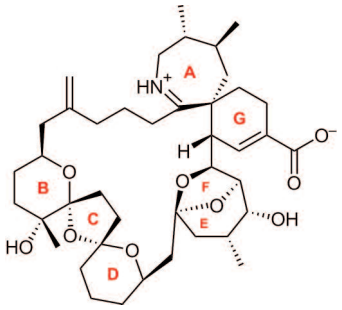
Total Synthesis of (+)-Pinnatoxin A

J. Am. Chem. Soc. **2008**, *130*, 3774–3776; *Synfacts* **2008**, 782 *(SYNFACT of the Month)*

According to Professor Armen Zakarian from the University of California at Santa Barbara (USA), from a certain perspective the total synthesis of complex natural products can be occasionally regarded as a 'guilty pleasure' of Organic Chemistry. "For example," he said, "for many people outside the field, it is sometimes not easy to imagine that the chemical synthesis of 0.9 mg of the powerful marine toxin palytoxin A would be anything more than a high-level chemical chess game, which requires a very expensive chess board with no apparent practical benefits." Possibly, one of the reasons is that the benefits, although substantial, are not direct. "Unlike aspirin," continued Professor Zakarian, "which can be used to relieve a headache, the anesthetic potential of palytoxin A is unlikely to attract consumers, not to mention its prohibitive cost." Another possible reason might be that the endeavor of complex molecule synthesis is largely unpredictable. "One has to have a rational plan," he explained, "but also anticipate that things are not going to go according to the plan. The important *specific* contributions resulting from the work culminating with the synthesis of, for example, palytoxin A, although quite logical in retrospect, could hardly be predicted at the onset of the endeavor. They are, however, now employed in the preparation of pharmaceuticals and many other useful organic materials."

The interest of Professor Zakarian and his group in the synthesis of pinnatoxin A began with a fascination with its chemical structure, while keeping its potent bioactivity in mind. The 27-membered all-carbon macrocyclic framework of the marine toxin incorporates several medium-sized rings, most notably a unique 6,7-spirobicyclic imine, which is a critical constituent of the pharmacophore. In addition, a 6,5,6-spirotricyclic bis-ketal and a dioxabicyclo[3.2.1]octane ring system are embedded in the macrocycle.

"It was pretty clear that our overall synthetic strategy would have to accommodate for the small size of the new group," said Professor Zakarian. "It was one of the very first projects for me as an Assistant Professor, so efficient use of resources was a crucial factor." Thus, an early strategic decision was to develop a convergent synthesis plan. According to Professor Zakarian, another easily identified challenge in the synthesis, based on both the structural analysis and prior art, was going to be the assembly of the spiroimine with its quaternary chiral center at the core. "Thus," he confirmed, "we planned to explore this challenge at the onset of the total synthesis, and our synthesis plan would have to allow for that."



Pinnatoxin A

"Because several groups investigated a Diels-Alder approach to form ring G and the quaternary stereocenter revealing its challenges," explained Professor Zakarian, "we became intrigued by the potential of a [3,3]-sigmatropic process as a solution to this synthetic problem. Our initially conceived tandem sigmatropic Claisen–Mislow–Evans rearrangement, developed by graduate student Matthew Pelc, was very successful in building the quaternary stereocenter and ring G." However, this strategy was ultimately abandoned because Zakarian and co-workers could not properly functionalize the product, in spite of extensive efforts. "Needless to say, it is times like these that put one's mental perseverance to the test," said Professor Zakarian. The group was able to redesign the synthesis almost completely, while keeping the Claisen rearrangement as a key concept behind the synthesis plan. Importantly, this exercise led to a solution for a long-standing limitation of the classic Ireland-Claisen rearrangement, which has previously had poor diastereoselectivity with α-branched esters. Highly stereoselective rearrangement could be achieved using readily available chiral Koga-type bases.

"The synthesis of the B,C,D-dispirotricylic fragment was achieved by Postdoc Chongdao Lu, who joined the group after obtaining his doctorate from the Chengdu Institute of Organic Chemistry, China," said Professor Zakarian. "The total synthesis was ultimately completed thanks to the skillful hands of another graduate student, Craig Stivala, whose previous athletic career in track and field fortunately [for me] ended with an injury in the pole vault," he concluded, "thus allowing him to pursue his true passion – Organic Synthesis!"

According to Dr. David Chen from the Chemical Synthesis Laboratory @ Biopolis, A*Star Singapore, an expert in the

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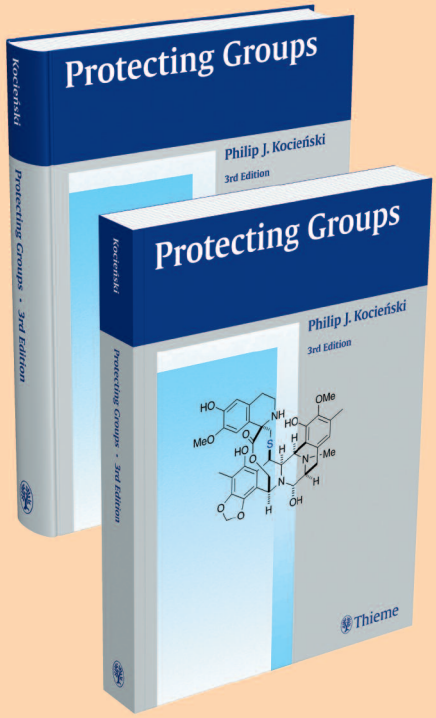
total synthesis of complex natural molecules, "chemical synthesis of marine toxins continues to serve as the cradle for the chemical and biological investigations of these harmful substances. The recent total synthesis of pinnatoxin A reported by Zakarian and Stivala illustrated, in a highly efficient and stereocontrolled manner, one of the most complex examples of chirality transfer by means of an Ireland–Claisen rearrangement. In a conceptually different approach to the pioneering synthesis reported Kishi and co-workers, the macrocyclic scaffold was casted by the venerable RCM reaction. The work reported by the Zakarian group," concluded Dr. Chen, "is a beautiful demonstration of the state-of-the-art technologies in complex natural product synthesis."

Matteo Zanda

From left: Prof. A. Zakarian, C. Stivala

INFORMATION ++++



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In the next issues:

SYNSTORIES

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(Focus on an article from the current literature)

Nickel-Catalyzed Cross-Coupling of Aryl Methyl Ethers with Aryl Boronic Esters
(Focus on an article from the current literature)

Pd(II)-Catalyzed Cross-Coupling of sp^3 C–H Bonds with sp^2 and sp^3 Boronic Acids Using Air as the Oxidant
(Focus on an article from the current literature)

Asymmetric Total Synthesis of (–)-Quinocarcin
(Focus on an article from the current literature)

Stereoselective Synthesis of β-L-Rhamnopyranosides
(Focus on an article from the current literature)

FURTHER HIGHLIGHTS

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Special Topic on "N-Heterocyclic Carbenes" in issue 17/2008

SYNLETT
Account on: Corrole: The Little Big Porphyrinoid
(by R. Paolesse)

SYNFACTS
Synfact of the Month in category "Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions":
Synthesis of Substituted Enol Ethers and Their Synthetic Application

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