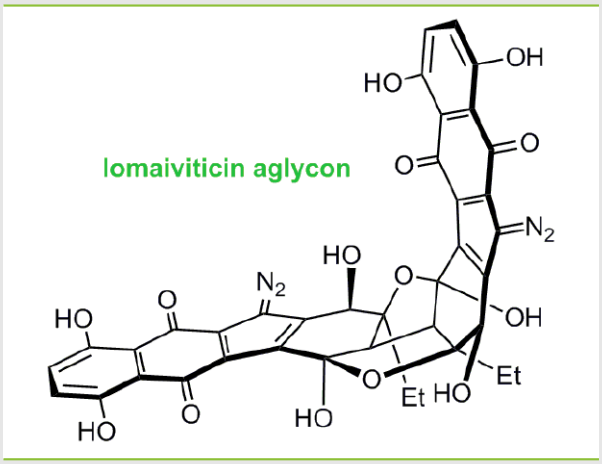
# SYNFORM

*People, Trends and Views in Synthetic Organic Chemistry*

*2011/08*


## SYNSTORIES

- **11-Step Enantioselective Synthesis of (–)-Lomaiviticin Aglycon**




- **Synthesis of *syn*- and *anti*-1,4-Diols by Copper-Catalyzed Boration of Allylic Epoxides**

- **SYNTHESIS/*SYNLETT* Advisory Board Focus: Professor Eugene Babaev (Moscow State University, Russian Federation)**

**CONTACT**

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




Thieme

***Dear readers,***

This is usually holiday time, at least in Europe. Schools are closed, cities become desert, beaches and mountains get very crowded. However, it's also a fantastic period to work in peace, without the hassle of administration and courses. Universities become much less crowded and researchers have more time to deal with the backlog, to perform experiments that were postponed for months, and to read literature and journals which piled up on the office table throughout the previous weeks. Personally, I really enjoy working in summertime! And those of you who are like me (I guess we are not a minority) might also find some time for a relaxed reading of this summer issue of ***SYNFORM***.

The first ***SYNSTORY*** describes the great piece of research performed by Dr. M. Tortosa (Spain) who developed a novel selective stereodivergent synthesis of 1,4-diols from allylic epoxides. The second covers an impressive and herculean synthetic effort performed by the group of Professor S. B. Herzon (USA) who developed an 11-step total synthesis of a fascinating butterfly-shaped dimeric molecule called Lomaiviticin aglycon. The third article is an Advisory Board Profile on Professor Eugene Babaev (Russia).

Enjoy your reading!

*Matteo Zanda*

*Editor of* ***SYNFORM***

## IN THIS ISSUE



**CONTACT**

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



***SYNFORM***, 2011/08
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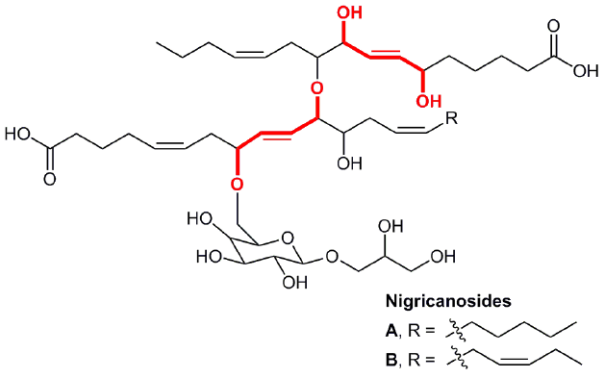
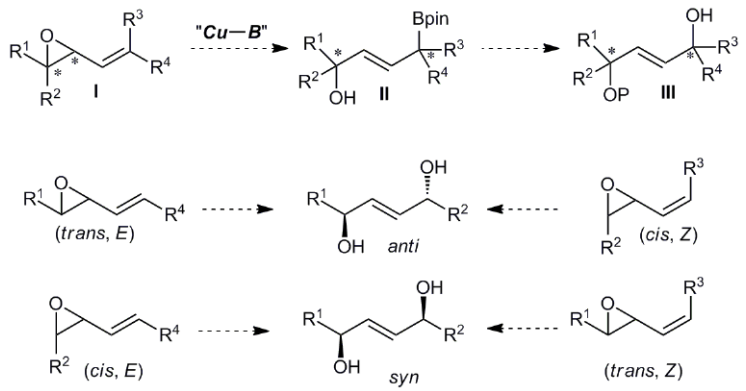
# Synthesis of *syn*- and *anti*-1,4-Diols by Copper-Catalyzed Boration of Allylic Epoxides

*Angew. Chem. Int. Ed.* **2011**, *50*, 3950–3953

The stereochemically defined 1,4-diol motif is frequently found in natural and biologically active molecules and therefore represents an attractive synthetic target. However, there are relatively few methodologies available to synthesize 1,4-diols in a stereocontrolled manner, and often these protocols are not applicable to complex or highly functionalized structural frameworks, such as those featured by many natural compounds. Recently, Dr. Mariola Tortosa from the Universidad Autónoma de Madrid (Spain) developed an interesting and original strategy to synthesize 1,4-diols in stereodivergent *syn* or *anti* configuration.




"From the outset, this project was inspired by a natural product," said Dr. Tortosa. "In 2007, while I was still a Postdoctoral Associate in Professor William Roush's group, Roberge and Andersen published the structures of nigricanosides A and B, two potent anticancer agents (*J. Am. Chem. Soc.* **2007**, *129*, 5822). These natural products contain two 1,4-diol subunits connected by an ether moiety. The structure intrigued me and led me to realize that there was a lack of general methods available in the literature for the stereocontrolled synthesis of 1,4-diols, especially compared with the large number of methods published for the preparation of 1,2-, 1,3- and 1,5-diols," she continued. According to Dr. Tortosa, most of the efforts in this field had been focused on the synthesis of symmetrical 1,4-diols. "These methods are important for the design of new ligands in asymmetric catalysis but are very difficult to apply to the total synthesis of complex molecules," she explained. "A logical method that Nature might use to synthesize the 1,4-diol fragments in the nigricanosides and other natural products would be the hydrolysis of vinyl epoxides. As is often the case, however, what Nature can do very easily is a major challenge in the lab." Dr. Tortosa explained that it is known that the hydrolysis of vinyl oxiranes under standard acidic conditions gives a 1:1 mixture of diastereomeric 1,4-diols.

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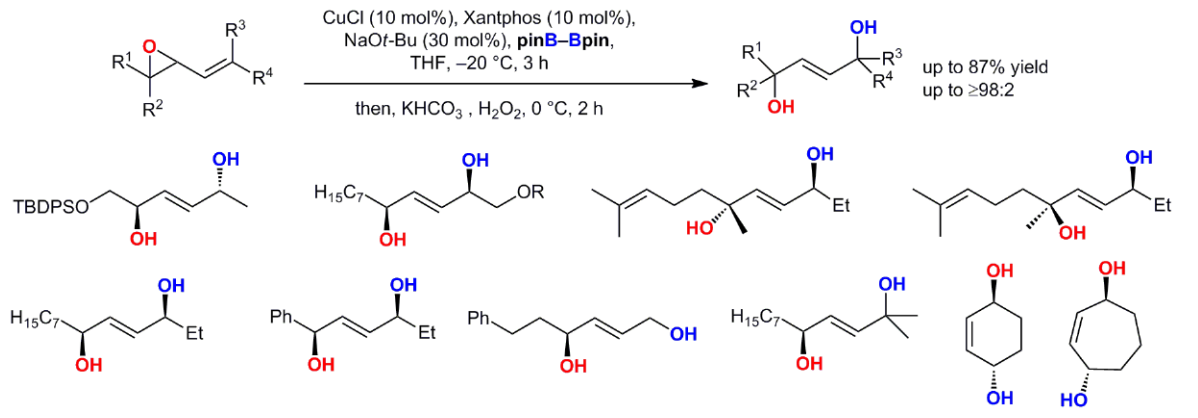
Around the same time as the isolation of the nigricanosides, copper-catalyzed borylations were emerging as a powerful new tool for forming carbon-boron bonds. "In this context," said Dr. Tortosa, "I thought the copper-catalyzed $S_N2'$ addition of diboronates to allylic epoxides was a potentially powerful transformation for the synthesis of 1,4-diols via the corresponding 1,4-hydroxyboronates." This method seemed particularly attractive because it would allow for the synthesis of both *syn*- and *anti*-1,4-diols by proper choice of the double bond and oxirane geometries. "Essentially, this method would constitute a formal stereocontrolled hydrolysis of vinyl epoxides," she added.

Dr. Tortosa revealed that it was not until a couple of years later that she had the chance to start working independently on this project. "Finding the right conditions (10 mol% CuCl, 10 mol% Xantphos, 30 mol% NaO*t*-Bu, –20 °C, 3 h) to carry out the reaction was not easy due to the instability of the 1,4-hydroxyboronate intermediate," she said. "I spent a good amount of time trying to isolate the 1,4-hydroxyboronate without any success. The obvious solution was to oxidize the carbon–boron bond in situ but this was not simple either." Dr. Tortosa explained that standard oxidation conditions, such as $NaOH/H_2O_2$ or $NaBO_3$, did not afford the 1,4-diols in good yield. The key point to solving this problem was to use a milder base such as $KHCO_3$ with $H_2O_2$. "The temperature also played an important role in the diastereoselectivity of the reaction," she continued, "and –20 °C provided a good balance between reactivity and diastereoselectivity. With the right conditions in hand, I could synthesize primary, secondary, and tertiary diols, both *syn* or *anti*, just by proper choice of the epoxide and double-bond geometry (Scheme 1)."

Despite these promising results, Dr. Tortosa was still disappointed by the fact that she could not isolate the 1,4-hydroxyboronates. "I reasoned that in situ protection of the hydroxy group prior to C–B oxidation could increase the stability of these compounds (avoiding intermolecular nucleophilic attack of the hydroxy group at the boron atom) and allow for their isolation. Indeed, I was delighted to find that the protected 1,4-hydroxyboronates were very stable (Scheme 2)." Dr. Tortosa explained that these are highly valuable intermediates that could be used in subsequent diastereoselective transformations such as the conversion of the C–B bond into a C–N to give 1,4-aminoalcohols, allylation of aldehydes and imines, and homologation reactions to afford 1,5-diols. "This observed stability is especially important because it allows a one-pot addition–protection–oxidation sequence to obtain orthogonally protected 1,4-diols in high yields and diastereoselectivities," she continued. "I believe this one-pot process will be useful in the preparation of a number of diol and triol targets where protecting group manipulation is often a challenge. We are currently exploring the reactivity of the 1,4-hydroxyboronates and their application to the synthesis of biologically active compounds."

"In the end," said Dr. Tortosa, "this study provides yet another example of the endless inspiration provided by natural products and of the enormous potential of copper-catalyzed borylation reactions. The seminal work of Professors Ito and Hosomi on α,β-unsaturated ketones (*Tetrahedron Lett.* **2000**, *41*, 6821) and their further development to the allylic substitutions in 2005 (*J. Am. Chem. Soc.* **2005**, *127*, 16034) opened a new area of research." Since then, according to Dr. Tortosa, the asymmetric addition of nucleophilic boron has




*Scheme 1*

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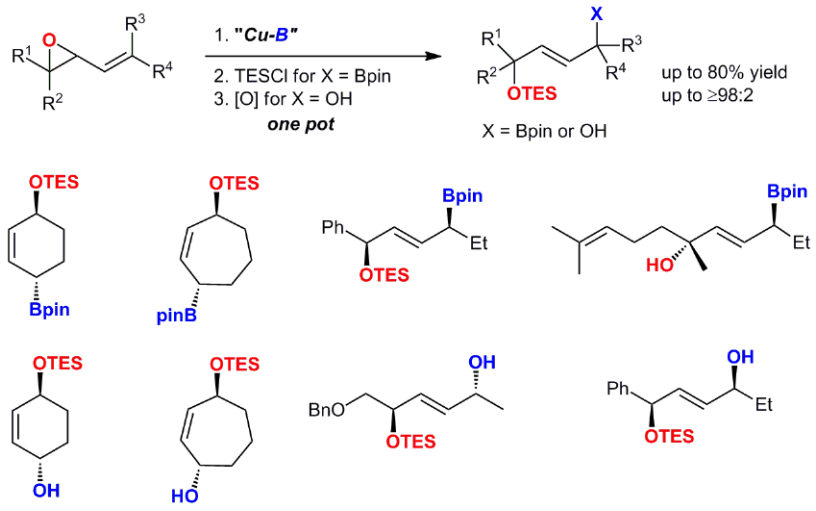


*Scheme 2*

experienced an immense growth and there are still new reactions to explore in this field. "In my opinion, one of the major challenges in this area is to find new ways to avoid the use of air- and moisture-sensitive copper alkoxides that are necessary to generate the boron–copper species. This type of improvement would definitely increase their applicability in industry," she concluded.

*Matteo Zanda*

## About the author

*Dr. M. Tortosa*

**Mariola Tortosa** was born in 1976. She obtained her B.S. in Chemistry from the Universidad Autónoma de Madrid (UAM) in 1999. She then joined the group of Dr. R. Fernández de la Pradilla at the Instituto de Química Orgánica General, CSIC (Madrid, Spain), to carry out her graduate work on the development of new asymmetric methods using chiral vinyl sulfoxides, for which she received the Lilly Young Researcher award. After obtaining her Ph.D. in 2005, she moved to The Scripps Research Institute in Florida (USA) to work as a Postdoctoral Fellow with Professor William R. Roush for three years. Her research in Florida was directed toward the completion of the total synthesis of the antitumor agent Superstolide A using a transannular Diels–Alder strategy. In 2008, she returned to the CSIC to work again with Dr. R. Fernández de la Pradilla. In January 2011, she moved to the Universidad Autónoma de Madrid as a Ramón y Cajal Fellow. Her research interests include boron chemistry and the synthesis of natural products.

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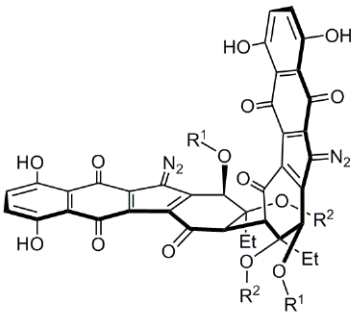
# 11-Step Enantioselective Synthesis of (–)-Lomaiviticin Aglycon

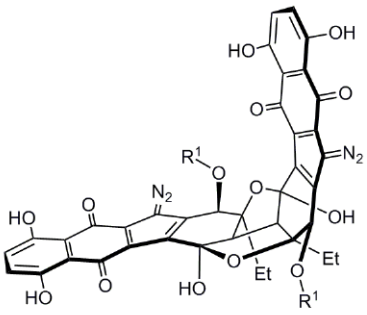
*J. Am. Chem. Soc.* **2011**, *133*, 7260–7263

Lomaiviticin aglycon, the des-carbohydrate derivative of the complex dimeric bacterial metabolites lomaiviticins A and B, is a fascinating butterfly-shaped dimeric molecule that is attracting the interest of many synthetic organic chemistry groups. The lomaiviticins are part of a small family of natural products, often referred to as diazofluorenes, which contain a (relatively) stable diazo functional group. The other well-known members in this family are the kinamycins. Recently, the group of Professor Seth B. Herzon from Yale University (New Haven, USA) reported the first synthesis of lomaiviticin aglycon by late-stage dimerization of two monomeric units.

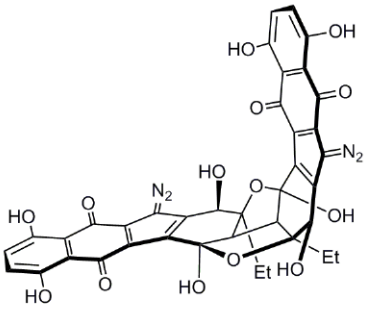
This accomplishment is the result of a herculean synthetic work that presented a number of formidable challenges. According to Professor Herzon, the two most critical parts of the work were (1) the development of a scalable synthesis of 'lomaiviticin monomers' and (2) the development of the dimerization reaction. "Concerning the former issue, we hypothesized that Nature prepares the lomaiviticins by late-stage dimerization of two identical monomers," said Professor Herzon. "This was the strategy we had in mind when we started, and so we set out to develop a method to prepare large quantities of synthetic 'lomaiviticin monomers' so that we could study their dimerization". However, this actually turned out to be quite challenging because the monomeric diazofluorenes, and their synthetic precursors, are relatively unstable. "We had to cycle through many iterations of protecting group schemes until we arrived at a suitable substrate," continued Professor Herzon. "Once we had access to the monomer, we made efforts to scale the chemistry so that we could prepare hundreds of milligrams of material and study the dimerization in detail."



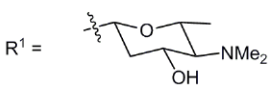
lomaiviticin A



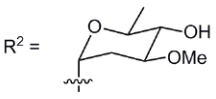
lomaiviticin B



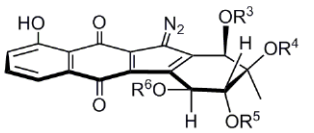
lomaiviticin aglycon



*N,N*-dimethyl-pyrrolosamine



oleandrose



| kinamycin | $R^3$ | $R^4$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| A | H | Ac | Ac | Ac |
| C | Ac | H | Ac | Ac |
| F | H | H | H | H |

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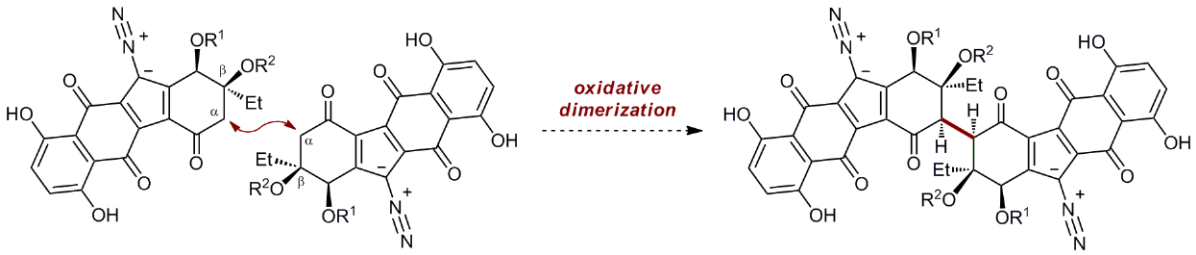
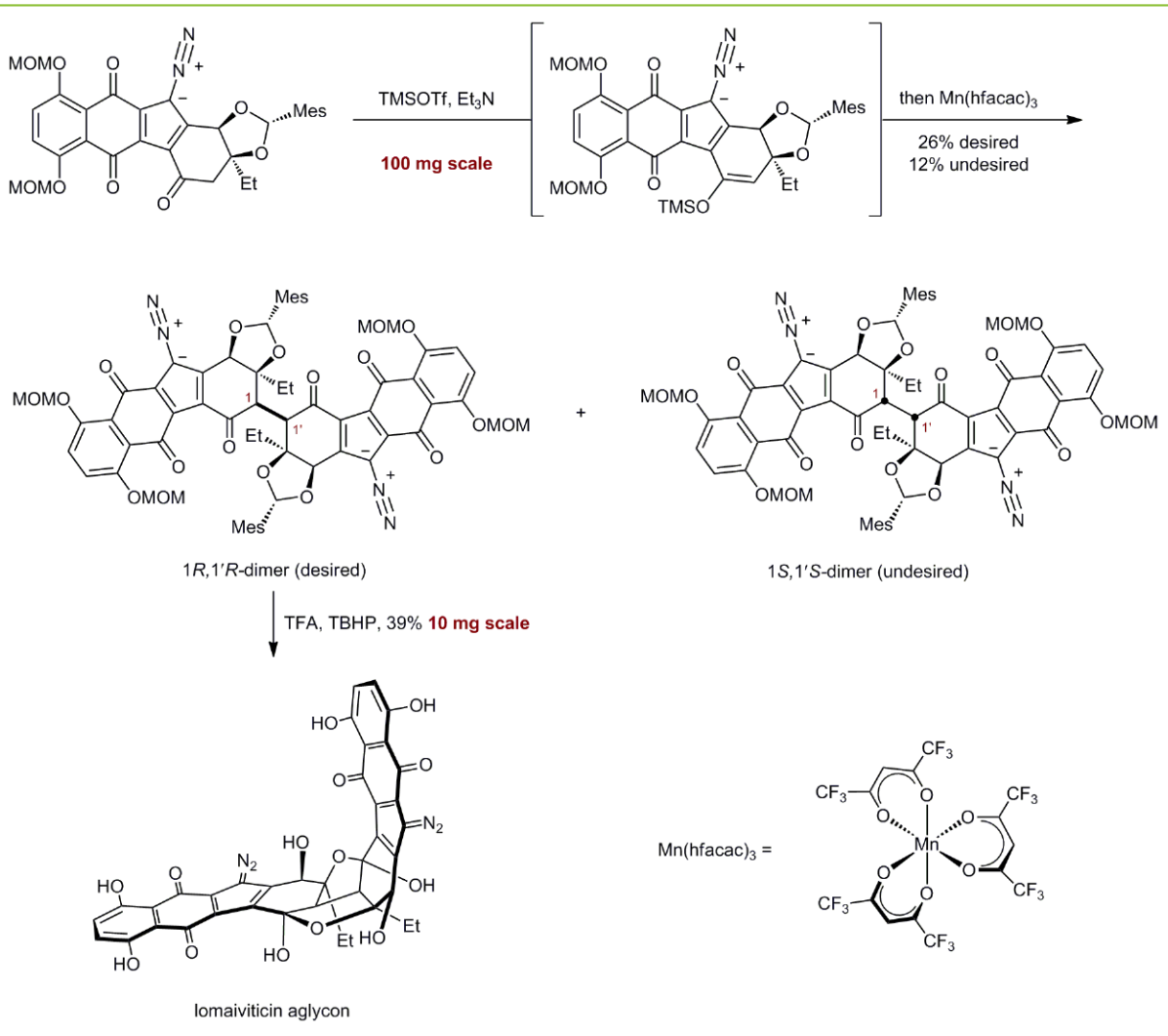



"Concerning the latter issue, namely the dimerization reaction, we examined many conditions to effect it," said Professor Herzon. "Formally, the reaction calls for the oxidative α-coupling of two ketones to form a 1,4-diketone. Many different methods to effect this reaction, involving coupling of ketones, enolates, and enoxysilanes, have been developed. In particular," he continued, "the Baran laboratory has utilized oxidative enolate coupling chemistry in several awesome natural product syntheses. In our system, the best coupling conditions we found involved the oxidation of the enoxysilane of our lomai-

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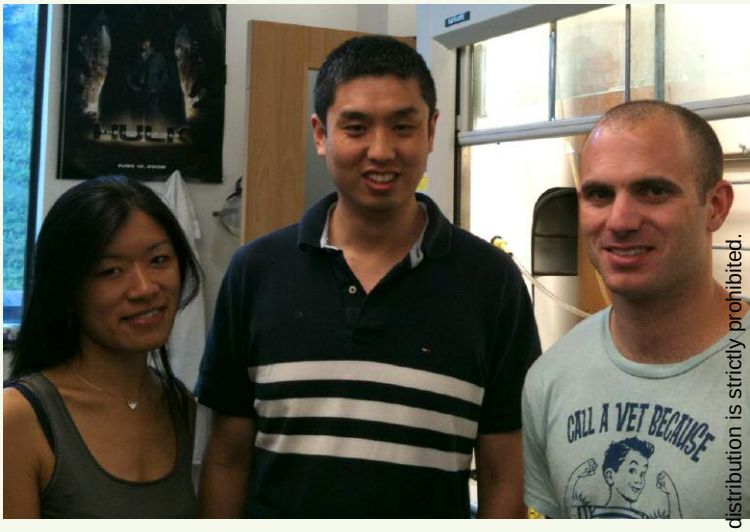
viticin monomers." However, all of the conventional oxidants the team of researchers looked at either led to no reaction or to elimination of the β-oxygen substituent. "We hypothesized that the elimination was due to the oxidant behaving as a Lewis acid toward the β-oxygen, so we began to search the literature for a single-electron oxidant that was powerful enough to effect the oxidative coupling but also less Lewis acidic," explained Professor Herzon. "During our search, we came across manganese tris(hexafluoroacetylacetonate). This is a very interesting complex. The chelating acac ligands render the manganese center coordinatively saturated, so we thought it would be less likely to behave as a Lewis acid toward the β-oxygen. Also, because these ligands are perfluorinated, the complex is a powerful one-electron oxidant," he said. "Jim Mayer had looked at C–H bond oxidations by $Mn(hfacac)_3$ and measured the oxidation potential –0.9 V, almost as powerful as CAN" (*Inorg. Chem.* **2002**, *41*, 2769). According to Professor Herzon, another feature of this oxidant is that it is soluble in non-polar solvents. "If you want to use CAN or copper triflate, you have to use a polar solvent, which may accelerate elimination pathways." he said. "We were able to run the oxidative coupling using the manganese complex in benzene, which may help to decrease the rate of elimination. Ultimately, we found that by controlling the stereochemistry of the acetal protecting group (using the *exo*-mesityl diastereomer) we could control the facial selectivity in the dimerization and obtain the desired coupling product. Although the yield is only modest (26–30%), the reaction is reproducible and scalable and provides a very direct pathway to the aglycon," said Professor Herzon.

Once the Yale researchers had the desired dimer in hand, they were able to work out conditions to effect the cleavage of all six protecting groups in one flask, to form the target aglycon and complete the synthesis.

If organic synthesis is an art, this must be a masterpiece!

**Matteo Zanda**

## About the authors




*From left to right: C. Woo, Dr. L. Lu, Prof. S. Herzon (not pictured: Dr. S. L. Gholap)*



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# SYNTHESIS/*SYNLETT* Advisory Board Focus: Professor Eugene Babaev (Moscow State University, Russian Federation)

**Background and Purpose.** ***SYNFORM*** will from time to time portrait **SYNTHESIS/*SYNLETT*** Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. In this issue, we present Professor Eugene Babaev, Moscow State University (Russian Federation).

## INTERVIEW

***SYNFORM*** | *Professor Babaev, what are your main current research interests?*

**E. Babaev** | It happened that all my life I am "sitting at two chairs" – doing experimental heterocyclic chemistry and developing novel topological concepts as a theoretical (better say mathematical) chemist. Sometimes, these two trends combine. Thus, in the 1990s I worked on the simplified computer description of very complex heterocyclic ring transformations. After this new systematic was built, we saw some "gaps" in it and published our prediction of yet un-

## BIOGRAPHICAL SKETCH

*Prof. E. Babaev*

**Eugene Babaev** was born in Solikamsk (the Ural Mountains, Russian Federation). He graduated from the Chemistry Department of Moscow State University (Lomonossov MSU) in 1982, and since that time has been working and teaching there at the Organic Chemistry Chair. He received his PhD degree from MSU in 1988 and his *Dr. Habilitus* honorable degree in 2007. Since 2001 he is the Head of the Combinatorial Chemistry Center (an educational/research unit of the Chair) and serves as the lecturer and supervisor of the practical combinatorial chemistry semester course. Since 1999 he is also co-employed at Moscow High Chemistry College as lecturer with semester courses on "Heterocyclic Chemistry". During 2008–2010 he co-served as the Head of Laboratory of Molecular Design at the Institute of Federal Ministry of Technology and Export. He worked as a Postdoctoral Fellow in organic chemistry with Professor J. Liebscher (Berlin, Germany, 1988) and in theoretical chemistry with Professors K. Jug (Hannover, Germany, 1993 and 1997–1998), A. Haas (Bochum, Germany, 1990), D. Bonchev (Burgas, Bulgaria, 1991) and R. Hefferlin (Chattanooga, USA, 1992). In 2001 he was a visiting professor in the laboratory of Prof. S. Kanemasa (Fukuoka, Japan).

In 1994 he received an Award from the Chemical Structure Association Trust (USA), in 1995 the Shuvalov's Award and medal (from MSU), in 1998 the International Award for innovation from SPECS Inc. (Netherlands), in 2009 the Mendeleev Award and medal (from the Mendeleev Legacy Foundation), and in 2010 the Innocentive Award.

He is author of more than 150 papers in scientific journals, one patent and several reviews and book chapters in the fields of organic synthesis, combinatorial chemistry, chemical topology and graph theory. He supervised six PhD and 30 Diploma works.

Since 1994 he received 11 research grants from national and international science foundations and 25 grants from industry (including Bayer, Degussa, Boehringer Ingelheim, Astra Zeneca, Nippon Soda, etc.) for his work focusing on the development of new synthetic approaches to molecules having biological and agricultural activities. In the project supported by Upstream Technologies his team prepared libraries of compounds, which displayed strong antileishmanial activity (tested *in vitro* in Canada and Pakistan and *in vivo* in Uganda).

Eugene Babaev was chairman of the series of National Meetings in Organic (2000–2003), Heterocyclic (2000, 2009) and Combinatorial Chemistry (1999–2004). He was founder and (co)chairman of a series of international biennial EuroAsian Meetings on Heterocyclic Chemistry (EAHM, 2000–2010) in Russia and abroad. He has given about 30 talks at universities and companies throughout the world and participated in >100 scientific meetings giving >50 invited/plenary lectures. Personal homepage: http://www.chem.msu.ru/eng/misc/babaev/

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known sub-families of rearrangements. Later (in the 2000s), my team filled some of these gaps: we discovered experimentally completely new families of recyclizations (e.g. oxazole-to-pyrrole, pyridine-to-oxazole, or pyrimidine-to-imidazole/oxazole). Although a recyclization of a heterocycle usually proceeds via a RORC sequence (Ring Opening – Ring Closure), we found that in the certain systems this mechanism can be reversed, being the opposite, RCRO, sequence. This led to a powerful synthetic strategy to some azoles by their conversion into α-fused azolo-azines, followed by (sometimes, spontaneous) azine ring cleavage.

Another of our directions in the design of novel reaction mechanisms is an attempt to find substrates for an elusive $S_{EN}$ mechanism, i.e. "electro-nucleophilic" double substitution. Among (hetero)aromatics the substitution of two groups at a time is common mainly for processes involving dehydrobenzenes via an elimination-addition (EE+AA) sequence. The opposite type ($A_EA_N$+EE) is yet unknown or very rare. We expect to find this new reactivity pattern among extremely dipolar π-amphoteric systems, preferably bicyclic, with strong charge separation, like in dipolar (pseudo)azulenes, indolizines or mesoionic structures. In such systems some familiar $A_E/S_E$ or $A_N/S_N$ reactions may proceed in an unusual way. Thus, common electrophilic substitution, Vilsmeier formylation using DMF, is here accompanied by nucleophilic amination. As we also found, some dipolar nitroindolizines are really "amphoteric", being soluble in acids and alkali (forming stable σ-complexes at different carbon atoms) and, furthermore, giving [8+2] cycloadducts by two opposite polar mechanisms.

**SYNFORM** | *What is your most important scientific achievement to date and why?*

**E. Babaev** | "Achievement" – is somewhat elusive; the recognition by *others* may not necessarily coincide with self-recognized achievement. Thus, finding higher citation of my papers on cross-coupling, I feel that the reason is, maybe, because it is a fashionable area itself. But there were other stories, when our finding of a novel reaction appeared to be of real need to others. Thus, when pharmaceutical chemists from Boehringer Ingelheim explored (in the finest details) our novel conversion of fused oxazoles into indolizines, I was flattered. Finding my pyridinium-oxazole rearrangement in the examination tasks in the US and Japanese universities was also a pleasure. Similarly, when I discovered the simplest route to the entire family of 2-aminoimidazoles, I was happy to see how this idea influenced several groups in the world who are working in marine alkaloid chemistry. This simple class was made before in 8–12 steps, whereas our RCRO methodology allowed for the synthesis of an alkaloid in two (!) steps, making it from 2-aminopyrimidines via imidazopyrimidines. I am glad that a brilliant current work in KU Leuven in this area is, in fact, "exported" as methodology from my Moscow lab (together with our former PhD student).

One result, which personally seems really significant to me, is my theoretical study of topology of the common Lewis formula. For me it was really unbelievable to find (and prove as a theorem) that such an invisible topological property, as is the Euler characteristic of molecular structures, is a novel invariant in chemistry, which is preserved in any reaction.

**SYNFORM** | *Can you mention a recent discovery in the area of organic chemistry, which you consider to be particularly important?*

**E. Babaev** | I was impressed by the recent discovery of carborane superacids, which are hundreds of times stronger than $HSO_3F$ and over a million times stronger than $H_2SO_4$. In contrast to $SbF_5$-containing magic acid mixtures they are kept in glass and give, by C-protonation, crystalline salts with benzene, isobutylene, and even fullerene. Before this work, we drew these carbocations only on paper, but now we may even recrystallize them! Changing $H^+$ in such acids to $CH_3^+$ led to super-methylating agents which have yet unexplored synthetic potential.

**SYNFORM** | *Do you have hobbies, besides chemistry?*

**E. Babaev** | There is a joke that science itself is a "salary-based" hobby for smart people. One of my hobbies is the history of science. I am especially interested in the epoch of Mendeleev and his life; I tried to write his biography and manage the web-project "Mendeleev online". Twice I was even filmed by BBC playing the role of this bearded man. I also enjoy traveling (somebody called it "science-tourism"), having visited about 230 cities in 37 countries.

**SYNFORM** | *What is the main goal in your scientific career?*

**E. Babaev** | To learn Nature by theory and experiment and discover its hidden laws, to share this knowledge with colleagues and pupils, and to encourage and improve the everyday life of people around me in these somewhat uncertain times.

*Matteo Zanda*

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## COMING SOON ►► COMING SOON ►►

# SYNFORM 2011/09 is available from August 19, 2011

### In the next issues:

#### SYNSTORIES

**Synthesis of Conolidine, a Potent Non-Opioid Analgesic for Tonic and Persistent Pain**
*(Focus on an article from the current literature)*

**Pd-Catalyzed Ring-Contraction and Ring-Expansion Reactions of Cyclic Allyl Amines**
*(Focus on an article from the current literature)*

**Enzyme-Catalyzed [4+2] Cycloaddition is a Key Step in the Biosynthesis of Spinosyn A**
*(Focus on an article from the current literature)*

## FURTHER HIGHLIGHTS

**SYNTHESIS**

**Special Topic on "C–H Functionalization/Activation" in issue 16/2011**

**SYNLETT**

**Account on: A Journey through Twelve Years of Interacting Molecules: From Artificial Amino Acid Receptors to the Recognition of Biomolecules and Switchable Nanomaterials**
*(by C. Schmuck)*

**SYNFACTS**

**Synfact of the Month in category "Synthesis of Heterocycles": Gold-Catalyzed Heteroannulation Route of N-Allylureas to Tricyclic Indolines**

## CONTACT

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