

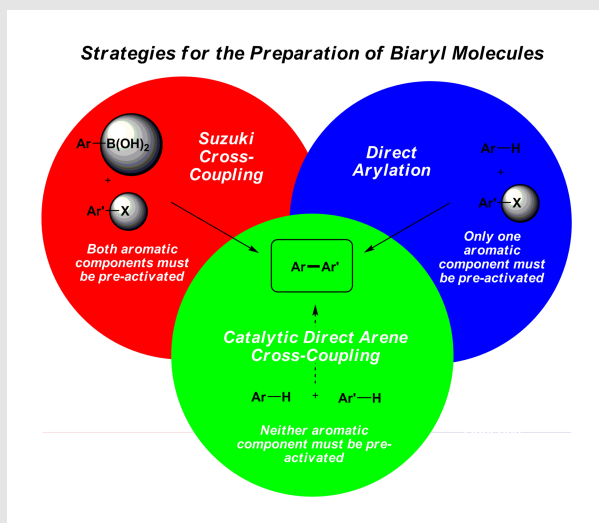
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2007 / 05

SYNSTORIES ■ ■ ■ ■

■ The Catalytic Cross-Coupling of Unactivated Arenes



■ Total Synthesis of (\pm)-Garsubellin A: A Successful Trial-and-Error Strategy

■ Tuning the Rotary Function of a Molecular Motor: Moving through a Loop

■ Design and Synthesis of 12-Aza-Epothilones (Azathilones) – Non-Natural Natural Products with Potent Anti-cancer Activity

CONTACT ++++

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



Dear readers,

The 15th European Symposium on Organic Chemistry 2007 was held from July 8–13, 2007 in Dublin (Ireland) with Professor Pat Guiry chairing the local organizing committee.

The symposium was very well organized in the superb venue of the University College Dublin and featured a strong scientific program including 44 oral lectures and high-level poster sessions. The weather, on the other hand, gave a very important contribution in keeping the attendees very much concentrated on the scientific program, effectively advising against any kind of trip in the beautiful and green Irish countryside.

This new issue of **SYNFORM** presents three **SYNSTORIES** based on very exciting communications presented at the ESOC 2007, namely a challenging total synthesis presented by the Shibasaki group in Japan, new epothilone derivatives disclosed by Altmann's group in Switzerland, and new functions of a molecular motor developed by the Feringa group in The Netherlands. This issue is completed by a **SYNSTORY** based on a recent publication by the group of Keith Fagnou in Canada on a tremendously exciting synthetic methodology that allows for the catalytic cross-coupling of two unactivated arenes. Enjoy your reading!

Matteo Zanda

Editor of **SYNFORM**

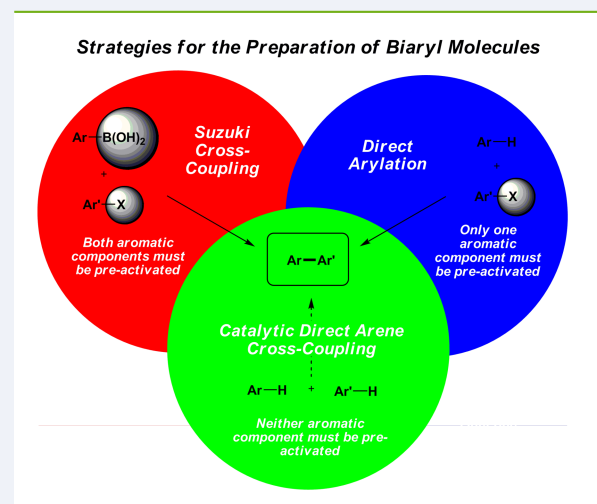
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If you have any questions or wish to send feedback, please write to Matteo Zanda at:
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The Catalytic Cross-Coupling of Unactivated Arenes

Science **2007**, *316*, 1172–1175

■ Biaryl molecules are prevalent in a wide range of molecules of societal importance including medicines, organic light-emitting diodes and electron-transfer devices. For this reason, methods enabling their rapid and cost-efficient synthesis are in high demand. Of the methods available to the synthetic chemist today, Suzuki couplings are arguably the most commonly employed and have had the greatest impact on our ability to prepare these molecules. These couplings are broad in scope, high-yielding and can frequently be performed with very low catalyst loadings. These traits set the bar very high for a new methodology, which aims to improve on the state-of-the-art.

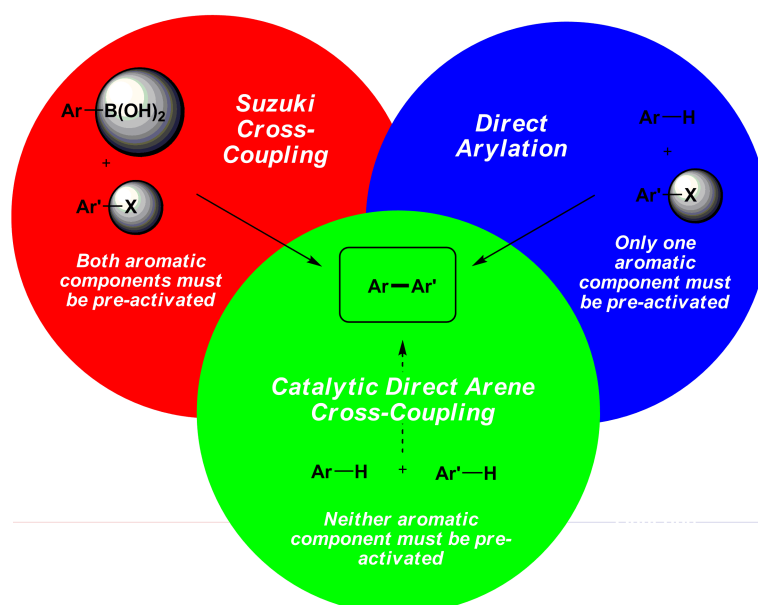
Now, Professor Keith Fagnou and David R. Stuart from the Chemistry Department of the University of Ottawa (Canada) have achieved a breakthrough discovery consisting of a palladium-catalyzed, completely selective, high-yielding cross-

coupling reaction involving a wide range of unactivated *N*-acetyl-indoles and benzenes.

“In our mind, the greatest weakness of Suzuki couplings and their related palladium-catalyzed cousins is the dependence on pre-activation of both aromatic coupling partners,” explained Professor Fagnou. “In the best cases, this reliance adds extra steps, increasing cost and waste. In the worst cases, the pre-activated arene may be synthetically inaccessible or too instable to participate in the cross-coupling. These were the problems that we aimed to study and hopefully resolve.”

“For four years, we have been working to advance the use of ‘direct arylation’ reactions which substitute the arylboronic acid reagent of a Suzuki coupling with the simple arene itself,” he continued. “Early on, we recognized that another strategy, the catalytic coupling of two simple arenes, would

Strategies for the Preparation of Biaryl Molecules

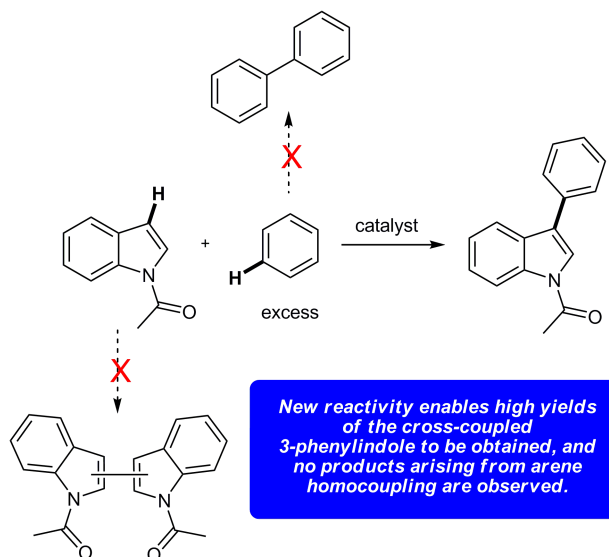


Strategies for the preparation of biaryl molecules

be an even better approach since it would obviate the need for arene pre-activation altogether. The problem was that, up to about one year ago, we had no idea how to achieve such a process in high yield.”

While it has been known for more than a quarter of a century how to oxidatively dimerize arenes, the mechanistic entry point that would allow such a process to be extended to cross-coupling had not been identified. According to Professor Fagnou, the key question that needed to be answered was “How, with two different arenes, can you achieve only cross-coupling and completely avoid unwanted arene dimerization that would lead to complex reaction mixtures and diminished yields?”

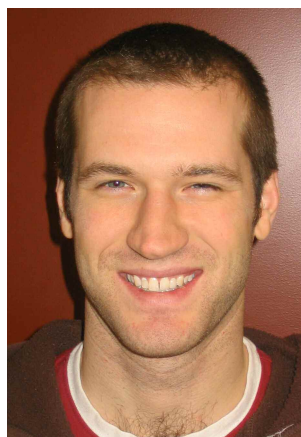
“A potential answer to this question came from our work on the direct arylation of perfluorobenzenes. In these studies, the reactivity of perfluoroarenes was found to be proportional to C–H acidity and diminishing electron density,” he added. “Such reactivity was inverse compared to that previously demonstrated with electron-rich azole substrates that react via an electrophilic aromatic substitution pathway. We reasoned that by appropriately selecting the arenes to predispose them to interact with the palladium catalyst via these dichotomous means the mechanistic entry point could be achieved. The palladium-catalyzed reactions between indoles and benzenes are a validation of this approach to biaryl synthesis.”



“We believe that these processes hold tremendous promise in the efficient synthesis of biaryl molecules,” concluded Professor Fagnou. “At the same time, we recognize the many

limitations that currently exist, including the use of stoichiometric metal oxidants, large excess of the benzene reagent, relatively high catalyst loadings, among others. Mindful of these issues, we are continuing to work to resolve these and other aspects – including broadening the scope, evaluating the regioselectivity, using oxygen (or air) as the terminal oxidant and making the reactions more synthetically useful. Nonetheless, we believe that it is the underlying reactivity that is the most interesting part of these new transformations, and that it is this reactivity that, we hope, will inspire other researchers to further develop these types of transformations.”

According to Professor Atsunori Mori, an expert in the field of arene coupling reactions from the University of Kobe (Japan), “Cross-coupling of aromatic compounds at both of the carbon–hydrogen bonds is a final goal in atom-economy-based synthetic efficiency. The success in the reaction of benzene and indole at the specific C–H bonds by Fagnou is, no doubt, a remarkable milestone in transition-metal catalysis. Further development of the synthetic method is expected to overcome remaining difficulties, for example, the employed amount of benzene and limitation for the second ArH species.”



D. R. Stuart



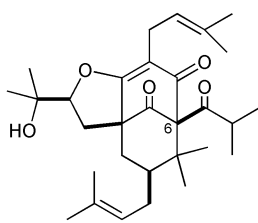
Prof. K. Fagnou

Matteo Zanda

Total Synthesis of (\pm)-Garsubellin A: A Successful Trial-and-Error Strategy

Selected presentation from the 15th European Symposium on Organic Chemistry, Dublin (Ireland), July 8–13, 2007

■ Garsubellin A, although a compact molecule, is one of the most daunting synthetic targets. Both bridgehead centers are quaternary, one of which is adjacent to another quaternary center. Furthermore, a tetrahydrofuran ring is fused with the central bicyclo backbone.



Garsubellin A

This compound potently induces choline acetyltransferase, therefore it is anticipated to be a drug lead for treating Alzheimer's disease. At the recent ESOC 15 conference, Akiyoshi Kuramochi, a PhD student from the group of Professor Masakatsu Shibasaki (University of Tokyo, Japan), brilliantly presented a new total synthesis of this target, that was experimentally carried out by A. Kuramochi himself, Dr. H. Usuda, Y. Shimizu, and K. Yamatsugu. "By the time we started this project," explained Mr. Kuramochi, "there was no completed total synthesis, although Nicolaou's group reported the synthesis of the fully functionalized bicyclic core of garsubellin A. So we aimed at the first total synthesis of this compound."

The key to success was the development of an effective methodology for the highly congested bicyclo skeleton based on a Claisen rearrangement and ring-closing metathesis. By facing many failures with strategies like aldol-type cyclizations, which worked nicely only in the model study, the Japanese team was able to establish a reliable methodology to access the bicyclo[3.3.1] core of polycyclic polyprenylated acylphloroglucinol (PPAP) products including garsubellin A. According to Akiyoshi Kuramochi, "The main problem was to construct the quaternary centers. As for the model studies^{1,2} toward 8-deprenyl garsubellin A, carried out by Dr. Usuda, we found that an intramolecular aldol cyclization was effective in the construction of the C-6 quaternary center. We thus wanted to apply this strategy to the real synthesis of garsu-

bellin A, however, this strategy didn't work at all. Even though we had investigated various aldol cyclizations with some substrates for a year, all of them turned out to be regrettable outcomes."

"Although we considered the situation to be desperate," continued Mr. Kuramochi, "we needed to think of other strategies to overcome the problem. We focused on a palladium-mediated Tsuji–Trost reaction, which was well suited to the cyclization with a diketone substrate. With some precursors for the reaction in hand, we performed various conditions, screening palladium catalysts, ligands, solvents, and so on, but nothing worked. Indeed, due to the crowdedness around the C-6 center, only O-allylation occurred."

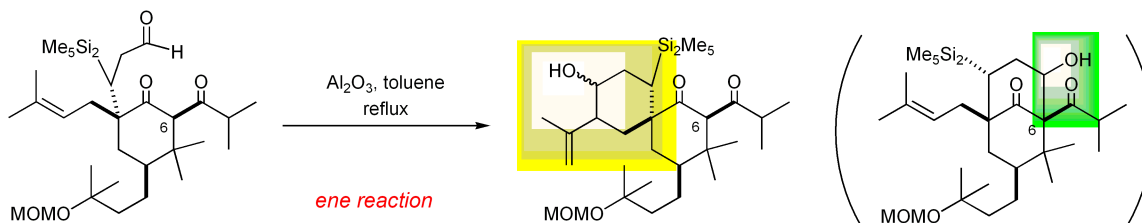
As the third strategy was chosen a Claisen rearrangement, which was not likely to be influenced by the steric factor, so that it would have been hopefully possible to construct the C-6 quaternary center. At this point, something interesting and unexpected occurred. "When we investigated the Claisen rearrangement with a model substrate," explained Mr. Kuramochi, "it, happily, worked well; however, surprisingly a Cope rearrangement occurred at the same time at a different part of the molecule. Although we couldn't obtain the desired product, we were delighted at facing the result because this unexpected event suggested that the Claisen rearrangement would have been effective. Soon after that, in fact, we succeeded in completing the total synthesis of garsubellin A."^{3,4}

As a perspective on this work, Akiyoshi Kuramochi points out that, "To accomplish asymmetric syntheses of PPAPs such as garsubellin A and hyperforin, Dr. Usuda and myself succeeded in developing a catalytic asymmetric Diels–Alder reaction using structurally complex dienes and dienophiles.⁵ With this strategy, highly functionalized PPAP intermediates can be accessed easily. We are now challenging the first catalytic asymmetric synthesis of hyperforin. Mr. Shimizu, Dr. Usuda, and myself are working toward a catalytic asymmetric synthesis of hyperforin."

About the authors. **Akiyoshi Kuramochi** (born 1981) is currently a graduate student in Professor M. Shibasaki's laboratory. He receives research fellowship for young scientists from JSPS. His research interest is developing efficient methodologies to construct complex molecules. **Yohei Shimizu** (born 1984) is currently a graduate student in Pro-

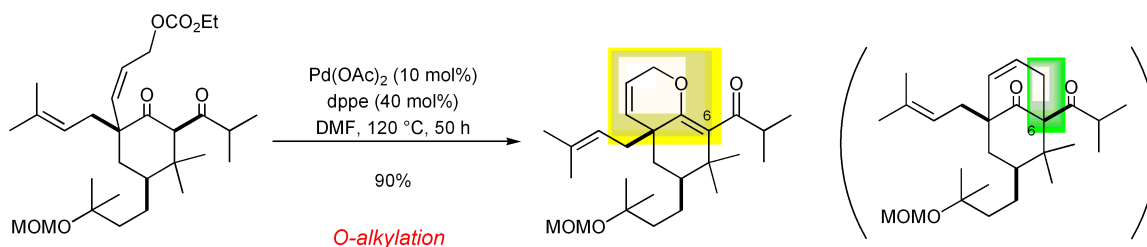
1st generation: Intramolecular aldol cyclization

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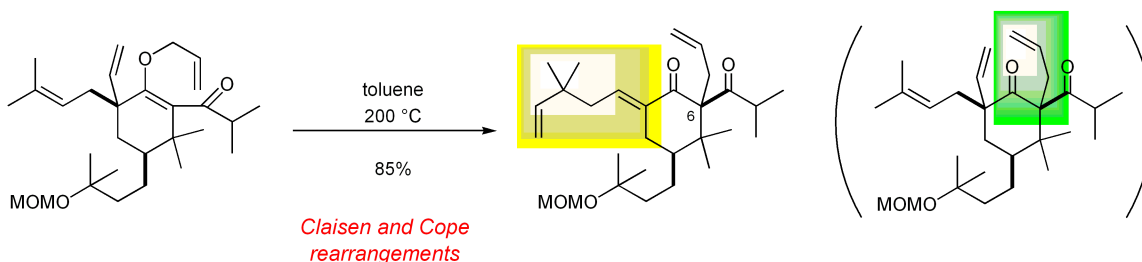
2nd generation: Palladium-mediated Tsuji–Trost cyclization

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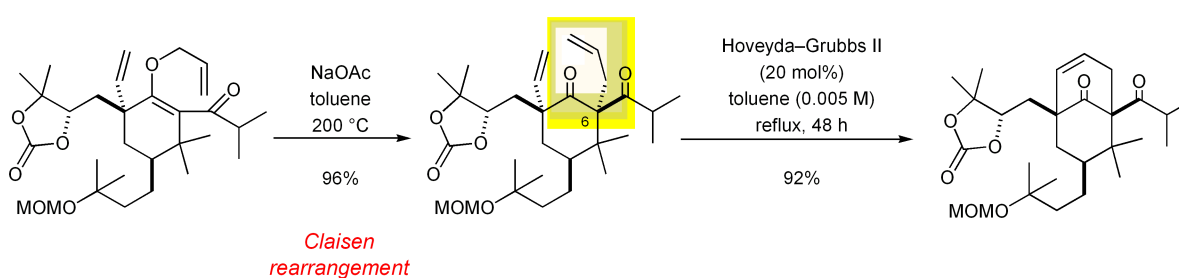


3rd generation: Claisen rearrangement (with a prenyl group)

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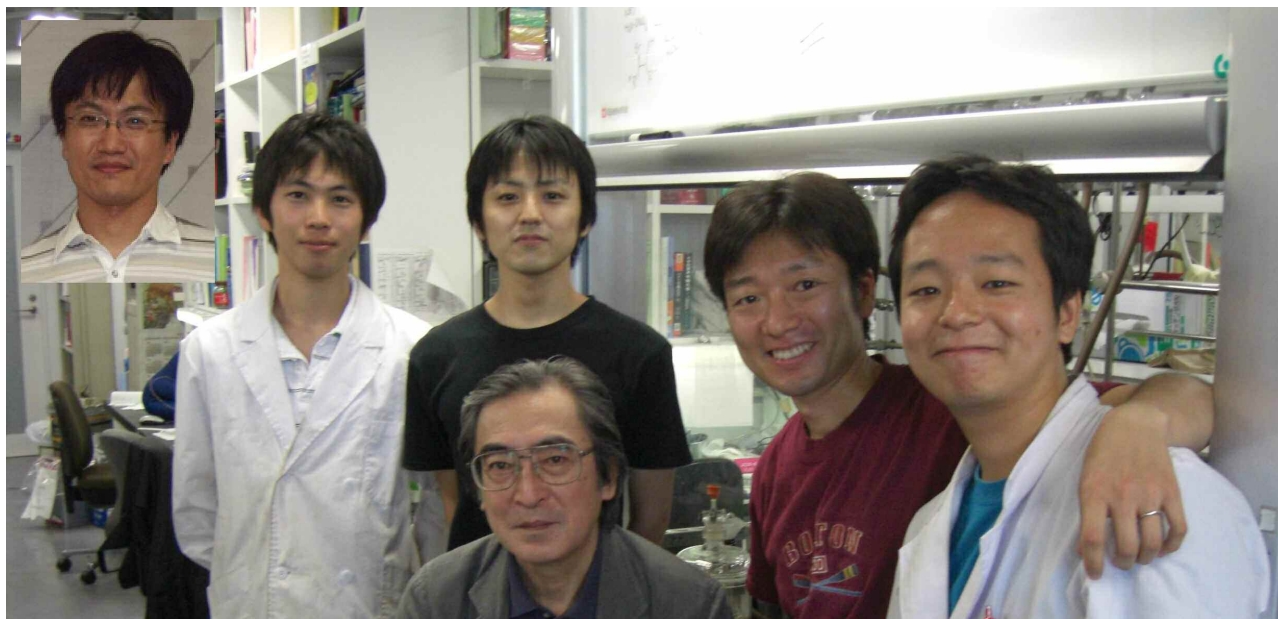


Final generation: Claisen rearrangement (without a prenyl group)



Professor M. Shibasaki's laboratory. His research interest is the biomimetic syntheses of complex molecules. **Kenzo Yamatsugu** (born 1982) is currently a graduate student in Professor M. Shibasaki's laboratory. He receives a research fellowship for young scientists from JSPS. His research interest is the

development of new methodologies to realize efficient syntheses. **Hiroyuki Usuda** (born 1977) received his PhD in 2004 under Professor M. Shibasaki's supervision, and was a post-doctoral fellow in Professor Matthew Shair's laboratory (Harvard University) in 2005. Since 2006, he has worked for



From left: Dr. H. Usuda (inset), Y. Shimizu, K. Yamatsugu, Prof. M. Shibasaki, Dr. M. Kanai, A. Kuramochi

Astellas pharmaceutical company. **Motomu Kanai** (born 1967) was an assistant professor in Professor Tomioka's laboratory (Osaka University) in 1992, and received his PhD in 1995. He joined Professor L. Kiessling's laboratory (University of Wisconsin–Madison) as a postdoctoral fellow in 1996–1997, and then returned to Japan to join Professor Shibasaki's group. He is currently an Associate Professor in the same laboratory. His awards include: Pfizer Award in Synthetic Organic Chemistry (2000), Pharmaceutical Society of Japan Award for Young Scientists (Japan), Thieme Journal Award (2003), and Merck–Banyu Lectureship Award (2005). **Masa-katsu Shibasaki** (born 1947) received his PhD in 1974 under the tutelage of Professor Yamada, and was a postdoctoral fellow in Professor E. J. Corey's laboratory from 1974–1977. He has been Professor at the University of Tokyo since 1991. His awards include: Pharmaceutical Society of Japan Award for Young Scientists (1981), Inoue Prize for Science (1994), Fluka Prize (Reagent of the Year, 1996), Elsevier Award for Inventiveness in Organic Chemistry (1998), Pharmaceutical Society of Japan Award (1999), Molecular Chirality Award (1999), Naito Foundation Research Prize for 2001 (2002), Arthur C. Cope Senior Scholar Award (2002), Medal with Purple Ribbon (2003), Toray Science and Technology Prize (2004), Japan Academy Prize (2005), Sankyo Takamine Memorial Award (2006), Shiohara Prize of Rare Earth Society (2006), and Centenary Medal and Lectureship (2007). ■

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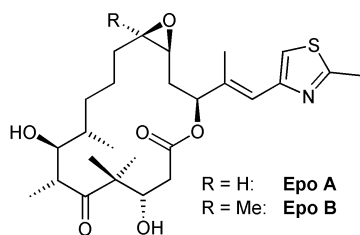
Matteo Zanda

Design and Synthesis of 12-Aza-Epothilones (Azathilones) – Non-Natural Natural Products with Potent Anticancer Activity

Selected presentation from the 15th European Symposium on Organic Chemistry, Dublin (Ireland), July 8–13, 2007

■ Natural products have proven to be valuable lead structures for anticancer drug discovery time and again and there can be no doubt that compounds originating from natural sources will continue to play an important role in the development of new medicines against cancer in the future. “On one hand, advances in isolation and analytical techniques and, in particular, the exploration of secondary metabolites from non-terrestrial organisms, will provide a continuous flow of new and diverse structures with various biological activities,” explained Prof. Karl-Heinz Altmann from the Department of Chemistry and Applied Biosciences of the Swiss Federal Institute of Technology (ETH) Zürich (Switzerland). “On the other hand, the design and synthesis of natural-product-inspired compound libraries by diversity- (DOS)¹ or biology-oriented synthesis (BIOS)² will lead to the creation of new (synthetic) leads for medicinal chemistry.”

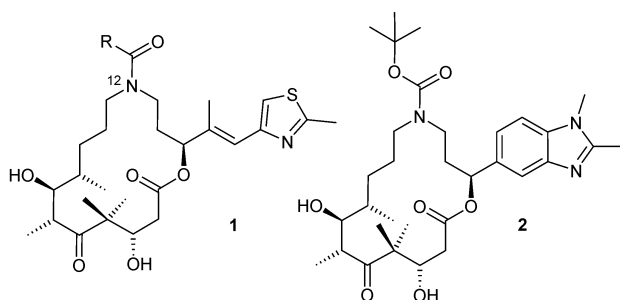
In cases where promising natural products could not be developed into medicines directly, natural-product-based drug discovery has traditionally been dominated by semi-synthetic approaches, which have produced a number of important anticancer drugs, including, for example, docetaxel [derived from paclitaxel or 10-deacetyl baccatin III (10-DAB), respectively], etoposide and teniposide (derived from podophyllotoxin), or irinotecan and topotecan (derived from camptothecin). Semi-synthesis also features prominently in the development of new anticancer drugs from the microtubule-stabilizing natural products epothilones A and B (Epo A and Epo B), with five out of seven epothilone-based agents in clinical trials being semi-synthetic derivatives (and one being the natural product Epo B).^{3,4}



“While semi-synthesis generally offers technical (fewer chemical steps) as well as economic (cost of goods) advantages over de novo total synthesis,” continued Prof. Altmann, “the array of accessible structural analogues is clearly more limited for the former. In our research on new and improved epothilone analogues, we have thus asked the question of whether it would be possible to create epothilone analogues with profound structural alterations that would still retain most of the desired activity of the original natural product.^{5,6} In other words, we wanted to explore the possibility of developing new structural scaffolds, or chemotypes, for microtubule stabilization that might serve as a basis for the discovery of new generations of anticancer drugs.”

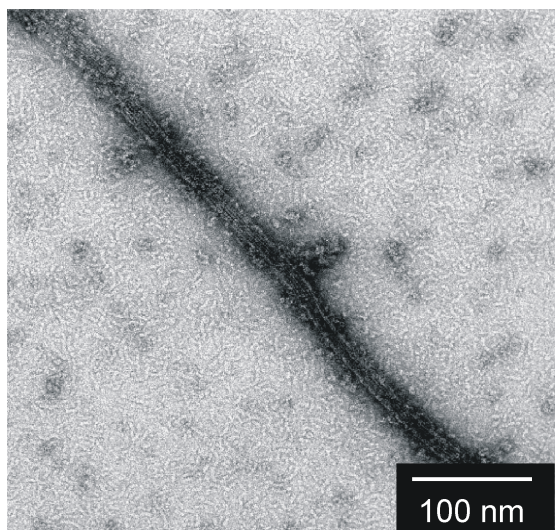
One avenue that Prof. Altmann’s group has followed in this research involves the synthesis and biological investigation of different types of aza-epothilones (“azathilones”), such as **1** or **2**, which are characterized by the replacement of a backbone carbon atom by nitrogen in the epothilone macrocycle.^{6,7} “In general, the potential of natural product analogues with backbone carbon → heteroatom replacements is largely unexplored,” said Prof. Altmann, “which is in spite of the fact that such changes could lead to improved synthetic accessibility and offer the potential to generate large sets of diverse analogues in a rather straightforward manner (for example, through acylation reactions or, in the case of nitrogen, reductive aminations). Perhaps more importantly, however, aza-epothilones such as **1** and **2** may be considered as “non-natural” natural products⁸ that still retain most of the overall structural characteristics of a natural product, but at the same time are structurally unique, as they are outside of the general scope of nature’s biosynthetic machinery for polyketide synthesis.”

Azathilones **1** and **2** are accessible through ring closure by ring-closing olefin metathesis (RCM);⁶ alternatively, **2** has been obtained based on a macrolactonization strategy and construction of the C11–N12 bond through reductive amination.⁶ “We have investigated a limited number of derivatives of type **1**, all of which showed moderate to good antiproliferative activity, with the corresponding *tert*-butyloxycarbonyl derivative (R = *t*-BuO) as the most potent compound,” conti-



nued Prof. Altmann. “Based on these findings, we prepared analogue **2**, which incorporates a potency-enhancing dimethylbenzimidazole side chain.⁶ Very intriguingly, this compound induces the polymerization of soluble tubulin into microtubule-like polymers with the same potency as Epo A or paclitaxel and it inhibits the growth of human cancer cell lines in vitro, with IC_{50} values in the low nanomolar range. Unfortunately, compound **2** shows significantly lower activity than Epo A against a P-glycoprotein-overexpressing multidrug-resistant cell line, but further optimization of **2** may alleviate this problem.”⁶

At the conceptual level, the elaboration of the natural product Epo A into the potent non-natural natural product **2** illustrates that (contrary to widely held belief) the creation of new biologically active scaffolds from natural product leads is a feasible endeavour. “As for every new lead structure, it



Electron-micrograph showing part of a single long microtubule formed from soluble tubulin in the presence of azathilone **2** (20 μ M porcine brain tubulin, 20 μ M **2**)



Prof. K.-H. Altmann

remains to be seen whether **2** and related structures will ultimately offer any true advantages over existing epothilone analogues at the pharmacological level,” concluded Prof. Altmann. “However, even if this were not the case, the results obtained in our studies so far provide a strong impetus for the continued investigation of hypermodified analogues of other natural products, which will allow the biological exploration of natural-product-like structural space beyond the products of nature’s biosynthetic machinery and their simple semi-synthetic derivatives.”

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Matteo Zanda

Tuning the Rotary Function of a Molecular Motor: Moving through a Loop

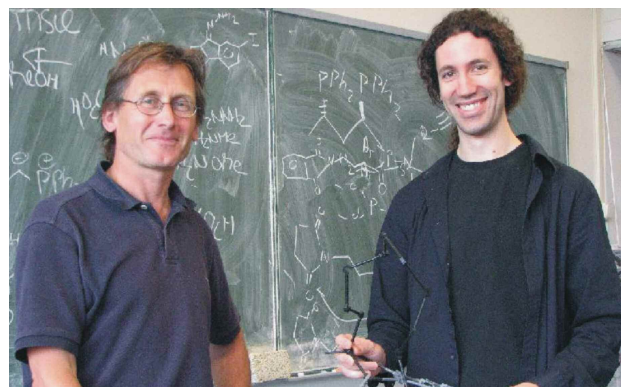
Selected presentation from the 15th European Symposium on Organic Chemistry, Dublin (Ireland), July 8–13, 2007

■ In 1999, the group of Professor Ben Feringa from the University of Groningen (The Netherlands) reported the first light-driven unidirectional molecular motor. The two halves rotate unidirectionally with respect to each other, by irradiation with UV light. “Before we can implement a molecular motor as motor in a nanodevice, we first need to understand their behavior in complex matrices,” explained Giuseppe Caroli, a PhD student in Prof. Feringa’s group. “We found, indeed, that the environment and conditions strongly affect their performance.”

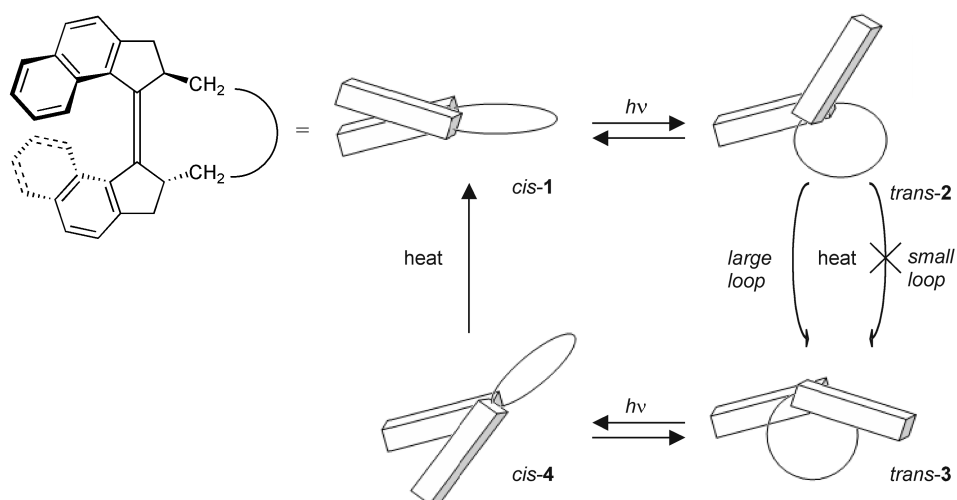
So, how does a motor operate when attached to another moiety? Will its photochemical features be affected? Will its speed change? Will it still be a motor at all? “To explore some of these points, we designed a molecular motor with a novel topology, attaching a loop between the two halves,” he continued. “For the motor to maintain its rotary function, half of it (a naphthalene moiety) must pass through the loop. We have found that a large loop can indeed let the naphthalene unit pass through. A molecular skipping rope? On the other hand, if the loop is small enough, the rotary function is expected to stop at some point.”

This is indeed what happens when the size of the loop is reduced significantly: after the photoisomerization from *cis*-1 to *trans*-2, thermal inversion was not observed. “What we

usually qualify as ‘unstable-*trans*’ (*trans*-2) was in this case found to be more stable than the classical ‘stable-*trans*’ conformation (*trans*-3),” concluded Giuseppe Caroli. “Effectively a molecular motor with a straitjacket, as the mechanical hindrance prevents it from rotating in the way expected. At the moment, we are testing different designs for analogous systems. The behavior of these motors is not always obvious, so new synthetic systems with original features can be expected.”



Prof. B. Feringa (left), G. Caroli (right)



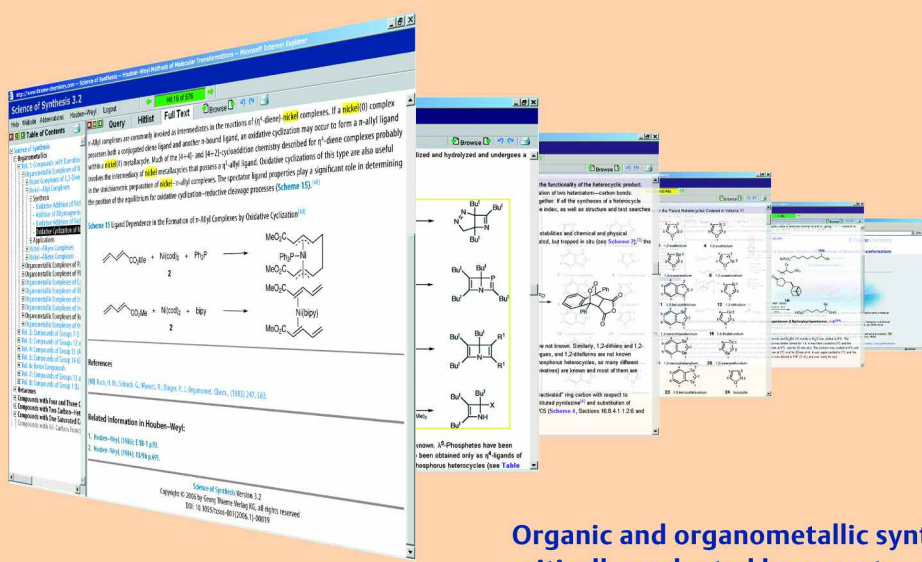
About the authors. **Ben Feringa** is the Distinguished van't Hoff Professor of Organic Chemistry at University of Groningen (The Netherlands). Among his many awards are the ACS James Flack Norris Award in Physical Organic Chemistry

(2006) and the Spinoza Award (2004). **Giuseppe Caroli** completed his undergraduate studies at the University of Bologna in 2002. Since 2004, he has been working towards his PhD under the guidance of Prof. B. Feringa.

Matteo Zanda

INFORMATION ++++

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SYNFORM 2007/06 IS AVAILABLE FROM October 23, 2007

In the next issues:

SYNSTORIES ■■■■

■ Enantio catalysis in Water

(Focus on a presentation at the 41st IUPAC Conference, Turin (Italy), August 5–11, 2007)

■ New Catalytic Transformations – On the Way to “Dream Reactions”

(Focus on a presentation at the 41st IUPAC Conference, Turin (Italy), August 5–11, 2007)

■ Direct Synthesis of Amides (and H₂) from Alcohols and Amines

(Focus on article from the current literature)

■ Snapshot of a Chemical Reaction Intermediate Using a Synthetic Receptor

(Focus on article from the current literature)

FURTHER HIGHLIGHTS +++++

SYNTHESIS

Review on: The Synthesis of Highly Functionalized Pyrroles: A Challenge in Regioselectivity and Chemical Reactivity

(by C. Schmuck)

SYNLETT

Account on: Metal-Catalyzed Asymmetric Synthesis of P-Stereogenic Phosphines

(by D. S. Glueck)

SYNFACTS

Synfact of the Month in category “Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions”: [Rh-Catalyzed Enantioselective Desymmetrization](#)

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