SYNTHESIS Best Paper Award 2015: Harnessing the Intrinsic Reactivity within the Aplysinopsin Series for the Synthesis of Intricate Dimers: Natural from Start to Finish

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Background. Thieme Chemistry and the Editors of SYNTHESIS and SYNLETT present the 'SYNTHESIS/SYNLETT Best Paper Awards'. These annual awards honor the authors of the best original research papers in each of the journals, considering their immediate impact on the field of chemical synthesis.
Erwan Poupon, Laurent Evanno and their co-workers from the Paris-Sud University (France) have won the inaugural SYNTHESIS Best Paper Award for the year 2015. The authors are recognized for their work on the synthesis of intricate dimers from aplysinopsin-type compounds. Paul Knochel, Editor-in-Chief of SYNTHESIS, remarked that the authors describe "in an elegant way how the consideration of biosynthetic aspects has led to the first total synthesis of dictazole B and its cyclobutane analogue. Their total synthesis of tubastrindole B has been achieved through a very original ring expansion starting from the dictazole precursor. In summary, a remarkable work clearly deserving the merits for best paper in 2015."
SYNFORM talked to Erwan Poupon and Laurent Evanno who were happy to share some background information regarding the prize-winning paper as well as their current research activities.

Biographical Sketches

Prof. E. Poupon

Erwan Poupon is full professor of pharmacognosy and natural product chemistry at Paris-Sud University, now part of Paris-Saclay University (France). He obtained his PharmD from the University of Rennes (France) in 1996 and his PhD from Paris-Descartes University (France) in 2000 under the guidance of Professor Henri-Philippe Husson. After a postdoctoral period in the group of Emmanuel Theodorakis (University of California San Diego, USA), he joined the faculty at Paris-Sud University. His scientific interests include all aspects of natural product chemistry from their origin and evolution to their total synthesis.

Dr. L. Evanno

Laurent Evanno received his PhD degree in 2007 from the Pierre et Marie Curie University, Paris (France), working on total synthesis under the supervision of Dr. Bastien Nay at the 'Muséum National d'Histoire Naturelle'. He then undertook postdoctoral research with Professor Petri Pihko at Helsinki University of Technology – TKK (Finland) in 2008 and with Professor Janine Cossy at ESPCI–Paris Tech (France) in 2009. Since 2010, he has been assistant professor at Paris-Sud University (France) and his research interests encompass synthesis and isolation of natural substances especially in the field of indole alkaloids.

Interview >

INTERVIEW

SYNFORM *Could you highlight the value of your award-winning paper with respect to the state-of-the-art, potential or actual applications, and explain the origin, motivations and strategy used for conducting the research?*

Prof. E. Poupon/Dr. L. Evanno We started the 'aplysinopsin project' in early 2013 and we quickly wanted to evaluate the possibility of total syntheses with a high degree of atom economy in a limited number of synthetic steps with a storyline deeply based on biosynthetic considerations. We naively tried to dimerize an aplysinopsin-type starting material: we made numerous unsuccessful and frustrating attempts at this. Mehdi Beniddir (who was a post-doc in the team) made a fortuitous observation that opened the way out of the maze. Indeed, a sample of our starting material left on the bench in front of a window for several months had a slightly different appearance when compared to a freshly prepared batch. A routine LC-MS analysis of the sample indicated the presence of a small, intriguing new peak that could be a new dimeric compound. To be able to isolate the dimer, a sample was crushed daily in a mortar and left directly under the sunlight for one month during August 2013. It was a great pleasure to isolate and characterize a dictazole-type adduct for the first time. The design of a photochemical reactor efficiently mimicking sunlight (just as in a coral reef environment?) was a pressing need. Adam Skiredj, the PhD student involved in the project, brought us the solution through his passion for tropical frogs. Indeed, UV-enriched lamps made for terrariums were used to create sorts of 'artificial lagoons' in the lab mimicking thereby an intense sunlight exposure. To realize the synthesis of dictazole B (a cyclobutane-centered molecule), to achieve a ring expansion toward tubastrindole B (a tetrahydrocarbazole) and to rationalize the 'aplysinopsin cascade', the hard work of optimization had to be done. The project permitted access to these unusual densely-functionalized scaffolds starting only from creatinine, iodomethane and formylindoles as the sole, costless starting materials. Ongoing prospects of the project include an asymmetric version of the sequence. The project excited the whole team for several months, making our nights quite short, and we now feel honored that SYNTHESIS selected our article for the Best Paper Award 2015.

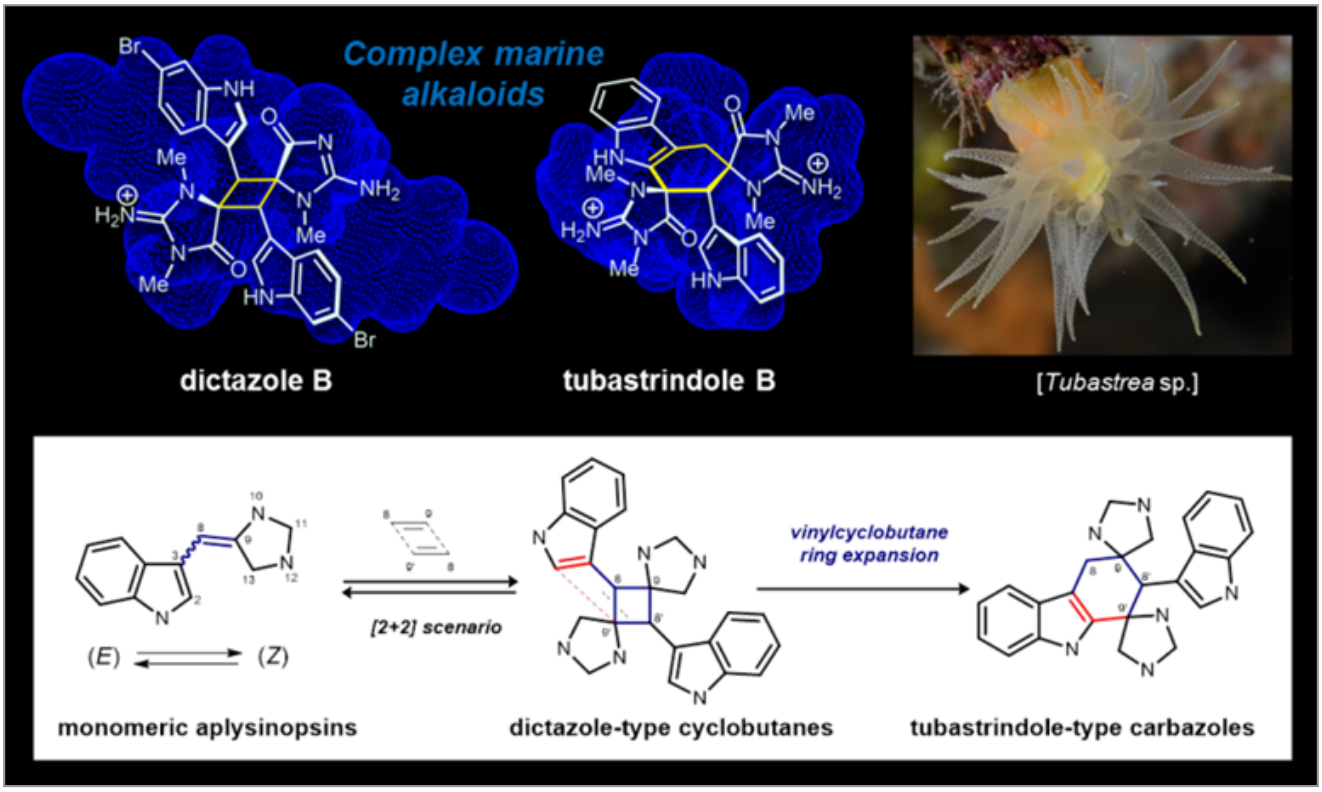

Figure 1 Overview of the project (picture: copyright debitus/IRD)

SYNFORM *What is the focus of your current research activity, both related to the award paper and in general?*

Prof. E. Poupon/Dr. L. Evanno We are fascinated by natural substances, whatever their origin (plants, marine invertebrates, insects, micro-organisms…). We are currently engaged in multidisciplinary projects: discovering new molecules from nature, drug-design projects from natural product scaffolds, answering chemical ecology issues… One of our main sources for reflection (and sometimes philosophical meditation) is trying to understand how **molecular complexity** is generated in nature and has emerged during evolution. For that, biomimetic strategies in total synthesis of complex molecules appear to us as not only a way to reach our synthetic targets, but also an ideal tool to dissect intimate mechanisms of biosynthetic pathways. Our challenge is to find targets that may deploy impressive cascades of reactions from simple building blocks to afford complex skeletons: in that way the 'aplysinopsin project' was ideal. A lesson we have learned in the last few years is that the simplest conditions are often the best in biomimetic strategies (no protecting group, room temperature, sunlight, air…).

SYNFORM *What do you think about the modern role, major challenges and prospects of organic synthesis?*

Prof. E. Poupon/Dr. L. Evanno Quite a difficult question to answer… let us put aside issues which are now consensual (environment-friendly chemistry, alternative carbon resources) and focus more specifically on natural product chemistry and biomimetic approaches. Facing the 'big data area', we wish to try to transfer the huge body of knowledge, techniques and ways of thinking acquired in recent decades in genomics, proteomics and metabolomics to the field of organic synthesis. For this, routine analysis of complex mixtures, chemistry in confined media, supramolecular bio-inspired catalysis and many other tools will undoubtedly be fully integrated in hyphenated projects in the coming years. Should our political and institutional leaders be conscious of the importance of fundamental and basic sciences, many discoveries, breakthroughs and surprises, as well as much fun, are waiting for curious and motivated students. Also, as professors, education is essential for us especially at a period of sometimes re-emerging scientific obscurantism.

The award-winning team, from left: A. Skiredj, Prof. E. Poupon, Prof. D. Joseph, Dr. M. Beniddir, Dr. L. Evanno, Dr. G. Bernadat

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