Biomimetic Synthesis of Bipleiophylline

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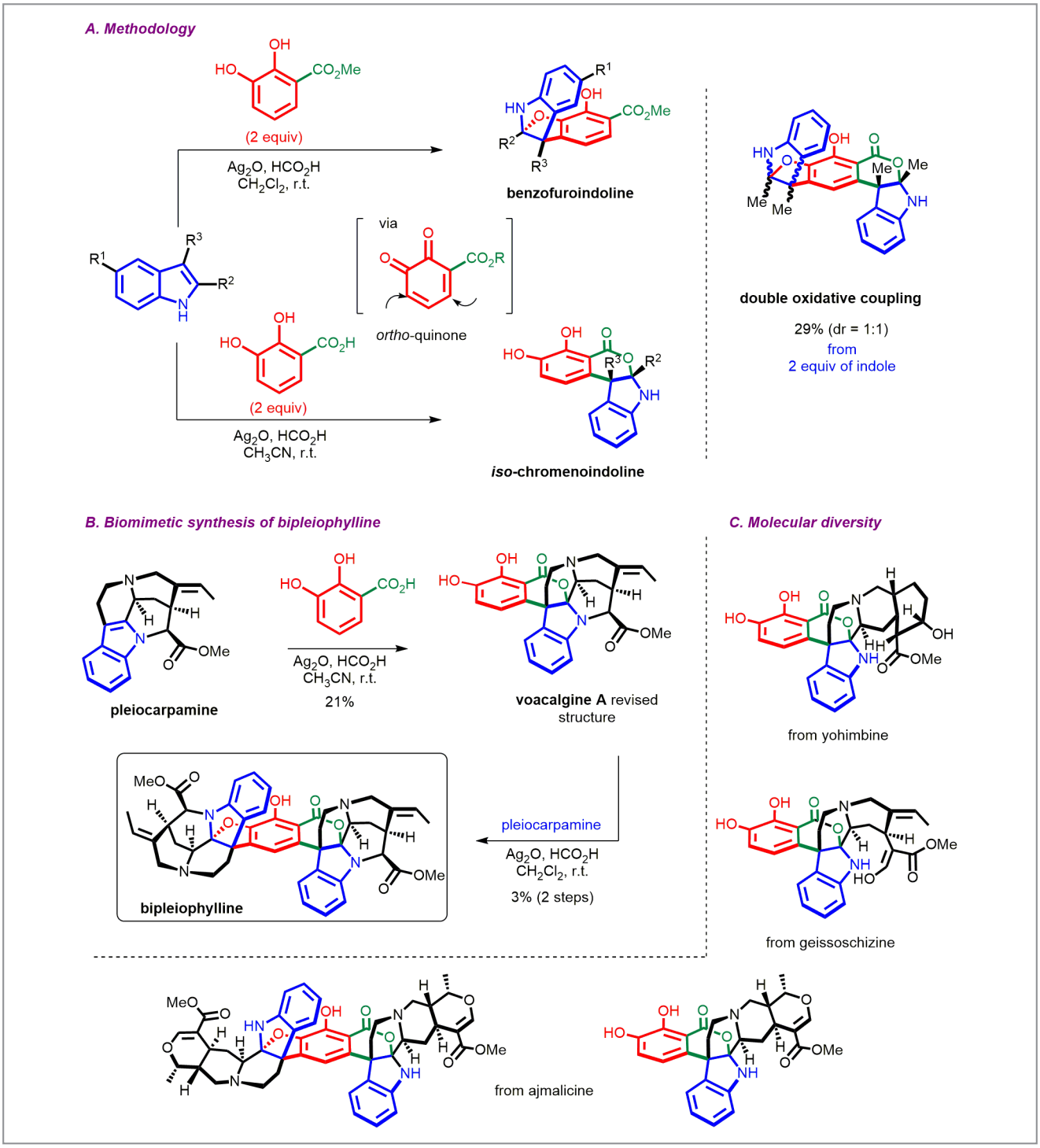
With over 2500 described structures, monoterpene indole alkaloids constitute a class of natural substances all derived from a single common precursor (strictosidine). These compounds are fascinating both in terms of complexity and diversity and are, needless to recall in detail, of great biological value, especially in the field of pharmacology. The synthesis of such molecules represents a challenging task for organic chemists, as well as an opportunity for developing innovative synthetic methods and strategies towards the assembling of these molecular scaffolds. Indeed, several research teams worldwide still consider monoterpene indole alkaloids as stimulating targets of choice in total synthesis. Even more challenging is the access to bis-indole alkaloids of this family. Among them, bipleiophylline, isolated from the bark of *Alstonia angustifolia* in Malaysia, has attracted attention since its discovery in 2008 due to its extreme complexity (*Org. Lett.* **2008**, *10*, 3749). "For instance, it was recently pictured on top of a mountain 'to climb' on the front cover of an authoritative book dealing with the design of synthetic strategies by Hanessian, Giroux and Merner (*Design and strategy in organic synthesis: from the chiron approach to catalysis*, Wiley-VCH, 2013)," confirmed Dr. Guillaume Vincent of the ICMMO, Université Paris-Sud, Faculty of Sciences (France). Pleiocarpamine, a known monoterpene indole alkaloid, emerges as a constitutive key substructure of bipleiophylline. Two units of this monomer are anchored to pyrochatechuic acid via a benzofuroindoline and an isochromenoindoline as heterocyclic linkers.

To tackle the challenge of synthesizing bipleiophylline, Dr. Vincent's group joined forces and knowledge with the team of Professor Erwan Poupon and Dr. Laurent Evanno (BioCIS, Université Paris-Sud, Faculty of Pharmacy, France) within the framework of a grant from the French National Research Agency (ANR).

"Importantly, our group holds expertise in synthetic methodology dealing with the indole nucleus, and has developed several methods to access the benzofuroindoline frameworks that can be found in bipleiophylline (*Angew. Chem. Int. Ed.* **2012**, *51*, 12546; *Angew. Chem. Int. Ed.* **2014**, *53*, 11881; *Org. Lett.* **2014**, *16*, 5752), and also benefits from the experience of Professor Cyrille Kouklovsky in all aspects of synthetic organic chemistry," said Dr. Vincent, who continued: "Furthermore, the group of Erwan Poupon and Laurent Evanno specialize in natural product chemistry and has recently reported the biomimetic transformation of indole natural products (*Angew. Chem. Int. Ed.* **2014**, *53*, 6419; *Eur. J. Org. Chem.* **2015**, 1894; *Eur. J. Org. Chem.* **2016**, 1494)."

The first task was to develop a synthetic method to access selectively both the benzofuroindoline and isochromenoindoline motifs from simple indole starting materials. "The previous methods published by our group proved to be unsuitable in the context of bipleiophylline and we decided to take advantage of the knowledge in biomimicry of our partners in the Poupon/Evanno group to adopt a bioinspired approach," said Dr. Vincent. Therefore, PhD student Natacha Denizot (ICMMO) generated a transient *ortho*-quinone with silver oxide from pyrocatechuic methyl ester on which a 2,3-disubstituted indole could undergo a 1,6-conjugate addition to deliver the benzofuroindoline part which corresponds to the first objective of the methodology. "We were surprised and thrilled to note that the isochromenoindoline part, our second objective, was obtained via a 1,4-conjugate addition, simply by starting from the free benzoic acid instead of its methyl ester," said Dr. Vincent, continuing: "The great potential of our method was demonstrated when we built, simultaneously, both the benzofuroindoline and the isochromenoindoline heterocyclic systems on the aromatic spacer when using an excess of the indole partner."

"The efficiency of this method had then to be evaluated on complex indole alkaloids," said Dr. Evanno and Professor Poupon. They revealed that postdoctoral researcher David Lachkar (BioCIS) first isolated tiny amounts of pleiocarpamine from *Pleiocarpa mutica* and *Alstonia undulata* (provided by Dr. Marc Litaudon and Dr. Vincent Dumontet, Institut de Chimie des Substances Naturelles, France) with the help of Dr. Mehdi Beniddir (BioCIS) and his students in the team. He then meticulously, and successfully, submitted this natural starting material to the oxidative coupling conditions with pyrochatechuic acid and silver oxide. The spectral data of the mono-coupling product corresponded to natural product voacalgine A (*Tetrahedron* 2013, *69*, 10869). The originally assigned structure of the latter was thought to contain a benzofuroindoline unit. "Based on the selectivity obtained during the method development, we decided to reinvestigate the structure of voacalgine A by 2D NMR including HMBC. Indeed, we reassigned its structure which proved to contain an isochromenoindoline," said Dr. Evanno and Professor Poupon. Finally, voacalgine A, the postulated biosynthetic precursor of bipleiophylline, was subjected to a second oxidative coupling


A. Methodology
(2 equiv)
Ag2O, HCO2H
CH2Cl2, r.t.
benzofuroindoline
via
ortho-quinone
(2 equiv)
Ag2O, HCO2H
CH3CN, r.t.
iso-chromenoindoline
double oxidative coupling
29% (dr = 1:1)
from
2 equiv of indole
B. Biomimetic synthesis of bipleiophylline
pleiocarpamine
Ag2O, HCO2H
CH3CN, r.t.
21%
voacalgine A revised
structure
bipleiophylline
pleiocarpamine
Ag2O, HCO2H
CH2Cl2, r.t.
3% (2 steps)
C. Molecular diversity
from yohimbine
from geissoschizine
from ajmalicine

Scheme 1

in the presence of pleiocarpamine which allowed the 'climbing partners' to reach their summit, since bipleiophylline was obtained in two steps and 3% yield from pleiocarpamine.

Dr. Vincent concluded: "To further demonstrate its synthetic potential, robustness and to access molecular diversity, the synthetic method was applied to a few indole alkaloids such as geissoschizine, yohimbine, and ajmalicine. Several isochromenoindoline natural-product-like derivatives were thus obtained."

About the authors

Dr. N. Denizot

Natacha Denizot was born in 1988 in Vienne (France). She obtained her Bachelor's degree in chemistry from the Université d'Avignon et Pays du Vaucluse (France) in 2009. She then was awarded her MSc degree from the Université Joseph Fourier, Grenoble (France) in 2012 with an internship at Givaudan (Switzerland) with Dr. Philip Kraft. In November 2015, she obtained her PhD under the direction of Dr. Guillaume Vincent on the synthesis of benzofuroindoline-containing natural products with a fellowship from the 'Fondation pour le développement de la chimie des substances naturelles et de ses applications sous l'égide de l'Académie des Sciences.'

Dr. D. Lachkar

David Lachkar received his MSc in organic chemistry from the Université Paris-Sud, Orsay (France) in 2011. He obtained a PhD degree working on polyoxometalate catalysis and supramolecular synthesis supervised by Dr. Emmanuel Lacôte at the Institut de Chimie des Substances Naturelles (ICSN-CNRS, France). Then he undertook postdoctoral research with Professor Erwan Poupon and Dr. Laurent Evanno, where he worked on extraction of marine natural products and biomimetic synthesis of indole alkaloids.

Prof. C. Kouklovsky

Cyrille Kouklovsky was born in Paris (France) and educated at the Université Paris-Sud (France). He defended his PhD in 1989 under the supervision of Professor Yves Langlois (CNRS, Gif-Sur-Yvette, France), working on the cationic asymmetric Diels–Alder reaction. Then he moved to a postdoctoral position in Professor Steven V. Ley's research group (University of Cambridge, UK), working on the total synthesis of rapamycin. In 1995, he was appointed as a 'Chargé de Recherche' CNRS at Université Paris-Sud (France), working on asymmetric dipolar cycloaddition reactions and their synthetic applications. He was promoted to Professor of Chemistry in 2003. His research interests are in the fields of synthetic methodology, asymmetric synthesis, and peptide synthesis. He is currently the President of the Organic Division of the French Chemical Society (SCF).

Dr. L. Evanno

Laurent Evanno received his PhD degree in 2007 from the Université Pierre et Marie Curie - Paris 6 (France), working on total synthesis under the supervision of Dr. Bastien Nay at the 'Muséum National d'Histoire Naturelle' (France). 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 the Université Paris-Sud (France). His research interests encompass biomimetic synthesis and isolation of natural substances.

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Prof. E. Poupon

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

Dr. G. Vincent

Guillaume Vincent was born in 1978 in Lyon (France). He graduated in 2002 from the Ecole Supérieure de Chimie Physique et Electronique de Lyon (CPE Lyon, France). During this period, he spent one year at the Dupont Pharmaceuticals Company in Wilmington (USA) working with Dr. Patrick Y. S. Lam. In 2002, he also obtained his MSc degree from the Université Lyon I (France), having worked in the group of Professor Marco A. Ciufolini. He completed his PhD in 2005 under the supervision of Professor Ciufolini. He then joined Professor Robert M. Williams at Colorado State University (USA) as a postdoctoral associate. At the beginning of 2007 he returned to France to the group of Professors Max Malacria and Louis Fensterbank at the Université Pierre et Marie Curie - Paris 6 (France). Finally, at the end of 2007 he was appointed 'Chargé de Recherche' by the CNRS at the Institut de Chimie Moléculaire et des Matériaux d'Orsay at the Université Paris-Sud working with Professor Cyrille Kouklovsky on nitroso-Diels–Alder cycloaddition and total synthesis of natural products. In 2011, he launched an independent research program towards synthetic applications and understanding of unusual reactivity of the indole nucleus.

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