

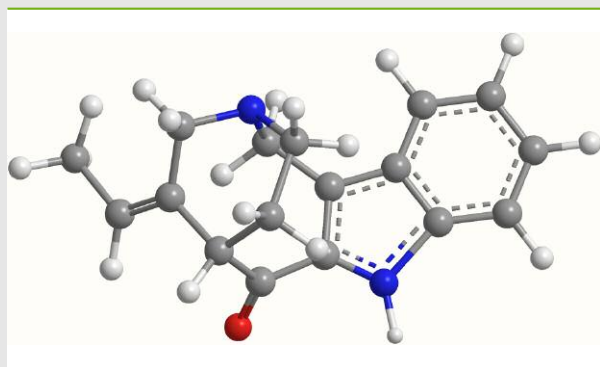
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2011/09

SYNSTORIES ■ ■ ■ ■

■ Synthesis of Conolidine, a Potent Non-Opioid Analgesic for Tonic and Persistent Pain



■ Catalytic Asymmetric Synthesis of Substituted Aziridines

■ Young Career Focus:
Dr. Rebecca Goss (University of East Anglia, Norwich, UK)

CONTACT ++++

Your opinion about SYNFORM is welcome, please correspond if you like:
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Thieme



Dear readers,

This issue of **SYNFORM** welcomes back an editorial feature which was first published long time ago, precisely in the second issue ever of **SYNFORM** (Issue 2, 2007): the **Young Career Focus**. At that time we wrote that “From this issue on, **SYNFORM** will regularly meet young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership.” Unfortunately, we could not manage to “regularly” publish those special **SYNSTORIES**, which now come back after more than four years with an interview to Dr. R. Goss (UK), a former Thieme Chemistry Journal Awardee. Further Young Career Focus articles are already in preparation, so this time we can dare to say again that this will become a regular feature of **SYNFORM**. The issue is completed by an overview of an outstanding piece of chemistry developed by the group of Professor G. C. Micalizio (USA) consisting in the total synthesis of the non-opioid analgesic conolidine, and by another **SYNSTORY** investigating the behind-the-scenes of the novel exciting methodology for the catalytic asymmetric synthesis of substituted aziridines developed by Professor W. Wulff (USA).

Enjoy your reading!

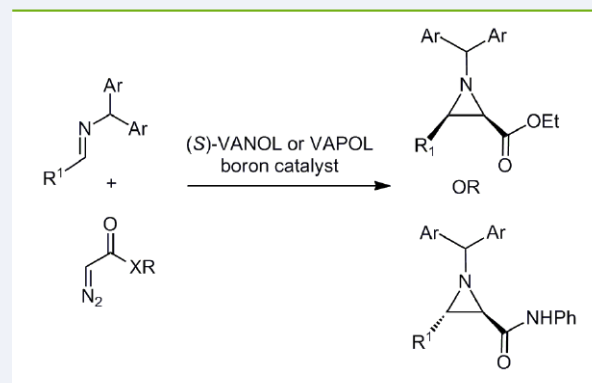
Matteo Zanda

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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NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■

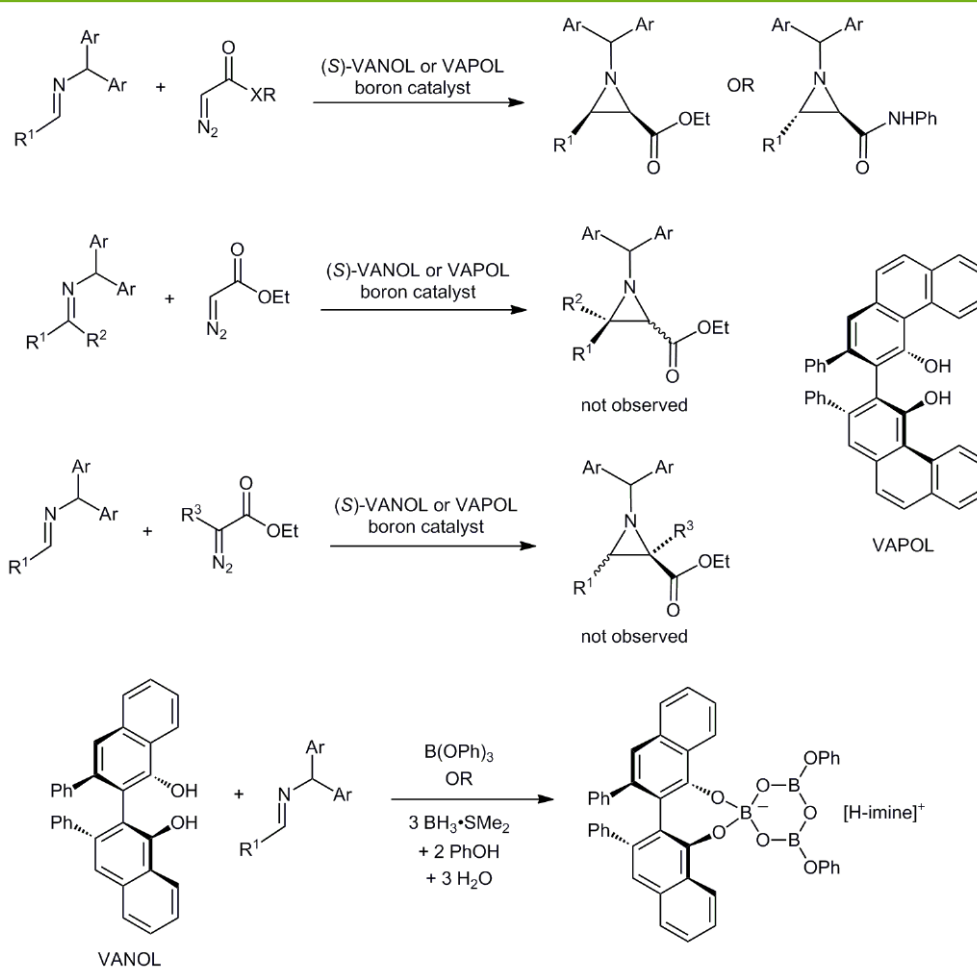
Catalytic Asymmetric Synthesis of Substituted Aziridines

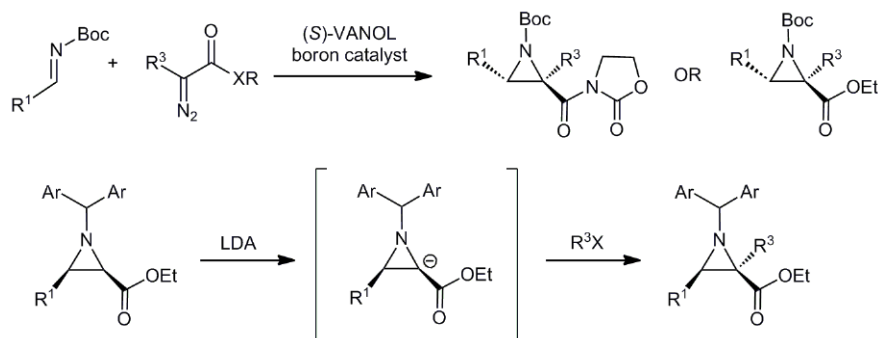
J. Am. Chem. Soc. **2011**, *133*, 8892–8895

■ The aziridine ring is present in a number of natural (such as the mitomycins) and bioactive substances. Furthermore, the strained aziridine ring is a versatile intermediate, for example of azomethine ylides, and can be useful as a precursor of other chemical functions, such as vicinal amino alcohols or diamines. It is therefore not surprising that a number of synthetic methods have been developed for the preparation of aziridines. Nonetheless the synthesis of non-racemic aziridines in a stereocontrolled manner remains a challenging endeavor and a truly

direct, efficient and general method for the stereoselective synthesis of aziridines is still lacking. Recently, an important contribution in this area has been achieved by Professor William Wulff and postgraduate student Li Huang from the Michigan State University (East Lansing, USA) who reported a novel methodology for the catalytic asymmetric synthesis of aziridines, including trisubstituted ones.

“In the past few years we have developed a catalytic asymmetric aziridination (AZ) reaction involving the reactions of





imines with diazo compounds,” said Professor Wulff. “This reaction allows access to aziridines in high yields with excellent diastereo- and enantioselection. The scope is broad and includes imines prepared from both aromatic and aliphatic aldehydes,” he continued. The reaction provides either *cis*-2,3-disubstituted aziridines from diazo acetates or *trans*-2,3-disubstituted aziridines from diazo acetamides. “The catalyst has been shown to be a chiral Brønsted acid having a boroxinate core whose assembly from the VANOL (or VAPOL, not shown) ligand and $B(OPh)_3$ occurs when and only when the imine substrate is added,” explained Professor Wulff.

According to the researchers from Michigan State University, all attempts to prepare trisubstituted aziridines with this reaction had failed in the past. “The reactions, either with imines in which the imine carbon is disubstituted, or with diazo compounds in which the diazo carbon is disubstituted, failed to proceed under normal conditions (room temperature)” said Professor Wulff. “Heating either reaction resulted in decomposition of either the diazo compound or the imine.”

The AZ reactions giving *cis*- and *trans*-disubstituted aziridines were performed on un-activated imines bearing a diaryl-methyl group on nitrogen. “The aryl group was fine-tuned to optimize reaction rates, diastereoselectivity and enantioselectivity,” said Professor Wulff. “It became obvious that to achieve a breakthrough to trisubstituted aziridines we would need to consider imines with an activating group on the nitrogen. We considered this proposition to be dicey since we were not sure if an activated imine would be basic enough to cause catalyst assembly. We had found that strong bases such as triethylamine would assemble the boroxinate core, but a weak base such as benzaldehyde would not.” Professor Wulff explained that *N*-Boc imines should be considerably less basic than a benzhydryl imine and, thus, there was much uncertainty whether they would work in this reaction. “It was at Li Huang’s insistence that these substrates be tried and her tenacity paid off,”

acknowledged Professor Wulff. Indeed, the reactions of *N*-Boc imines with diazo compounds where the diazo carbon was disubstituted proceeded to give trisubstituted aziridines in high yields with excellent enantioselectivities. The yields were lower for diazo esters while optimal yields were found with the *N*-acyloxazolidinone diazo compounds. “The diastereoselectivity is $\geq 100:1$ for the diastereomer shown,” said Professor Wulff. “Access to its diastereomer is possible from the *cis*-disubstituted aziridine which we had previously shown can be alkylated with retention of configuration at carbon-2. The question left to address is what the actual catalyst for this reaction is. Is it a boroxinate-based Brønsted acid or some other structure that perhaps is a chiral Lewis acid?” he concluded.

Matteo Zanda

About the authors



From left: Prof. W. Wulff, L. Huang

>>

Li Huang received her B.Sc. and M.Sc. degrees in medicinal chemistry from Fudan University (P. R. of China) in 2002 and 2005, respectively. After working one year as a research assistant in Shanghai Hengrui Pharmaceutical Company, she moved to Michigan State University (USA) in 2006. Since then, she has been a doctoral student in organic chemistry under the supervision of Professor Wulff.

William Wulff was born and raised near Eau Claire, Wisconsin (USA). Professor Wulff obtained his BS degree in chemistry at the University of Wisconsin at Eau Claire in 1971 doing research with Professor Larry Schnack. After completing the required service in the US Army, his doctoral education was pursued at Iowa State University (USA) under the direction of Professor Thomas Barton. After a postdoctoral stint at Princeton University (USA) with Professor Martin Semmelhack, Professor Wulff finally became a tax-payer in 1980 upon assuming a position of Assistant Professor of Chemistry at the University of Chicago (USA). In 1999, Professor Wulff took up his present position of Professor of Chemistry at Michigan State University.

Synthesis of Conolidine, a Potent Non-Opioid Analgesic for Tonic and Persistent Pain

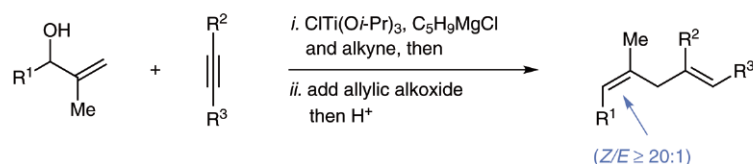
Nat. Chem. **2011**, *3*, 449–453

Traditional biomedical treatments for chronic pain have been largely unsuccessful in bringing pain relief to patients; therefore, chronic pain remains an area of substantially unmet clinical need. Opioid analgesics are typically used to treat chronic pain; however, their therapeutic profile is far from ideal: addiction, tolerance and a number of other side-effects including depression of breathing and nausea are some of the very severe drawbacks of opioids in clinical practice. Replacement of opioids with alternative analgesic agents clearly remains an important goal in the therapy of chronic pain. In traditional Chinese, Ayurvedic and Thai medicines the flowering tropical plant *Tabernaemontana divaricata* has been used for the treatment of fever, pain, and dysentery. A vast array of structurally diverse indole alkaloids possessing a range of different biological profiles were isolated from *T. divaricata*. Among them, conolidine is an exceedingly rare component,

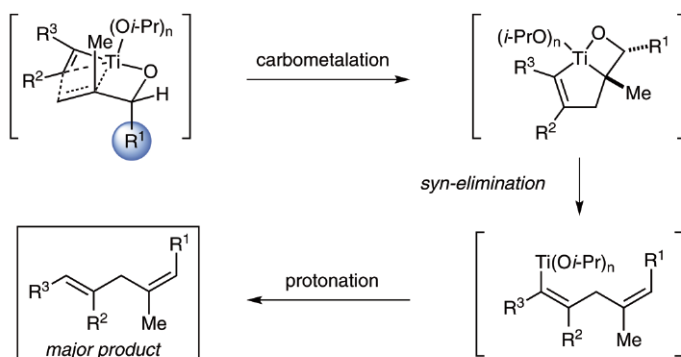
isolated in only 0.00014% yield from the stem bark of this plant. Conolidine belongs to the C5-nor stemmadenine class of natural products, and nothing was known about the biological or medicinal properties of conolidine until the recent work published by the group of Professor Glenn C. Micalizio from the Scripps Research Institute (Jupiter, Florida, USA), which performed the total synthesis of conolidine and established that this natural product is a potent non-opioid analgesic showing great efficacy in animal models of tonic and persistent pain.

“Our interest in the C5-nor stemmadenines began in 2008 after our publication of a reaction method suitable for the synthesis of 1,4-dienes through the direct coupling of allylic alcohols with alkynes,” said Professor Micalizio (*J. Am. Chem. Soc.* **2007**, *129*, 15112) (Figure 1A). “1,4-Dienes are a structural motif found within a great variety of bioactive natural

A: Titanium-mediated reductive cross-coupling for 1,4-diene synthesis



B: Empirical model for stereoselection based on a boat-like transition state and minimization of A-1,2 interactions



C: Some C5-nor stemmadenines

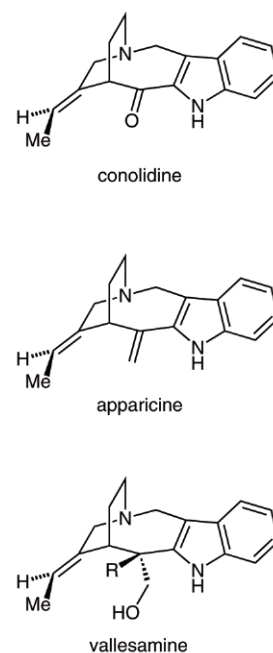


Figure 1 Titanium-mediated reductive cross-coupling of allylic alcohols with alkynes – a stereoselective approach to the synthesis of 1,4-dienes; and an introduction to the structure of C5-nor stemmadenine

products ranging from fatty acids and terpenes to complex polyketides and alkaloids,” he explained. “The chemical method delivers 1,4-dienes with exquisite levels of stereocontrol and, in a subset of cases, with exceptional selectivity for the synthesis of *Z*-trisubstituted alkenes” (Figure 1A and 1B). With this new chemical method in hand, Professor Micalizio and his coworkers began to contemplate the application of this technology in natural product synthesis. “During the process of considering potential classes of natural products to pursue, the C5-nor stemmadenines (Figure 1C) rapidly rose to the top of our list,” he said.

“First, we recognized the great challenge associated with establishing the ring system common to this family, and appreciated that no total synthesis of any member of the class had been described (the first total synthesis of a racemic C5-nor stemmadenine, (\pm)-apparicine, appeared during the course of our studies: *Chem. Commun.* **2009**, 3372 and *J. Org. Chem.* **2009**, 74, 8359),” said Professor Micalizio. “Second, potent analgesic properties had been reported for members of this natural product class (*J. Pharm. Pharmacol.* **1999**, 51, 1441 and *J. Med. Plants Res.* **1982**, 46, 210),” he continued. Professor Micalizio explained that in early reports that described apparicine as an opioid analgesic, *in vivo* analgesic efficacy was demonstrated to be nearly as potent as morphine, yet *in vitro* biochemical experiments demonstrated that apparicine was a relatively poor ligand to opiate receptors. “Based on these observed differences in activity (*in vivo* vs. *in vitro*), we reasoned that C5-nor stemmadenines (like apparicine) may

operate through a non-opioid mechanism, and therefore represent a potential lead for the development of a natural-product-inspired and clinically relevant non-opioid analgesic agent,” he said.

Professor Micalizio revealed that his laboratory’s efforts from the outset were focused on employing allylic 1,3-strain to control the conformation of a late-stage intermediate to enable facile construction of the azabicyclo[4.2.2]decane system common to this class of natural products (Figure 2). “With this as a central design, our first-generation strategy aimed to employ a Ti-mediated allylic alcohol–alkyne reductive cross-coupling reaction to unite a functionalized allylic alcohol (as depicted in Figure 2) with an indole-containing alkyne (not depicted),” he said. “Unfortunately, all attempts to accomplish this type of bond construction were met with failure, as the heterocycle-containing allylic alcohol of interest proved to be resistant to metal-mediated reductive cross-coupling chemistry.”

Professor Micalizio explained that while disappointed by the inability of their Ti-mediated reductive cross-coupling process to generate the desired cyclization substrate, their interest in the biological activity associated with the C5-nor stemmadenines, and the lack of a chemical solution to the total synthesis of any member of the class, kept their focus tuned to developing an efficient laboratory entry to the class. “Moving away from reductive cross-coupling chemistry, we searched for another reaction suitable for converting the heterocycle-containing allylic alcohol into the desired stereo-

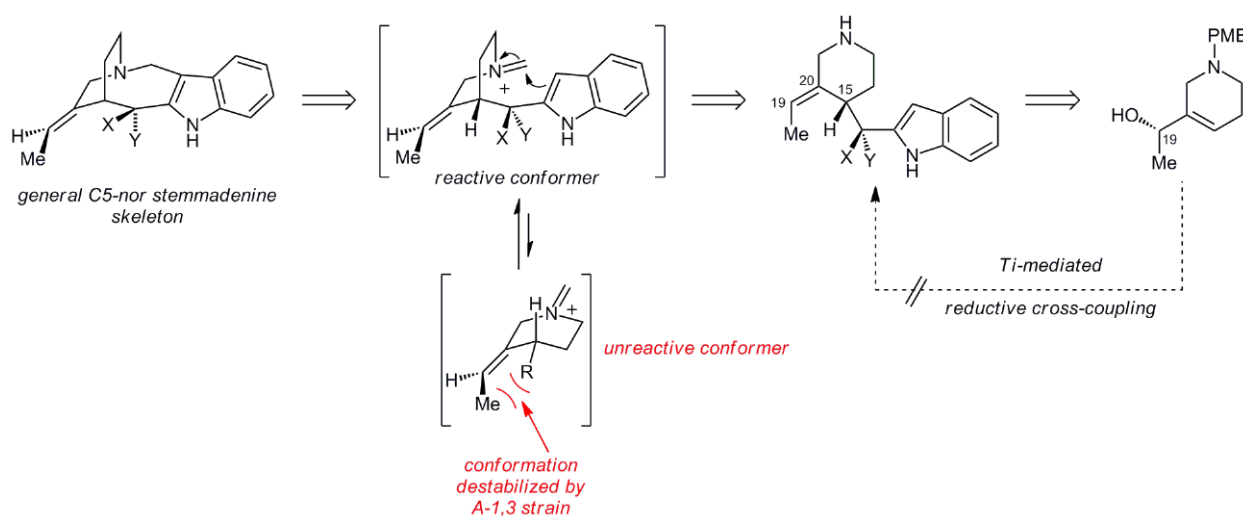


Figure 2 General retrosynthetic strategy, where conformational biasing of a late-stage intermediate would be employed to facilitate the formation of the azabicyclo[4.2.2]decane core, and inability to access a cyclization precursor via Ti-mediated reductive cross-coupling chemistry

defined cyclization substrate,” he said. According to the Scripps researcher, this search quickly led to favoring the use of sigmatropic rearrangement chemistry, and further on the identification of Still’s stannylmethyl ether based [2,3]-Wittig rearrangement as a potentially ideal solution (*J. Am. Chem. Soc.* **1978**, *100*, 1927). “This sigmatropic rearrangement reaction is known for its unique stereochemical course (when first published, this reaction was discussed in the context of converting acyclic allylic alcohols into *Z*-trisubstituted alkenes) – a characteristic that we hoped would prove useful for establishing the desired C19–C20 alkene of the C5-nor stemmadenines, yet few demonstrations of this stereoselectivity had been described with related cyclic substrates,” explained Professor Micalizio.

Fortunately, the stannylmethyl ether based [2,3]-Wittig rearrangement proceeded with good levels of stereochemical control and delivered the desired C19–C20 alkene (ratio of olefin isomers = 12:1, Figure 3). “Moving on, a simple five-step sequence was employed to convert the primary alcohol product into the desired cyclization substrate, and subsequent reaction with formaldehyde generated the first synthetic sample of the rare C5-nor stemmadenine (\pm)-conolidine. Overall, these investigations demonstrated a limitation in the use of Ti-mediated reductive cross-coupling chemistry, yet established a viable synthetic strategy for creating the central azabicyclo[4.2.2]decane system common to the C5-nor stemmadenine family of natural products,” said Professor Micalizio.

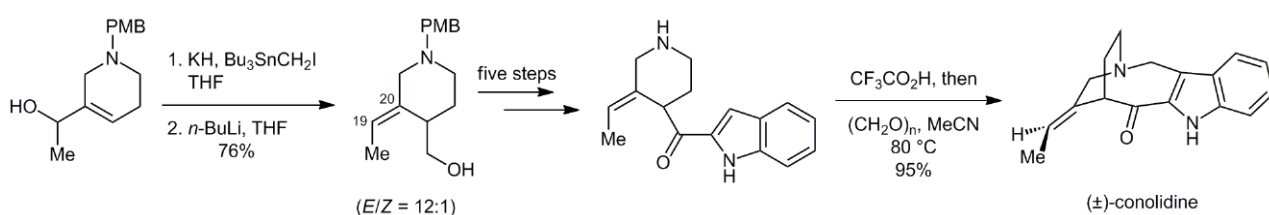
“Following this success, a means for resolving the starting heterocycle-containing allylic alcohol was employed (*Tetrahedron: Asymmetry* **1992**, *3*, 827), and the synthetic sequence depicted in Figure 3 was used to prepare (+)- and (–)-conolidine (ee of each sample $\geq 90\%$ by HPLC analysis),” he said. This accomplishment defined the first asymmetric total synthesis of any C5-nor stemmadenine.

Pleased with their relatively efficient solution to the synthesis of conolidine (nine steps, 18% overall yield), Professor Micalizio and coworkers directed their attention to the poten-

tial non-opioid analgesic properties of conolidine. “In order to address this hypothesis, we established a collaboration with Professor Laura Bohn in the Department of Molecular Therapeutics at Scripps, Florida,” he said. “The biological evaluation that followed examined the analgesic profile of our synthetic samples of (\pm)-, (+)-, and (–)-conolidine in established models. The results of these studies confirmed that conolidine 1) possesses potent analgesic properties in vivo, 2) is not an effective ligand for the μ -opioid receptor, 3) lacks affinity or efficacy for κ - and δ -opioid receptors, 4) readily enters the brain, and 5) does not affect locomotor activity in C57BL/6J mice.”

Interestingly, these studies demonstrated that both enantiomers of conolidine have similar analgesic properties. “At first we were surprised by this observation, but after considering the structural features of this natural product, we settled on a reasonable hypothesis,” confirmed Professor Micalizio. “The origin of chirality in conolidine is based on the disposition of the ethylidene side chain about an otherwise symmetric azabicyclo[4.2.2]decane. As such, the similar analgesic properties of each enantiomer of conolidine may derive from a common mechanism of action whereby the ethylidene side chain does not play a substantial role in binding. Alternatively, each enantiomer may operate through an independent pharmacological mechanism of action,” he argued.

According to Professor Micalizio, the in vivo profile of conolidine is interesting, showing similar potency to morphine in a pain model designed to assess both acute tonic and persistent responses (the formalin test), as well as the writhing assay, yet is not effective in models of pain that evaluate response to acute thermal stimulation (specifically, the hot plate or warm water tail immersion assay). “Efforts to determine the pharmacological mechanism of action associated with conolidine’s potent analgesic properties have been ongoing in the Bohn laboratory in the Department of Molecular Therapeutics at Scripps, Florida, facilitated by generous data from the Psychoactive Drug Screening Program (PDSP) [sponsored by the National Institute of Mental Health



(Bethesda, Maryland)],” he said. “While over fifty potential targets have been evaluated to date, with no reasonable biological target yet emerging, we are encouraged by conolidine’s lack of affinity to the many targets that have been assessed, as this data supports the hypothesis that this rare natural product may be operating through a very selective and potentially unique pharmacological mechanism of action. These studies,” concluded Professor Micalizio, “provide another example where triumphs in chemical synthesis have led the way to medically relevant discoveries and have established a means to pursue drug discovery and development.” ■

Matteo Zanda

About the author



Prof. G. C. Micalizio

Young Career Focus:

Dr. Rebecca Goss (University of East Anglia, Norwich, UK)

■ **Background and Purpose.** *SYNFORM* will from time to time meet young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This *SYNSTORY* with a **Young Career Focus** presents Dr. Rebecca Goss, Lecturer in Organic Chemistry at the University of East Anglia, UK.

INTERVIEW

SYNFORM | Dr. Goss, what is the focus of your current research activity?

Dr. Goss | My group's research includes a diverse array of projects with natural products as the focus. Research within my group falls within four complementary and overlapping themes (Figure next page): We are interested in the discovery of novel bioactive natural products, elucidating biosynthetic pathways, developing individual enzymes as tools for organic synthesis and harnessing entire biosynthetic pathways as a rapid means of accessing libraries of otherwise synthetically

BIOGRAPHICAL SKETCH



Dr. R. Goss

Rebecca Goss grew up on the Isle of Man living in a converted steam railway station close to the sea. She completed her undergraduate studies in chemistry at the University of Durham between 1994 and 1997. She then carried out her PhD on the biosynthesis of various natural products, including an investigation into the stereochemistry of enzymatic fluorination in fluoroacetate biosynthesis, under the supervision of Professor David O'Hagan (University of Durham, UK, awarded in 2001). In 2000 Dr. Goss moved to the University of Cambridge (UK) to study the chemistry and molecular biology of polyketide biosynthesis in the research group of Professors Jim Staunton, FRS and Peter Leadlay, FRS. In 2002, Dr. Goss moved to an independent position within the Department of Chemistry at the University of Nottingham (UK). After receiving a Royal Society BP Dorothy Hodgkin Fellowship in 2003 she moved to the University of Exeter (UK). The Goss research group then moved to the University of East Anglia in 2005.

In 2007 Dr. Goss was awarded the RSC Meldola prize for her excellent contributions at the interface of organic chemistry and molecular biology. She is a recipient of the Thieme Chemistry Journal Award 2011.

Apart from chemistry she has interests in hill walking, running and painting and enjoys the company of her two-year-old daughter, Esther.

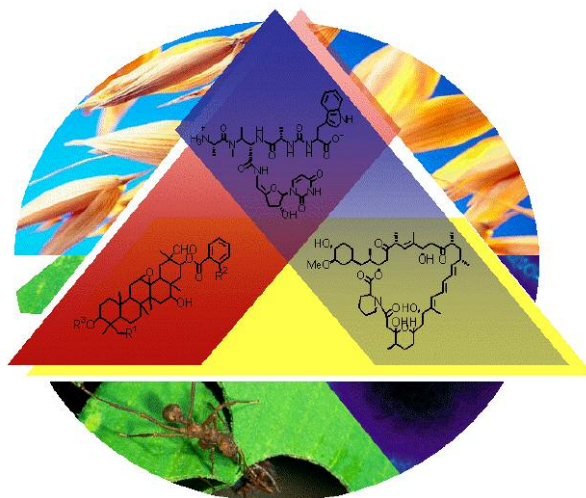


Figure Complementary chemical biology research projects within the Goss group utilizing overlapping tools of organic synthesis and molecular biology.

intractable natural products with which to probe structure-activity relationships.

SYNFORM | *When did you get interested in synthesis?*

Dr. Goss | I've been interested in rudimentary synthesis since my childhood, but my interest in organic chemistry and the possibilities that organic synthesis affords really started to develop during a vacation research project during my undergraduate studies.

SYNFORM | *What do you think about the modern role and perspectives of organic synthesis?*

Dr. Goss | Organic synthesis remains vital to society from energy, agriculture and food to materials and medicine. Perhaps due to the pervasive nature of the subject it is taken for granted.

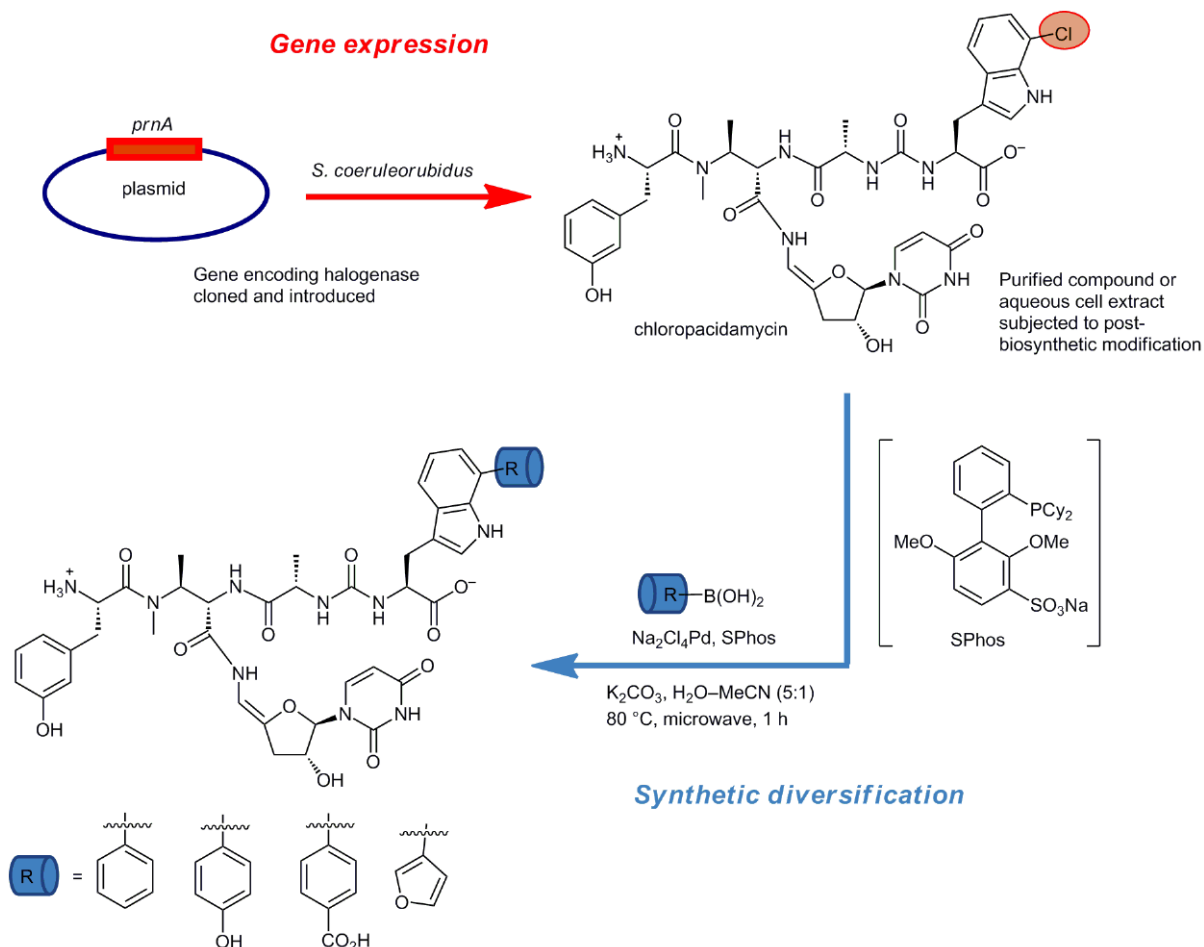
It is now a really exciting time to be an organic chemist, the increasing ease of acquiring relatively inexpensive genome sequences means that chemists can very rapidly gain information as to how natural products are assembled. It is possible to search for genes and therefore enzymes that mediate certain reactions, and harness these enzymes as tools for synthesis.

SYNFORM | *Your research group is active at the frontier of organic synthesis and biological sciences. Could you tell us more about your research and its aims?*

Dr. Goss | We are particularly interested in understanding how bioactive natural products with biosynthetically exotic motifs are assembled. A significant number of drugs in the clinic are based on natural products, however, in recent years natural products have lost popularity with the pharmaceutical industry due in part to the perceived problems with their "medchem ability" – series of analogues are synthetically intractable using conventional approaches. We are interested in combining synthesis and biosynthesis in order to generate series of analogues, and have recently established a new paradigm in natural product analogue generation which we have been calling "Chemogenetics". Using this approach we have been recruiting genes from various microbes and installing them out of context into organisms that make natural products that we are interested in. By controlling gene expression we are able to coerce the foreign enzyme to act in concert with the existing biosynthetic pathway so as to insert a selectively functionalizable handle into the natural product. The handle is chemically orthogonal to the other functional groups within the natural product and may therefore be used for selective derivatization and access to extensive libraries of analogues (*J. Am. Chem. Soc.* **2010**, *132*, 12243, Highlighted in *C&EN News*, August 23rd, 2010).

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

Dr. Goss | We are having a lot of fun combining synthetic biology and chemistry; this is enabling us to selectively dial-



Scheme Chemogenetics: a new paradigm in natural product analogue synthesis. The introduction of *prnA*, a gene encoding a halogenase, into the pacidamycin producer results in the generation of chlorinated pacidamycins. The chlorine may be used as a selectively functionalizable handle enabling further synthetic diversification.

in to bioactive natural and unnatural products. We hope to use these compounds to pinpoint exact molecular modes of action (see for example: *Chem. Sci.* **2011**, DOI: [10.1039/C1SC003783](https://doi.org/10.1039/C1SC003783), Highlighted in *RSC Chemistry World*).

Matteo Zanda

COMING SOON ►► COMING SOON ►►

SYNFORM 2011/10 is available from September 20, 2011

In the next issues:

SYNSTORIES ■ ■ ■ ■

■ Copper-Catalyzed Aerobic Oxidation of Hydroxamic Acids Leading to a Mild and Versatile Acylnitroso Ene Reaction

(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 – A Key Step in the Biosynthesis of Spinosyn A

(Focus on an article from the current literature)

FURTHER HIGHLIGHTS + + + +

SYNTHESIS

Review on: Total Synthesis of Polypropionate-Derived γ -Pyrone Natural Products

(by J. E. Moses)

SYNLETT

Account on: Exploring a Unique Reactivity of 6 π -Azoelectrocyclization to Enzyme Inhibition, Natural Products Synthesis, and Molecular Imaging: An Approach to Chemical Biology by Synthetic Chemists

(by K. Tanaka)

SYNFACTS

Synfact of the Month in category "Metal-Mediated Synthesis":

Rh-Catalyzed Asymmetric Addition of Trifluoroborates to Sulfonylketimines

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