Intermolecular Radical Mediated Anti-Markovnikov Alkene Hydroamination Using N-Hydroxyphthalimide

Highlighted article by S. W. Lardy, V. A. Schmidt
Dear Readers,

Yesterday was my first day in my new academic position, today I am writing this Editorial in my new office in the brand new, state-of-the-art Chemistry Department of Loughborough University. I do not mind being here during the weekend, because this place is so functional and comfortable that even working out-of-hours becomes a pleasure! It will take some time to be fully up-and-running with my new group and research – at the moment I am still emptying crates and moving stuff into my office – but SYNFORM is an excellent way to feel continuity even in the middle of a move. So, let’s have a look at this February issue, which starts with the synthesis of the tantalizingly complex polycyclic terpenes Shizukaols A and E achieved by X.-S. Peng (P. R. of China) and co-authors. The next article is an interesting YCF interview with J. Cornellà (Germany), while the following contribution reports on the radical alkene hydroamination by V. A. Schmidt (USA) published in J. Am. Chem. Soc. Finally, the key duty of closing the issue is in very good hands: I. Seiple (USA) – a recent Thieme Chemistry Journal Awardee – with his synthesis and structural re-assignment of 2,18-seco-lankacidinol B.

And this is me wrapping up this weekend working day and heading for a well-deserved pint!

Enjoy your reading!!

Contact
If you have any questions or wish to send feedback, please write to Matteo Zanda at: synform@outlook.com
Total Syntheses of Shizukaols A and E

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Biologically active natural products are often used as starting points and potential sources for drug discovery, along with being critical tools for learning about biologically important processes. Unfortunately, natural products can generally only be isolated in very minute quantities from natural sources, so supplies with which to carry out a full physiological and biological assessment are often extremely scarce. Even when promising leads or potential drugs are identified among these natural products, the lack of availability and scalability represents a formidable barrier to their further development and evaluation in drug discovery. Fortunately, chemical synthesis has the potential to solve the supply problem by providing larger quantities of natural products and their analogues in a more efficient and scalable manner, thus enabling a better understanding of their biological action and biogenetic synthesis. Furthermore, chemical manipulation presents opportunities for modifying the structure of natural products, with the ultimate aim of improving their activity or physicochemical/biological properties.

Shizukaols A and E, two dimeric lindenane-type terpenes, were isolated from _Chloranthus japonicas_. Both possess a common heptacyclic framework containing more than 10 contiguous stereocenters with potential biological activities, which has attracted a considerable amount of interest from synthetic chemists. However, only one total synthesis of two dimeric members, shizukaol D and sarcandrolide J, was reported by Professor Bo Liu and co-workers in 2017. Recently, Professor Xiao-Shui Peng from The Chinese University of Hong Kong, together with Dr. Bencan Tang from the University of Nottingham Ningbo China (P. R. of China), have reported the total syntheses of shizukaols A and E via a biomimetic synthetic approach. Among the research priorities of the authors are, in fact, the design and accomplishment of a “bio-inspired” total synthesis of structurally complex and biologically significant natural products, and a better understanding of their biological action and biogenetic synthetic approach. This project was initiated in 2010, when Dr. Yin-Suo Lu enrolled as a PhD student in the group of Professor Henry N. C. Wong at The Chinese University of Hong Kong (P. R. of China). Professor Peng explained: “In the early stage of his PhD studies, Dr. Lu achieved quite exciting preliminary results on the generation of an endo-type core for shizukaol family members (_Org. Lett._ **2011**, *13*, 2940–2943 and _Org. Lett._ **2016**, *18*, 5447–5448). Based on these initial studies, Dr. Lu then achieved the crucial endo-cyclization product 5 through Diels–Alder reaction between diene 3 and dienophile 4 (Scheme 1). However, despite considerable experimentation, the conversion of the hydroxyl group of endo-cyclization product 5 into the carbonyl group in 6 could not be achieved.”

**Figure 1** Structures of shizukaols A and E

![Structure of shizukaol A](image1)

**Scheme 1** Unsuccessful transformation of the hydroxyl group into a carbonyl group

![Scheme 1](image2)
In 2013, Dr. Jian-Li Wu joined this shizukaol project after the first target molecule, bolivianine, was synthesized by Professor Bo Liu of Sichuan University (P. R. of China), and he started investigating the endo-selectivity of the Diels–Alder reaction and the improvement of synthetic efficiency in late-stage functionalization. “Dr. Wu’s investigation proved that the late-stage conversion of the epoxy unit (Schemes 2 and 3) into the hydroxy keto ester unit of shizukaols A (1) and E (2), a common framework of the dimeric family members, was a more step-economic strategy for total synthesis. Thus, according to the structural features of the shizukaol family, Dr. Wu synthesized more suitable precursors 7, 8, and 13, being at least biogenetically much closer to intermediates suitable for further transformations through either a highly Z-selective olefination of α-siloxy ketone with ynolate anions or an intramolecular Horner–Wadsworth–Emmons olefination from commercially available Wieland–Miescher ketone,” explained Professor Peng.

He continued: “As expected, the Diels–Alder reaction between 7 and 8, 8 and 13, respectively, worked well to afford the desired products (9, 14) with endo selectivity. However, efforts to invert the secondary α-hydroxy group in 11 or 15 were unsuccessful, probably due to the fact that the key hydroxy group at C9 was sterically hindered.” The authors found that even the corresponding mesylate and triflate, which were easily epimerized, did not give positive results when treated with alkaline reagents such as DBU and KNO₂. Therefore, oxidation of alcohols 11 or 15 with Dess–Martin periodinane, respectively, led to diones 12 and 16. Treatment of dione 12 with Zn[BH₄]₂ eventually gave the synthetic shizukaol E (2) with a C9 β-hydroxy group, together with recyclable compound 11 in 92% yield with an α/β ratio of 2.8:1. Simil-

Scheme 2 Total synthesis of shizukaol E (2); BHT = butylated hydroxytoluene, DMP = Dess–Martin periodinane, DMAP = 4-dimethylaminopyridine
Early, oxidation of 15 with Dess–Martin periodinane, followed by reduction of dione 16 with Zn(BH₄)₂, eventually achieved shizukaol A (1) and alcohol 15 in 95% yield with an α/β ratio of 4.6:1. “Presumably, the stereoselectivity of these reductions results from coordination between Zn(BH₄)₂ and the two carbonyl groups at C8 and C9 in diones 12 and 16. The relevant DFT calculations of the reduction of diones 12 and 16 with Zn(BH₄)₂, performed by Dr. Bencan Tang, supported the observed stereoselectivity,” said Professor Peng.

“In summary, the first total syntheses of shizukaols A (1) and E (2) were accomplished from commercially available Wieland–Miescher ketone in 0.1% overall yield over 24 steps and 0.15% overall yield over 28 steps in the longest linear sequences, respectively, involving a modified biomimetic Diels–Alder reaction and a biogenetic transformation of an epoxy unit to the common hydroxy keto ester species of the shizukaol family,” remarked Professor Peng. He continued: “This synthetic approach should open up a practical avenue for the total syntheses of the intriguing chloranthaceae family members, and should facilitate as well the understanding of their relevant biological action in nature.”

Professor Peng concluded: “Last but not least, we would like to express our sincere gratitude to Professor Henry N. C. Wong for his invaluable comments, which effectively helped us in achieving our synthetic goals, as well as for his great contribution to the development of organic chemistry in China, on the occasion of his retirement from the Chinese University of Hong Kong after a career spanning over 35 years.”

Scheme 3 Total synthesis of shizukaol A (1); BHT = butylated hydroxytoluene, DMP = Dess–Martin periodinane
About the authors

Jian-Li Wu grew up in Wuhan, Hubei (P. R. of China) and obtained a B.Sc. in chemistry from Nanjing University (P. R. of China) in 2012. Then he moved to The Chinese University of Hong Kong (P. R. of China) as a PhD student, obtaining his PhD there in 2016, where he worked on the total syntheses of shizukaols A and E under the supervision of Professors Henry N. C. Wong and Xiao-Shui Peng. Now, he works in new drug discovery in Shenzhen.

Yin-Suo Lu was born and raised in Jiangsu province (P. R. of China) and earned a B.Sc. in pharmaceutical science from Peking University (P. R. of China). He continued with his M.S. studies at the same university under the direction of Professor Xin-Shan Ye in the research field of carbohydrate chemistry. He obtained his PhD from The Chinese University of Hong Kong (P. R. of China), where he worked on the total syntheses of shizukaols A and E under the supervision of Professors Henry N. C. Wong and Xiao-Shui Peng. Now, he works in new drug discovery in Shenzhen.

Bencan Tang grew up in Panxian City, Guizhou Province, P. R. of China, and obtained her B.Sc. in analytical chemistry from Lanzhou University (P. R. of China) in 2000. Subsequently, she obtained her M.Sc. in 2003 from Lanzhou University under the direction of Professor Weidong Li. She then moved to the University of Nottingham (UK) in 2004, to start a PhD study with Professor Gerry Pattenden (FRS), working on the biomimetic synthesis of marine natural products, and was awarded a Ph.D. in 2008. After postdoctoral work with Professor David Harrowen at the University of Southampton (UK) from 2009 to 2011, she was hugely attracted by computational chemistry, so in 2011, she joined Professor Rob Paton's group at Oxford University (UK) to focus on computational studies of organic reactions, where she stayed for two years. In 2014, Bencan became an assistant professor at the University of Nottingham Ningbo China, where she explores the biomimetic synthesis of marine natural products, as well as novel metal-catalyzed organic reactions, mainly computationally.

Xiao-Shui Peng received his BSc and MSc degrees from Lanzhou University (P. R. of China) in 1999 and 2002, respectively, under the guidance of Professor Xin-Fu Pan. In 2006, he obtained his PhD from The Chinese University of Hong Kong (P. R. of China), where he worked on the total synthesis of pallavicinin under the supervision of Professor Henry N. C. Wong. After completing his postdoctoral research fellowship with Professor K. C. Nicolaou and Dr. David Y. K. Chen on the cortistatins project at CSL@Biopolis, Singapore, he returned to CUHK as a Research Assistant Professor in 2009. He is now Research Associate Professor and is focusing his research themes on the development of novel bio-inspired strategies and methodologies for the total synthesis of structurally complex and biologically significant natural products.
Young Career Focus: Dr. Josep Cornella (Max-Planck-Institut für Kohlenforschung, Germany)

Background and Purpose. SYNFORM regularly meets 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 Young Career Focus presents Dr. Josep Cornella (Max-Planck-Institut für Kohlenforschung, Germany).

INTERVIEW

**SYNFORM** What is the focus of your current research activity?

**Dr. J. Cornella** The main focus of our research group is the development of rapid, practical and efficient methodologies for organic synthesis based on sustainable and cheap catalysts, towards more sustainable chemical processes. In addition to efficiency and practicality, we are highly interested in discovering new reactivity with the aim of unveiling novel transformations. More specifically, our group’s interests are in the fundamental understanding and application of catalytic processes and the development of simple reagents for organic synthesis. We believe that these two approaches have enormous potential with potential impact across the chemical sciences.

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

**Dr. J. Cornella** I was first fascinated by synthesis in my undergraduate courses at the Universitat de Barcelona, where I undertook the class “Síntesi Orgànica” with Prof. Albert Moyano. There, I discovered the beauty and fun of constructing molecules and the plethora of possibilities for connecting and disconnecting bonds. Then, during my PhD and postdoc I learned how metals and catalysis can influence such disconnections, ultimately leading to extremely straightforward methodologies. I was fascinated by the idea of using transition metals to dramatically shorten a synthesis that required several steps and a tremendous amount of effort, time and resources. With this idea in mind, we are trying to add another variable to the equation: sustainability. In addition to streamlining synthesis, we are also attempting to provide sustainable approaches to these processes. In our laboratory, this implies the design of simple and readily available reagents or earth-abundant metals as catalysts.

Biographical Sketch: Dr. Josep (Pep) Cornella

Dr. Josep (Pep) Cornella studied chemistry at the University of Barcelona (Spain). His MSc studies in the Department of Organic Chemistry investigated the chemistry of allylboron reagents. After completing his Master’s thesis in 2008, he moved to the United Kingdom to pursue doctoral studies in the group of Prof. Igor Larrosa at Queen Mary University of London (QMUL) where he focused on the use of aromatic carboxylic acids as aryl donors in metal-catalyzed decarboxylative reactions. In 2012, he received a Marie Curie Fellowship to pursue postdoctoral studies in the group of Prof. Ruben Martin at the Institut Català d’Investigació Química (ICIQ, Spain) where he focused on the development of Ni-catalyzed transformations for the activation of C–O bonds and carbon dioxide (CO2) insertion. In 2015, he obtained a Beatriu de Pinós Fellowship to carry out further postdoctoral studies in the group of Prof. Phil S. Baran at The Scripps Research Institute, California (USA), where he developed novel transformations based on the concept of “redox-active esters” as radical coupling partners for Ni- and Fe-catalyzed cross-couplings.

In spring 2017, he was appointed as a Max Planck Group Leader in the Department of Organometallic Chemistry at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr (Germany). He has been a Max Planck Research Group Leader (MPRGL) since the summer of 2017 at the same Institute, where he leads the Laboratory for Sustainable Homogeneous Catalysis, and was the recipient of the Thieme Chemistry Journals Award in 2017.
SYNFORM  What do you think about the modern role and prospects of organic synthesis?

Dr. J. Cornella  Organic synthesis is truly vivid and alive. More specifically, homogeneous catalysis has become an indispensable tool for organic synthesis. New methodologies to assemble molecular entities appear every day from researchers around the world at an incredible pace. Thousands of methods are published every year, thus highlighting the richness and wide interest in this area. However, it seems that these fast-growing and large number of efficient and available methods do not translate when looking at applications in industrial contexts. A recent report from medicinal chemists revealed that industry relies mainly on a small and specific set of reactions to synthesize their libraries of compounds. Although many factors can contribute to this, a determining factor is that the methods of choice (namely Suzuki cross-coupling, amide bond formation, enantioselective hydrogenation, etc.) are those which are simple, robust, scalable and reliable, especially when applied in complex synthetic contexts. In this regard, our research group places particular emphasis on covering the largest chemical space possible when developing new strategies (presence of a large variety of heterocycles and sensitive functional groups) to be able to achieve the maximum translational potential possible.

SYNFORM  Your research group is active in the area of catalysis applied to organic synthesis. Could you tell us more about your research and its aims?

Dr. J. Cornella  In particular, we are interested in developing methodologies based on cheap and abundant Ni salts for the decoration of heterocycles, which are of major importance in pharmaceutical and agrochemical settings. We have developed a methodology for the functionalization of C–F bonds with alkyl Grignard reagents in a regioselective fashion to construct new C–C bonds.2 In addition to the activation of challenging and strong C–F bonds, we have identified a feature in the ligand (Thorpe–Ingold effect) that minimizes the formation of the commonly obtained by-products through β-hydride elimination/insertion events. This allows a rapid construction of non-planar structures which are of great interest to medicinal chemists to design and modify protein–drug interaction sites (Scheme 1).

Another area we are interested in is the development of practical reagents for organic synthesis. In this regard, we have recently developed a pyrylium reagent (Pyry-BF₄) which is capable of targeting amino groups C(sp²)–NH₂, which are prevalent in a wide variety of chemical compounds. The reagent reacts preferentially with these functionalities, thus priming them for a simple and robust nucleophilic aromatic substitution (S_NAr).3 Prior to our work, such reactivity was rather limited to the use of polyalkylated amines or diazo compounds, which are either explosive or unselective. The protocol developed by our group proceeds with extreme chemoselectivity and this permits the modification of C(sp²)–NH₂ bonds in late-stage functionalization contexts as demonstrated by the successful modification of densely functionalized molecules such as ibrutinib (anticancer), prazosine (antianxiety) and adenosine (DNA-building material) (Scheme 2).

Another research line we are currently exploring is the study of the chemistry of low-valent elements. For example, we are interested in highly reduced species of Ni and their capabilities as catalysts. While the high oxidation states of

Scheme 1 Ni-catalyzed branch-selective alkylation of C–F bonds
Ni – Ni(IV) to Ni(0) – are well-known in the literature, little is known about the highly reduced species of Ni in the context of cross-coupling. In traditional cross-couplings the electron density is provided by the ancillary ligand: we wondered what would happen if this process is reversed, and the electron density is mainly supplied by the metal center. Inspired by the seminal work from Jonas and Pörschke in the 1970s at MPI Kohlenforschung, we were able to identify a highly reduced Ni–Li–olefin complex [formally a Ni(-II)], which is capable of catalyzing Kumada–Corriu cross-couplings at cryogenic temperatures. The unprecedented activity of this Ni(-II) complex at low temperatures allowed the coupling of moieties bearing sensitive functional groups, which would react with the Grignard at higher temperatures, such as esters and nitriles. Although preliminary studies point towards the possibility of a low-valent catalytic cycle involving Ni(-II) species to forge C–C bonds, details on a full mechanistic picture are still under investigation (Scheme 3).

**Scheme 2** Development of a pyrylium reagent for the activation of C–NH$_2$ in aminoheterocycles

**Scheme 3** Formal Ni(-II) precatalyst for Kumada cross-coupling
SYNFORM  What is your most important scientific achievement to date and why?

Dr. J. Cornella  The most important scientific contribution is always yet to come. However, I am very proud of the contributions we have made in such a short time. The discovery of a branch-selective alkylation of C–F bonds disclosed an unknown Thorpe–Ingold effect in the ligand which led to complete retention over isomerization. The catalytic activity of a formal Ni(II) complex has led to a reconsideration of the role of the ligands in Kumada cross-coupling and the consideration of low-valent species involved in catalytic cycles. And finally, the development of the Pyry-BF$_4$ has permitted a safe, selective and scalable S$_{Ar}$ into C(sp$^2$)–NH$_2$ bonds, which has been elusive to date. Although all these results have been small contributions to each particular field, I believe our continuous work in this area will open new vistas and I am convinced (as is every chemist) that great things to discover lie ahead of us.

REFERENCES

Nitrogen atoms are ubiquitous in pharmaceuticals, natural products, materials, and commodity chemicals. The simplest amine – ammonia – is central to life since its use as fertilizer quite literally feeds the world. Biological systems are finely tuned to use ammonia as a building block for complex molecule synthesis, but the use of ammonia in the laboratory is met with many obstacles ranging from the conceptual to the practical. “Ammonia is a flammable and highly corrosive gas. It also reacts readily with many common reagents and forms stable, and often inert, Werner complexes in the presence of many transition metals. These obstacles have impeded the usage of ammonia directly in synthetic methodology development,” said Professor Valerie A. Schmidt from the University of California, San Diego (USA). The Schmidt group considered that an inexpensive ammonia surrogate could be used to create new C–N bonds via alkene hydroamination.

In an effort to realize this, the authors investigated N-hydroxyphthalimide (NHPI) as a potential ammonia surrogate. “We reasoned that – if a suitable deoxygenation procedure was identified and hydroamination occurred – the alkyl
Phthalimide products could be hydrolyzed to the corresponding primary amines," said Professor Schmidt. She continued: "The overall transformation achieved would be the formal addition of ammonia across a C–C double bond."

To achieve this, the group developed a dual radical atom and group transfer approach using phosphorus(III) reagents. Professor Schmidt explained: "This strategy leverages the relatively weak O–H and N–O bonds of NHPI to forge strong N–C, C–H, and phosphoranyl units. Because our dual transfer approach would generate an N-centered, phthalimidyl radical, alkene addition should preferentially result in the formation of the anti-Markovnikov regioisomeric amine products."

Professor Schmidt concluded: "This is a user-friendly, two-step procedure to access primary amines from unactivated and functionalized alkenes with a bench-stable, solid ammonia surrogate and inexpensive phosphite reagent. We are now investigating the kinetic and thermodynamic limits of this reaction as well as the generality of this mechanistic approach with other functional groups."

**About the authors**

**Samuel W. Lardy** grew up in Edina, Minnesota (USA) and obtained a Bachelor's degree in chemistry from Loyola Marymount University (USA) in 2016. As an undergraduate student, he performed research under the supervision of Dr. Jeremy McCallum. He started his graduate studies at the University of California, San Diego (USA) in 2017 under the leadership of Dr. Valerie Schmidt. His research focus is on phosphorus(III)-mediated atom- and group-transfer methodology development.

**Valerie A. Schmidt**, originally from Maryland (USA), earned her undergraduate degree in chemistry from Towson University, Maryland (USA). She then pursued graduate studies under the supervision of Prof. Erik Alexanian at the University of North Carolina at Chapel Hill (USA). As a Burroughs–Wellcome and Venable Fellow, she studied radical-mediated hydrocarbon functionalizations. She then moved to the laboratory of Prof. Paul Chirik at Princeton University (USA) as a Ruth L. Kirschstein National Institutes of Health Postdoctoral Fellow focusing on development of alkene cycloadditions and hydrovinylations catalyzed by reduced iron and cobalt compounds supported by redox-active ligands. She began her independent career in 2016 in the Department of Chemistry and Biochemistry at the University of California, San Diego (USA). The Schmidt lab is focused on the development of new synthetic methodologies by accessing reactive intermediates with unpaired electrons and studying their mechanisms.
Bacteria are becoming increasingly resistant to antibiotics in all parts of the world. New resistance mechanisms are emerging and spreading globally, thus threatening our capacity to treat even the most common infectious diseases. While bacterial infections such as pneumonia, tuberculosis and sepsis are becoming harder, and sometimes impossible, to treat as antibiotics currently in use become less effective, there is a growing need for new classes of antibiotics that can overcome resistance.

The group of Professor Ian Seiple from the University of California, San Francisco (USA) has a longstanding interest in antibiotics that inhibit protein synthesis by binding to the catalytic center of the bacterial ribosome. These include many FDA-approved classes such as the streptogramins, oxazolidinones, macrolides, lincosamides, pleuromutilins and amphenicols. “There are other classes that target the same site that show enormous potential but that have liabilities preventing their advancement as human therapies,” explained Professor Seiple. He continued: “First and foremost among these classes are the lankacidins, which have attracted interest from academia and industry for decades as a potential treatment for multidrug-resistant Gram-positive infections.1 Unfortunately, this class is chemically unstable in both acidic and basic environments, greatly limiting its chemical modification by semisynthesis as well as its advancement to the clinic. We sought to develop a modular synthesis of lankacidin antibiotics that would allow us to develop chemically stable analogues with improved potency.”

When the first report of seco-lankacidins appeared in the literature in January 2018,2 the group had been working on a synthesis of the lankacidin backbone for over a year. Professor Seiple explained: “Much to our surprise, we had already prepared a silyl-protected version of 2,18-seco-lankacidinol B en route to the cyclic members of the lankacidin class. We immediately removed the silyl protecting groups, and we were very surprised to find that the 1H and 13C NMR spectra of the product did not match the published spectra! Initially, we were very concerned that we had misassigned the stereochemistry of some of our intermediates, but we quickly convinced ourselves by 2D NMR that our assignments were correct. Additionally, we noticed that no 2D NMR data was included in the publication describing the isolation,2 and thus we assumed that they had assigned the stereochemistry by analogy to the rest of the class.”

He continued: “After careful analysis, we noticed that the largest discrepancies in spectral data occurred for atoms near and around the six-membered lactone ring, which contains two stereocenters. We then set out to synthesize all four possible diastereomeric combinations of these two stereocenters, with the hope that the spectra of one of these derivatives would match the spectra of the natural product.”

Much to the authors’ delight, the spectra of one of the four diastereomers they synthesized matched perfectly with the published data. This analogue was epimeric at the C4 position compared to the reported structure. This conclusion was supported by 2D NOE data, but the group sought further confirmation by X-ray crystallography. Professor Seiple remarked: “Unfortunately, we were unable to obtain X-ray-quality crystals of any of the final analogues (or of derivatives there-
We were successful, however, in crystallizing a derivative of an intermediate that contained the full lactone core. Taken together with the other spectral data, we believe there was sufficient evidence to call for a structural reassignment of 2,18-secologacidinol B, revising the stereochemistry at C4. In addition to reassigning the structure, the authors were interested in the antibacterial activity of acyclic members of the lankacidin class. They measured the activity of lankacids against a panel of five Gram-positive and five Gram-negative pathogens. “Perhaps unsurprisingly, the four acyclic lankacidin derivatives displayed weak-to-no activity against these bacteria. The lack of activity is most likely due to the absence of the macrocycle, which presumably grants a favorable conformational disposition for the binding site in the ribosome,” said Professor Seiple. He continued: “It is also possible, however, that the lack of the pyruvamide sidechain contributes to the lack of activity, as this sidechain is present in the structures of all of the cyclic members.”

Professor Seiple said: “This structural reassignment raises a number of questions. 2,18-secologacidinol B is the only member of the lankacidin class that has been shown to have S stereochemistry at C4. Have any other members of the lankacidin class been misassigned? Does the stereochemical inversion offer any functional advantages to the molecule? Is it possible that the C4 stereochemistry actually exists in an S configuration during the biosynthesis for the entire class, only to be converted into R after cyclization (enzymatically or non-enzymatically)? Would cyclized lankacids with inverted C4 stereochemistry still inhibit the ribosome? Would they be more structurally stable?”

Professor Seiple concluded: “We are currently pursuing the answers to these questions by developing syntheses of both natural and non-natural lankacids. We are excited to report the results of these studies in the near future.”

REFERENCES

About the authors

**Ian Seiple** received his BS from the University of California at Berkeley (USA) under the tutelage of Dirk Trauner, and in 2006 joined the laboratory of Phil Baran at the Scripps Research Institute (USA) as an NSF Predoctoral Fellow. During his graduate studies he developed fully synthetic routes to pyrrole-imidazole alkaloids, including palau’amine. In 2011 he moved to Harvard University (USA), where he worked on the synthesis of novel macrolide antibiotics as an NIH postdoctoral fellow in the laboratory of Andy Myers. He started his independent laboratory at the University of California, San Francisco (USA) in 2015, and focuses on the development of modular routes to complex small molecules with therapeutic potential.

**Yanmin Yao** received his BS from Shandong Normal University (P. R. of China), and in 2008 he started at Nankai University (P. R. of China) for his graduate studies. He joined the group of Guangxin Liang, where his research focused on total synthesis of bioactive alkaloids and terpenoids including (+)-agelastatins A and B, longifolene and (+)-minfiensine. In 2014, he joined Pharmaron Beijing, Co. Ltd. (P. R. of China) as a researcher in process chemistry. At the end of 2015, he joined the laboratory of Ian Seiple at UCSF (USA) as a postdoctoral fellow, where he works on the synthesis and modification of antibiotics.

**Lingchao Cai** received his BS and MS from Nankai University (P. R. of China). He did his graduate research at the University of California, Los Angeles (USA) under the direction of Professor Ohyun Kwon focusing on the total synthesis of indole alkaloids. After graduation, he moved to UCSF (USA) and joined Ian Seiple’s lab for his postdoctoral research, focusing on synthesis and development of lankacidin antibiotics.
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