Synthesis, Structural Reassignment, and Antibacterial Evaluation of 2,18-*Seco*-Lankacidinol B

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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 ^{1}H and ^{13}C 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

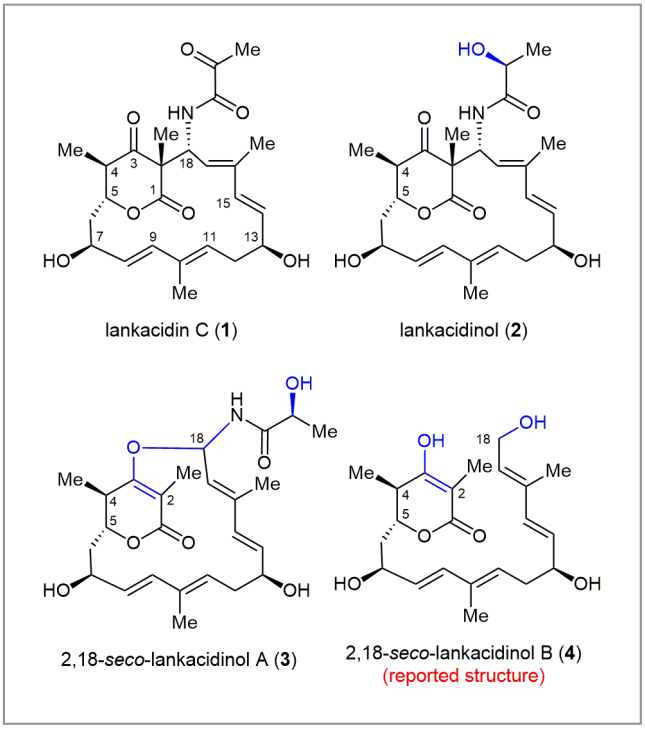
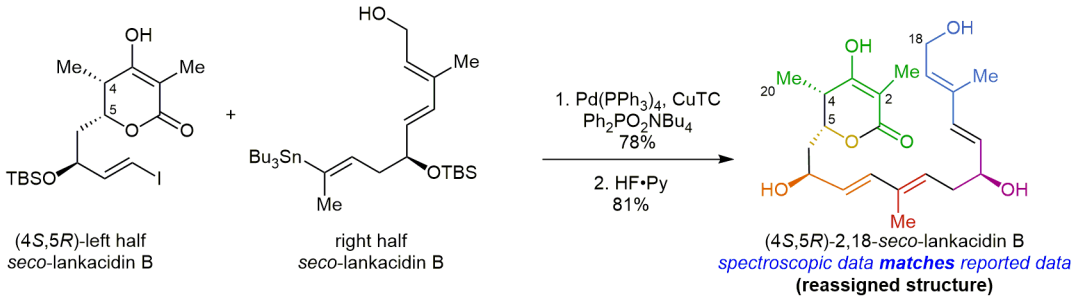


Figure 1 Lankacidin antibiotics

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-



Scheme 1 Completion of the synthesis: assembling of left and right half of seco-lankacidin B

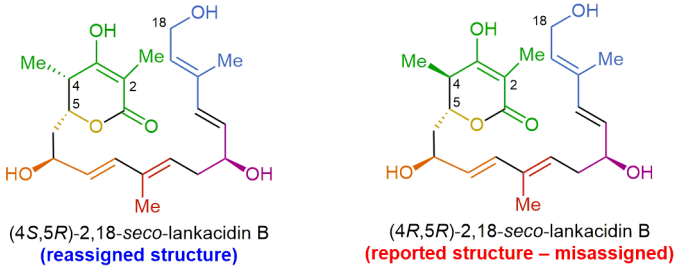


Figure 2 Correct and previous misassigned seco-lankacidin B structures

of). 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-*seco*-lankacidinol 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 lankacidins 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-*Seco*-lankacidinol 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 lankacidins 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 lankacidins. We are excited to report the results of these studies in the near future."

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(2) C. Lu, J.-M. Li, H. Qi, H. Zhang, J. Zhang, W. S. Xiang, J. D. Wang, X. J. Wang *J. Antibiot.* **2018**, *71*, 397–401.

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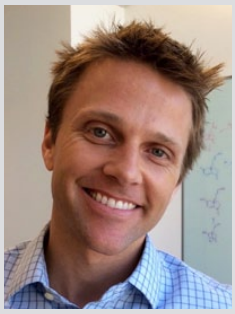
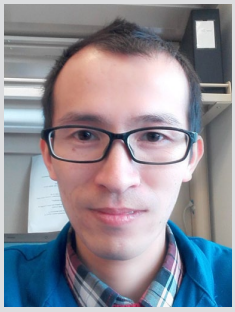


Prof. I. Seiple

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.



Dr. Y. Yao

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.

Dr. L. Cai

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.