

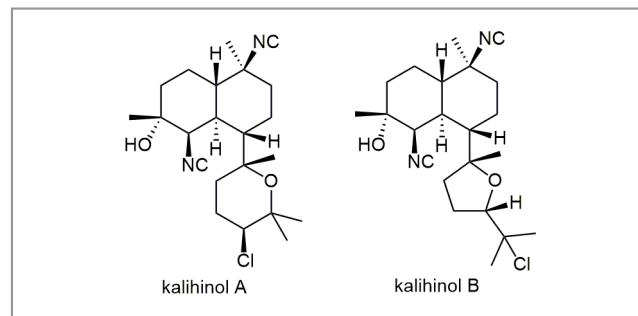
Synthesis and Potent Antimalarial Activity of Kalihinol B

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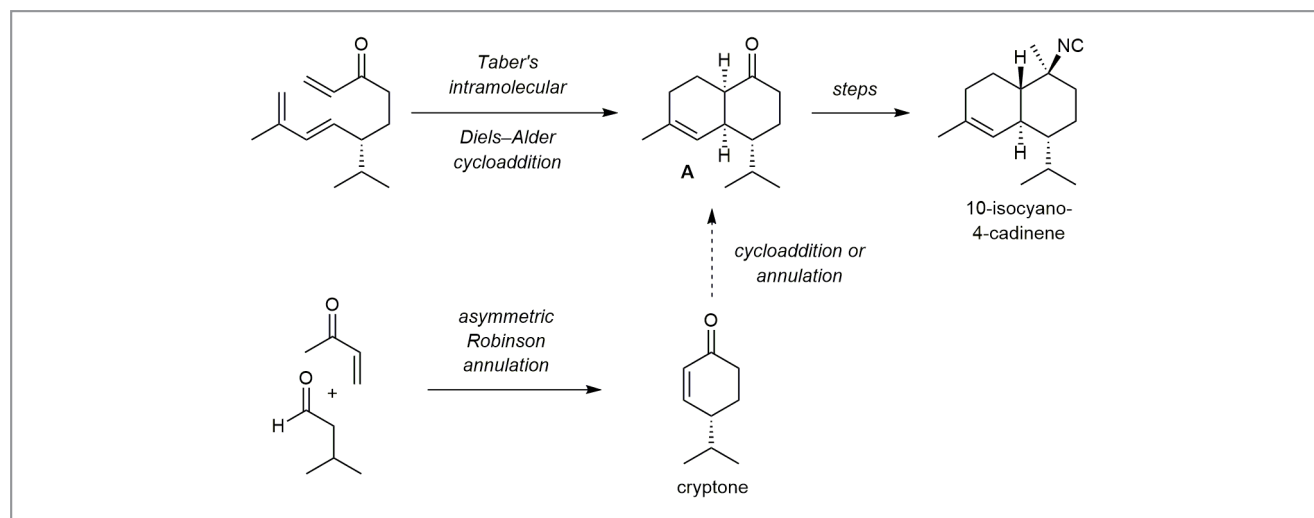
The treatment of malaria remains a medical challenge and the current best practice relies on combination therapy, namely the use of two or more drugs mostly for reducing the risk of therapy failure and developing resistance. Access to a broad portfolio of effective antimalarial drugs is an urgent medical need; therefore, the discovery and development of novel affordable antimalarial drugs continues to be a vibrant research area. Sponge-derived kalihinanes have been reported to have antimalarial activity; however, a systematic study of kalihinanes as antimalarial agents has not been described. Recently, Professor Christopher D. Vanderwal from the University of California (Irvine, USA), described a 12-step synthesis of kalihinol B, which was found to have potent antimalarial properties.

Professor Vanderwal said: “Although there had been synthesis work on the kalihinanes before by the Wood and Miyaoka groups (see the original JACS paper for references), my PhD student Mary Beth Daub and I began our studies because we believed that a general approach to many members of the family might offer a better understanding of the mechanism of action of these potent antimalarials, assuming that we could engage excellent collaborators (which we have, in Professor Karine Le Roch and Jacques Prudhomme!). After all,” he continued, “there are over 50 known naturally occurring kalihinanes at the last count and, because the antimalarial activity of kalihinol A ($EC_{50} = 1.2$ nM against a drug-resistant malaria parasite) was reported after many of these com-

pounds were discovered, only five natural products had been tested for antimalarial activity.”



The group's synthesis strategy arose from a 'Molecule of the Quarter' challenge, in which the group breaks up into teams, each of which develops a strategy for the synthesis of the target molecule. Professor Vanderwal explained: “Kalihinol A, with its incredible antimalarial activity, was the target. The key idea came from a different way of looking at the simpler but related sesquiterpene, isocyanocadinene.” The Wood and Shenvi groups had made this molecule previously by application of an intramolecular Diels–Alder cycloaddition originally described by Taber for his synthesis of torreyol. That same type of cycloaddition also featured in the Wood and Miyaoka syntheses of the kalihinanes. Professor Vanderwal said: “We looked at the decalone cycloadduct **A** as a possible

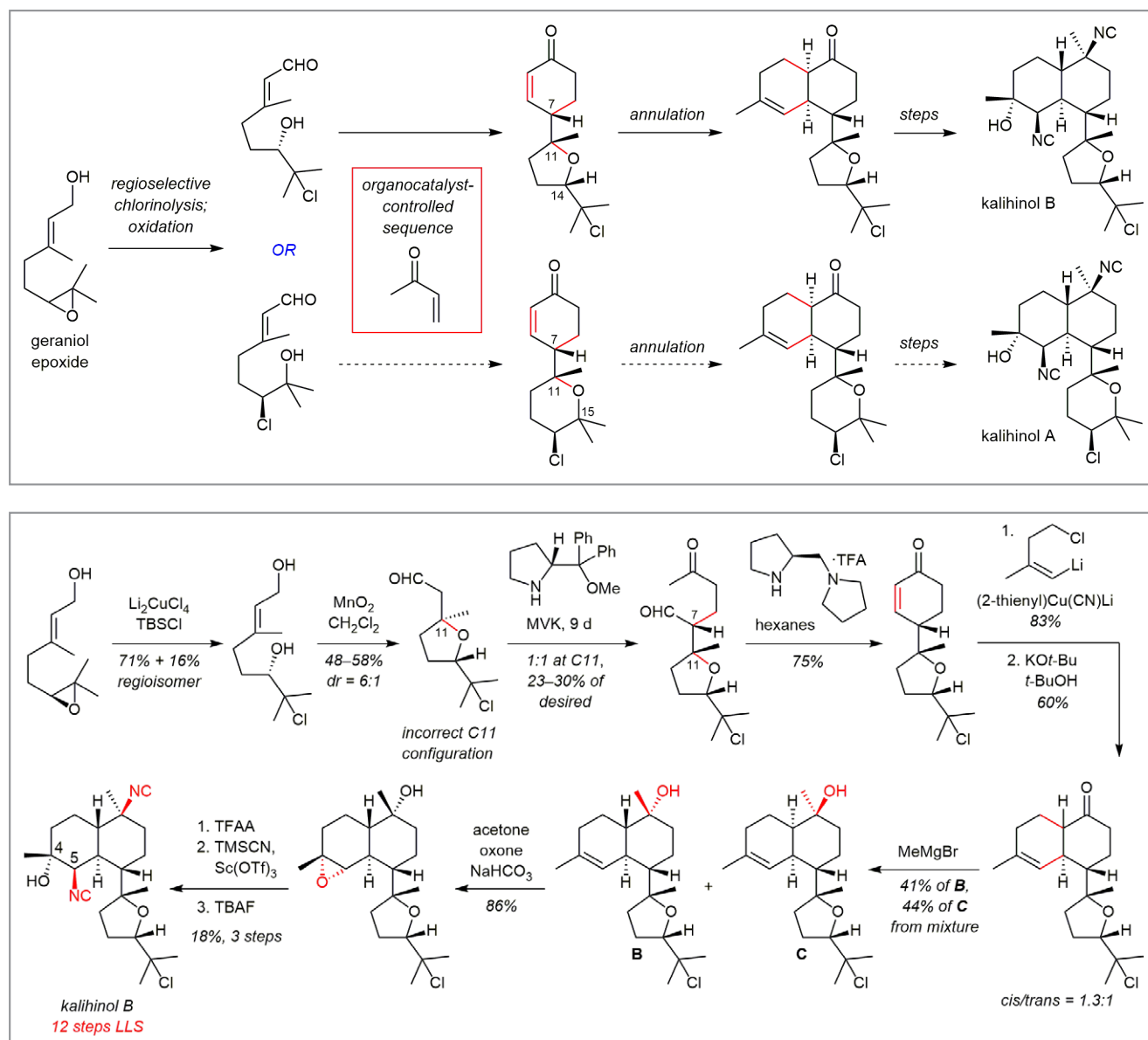


product of an annulation or cycloaddition onto cryptone, a known building block available in enantiopure form by asymmetric organocatalytic Robinson annulation.”

He continued: “That was the insight we needed to be able to connect the oxygen-heterocycle synthesis with the ‘B’-ring synthesis via a sequence of oxa-Michael addition and Robinson annulation. The possibilities for organocatalytic stereo-control of the C7,C11 relationship, which admittedly didn’t work out quite perfectly, were really exciting. We felt that this approach to the synthesis of the pendant heterocycle – targeting the C11–O bond whereas Wood and Miyaoka forged the C14(15)–O bond (likely also the biosynthetic process) – set

our approach apart from the previous work and offered the possibility of a very short synthesis. Fortunately, Mary Beth was able to reduce this relatively simple idea to practice in a way that I am very proud of.”

According to Professor Vanderwal, the short step count (12 or 13 steps, depending upon the starting epoxidation) would not have been possible without application of the excellent invertive isocyanation of tertiary trifluoroacetates developed by Shenvi and Pronin. “We have the good fortune of being friendly with Professor Shenvi and of having Professor Sergey Pronin as our newest colleague here at UCI,” said Professor Vanderwal. “At the outset of our work, we anticipated needing to de-



velop this type of reaction; having been beaten to it so nicely obviated any work by us in that area. We can tell you, that reaction works as advertised! What was so fortunate for us was that the conditions developed by Shenvi and Pronin also behaved well in the epoxide isocyanolysis. If that hadn't worked out, our endgame would have been much, much longer."

"We were ecstatic to learn that our synthetic sample of kalihinol B had nearly identical activity against drug-resistant

malaria parasite to that reported for kalihinol A," said Professor Vanderwal, who concluded: "That is the first of many SAR data points that we hope to add to the literature as we work with Jacques and Karine to understand how some of the kalihinanes exert their exciting antimalarial activity."

Matthew Fenske

About the authors



M. B. Daub

Mary Beth Daub was born and raised in Claremont, California (USA). She received a B.A. in chemistry from Williams College in Williamstown, MA (USA) in June 2011, where she worked towards the synthesis of polyketide natural products in the lab of Professor Thomas E. Smith. She is currently a fourth-year Ph.D. student at the University of California, Irvine (USA) working under the direction of Professor Chris Vanderwal. Her research in the Vanderwal group focuses on the development of a unified synthetic approach towards the kalihinane family of antimalarial isocyanoterpene natural products.



J. Prudhomme

Jacques Prudhomme was born in Los Angeles, California (USA). After earning his B.Sc. degree in biochemistry at the University of California, Riverside (UCR, in the USA), he joined the laboratory of Professor Irwin Sherman studying the cytoadherent properties of the malaria parasite, *Plasmodium falciparum*, as well as the endothelial cells with which they interact. In 2006, he joined the laboratory of Professor Karine Le Roch and began evaluating the effect of natural products and chemical compounds on *Plasmodium* parasites and their potential as novel antimalarial agents. He is a Research Associate in the Department of Cell Biology and Neuroscience at UCR and is well published with over 25 years experience working with malaria parasites.

Karine Le Roch is an Associate Professor at the University of California, Riverside (UCR, in the USA). She obtained her Master's degree in parasitology at the University of Lille II (France) and the University of Oxford (UK) in 1997. She completed her Ph.D.



Prof. K. Le Roch

in June 2001 at the University of Paris Sorbonne (France), working on the cell cycle of the human malaria parasite, *Plasmodium falciparum*. In 2001, as a postdoctoral fellow, she joined the Scripps Research Institute, San Diego, California (USA) to carry out the functional analysis of the *P. falciparum* genome using microarray technologies. She joined the Genomics Institute of the Novartis Research Foundation (California, USA) in January 2004 where she developed the malaria drug discovery program. Since April 2006 at UCR, Karine Le Roch is using functional genomics and system biology approaches to elucidate critical regulatory networks driving the malaria parasite life cycle and identify novel drug targets.



Prof. C. D. Vanderwal

Christopher D. Vanderwal received B.Sc. (biochemistry, 1995) and M.Sc. (chemistry, 1998) degrees from the University of Ottawa (Canada). He then moved to the Scripps Research Institute (La Jolla, USA) for doctoral studies in the group of Professor Erik Sorensen. After obtaining his Ph.D. in 2003, Chris joined the group of Professor Eric Jacobsen at Harvard University (USA) as a Jane Coffin Childs Postdoctoral Associate. In 2005, he began his independent academic career at the University of California, Irvine (USA). In 2011, Chris was promoted with tenure to Associate Professor and was named a UCI Chancellor's Faculty Fellow, and in 2013, he was promoted to Professor and Vice Chair of Chemistry for Graduate Affairs. His research group at UC Irvine aims to develop practical and divergent syntheses of complex, bioactive natural products.