

## Total Synthesis of Linear Polythiazole/Oxazole Plantazolicin A and Its Biosynthetic Precursor Plantazolicin B

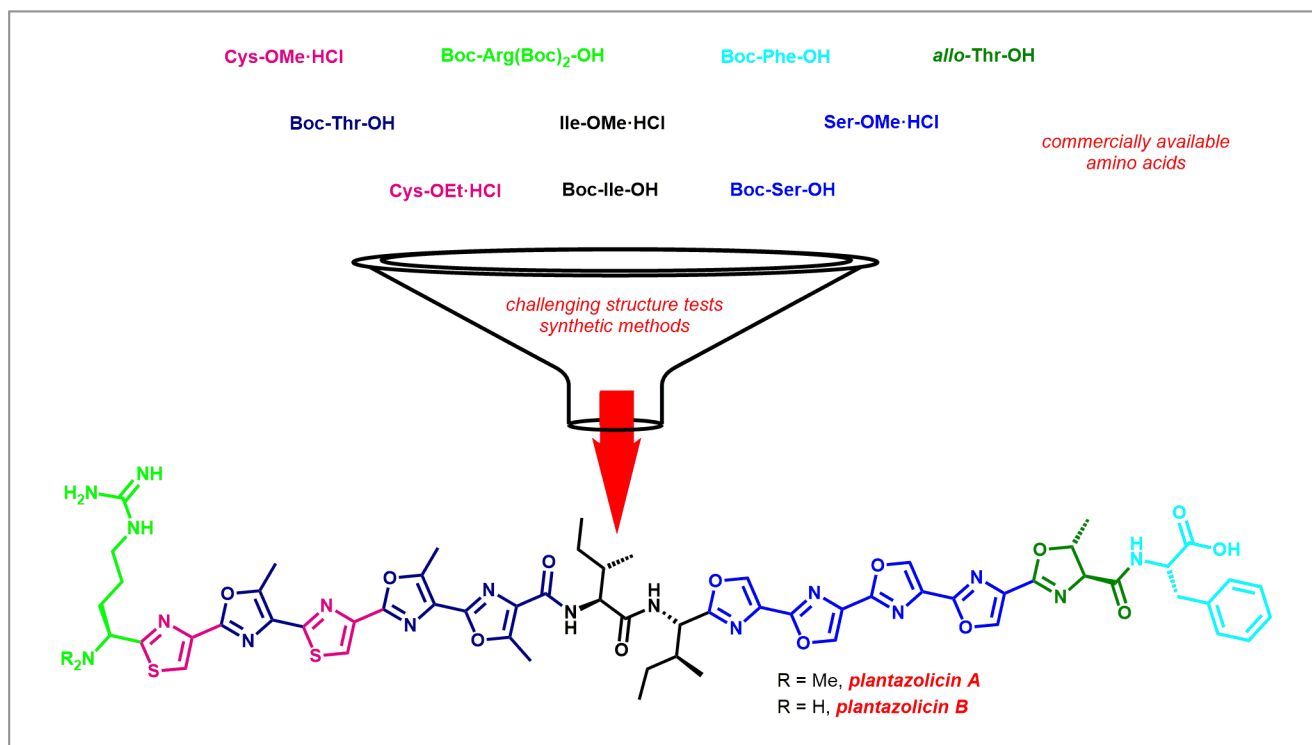
*Angew. Chem. Int. Ed.* **2015**, *54*, 1284–1288

Plantazolicin A has garnered much interest since its structure was first reported in 2011 due to its highly selective activity against the causative agent of anthrax toxicity, *Bacillus anthracis*. With ten heterocyclic rings, including one which is saturated, plantazolicin A and its biosynthetic precursor plantazolicin B offer a significant challenge to the synthetic chemist, and the successful synthesis of these molecules by the group of Professor Steven Ley at the University of Cambridge (UK) is a reminder of the power of modern synthetic methods. Professor Ley said: “This was by no means a straightforward synthesis – the final coupling step to join the two large pieces was first attempted in May 2013; it took over 1.5 years to optimize this step and the deprotection and purification of the resulting natural products.”

Professor Ley continued: “One of our key considerations was that we wanted to have very strong support for our synthesis in the form of robust characterization of all intermediates and independent full characterization of the final

natural products, as there was some variability and omissions in the reported data for plantazolicin A across the literature, and full characterization of plantazolicin B had not previously been reported. This led to a supporting information section larger than some theses at 130 pages! The advice of Professor Douglas Mitchell at the University of Illinois at Urbana-Champaign (USA) on the purification of the natural products, as well as the provision of an authentic sample of plantazolicin A to enable comparison, was greatly appreciated.”

This project was originally proposed by Dr. Sabine Fenner in her application for a German Academic Exchange service (DAAD) fellowship and she was joined on the project by Dr. Zoe Wilson. Professor Ley told SYNFORM that Sabine largely focused on the synthesis of the common right-hand-side molecule while Zoe focused on the synthesis of appropriate left-hand fragments to allow the synthesis of both plantazolicin A and B. They then collaborated closely on the final coupling and deprotection steps to give the natural products.



Professor Ley revealed that some of the group's key aims were to gain access to both plantazolicin A and plantazolicin B via a common convergent route, and additionally to make the approach as applicable to the future synthesis of analogues as possible: "The application of dicyclizations of two amino acid residues simultaneously at two stages of the synthesis allowed us to form concatenated rings in a single step, which contributed to an overall longest linear step count of only 14 (plantazolicin B) or 15 (plantazolicin A) steps," he commented. In order to make the synthesis as cost-effective as possible, commercially available protected amino acids were used as starting materials, with all but one being of the natural L configuration (the mechanism of cyclization using Deoxo-Fluor requiring the use of *allo*-threonine in synthesizing the oxazoline ring). Rather than using the more conventional Hantzsch-type thiazole synthesis from thioamides, which often necessitates the use of unpleasant sulfurating agents, the condensation of cysteine esters with amino aldehydes followed by the oxidation of the resulting thiazolidine to the thiazole using manganese dioxide readily gave access to the desired thiazoles. This method was especially beneficial for the synthesis of the key arginine-derived thiazole residue which proved to be very challenging.

"With the synthesis for these natural products successfully established, we now have access to analogues and simplified fragments which are unavailable through biological methods such as codon reprogramming," said Professor Ley, continuing: "It is hoped that these can be used to help further establish the structure–activity relationship for plantazolicin A."

Additionally, this paper has the distinction of being Professor Ley's 800<sup>th</sup> publication. Dr. Zoe Wilson commented: "The entire Ley group was looking forward to the champagne party on the 20<sup>th</sup> of March."

Professor Dieter Enders, a synthetic organic chemistry expert from Aachen University (Germany) and Editor for Reviews of SYNTHESIS, commented: "With the total synthesis of plantazolicin A and B, the Ley group has added yet another masterpiece to their impressive list of numerous elegant and very efficient syntheses of biologically active natural products. The convergent route starting from commercially available amino acids carried out by Dr. Zoe Wilson and Dr. Sabine Fenner is most convincing and will certainly allow access to analogues of these important compounds. Being almost of the same age as Steve, I know what it means to have published 800 papers in the field of synthetic chemistry. This is a paramount accomplishment and indeed deserves a lot of champagne!"

*Dieter Enders*

### About the authors



Prof. S. V. Ley

**Steven Ley** is currently Professor of Chemistry and Director of Research at the University of Cambridge (UK), where he is a Fellow of Trinity College. He was BP 1702 Professor of Chemistry for 21 years. Steve obtained his PhD from Loughborough University (UK) with Professor Harry Heaney and afterwards carried out postdoctoral research with Professor Leo Paquette (Ohio State University, USA), then Professor Derek Barton (Imperial College, UK). He was appointed as a Lecturer at Imperial College in 1975, promoted to Professor in 1983, and then to Head of Department in 1989. In 1990 he was elected to the Royal Society (London) and was President of The Royal Society of Chemistry from 2000–2002. Steve's research interests are varied and span many disciplines including new synthetic methodologies, the total synthesis of natural products and the development of enabling technologies for chemical synthesis especially in the area of flow chemistry technologies. He has published nearly 800 papers and has gained 50 major awards including the Tetrahedron Prize for Creativity in Organic Chemistry (Elsevier); Heinrich Wieland Prize (Boehringer Ingelheim, Germany); The Paracelsus Prize (Swiss Chemical Society); The Royal Medal (The Royal Society, London) and, most recently, The Longstaff Prize (The Royal Society of Chemistry).



Dr. Z. Wilson

**Zoe Wilson** grew up in the small town of Warkworth, New Zealand. She attended the University of Auckland (New Zealand) where she completed a Bachelor of Science in Medicinal Chemistry, then a BSc (Hons) in Medicinal Chemistry (researching the synthesis of anti-*Helicobacter pylori* compounds) and a PhD in synthetic chemistry (working on the synthesis of the natural product berkelic acid) with Professor Margaret Brimble. Upon completion of her PhD in 2010 she was awarded a Newton International Fellowship from the Royal Society to join the research group of Professor Steven V. Ley. Upon completion of the fellowship, she was then employed as a Postdoctoral Research Associate to continue working in the Ley group. Her interests lie in the areas of

>>

natural product synthesis and how this leads to the development of novel chemistry. Additionally, Zoe has been a College Lecturer and Fellow at Murray Edwards College at the University of Cambridge since October 2013.



Dr. Z. Wilson

**Sabine Fenner** was born in Homberg/Efze (Germany). She studied chemistry at the Georg-August-University of Göttingen (Germany) with an internship at Sanofi-Aventis, Frankfurt am Main (Germany) in 2007. Under the guidance of Professor Lutz Ackermann she received her Diploma in 2008 and her PhD in 2012 (with distinction *summa cum laude*) for investigations into transition-metal-catalyzed C–H bond functionaliza-

tion. She then joined the group of Professor Steven V. Ley at Cambridge University as a Postdoctoral Fellow of the German Academic Exchange Service (DAAD), focusing on the total syntheses of the natural products plantazolicin A and B. In 2014 she assumed her current position in the Process Development department of GlaxoSmithKline, Stevenage (UK).