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.

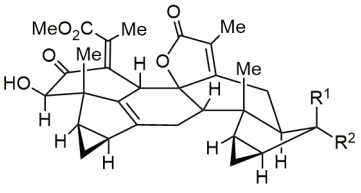
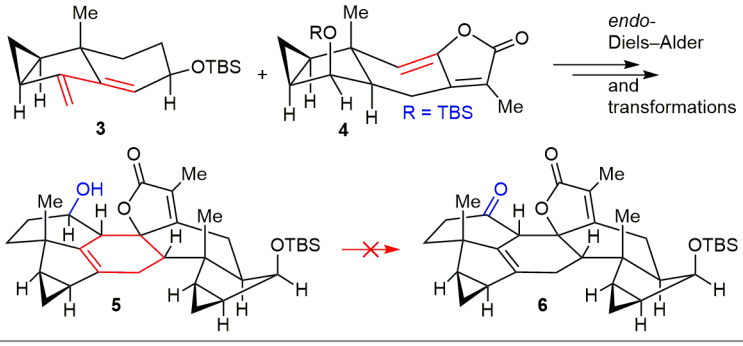


Figure 1 Structures of shizukaols A and E

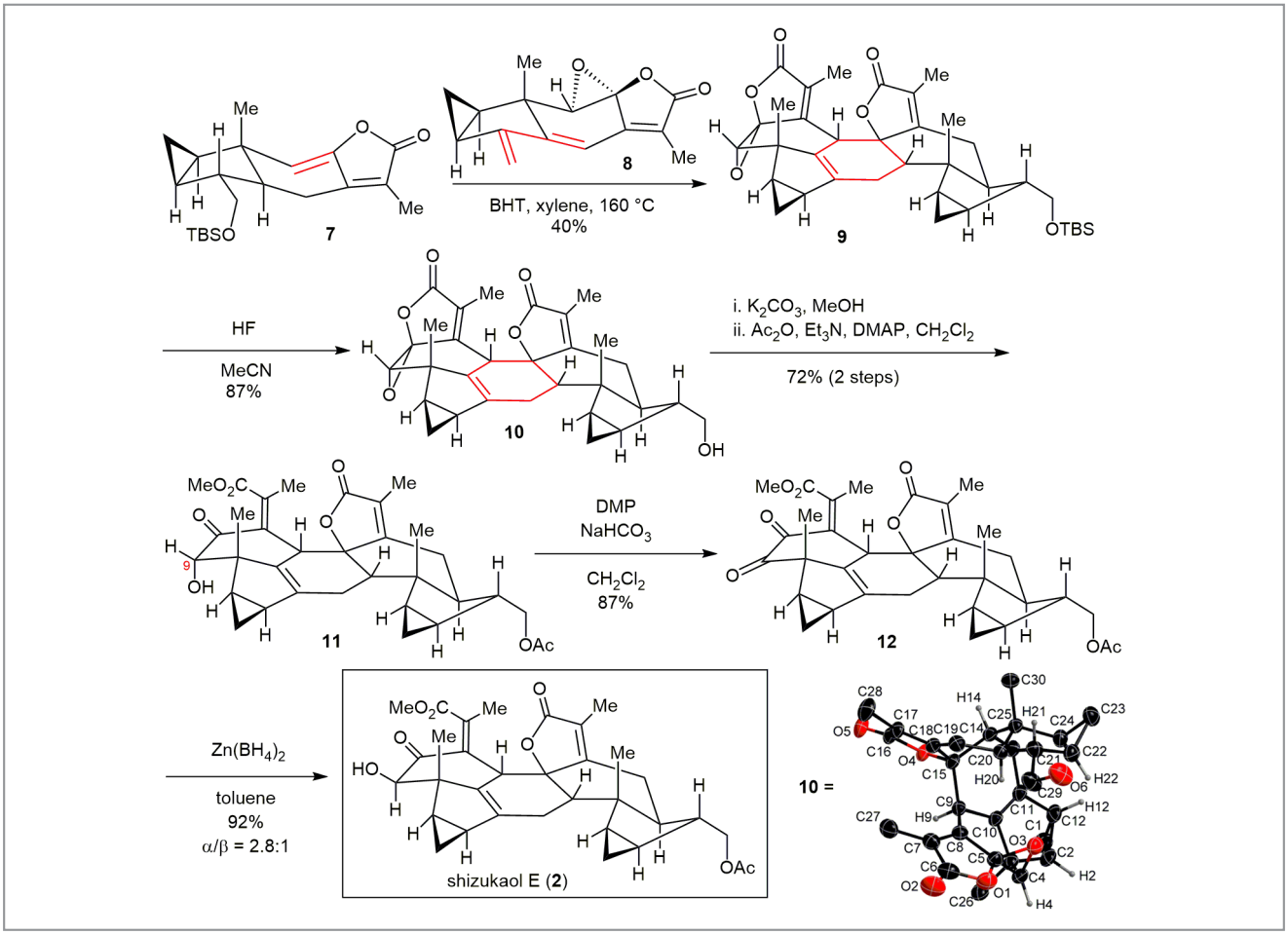
Shizukaols A and E, two dimeric lindenane-type terpenes, were isolated from *Chloranthus japonicas*. Both possess a common heptacyclic framework containing more than 10 contiguous stereocenters with potential biological activities, which has attracted a considerable amount of interest from synthetic 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."



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

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 KNO_2. Therefore, oxidation of alcohols **11** or **15** with Dess–Martin periodinane, respectively, led to diones **12** and **16**. Treatment of dione **12** with $Zn(BH_4)_2$ 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-

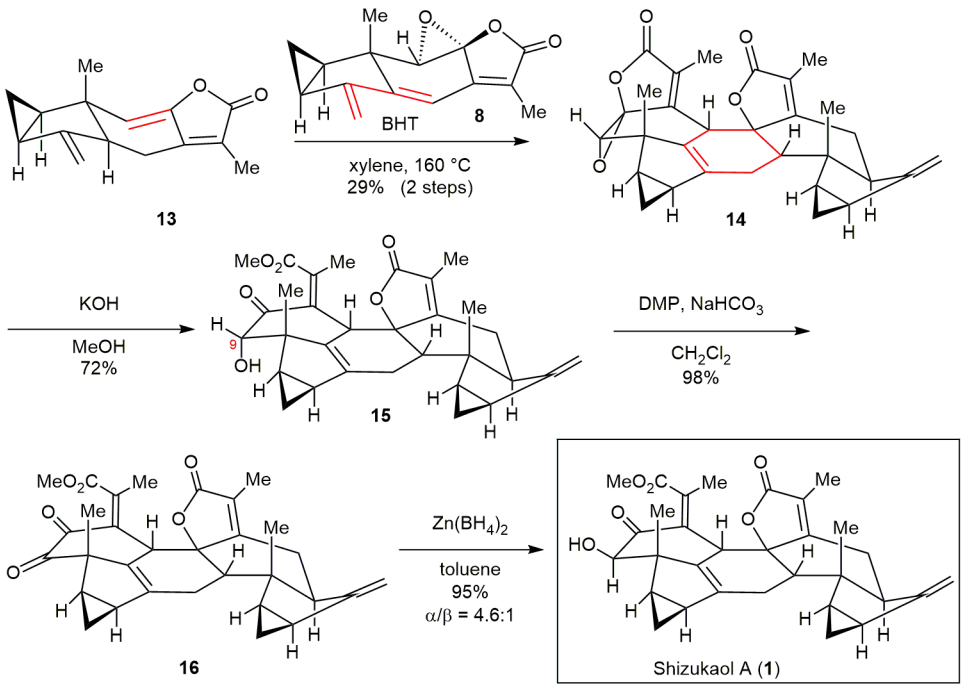


Scheme 2 Total synthesis of shizukaol E (**2**); BHT = butylated hydroxytoluene, DMP = Dess–Martin periodinane, DMAP = 4-dimethylaminopyridine

arly, oxidation of **15** with Dess–Martin periodinane, followed by reduction of dione **16** with $Zn(BH_4)_2$, 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 $Zn(BH_4)_2$ 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 $Zn(BH_4)_2$, 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

Dr. J.-L. Wu

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.

Dr. Y.-S. Lu

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. After that, he worked at the Hong Kong Polytechnic University (P. R. of China) from 2014 to 2016 as a postdoctoral fellow studying transition-metal-catalyzed methodology under the direction of Professor Wing-Yiu Yu. Since 2016, he has been a researcher in pharmaceutical industry. Now, he is working in the department of Innovative Drug R&D Center of Shenzhen Salubris Pharmaceutical Co., LTD (P. R. of China).

Prof. B. Tang

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 Harrowven 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.

Prof. X.-S. Peng

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.

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