Total Synthesis of (±)-Atropurpuran

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Plants of the genera *Aconitum* and *Delphinium* are widely distributed in the northern hemisphere and many of them have been employed in folk medicine to treat pain, rheumatism and neurological disorders. These species provide various groups of diterpenoid alkaloids possessing polycyclic and complex structures and a range of intriguing bioactivities. Professor Yong Qin's group at Sichuan University (P. R. of China) began to study the total synthesis of atropurpuran in the summer of 2009. Professor Qin explained the origins of their interest: "Professor Feng-Peng Wang (from the same department) is a respected colleague and globally well-known phytochemist who has consistently and extensively investigated the chemistry and biology of diterpenoid alkaloids for over 30 years (*Nat. Prod. Rep.* **2010**, *27*, 529–570). In 2006, Professor Wang's group isolated a pentacyclic diterpenoid named atropurpuran from *Aconitum hemsleyanum* var. *atropurpureum*; however, this was not published until 2009 after they successfully obtained X-ray crystallographic data to fully verify its cage-like and congested architecture. This compound was considered a biosynthetic precursor of related diterpenoid alkaloids (e.g., arcutine and acrutinine). In view of its interesting structure and unexplored bioactivity, atropurpuran seemed likely to be a research focus for synthetic chemists (see the original paper for references)."

Professor Qin continued: "It was in the summer of 2009 during a chat with Professor Wang that he speculated whether I could conquer the two molecules: atropurpuran and aconitine. That was the starting point of this synthetic adventure." The first version of the synthetic endeavor towards atropurpuran relied on the original biosynthetic pathway proposed by Professor Wang and was mainly carried out by PhD student Huan Chen. "In this context, we synthesized two intermediates (**A** and **B**) employing different organocatalytic Michael addition reactions as key steps, respectively," said Professor Qin. "Unfortunately, neither compound is suitable to be advanced to the target since their preparation suffers from tedious synthetic steps and low efficiency."

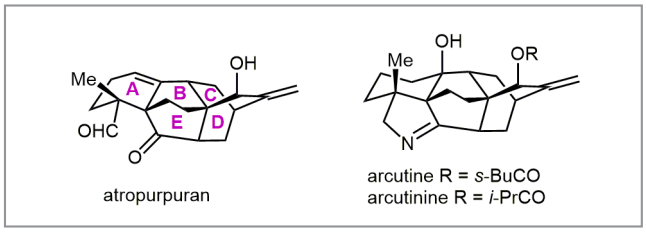


Figure 1

After an extremely challenging five-year effort, the turning point for the project came in March 2014 when the group designed a different synthetic route, finally leading to success. Professor Qin remarked: "Another two researchers became the main force of the new strategy: Jing Gong, another PhD student under my supervision, and Dr. Xiao-Yu Liu, a former PhD student of Professor Wang, who joined my group as an associate professor. As expected, a tandem oxidative dearomatization/intramolecular Diels–Alder cycloaddition reaction took place smoothly to afford compound **C** in decagram quantities, which we considered to be a cornerstone for the whole synthesis. We actually did not have much trouble before we started to assemble the final ring (ring B) of the target molecule." Unfortunately, various conditions for the ketyl-olefin cyclization of intermediate **D** to form ring B proved unsuccessful. By carefully checking the reaction transition state, the authors believed that a bulky group at C20 would not only interrupt the undesired intramolecular H-bonding but also force ring E to adopt a boat conformation, thus favoring the spati-

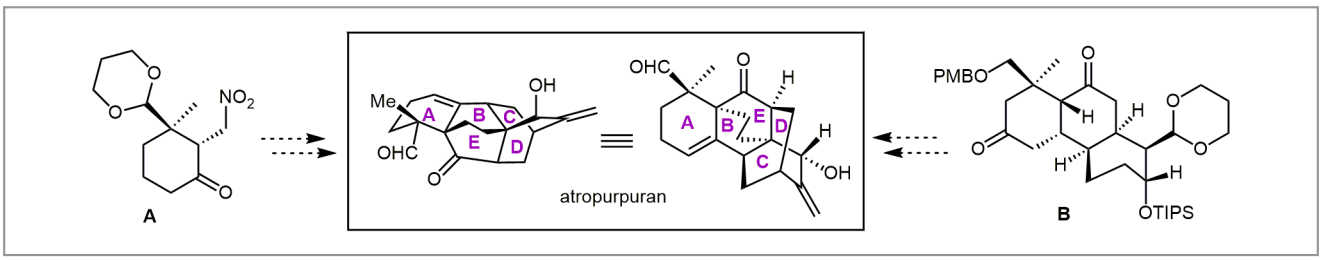
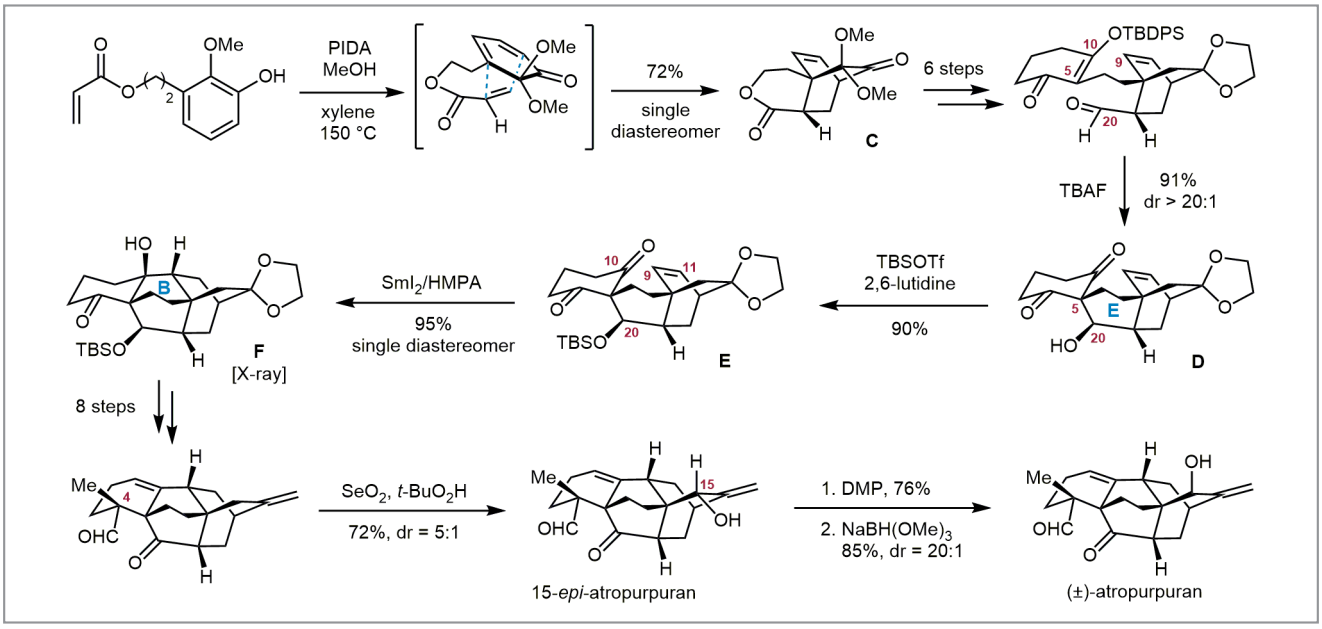


Figure 2



Scheme 1

al proximity between C10 ketyl with C9[9,11] and enabling the cyclization (see the original paper for details). As a result, by installing a bulky *tert*-butyldimethylsilyl (TBS) group on C20 alcohol, Professor Qin and co-workers were able to reach the atropurpuran core (intermediate **F**) from **E** via a ketyl-olefin cyclization in an efficient manner.

"The endgame of our synthesis was more challenging than we anticipated, with some simple reactions failing to work, probably because of the rigid nature of the core structure," said Professor Qin. "To our delight, after extensive experimentation, we ultimately figured out a sequence to atropurpuran. Of note, a chemoselective and stereoselective reduction was achieved to install the requisite hydroxyl group at C15 of the target natural product in the last step of the synthesis."

"We believe this is an interesting story on natural product research where a natural product was isolated and synthesized through a *de novo* route in the same department, which we are very proud of," said Professor Qin, who concluded: "In the long run, development of an entry to optically pure atropurpuran and arcutinine, as well as exploration of their biological profiles would be desirable. Additionally, the accomplishment of this work sheds light on the importance of strategic rational design which would greatly facilitate total synthesis of such three-dimensionally complex and cage-like molecules."

About the authors

J. Gong

Jing Gong was born in Sichuan (P. R. of China). He received his B.Sc. degree in chemistry at Sichuan University (P. R. of China) in 2013. In the same year he joined the group of Professor Yong Qin at Sichuan University to pursue his Ph.D. degree. His research focuses on the total synthesis of complex natural products.

Dr. H. Chen

Huan Chen was born and raised in Chengdu of Sichuan Province (P. R. of China). He obtained his B.Sc. degree in pharmacy from Sichuan University (P. R. of China) in 2009. He then began his doctoral research in Professor Yong Qin's group, working on the total synthesis of atropurpuran. In 2006, he received his Ph.D. degree in chemistry of medicinal natural products from Sichuan University.

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Prof. X.-Y. Liu

Xiao-Yu Liu received his Ph.D. degree in 2012 under the supervision of Professor Feng-Peng Wang at Sichuan University (P. R. of China). After conducting postdoctoral research in the group of Professor David Y.-K. Chen at Seoul National University (Korea), he joined the faculty of Sichuan University in 2014 working with Professor Yong Qin. His research interests include target- and diversity-oriented synthesis based on complex natural products, especially various groups of diterpenoid alkaloids and related diterpenes.

Prof. Y. Qin

Yong Qin received his B.Sc. degree from Yunnan University (P. R. of China) in 1989 and his Ph.D. from the Institute of Chemistry, Chinese Academy of Sciences (P. R. of China) in 1995. From June 1995 to August 1996, he worked at the Chengdu Institute of Organic Chemistry (P. R. of China) as an assistant and associate professor. From August 1996 to August 2000, he worked with Professor Martin E. Kuehne as a postdoctoral associate at the University of Vermont (USA). Then he moved to San Diego (USA) and worked as a research scientist at Triad Therapeutics Inc. In 2003, he joined the faculty of West China School of Pharmacy, Sichuan University (P. R. of China) as a full professor. Since 2011, he is an adjunct professor at the Innovative Drug Research Centre, Chongqing University. His research has been focused on the total synthesis of bioactive natural products and medicinal chemistry.