Total Synthesis and Anti-inflammatory Activity of Stemoamide-Type Alkaloids Including Totally Substituted Butenolides and Pyrroles

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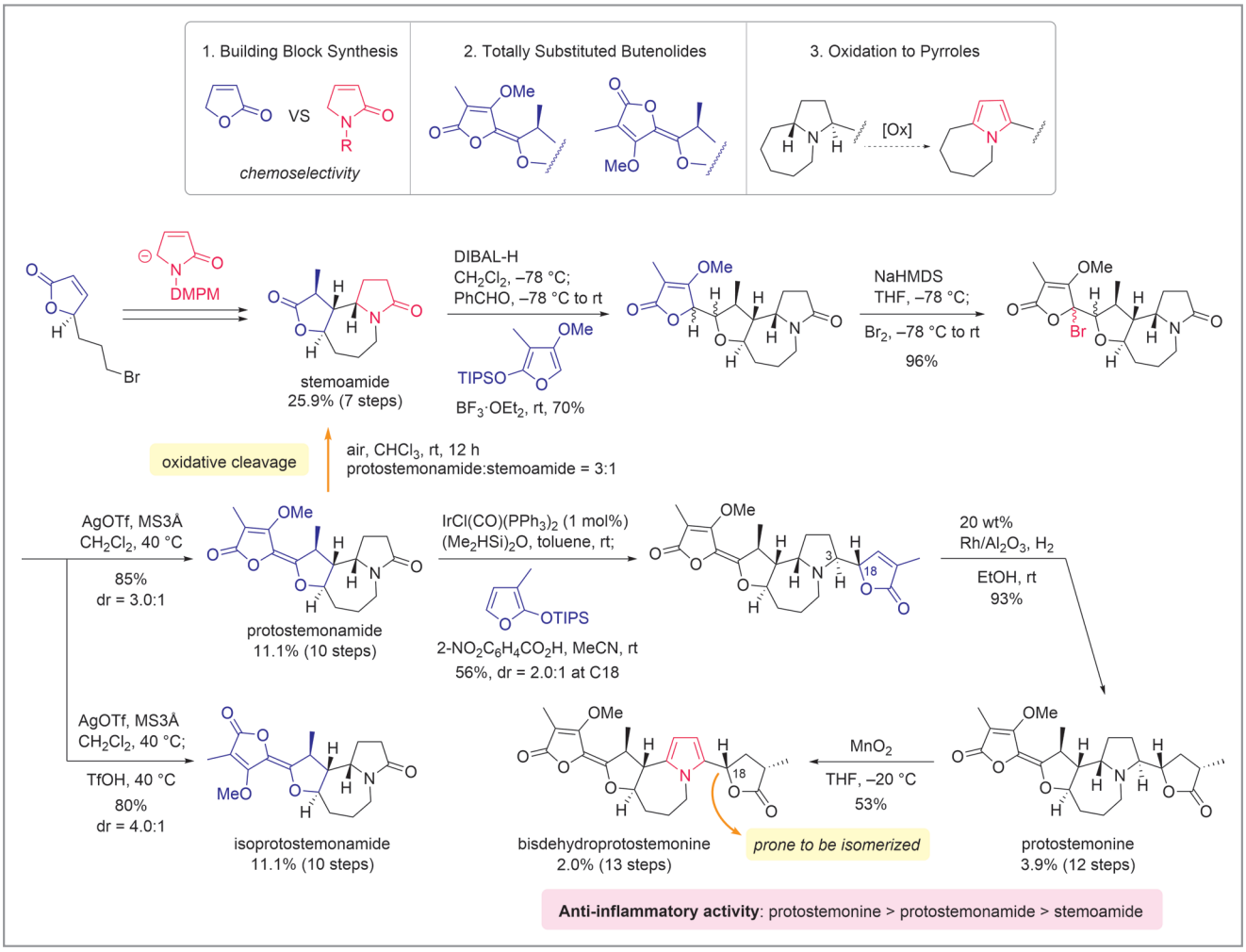
Tricyclic stemoamide has been recognized as a very popular target for total synthesis. Indeed, many research groups have reported the total synthesis of this relatively simple natural product to demonstrate the utility of their own synthetic method. However, none had accomplished the total synthesis of the pentacyclic stemoamide-type natural products, despite the fact that pentacyclic protostemonine is known to show much better biological profiles, such as protective effects on acute liver failure and acute lung injury in mice. Some time ago, the group of Professor Takaaki Sato at Keio University (Yokohama, Japan) started a project that led to the publication of this SYNTHESIS paper. Professor Sato explained: "In this study, we developed three key methods: 1) the chemoselective assembly of five-membered building blocks by iridium-catalyzed reductive nucleophilic addition (examples: *J. Am. Chem. Soc.* **2017**, *139*, 18386–18391; *Org. Lett.* **2020**, *22*, 7502–7507), 2) the three-step stereodivergent synthesis of the totally substituted butenolides, and 3) the direct oxidation of the pyrrolidine groups to the corresponding pyrroles with MnO_2. These methods enabled us to achieve the unified total synthesis of stemoamide-type alkaloids and demonstrate the systematic structure–activity relationship involving the anti-inflammatory activities by inhibition of iNOS expression in macrophage cell line RAW264.7. We believe that our study opens up a whole new research chapter in the field of *Stemona* alkaloids, in terms of both synthesis and biological activity."

Professor Sato recalled that the original idea of this project arose in 2013. He commented: "My kid, two years old at that time, showed no interest in my research, but loved LEGO®-blocks. I thought: 'OK, my kid is playing with LEGO®-blocks, and his dad is playing with building blocks in chemistry. He would love me and my job!'" Professor Sato's motivation was simple, but as he commented, a project must contribute to solving issues in modern organic synthesis, in this case, the building block synthesis of stemoamide-type alkaloids by precise control of the chemoselectivity (amide vs ester). "I am very proud of my students, who have made accomplishments based on the initial rough sketch of my ideas," said Professor Sato. He continued: "I also appreciate the contribution of the groups of Prof. Urabe, Prof. Oishi and Prof. Simizu, who are wonderful collaborators. Unfortunately, total synthesis takes time. My kid grew up quickly, and is not playing with LEGO®-blocks anymore."

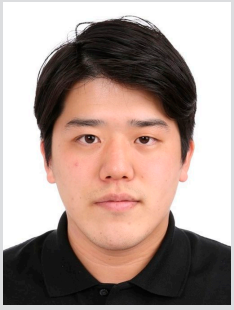
Mr. Soda, first author on the paper, said: "I felt very confident that our team would achieve this project when I found that the bromo group could be regioselectively installed into the tetracyclic intermediate, derived from tricyclic stemoamide. However, that was just the beginning." Mr. Soda explained that the most difficult part was the instability of each natural product. The following silver-mediated elimination provided tetracyclic protostemonamide, including the totally substituted butenolide. "I was so excited, and collected the NMR data overnight," remarked Mr. Soda. He went on: "I went to the NMR room to pick up the sample the next day and realized that the color of the sample had gained yellow. Reexamination of the TLC and NMR revealed that most of the sample had returned to the tricyclic stemoamide. It was a nightmare. Our sample spontaneously reverted back." Subsequently, Mr. Soda found that the oxidative cleavage of the tetrasubstituted olefin took place under aerobic atmosphere. The oxidation of the pyrrolidine group was also a tough step. "After oxidation of the pyrrolidine, the crude sample was pure, but various attempted purifications always led to the isomerization of the desired product," said Mr. Soda. He continued: "Finally, I obtained the pure spectroscopic data by super-quick filtration through a short pad of basified silica gel (1% Et_3N) within 20 seconds, and subsequent GPC (Gel Permeation Chromatography). Do not forget filtration of $CDCl_3$ through basic alumina before use upon measuring NMR. I learned a lot from these tough natural products."

Professor Sato said: "The key to success of this project was the development of nucleophilic addition to amide carbonyls. This reaction had received less attention than their construction due to their high stability. However, an amide group is one of the most abundant functional groups in organic synthesis, which means that it has a high potential for a broad range of applications such as total synthesis of complex natural products, late-stage modification of peptides and proteins, and supply of functional materials." Professor Sato concluded: "Currently, a number of research groups – including our group – have been engaged in this field, and further significant progress will be made in the near future."



Scheme 1 Unified total synthesis and anti-inflammatory activity of stemoamide-type alkaloids

About the authors



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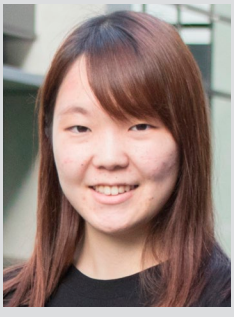

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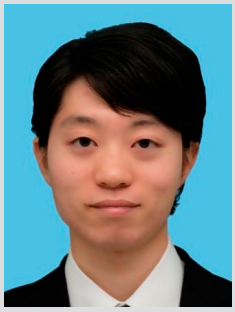

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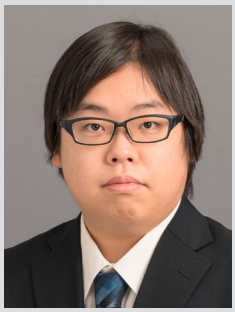
Takeshi Oishi received his Ph.D. degree in 2002 from Keio University (Japan) under the supervision of Professor Noritaka Chida. Then he worked at the National Institute of Advanced Industrial Science and Technology (AIST, Japan) as a research fellow for two years. In 2005, he joined the School of Medicine, Keio University (Japan) as an assistant professor.



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Professor S. Simizu

Siro Simizu received his B.Sc. degree in 1993 from Keio University (Japan), and his Ph.D. degree in 1998 from the same university under the supervision of Professors Kazuo Umezawa and Masaya Imoto. He spent 12 years in Professor Hiroyuki Osada's group at RIKEN (Japan) as a researcher. He joined the Department of Applied Chemistry, Keio University as a lecturer in 2010. He was promoted to Professor in 2017. He was awarded the Young Investigator Awards of the Japanese Cancer Association in 2004, and the Young Investigator Awards of the Japanese Association for Metastasis Research in 2011.

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Noritaka Chida received his B.Sc. degree in 1979 from Keio University (Japan), and Ph.D. degree in 1984 from Tohoku University (Japan, under Professor Akira Yoshikoshi). From 1984 to 1987, he worked for Mercian Co. Ltd., as a researcher. In 1987, he joined the Department of Applied Chemistry, Keio University as a research assistant, and in 1988–1989, he spent one year as a postdoctoral researcher at the University of Pennsylvania (USA) with Professor A. B. Smith, III. He was promoted to Professor of Keio University in 2003. He retired in 2022, and is currently professor emeritus at Keio University. He was awarded the "BCSJ Award" from the Chemical Society of Japan in 2002, 2015 and 2017, and the Keio Gijuku award in 2021.

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Takaaki Sato received his B.Sc. degree in 2001 from Tohoku University (Japan) and his Ph.D. degree in 2006, also from Tohoku University (supervisor: Professor Masahiro Hirama). He spent two years in Professor Larry E. Overman's group at the University of California, Irvine (USA) as a JSPS fellow. He joined the Department of Applied Chemistry, Keio University (Japan) as an assistant professor in 2008. He was promoted to Associate Professor in 2016. In 2022, he started his independent career at Keio University. He was awarded the Otsuka Pharmaceutical Co. Award in Synthetic Organic Chemistry, Japan in 2008, the Young Scientist's Research Award in Natural Product Chemistry in 2014, the Incentive Award in Synthetic Organic Chemistry, Japan in 2016, and the Thieme Chemistry Journals Award in 2019.

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