SYNTHESIS Best Paper Award 2023: Total Synthesis and Anti-inflammatory Activity of Stemoamide-Type Alkaloids Including Totally Substituted Butenolides and Pyrroles

Synthesis **2023**, *55*, 617–636

Background. Thieme Chemistry and the Editors of SYNTHESIS and SYNLETT present the 'SYNTHESIS/SYNLETT Best Paper Awards'. These annual awards honor the authors of the best original research papers in each of the journals, considering their immediate impact on the field of chemical synthesis.

A collaborative team from Keio University and Toyama Prefectural University (Japan) led by Takaaki Sato have been awarded the SYNTHESIS Best Paper Award 2023. The authors are recognized for their detailed synthetic study of the stemoamide class of heterocycles including tricyclic, tetracyclic and pentacyclic frameworks. The paper includes a stereodivergent strategy in the creation of a fully substituted butenolide. A comprehensive investigation that outlines several optimization reactions, careful structure elucidation and discussion, and anti-inflammatory assays, are highlights on this exciting study. This paper was the subject of a previous SYNFORM News announcement and a SYNTHESIS Highlight article (*Synform* **2022**, *12*, A202; DOI: 10.1055/s-0040-1720579) wherein the background and research were discussed in more detail.

SYNFORM spoke with Professor Takaaki Sato, who was happy to both share some additional insight into the prize-winning paper and to answer a few other questions on research in his group and total synthesis in general.

Biographical Sketch

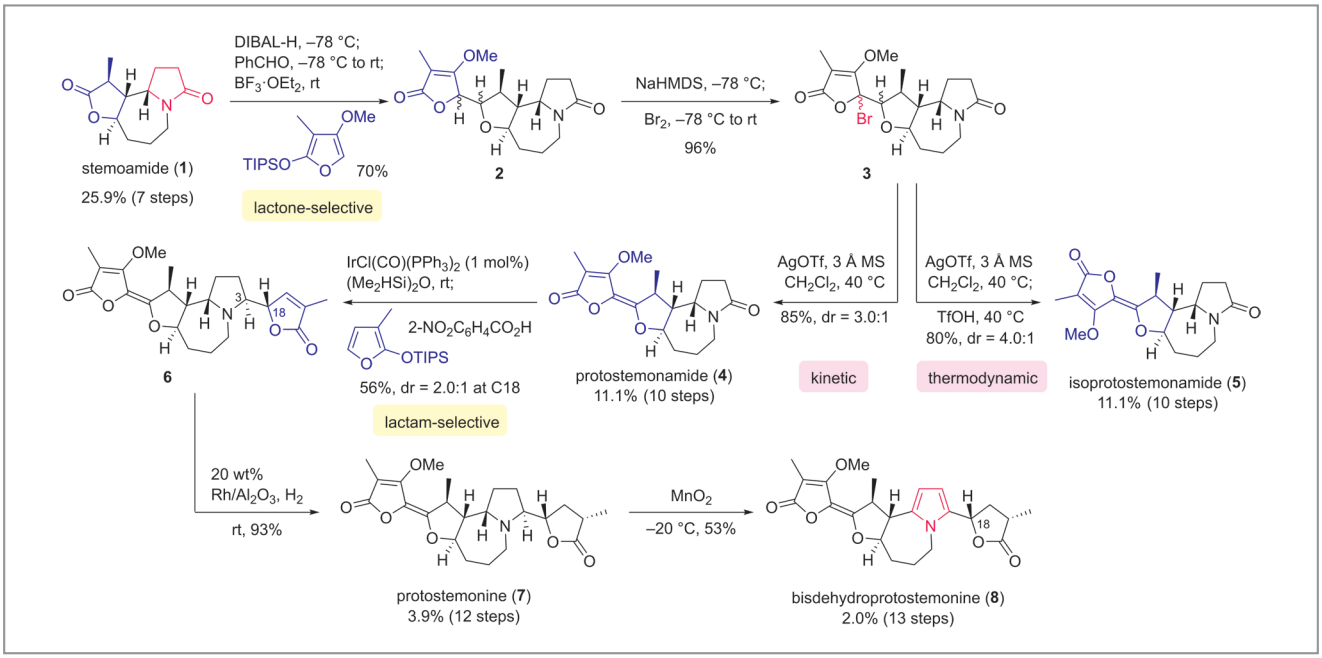
Top, from left: Yasuki Soda, Yasukazu Sugiyama, Kana Shibuya, Shunsei Sato, Junya Saegusa, Tomoe Matagawa, Sayaka Kawano
Bottom, from left: Prof. Makoto Yoritate, Prof. Keisuke Fukaya, Prof. Daisuke Urabe, Dr. Kento Mori, Prof. Siro Simizu, Prof. Noritaka Chida, Prof. Takaaki Sato (Dr. Takeshi Oishi not shown)

Takaaki Sato received his B.Sc. degree in 2001 from Tohoku University (Japan), and his Ph.D. in 2006 from the same university (Professor Masahiro Hirama). He the 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 and 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 a Thieme Chemistry Journals Award in 2019.

INTERVIEW

SYNFORM *Could you highlight the value of your award-winning paper with respect to the state-of-the-art, as well as the potential or actual applications?*

Prof. T. Sato The stemoamide-type alkaloids have been recognized as one of the most popular synthetic targets due to recent biological studies involving anti-inflammatory effects such as LPS-induced acute lung injury in mice. However, the structure–activity relationship (SAR) had not been demonstrated, especially for libraries including pentacyclic natural products. Structurally, stemoamide-type alkaloids consist of various five-membered heterocyclic rings. However, a building block strategy using five-membered rings had not been realized, since differentiation between γ-lactones and γ-lactams was highly challenging. We achieved the collective total synthesis of the stemoamide-type alkaloids by chemoselective assembly of five-membered building blocks (Scheme 1). The lactone selectivity was relatively easy to achieve by taking advantage of the inherent electrophilicity of the lactone (**1**→**2**). In contrast, the lactam selectivity was realized by iridium-catalyzed reductive nucleophilic addition (**4**→**6**). Another conspicuous transformation was the stereodivergent construction of the totally substituted butenolides. While elimination of bromide **3** with AgOTf under kinetic conditions provided protostemonamide (**4**) as a major product, elimination and subsequent acid-mediated isomerization gave isoprotostemonamide (**5**) as a thermodynamic product. These methods enabled us to determine the systematic SAR, revealing that the pentacyclic framework including the totally substituted butenolide is crucial for anti-inflammatory activities.



Scheme 1 Total synthesis of stemoamide-type alkaloids

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SYNFORM *What is the focus of your current research activity?*

Prof. T. Sato Currently, one of our research topics is the development of reactions including a crystallization process to control unsolved selectivity, and its application to total synthesis of natural products. When you read a textbook of organic synthesis, you can find two basic approaches to control selectivity. The first one is kinetic control, which favors a product via the most stable transition state under irreversible conditions. The other is thermodynamic control, in which the lowest-energy product predominates under reversible conditions. In total synthesis of complex molecules, we are often faced with reactions showing unfavorable selectivity even if both approaches are attempted. Our focus is to come up with an alternative solution utilizing crystallization. Although crystallization itself is a well-studied process, the combination of a reaction process in solution with simultaneous crystallization could provide new selectivity (for selected examples, see: Walsh & Kitching, *JACS Au* **2022**, *22*, 2235–2250). In addition, these types of reactions result directly in crystallized product, and thus can potentially be applied to process chemistry. Prediction of crystallization from molecular structures remains challenging, requiring trial and error. However, we believe that in the near future, more intentional design of selective reactions – including crystallization process – will be feasible by computational approaches.

SYNFORM *What do you think about the modern role, major challenges and prospects of total synthesis?*

Prof. T. Sato Total synthesis of natural products has a long history, starting from the synthesis of urea by Wöhler in 1828. One of my favorite syntheses is the total synthesis of reserpine by Woodward in 1958. Although traditional, the area still remains a rich source of discoveries, providing opportunities for significant progress of organic synthesis. Historically, total synthesis has advanced with the development of new methods controlling 'selectivity'. For example, synthetic chemists in the 1950s and 1960s used the conformation of cyclic compounds to control stereoselectivity. However, direct stereocontrol of acyclic compounds was developed due to the need for the synthesis of products such as polyketides. What I focused on, in the unified total synthesis of the stemoamide-type alkaloids, was 'chemoselectivity'. While control of stereoselectivity contributes in improving the yield of a reaction itself, control of chemoselectivity not only does that, but may also impact efficiency in the synthetic route, reducing the number of steps required by avoiding inefficient reactions. To be more specific, transformation of the target functional group in natural products often requires protecting group manipulation of more reactive functional groups, causing an increase in the total steps. However, realization of lactam-selective reductive nucleophilic addition in the presence of more electrophilic lactones acted as a game-changer, which enabled quick access to a variety of tetra- and pentacyclic natural products from simple tricyclic stemoamide. The late-stage oxidation of pyrrolidines to pyrroles without affecting other functional groups was also crucial to the concise total synthesis. Through our work, we were able to demonstrate the effectiveness of chemoselectivity and we are certain that this is one way of opening new and innovative routes in the synthetic world. Reactions in the presence of free alcohols, carboxylic acids and primary amines are still limited for synthetic organic chemists.

SYNFORM *What does this award mean to you/your group?*

Prof. T. Sato Ultimate goals that lie ahead of total synthesis are contributions to human society, such as human health with medicinal drugs and global food problems with agricultural chemicals. On the other hand, I believe that synthetic organic chemists still enjoy total synthesis, almost as if it is an Olympic event! Who achieved the first total synthesis of this complex natural product in the world? Who developed the shortest synthetic route? Who accomplished it in the highest total yield? Who came up with the most elegant solution? When I came up with the chemoselective assembly of five-membered building blocks to approach stemoamide-type alkaloids, it brought me the feeling that our group may be nominated for a synthetic 'Olympic event'! It has been more than ten years since our program started in 2013. The project was finally completed with my talented students and wonderful collaborators. We are not sure whether our synthesis is the best or not, but I feel like we won an Olympic medal, being selected as the Synthesis Best Paper Award 2023.

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