A Femtomolar-Range Suicide Germination Stimulant for the Parasitic Plant *Striga hermonthica*


*5DS* (5-deoxy*strigol*) representative natural SL

SAM690 (from screening)  MEC = 1 µM

*SPL7* (introduction of 4'-methyl group to butenolide)  MEC = 10 nM

H-SPL7 (synthetic by-product)  MEC = 10 pM

**Contact**

Your opinion about Synform is welcome, please correspond if you like: marketing@thieme-chemistry.com
Dear Readers,

I am on a night-flight back to Europe, currently at an altitude of 11,200 meters, right in the middle of the Atlantic Ocean. I am in economy class, so it’s not that comfy here... I really wish I could stretch my legs and back... on my left a gentleman who is not asleep either and is watching a TV series, occasionally laughing pretty loudly; on the right – lucky me – the aisle; behind, someone is snoring, while in front sits a teenager playing some sort of video game. I am not a fan of flying, I never feel totally relaxed, even more so if I start thinking that 10 kilometres below me there is a deep and almost unimaginable immensity of dark cold water... suddenly I feel the need for a drink, so I’ll just crack on with this Editorial, then I’ll head to the spot where the flight attendants are quietly chatting and I’ll buy some spirits... yes, buy, because the glorious days when one was entitled to get pretty much any complimentary drink during the flight are long gone, now you are lucky if you get some water and a frugal meal during a transatlantic flight. Okay, let’s try not to think about the hungry marine monsters below me for a moment, and focus on something positive: this issue of Synform – what else! The start could not be any better: an interview with Professor Tehshik Yoon, University of Wisconsin – Madison (USA), who is the recipient of the SYNTHESIS Best Paper Award 2018. Quite unusually, both the second and the third articles are back-to-back YCF interviews, the first with Jie Wu (Singapore) and the second with Jia Niu (USA), who tell us about their views on chemistry, their career ambitions and their research. The final contribution is a Literature Coverage article covering the recent work by Uraguchi and colleagues (Japan) on a highly potent suicide germination stimulant for combatting a parasitic plant that poses significant threats to food security in Africa.

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A Femtomolar-Range Suicide Germination Stimulant for the Parasitic Plant Striga hermonthica

Coming soon

Contact
If you have any questions or wish to send feedback, please write to Matteo Zanda at: synform@outlook.com

Okay, I really need that drink now...
Enjoy your reading!!!

Synthesis 2018, 50, 539–547

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. Tehshik Yoon and co-workers, from the University of Wisconsin-Madison in the USA, are the recipients of the SYNTHESIS Best Paper Award 2018. The authors are recognized for their application of tandem Lewis acid photoredox catalysis. According to SYNTHESIS Editor-in-Chief Paul Knochel “It is a paper that is especially appealing since it describes a very general method for performing a radical anion [3+2] cycloaddition leading to highly substituted polyfunctional cyclopentane derivatives starting with readily available styrenes and cyclopropyl phenyl ketones. The tandem Lewis acid/photoredox catalyst is very convenient to prepare and highly effective. It is certainly a very valuable extension of dipolar cycloadditions using photoredox catalysis.” SYNFOM FORM spoke with Prof. Tehshik Yoon, who was happy to share some background information regarding the prize-winning paper as well as current research activities ongoing in his group.

Biographical Sketch

Tehshik Yoon is a Professor of Chemistry at the University of Wisconsin-Madison (USA). He received his bachelor’s degree in chemistry from Harvard University (USA), where he performed undergraduate research with Prof. David Evans, and his master’s degree from Caltech (USA) under the supervision of Prof. Erick Carreira. His Ph.D. thesis with Prof. David MacMillan, first at Berkeley (USA) and then at Caltech, focused on the development of chiral Lewis acids for enantioselective Claisen rearrangements. After finishing graduate school in 2002, he became an NIH postdoctoral fellow in the laboratory of Prof. Eric Jacobsen at Harvard, where his research involved the development of a hydrogen-bond-donating catalyst for asymmetric nitro-Mannich reactions. Tehshik has been on the faculty at UW-Madison since 2005. His research group has broad interests in organic synthesis and catalysis. In particular, the Yoon group has been pioneering the use of transition-metal photocatalysts in synthetically useful transformations promoted by visible light. Tehshik’s efforts in teaching and research have earned him a variety of prestigious awards, including an NSF CAREER Award (2007), the Research Corporation Cottrell Scholar Award (2008), the Beckman Young Investigator Award (2008), the Amgen Young Investigator Award (2009), an Alfred P. Sloan Research Fellowship (2009), an Eli Lilly Grantee Award (2011), a Friedrich Wilhelm Bessel Award from the Humboldt Foundation (2015), and an ACS Cope Scholar Award (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. Tehshik Yoon We often hear the Diels–Alder cycloaddition referred to as the "most powerful organic reaction." Whether or not this assessment is still true in 2019, it is certainly the case that a large variety of six-membered carbocycles can be synthesized in a straightforward manner using Diels–Alder cycloaddition chemistry. Five-membered carbocycles, on the other hand, are comparatively more difficult to assemble. The purpose of the study reported in our paper was to explore the scope of a formal [3+2] cycloaddition that my co-workers had discovered. The reaction involves a novel radical mechanism, which we thought might allow a broad range of reaction partners to participate in the cycloaddition. Our hope was to demonstrate that this new method could start bridging the gap between the capabilities of existing [3+2] cycloaddition methods and reactions as powerful as the Diels–Alder reaction.

SYNFORM Can you explain the origin, motivations and strategy used for conducting the award-winning research?

Prof. Tehshik Yoon This [3+2] reaction was originally inspired by an analogy to the photocatalytic [2+2] cycloaddition that was our first contribution to the field of photoredox catalysis. Our previous work had shown that photoredox reduction of enones afforded reactive radical anions that would react with electron-deficient alkene reaction partners, while the [2+2] cycloaddition works only with electron-deficient enone-type structures. This paper’s objective was to ascertain how broad the scope of the [3+2] cycloaddition might be.

SYNFORM What is the focus of your current research activity, both related to the award paper and in general?

Prof. Tehshik Yoon My laboratory is broadly interested in photochemistry as a tool for organic synthesis. One major thrust of our research is the use of catalysts or other reagents to control the reactivity of photochemically generated reactive intermediates. For instance, we have developed a general strategy for controlling the stereochemistry of photochemical reactions that uses chiral Lewis acids in conjunction with transition-metal photoredox catalysts. Other students in the group are studying how copper salts can divert radical photoredox reactions towards carbocation reactivity.

SYNFORM What is the focus of your current research activity, both related to the award paper and in general?

Prof. Tehshik Yoon I think the modern role of organic synthesis remains rooted in its historical role. Synthetic chemistry is indispensable to contemporary science because the structure of a molecular entity dictates its useful physical, electronic, and biological properties. Research at the forefront of the molecular sciences requires access to new molecular compounds, and synthetic organic chemists are unique in their ability to predictably deliver these new structures in practical ways. So the central questions motivating synthetic research remain the same: How do we synthesize new compounds, and how do we synthesize them more efficiently and with better control?

As organic chemistry has matured, it has grown to embrace a much greater variety of technologies and reaction types. For example, one could not be a practicing synthetic organic chemist today without at least a rudimentary grasp of organometallic chemistry, because reactions like cross-coupling and olefin metathesis reactions have become such essential tools in synthesis. So it’s gratifying to be a synthetic photochemist during a period when the broader community of synthetic organic chemists are beginning to recognize the capabilities that photochemistry offers; I am optimistic that the tools we are developing will become equally integrated into the arsenal of standard synthetic methods. It’s also...
exciting to observe the growth of interest in biocatalysis, electrochemistry, and flow chemistry. What makes us synthetic chemists is not any commitment to a specific set of techniques or approaches, but rather the mindset that the construction of complex molecules is an important goal. Any new strategy that makes synthesis more powerful or more efficient, therefore, is a valuable contribution to our field.

This openness to new ideas makes it difficult to offer predictions about the long-term evolution of organic synthesis as a field. Ours is a discipline that has always valued the creativity of its practitioners, and the nature of creativity is to be somewhat unpredictable. But however organic synthesis continues to grow, it will remain a central contributor to the world so long as social problems have molecular solutions.

[Signature]
Young Career Focus: Dr. Jie Wu  
(National University of Singapore, Singapore)

**Background and Purpose.** SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Dr. Jie Wu (National University of Singapore, Singapore).

**Biographical Sketch**  
**Jie Wu** was born in 1983 and raised in Sichuan Province (P. R. of China). He received his B.S. degree in chemistry from Beijing Normal University (P. R. of China) in 2006. He then moved to Boston University (USA) to obtain a Ph.D. under the supervision of Prof. James S. Panek in 2012, focusing on natural product synthesis. From 2010 to 2012, during his Ph.D. studies, he also worked at the Boston University Center for Chemical Methodology & Library Development (BU-CMLD), directed by Prof. John A. Porco. He then was appointed as SkolTech Postdoctoral Fellow with Prof. Timothy F. Jamison and Prof. T. Alan Hatton at MIT (USA) from 2012 to 2014, where he worked on the development of continuous-flow synthetic methods. After working as a senior scientist in Snapdragon Chemistry Inc., he joined the department of chemistry at the National University of Singapore (Singapore) as an assistant professor in 2015. His research interests explore the broad areas of flow chemistry, photochemistry, and green chemistry. In 2017, he was awarded the 4th Green & Sustainable Manufacturing Award from GSK-Singapore, and the Asian Core Program Lectureship Award from China. In 2018, he received the Young Chemist Award from the Department of Chemistry at the National University of Singapore, and an Asian Core Program Lectureship Award from Taiwan and Thailand. In 2019, he received the Thieme Chemistry Journals Award.

**INTERVIEW**

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

**Dr. Wu**  
The overarching goal of my research group is to apply advanced engineered micro-tubing reactors to serve as better platforms to perform new chemical transformations and sustainable manufacturing with relevance to contemporary problems. Our lab is focusing on exploring new fundamental reactions that can directly transform abundant and inexpensive feedstocks (natural gases, unfunctionalized alkanes and silanes) into value-added products in an atom- and step-economic fashion, and to harvest visible light by chemical means and to use light as the energy source for chemical transformations. We are also interested in end-to-end synthesis of APIs in an automated fashion.

Our approach is unique in the sense that we position ourselves at the interface of organic synthesis and chemical engineering. I was trained as a joint postdoc in the chemistry and chemical engineering departments at MIT, and I obtained my Ph.D. by conducting natural product total synthesis. My research group aims to be multidisciplinary, and to tackle problems from a different angle, not just from the traditional organic synthesis one.

**SYNFORM**  
*When did you get interested in synthesis?*

**Dr. Wu**  
I got deeply interested in organic synthesis during my Bachelor’s studies at Beijing Normal University. There were frequent invited seminars from prominent professors in chemistry. I was captivated by Prof. Lin Guoqiang’s seminar talk on natural product synthesis. It left me with a deep impression of “Wow, we can build lego at the molecular level!” I fell in love with organic synthesis in an instant as I felt excited to be able to translate any molecule I draw on paper into reality, once I became a master of it. After my undergraduate stu-
dyads, I chose to perform my Ph.D. research on natural product synthesis at Boston University under Prof. James S. Panek’s supervision, where I completed the total synthesis of (−)-virginiamycin M, I enjoyed the experience in multistep synthesis, and believe synthetic chemistry is an art. Then I moved to MIT for postdoctoral studies under Prof. Timothy Jamison and Prof. Alan Hatton, where I started to learn continuous-flow synthesis for the first time. I feel privileged to be involved in some of the most advanced technology, which may be a future trend in the pharmaceutical industry. With my experience in total synthesis, I joined the team at MIT and focused on endto-end API synthesis. This was a tremendous experience for me as I saw the potential of combining chemistry and chemical engineering, which can really change the way we conduct chemistry in the future.

**SYNFORM** What do you think about the modern role and prospects of organic synthesis?

**Dr. Wu** I believe that organic synthesis belongs to fundamental science, which builds the base for many related disciplines, such as chemical biology, materials science, polymer science, medicinal chemistry, agricultural chemistry, and environmental science, and supports the development of our society. By studying reactivity and reaction mechanisms, organic chemists can facilitate efficient bond formation and create new valuable molecules. I believe one important continuing goal in organic synthesis is to construct or cleave chemical bonds more effectively in a controllable and sustainable way. Photochemistry and electrochemistry have become emerging technologies in the past decade to achieve mild and green chemical synthesis. Another important aspect will be automation, which will effectively save time and labor-intensive synthetic laboratory work. I expect that this will be a trend for the pharmaceutical and chemical industries in the future. In this context, continuous-flow synthesis will play a significant role in future development of synthetic chemistry, which is naturally suitable for automation. Machine learning can be another future direction for organic synthesis, where high-throughput technology will be important to gather enough data to teach machines in order to build a reliable model for prediction.

**SYNFORM** Your research group is active in the areas of photocatalysis and flow technology. Could you tell us more about your research and its aims?

**Dr. Wu** Due to my experience with continuous-flow technology during my postdoc studies, I decided to build my research group focusing on flow synthesis from the start of my independent academic career in 2015. Continuous-flow synthesis provides a platform to bridge the gap between fundamental studies in organic synthesis and applied chemical manufacturing. It appears to be particularly well poised to contribute to the movement toward green and sustainable processes. Flow technique has also been utilized to enable challenging reactions that are difficult to conduct using conventional batch equipment. However, there is one big hurdle in continuous-flow synthesis: it is not efficient for small-scale reaction evaluation. A good chemist can screen more than 10 reactions under batch conditions per day for methodology development. However, the same chemist can probably conduct only one flow reaction in terms of investigating the discrete variables such as catalysts, substrates and solvents. This limits the efficiency of using continuous-flow technology to develop new synthetic methodologies. In 2017, my group invented a “stop-flow” micro-tubing (SFMT) reactor platform, which combines elements from both continuous-flow and conventional batch reactors. It is a batch reactor, but substituting the flasks with sealed micro-tubing. With this newly developed technology, we aim to achieve reactions that were difficult or even unachievable before.

Sunlight is an environmentally benign and endless source of clean energy. The past decade has witnessed a rapid growth in the field of visible-light photoredox catalysis. We think that the photoreaction is a natural complement to microtubing reactors due to the Beer–Lambert Law. Moreover, our SFMT reactor serves as an ideal platform to conduct gaseous-reagent-involving transformations under light irradiation, especially at high pressure. My group has developed several new fundamental reactions that directly convert inexpensive gaseous feedstocks in order to synthesize valuable chemicals using visible light as the energy source, including the vinylation of fluorinated aryl bromides using acetylene, heterocycle synthesis using CO₂, difunctionalization of electron-deficient alkenes using CO₂, divergent synthesis using ethylene, and using ethane as the ethylation reagent. Most of these reactions are not possible without the use of the SFMT reactor. We also worked on C–H activation under photo-irradiation for green synthesis. In particular, we are the first to disclose that neutral eosin Y can be utilized as an effective direct hydrogenatom-transfer photocatalyst to activate a wide range of native C–H bonds in a green and sustainable fashion. We also found that HCl can be applied in SFMT reactors as a hydrogen–atom-transfer catalyst after it has been activated by a photoredox catalyst. A wide range of alkanes, especially those with unactivated C–H bonds, can be activated using this protocol.
SYNFORM  What is your most important scientific achievement to date and why?

Dr. Wu  Our recent development of the “stop-flow” micro-tubing (SFMT) reactor platform is something I feel is special (Chem. Sci. 2017, 8, 3623–3627). This SFMT platform addresses many limitations in both batch and flow reactors, and has proved to be quite efficient and effective during screening for gas/liquid and light-mediated reactions. It is also an easy-to-handle apparatus for high-pressure reactions. We have proven in several of our projects that the SFMT works more effectively with reactions involving gases, as the gas/liquid interfacial contact is significantly improved in the micro-reactor, and the high pressure can be maintained while sealing. Photoreactions performed better in our studies, as the photon fluxing is more efficient for microtubing reactors, and it also provides an easy platform for utilizing gas reagents under photo-irradiation at high temperature or high pressure. Owing to its ease of access and operation, high efficiency, enhanced safety, and green nature, the SFMT platform promises to become an important method complementary to the current reaction apparatuses utilized in organic laboratories.
Young Career Focus: Dr. Jia Niu (Boston College, USA)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Dr. Jia Niu (Boston College, USA).

Biographical Sketch

Jia Niu was born and raised in Shijiazhuang, Hebei Province (P. R. of China) and obtained a Bachelor of Science degree with the highest honor in chemistry from Tsinghua University (P. R. of China) in 2005. After completing a Master of Science degree under the guidance of Professor Xi Zhang in 2008, also at Tsinghua, he moved to the United States and joined Professor David R. Liu’s group at Harvard University to pursue his Ph.D. degree. In the Liu group, he developed an enzyme-free strategy capable of translating DNA templates to sequence-defined synthetic polymers structurally unrelated to nucleic acids – essentially an artificial translation system that did not need ribosomes in spite of other necessary restrictions. After graduate school, he became a joint postdoctoral scholar with Professor Craig J. Hawker and Professor H. Tom Soh at University of California, Santa Barbara (USA) in 2014. During his postdoc, Jia led two technology development projects: (1) a strategy to engineer live cell surface with functional polymers via light-mediated, cyto compatible controlled radical polymerization; and (2) a platform to discover carbohydrate-modified aptamers for lectin recognition with high specificity. The graduate and postdoctoral training experiences have shaped Jia’s interests in combining organic chemistry approaches with polymer synthesis to generate novel polymeric structures, and he uses them to address pressing needs in biomedicine, materials, and environmental sciences. Jia started his current assistant professor appointment in Boston College, USA in the summer of 2017. He is the recipient of the 2019 Thieme Chemistry Journals Award.

INTERVIEW

SYNFORM What is the focus of your current research activity?

Dr. Niu Research in the Niu group is currently focused on the development of strategies for the synthesis of macromolecules with novel architectures, functions, and sequences, and the use of these polymeric materials in applications ranging from biomedicine to environmental sciences. Our approach is centered around integrating cutting-edge synthetic organic chemistry principles with macromolecule synthesis towards generating novel macromolecules with bioactive functions or high material performance – essentially positioning our research activities at the interdisciplinary interfaces of organic chemistry, polymer science, and chemical biology (Figure 1).

SYNFORM When did you get interested in synthesis?

Dr. Niu I became interested in organic synthesis and polymer chemistry when conducting undergraduate research in Professor Xi Zhang’s group at Tsinghua University. My research project at the time involved fabricating polyelectrolyte thin films by iteratively depositing two polyelectrolytes carrying opposite charges onto a substrate, also known as the Layer-by-Layer (LbL) technique. I was awed by the polymer chemist’s ability to design and manipulate the backbone and side-chain structures of the polyelectrolytes and use them to fabricate polymer thin films for a variety of applications ranging from building uniquely shaped cavities for molecular recognition to fabricating materials with special wetting properties that mimic the body coatings of the water strider bug. I also realized that despite these impressive capabilities, compared to biopolymers such as DNA, proteins, and polysaccharides, synthetic polymers still lack the critical control over sequence, structure, or molecular weight. I thought that this discrepancy created great opportunities in polymer chemistry for the synthesis of precision macromolecules that approach the structural and functional prowess of biopolymers, and decided to pursue polymer synthesis in my further studies.
What do you think about the modern role and prospects of organic synthesis?

Dr. Niu Organic synthesis, and the tools chemists have developed to enable its execution, have fundamentally changed almost all aspects of modern life and industries. Because of the vast scope of organic synthesis and the great diversity of innovations taking place in this field, it is difficult for one to predict a general prospect of organic synthesis. I can only discuss my somewhat narrow perspective on this topic. There are two research areas in organic synthesis that motivate me the most: first, discovery of synthetic small molecules and macromolecules that can help to reveal the underlying molecular principles of life and/or can serve as tools to manipulate...
the biological processes governed by these principles; second, development of the methodologies that can make organic synthesis and its products sustainable, through the use of renewable raw materials, attaining high atom-economy, developing efficient catalysts, or enabling recycling or controlled degradation of the organic materials. While much progress has been made in these research directions, greater advances are still urgently needed to address some of the most pressing challenges our society faces both currently and in the future.

SYNFORM Your research group is active at the interface of organic synthesis with chemical biology. Could you tell us more about your research and its aims?

Dr. Niu Given the short history of our research group, we are only at the beginning of our exploration at the interface of chemistry and biology. One specific direction of our research is to develop novel glycomimetic polymers with unique architectures and sequences for studying the guiding principles of the interactions between polysaccharides and carbohydrate-binding proteins. The interactions of polysaccharides with their cognate protein receptors are essential in many important cellular processes, but how the structures and sequences of polysaccharides regulate these interactions remains poorly understood to date. Central to this limitation is the highly heterogeneous and dynamic nature of polysaccharides in vivo, and our current inability to generate synthetic analogues of the natural polysaccharides with fully controlled structures and sequences. We hope that some of the polymer synthesis strategies recently developed in our lab can be extended to address this important challenge, leading to next-generation glycomimetic polymers with controlled architectures and sequences to facilitate our future investigations into polysaccharide-carbohydrate-binding protein interactions.

Another specific direction we are pursuing is the synthesis of precision sustainable polymers from simple, readily available bio-based building blocks. Sustainable polymers made from renewable resources provide a promising solution to the current environmental issues associated with the conventional petroleum-based polymers. We are currently investigating the synthesis of precision polymers with tailored structural motifs in both the backbone and side chain, while maintaining control over polymer molecular weight, chain end groups, and dispersity. We hope these sustainable precision polymers will be able to compete with conventional polymers in the realm of high-performance materials.

SYNFORM What is your most important scientific achievement to date and why?

Dr. Niu I am excited about our recent report on the principle of radical cascade-triggered ring-opening polymerization (J. Am. Chem. Soc. 2018, 140, 10402–10406) (Figure 1, top). The radical cascade reaction is a powerful approach that organic chemists adopt to facilely construct complex molecular structures. We demonstrated that this chemistry can also be used to provide the key driving force for the ring-opening polymerization—a process that was traditionally driven by the relief of ring strain in cyclic monomers. To our knowledge, this work represents the first system that allows radical ring-opening polymerization of macrocyclic monomers with low ring strain to be well controlled in either homopolymerization or block copolymerization. In a second recent paper, we described a simple approach for the synthesis of sequence-regulated polymers via orthogonal CuAAC and SuFEx click reactions (Angew. Chem. Int. Ed. 2018, 57, 16194–16199; corrigendum: Angew. Chem. Int. Ed. 2019, 58, 655–655) (Figure 1, bottom). The perfect orthogonality of these two click reactions enabled one-pot step-growth polymerization to generate periodic sequence-controlled polymers with high sequence complexity, as well as solid-phase iterative coupling of building blocks to yield sequence-defined oligomers without the need of protecting groups. Taken together, these polymer synthesis technologies open new avenues for many future directions of our group spanning polysaccharide-mimicking polymers and sustainable polymers.

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Striga hermonthica (Striga), a parasitic plant commonly called “Witchweed”, represents a major threat to food security in Africa; however, despite its scale, the problem is not well recognised by the general public. Striga is an obligate root hemiparasitic plant that makes a host plant wither. Although tiny Striga seeds are difficult to remove directly from the soil in order to protect crops, they can be killed by inducing their germination in the absence of host plants, which is known as a suicide germination strategy. Since the strigolactones (SLs), a group of plant hormones produced by host plant roots, were discovered as germination stimulants of Striga in 1966, they have been attractive lead molecules for designing Striga suicide germinators and major efforts have been made to develop synthetic SLs by modifying their structures. However, none has had the high potency, target (plant) selectivity and low synthetic costs required for further development. An interdisciplinary team led by researchers at Nagoya University (Japan) has tackled the Striga infection problem and found a highly potent SL mimic as a candidate of an ideal suicide germination stimulant.

Plant biologist Dr. Yuichiro Tsuchiya (now at Nagoya University, Japan) had reasoned that the major issue in SL research for tackling the Striga infection is a lack of basic information, such as the identity of SL receptors, which hinders development of suicide germination molecules through rational molecular design. He said: “Because I had experience in identifying a receptor of Arabidopsis through chemical screening to find its seed germinators, we had a strong belief that we might be able to identify SL receptors in Striga as well.” His team had decided to investigate and collect basic information about how Striga senses SLs and germinates. However, this turned out to be a very challenging task because, in Striga, it is impossible to conduct conventional biological assays using genetics, such as mutational studies, transformations, and gene editing. Dr. Tsuchiya explained: “A breakthrough came when I moved to the Institute of Transformative Bio-Molecules (WPI-ITbM) at Nagoya University, where chemists and biologists work together to crack unsolved issues.” His team in Nagoya was eventually able to determine 11 SL receptors in Striga (ShHTLs) in 2015, by means of a synthetic SL with fluorescence turn-on property, now called Yoshimulactone green (YLG), which was designed and synthesized by two ITbM chemists, Drs. Shinya Hagihara and Masahiko Yoshimura.

The fluorescence probe made it extremely easy to analyze SL receptors biochemically and understand their biological functions, and indeed, the discovery of YLG enabled the
team to develop, for the first time, suicide germination molecules based on the ligand–receptor interactions. The present research was initiated by the chemical screening of small molecules to find receptor-selective Striga germinators, and subsequent structural modification of hit molecules by the Ooi group led to the serendipitous discovery of a femtomolar-range suicide germination stimulant for Striga, sphyanolactone-7 (SPL7). “The development of SPL7 as a highly potent germination stimulant is a monument to the efforts we have made over 15 years and now one of my dreams is coming true!” exclaimed Dr. Tsuchiya, with feeling.

Organic chemist Prof. Takashi Ooi took up the tale: “My research group (Daisuke Uraguchi, Sathiyanarayanan AM, and Rie Yamaguchi) introduced chemical viewpoints to Yuichiro’s study on parasitic plants, specifically Striga, and helped open up a new avenue to understand and combat the Striga infection.” Dr. Daisuke Uraguchi (organic chemist) echoed this statement: “I believe that our experience with homogeneous catalysis in organic chemistry really helped the investigation of biological reaction mechanisms relating to the Striga germination process.” For instance, their approach enabled an investigation into how Striga’s SL receptors (ShHTLs), having hydrogenase activity, recognize and react with ligands and transmit germination signaling through the alteration of their three-dimensional structures, which finally led them to propose a cumulative activation scenario. Dr. Uraguchi described: “A cumulative model for switching-on the germination signaling was proposed through monitoring the intermediate of the process by LC-MS, which is somewhat similar to the mechanistic study of organic transformations.” Furthermore, during structure–activity relationship studies of Striga germinators, the group found that an impurity of a synthetic germinator (H-SPL7) was an unprecedentedly potent molecule, providing a basis for development of the key molecule named sphyanolactone-7 (SPL7). “We did not neglect inconsistencies in the data from biological experiments – namely, in the evaluation of the activity of germination stimulants – and hypothesized this could be due to contamination by a trace amount of a highly potent molecule. We had this idea thanks to our experience in catalysis, where the influence of a small amount of impurity can cause a lot of trouble!” he said. On the basis of the experimental results, they realized that the contaminant (H-SPL7) seemed to be generated via autooxidation of the target molecule (one of the SAM molecules), which was a derivative of the hit molecule in the initial chemical screening. Dr. Uraguchi continued: “I feel that Nature suitably derivatized our molecule on our behalf and then we serendipitously found it as a gift from Nature!” The process of identifying the contaminant was similar to the isolation of natural products and its actual structure convinced the group of its extraordinary potency. The core skeleton of the SAM molecules was hybridized with a butenolide ring, which has been regarded as a critical part of SLs for stimulating Striga germination. “This structural characteristic motivated us to name it sphyanolactone-7 (SPL7), whose pronunciation is derived from ‘sphinx’, the hybrid of a human head and a lion body, guardian of a pyramid in Africa, and specifically in Egypt,” he said. Prof. Ooi further noted: “Since SPL7 selectively activates/binds one of the ShHTLs, ShHTL7, we believe it will be a powerful tool for elucidating the biological systems behind germination signaling.” Dr. Uraguchi followed: “Hereafter, by taking advantage of the receptor selectivity of SPL7, we will further tackle the mysteries of Striga; for example, how the germination signal is transmitted and why Striga has many SL receptors. Through this challenge, I hope that our study will eventually contribute to solving the current serious Striga problems for African food security.” Prof. Ooi continued: “More importantly, SPL7 is a promising candidate for a Striga herbicide, relying on the suicide germination process. Since the danger to food security in Africa originates largely from the damage to food production caused by Striga infection – as detailed in United Nations documents – if SPL7 provides a definitive solution to this problem, this work would have an enormous impact on society. He concluded: “We are going to pursue a field test of SPL7 as a Striga suicide germinator in Africa (Kenya) and hope to develop an agrochemical for ensuring food security in Africa within the next decade. For us, as chemists, the collaboration with biochemists has been a real pleasure.”
About the authors

Yuichiro Tsuchiya (middle), born in 1974 in Hokkaido (Japan), initiated his career as a plant scientist in Eiji Nambara’s group while he was an undergraduate at Hokkaido University (Japan). He earned his PhD in agriculture in 2002 under the supervision of Peter McCourt at the University of Toronto (Canada) and Satoshi Naito at Hokkaido University. After experiences as a postdoctoral researcher in Peter McCourt’s laboratory, Yuji Kamiya’s group in Riken (Japan) and Toshinori Kinoshita’s group at Nagoya University (Japan), he became a designated associate professor at the Institute of Transformative Bio-Molecules (WPI-ITbM) at Nagoya University in 2015. His lab’s research has focused on elucidating the mechanism of seed germination in the parasitic plant *Striga hermonthica* using small-molecule probes.

Takashi Ooi (left) is a professor at Nagoya University (Japan). He was born in 1965 in Nagoya and received his B.Eng. (1989) and Ph.D. (1994) degrees from Nagoya University under the supervision of Professor Hisashi Yamamoto. After working as a JSPS postdoctoral fellow with Professor Julius Rebek, Jr. at the Massachusetts Institute of Technology (USA), he started his academic career as an assistant professor in Professor Keiji Maruoka’s group at Hokkaido University (Japan) in 1995. In 2001, he was appointed as an associate professor at Kyoto University (Japan). He was then promoted to professor at Nagoya University in 2006. From 2012, he has been one of the principal investigators at the Institute of Transformative Bio-Molecules (WPI-ITbM) at Nagoya University. He has received several awards, including the Chugai Pharmaceutical Co., Ltd. Award in SSOCJ (1996), the CSJ Award for Young Chemists (1999), the Thieme Chemistry Journals Award (2006), the JSPS Prize (2010), the IBM Japan Science Prize (2011), the Inoue Prize for Science (2013), and the SSOCJ Daiichi-Sankyo Award for Medicinal Organic Chemistry (2017), and was named a Fellow of the RSC (FRSC) in 2014. His research interests are general synthetic organic chemistry.

Daisuke Uraguchi (right) is an associate professor at Nagoya University (Japan). He was born in 1974 in Hokkaido (Japan) and received his B.Sc. (1997) and Ph.D. (2002) degrees from Hokkaido University (Japan) under the guidance of Professor Keiji Maruoka. He gained substantial experience working as a JSPS postdoctoral fellow (2002–2004) with Professor P. Andrew Evans at Indiana University (USA) and with Professor Masahiro Terada at Tohoku University (Japan). Then, he moved to the Sagami Chemical Research Center (Japan, 2004–2006). In 2006, he became an associate professor in the research group of Professor Takashi Ooi at Nagoya University, and was promoted to associate professor in 2008. He has received the Takeda Pharmaceutical Co., Ltd. Award in SSOCJ (2008), the CSJ Award for Young Chemist (2010), the Young Scientists’ Prize from MEXT (2011), the Banyu Chemist Award (2012), the MBLA Lecture Award (2013), and the Thieme Chemistry Journals Award (2014). His current research interests include the chemistry of organic ion-pair catalysis.
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