Press Release

Selective Functionalization Synthesizes Chemotherapeutic Natural Products

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Through an extensive international collaboration, scientists at the Center for Selective C–H Functionalization (CCHF), Emory University and the Institute of Transformative Bio-Molecules (ITbM), Nagoya University have synthesized marine alkaloids with anti-cancer and therapeutic properties through a sequential C-H functionalization strategy.

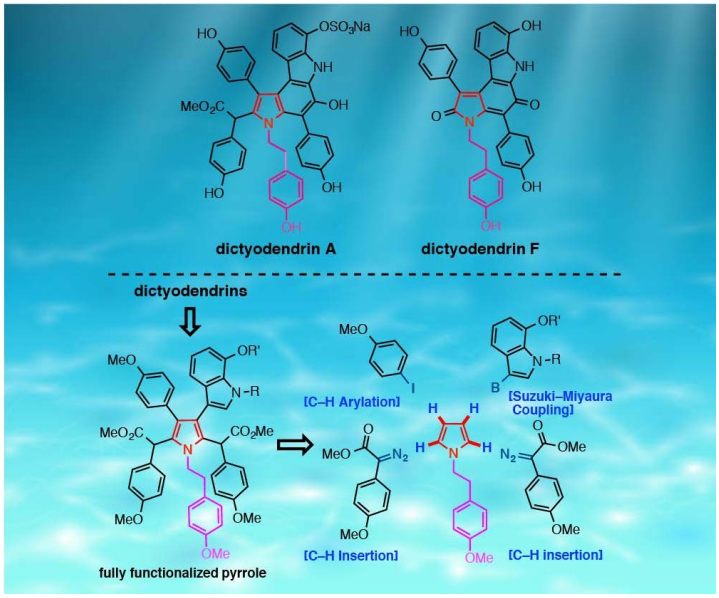

Figure 1. Synthesis of marine alkaloid, dictyodendrin using selective C-H functionalization strategies

Atlanta, USA and Nagoya, Japan – Professor Huw Davies and Katie Chepiga of Emory University, along with Professor Kenichiro Itami, Junichiro Yamaguchi and Atsushi Yamaguchi at the Institute of Transformative Bio-Molecules (ITbM) of Nagoya University, have together developed a novel concise entry to a family of natural products, the dictyodendrins, using C–H functionalization. The power of this strategy has been demonstrated through the synthesis of dictyodendrin A and F. The dictyodendrin family was first isolated from a marine sponge in 2003 and various structural derivatives have been identified. This family of marine alkaloids exhibits interesting biological activities, including the inhibition of telomerase and a β-site amyloid-cleaving enzyme 1 (BACE) with potential for cancer chemotherapy and treatment of Alzheimer's disease, respectively. Application of Davies' and Itami's C-H functionalization chemistry has led to the concise synthesis of dictyodendrins A and F. The study, published online on January 6, 2015 in the *Journal of the American Chemical Society*, demonstrates how sequential functionalization can streamline the construction of complex structures, offering possibilities towards the development of novel synthetic routes for other significant organic molecules.

Dictyodendrins share a common structure, consisting of a highly substituted pyrrole core, i.e. a five-membered aromatic ring containing a nitrogen atom. Arising from their complex structure and potent biological activity, this family of molecules has attracted much attention from the scientific community. The groups of Davies and Itami have worked on synthesizing dictyodendrins through combining their expertise on C-H functionalization chemistry, which involves substituting the hydrogen atom attached to a carbon by another functional group. This was achieved by the collaboration between two graduate students, Katie Chepiga from the Davies group and Atsushi Yamaguchi from the Itami group, who both participated in an exchange program at each other's institute. The two graduate students speak of their experience on accomplishing the total synthesis of the two dictyodendrins.

“Originally, Atsushi had started to work on the synthesis of dictyodendrins at Emory. We wanted to functionalize the molecules at all four of the C-H bonds on the pyrrole ring to make the core of dictyodendrin. Atsushi had first optimized the first C-H arylation reaction with the Itami group chemistry and he had worked on optimizing some Davies group chemistry to apply the first carbenoid C-H functionalization reaction. My role was to optimize the two rhodium carbenoid C-H functionalization reactions, which is the Davies group chemistry,” says Chepiga.

“I was involved in carrying out the direct C-H arylation of the pyrrole ring and the total syntheses of the dictyodendrins. The double C-H insertion reaction optimized by Katie was necessary for the synthesis of these compounds, so without her help, I couldn’t have completed this project,” says Atsushi Yamaguchi.

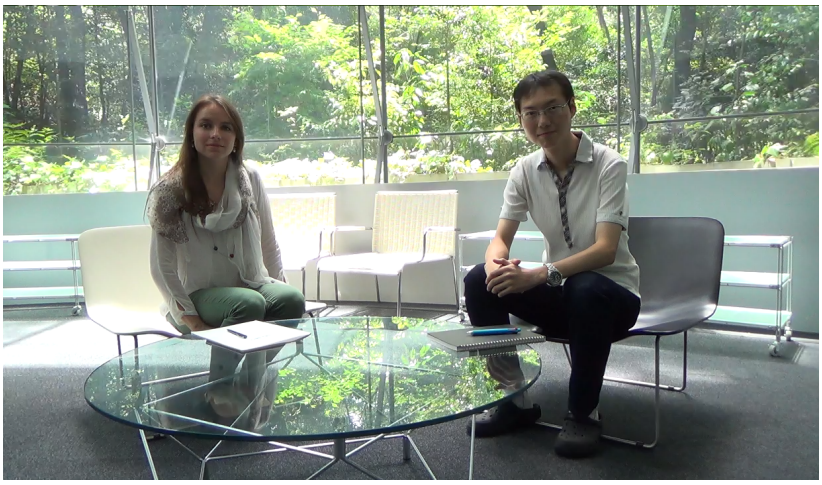

Figure 2. Katie Chepiga from Emory University (left) and Atsushi Yamaguchi from Nagoya University (right)

In order to attach different functional groups at specific positions on the pyrrole core, the sequence and selection of coupling reactions are highly significant. As the molecule becomes more complex, the molecule changes its reactivity and spatial environment, making the following reactions more challenging. Therefore, developing appropriate conditions with high reactivity and regiocontrol were crucial to achieve the total synthesis of dictyodendrins. “After extensive screening of catalysts and conditions, it was found that the Davies’ group and our catalyst were the best to achieve the two types of C-H functionalizations that enabled selective installation of the desired functional groups,” say Profs. Itami and Junichiro Yamaguchi, who led this research. Through sequential C-H functionalization of the pyrrole core, an efficient formal synthesis of dictyodendrin A and F was achieved in relatively a short number of linear steps.

This work is an outcome from the collaboration between Profs. Davies and Itami. Prof. Davies’ lab at Emory University is a member site of the National Science Foundation’s Center for Selective C-H Functionalization (CCHF) in the United States and Prof. Itami’s lab at Nagoya University is a member site of the World Premier International Research Center Initiative’s Institute of Transformative Bio-Molecules (ITbM). The CCHF and ITbM are currently partner institutes in the Virtual Institute for C–H Functionalization (VICHF), exchanging students/faculty and carrying out collaborative projects. Atsushi, Katie and Prof. Davies comment on this international collaboration that led to this study.

“Prof. Itami suggested this exchange, as he knew Prof. Davies well. At that time, the connection between ITbM and CCHF was not as strong and this was the first opportunity for collaboration between the two centers,” says Atsushi, who was the first member to be involved in this exchange program.

“It’s really obvious that through the collaboration of the CCHF and ITbM, we can achieve a lot more that we can achieve as individual groups and we can get to the goals that we really want to achieve a lot more, faster and more efficiently than working alone in separate labs,” says Chepiga, who worked in Prof. Itami’s lab as part of the exchange.

“This work shows the accomplishment of a successful global exchange and we would like to see if we can develop other projects that combine our respective C-H functionalization strategies,” says Prof. Davies, who co-led this work.

This article “Concise Syntheses of Dictyodendrins A and F by a Sequential C–H Functionalization Strategy” by Atsushi D. Yamaguchi, Kathryn M. Chepiga, Junichiro Yamaguchi, Kenichiro Itami, and Huw M. L. Davies is published online on January 6, 2015 in the *Journal of the American Chemical Society*.
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About WPI-ITbM (http://www.itbm.nagoya-u.ac.jp/)
The World Premier International Research Center Initiative (WPI) for the Institute of Transformative Bio-Molecules (ITbM) at Nagoya University in Japan is committed to advance the integration of synthetic chemistry, plant/animal biology and theoretical science, all of which are traditionally strong fields in the university. As part of the Japanese science ministry’s MEXT program, ITbM aims to develop transformative bio-molecules, innovative functional molecules capable of bringing about fundamental change to biological science and technology. Research at ITbM is carried out in a “Mix-Lab” style, where international young researchers from multidisciplinary fields work together side-by-side in the same lab. Through these endeavors, ITbM will create “transformative bio-molecules” that will dramatically change the way of research in chemistry, biology and other related fields to solve urgent problems, such as environmental issues, food production and medical technology that have a significant impact on the society.

About NSF-CCHF (http://www.nsf-cchf.com/)
The NSF Center for Chemical Innovation on Selective C-H Functionalization is comprised of 23 collaborating research groups located at 15 universities within the US. The goal of the Center is to leverage its collaborative potential to develop technology for selective C-H functionalization that will revolutionize the practice and reshape the teaching of chemical synthesis, empowering end users in materials science, fine chemicals development, and drug discovery.

About The Virtual Institute for C–H Functionalization (VICHF) (http://nsf-cchf.com/vichf/)
The Virtual Institute for C–H Functionalization (VICHF) has been established to act as a collaborative forum for international research partners to encourage the exchange of ideas and students and to harbor a global research community for this developing field of chemistry.


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