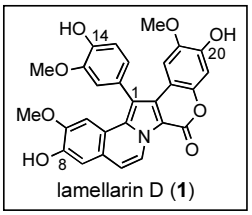
Design and Synthesis of Novel Lamellarin D Analogues Targeting Topoisomerase I

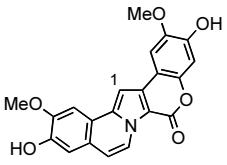
Takeshi Ohta[1], Tsutomu Fukuda[1], Fumito Ishibashi[1] and Masatomo Iwao[2]*
[1]*Graduate School of Science and Technology and*
[2] *Department of Applied Chemistry, Faculty of Engineering,*
Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan
**Tel: +81-95-819-2681, Fax: +81-95-819-2681, E-mail: iwao@nagasaki-u.ac.jp*



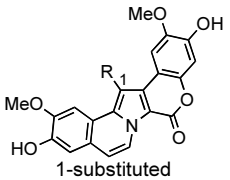
lamellarin D (**1**)

Lamellarin D (**1**), a pentacyclic marine natural product, has attracted considerable attention due to its unique structure and highly useful biological activities such as potent cytotoxicity on P-glycoprotein-mediated multidrug-resistant (MDR) cancer cells.

In 1997, we have reported the first total synthesis of **1** using *N*-ylide-mediated cyclization of a benzylisoquinoline derivative as the key ring-construction procedure.[1] By using this strategy, we have synthesized ten lamellarin D analogues and carried out a structure-activity relationship (SAR) study.[2] In this study, we revealed that the hydroxyl group at C-8 and C-20 positions are essential for cytotoxicity. Recently, Bailly et al. have reported the major molecular target of **1** in cancer cell is topoisomerase I. They also presented a theoretical model of **1**-DNA-topoisomerase I ternary complex.[3] The model is in perfect agreement with our SAR study.



1-dearyllamellarin D (**2**)



1-substituted
1-dearyllamellarin D **3**

Based on these previous studies, we designed 1-dearyllamellarin D (**2**) and its C-1 substituted derivatives **3** as topoisomerase I inhibitors. The synthesis of **2** has been achieved by combinational use of regioselective lithiation, Suzuki-Miyaura coupling, Mitsunobu type reaction, and intramolecular Heck reaction as key reactions. Electrophilic substitution of *O*-protected **2** proceeded at 1-position selectively. These reactions allowed to produce a number of C-1 substituted **3**.[4] Evaluation of topoisomerase I inhibitory activity of **2** and **3** are in progress.

References

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