Synthesis of the Macrocyclic Core of the Solomonamides, a New Class of Cyclopeptides of Marine Origin

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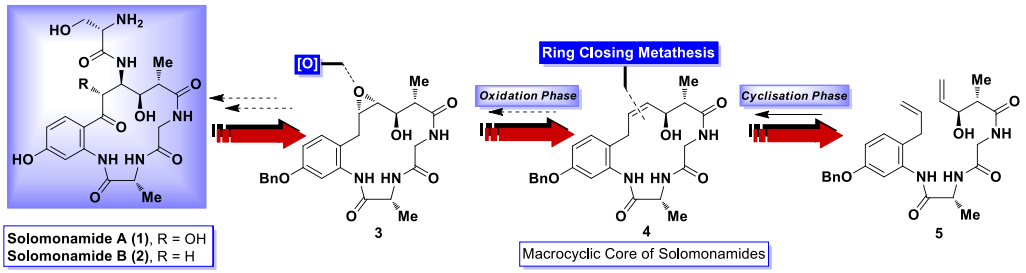
SUMMARY:

Two unprecedented cyclic peptides, Solomonamides A (**1**) and B (**2**), were recently isolated from the marine sponge *Theonella swinhoei* [1] by the Zampella's group [2]. Preliminary structural studies revealed a novel cyclic peptide type structure, whose absolute configuration must be still confirmed. Interestingly, solomonamide A exhibits anti-inflammatory activity, showing significant reduction (60%) of inflammation at a very low concentration of 100 µg/kg in animal models. On the other hand, the scarcity of these compounds from their natural sources has been a drawback for further pharmacological assays. This difficulty to access large amounts of these compounds makes quite difficult to gain insight into their biological profiles and mechanism of action and justifies the chemical synthesis of this new class of cyclic peptides. As a consequence, the solomonamides have been the subject of several synthetic efforts [3], however any total synthesis has not been reported to date. Recently, we have engaged in a project directed towards their total synthesis. To this aim, we have developed a new synthetic strategy which involves a key ring closing metathesis reaction (RCM) to construct the macrocyclic core of the solomonamides in form of compound **4** (Scheme 1). The RCM proceeded in a stereoselective manner to provide exclusively the *Z*-isomer in high yield. Thus, we designed a synthetic plan to be executed in two phases, the first initiated with a cyclisation phase, via a ring closing metathesis, and the second, an oxidation phase of the resulting macrocyclic product to install the functional groups in order to obtain the final compound. In this communication, we wish to present our synthetic studies about these natural products in order to validate the designed strategy.



Scheme 1. Structures of the Solomonamides and Retrosynthetic Analysis.

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