Subject area: Organic
Symposia: Molecular Function of Natural Products: Advances towords Chemical Biology

Authors: Hajime Sugahara, Kazunori Otsuka, Yuichi Ishikawa, Masato Oikawa

Synthetic studies of protoaculeine B

Protoaculeine B (pACU-B) is the *N*-terminal fragment amino acid of aculeine B, a cytotoxic peptide isolated from marine sponge *Axinyssa aculeata* collected at Iriomote, Okinawa, Japan. pACU-B is composed of a novel heterotricyclic amino acid (HTAA) which would be derived from L-tryptophan, and a long chain polyamine (LCPA). pACU-B has been suggested to be cytotoxic to nerve cells but the mechanism of the action is unknown because of the limited availability. We, therefore, have started our synthetic studies of pACU-B, to establish synthetic route toward the novel structure and to implement evaluation of the biological activity.

Retrosynthetically, we thought that pACU-B would be synthesized be coupling of the HTAA and the LCAA moieties. As for the synthesis of the former moiety, L-tryptophan was chosen as the starting material. The key for the successful synthesis was, 1) construction of the piperidine ring fused to indole, 2) stereochemical control of the amino group on the piperidine ring, and 3) introduction of the LCPA to the piperidine ring.

The synthesis of the HTAA moiety was first achieved in total 13% yield over 13 steps starting from L-tryptophan employing reductive amidation of oxime followed by diastereoselective hydrogenation of enamide.

Introduction of polyamine to the HTAA was next attempted. We focused on the enamide structure, which may be a reactive functionality. In fact, enamide was proven to be efficient in aza-Michael reaction as well as aza-Mitsunobu reaction from our model study using α-tetralone. Application of the method toward pACU-B will be also presented.
(248word)