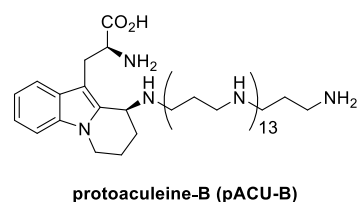


# Synthetic Studies on Marine Natural Polyamine Protoaculeine–B

(Yokohama City University) ○Hiroki Shiozaki, Yuichi Ishikawa, Masato Oikawa

**Keywords:** Polyamine; Protoaculeine; Enamide; Bromination; Neurotoxin

Protoaculeine–B (pACU–B) was isolated in 2014 by Sakai et al from marine sponge *Axinyssa aculeata* collected at Iriomote island, Okinawa, Japan.<sup>1</sup> pACU–B is composed of heterotricyclic amino acid which would be derived from L–tryptophan, and a long chain polyamine (LCPA). pACU–B is expected to be neuroactive, because some naturally occurring neuroactive agents such as JSTX and PhTX share amino acid and polyamine motifs. We have started our synthetic study on pACU–B to 1) establish the novel structure, 2) collect the data on the structure–activity relationships, and 3) clarify the mode of action of synaptic receptors in the central nervous system.



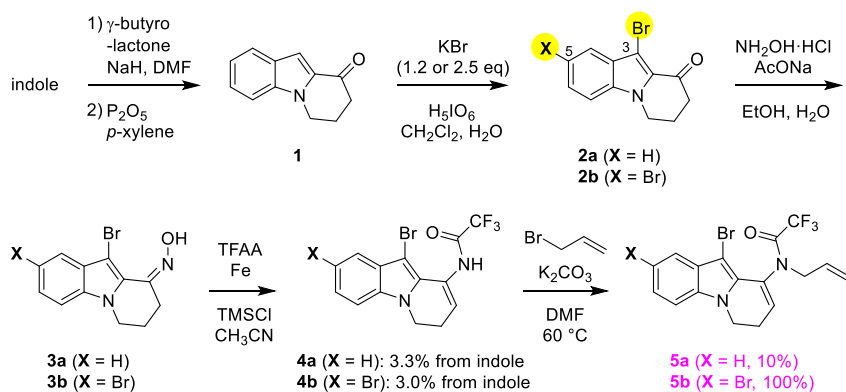
In this study, we tried to establish the synthetic route that would be also applicable to the analog synthesis. To conjugate the core heterotricyclic skeleton with LCPA, we have successfully developed an *N*–alkylation strategy employing TFA enamide, as follows.

Starting from indole, introduction of butyric acid followed by cyclization reaction was conducted according to the known procedure to furnish **1** bearing the third pyrrolidine ring. We next introduced bromo group in order to acquire the high reactivity in the *N*–alkylation. It was found that the number of the bromo group introduced can be controlled by the amount of KBr used, giving rise to two bromides **2a/2b** selectively. Key heterotricyclic TFA enamides **4a/4b** were then constructed over two steps via oxime **3a/3b** (3.3% / 3.0% from indole for 5 steps).

After extensive examinations, the key *N*–

alkylation was found to proceed smoothly when a combination of alkyl halide and  $K_2CO_3$  was applied

on the dibromide **4b**. The coupling of **4b** with other alkyl halides, as well as our endeavors toward pACU–B will be reported.



1) S. Matsunaga et al, *Org. Lett.* **2014**, *16*, 3090–3093.