Unified Total Synthesis of Pentacyclic Stemoamide-type Alkaloids

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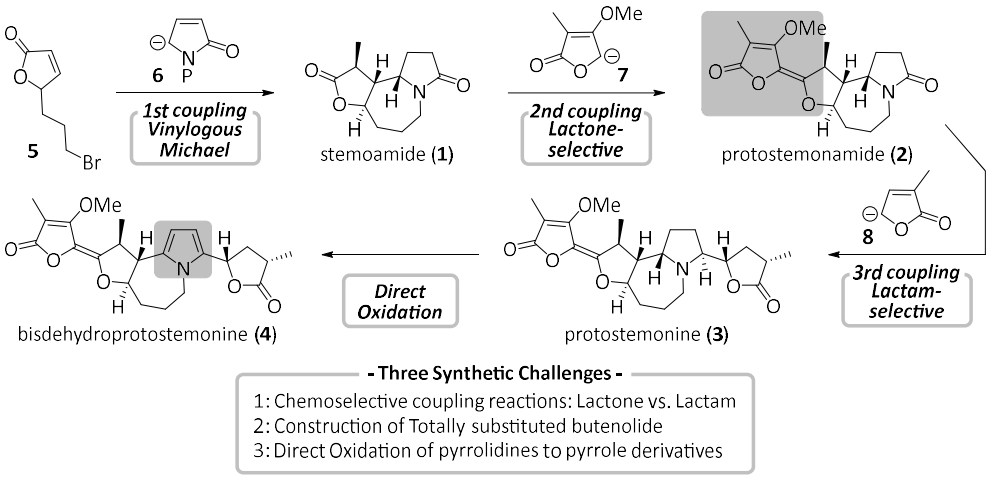
Stemomaide-type alkaloids comprise one of the largest groups in *stemona* family. While tricyclic stemoamide (**1**) does not exhibit any pivotal biological activity, protostemonine (**3**) is known to show diverse biological activities such as anti-inflammatory effect. These facts suggest that complex pentacyclic derivatives might possess better biological profiles than tricyclic and tetracyclic stemoamide-type alkaloids. However, comprehensive biological studies have been prohibited owing to the structural complexity of pentacyclic alkaloids. Here, we disclose a unified total synthesis of pentacyclic stemoamide-type alkaloids.

The unified total synthesis must overcome three synthetic challenges. The first challenge was development of three chemoselective coupling reactions using five-membered heterocyclic rings (**5**→**1**, **1**→**2**, **2**→**3**). The lactam-selective coupling was challenging because a lactone is more electrophilic than a lactam (**2**→**3**). We solved this issue by an iridium-catalyzed reductive nucleophilic addition.[1] The second challenge was construction of a totally substituted butenolide embedded in **2**, **3** and **4**. This structure is highly oxygenated and contains two tetrasubstituted olefins, one of which requires stereocontrol. The third challenge was direct oxidation of pyrrolidines to pyrroles (**3**→**4**). Establishment of mild oxidation was required without affecting tertiary amine and the ene-diol structure. The developed strategy was highly effective, resulting in the total syntheses of eight pentacyclic alkaloids within 13 steps.[2,3]



1) T. Sato, N. Chida, *Chem*. *Lett*. **2019**, *48*, 1138. 2) T. Sato, N. Chida, *J*. *Am*. *Chem*. *Soc*. **2017**, *139*, 18386. 3) T. Sato, N. Chida, *Org*. *Lett*. **2020**, *22*, 7502. *Current position of Makoto Yoritate: Graduate School of Pharmaceutical Sciences, Kyushu University