Studies Toward the Total Synthesis of the Stemona Alkaloids

\((\pm\))-Stemoamide and \((\pm\))-Parviestemoamide

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\((-\))-Parviestemoamide \hspace{2cm} \((-\))-Stemoamide

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Stemona alkaloids: Introduction

- Herbal extracts from plants belonging to the **Stemonaceae family** have been used in folk medicine in East Asia for a thousand years.

- Stemona alkaloids exhibit **coughing supression**, **antituberculosis**, **antibacterial**, **antifungal** and **anthelmintic** properties.

- They currently comprises ~**150 compounds** (139 as of the last review)

*Nat. Prod. Rep. 2010, 27, 1908*
Most of **Stemona alkaloids** have a **pyrrolo [1,2-\(a\)]azapine** or a **pyrido [1,2-\(a\)]azapine nucleus** (either exposed or hidden).

I: Stenine  
II: Stemoamide  
III: Tuberostemospironine  
IV: Stemoamine  
V: Parviestemoline  
VI: Stemofoline  
VII: Stemocurtisine

**Fig. 1**  *Stemona* alkaloid groups.

*Nat. Prod. Rep.*** **2000, 17, 117**

(-)-**parviestemoamide** (?)

(-)-**stemoamide**
Stemona alkaloids: Parviestemoamide

- Isolated as a minor component from the roots of *Stemona parviflora* $[^{[\alpha]}_D] = -211.2$ (MeOH, $c = 0.25$)

- **Antihelmintic** properties

- **Absence** of the pyrrolo[1,2-\(a\)]azepino nucleus

- Xu and coworkers first suggested the structure \(1a\)\(^1\) and later on structure \(1b\)\(^2\)

- **4 contiguous stereogenic centers** and a 10 membered \textbf{lactam trans} fused with the \textbf{lactone core} which represents the synthetic challenge.

Strategies based on **macrolactamization** or intramolecular **Michael addition** have been not successful to reach the desired targets which could be converted into **parviestemoamide**.
Radical cyclization in Wipf group: Tuberostemonone project

The Reformatsky reaction didn’t provide the desired lactone.

Stemona alkaloids: Stemoamide

- Isolated from *Stemona tuberosa* and characterized by Xu and Co-workers in 1992\(^1\)
- More than a **dozen synthetic routes**\(^2\) have been reported (total, formal and epimers)
- Simplest Stemona alkaloid; Bowl-shaped lactone-fused *pyrrolo [1,2-a] azapine* (4 stereogenic centers);  

\[ \text{Protostemonamide} \]  
\[ \text{Stemonine} \]  
\[ \text{Saxorumamide} \]  
\[ \text{(-)-Stemoamide} \]  
\[ \text{Stemocochinin} \]  
\[ \text{Isosaxorumamide} \]

Stemoamide: Previous syntheses

TL 2012, 53, 2647

TL 1994, 35, 6417


JOC 1996, 61, 8356

JACS 1997, 119, 3409;
JACS 2000, 122, 4295

Org. Biomol. Chem 2011, 9, 673

TL 2002, 43, 295

JOC 2007, 72, 4246

JOC 2006, 71, 3287

Synlett 2004, 1211
Stemoamide: Previous syntheses

(-) and (±)-stemoamide
7 steps; 20 % overall yield


(±)-stemoamide
8 steps; 37 % overall yield

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