Studies Toward the Total Synthesis of the Stemona Alkaloids (±)-Stemoamide and (±)-Parviestemoamide

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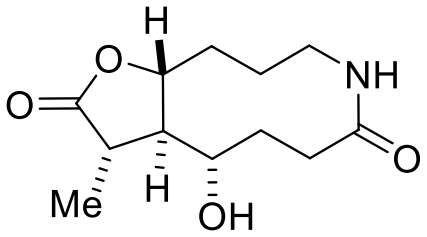
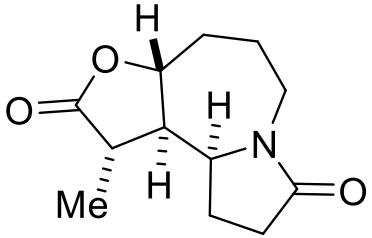
Wipf Group Research Topic Seminar



(-)-Parviestemoamide



(-)-Stemoamide

12/21/2013

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 antihelmintic** properties.

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

Nat. Prod. Rep. **2010**, *27, 1908*

Stemona alkaloids: Introduction

- Most of **Stemona alkaloids** have a **pyrrolo [1,2-*a*]azapine** or **a pyrido [1,2-*a*]azapine nucleus** (either exposed or hidden).

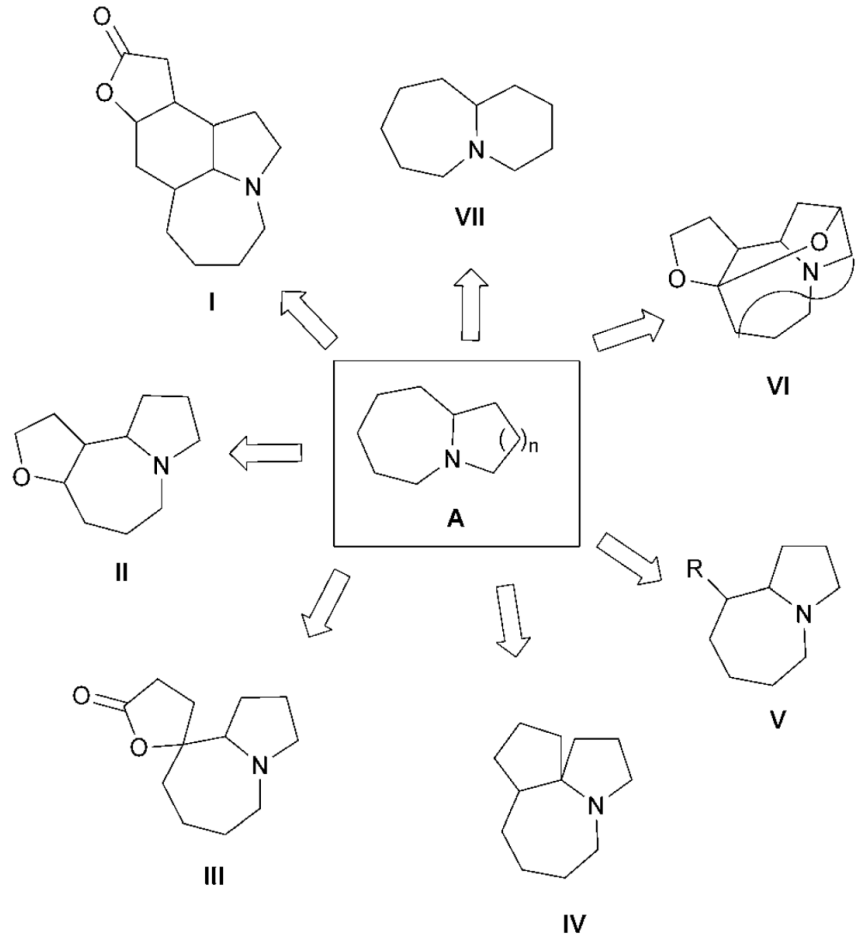
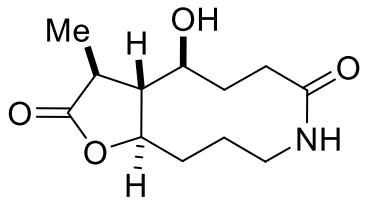
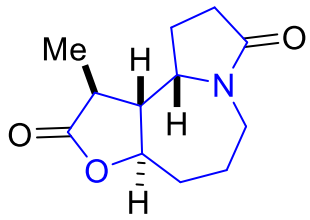


Fig. 1 *Stemona* alkaloid groups.

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



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

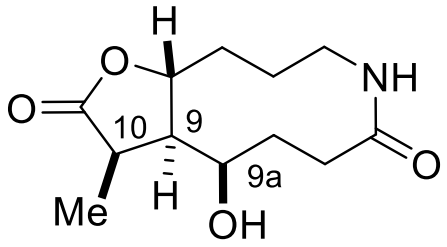


(-)-**stemoamide**

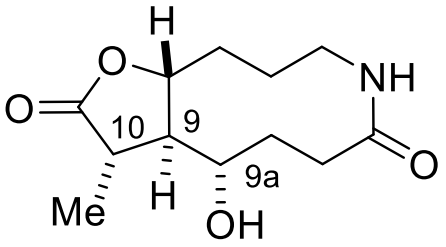
Nat. Prod. Rep. **2000**, *17, 117*

Stemona alkaloids: Parviestemoamide

- Isolated as a minor component from the **roots** of *Stemona parviflora* $[\alpha]_D$=-211.2 (MeOH, c = 0.25)
- **Antihelmintic** proprieties
- **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 **lactam** ***trans*** fused with the **lactone core** which represents the synthetic challenge.



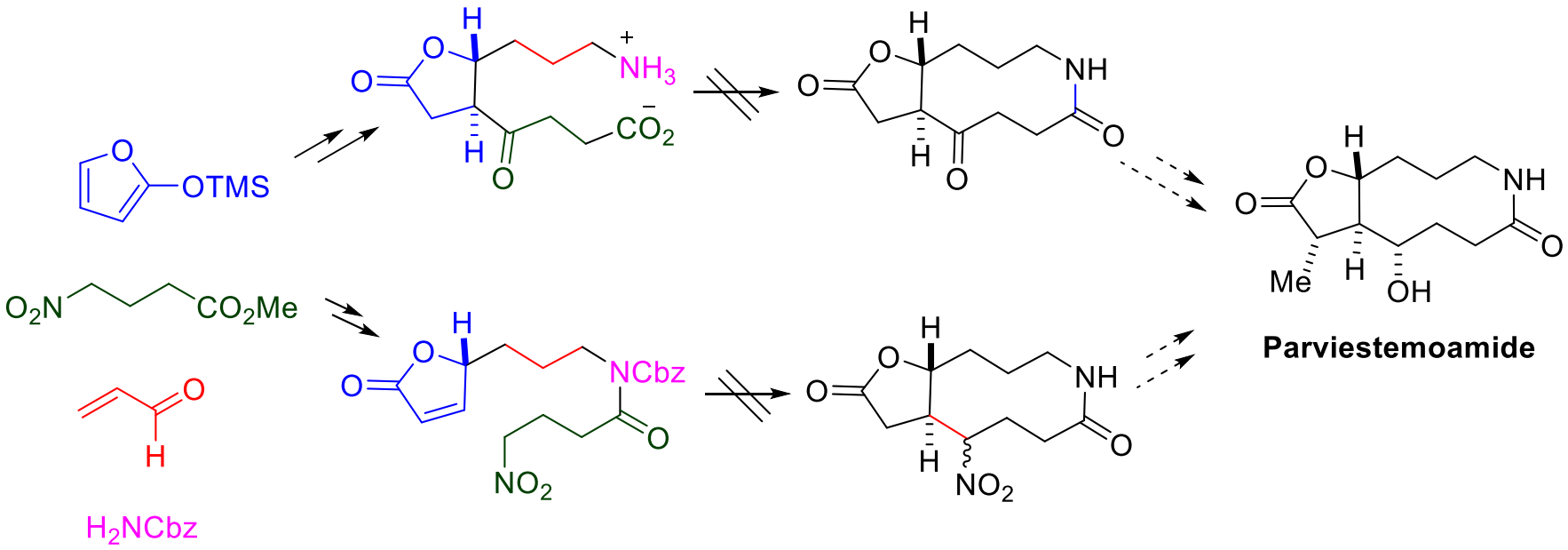
1a



1b

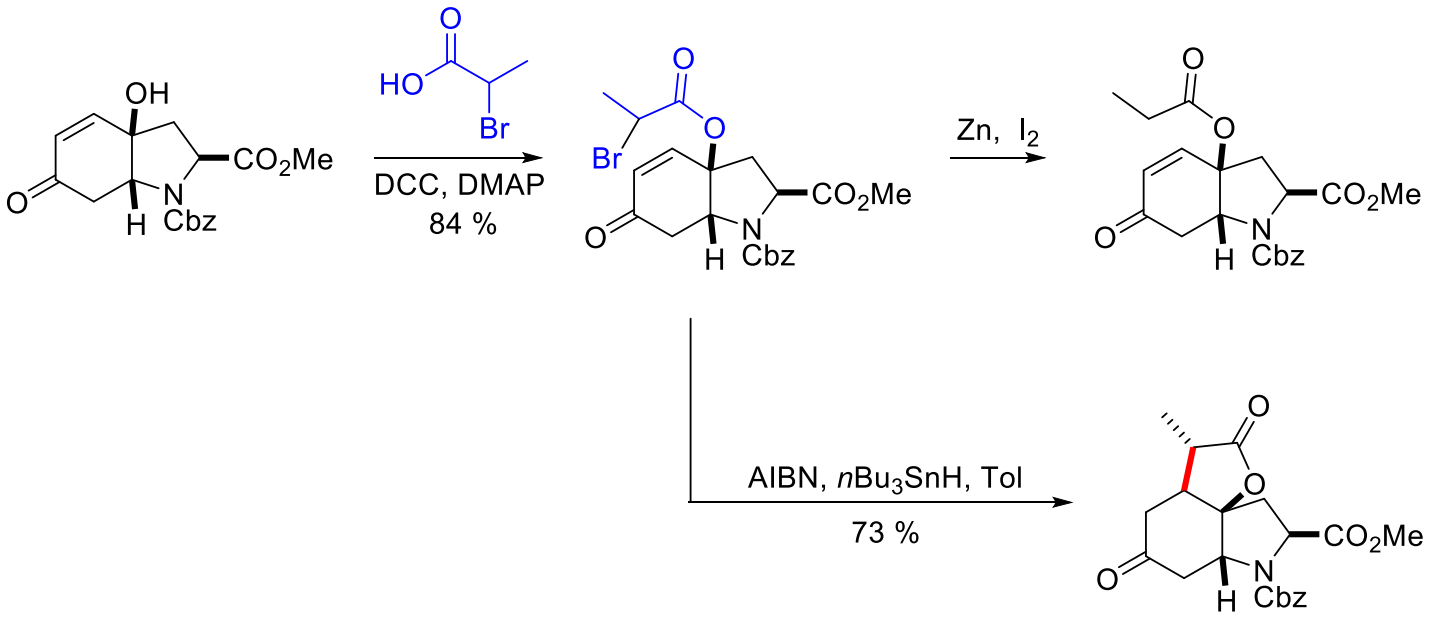
1 - *Acta Chim. Sinica* **1991**, *49*, 927.
2 - *Mem. Inst. Oswaldo Cruz* **1991**, *86*, 55.

Parviestemoamide: Previous work

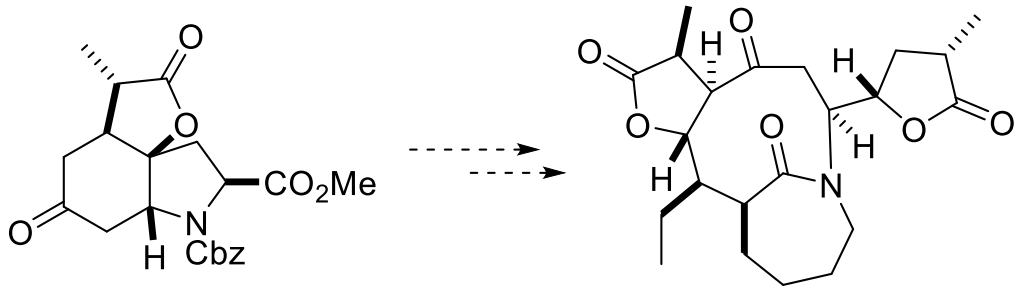


- Strategies based on **macrolactamization** or intramolecular **Michael addition** have been not successful to reach the desired targets which could be converted into **parviestemoamide**

Radical cyclization in Wipf group: Tuberostemonone project



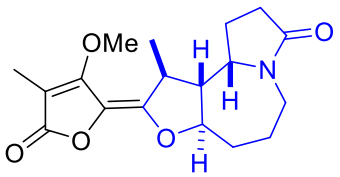
- The **Reformatsky** reaction didn't provide the desired **lactone**.



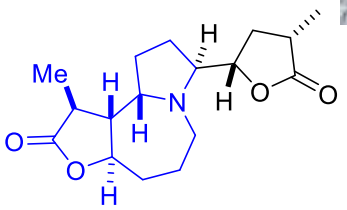
Pierce, J. G. Ph.D. Dissertation, University of Pittsburgh, 2008.

Stemona alkaloids: Stemoamide

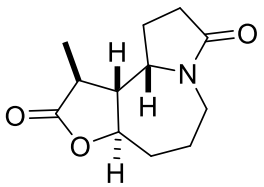
- Isolated from ***Stemona tuberosa*** and characterized by Xu and Co-workers in 1992[1]
- More than a **dozen synthetic routes**[2] have been reported (total, formal and epimers)
- Simplest Stemona alkaloid; Bowl-shaped lactone-fused **pyrrolo [1,2-a] azapine** (4 stereogenic centers);



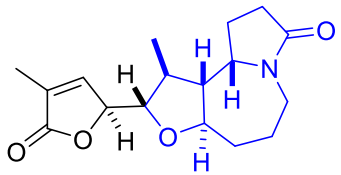
Protostemonamide



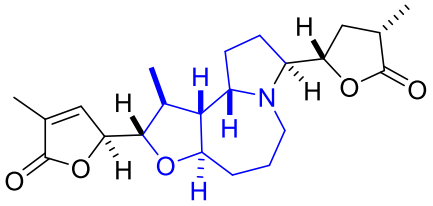
Stemonine



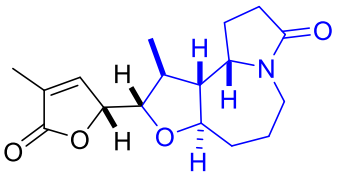
(-)-**Stemoamide**



Saxorumamide



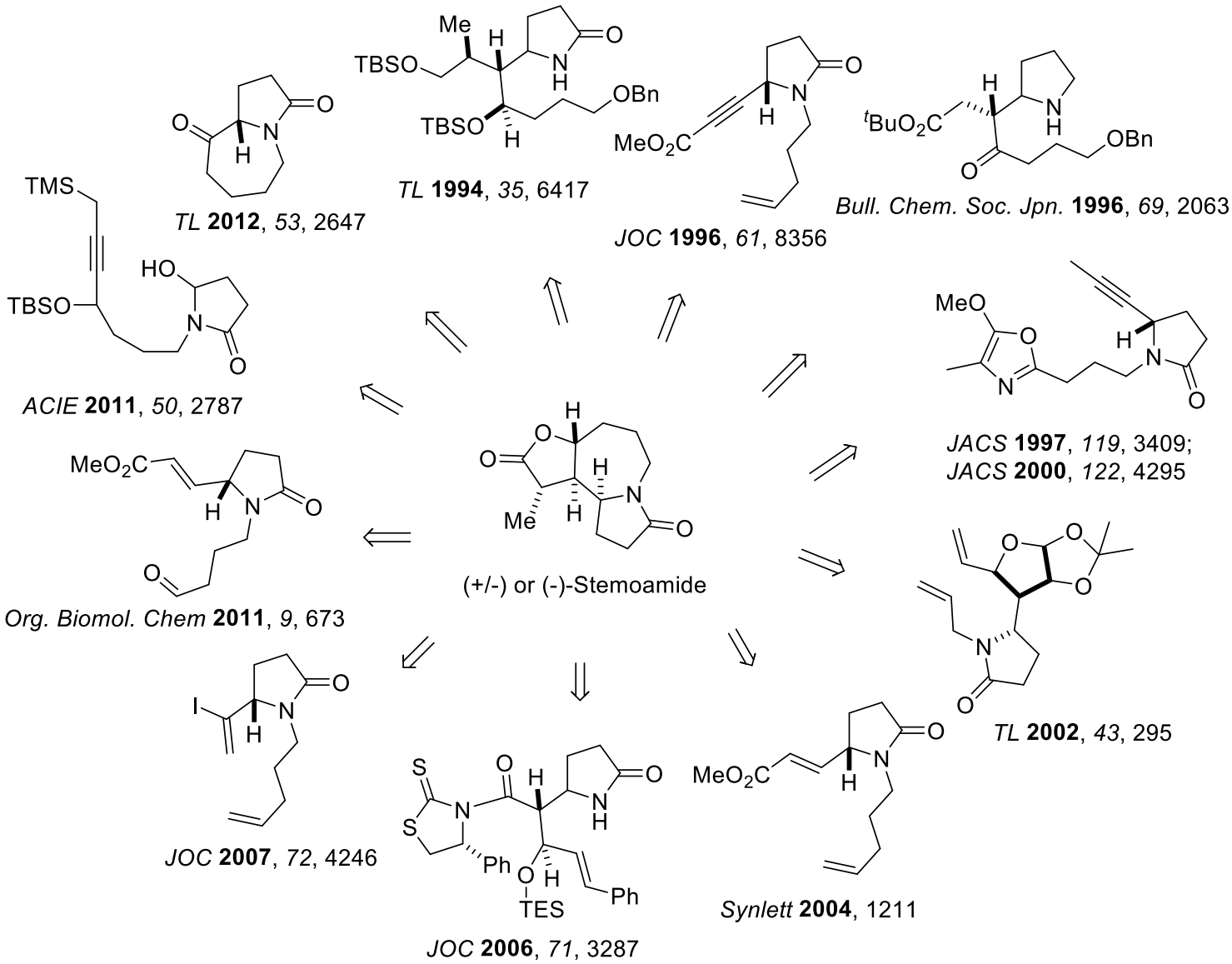
Stemocochinin



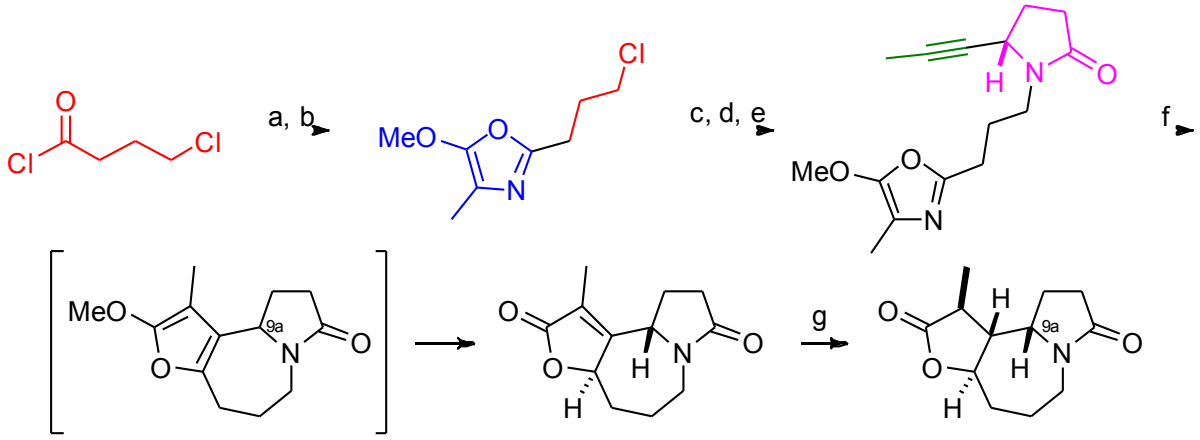
Isosaxorumamide

J Nat. Prod. **1992**, 55, 571-576.

Stemoamide: Previous syntheses



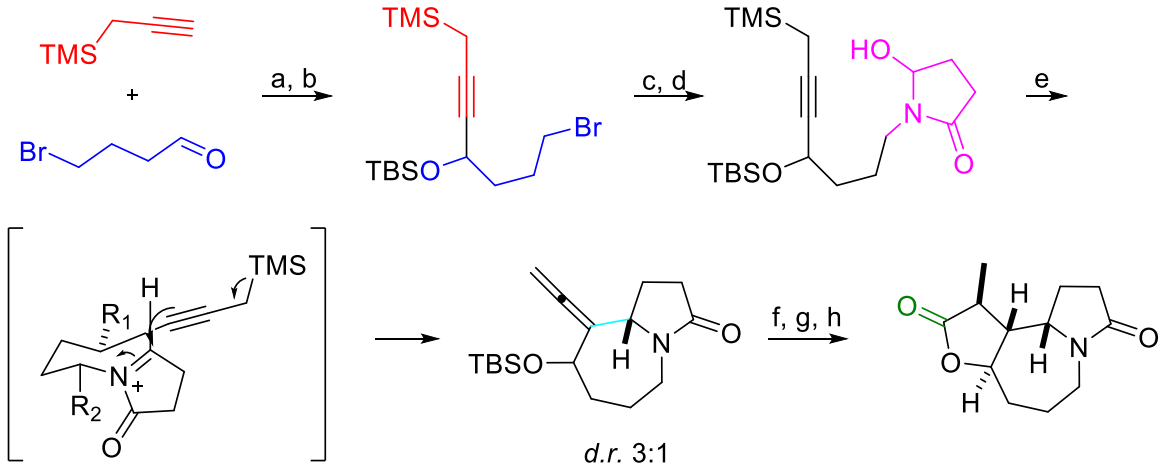
Stemoamide: Previous syntheses



a) methylalaninate , Py; b) P_2O_5, 80 % (2 steps); c) succinimide, 97 %; d) $NaBH_4$, MeOH, 72 %
e) $SnBu_3$, $BF_3.Et_2O$, 92%; f) 182 ºC, ethylbenzene, 53 %; g) $NaBH_4$, $NiCl_2$ 73 %.

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

J. Am. Chem. Soc. **1997**, 119, 3409-3410; *J. Am. Chem. Soc.* **2000**, 122, 4295



a) *n*BuLi, -78 ºC, 93 %; b) TBSCl, DBU, 87 %; c) succinimide, K_2CO_3; d) $NaBH_4$, EtOH, 93 % (2 steps);
e) $FeCl_3$, 0 ºC, 86 %; f) TBAF, 96 %; g) $[Ru(CO)_{12}]$, CO, 100 ºC 81 %; h) $NaBH_4$, $NiCl_2$, MeOH, 74 %.

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

Angew. Chemie. Int. Ed. **2011**, *50*, 2787-2790.

Acknowledgments

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