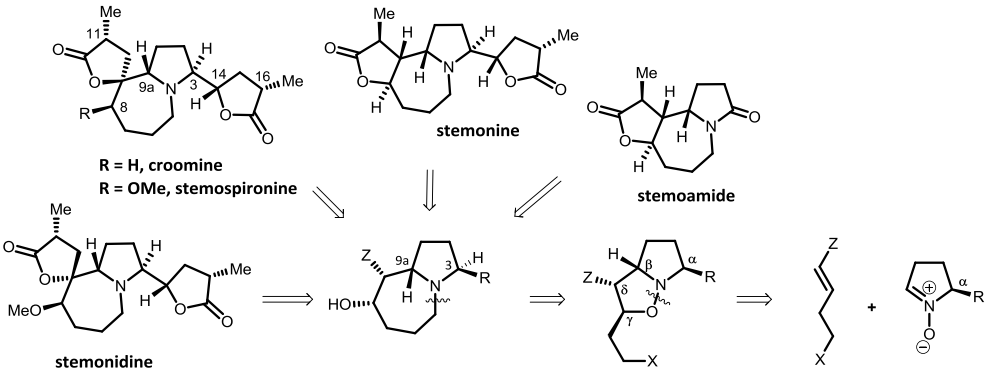
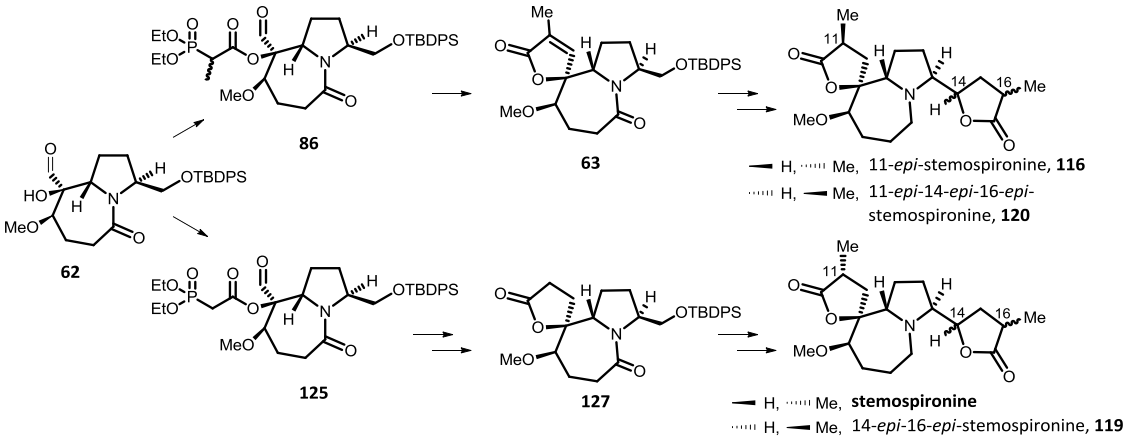
FLEXIBLE APPROACH TO *STEMONA* ALKALOIDS: TOTAL SYNTHESES OF (–)-STEMOSPIRONINE AND THREE NEW DIASTEREOISOMERIC ANALOGS

The extracts of several plants of the *Stemonaceae* family have long been used in Asian countries against different diseases and for their antiparasitic properties. Significant constituents of these extracts are a series of structurally related secondary metabolites named as *Stemona* alkaloids.[1] All the *Stemona* alkaloids are polycyclic and most of them present a central pyrrolo[1,2-*a*]azepine system as a characteristic structural feature. The majority also incorporate at least one substructure of α-methyl-γ-butyrolactone. Our research group designed a strategy in which the pyrroloazepine system is generated at an early stage of the sequence and the other specific fragments are then incorporated, with the aim of developing a flexible approach, with some intermediates being common precursors for various alkaloids. The typical pyrroloazepine core is synthesized through a 1,3-dipolar cycloaddition reaction between a chiral nitrone and an electrondeficient olefin.



In this thesis, the syntheses of stemospironine and three new diastereoisomeric analogs, **116**, **119** and **120** have been achieved.[2] Thus, spirolactonization in the key intermediate **62** was accomplished by esterification of the tertiary alcohol followed by basic treatment of the phosphonate **86**, yielding lactone **63**. After removal of the silyl protection, the alcohol was oxidized, and the corresponding aldehyde was treated with ethyl bromomethylacrylate and zinc furnishing a 1:1 mixture of bislactones. Once the hydrogenation of C-C double bonds was accomplished, each bislactone was converted to amines **116** and **120**, respectively. On the other hand, spirolactonization of **125** furnished an unsaturated lactone, which was hydrogenated to yield **127**. A stereoselective α-methylation rendered the stemospironine-like configuration at C_{11}. Then, the remaining transformations were performed as before, affording stemospironine and its analog **119**. The analytical data of the synthetic stemospironine are in total agreement with those described for the natural alkaloid.[3]



1) Alibés, R.; Figueredo, M. *Eur. J. Org. Chem.* **2009**, 2421-2435.
2) Bardají, N.; Sánchez-Izquierdo, F.; Alibés, R.; Font, J.; Busqué, F.; Figueredo, M. *Org. Lett*. **2012**, *14*, 4854-4857.
3) Sakata, K.; Aoki, K.; Chang, C.-F.; Sakurai, A.; Tamura, S.; Murakoshi, S. *Agric. Biol. Chem*. **1978**, *42*, 457-463.