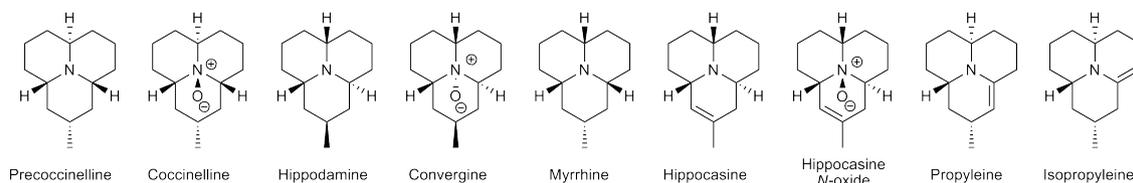


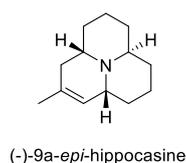
# Iterative Synthetic Strategy for Azaphenalene Alkaloids. Total Synthesis of (-)-9a-*epi*-hippocasine

Ladybugs belong to Coccinellidae family. Most of these species eat aphids and mites, which are especially damaging for several kinds of crops. Taking advantage of this fact, there are some approaches where *Coccinellidae* family insects are used as biological control of agricultural pests.<sup>1</sup> Ladybugs protect themselves against predators by its coloration, especially when they form aggregations. Reflex bleeding is another known method of protection; it consists in an orange fluid secretion, which has a bitter taste. From this fluid, several alkaloids have been isolated. An example of these are azaphenalene alkaloids, which are a family of compounds presenting a common feature based on perhydro-9b-azaphenalene (Figure 1). Until now, there are only two published syntheses of these alkaloids in enantiopure form.<sup>2,3</sup>



**Figure 1.** Isolated alkaloids with perhydro-9b-azaphenalene structure.

In this thesis, the enantioselective total synthesis of the non-natural alkaloid (-)-9a-*epi*-hippocasine is described (Figure 2). An iterative strategy has been developed, where the key steps are a palladium catalyzed asymmetric allylic alkylation reaction of glutarimide, two diastereoselective nucleophilic allylation reactions and two ring closing metathesis processes.



**Figure 2.** Structure of (-)-9a-*epi*-hippocasine.

Further studies directed to the synthesis of other members of this alkaloids family were also undertaken.

<sup>1</sup> Angela Glisan King, Jerrold Meinwald, *J. Chem. Rev.* **1996**, *96*, 1105-1122.

<sup>2</sup> Trevor C. Sherwood, Adam H. Trotta, Scott A. Snyder, *J. Am. Chem. Soc.* **2014**, *136*, 9743-9753.

<sup>3</sup> Marta Guerola, María Sanchez-Roselló, Cristina Mulet, Carlos del Pozo, Santos Fustero, *Org. Lett.* **2015**, *17*, 960-963.