A CONCISE SYNTHESIS OF 8a-*epi*-SWAINSONINE ANALOGUE

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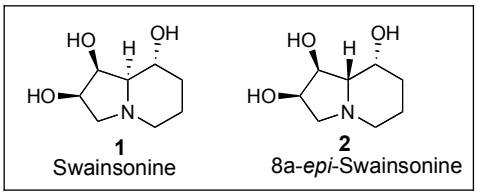
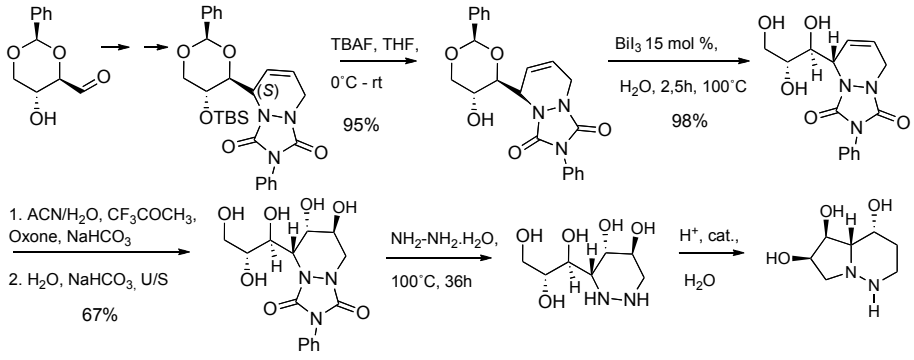
Abstract

Swainsonine **1**, a naturally occurring polyhydroxyindolizidine, has attracted much attention for being an effective inhibitor of α-D-mannosidases, including the glycoprotein-processing enzyme mannosidase II, exhibiting important antimetastatic, antitumor-proliferative, anticancer, and immunoregulating activities.[1] Swainsonine **1** was also the first inhibitor to be selected for testing as an anticancer drug, reaching phase II clinical trials in the US. Furthermore, considerable structural variants (epimers, and structural analogues) have also been prepared in order to try to improve the biological activity and/or the selectivity of the natural compound. Several of these diastereomers demonstrated comparable α-D-mannosidase inhibitory activity to Swainsonine **1**, *e.g.* 8a-*epi*-swainsonine (**2**) has 93% the activity of Swainsonine (**1**).[2]



This work results of an extension of a Diels-Alder cycloaddition of a derivative diene with PTAD obtained in excellent yield and total selectivity.[3] Removal of the alcohol functions protections and after removal of the urazole moiety we are a step away of obtaining an analogue of 8a-*epi*-Swainsonine that will be submitted to inhibitory activity of mannosidases and to docking studies on the respectives enzymes. The Scheme below shows the chemical sequence and the yields obtained so far.



References

[1] J.Bi, V.K. Aggarwal *Chem. Comm.*, **2007**, 120-122. [2] J.N. Abrams, R.S. Babu, H. Guo, D. Le, J. Le, J.M. Osbourn, G.A. O'Doherty, *J. Org. Chem.*, **2007**, 1935-1940. [3] M.J. Alves, Vera C. M. Duarte, H. Faustino, A. Gil Fortes *Tetrahedron Asymmetry*, **2010**, *21*, 1817-1820.