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Towards the total synthesis of the labdane diterpenes Cacofurans A and B.

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Abstract

Cacospongia sp. is a species of marine sponge that produces labdane-class diterpens known as Cacofurans A and B, which show cytotoxic activity in vitro. In this work, we present the synthetic pathway of Cacofurans A and B in ten and nine steps, respectively. Five steps of the synthetic proposal were completed, with 25% overall yield, including the formation of a five-membered ring using the Suárez reaction. After the completion of the total synthesis, the cytotoxic potential of Cacofurans A and B will be evaluated.

Key words: *Total Synthesis, cacofurans, diterpens.*

Introduction

More than half of simple molecules approved as drugs between 1981 and 2014 are natural products or derived from them, and when it comes to cancer treatment, this number increases to 80%.[2] Cacofurans A and B are a labdane-class of diterpenes found in a marine sponge of the gender *Cacospongia*, which are known to possess cytotoxic properties.[1] In this work, we developed a synthetic method towards the synthesis of Cacofurans A and B and further evaluation of their cytotoxic properties.

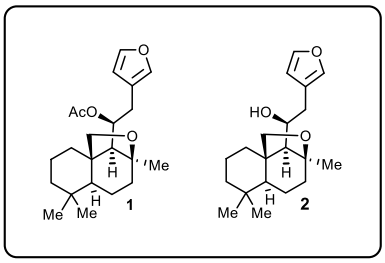
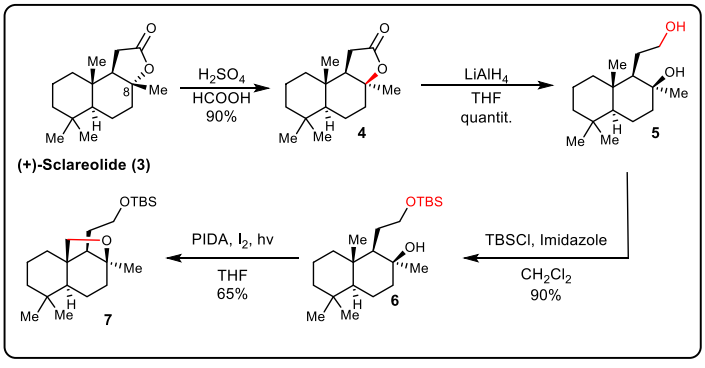


Figure 1. Cacofurans A (**1**) and B (**2**).

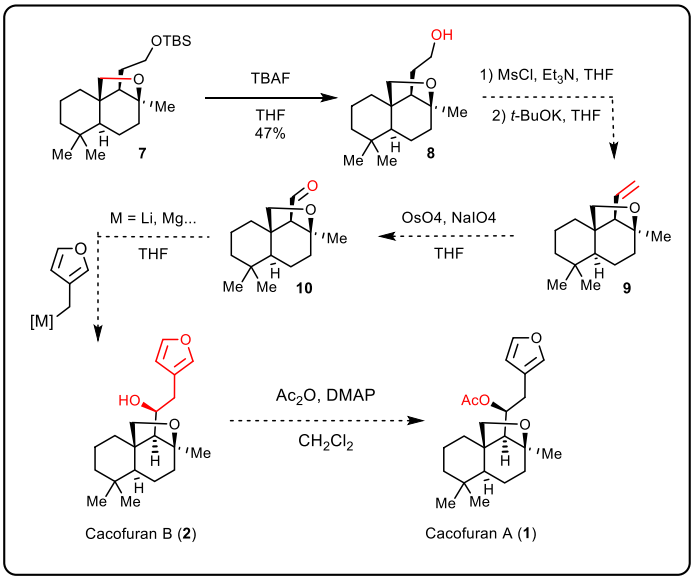
Results and Discussion

The synthetic route begins with an epimerization in C8 of the compound **3** to obtain **4** in 90% yield. A reduction of the lactone moiety using $LiAlH_4$ allows the obtention of **5** in quantitative yield. Several protecting groups were evaluated to protect the primary hydroxyl group of **5**, and TBS showed the best results with 65% yield when applied in the formation of **7** using the Suárez reaction.



Scheme 1. Synthesis of the key intermediate **7**.

Next, the synthetic sequence for the formation of Cacofurans A and B encompasses the deprotection of **7** furnishing the compound **8** in 47% yield. Then, the next steps under evaluation involve a mesylation reaction of the hydroxyl group of **8** and an elimination reaction to obtain the terminal olefin **9**, followed by a oxidative cleavage for the production of aldehyde **10**. The Cacofuran B (**2**) may be achieved by a nucleophilic addition employing an organometallic reagent to the carbonyl group of **10**. The Cacofuran A (**1**) may be obtained with an acetylation of the secondary alcohol of **2**.



Scheme 2. Final steps towards Cacofuran A (**1**) and B (**2**).

Conclusions

In conclusion, five steps were already accomplished in 25% overall yield to afford compound **8**. Work is now in progress to complete the total synthesis of Cacofurans A and B, and their cytotoxicity will be evaluated against tumor cells.

Acknowledgement

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[1] Higa, T.; Musman, M.; Tanaka, J. *J. Nat. Prod.*, **2001**, *64*, 1468.

[2] Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2016**, *79*, 629.