Chemoenzymatic synthesis of bis-THF rings present in acetogenins

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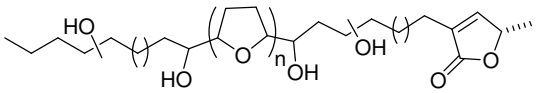
INTRODUCTION

Acetogenins belong to a family of natural products of general formula **I**, endowed with high cytotoxic activity.[1,2] They contain a cyclic THF core flanked by two long hydrocarbon side chains. In addition to the more common mono-THF, bis-THF structures are also found in nature, and display a similar activity profile. The configuration of the THF rings in natural acetogenins is usually *R*,*R*, as found in the bis-THF cores of Asimisin and Guanaconetin, Figure 1.



general formula of acetogenins, **I**

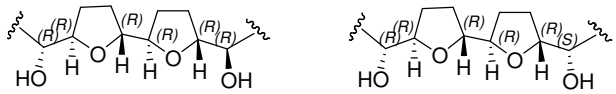


Figure 1. Bis-THF cores of Asimisin and Guanaconetin

We decided to prepare the bis-THF rings present in these natural products using an iterative strategy based on the iodoetherification of 3-butenyl carbinols, such as **2** and **4**, Figure 2.

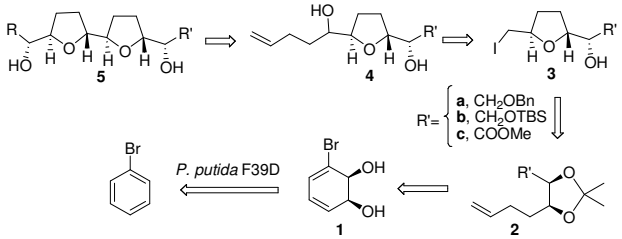


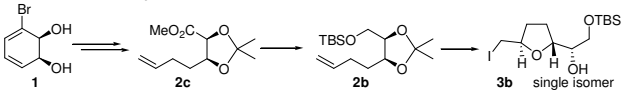
Figure 2. Analysis of the bis-THF core of acetogenins

RESULTS AND DISCUSSION

a) *Synthesis of trans-THF* **3**.

Starting from enantiopure diol **1**, obtained by microbial oxidation of bromobenzene using a mutant strain of *P. putida*, protected carbinol **2c** was prepared in 48% overall yield through a 4 step sequence, Scheme 1. The cyclization was performed using different oxygenated groups R' in **2** and the best selectivity was obtained using **2b**, giving 100% *trans* THF, Scheme 1.

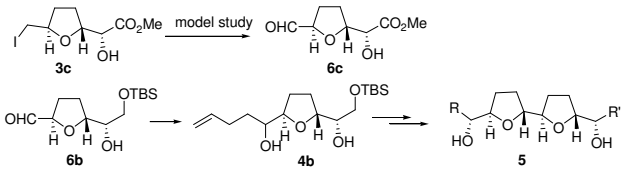
Scheme 1. Synthesis of *trans* THF, **3**.



b) *Approach to the synthesis of the bis-THF core*, **5**.

In order to perform the iterative methodology, the primary iodide **3** has to be oxidized to aldehyde **6** and then submitted to a Grignard-type alkylation to give **4**.
The oxidation was optimized using the iodide **3c** as a model study. Using the best conditions, the isomer **3b** was converted to aldehyde and alkylated to give carbinol **4b**, precursor of the cyclization, Scheme 2.
Details for these transformations, together with the proposed cyclization to **5**, will be presented.

Scheme 2. Approach to the synthesis of the bis-THF core, **5**



CONCLUSION

An iterative methodology to the bis-THF core of natural acetogenins has been proposed. The starting compound derives from enantiopure diols obtained by microbial dioxygenation of bromobenzene.

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[2] Bermejo, A.; Figadere, B.; Zafra, M.-C.; Barrachina, I., Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269-303