Chemoenzymatic synthesis of bis-THF rings present in acetogenins

Juan C. Ramos, Margarita Brovetto, Gustavo Seoane*

Departamento de Química Orgánica. Facultad de Química. Universidad de la República. Montevideo-Uruguay.

*Corresponding author. Tel.: +(5982)-924-4066 Fax: (5982)-924-1906; gseoane@fq.edu.uy

Keywords: Acetogenins, cis-ciclohexadienols, tetrahydrofurans

INTRODUCTION

Acetogenins belong to a family of natural products of general formula 1, endowed with high cytotoxic activity. 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.

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.

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.


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.

ACKNOWLEDGEMENTS

ANII, Uruguay.
PEDECIBA, Uruguay.
Mr. Horacio Pezaroglo (for NMR experiments).

REFERENCES