Synthesis and Biological Activity of Fostriecin Analogs

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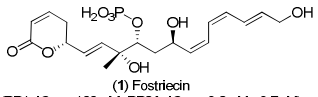
INTRODUCTION

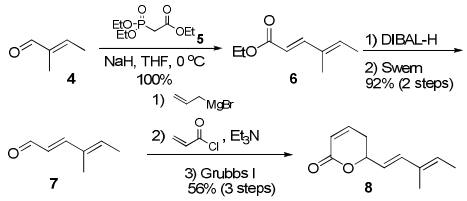
Fostriecin (**1**) is a phosphate monoester produced by *Streptomyces pulveraceus*[1] that displays promising antitumor activity.[2] It has entered NCI-sponsored clinical trials, but the studies were discontinued due to its storage instability and unpredictable chemical purity.[2] In this context, more stable derivatives of fostriecin (**2** and **3**) have been proposed in order to evaluate the cytotoxic activity and try to understand the molecular requirements for inhibition of protein phosphatase.



(**1**) Fostriecin
(PP1, IC_{50} > 100 μM; PP2A, IC_{50} = 3,2 nM - 3,7 μM)

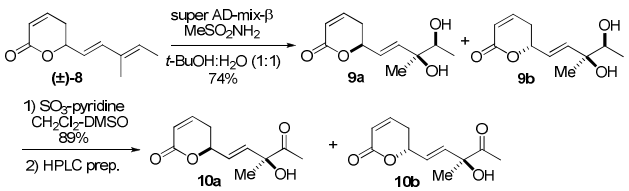
RESULTS AND DISCUSSION

The synthesis of **2** and **3** began with the preparation of lactone (±)-**8** in 52% yield over 6 steps (**Scheme 1**).



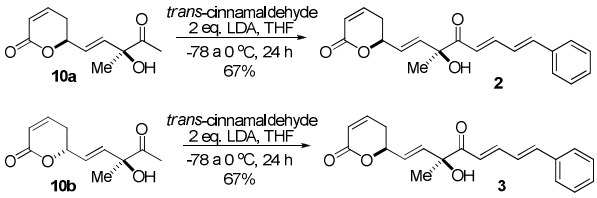
Scheme 1. Synthesis of lactone **8**.

Lactone (±)-**8** was converted into diastereoisomers **9a** and **9b** under Sharpless asymmetric dihydroxylation conditions. Subsequently, oxidation of the primary alcohol provided methyl ketones **10a** and **10b**, which were separated using preparative HPLC (**Scheme 2**).



Scheme 2. Synthesis of intermediates **10a** and **10b.**

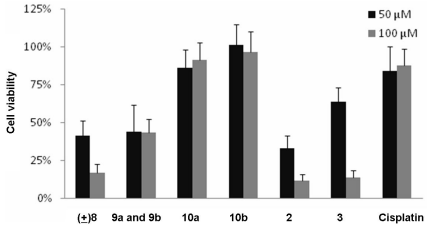
The desired compounds **2** and **3** were formed after aldol condensation reaction with *trans*-cinnamaldehyde in 67% yield.



Scheme 2. Synthesis of compounds **1** and **2**.

The cytotoxic activity of **2** and **3** and the synthetic intermediates **8**, **9** and **10** were evaluated by cell viability assay, using PC-03 (prostate) cell lines. These cell lines are resistant to cisplatin[3] and overexpress low molecular weight protein tyrosine phosphatases (LMW-PTPs), acting as positive tumor regulator.

Figure 1. Tumor PC-03 cell viability after treatment with synthesized compounds.



CONCLUSION

Compounds **2**, **3**, **8** and **9** are cytotoxic to PC-03 tumor cells that overexpress LMW-PTP, suggesting a strong relationship between cell death and inhibition of this enzyme.

ACKNOWLEDGEMENTS

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