Synthesis of Novel Goniothalamin Analogs

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INTRODUCTION

The styryl lactone goniothalamin (**1**) is a secondary metabolite distributed among the plants of the genus *Goniothalamus* which has cytotoxic and antiproliferative properties.[1,2]

Given the interest of our research group to pursue studies of the biological activity of compounds based on its structure, we proposed the synthesis of hydrophilic analogs (**2a-c**).

Moreover, the incorporation of fluorine into molecules has become a common tool in medicinal chemistry for improving the pharmacological profile of bioactive compounds.[3-5] Thus, we proposed the synthesis of compounds (**2d-e**) containing the trifluoromethyl groups.

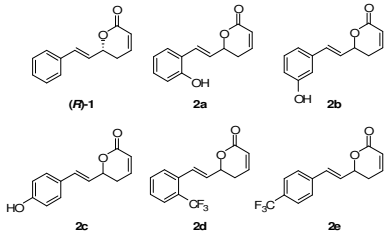
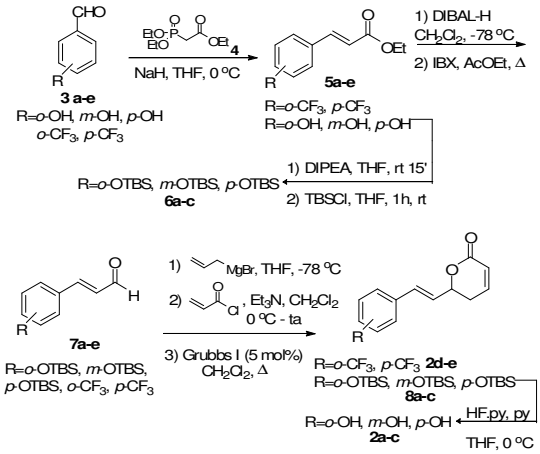


Figure 1. (*R*)-goniothalamin (**1**) and analogs (**2a-e**).

RESULTS AND DISCUSSION

The general synthetic route to achieve analogs **2a-e** is represented in Scheme 1.



Scheme 1. General synthetic route for goniothalamin analogs **2a-e.**

The synthesis of lactones **2a-e** began with the preparation of aldehydes **7a-e**. Reagent **4** was used to homologate commercial aldehydes **3a-e** by the HWE reaction, followed by reduction of esters **5a-e** with DIBAL-H and oxidation with IBX, leading to the corresponding aldehydes **7a-e**. The hydroxyl groups were protected using TBSCl and DIPEA.

Allyl Grignard was added to generate the homoallylic alcohols which were reacted with acryloyl chloride leading to the corresponding esters. Finally, the lactone analogs were achieved by treating the dienes with Grubbs I catalyst (5 mol%). The TBS groups were removed using solution of HF in pyridine. The overall yields are summarized in Table 1.

Table 1. Overall yields for goniothalamin analogs **2a-e**.

Analogs	R	Overall yields
2a	*o*-OH	22%*
2b	*m*-OH	38%*
2c	*p*-OH	17%*
2d	*o*-CF_3	15%**
2e	*p*-CF_3	17%**

*Over eight steps.
**Over six steps.

CONCLUSION

The present work discloses the synthesis of five novel lactone analogs (**2a-e**) of goniothalamin. These compounds will be evaluated *in vitro* against human tumor cell lines in an antiproliferative assay and also for the inhibition of protein phosphatase.

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