Synthesis of Lactam Derivatives of Goniothalamin

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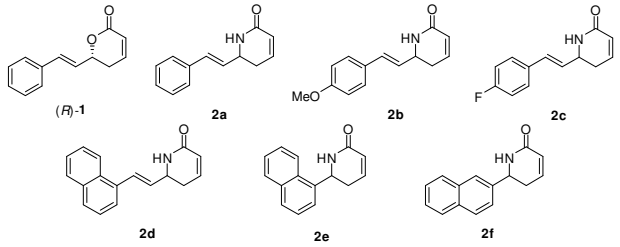
INTRODUCTION

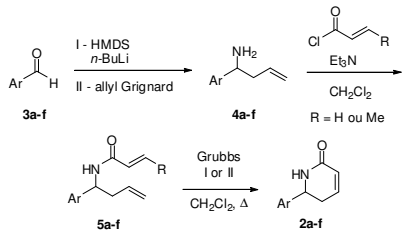
(*R*)-Goniothalamin (**1**) is a natural product isolated from plants of the *Goniothalamus* gender. The natural enantiomer presents antiproliferative activity against the following tumor cell lines: cervical (HeLa), kidney (786-0) and adriamycin resistant ovary (NCI-ADR/RES).[1] Posterior reports indicate that goniothalamin may act in the apoptotic process in cancer cells via different mechanisms.[2]

Based on the presence of lactam moieties in several biologically active natural product, we decide to search for compounds displaying enhanced cytotoxicity and selectivity. Therefore, we propose the synthesis of lactam derivatives (**2a**-**f**) based on the goniothalamin structure.



RESULTS AND DISCUSSION

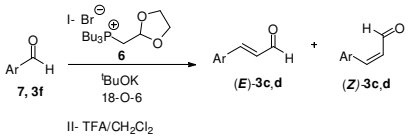
The general synthetic route to achieve the derivatives **2a**-**f** stated with aldehydes **3a**-**f** (Scheme **1**).



Scheme 1. General synthetic route for derivatives **2a**-**f**.

To prepare the non-commercial aldehydes **3c** and **3d**, we used the methodology described in Scheme **2**. Reagent **6** was used to homologate the commercial aldehydes **7** and **3f**, following deprotection of the acetal to deliver the desired aldehydes.

Aldehyde **3c** was obtained in 64% yield with a diastereoisomeric ratio of >99:1, and **3d** was obtained in 59% yield with a diastereoisomeric ratio of 16:1.



Scheme 2. Aldehyde homologation.

The synthesis of lactams **2a**-**f** began with the formation of imine from aldehyde (**3**) and LHMDS, followed by the addition of allyl Grignard to generate the primary amine **4**. The next step involved the reaction of the amine with acryloyl or crotonoyl chloride leading to the corresponding amide (**5**). Finally, the lactam derivatives **2** were achieved by treating the corresponding amide with Grubbs' catalyst.

All conditions used and the overall yields are summarized in Table **1**.

Table 1. Experimental conditions for derivatives **2a**-**f**.

2	R	Catalyst (mol%)	Overall yield (3 steps)
a	H	Grubbs I (10)	20%
b	H	Grubbs II (3x3)	26%
c	Me	Grubbs II (2x3)	18%
d	Me	Grubbs II (2x3)	30%
e	Me	Grubbs II (2x3)	45%
f	Me	Grubbs II (2x3)	42%

CONCLUSION

To sum up, it was possible to synthesize lactam derivatives of goniothalamin in good overall yields over 3 steps (18-45%). These derivatives are under *in vitro* evaluation against human tumor cell lines in an antiproliferative assay.

ACKNOWLEDGEMENTS

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