Synthesis of 3,4-Dihydro-γ-Pyrone Analogues of Goniothalamin

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Keywords: goniothalamin, analogues, 3,4-dihydro-γ-pyrones

INTRODUCTION

In an ongoing program to identify new candidates for cancer treatment, goniothalamin **1** (Figure 1) was recognized as a good lead compound with significant cytotoxicity against a variety of cancer cell lines, including cervical, kidney, prostate, breast carcinoma and leukemia.[1] In an attempt to develop new analogues with higher activity and selectivity, we decided to prepare 3,4-dihydro-γ-pyrone analogues of goniothalamin.

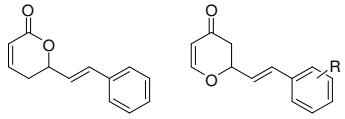
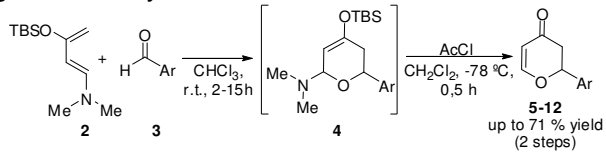


Figure 1. Goniothalamin and 3,4-dihydro-γ-pyrones.

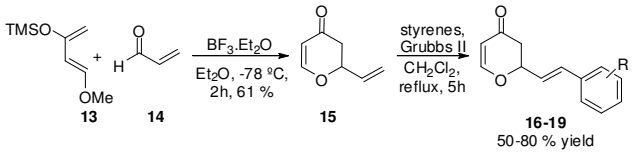
RESULTS AND DISCUSSION

The synthetic strategy aiming the preparation of 3,4-dihydro-γ-pyrones is based on the methodology described by Rawal.[2] The hetero Diels-Alder (HDA) reaction of 1-amino-3-siloxy-1,3-butadiene **2** with a range of aldehydes **3** proceeded readily at room temperature and in the absence of a Lewis acid (Scheme 1). The cycloadducts **4** could be converted directly to the corresponding 3,4-dihydro-γ-pyrones **5-12** in a one-pot procedure using acetyl chloride, in good overall yields.



Scheme 1. General route for the 3,4-dihydro-γ-pyrones.

Initially, analogues **5-9** lacking the styryl moiety were prepared. Inspired by the work of Kasaplar,[3] who found that 1-naphthyl substitution in the lactone ring of goniothalamin dramatically enhanced the activity, the 1- and 2-naphthyl substituted analogues **10-12** were also synthesized. Regarding the styryl series, the synthetic sequence described above using *trans*-cinnamaldehyde as dienophile was ineffective leading to a mixture of products due to the low chemoselectivity of the Diels-Alder reaction. To surpass this limitation, another synthetic route was envisioned (Scheme 2). 6-Vinyl-3,4-dihydro-γ-pyrone **15** was prepared using the HDA reaction of Danishefsky´s diene **13** with acrolein **14** catalyzed by boron trifluoride in 61 % yield. With this olefin in hand, cross metathesis reaction with styrenes in the presence of Grubbs´ second-generation catalyst (5 mol%) in refluxing CH_2Cl_2 afforded the desired 2-styryl-3,4-dihydro-γ-pyrones **16-19** in moderate to good yields.



Scheme 2. Alternative route for the styryl series.

Figure 2 shows selected examples of the 3,4-dihydro-γ-pyrones prepared using both strategies.

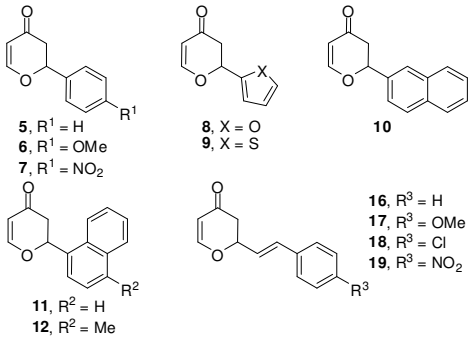


Figure 2. Examples of 3,4-dihydro-γ-pyrones synthesized.

CONCLUSION

In conclusion, a series of 3,4-dihydro-γ-pyrones were prepared using the HDA reaction of Rawal´s diene with several aldehydes and subsequent elimination of the amino group. Alternatively, the styryl derivatives could be obtained by means of a HDA reaction between Danishefsky´s diene and acrolein, followed by olefin cross metathesis with styrenes. These analogues are under *in vitro* evaluation against human tumor cell lines and in phosphatase inhibition assays.

ACKNOWLEDGEMENTS

We thank FAPESP and CNPq for financial support.

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