A tandem ring-closing/cross-coupling metathesis reaction toward the short synthesis of goniothalamin analogs

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INTRODUCTION

In view of preparing furanone analogs – exemplified by compound **1**- of the cytotoxic naturally occurring styryl lactone goniothalamin (**2**),[1] we envisioned a key cross-coupling metathesis reaction between vinyl furanone **3** and a range of styrenes.

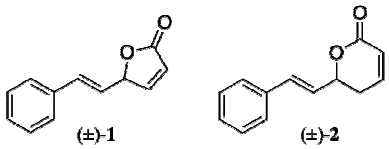
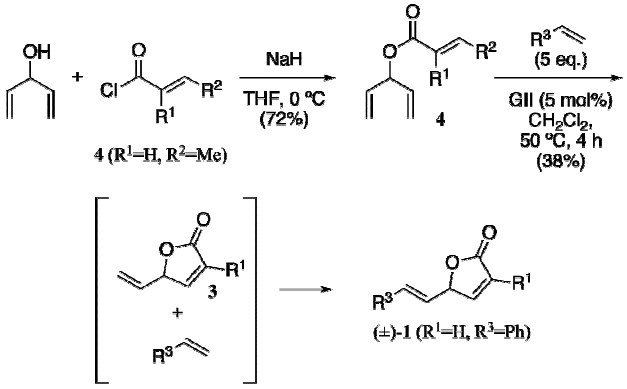


Figure 1. Cytotoxic goniothalamin (**2**) and an analog (**1**).

Inspired by the work of Piva *et al*,[2] where **3** would be formed *in situ* via ring-closing metathesis of triene **4**, we herein report the short synthesis of a variety of styryl furanones using a key tandem ring-closing/cross-coupling metathesis (RCM/CCM) step.

RESULTS AND DISCUSSION

Pentadienyl ester (**4**, R^1=H, R^2=Me) was readily prepared from pentadienyl-3-ol and crotonoyl chloride upon treatment with sodium hydride. Reacting a mixture of compound **4** and excess styrene with Grubbs' second-generation catalyst (GII) under highly diluted conditions at reflux, delivered the desired styryl butenolide (**1**).



Scheme 1. Short synthetic route to styryl furanones.

Although the conversion of the starting ester **4** appeared complete by TLC analysis, the yield of the desired furanone was generally poor (<30%), mostly due to partial decomposition on silica gel (as demonstrated by 2D-TLC).

The process was repeated using different styrenes (R^3-vinyl), that were either commercially available or readily prepared from the corresponding aldehydes via Wittig olefination.

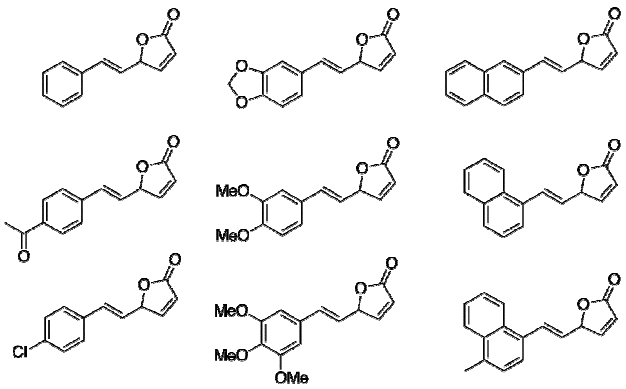


Figure 2. Goniothalamin analogs prepared.

CONCLUSION

A group of styryl furanones was prepared via a highly convergent strategy using tandem metathesis reactions as key step. Although the yields are low, this is a rapid way to access substrates for evaluation of their cytotoxicity toward a range of cancer cell lines.

Future work will probe the stability of α-phenyl-substituted analogs (R^1 = Ph), using the same tandem reaction under appropriate conditions (solvent / temperature, catalyst).

ACKNOWLEDGEMENTS

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REFERENCES

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