Integrated Batch and Continuous Flow Process for the Synthesis of Goniothalamin

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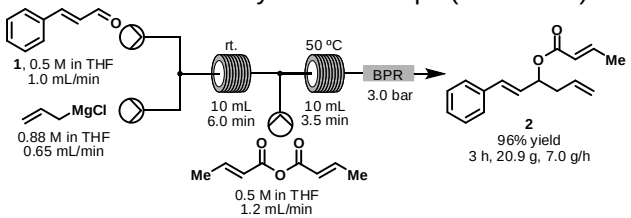
INTRODUCTION

Continuous-flow techniques can often provide better mixing and heat transfer, precise control over concentrated or hazardous reaction streams, reduced solvent waste and synthetic shortcuts.[1] Moreover, the rapid process optimization of synthetic steps on a small scale, combined with the telescoping of steps together in a continuous mode, enables more elaborate multistep sequences to be performed, leading directly to drug molecules or even natural products.[2] Bearing this in mind, we aimed at developing a continuous flow process for the synthesis of goniothalamin (**3**), which presents potent *in vivo* antitumor activity.[3]

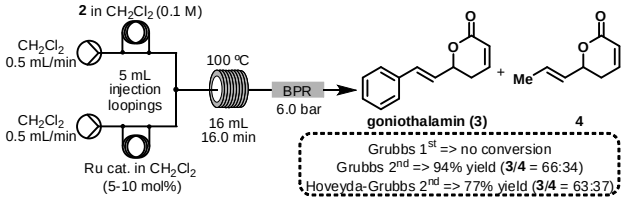
RESULTS AND DISCUSSION

Initially, addition of allylMgCl to cinnamaldehyde (**1**) was investigated and full conversion could be obtained at room temperature. The alkoxide intermediate was then acylated in line by the addition of a third stream containing crotonic anhydride. Once the flow equipment and reaction parameters were optimized, the telescoped process for the preparation of ester **2** was run continuously over 3 h to generate 20.9 g of the product, which was obtained in 96% yield for 2 steps (Scheme 1).



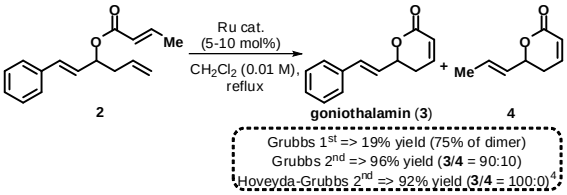
Scheme 1. Continuous flow synthesis of ester **2**.

Next, ring-closing metathesis reaction was evaluated in segmented flow conditions (Scheme 2). Although full conversion could be achieved in a short residence time using either Grubbs or Hoveyda-Grubbs second-generation catalysts, selectivity was adversely affected by co-entrapment of propylene with catalyst and product in the traveling "plug". Indeed, the evolving gas underwent an olefin cross-metathesis reaction with the styryl moiety of goniothalamin (**3**) affording lactone **4**.



Scheme 2. RCM reaction of ester **2** in flow conditions.

Ring-closing metathesis was then performed in batch mode (Scheme 3). Grubbs first-generation catalyst afforded the dimer as the major compound. Gratifyingly, more active catalysts gave goniothalamin in a good selectivity and yield. Owing to the limitation imposed by the formation of lactone **4**, a large scale synthesis of goniothalamin (**3**) was performed in batch mode using optimized conditions to afford goniothalamin (**3**) in 78% yield and a sample of 8.0 g was prepared.



Scheme 3. RCM reaction of ester **2** in batch mode.

The asymmetric version of this route was also investigated using Brown allylation. Both batch and flow methods gave essentially the same results in terms of yield and enantioselectivity (92% ee).

CONCLUSION

In conclusion, we demonstrated that integration of batch and flow chemistry platforms is a powerful strategy aiming at the preparation of gram quantities of important molecules, as exemplified for the synthesis of the natural product goniothalamin.

ACKNOWLEDGEMENTS

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REFERENCES

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