Studies of continuous-flow synthesis of nonpeptidal bis-tetrahydrofuran moiety of Darunavir

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Keywords: continuous-flow, bis-THF, Darunavir, HIV protease

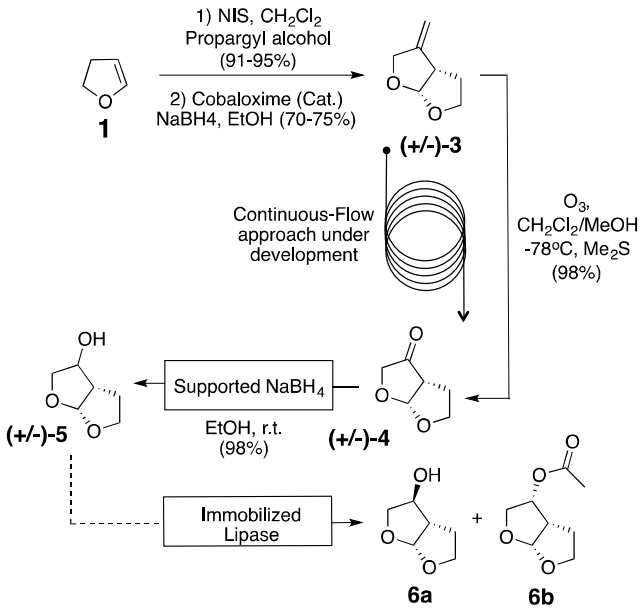
INTRODUCTION

The AIDS (acquired immunodeficiency syndrome) has become one of the most pressing medical concerns of our time. Specifically, the critical function of HIV protease has made it an important target for the treatment of HIV/AIDS.[1-3] The approval of the first protease inhibitor (PI), saquinavir and its introduction into highly active antiretroviral therapy (HAART), with reverse transcriptase inhibitors, led to significantly enhanced HIV management and improved the quality of life of HIV/ AIDS patients. The future management of HIV/AIDS should rely upon the development of therapies that are less toxic and more effective in combating drug-resistance.[1] In this context, the Darunavir have enjoyed a surge in popularity as a new generation of PIs bearing a structure-based designed bis-THF ligand that effectively fills in the hydrophobic pocket and maximizes hydrogen bonding interactions with the backbone atoms of the S2-site.[1] A number of bis-THF-derived inhibitors are exceedingly potent and have maintained very impressive potency against multidrug-resistant HIV-1 variants.[1-3] We are interested in the use of continuous-flow approach in order to prepare the bis-THF moiety of PIs. This approach will allow a cascade effect by doing the reduction and the acetylation steps in a closed system.

RESULTS AND DISCUSSION

The functionalization of 2,3-dihydrofuran (**1**) led to the iodo ether intermediate as already stated in the literature (Scheme 1). [2] The subsequent radical cyclization produced the bicyclic acetal **3**, which was converted to the ketone **4** upon ozonolysis in standard batch reactors.[2] Herein we introduced a new approach by continuous flow ozonolysis of intermediate **3**, followed by reduction of the carbonyl ketone of **4** with immobilized borohydride and subsequent resolution by immobilized lipase. As well as the use of $NaBH_4$ described in the literature, this novel condition reaction led to the alcohol **5**. This novel procedure can allow the use of continuous-flow conditions to reach compound **5**.

The literature states that the esterification of the alcohol 5 with lipase P30 leads a mixture of **5** and **6**. [2] This reaction with lipase N435 to produce the acetate **6** as a sole product is under investigation and the success in this step can allow to the use of continuous-flow conditions to synthesize the bis-THF **6**.



Scheme 1: Racemic synthesis, enzymatic resolution route and proposed in the continuous-flow synthesis of bis-THF.

CONCLUSION

The results on the reduction of **4** with immobilized borohydride are promising and can lead to an efficient synthesis of oxygenated bis-THF structures.

ACKNOWLEDGEMENTS

The authors thank CAPES, CNPq, and FAPERJ.

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