Stereoselective Synthesis of an Analogue of the Macrolactone of Isomigastatin

Luiz C. Dias*a, Giovanni W. Amarante*b, Leila S. Conegero, a Fernanda G. Finelli and Gustavo C. Monteiro

*aUniversity of Campinas – Institute of Chemistry – Campinas, SP; bFederal University of Juiz de Fora – Chemistry Department – Juiz de Fora, MG – Brazil

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INTRODUCTION

Isomigastatin (1) was first isolated in 2002 from cultures of Streptomyces platensis (strain NRRL 18993) by Kosan Biosciences researchers (Figure 1). This natural product belongs to the glutarimide polyketide family and it is a precursor of migastatin in its biosynthetic pathway.

![Figure 1. Isomigastatin (1).](image)

Recently, our group developed an approach for the synthesis of the macrolactone of migastatin and analogues. Regarding the biological importance of these skeletons and taking into consideration that isomigastatin analogues have not been explored yet, we decided to extend this strategy in the synthesis of an analogue of the macrolactone of isomigastatin.

RESULTS AND DISCUSSION

Our studies began with an asymmetric aldol addition between acrolein and the titanium enolate derived from N-propionylloxazolidinone to provide the aldol adduct 6 in 87% yield (>95:05 dr). After protection with a silyl group, a stereoselective dihydroxylation of 7 using OsO4/NMO system gave the lactone 8, in 70% yield (>95:05 dr). Protection of 8 with 2,2,2-trichloroacetimidate of PMB in acidic conditions, followed by lactone opening in the presence of excess of LiAlH4 gave the diol 10, in 64% overall yield for two steps (Scheme 1).

![Scheme 1. Preparation of fragment C7-C11 (10).](image)

Selective protection of the hydroxyl group of 10 with TBSCI/imidazole gave the alcohol 11, in 86% yield. Methylation of 11 in the presence of proton sponge and Me2OBF4, followed by removal of PMB using DDO/H2O provided 12, in 79% yield (2 steps). Oxidation of the alcohol with NMO and TPAP gave the corresponding aldehyde, which was used as substrate in the Petasis and Bzowej olefination reaction. The olefin 13 was then obtained in 45% yield (2 steps). Selective deprotection of the silyl group in the presence of a mixture of HF-Py-THF gave the alcohol 14 in 72% yield (Scheme 2).

![Scheme 2. Preparation of macrolactone (17).](image)

Treatment of alcohol 14 with 6-heptenoic acid, DCC and DMAP gave the ester 15, in 87% yield. The alkene ring closing metathesis was performed by using 20 mol% of the Grubbs catalyst II to give 16, in 65% yield. To accomplish the synthesis, the TBS protecting group was removed in presence of HF solution.

CONCLUSION

In summary, a new analogue of the macrolactone of isomigastatin 17 was synthesized in 14 steps with an overall yield of 0.85%. The strategy was based on an efficient asymmetric aldol addition, a highly stereoselective dihydroxylation and a ring closing metathesis. The antitumoral activity of the final product is ongoing and will be reported in due course.

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REFERENCES