Stereoselective Synthesis of an Analogue of the Macrolactone of Isomigrastatin

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INTRODUCTION

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

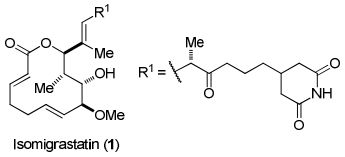
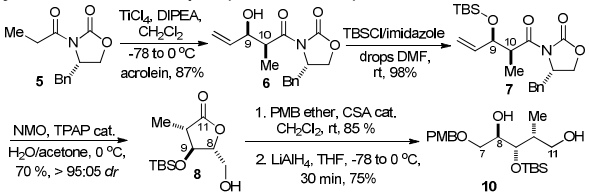


Figure 1. Isomigrastatin (**1**).

Recently, our group developed an approach for the synthesis of the macrolactone of migrastatin and analogues.[2] Regarding the biological importance of these skeletons and taking into consideration that isomigrastatin analogues have not been explored yet, we decided to extend this strategy in the synthesis of an analogue of the macrolactone of isomigrastatin.

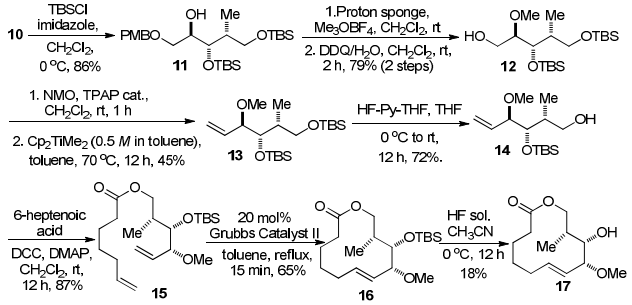
RESULTS AND DISCUSSION

Our studies began with an asymmetric aldol addition between acrolein and the titanium enolate derived from *N*-propionyloxazolidinone to provide the aldol adduct **6** in 87% yield (>95:05 dr). After protection with a silyl group, a stereoselective dihydroxylation of **7** using OsO_4/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 $LiAlH_4$ gave the diol **10**, in 64% overall yield for two steps (Scheme 1).



Scheme 1. Preparation of fragment C7-C11 (**10**).

Selective protection of the hydroxyl group of **10** with TBSCl/imidazole gave the alcohol **11**, in 86% yield. Methylation of **11** in the presence of proton sponge and Me_3OBF_4, followed by removal of PMB using DDQ/H_2O 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**).

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 isomigrastatin **17** was synthetized 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.

ACKNOWLEDGEMENTS

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REFERENCES

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