Synthesis of Polyketide Fragments in Order to Study the Elaiophylin Biosynthesis

Patrícia Prediger,[1] Luiz Carlos Dias.[1,*]

[1] *Instituto de Química, Universidade Estadual de Campinas, UNICAMP, C.P. 6154, 13084-971 Campinas, SP, Brasil.*

**e-mail ldias@iqm.unicamp.br*

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INTRODUCTION

Elaiophylin (**1**), a glycosidic polyketide, was first isolated from the cultures of Streptomyces melanosporus by Arcamone et al.[1a] and by Arai[1b] from a related microorganism. Elaiophylin is a 16-membered macrolide which displays a wide range of bioactivities such as antimicrobial, cell cycle inhibition, apoptosis induction, immunosuppressive, anthelmintic, inhibition of K^+-dependent adenosine triphosphatases, and plant growth inhibition.[2]

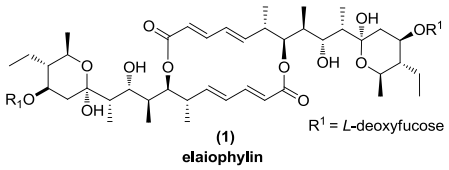


Figure 1. Elaiophylin (**1**).

Due to the pronounced activity showed by this macrolide, we are interested in to investigate its biosynthesis by analyzing the interaction between the elaiophylin enzyme thioesterase and the fragments **2**-**5**.[3]

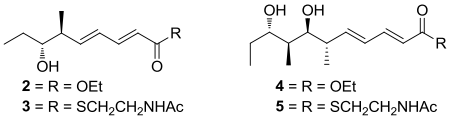
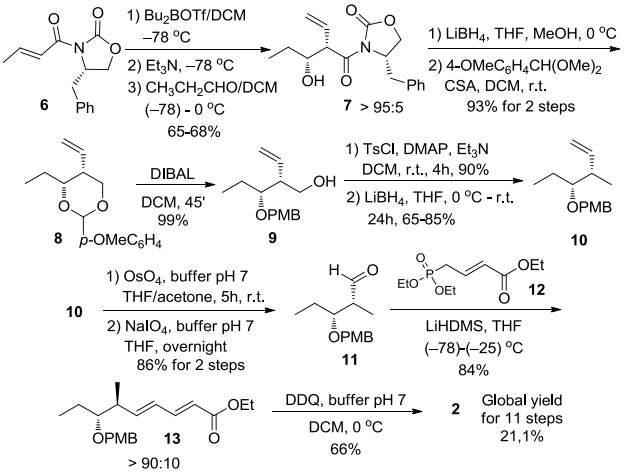


Figure 2. Fragments for studying elaiophylin biosynthesis.

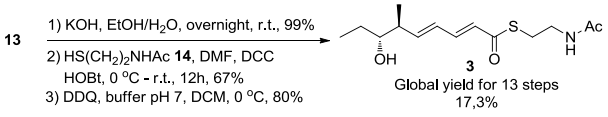
RESULTS AND DISCUSSION

We started our synthesis with an Evans' asymmetric aldol reaction of chiral crotonate imide **6** and propionaldehyde (Scheme 1). The *syn* aldol adduct **7** was obtained in good yield with >95:5 diastereoselectivity. Reductive removal of the chiral auxiliary with $LiBH_4$, followed by diol protection, provided the acetal **8** in 93% yield for 2 steps. The selective reduction of **8** was carried out with DIBAL, furnishing the alcohol **9** in 99% yield. Tosylation of the hydroxyl group under standard conditions followed by reduction of the tosylate using $LiBH_4$ gave **10** in the range of 65-85% yield. We then submitted **10** to the dihydroxylation/oxidative cleavage of the vinyl group, which provided aldehyde **11** in 86% yield for 2 steps. Thus, the HWE olefination with the phosphonocrotonate **12** was carried out to afford the *E*,*E* diene **13** in 84% yield. Finally, **13** was treated with DDQ for the oxidative deprotection in 66% yield.



Scheme 1. Synthesis of fragment **2**.

Aiming the synthesis of fragment **3**, the ester **13** was hydrolyzed and then submitted to the coupling reaction with the thioacetamide **14** in the presence of DCC and HOBt (Scheme 2). The thioester was obtained in 67% yield. DDQ oxidative deprotection provided the desired fragment **3** in 80% yield.



Scheme 2. Synthesis of fragment **3**.

CONCLUSION

We successfully achieved the synthesis of two fragments which will be employed to study the elaiophylin biosynthesis.

ACKNOWLEDGEMENTS

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[2] Hammann, P.; Kretzschmar, G.; Seibert, G. *J. Antibiot.*, **1990**, *43*, 1431.
[3] The biological essays are in progress at University of Cambridge by Dr. Yongjun Zhou and Prof. Dr. Peter F. Leadlay.