Studies toward total synthesis of tautomycetin

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INTRODUCTION

Tautomycetin is a polyketide natural product recognized as an inhibitor of serine/threonine phosphatases type I.[1] In spite of this important activity, there is no total synthesis described in the literature.[2] For this reason, we have proposed a project aiming to the total synthesis of tautomycetin. We wish to describe here our approach to fragments C7'-17 and C1-C12 of tautomycetin.

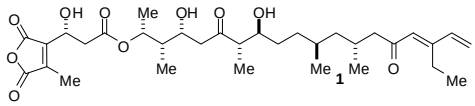
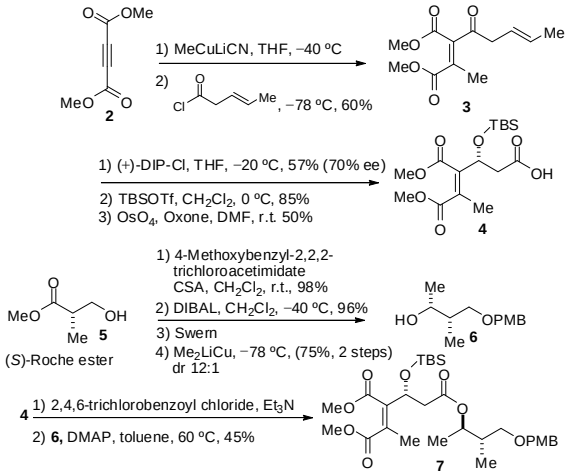


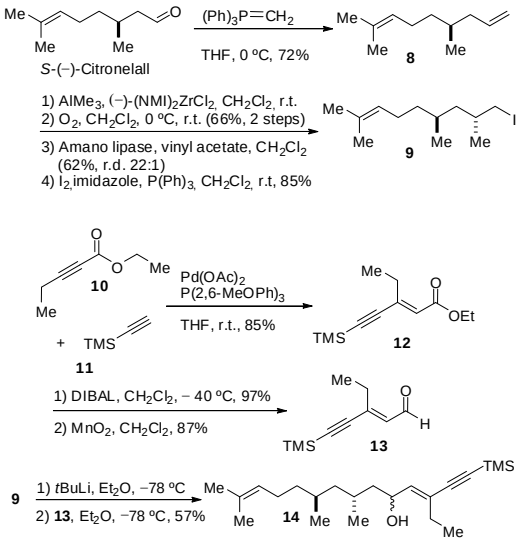
Figure 1. Tautomycetin **1**.

RESULTS AND DISCUSSION



Scheme 1. Synthessis of the C7'-17 fragment **7**.

Alkyne **2** was added to MeCuLiCN followed by addition of penten-3-enoyl chloride to afford **3**. Compound **3** was converted into **4** through asymmetric reduction, protection of the hydroxyl group and oxidative cleavage of the olefin moiety. Alcohol **6** was synthesized from Roche ester through protection of its primary hydroxyl group, reduction of the ester group, oxidation and Me_2LiCu addition to the intermediate aldehyde. Compounds **4** and **6** were coupled by Yamaguchi esterification to afford the C7'-17 fragment **7** (Scheme 1).



Scheme 2. Synthesis of C1-C12 fragment **12**.

S-(–)-citronellal was converted into terminal olefin **8**, by Wittig reaction. This olefin was the substrate for the ZACA reaction which lead to asymmetric methyl addition with concomitant primary hydroxyl formation.[3] Finally, modified Appel reaction changing the hydroxyl for iodine provided iodide **9**. The ester **12** was prepared by a cross coupling reaction between compounds **10** and **11**. The aldehyde **13** was synthesized from ester **12**, through reduction followed by oxidation. Compounds **9** and **13** were coupled by halogen-lithium exchange of **9**, followed by addition of **13** providing **14** in 57% yield (scheme 2).

CONCLUSION

We successfully achieved the synthesis of two large fragments of Tautomycetyn.

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