Chemoenzymatic synthesis of the C_{14}-C_{21} fragment of the Amphidinolides T Series

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INTRODUCTION

Dinoflagellates of the genus *Amphidinium* posses a particularly prolific biosynthetic machinery.[1] For instance, over thirty macrolides have been isolated from *Amphidinium* strains, displaying extremely potent cytotoxicity against tumor cell lines.[2] Among them, the Amphidinolide T family comprises 19-membered macrolactones possessing seven or eight stereogenic centers, a highly substituted tetrahydrofuran ring, an α–hydroxy ketone, an exocyclic methylene group and a homoallylic ester linkage.[3] Due to their high biological activity and intriguing polyoxygenated structure, we became interested in their preparation and designed a chemoenzymatic approach to the C_{14}-C_{21} fragment, using as starting material cyclohexadienediol **1** produced by biotransformation of bromobenzene, as shown in Fig.1.[4]

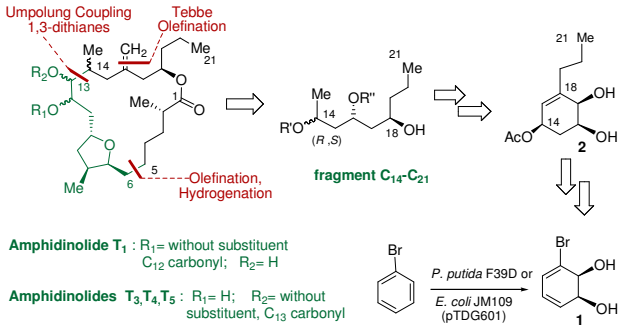
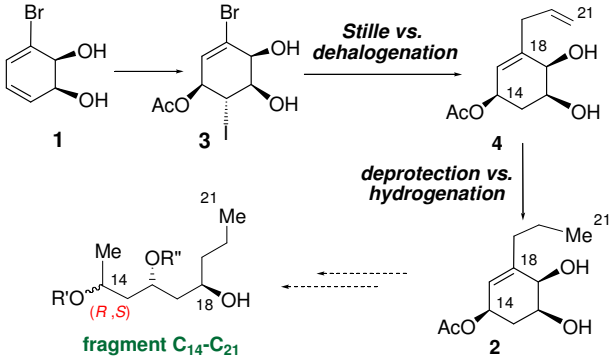


Figure 1. Approach to the C_{14}-C_{21} fragment of the Amphidinolide T series from monosubstituted arenes.

RESULTS AND DISCUSSION

Precursor **2** is an advanced intermediate of the synthetic route. It was prepared in very good yield, 47%, through a seven step sequence from bromobenzene. Different approaches to this compound were designed, based on changing the order of some reactions of the synthetic sequence. For instance, the Stille reaction and the dehalogenation were switched in the synthesis of compound **4**; similarly diol deprotection and hydrogenation were switched for compound **2**, Scheme 1.

Starting from enantiopure diol **1**, the best sequence includes protection of diol, halohydrin formation (Prevost), dehalogenation, and then Stille reaction, followed by deprotection of the diol group and final hydrogenation of the terminal olefin.



Scheme 1. Stereocontrolled synthesis of **2**, strategies toward C_{14}-C_{21} fragment.

Details of the optimization to prepare intermediates **4** and **2**, will be presented.

CONCLUSION

Intermediate compound **2** is prepared in very good yield from cyclohexadienediols of microbial origin.

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