Chemoenzymatic Approach to the stereoselective synthesis of C_6-C_{13} fragment of Amphidinolides T Series

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INTRODUCTION

In the search for novel bioactive compounds, natural products isolated from marine organisms show a wealth of pharmacological and structural diversity.[1] Amphidinolide-T, marine macrolide, exhibit extremely potent cytotoxicity against tumor cells lines.[2] These natural products are 19-membered macrolides, 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]

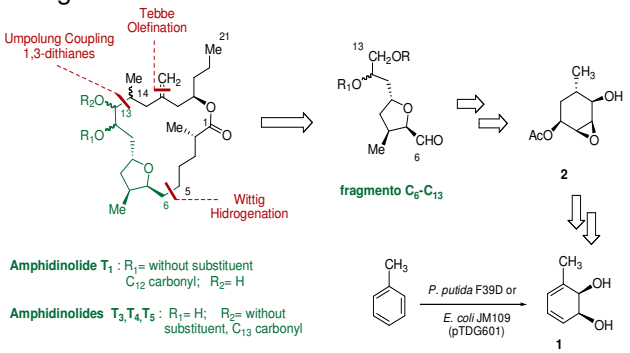


Figure 1. Approach to Amphidinolides T Series and C_6-C_{13} fragment from monosubstituted arenes

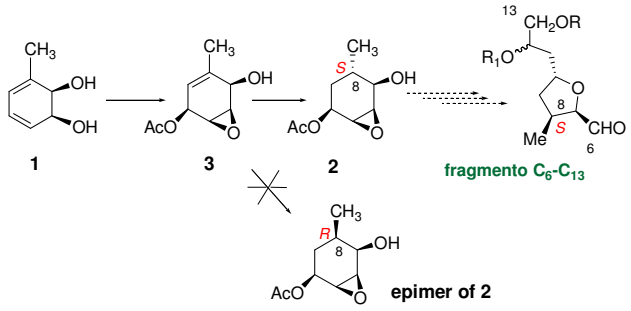
Due to its high biological activity and intriguing polyoxygenated structure we became interested in its preparation and designed a chemoenzymatic approach to its C_6-C_{13} fragment, using as starting material cyclohexadienediol **1** produced by biotransformation of toluene, as shown in Fig.1.[4]

RESULTS AND DISCUSSION

Starting from toluene, epoxide **3** was prepared in 50% overall yield from enantiopure diol **1** through a concise sequence consisting of diol protection, regio and stereoselective halohydrin formation (Prevost), deprotection of diol system and basic conditions to afford β-epoxide. For stereoselective hydrogenation of **3**, different type of catalyst, as well as % of them, solvents and hydrogen pressure were tested.

Compound **2** has to be persuade with absolute configuration "*S*" at C_8. Whereas some solvent conditions afford C_8 with the desired configuration *S*, other solvents give the epimer at C_8, Scheme 1.

Best conditions found to produced intermediate **2,** will be discussed. Within NMR, nOe and europium complex studies, done for determination of absolute configuration at C_8 for both compounds, **2** and its epimer.



Scheme 1. Stereoselective hydrogenation step, proposed synthesis of C_6-C_{13} fragment

CONCLUSION

Epoxide **3**, precursor in the approach to fragment C_6-C_{13} of Amphidinolides T series, was prepared in four steps, with good yield from cyclohexadienediol **1** of microbial origin.

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REFERENCES

1. Ireland, C.; Copp, B.; Foster, M.; Mc Donald, A.; Radisky, D.; Swersey, J. In *"Marine Biotechnology"* Plenum Press: New York, **1993**; Vol. 1, cap. I.
2. a)Chakraborty, T. K.; Das, S. *Curr. Med. Chem. – Anti-Cancer Agents.* **2001**, *1*, 131. b) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77.
3. Kobayashi , J.; Kubota, T.; Endo , T.; Tsuda , M. *J. Org. Chem.* **2001**, *66*, 134.
4. Carrera I.; Brovetto M.; Seoane G.;*Tetrahedron* **2007**, *63*, 4095.