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Asymmetric synthesis of a model compound for the cyclohexenone core of ambuic acid

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Abstract—A model compound for the central core of ambuic acid has been prepared chemoenzymatically from toluene in enantiomerically pure form. An approach to the introduction of the C-9 side chain has also been investigated.

1. Introduction

A group of molecules with highly functionalized cyclohexenone cores and bearing several stereogenic centers in their structures have been found in Nature, isolated mainly from fungal sources.[1–5] They exhibit interesting biological properties such as antibiotic, antimicotic, and antitumoral activity, among others.[6]

Ambuic acid **1** belongs to this group of molecules (Fig. 1). It has been isolated from *Pestalotiopsis* spp. and from one *Monochaetia* sp.,[7] which are found as endophytic fungi in several plants;[8] it has shown an interesting antifungal activity toward several species of fungal plant pathogens, thus suggesting a symbiotic association. Its structure[9] consists of a highly functionalized cyclohexenone bearing three side chains.

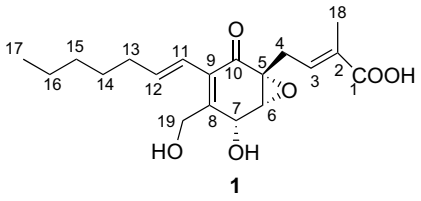

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Figure 1. Ambuic acid structure and numbering.

Since only a few syntheses of this molecule have been reported,[10,11] it was interesting for us to propose the construction of a simple, but homochiral model, by means of an efficient and well-known chemoenzymatic methodology[12] using a mutant strain of *Pseudomonas*, *Pseudomonas putida* F39/D.[13,14]

In the previous work, we have reported the preparation of polyhydroxylated chiral enones of type **I** from aromatic compounds.[15] The trihydroxyenone prepared from toluene ($R = CH_3$, Scheme 1) is a suitable starting material for preparing a chiral model for (+)-ambuic acid, bearing a methyl group on carbon 5 and lacking the side chains on carbons 8 and 9 as shown in the retrosynthetic analysis (Scheme 1). The appropriate starting material for ambuic acid total synthesis would be an enone of type I obtained from a microbial metabolite derived from phenylacetaldehyde (Scheme 1).

Starting from enone **2**, we are able to perform convenient protection–deprotection steps in order to achieve oxirane ring closure to give **5**. With subsequent inversion of the configuration of the carbon, which bears the hydroxyl group, we are able to obtain the desired model molecule for ambuic acid **7**.

2. Results and discussion

According to the synthetic plan shown in Scheme 2, trihydroxyenone **2** was selectively protected on the less hindered secondary hydroxy group by forming a silylether with bulky dimethylthexylsilyl chloride (THSCl) to give **3**.[16] Next, the remaining secondary alcohol on **3** was

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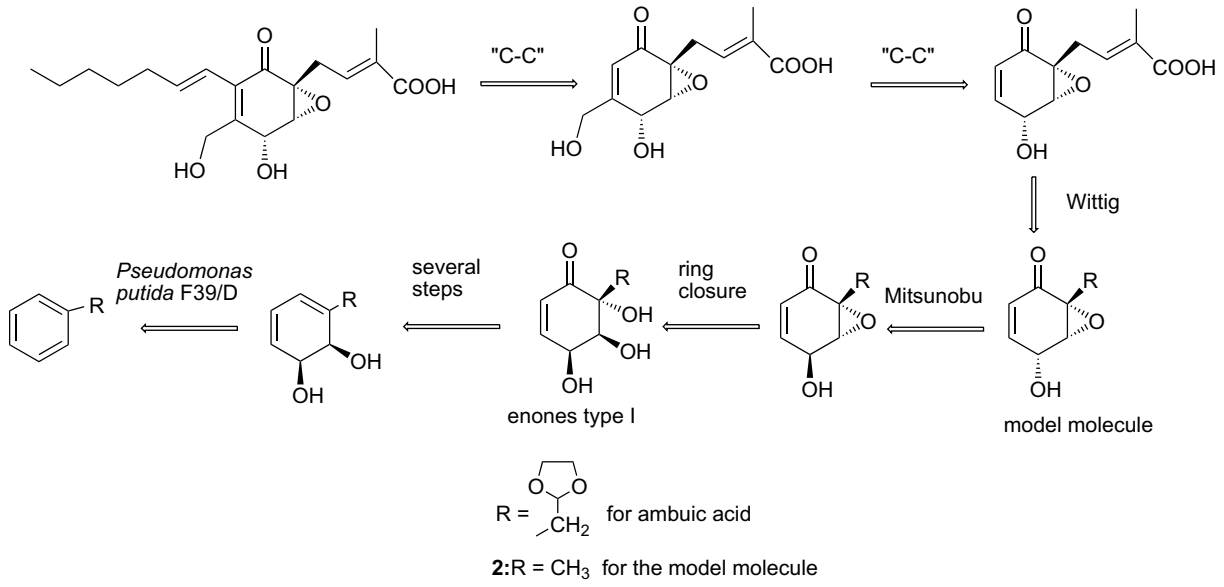
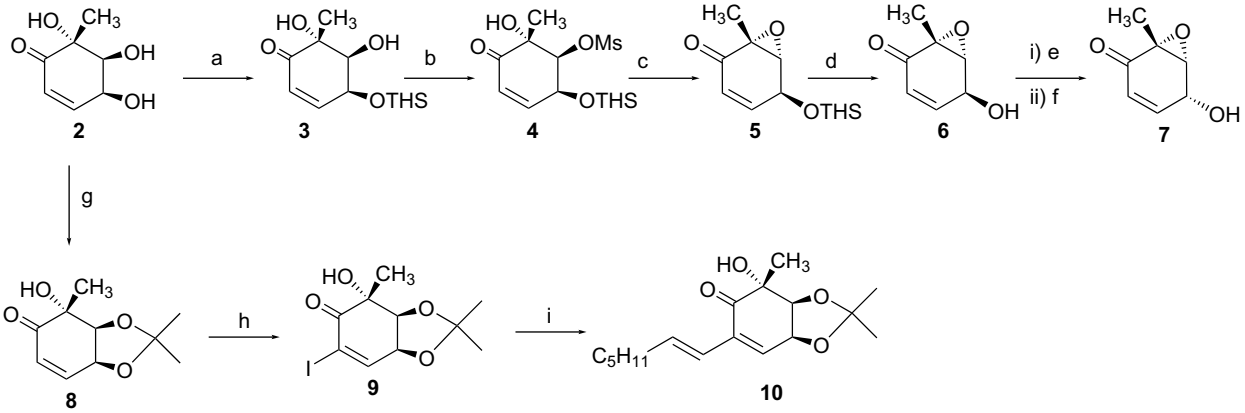


Scheme 1. Retrosynthetic analysis of ambuic acid.



Scheme 2. Preparation of model molecules. Reagents and conditions: (a) THSCl, imidazole, DMF, 0 °C, 98%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 45%; (c) K_2CO_3, 18-crown-6, THF, 0 °C, 76%; (d) Py-HF, THF, 0 °C to rt, 64%; (e) PPh_3, benzene, rt, then *p*-nitrobenzoic acid, rt, then DEAD, rt; (f) K_2CO_3, MeOH, −20 °C, 22%; (g) DMP, acetone, rt, 95%; (h) I_2, DMAP, CH_2Cl_2, 50 °C, 77%; (i) *trans*-1-heptenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, THF–H_2O, reflux, 50%.

mesylated to **4**, to provide a good leaving group for the ring closure to **5**.

Several reagents were assayed for the introduction of the leaving group on carbon 3 (Table 1).

Neither triflate nor tosylate could be obtained with satisfactory yields, but the mesylation of **3** under the conditions shown in entry 2 was carried out with acceptable results.

The treatment of **4** in basic medium permitted oxirane ring closure, leading to compound **5** and thus demonstrating that the proposed methodology is useful for the preparation of chiral epoxyenones. The following steps consisted of the deprotection of the silylated hydroxyl group and further the inversion of configuration through a Mitsunobu reaction, leading to the desired model molecule of the central core of ambuic acid **7**. The Mitsunobu reaction proved

Table 1. Reagents and conditions for introducing a good leaving group on carbon 3

Entry	Reagents and conditions	Products
1	*p*-Toluensulfonylchloride, Py, rt	No reaction in 72 h
2	CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C	**4** (45%) + **5** (39%)
3	CH_3SO_2Cl, Py, CH_2Cl_2, 0 °C	**4** (13%) + decomposition products
4	$(CF_3SO_2)_2O$, DMAP, CH_2Cl_2, 0 °C	**4** (20%) + **11** (traces)* + decomposition products

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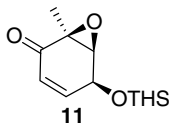

troublesome, although it could be optimized by the addition of *p*-nitrobenzoic acid before DEAD with acceptable yield (Scheme 2).

We also investigated the introduction of a heptenyl side chain corresponding to carbon 9 of the ambuic acid, on acetonide **8**, as shown in Scheme 2. This was successfully achieved by α-iodination[17] and further Suzuki coupling[18] with *trans*-1-heptenylboronic acid[19] in 39% overall yield.

All the compounds were purified by column chromatography, their optical rotations were determined and they were fully characterized by spectroscopic methods.

3. Conclusion

We have developed a chemoenzymatic synthetic methodology for the synthesis of chiral epoxy enones, thus obtaining a valuable chiral model molecule for ambuic acid. We have also demonstrated the introduction of alkene side chains by means of Suzuki C–C coupling on this highly functionalized core. We are currently investigating the total synthesis of ambuic acid using sulphonylcarbanion chemistry for the introduction of the hydroxymethylene group on carbon 8.[20] We are also attempting the synthesis of other natural epoxyenones[6] such as bromoxone and parasitenone.

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