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Microbiological Transformations. 30. Enantioselective hydrolysis of racemic epoxides : the synthesis of enantiopure Insect Juvenile Hormone Analogs (Bower's compound)

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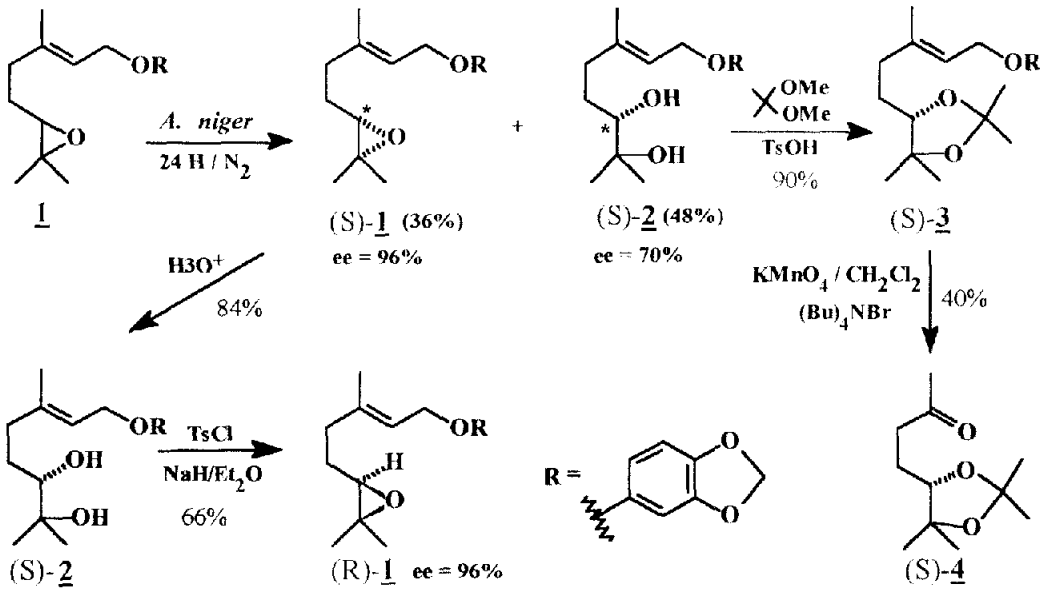
Abstract : The enantioselective epoxide biohydrolysis of the racemic benzodioxole 6,7-epoxygeraniol derivative **1** has been achieved using the fungus *A. niger*. This new type of preparative scale bioconversion allows the synthesis of both enantiomers of Bower's compound, an analogue of insect juvenile hormone. Biological tests showed that the 6(R) enantiomer was about ten times more active than the 6(S) enantiomer against the yellow meal worm *Tenebrio molitor*.

As stereochemistry governs the biological activity of many compounds, chirality is emerging as a key issue in pharmaceutical or agrochemical research. Because of their high synthetic versatility, and also since some of them are potent biologically active compounds, many efforts have been devoted to the preparation of epoxides of high enantiomeric purity. In the course of our studies aimed to perform the preparation of such enantiopure products, we have recently described a new preparative scale bioconversion method allowing for the microbiologically mediated hydrolysis of several epoxides[1,2]. Interesting results have been obtained in this context, that suggest that biohydrolysis of racemic epoxides could be a new tool of high preparative value to the organic chemist. We described here an application of this enantioselective biohydrolysis, using the fungus *Aspergillus niger* (LCP 521), to the synthesis of either enantiomer of Bower's compound **1** that is known to be a potent analogue of insect juvenile hormone[3]. These hormones are necessary in insect development for the maintenance of larval characteristics and for egg maturation[4]. Some racemic radiolabeled analogues carrying a photoactivable group have been recently synthesized in order to allow tagging of the juvenile hormone receptors[5]. Obviously, it was of interest to prepare specifically both enantiomers of these compounds in enantiopure form, in order to test them separately and to use the (possibly) more potent enantiomer as a precursor for further synthesis of photoaffinity labels.

When submitted to a buffered (pH 7) suspension of the fungus *A. niger* for 22 hours under anaerobic conditions (N_2), racemic[6] Bower's compound **1** (0.5 g) was partially hydrolyzed to diol **2** (48% isolated yield). The remaining epoxide **1** (36% isolated yield) showed an excellent enantiomeric purity (ee = 96%) and the formed diol was also optically active (ee = 77%).

The enantiomeric excess of diol **2** was determined by HPLC analysis of its (-)- camphanyl derivative[7]. Similarly, the ee of **1** was determined after acid hydrolysis to its diol. As we showed previously, this does not alter the stereochemistry at C(6)[7]. The absolute configuration at C(6) was determined by using a chemical correlation of **2** with the corresponding keto-acetonide **4**, which has been previously described by Koga et al.[8]. Thus, diol **2** was transformed into its acetonide **3**, which was oxidized, via a phase-transfer technique, to the keto-acetonide **4** ($[\alpha]_D^{25}$ = -10 (c 1.95; MeOH) (lit.[8] $[\alpha]_D^{27}$ = -14.8 (c 1.4; MeOH)). This result allowed the assignment of the (S) absolute configuration at the carbon atom C(6) of diol **2** and of the remaining epoxide **1**.



The other enantiomer of Bower's compound (the 6(R)-epoxide **1**) could be easily obtained from 6(S)-**1**. Indeed, acid hydrolysis of 6(S)-**1** (ee = 96%) led to 6(S)-**2**, which, upon reaction with tosylchloride in the presence of sodium hydride, afforded 6(R)-epoxide **1** (ee = 96%) after cyclisation involving total inversion at the stereogenic C(6) carbon atom.

Each (6S)-**1** and 6(R)-**1** enantiomer of Bower's compound was tested for its juvenile hormone activity. Thus, exposure of *Tenebrio molitor* pupae at 10 ng/pupae to 6(R)-**1** is enough to induce morphogenic activity, whereas 100 ng/pupae of 6(S)-**1** must be used to obtain the same biological effect. Therefore, we can conclude that there is a biological specificity to the 6(R) enantiomer, this one being superior to the 6(S) enantiomer by a factor of about 10.

As a conclusion this work shows that enantioselective biohydrolysis of racemic epoxides can be very easily and conveniently achieved at the preparative scale, just by using a suspension of the fungus *A. niger* cells. This very efficient method thus constitutes a very powerful tool allowing for the synthesis of optically active epoxides via an environmentally gentle methodology. Work is in progress in our laboratory in order to explore, using several other racemic or prochiral epoxides, the scope and limitations of this highly interesting microbiological transformation.

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