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Preparation of Optically Active Cyclohexanediols and (+)-α-Hydroxycycloheptanone by an Enzyme Catalysed Stereoinversion/Oxidation Process

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Abstract: (±)-*trans* and *cis* Cyclohexane-1,2-diols have been shown to undergo a double stereoinversion process to give *trans* (*S,S*)-cyclohexane-1,2-diols on incubation with the fungus *C. cassiicola*.

Optically active diols which possess a C_2-axis of symmetry are compounds which can serve as chiral starting materials or as chiral auxiliaries in asymmetric synthesis.[1] For example, enantiomerically pure *trans* cyclohexane-1,2-diol **1**[2] has been employed in asymmetric alkylations,[3] conjugate additions to α,β-unsaturated esters[4] and for the preparation of chiral phosphines[5] and crown ethers.[6]

In connection with our work on the enzyme catalysed hydrolysis of cyclohexene epoxide with various fungi we made the unexpected observation that the microorganism *Corynosporium cassiicola* was able to interconvert the 1(*R*,), 2(*R*) and 1(*S*), 2(*S*) enantiomers of the product, *trans* cyclohexane-1,2-diol. As the reaction proceeded the 1(*R*), 2(*R*) enantiomer was converted to the 1(*S*), 2(*S*) enantiomer (Figure 1). To our knowledge the only other interconversion of this type was reported by Hasegawa and coworkers. They documented a microbial stereo-inversion, catalysed by two dehydrogenase enzymes in the fungus *Candida parapsilosis*, in which terminal (*R*) -1,2-diols can be converted into (*S*)-1,2-diols in high molar yields.[7]

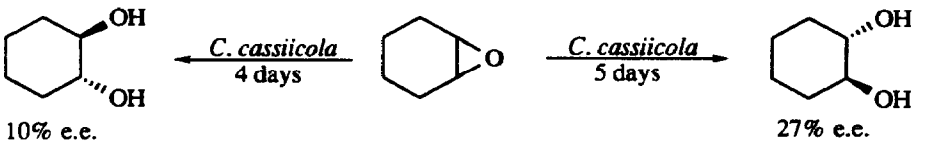


Fig. 1.

From our initial result we became interested in the possibility of obtaining optically active cyclic 1,2-diols by a microbial double stereoinversion process which would allow access to a single enantiomer of a *trans* cyclo-

alkanediol from its antipode or racemate obviating the need to discard an unwanted enantiomer. Incubation of the (±)-*trans* diol **1** or *meso cis* diol **2** with whole cells of *Corynosporium cassiicola* over 5 days gave optically pure (>99% e.e.)[8] (+)-1(*S*), 2(*S*)-**1** in 50% and 41% yield respectively (Figure 2). In a control experiment, incubation of the 1(*R*), 2(*R*)-diol **1** over 4 days gave the *meso* diol **2** (26%) and the 1(*R*), 2(*R*)-*trans* diol **1** (27%, 48% e.e.) while incubation of the 1(*S*), 2(*S*)-diol **1** over the same time period showed no loss of optical purity.

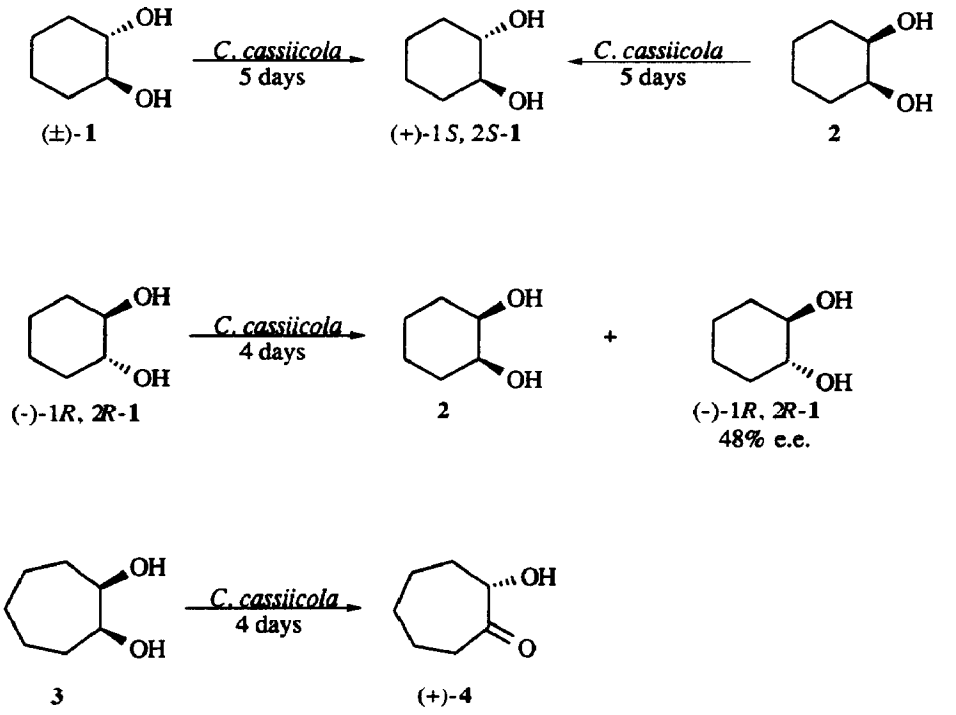
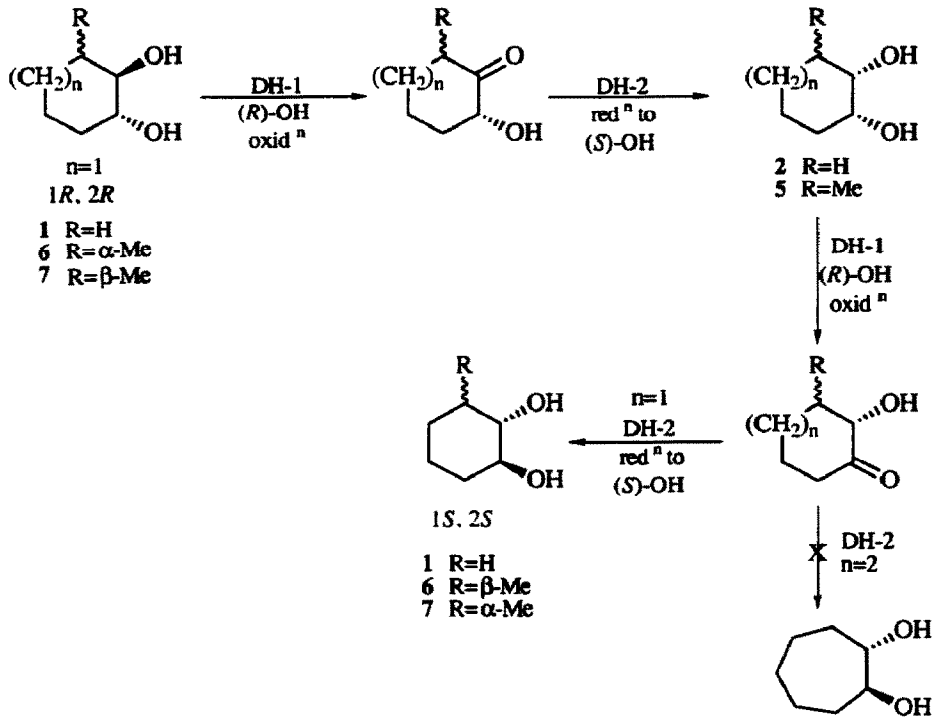


Fig. 2. Some biotransformations catalysed by *C. cassiicola*

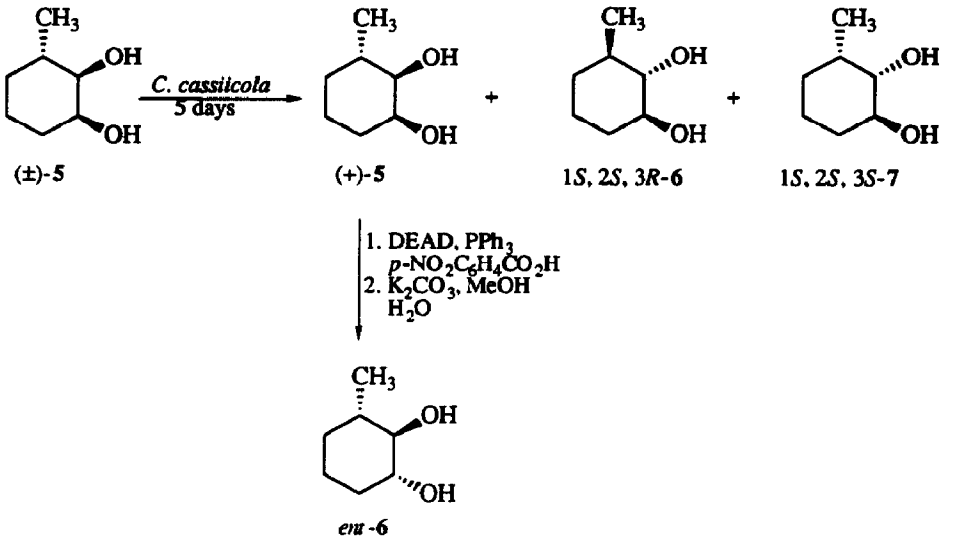
It must be assumed from these biotransformations that two or more dehydrogenase enzymes (DH-1 and DH-2) in this microorganism catalyse the irreversible formation of the 1(*S*), 2(*S*) isomer of the diol **1** *via* tandem oxidation-reduction reactions (Scheme 1). Interestingly, *cis* cycloheptane-1,2-diol **3**[9] gave the (+)-(*S*)-α-hydroxyketone **4**[10] (50%, 83% e.e.). The absolute configuration of compound **4** was determined by comparison of its c.d. curve, which exhibited a positive Cotton effect, with that of (*R*)-acetoin.[11] Evidently compound **4** is not a substrate for the second enzymic transformation mediated by DH-2. Biotransformation of the non symmetrical (±)-*cis, trans* 3-methylcyclohexane-1,2-diol **5** gave recovered starting diol (+)-1(*S*), 2(*R*), 3(*S*)-**5** (32%, 40% e.e.). The absolute configuration of this dextrorotatory diol was deduced using

established data.[12] In addition, two *trans* diols 1(*S*), 2(*S*), 3(*R*)-**6** (81% e.e.) and **7**[13] (88% e.e.) (17% combined yield; ratio **6**:**7**; 1:1.5) were isolated (Scheme 2). The racemic diols **6** and **7** (61% yield, ratio **6**:**7**; 1:4) were made as standards by performic acid oxidation of 3-methylcyclohexene followed by hydrolysis of the formate esters. The absolute configuration of the 1(*S*), 2(*S*), 3(*R*)-diol **6** was determined by Mitsunobu inversion of the C-1 hydroxyl group of the optically active recovered (+)-diol **5** to give *ent* **6**. While the absolute configuration of the diol **7** remains undetermined we surmise that the major enantiomer present in the mixture is the 1(*S*), 2(*S*), 3(*S*)-diol (see Scheme 2).



Scheme 1

Thus we believe the process for **5** is enantioselective, the 1(*R*), 2(*S*), 3(*R*) enantiomer being processed more rapidly. However, each enantiomer gives a different diastereomeric diol product. Hence the (*R*)-selective DH-1 and (*S*)-selective DH-2 can accept both (*R*) and (*S*) orientations of the methyl group. We are currently extending the range of substrates which will be accepted by this microorganism to give new chiral diols/α-hydroxyketones for use as novel chiral auxiliaries.



Scheme 2

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8. The enantiomeric excess of the diols **1**, **6** and **7** was determined by conversion to the corresponding di-1,2-O-trifluoroacetates and comparison to their racemic counterparts by gas chromatography (G. C.) over a chiral stationary phase (Lipodex D).
9. Diols **3** and **5** were prepared from the corresponding alkenes (OsO_4, acetone/water, NMO).
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