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MICROBIALLY MEDIATED ENANTIOSELECTIVE HYDROLYSIS OF RACEMIC ACETATES

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ABSTRACT: The enantioselective hydrolyses of a series of racemic hydroaromatic acetates by Rhizopus nigricans to produce optically active alcohols are described. A rule predicting the absolute stereochemistry of the resulting alcohols is proposed.

While a variety of methods exist for resolving compounds and for establishing their absolute stereochemistry, there are very few techniques that permit simultaneous solution of both problems. In this communication we wish to describe a method for resolving esters and assigning the absolute configuration about the carbinol carbon through the use of a microbially mediated hydrolysis. For some time we have been interested in determining the absolute stereochemistry of metabolites obtained from aromatic substrates;[2] in the course of these studies the need for preparing useful quantities of optically active transformation products of these metabolites became apparent. A preparative method utilizing microorganisms, or enzymes, appeared capable of yielding optically active alcohols whose configurations could be predicted with greater certainty than those of alcohols obtained by other methods. Although many enantioselective hydrolyses of methyl and ethyl esters of racemic acids have been reported,[3] there were few reports of the hydrolyses of acetates or benzoates of racemic alcohols.[4] One report by McGahren et al.[4b] on the enantioselective hydrolysis of 1-octyn-4-yl benzoate, using a strain of Rhizopus nigricans, prompted our use of this organism for the work described here.[5] In order to determine whether the enzyme(s) present in R. nigricans (R-70) would enantioselectively hydrolyze acetates, as well as benzoates, we examined the hydrolyses of the benzoate and acetate of methyl phenyl carbinol and found that the enantiomeric excesses (e.e.) of 1 obtained from hydrolysis of the acetate was greater than that obtained from the benzoate. This result led us to examine the enantioselective hydrolyses of the acetates listed in Table 1 in preference to other esters. For data on the absolute configuration of compounds investigated see literature references in Table 1.

The absolute configurations of the carbinols produced were consistently the ones shown in Fig. 1. In the Cahn-Ingold-Prelog convention, this is the one designated as R in most cases, but in one instance (compound 3) the rules of this convention require the S designation. The configurations were unaffected by variations in ring size (compounds 5, 6 and 7) or by the acyclic nature of some of the compounds. When the methylene group adjacent to the carbinol of

the cyclic esters was substituted with a trans-disposed bromine atom, the relative size of the substituted methylene is "effectively larger" than that of the fused aromatic ring. In the case of the acyclic compounds, replacement of the hydrogen on the methyl group of compound 1 by a chloride atom (2) or methyl acetylene (3) does not affect the relative sizes of the aromatic ring and the methylene group. On the basis of these results we propose a rule which states that the enantiomer shown in Fig. 1 is more rapidly hydrolyzed than its antipode, if R_1 is "effectively larger" (bulkier) than R_2. For the compounds in Table 1 a methylene group was always "effectively smaller" than a fused aromatic moiety. While most of substrates described here are benzylic acetates, the results of the hydrolysis of compound 12 suggest that the enzyme also functions with non-aromatic acetates.

In addition to verifying the configurations assigned on the basis of these hydrolysis experiments, it is also important to compare these results with those obtained using the most reliable general chemical method available, i.e. Horeau's method.[12] This method has been used to assign the configurations of compounds 1, 5 and 7. The configuration of 1 and 5 agree with tnose assigned by the microbial hydrolysis procedure, while the configuration assigned to 7 using Horeau's method was shown to be incorrect.[6] Enantioselective hydrolysis, however, correctly assigns the configuration of 7 although the e.e. obtained is less than that noted for the other alcohols.

Since the absolute stereochemistry of the alcohol 3 was unknown, its configuration was determined by chemical transformation to (S)-methyl O-acetyl mandelate [11] (Fig. 2).

Mori and Akao[4a] have recently described the use of Bacillus subtilis var. niger to hydrolyze a series of acetates of alkyl/alkynyl carbinols, α-hydroxy esters and 1. In the latter case the configuration of the alcohol formed is S, i.e. opposite to that observed in our hydrolyses. The two sets of results suggest that the configuration of the alcohol that forms in the hydrolysis can be controlled by an appropriate choice of the microorganism.

Figure 1

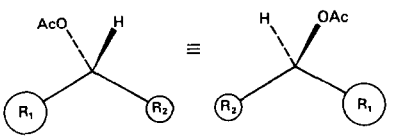
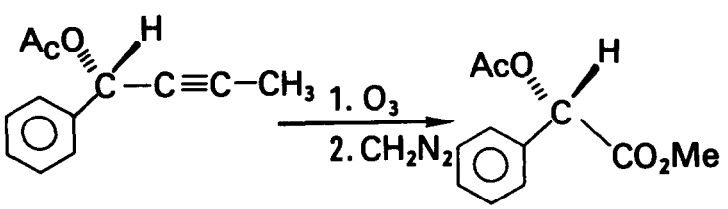
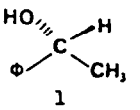


Figure 2



Microbially Mediated Hydrolyses[16] of Racemic Acetates

Compound formed	Config.	ee	ref.	Compound formed	Config.	ee	ref.
1	R	78	7	7	R	28	6
2	R	62	13	8	R	43	6
3	S	51	11	9	R	54	6
4	R	71	9	10	1R, 2R	58	14
5	R	78	10	11	1R, 2R	98	2a
6	R	83	6	12	1R, 2R	50	15



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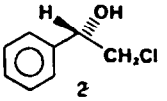

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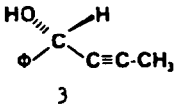

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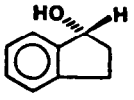

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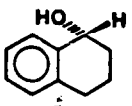

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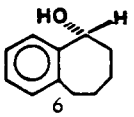

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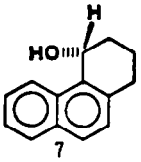

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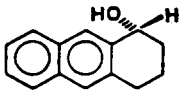

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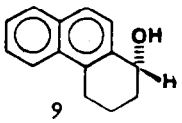

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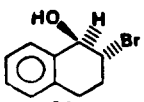

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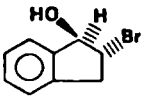

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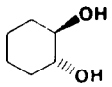

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11. The absolute stereochemistry of the alcohol [α_D = -8.6° ($CHCl_3$, C = 1.75, e.e. 61%] was established by ozonolysis of the acetate and methylation of the resulting acid to yield (+)(S)-methyl O-acetyl mandelate $[\alpha]_D^{25}$ +87.6° ($CHCl_3$, C = 0.36). L-(+)-mandelic acid was methylated with diazomethane and acetylated with acetic anhydride in pyridine to yield (+) (S)-methyl O-acetylmandelate $[\alpha]_D^{25}$ +144.4° ($CHCl_3$, C = 2.26).
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14. The configuration of this compound was determined by acetylation and reduction of the bromo acetate to [S]-tetral-1-ol of established configuration.
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16. The hydrolyses were carried out by adding approximately 250 mg of the appropriate acetate (either neat or in 1 ml of THF) to a 2-day shake culture (250 ml in a 1-l Erlenmeyer) of R. nigricans grown on potato dextrose broth. The broth was prepared by filtering a boiled suspension of 400 gm of diced potatoes, 40 gm glucose and 2l of distilled water. After inoculation, the flask was shaken for 2 days and the substrate added. Shaking was resumed for 8-16 hrs or until approximately 1/3 of the racemic acetate had been hydrolyzed. The mixture was then extracted with ethyl acetate and the alcohol and unhydrolyzed acetate separated by thick layer chromatography.

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