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BIFUNCTIONAL CHIRAL SYNTHONS VIA BIOCHEMICAL METHODS.
VII. OPTICALLY-ACTIVE 2,2'-DIHYDROXY-1,1'-BINAPHTHYL.[1]

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Summary: Optically-active binaphthols (1R and 1S) have been prepared via microbial enantiospecific hydrolysis of axially-disymmetric (±)-2,2'-diacetoxy-1,1'-binaphthyl.

A variety of stereochemical investigations have been successfully conducted using the optically active 2,2'-dihydroxy-1,1'-binaphthyls (binaphthols). For example, the chiral binaphthols, 1R and 1S can be converted into chiral catalysts for asymmetric hydrogenation[2] or into chiral crown ethers[3], useful as stereoselective complexing agents. Moreover, they can serve as chiral auxiliaries to form chiral hydride reagents, important in the commercial synthesis of prostaglandins[4]. Until now the racemic binaphthol has been resolved only by classical means involving the tedious separation of the diastereomeric derivatives[5], or via chromatographic resolution upon an HPLC column packed with chiral stationary phase[6]. Herein, we report a facile method for the preparation of 1R and 1S of high optical purity via microbial enantiospecific hydrolysis of (±)binaphthol diacetates (2).

Two kinetic resolution steps are operating in tandem during the enzymatic hydrolysis of racemic axially-disymmetric diacetates (A and B).

$$A \xrightarrow{k_1} P \xrightarrow{k_2} R$$

$$B \xrightarrow[k_3]{} Q \xrightarrow[k_4]{} S$$

The enantiomeric monoacetates (P and Q) are formed at varying rates; in turn, they are further hydrolyzed to the diols (R and S) as shown. The optical purity of each fraction is dependent on the magnitude of the four relative second order rate constants[7] (k_1, k_2, k_3 and k_4). When the enzyme retains the same stereochemical preference ($k_1 > k_3$ and $k_2 > k_4$) and the rate constants of the second parallel steps are greater or equal to those of the first ($k_2 \geq k_1$ and/or $k_4 \geq k_3$), only then can B and R accumulate in optically pure forms. This kinetic pattern is illustrated by the ensuing examples. Although a wide variety of microorganisms were found to cleave the diacetoxy groups of (±)2, two fungi, *Absidia glauca* ATCC 6776a[8] and *Rhizopus arrhizus* ATCC 11145, were uniquely suited to catalyze this stereospecific hydrolysis in high yields. In a typical experiment, (±)2 (200 mg) was exposed to *A. glauca* in 200 ml of Vogel's medium[9] at pH 5.5. At various intervals, the extent of conversion and the enantiomeric excess (*ee*) of the diacetate (2S + 2R), monoacetate (3S + 3R) and diol (1S + 1R) fractions were determined[10] (Fig. 1). Termination of the reaction at approximately 50% conversion afforded 1S (72 mg) ($[\alpha]_D^{25}$ = -34.2°, THF; lit.[11], $[\alpha]_D^{23}$ = -38°, THF) and 2R (68 mg) with *ee* of 0.90 and 0.74 respectively. The apparent relative rate constants[11] were calculated to be: $k_1 = 12.5 \pm 4.1$; $k_2 = 205 \pm 8$;

$k_3 = 1$; $k_4 = 3.7 \pm 1.3$. Based on the computer generated graphs (Fig. 1A, 1B), the maximal chemical yields obtainable for the diacetate (**2R**) and the diol (**1S**) with *ee* of 0.95 are in the range of 40% for each species. *R. arrhizus* also preferentially hydrolyzed the *S*-acetoxy groups of (±)**2** and gave the apparent relative kinetic constants of $k_1 = 10.7 \pm 1.0$, $k_2 = 308 \pm 35$, $k_3 = 1$, and $k_4 = 9.3 \pm 1.0$.

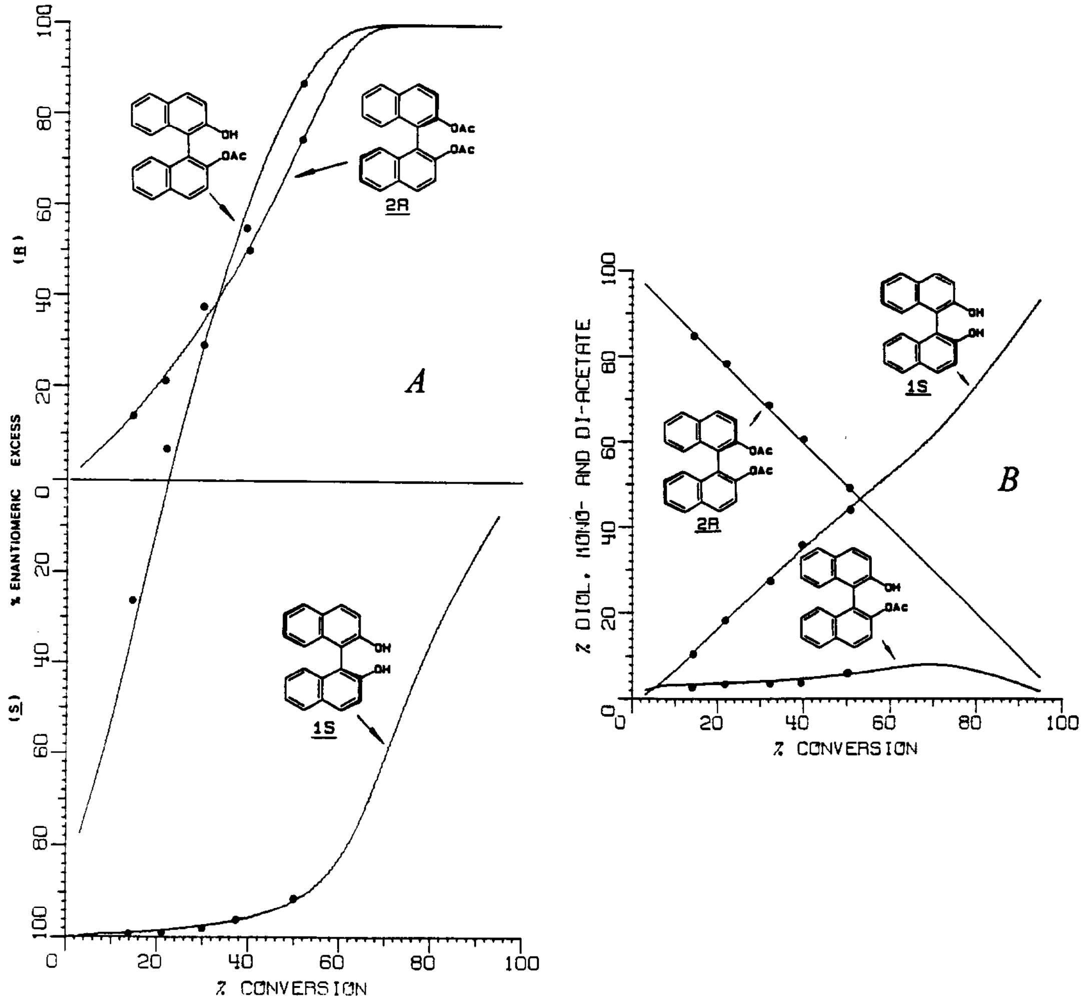
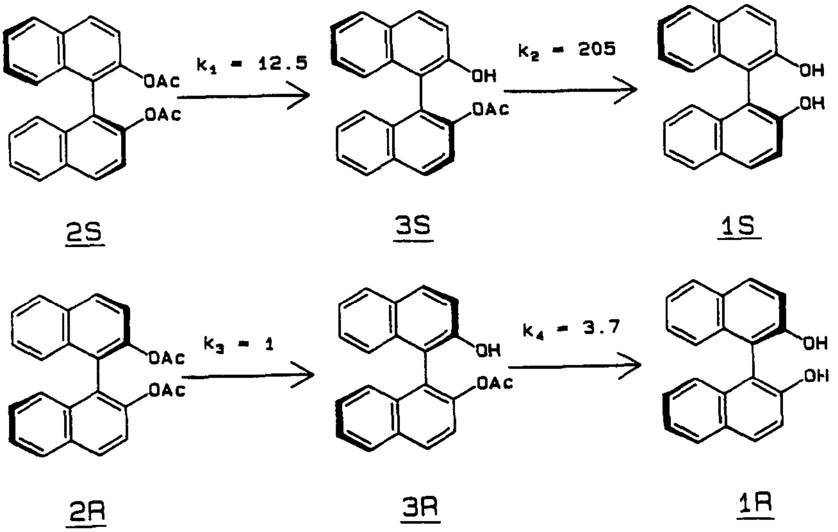


Fig. 1A. Plot of percent enantiomeric excess of diacetate, monoacetate or diol as a function of percent conversion ($C = 1 - \{[A + B]/[A_0 + B_0]\}$. The curves are computer generated[7] using the constants: $k_1 = 12.5$, $k_2 = 205$, $k_3 = 1$, and $k_4 = 3.7$. ● Experimentally determined values. 1B: Percent diacetate, monoacetate or diol as a function of percent conversion.



Quantitative definition of the requisite kinetic parameters allows the prediction of the ee of any chiral species for a given conversion, as well as the optimization of chemical and optical yields. Further, the apparent amplification of enzymic enantiospecificity as a consequence of the synergistic interaction of the relative rate constants facilitates the preparation of axially-disymmetric compounds in their chiral forms.

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12. Since microorganisms may contain more than one ester hydrolase, these values are apparent relative rate constants.

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