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SYNTHESIS OF CHIRAL BUILDING BLOCKS FOR SELECTIVE ADENOSINE RECEPTOR AGENTS. LIPASE-CATALYZED RESOLUTION of 2-BENZYLPROPANOL AND 2-BENZYLPROPIONIC ACID.

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Abstract: Both enantiomers of 2-benzylpropanol and 2-benzylpropionic acid have been synthesized using a lipase-catalyzed resolution in an organic solvent and in water.

The interaction between a drug and its bological receptor is usually affected by the absolute configuration of the drug[1]. 2-Benzylpropanol (**1**) or 2-benzylpropionic acid (**4**) are potentially useful compounds for incorporating chiral recognition units in adenosine receptor agonists[2] and antagonists[3]. The attempts to synthesize this unit via 2-benzylpropionaldehyde, obtained by a Sharpless epoxidation procedure, resulted in modest stereoselectivity[4]. Until now the best method for the preparation of (R) or (S)-**1** has been the repeated recrystallization of (+)-methylbenzylamine and/or quinine salts of **4**, followed by $LiAlH_4$ reduction of the optically pure acid[4].

Here we report a more convenient technique based on a lipase-catalyzed resolution[5] of **1** and **3**. A typical experiment is outlined in Fig 1.[6] Despite the one C-C bond distance between the primary hydroxyl group and the chiral center in **1**, the lipase from *Pseudomonas* sp. (Amano) acts stereoselectively (E= 12)[7] in *tert*-butyl methyl ether (*t*-BuOME). The (R)-alcohol has been prepared in 97% ee and 43% yield using this enzyme[8]. The (S)-alcohol has been synthesized by enzymatic hydrolysis of the (S)-enriched ester (**2**) in water to give (S)-**1** in 93% ee and 35% yield.

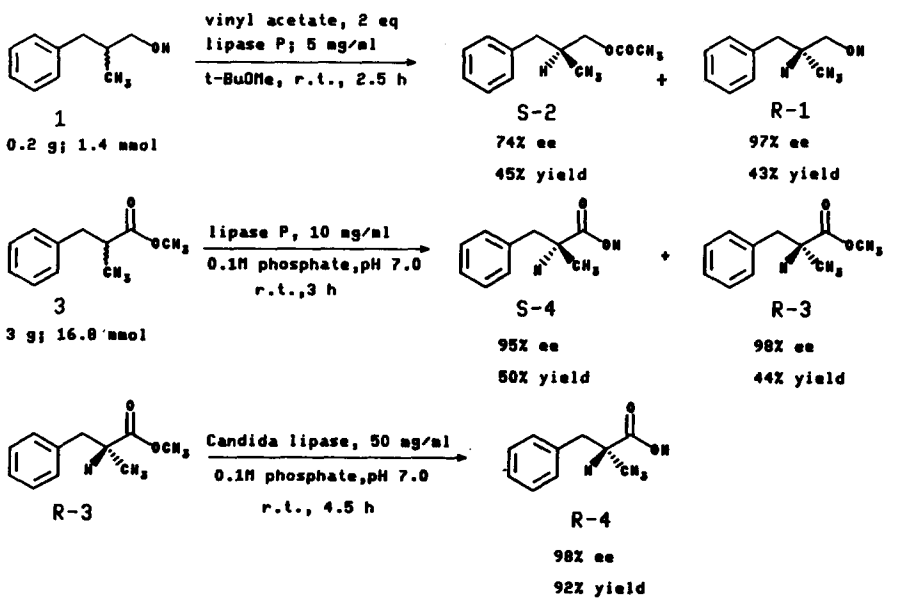

Figure 1

In **2** the chiral unit forms the alcohol part of the ester and the scissile bond is also one C-C bond away from the chiral center.

The enzymatic hydrolysis also was carried out on ester **3** in which the chiral unit was located in the acid part of the molecule (Fig 1). This method is highly stereoselective (E=145) and gives R-ester (R)-**3** and S-acid (S)-**4** both with ee > 95% in excellent yield[9]. If R-acid (R)-**4** is required for subsequent synthesis, it can be produced from the corresponding ester. Since (R)-**3** is prone to racemization, hydrolysis cannot be carried out under basic conditions. We have found that another lipase from *Candida cylindracea* easily hydrolyzes (R)-**3** without racemization to give (R)-**4** with 98% ee in good yield.

In summary, the combination of lipase-catalyzed hydrolysis in water and transesterification in an organic solvent allows the synthesis of all possible enantiomers of the alcohol **1**, ester **3**, and acid **4**, with the exception of (S)-**3**[10] which can be prepared by HCl-catalyzed esterification of (S)-**4**. It should be stressed that these enzymatic reactions are fast, employ inexpensive commercially available enzymes, require minimal work-up and can therefore, easily be performed on a large scale.

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6. Enantiomeric excess of **1** and **3** was determined by HPLC using Chiralcel OD column (Daicel) with a mobile phase of hexane:2-propanol:diethylamine (80:20:0.1). **2** and **4** were converted to **1** prior to HPLC analysis by basic hydrolysis or reduction with $LiAlH_4$, respectively.
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8. 0.2 g of **1**, Vinyl acetate (2 eq; 0.26 mL) and 70 mg lipase P were combined in 14 mL *t*-BuOMe and mixture was stirred. After 2.5 h, reaction was stopped by filtering enzyme. Products were separated by radial chromatography (5% EtOAc/hexane).
9. 3g of **3** was suspended in 300 mL buffer, enzyme (3g) was added, and mixture was stirred. After 3 h, ester was extracted with hexane from basic solution (pH 8-9) and acid was extracted with EtOAc from acidic solution (pH 2).
10. All compounds have been fully characterized by ^1H NMR, MS and elemental analysis. Data for optical rotations are as follows: $[\alpha]_D^{20}$ = + 16.5 (R)-**1** and -15.6 (S)-**1**, (c 0.6; EtOH); $[\alpha]_D^{25}$ = -26.2 (R)-**4** and +25.6 (S)-**4** (c 1; $CHCl_3$); $[\alpha]_D^{25}$ = -33.7 (R)-**3** and +35.9 (S)-**3** (c 1; $CHCl_3$).

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