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## Highly Efficient Enzymatic Resolution of Homoallyl Alcohols Leading to a Simple Synthesis of Optically Pure Fluoxetine and Related Compounds

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Abstract : A practical method for enzymatic resolution of homoallyl alcohols and its utility in the synthesis of optically pure fluoxetine and related compounds is reported. Copyright © 1996 Published by Elsevier Science Ltd

Because of the interesting biological activities of fluoxetine against a wide range of symptoms like depression, anxiety, alcoholism, obesity, chronic pain and bulemia<sup>1</sup>, the synthesis of both the enantiomers of this drug and related compounds has attracted considerable attention<sup>2</sup>. In continuation of our studies<sup>3</sup> on enzymatic kinetic resolutions and their use in the synthesis of biologically active compounds we have now developed a simple synthesis of optically active fluoxetine starting from 1-phenyl-3-buten-1-o1 (1a), the subject of the present communication. The key step of this new approach is the highly efficient *Pseudomonas cepacia* (Amano PS)<sup>4</sup> catalyzed acylation of racemic 1a, under non-aqueous conditions, to give 98% optically pure (R)-1a acetate in >47% isolated yield. It is interesting to note that the selectiveity of lipase PS<sup>24,56</sup> for (R) -1a is so high that the acylation stops after 50% conversion on racemic 1a. The recovered unreacted alcohol had (S)-configuration and high optical purity (91% ee.). The generality of this approach has also been established by screening various homoallyl alcohols and the details are given in the **Table**. The other reported enzymatic synthesis of similar homoallyl alcohols deal with the PLE and CCLE catalyzed hydrolysis of racemic acetates in aqueous solution<sup>7</sup>.

The optically pure (S)-1 was conveniently converted to the (S)-3-phenyl-1, 3-propanediol (2) by ozonolysis in CH<sub>2</sub>Cl<sub>2</sub> at -78°C followed by NaBH<sub>4</sub> reduction of the crude aldehyde obtained and usual work-up in 62% overall yield, { $[\alpha]_D^{25} = -64.9^\circ (c=2.7, CHCl_3)$ ; Lit<sup>8</sup>  $[\alpha]_D^{25} = -63.0^\circ$ , (c=0.958, CHCl<sub>3</sub>)}. (R)-3-phenyl-1, 3-propane diol was similarly prepared from (R)-1 (obtained by basic hydrolysis of (R)-1 acetate) in 64% yield;  $[\alpha]_D^{25} = +65.5^\circ (c=2.4, CH_2Cl_2)$ . Since these diols (R)-1 and (S)-1 are known precursors for optically pure fluoxetine and tomoxetine our route also contributes to a formal synthesis of these molecules.



Ph $OH$ $OH$ $OH$ $OH$ $OH$ $OH$ $OH$ $OH$								
(K,S)-1				(3)-1		(K)-I acetate		
		Reaction		Unreacted		Products		a
Compd.	Ph			alcohols		(acetates)		E
Nos.		Time (h)	Conv. Ratio (OH: OAc <sup>b</sup> )	$\left[\alpha\right]_{\mathrm{D}}^{25^{\mathrm{c,d}}}$	eee	$\left[\alpha\right]_{D}^{25^{d}}$	ee <sup>e.f</sup>	
1a.	Phenyl	30	50:50	-45.5	91	+75.5	98	>100
1b.	<i>p</i> -chlorophenyl	30	49:51	-29.1	82	+87.7	91	>100
1c.	<i>p</i> tolyl	48	50:50	-44.0	93	+ 93.7	91	>100
1d.	<i>p</i> anisyl	38	47:53	-32.3	81	+102.8	89	46.6
1e.	<i>p</i> -trifluorotolyl	96	48:52	-25.4	73	+53.4	90	49.4
1f.	3,4-dichlorophenyl	30	43:57	-16.7	57	+66.9	76	12.9

## Table : Enzymatic acylation of homoallyl alcohols<sup>a</sup>.

(a) Typical experimental details: A mixture of racemic alcohol (2.5 mmol), vinyl acetate (7.5 ml), and lipase PS (125 mg) was stirred atroom temp. until the required conversion was achieved. Enzyme was removed by filtration and the residue after concentration was purified by column chromatography. The isolated yields of products (acetates) and unreacted alcohols were found to be in the range from 45-47.5%. (b) determined by GC analysis. (c) Absolute configurations were assigned based on chiral HPLC analysis. (d) Specific rotations were measured in benzene. (e) estimated by chiral HPLC analysis using a (250 x 4.6mm) column: Pirkle cov. Ph. Gly.; Chiral stationary phase: (R)-(3,5-dinitrobenzyl) phenyl glycine covalently bonded to aminopropyl silica, (particle size  $\beta_{\mu}$ ; eluent: 5% IPA in hexane; flow rate: 1 ml/min; detection:  $\lambda = 254$ nm; column supplier: Chromopak. (f) confirmed by hydrolysing (K<sub>2</sub>CO<sub>3</sub>/MeOH) acetates to the corresponding alcohols followed by chiral HPLC analysis. (g) Enantiomeric ratio (E) were calculated following Sih's method<sup>9</sup>.

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