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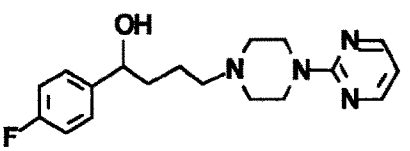
Enzymatic Preparation of Optically Active 4-Chloro-1-phenyl-1-butanol Derivatives

Daniele Bianchi*, Paola Moraschini, Aldo Bosetti and Pietro Cesti

EniChem-Istituto Guido Donegani, Via Fauser 4, 28100 Novara, ITALY

Abstract: The enantiomers of substituted 4-chloro-1-phenyl-1-butanol were prepared by stereoselective lipase-catalyzed resolution of the corresponding esters and alcohols, in water and in organic solvent, respectively.

The synthesis of homochiral drugs is a major challenge in medicinal chemistry since enantiomers may have different biological activities and be responsible for toxic side effects.[1] Recent advances in the synthesis of homochiral compounds, such as chemical asymmetric synthesis, catalytic kinetic resolutions, stereoselective crystallization and chiral chromatography, make the preparation of large quantities of enantiomers possible. Among these methods, biocatalytic procedures using hydrolytic enzymes both in aqueous and in organic solvents, are playing an increasingly important role.[2] One of the major advantages of enzymes with high enantioselectivities is their ability to produce both enantiomers of a given compound. This feature is extremely important during early stages of drug development when both the stereoisomers are needed for comparative testing. In the present work we report the lipase-catalyzed resolution of a series of 4-chloro-1-phenyl-1-butanol derivatives (**4a,c**), versatile intermediates in the synthesis of enantiomerically pure drugs, such as the antipsycotic agent α-(4-fluorophenyl)-4-(2-pyrimidynyl)-1-piperazinebutanol[3] (**1**) and the H_1 antistamine agent α-[4-(1,1-dimethylethyl)phenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol[4] (Terfenadine) (**2**).



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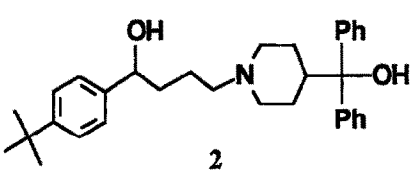

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In the literature the preparation of pure enantiomers of **1** and **2** through stereoselective chemical reduction using chiral borane derivatives has been reported[4,5]. The single enantiomers were tested, showing a different biological response. Firstly we investigated the lipase-catalyzed hydrolysis of the unsubstituted (RS)-**3a** (Scheme 1) using a series of commercially available lipases. Hydrolytic reactions were carried out in an emulsion of oily substrate in phosphate buffer, at 30°C, keeping the pH constant at 7. The absolute configuration of the alcohol produced was determined after transformation of (R)-**4a** into the known (R)-1-

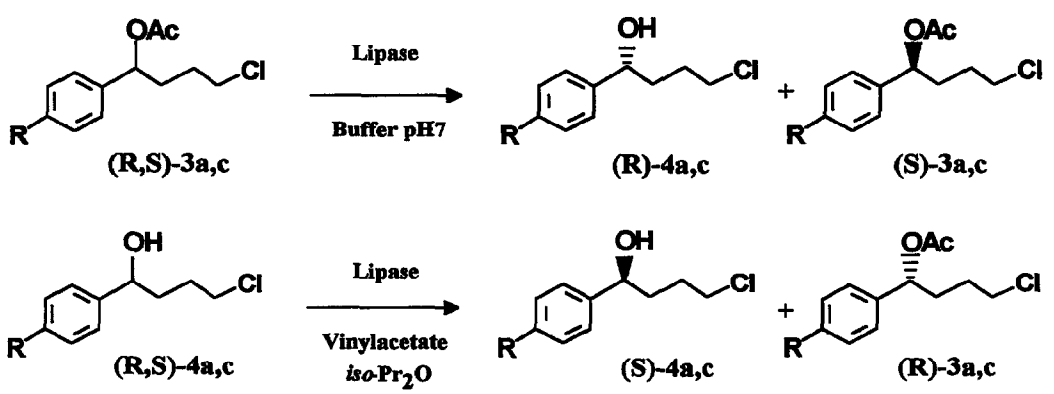
phenyl-1-butanol[6] by reduction with sodium borohydride in DMF[7]. The e.e. of both **3a** and **4a** was determined by HPLC using a chiral column Daicel Chiralcel OB.

Table 1. Enzymatic hydrolysis of (R,S)-**3a**[a]

Lipase source	Time (hours)	Conv. (%)	e.e (conf.) ester	e.e. (conf.) alcohol	E[b]
Aspergillus niger	24	25.7	69.3 (R)	27.0 (S)	7
Rhizopus delemar	48	23.9	18.0 (R)	57.3 (S)	4
Pseudomonas cepacia	48	47.0	80.1 (S)	89.2 (R)	41

(a) substrate (1 g), lipase (1 g), phosphate buffer 0.01 M, pH 7 (100 ml), 30°C; (b) Enantiomeric ratio[8].

As shown in Table 1, the best results in terms of enantioselectivity were obtained with lipase Amano PS from *Pseudomonas cepacia*. The stereoselectivity was lower than that displayed by the same enzyme in the hydrolysis of racemic 2-chloro-1-phenyl-1-ethanol[9] and 3-chloro-1-phenyl-1-propanol[10] which may be a consequence of the smaller difference in size of the aliphatic substituent on the stereogenic center (-CH_2Cl, volume = 35.9 Å^3; -$CH_2CH_2CH_2Cl$, volume = 69.0 Å^3)[11] with respect to the aromatic one (-Ph, volume = 70.4 Å^3). Given the similar volume of the substituents, the enantiodiscrimination is still remarkable, and this is probably due to the different conformational flexibility of the two chains which is the main parameter determining the interaction with the enzyme's active site[12]. In the case of the *para*-substituted substrates **3b** (4-F-Ph, volume = 75.8 Å^3) and **3c** (4-*tert*-Bu-Ph, volume = 111.4 Å^3), the difference in size is higher and consequentely the enantiomeric ratio increases from 41 to 66 and above 500, respectively (Table 2).



Scheme 1. Hydrolysis and transesterification reactions. (a): **R** = H, (b): **R** = F, (c): **R** = *tert*-Butyl.

In a second approach the transesterification of (RS)-**4a,c** was carried out by suspending lipase PS in a solution of the substrate with vinylacetate, as the irreversible acylating agent, in anhydrous *iso*-propylether, at 30°C (Scheme 1). In order to avoid diffusional limiting phenomena, the enzyme was immobilized onto celite.[13]

Table 2. Lipase PS-catalyzed resolution of 4-chloro-1-phenyl-1-butanol derivatives

Substrate	Conv. (%)	Ester 3 $[\alpha]_D^{25a}$	Ester 3 conf.	Ester 3 e.e.	Alcohol 4 $[\alpha]_D^{25a}$	Alcohol 4 conf.	Alcohol 4 e.e.	E[b]
3a[c]	47	-63.0	S	80.1[d]	+39.7	R	89.2[d]	41
3b[c]	46	-60.4	S	78.0[e]	+76.3	R	92.7[e]	66
3c[c]	50	-72.0	S	>95[e]	+30.9	R	>95[e]	>500
4a[f]	55.8	+62.1	R	79.0	-44.5	S	>95	82
4b[f]	50	+77.0	R	>95	-82.0	S	>95	>500
4c[f]	50	+72.0	R	>95	-30.9	S	>95	>500

(a) [C=1, $CHCl_3$]; (b) Enantiomeric ratio[8]; (c) Hydrolysis: substrate (1 g), lipase PS (1 g), phosphate buffer 0.01 M pH 7 (100 ml), 30°C; (d) Determined by HPLC (chiral column Daicel Chiralcel OB); (e) Determined by HPLC (chiral column Daicel Chiralcel OD); (f) Esterification: substrate (1 g), lipase PS (1.9 g), vinylacetate (9.4 ml), *iso*-propyl ether (180 ml), 30°C.

As reported in Table 2, the enantioselectivity in organic media is higher than that displayed in water. This different behaviour is presumably due to the higher rigidity of the enzyme in anhydrous organic solvent with respect to the water, where the increased protein's flexibility results in a relaxation of stereoselectivity.[14]

The thus obtained **4b** and **4c** can be converted into the homochiral **1** and **2** by substitution of the chlorine atom with 2-(1-piperazinyl)pyrimidine and α,α-diphenyl-4-piperidinemethanol, respectively, using the procedure described in the literature[4,5].

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