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Chemoenzymatic Route to ß-Blockers *via* 3-Hydroxy Esters

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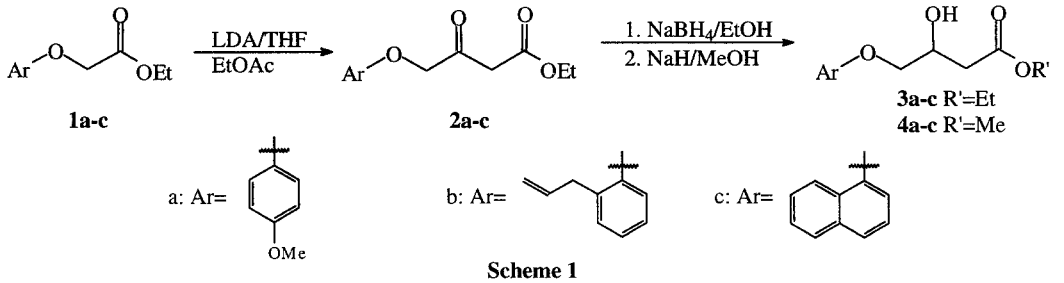
Abstract: Enantiomerically pure precursors of ß-blockers (propranolol, alprenolol and 1-(isopropylamino)-3-*p*-methoxy-phenoxy-2-propanol) were synthesized. Key step is the lipase-catalyzed kinetic resolution of *rac*-3-hydroxy esters either by O-acylation using vinyl acetate or by hydrolysis of the ester group. Both approaches were highly enantioselective (> 95 %ee) with E-values > 150 using lipase from *Pseudomonas cepacia.* The formal synthesis of (-)-(S)-propranolol was developed in subsequent steps.

INTRODUCTION

ß-Blockers are among the top twenty drugs based on their world wide sales. For example, the sales of atenolol valued more than 1 million US$ in 1990.[1] Although the (S)-enantiomers are much higher biologically active than the (R)-enantiomers and in some cases the (R)-enantiomer shows contraceptive actions, most ß-blockers are still sold as racemates. Both chemical and chemoenzymatic methods can yield enantiomerically pure ß-blockers. For example, Bevinakatti and Banerji resolved 1-chloro-3-(aryloxy)-2-propanol derivatives by lipase-catalysed hydrolysis or acylation for the preparation of (S)-propranolol, (S)-atenolol and (S)-practolol.[2] In another approach N-substituted acetates of propranolol were hydrolysed by several esterases, however only moderate enantioselectivities and a preference for the unwanted (R)-enantiomer were reported.[3] The preparation of (S)-propranolol via lipase-catalyzed resolution of glycerol derivatives[4] and cyanohydrins[5] was also performed. 3-(Aryloxy)-1,2-propanediol derivatives were used to develop an improved active site model of lipase from *Pseudomonas* cepacia.[6] In an earlier study[7], we have used 3-hydroxy esters for the investigation of factors affecting the enantioselectivity in the kinetic resolution by lipase catalysis in organic solvents. It turned out, that according to Kazlauskas' rule[8] for secondary alcohols, 3-hydroxy esters with a large aromatic group (namely 4-(1-naphthyloxy)-3-hydroxybutyric acid methyl ester) have been much better substrates and high enantioselectivities were observed.[7] In the present report, these findings were extended to the lipase-catalyzed resolution of other 4-(1-aryloxy)-3-hydroxybutyric acid esters. These can be transformed into the corresponding ß-blockers as has been elaborated in this paper for propranolol.

RESULTS

The 3-hydroxy ethyl esters **3a-c** were synthesized from the 2-aryloxy-acetic acid ethyl esters **1a-c** (Scheme 1) in two steps in about 80 % overall yield. It turned out, that methyl esters were better substrates and therefore we also performed later ester exchange with NaH in methanol to yield **4a-c**.



Scheme 1

Screening of suitable lipases

Typical results of the screening using commercial lipases are shown in Table 1 for the hydrolysis of the ethyl ester of **3c**. In all cases the product **5c** had the S-configuration (Scheme 3). This was confirmed by chiral GC analysis, chiral shift NMR spectroscopy and chemical correlation (see experimental). It is obvious from Table 1, that best results were achieved with lipase from *Pseudomonas cepacia* (PCL), giving an E-value of more than 150, which should allow the isolation of enantiomerically pure substrate and product. Another good lipase was from *Chromobacterium viscosum* (CVL). This may be due to the very high sequence homology to the *Pseudomonas sp.* lipase family.[9] PCL was used throughout all subsequent experiments.

Table 1: Screening of lipases *via* hydrolysis of **3c**

Lipase	%ee **5c** (S)	%ee **3c** (R)	Time (h)	c* (%)	E*
PPL	92	96	69	35	15
PCL	90	96	22	48	>150
CRL	10	22	137	32	3
CVL	78	93	69	46	79
RML	9	13	137	55	< 2

*calculated from the enantiomeric excess according to Chen *et al.*[10]

*Resolution of the 3-hydroxy methyl esters **4a-c***

Compounds **4a-c** were subjected to either lipase catalyzed hydrolysis in aqueous phosphate buffer / toluene or acylation with vinyl acetate in hexane using PCL (Scheme 2). The hydrolysis of the three 3-hydroxy methyl esters **4a-c** resulted in all cases in the formation of highly pure acid in the desired (S)-configuration. The enantioselectivity was high in all cases and the reactions virtually stopped around 50 % conversion. The fasted reaction was observed with compound **4a**. On the other hand we found that the acylation with vinyl acetate was even more enantioselective and even faster, yielding the acetate in (R)-configuration. In the case of compounds **4a** and **4b** the reaction progress could be monitored by gas chromatography (GC) on a chiral column thus allowing the almost exact determination of 50 % conversion.