

ENZYMATIC RESOLUTION OF AN ARYLPIPERIDINE DERIVATIVE
UTILIZING LIPASE CATALYZED HYDROLYSIS

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ABSTRACT: Enantiospecific hydrolysis of the acetate of 1 was carried out on a multigram scale utilizing a lipase from *Aspergillus niger*. Both stereoisomers R-(+) and S-(-) were obtained with high enantiomeric purity ($\geq 97\%$ ee).

Recent work in our laboratories identified 1 as an antiarrhythmic agent^{1a,b} and a potent, selective antagonist at the 5-HT₂ receptor.² Studies concerned with providing a preferred bio-active isomer of 1 warranted the preparation of useful amounts of both enantiomers. The use of enzymes for the procurement of chirally pure compounds has gained attention and their use in such a manner here was attractive.³ Outlined here is the utilization of lipase catalyzed hydrolysis of esters for the resolution of 1 into its optical isomers on a multigram scale.

Racemic 1 (α -phenyl-1-(2-phenylethyl)-4-piperidinemethanol)⁴ was first acylated following a standard procedure to give racemic acetate 2. Ester 2 was adsorbed onto silica gel and subjected to the action of a lipase from *Aspergillus niger* (Amano AP-12)⁵ in 0.1N phosphate buffer (pH=6.5). The lipase preferentially hydrolyzed the (-)-enantiomer of ester 2 delivering an easily separable mixture of (-)-1 and (+)-2. Use of silica gel as an adsorbent allowed for more homogenous and efficient mixing, and a greater surface area for contact between the buffer, enzyme and water insoluble ester 2.⁶ After a reaction time of one to three days, the suspension was filtered and washed with water. Separation of products from the silica gel with common organic solvents, followed by chromatographic separation, provided alcohol (-)-1 and acetate (+)-2. Saponification of (+)-2 yielded (+)-1. Although the course of the enzyme catalyzed reaction could be monitored for ~50% hydrolysis by HPLC, the following simple approach allowed for expedient yet uncompromising results. Long reaction times (~3 days) resulted in the hydrolysis of all of (-)-2 and a small amount of (+)-2 which, after chromatographic separation, delivered pure (+)-2 [saponification yielding (+)-1] and alcohol 1 enriched in the (-)-enantiomer. This alcohol was reacylated to acetate 2 [now enriched in the (-)-enantiomer] and resubjected to lipase hydrolysis for a shorter reaction time (~1 day). Chromatographic separation now gave rise to pure alcohol (-)-1 and a small amount of 2. Using this protocol, 13.0 g of (-)-1 ($[\alpha]_D^{20} = -29.9$, $c=1.0$ CHCl₃) and 10.3 g of (+)-1 ($[\alpha]_D^{20} = +28.8$, $c=1.0$ CHCl₃) were prepared from 46.0 g of (\pm)-2.⁷ The high enantiomeric purity ($\geq 97\%$ ee) for each enantiomer was determined by ¹⁹F NMR analysis of their respective α -methoxy- α -trifluoromethyl-phenyl acetate esters.⁸

