Pergamon

*Tetrahedron: Asymmetry*, Vol. 7, No. 9, pp. 2485-2488, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00313-8

# A New Application of *Candida Antarctica* Lipase for Obtaining Natural Homochiral BBAs Aryloxypropanolamine

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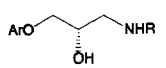
**Abstract:** CAL offers increased ee, together with broad substrate structural tolerance that makes it a firm candidate for the resolution of BBAs of type **1**.

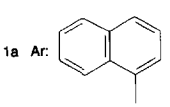

## Introduction

The close correlation between chemical structure and biological activities of molecules is a well verified fact. In particular the absolute configurations of molecular structures determine clear contradictions in the pharmacological activities of many therapeutics groups. A clear example is constituted by the aryloxypropanolamine group of BBAs **1**, whose therapeutical effects reside largely in the (S)-enantiomers[1].

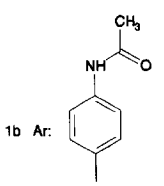
Of the synthetic approaches leading to this type of structure in high enantiomeric purity those based on asymmetric synthesis[2] or biotechnological methods[3] deserve special consideration. Without doubt, the strategies based on the use of glycidol and derivatives as C-3 synthons, have been shown to be the most useful for the introduction of the 2-propanol chain on the aromatic system. Moreover, resolution at the C-2 level of the side-chain, can easily be accomplished by enantioselective hydrolysis/synthesis with a wide variety of lipases from various



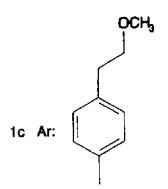

1



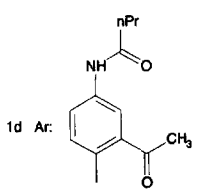

(Propranolol)




(Practolol)




(Metoprolol)




(Acebutolol)

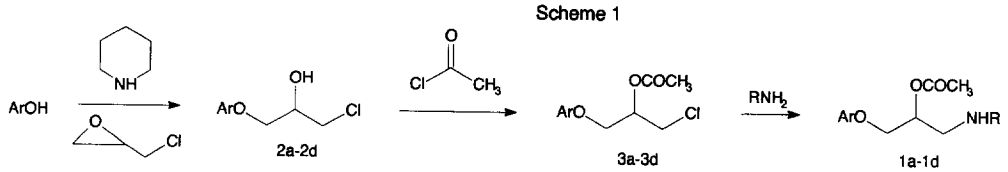
sources[4], and on synthetic intermediates, since the inefficiency in the resolution of the final products of type **1** has been shown. However, from previous papers the relationship between the enantiomeric excess and the type of enzyme used, with the same substrate, is unclear. Thus, a wide variety of results depending on the enzyme used have been reported, which cannot be "extrapolated" for other substrates. This problem is even more important, if we consider the wide variety of structures includes BBAs of type **1**, whose cardioselectivity is conditioned by the substituted aromatic system[5]. Consequently, the objective of our work has been the search for a new and powerful

catalyst, generally useful for a great variety of structures, offering comparable enantiomeric excesses and largely independent of the sustrate employed.

**Results and Discussion**

The general synthesis route is shown in Scheme 1. The Ar group selection is based to be representative of non-selective BBA drugs (propranolol) and β1 cardioselective BBAs (practolol, metoprolol and acebutolol). The enantioselective resolution has been accomplished using native Lipase B from *C. antarctica*. Due to the high enantioselectivity described in the resolution of racemic alcohols using this enzyme[6], we have analyzed the resolution of the (*RS*)-1-aryloxy-3-chloropropan-2-ols and their corresponding (*RS*)-O-acetoxy derivatives [7] which are beta-blocker precursors.

Scheme 1




Two different strategies have been examined for the resolution of these compounds : 1. Hydrolysis/Alcoholysis of racemic O-acetate; 2. Acylacion of racemic alcohol. Results obtained for the resolutions of these compounds are shown on Table 1. Water, methanol and butanol were tried as nucleophiles. The best yield and enantioselectivity for substrate **3a** and reaction product were obtained at 25°C under hydrolysis conditions (5 equiv. of water). Enantioselectivity was only moderately affected by increasing temperature (37°C). Shorter reaction times were performed for n-buthanol than methanol, but better enantioselectivity was observed for the latter.

The alcohol obtained was assigned as the (*S*)-enantiomer on the basis of its specific rotation [7]. Acylation of **2a** was tried with lipase B and vinyl acetate as the acyl donor (Table 1). In order to demonstrate the application of *C. antarctica* lipase for the asymmetric synthesis of beta-blocker precursors, resolutions of **3b-3d** and **2b-2d**, was assayed with similar results. The enantiomeric purities were determied by HPLC on a chiral support (Chiracel OD)[8].

**Conclusions**

From the data on Table 1, the low dependence showed by the lipase of C. antarctica with respect to the ee and the aromatic region of the BBA molecule can be deduced, working quite unspecifically with groups of very different physico-chemical characteristics, which suggests a wide structural tolerance near the active site of this lipase. This confirms previous studies by us[10], and demonstrates the suitability of this enzyme for the resolution of arylpropanolamine structures 1, and being much better to date than other biocatalysts, opens new possibilities for biotechnology to access homochiral beta-blockers.

Table 1.

| Comp | T[a] | Reaction medium | time (h) | % | $ee_s$ | isomer | $ee_p$ | isomer | E[(9)] |
|---|---|---|---|---|---|---|---|---|---|
| 3a | 25° | 5 H2O | 144 | 47 | 95 | (-)-R | 95 | (+)-S | 146 |
| | 37° | 5 H2O | 48 | 50 | 95 | (-)-R | 95 | (+)-S | 70 |
| | 25° | 20 H2O | 168 | 13 | 20 | (-)-R | 95 | (+)-S | 47 |
| | 25° | 10 H2O | 168 | 37 | 67 | (-)-R | 95 | (+)-S | 79 |
| | 25° | 5 MeOH | 168 | 39 | 77 | (-)-R | 95 | (+)-S | 91 |
| | 25° | 5 BuOH | 6 | 39 | 59 | (-)-R | 71 | (+)-S | 11 |
| 3b | 25° | 5 H2O | 168 | 40 | 79 | (-)-R | 95 | (+)-S | 94 |
| 3c | 25° | 5 H2O | 144 | 37 | 70 | (-)-R | 95 | (+)-S | 124 |
| 3d | 25° | 5 H2O | 168 | 39 | 77 | (-)-R | 95 | (+)-S | 77 |
| 2a | 25° | 3 VA | 72 | 26 | 28 | (-)-R | 88 | (+)-S | 21 |
| | 37° | 3 VA | 96 | 3 | 27 | (-)-R | 95 | (+)-S | 51 |
| 2b | 25° | 3 VA | 168 | 5 | 18 | (-)-R | 95 | (+)-S | 47 |
| 2c | 25° | 3 VA | 144 | 5 | 20 | (-)-R | 95 | (+)-S | 102 |
| 2d | 25° | 3 VA | 168 | 10 | 18 | (-)-R | 95 | (+)-S | 42 |

Reaction carried out with 10 ml of t-BuOMe, 5 mg of native lipase.

**Acknowledgment**: This work was supported by a grant from C.I.C.Y.T. (Ministerio de Educacion y Ciencia. Spain) Project PB-93-0469.

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(*Received in UK* 24 *June* 1996)