Enantioselective Hydrolysis of 1-Aryl-2-chloroethyl propanoate Mediated by Burkholderia cepacia and Candida rugosa Lipases.

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Abstract
Enantioselective hydrolysis of racemic compounds 4a-b by lipases from Burkholderia cepacia and Candida rugosa afforded the corresponding alcohols in 79-91%, isolated yield, that can be used as building blocks for stereoselective syntheses of pharmaceuticals compounds as Sotalol and Sertraline.

Key words: Burkholderia cepacia lipase, Candida rugosa lipase, asymmetric synthesis, biocatalysis.

Introduction
Chiral secondary alcohols as important and valuable building blocks for pharmaceuticals, agricultural and other fine chemicals products, such as Sotalol - Sotagard®, a β-adrenergic receptor blocker, and Sertraline - Zoloft®, anti-depressant agent1-2, Image 1.

Image 1. Pharmaceuticals products: Sotalol and Sertraline.

In this work, we report a production of chiral intermediates for synthesis of Sotalol and Sertraline in excellent yields and good enantiomeric excess (ee).

Results and Discussion
The halohydrins (±)-3a-b was synthesized using acetophenones 1a-b, NH4Cl and Oxone® in dichloromethane at room temperature3 and subsequent reduction using NaBH4 in methanol, Image 1. The esterification reaction of halohydrins (±)-3a-b furnished the compounds (±)-4a-b by using butyric anhydride and DMAP in dichloromethane.

Image 2. Enantioselective synthesis of secondary alcohols mediated by Burkholderia cepacia and Candida rugosa Lipases.

The preliminary results of biocatalytic process for production of chiral pharmaceuticals intermediates 3a-b by using Burkholderia cepacia and Candida rugosa Lipases were demonstrated in Chart 1. The enantioselective hydrolysis of compounds (±)-4a-b furnished the halohydrins (R)-3a-b in excellent isolated yields and the intermediate (R)-3b was obtained with excellent ee, >99%.

Chart 1. Enantioselective hydrolysis of (±)-4a-b butanoate esters mediated by Burkholderia cepacia and Candida rugosa Lipases.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Lipase</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>E (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>B. cepacia</td>
<td>(R)-3a</td>
<td>80</td>
<td>46</td>
<td>3.6</td>
</tr>
<tr>
<td>1a</td>
<td>C. rugosa</td>
<td>(R)-3a</td>
<td>86</td>
<td>8.1</td>
<td>1.2</td>
</tr>
<tr>
<td>1b</td>
<td>B. cepacia</td>
<td>(R)-3b</td>
<td>78</td>
<td>&gt;99</td>
<td>&gt;200</td>
</tr>
<tr>
<td>1b</td>
<td>C. rugosa</td>
<td>3b</td>
<td>91</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a 0.7 mmol of substrate dissolved in 3 mL of diisopropyl ether was added in 3 mL of phosphate buffer 0.1M, pH 7, containing 1.2 M of MgCl2 and Lipase, and stirred for 12 h at 30°C. The products were purified in chromatographic system Biotage using hexane/acetone gradient. The absolute configuration was compare with literature3,4 and the enantiomeric excess was performed using HPLC by chiral column.

Conclusions
Enantioselective hydrolysis of compounds (±)-4a-b mediated by lipases from Burkholderia cepacia and Candida rugosa furnished the chlorohydrins (R)-3a-b in excellent yields, and the studies are been conducted to optimize the biocatalytic process.

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