ENANTIOSELECTIVE PRODUCTION OF BETA-HYDROXY PHOSPHONATES BY SACCHAROMYCES CEREVISIAE

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Abstract
Enantioselective reduction of beta-ketophosphonates 1a-b by Saccharomyces cerevisiae afforded building blocks for the stereoselective syntheses of fosfomycin, an important pharmaceutical compound, isolated in excellent yield (89-92%).

Key words: beta-hydroxy phosphonates, fosfomycin, asymmetric synthesis.

Introduction
Optically active beta-hydroxyalkanephosphonic acid derivatives are important precursors for pharmaceuticals compounds1 and fosfomycin, Figure 1, is an antibiotic used as an effective treatment for urinary tract infections, particularly since it is highly effective when applied as a single dose.2

Figure 1: Fosfomycin sodium salt.

In this work, we report the preliminary enantioselective bioreduction of beta-ketophosphonates 1a-b using whole cells of Saccharomyces cerevisiae in excellent yield. Compound 2b will be used to prepare fosfomycin.

Results and Discussion
The beta-ketophosphonate 1a was synthesized using chloroacetone, trimethylphosphite and potassium iodide in dichloromethane at room temperature3; and beta-ketophosphonates 1b by chlorination of 1a using HCl 2N and oxone® in dichloromethane at room temperature4. Enantioselective reduction of compounds 1a-b mediated by Saccharomyces cerevisiae, Figure 2, provided the beta-hydroxy phosphonates 2a-b in excellent yields, Table 1.

Table 1. Bioreduction of beta-ketophosphonates 1a-b by Saccharomyces cerevisiae.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Isolated Yield (%)</th>
<th>[α]D20</th>
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<tbody>
<tr>
<td>1a</td>
<td>(R)-2a</td>
<td>92 -15</td>
<td>-</td>
</tr>
<tr>
<td>1b</td>
<td>2b</td>
<td>89 +2,7</td>
<td></td>
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</tbody>
</table>

* 6 mmol of substrate in 0.5 mL of ethanol was added to a suspension of 4 g of whole cells in 100 mL of water. Reaction time: 14h; temperature: 30°C; orbital shaker: 200 rpm. The configuration of β-hydroxyl phosphonates was determined by comparison of the [α]D20 with literature5.

Conclusions
The enantioselective reduction beta-ketophosphonates 1a-b mediated by Saccharomyces cerevisiae provided corresponding alcohols in excellent isolated yields. Studies are been conducted to determine the enantiomeric excess (ee) of beta-hydroxy phosphonates 2a-b and absolute configuration of 2b.

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