Bioreduction of beta-Ketophosphonates by Sacharomyces cerevisiae.


Abstract
The bioreduction of beta-ketophosphonates 1a-d by Sacharomyces cerevisiae furnished intermediates in high isolated yield and ee, which may be used for synthesis of fosfomycin - Morunol®, a potent antibiotic.

Key words:
Sacharomyces cerevisiae, beta-ketophosphonates, fosfomycin, asymmetric synthesis, biocatalysis.

Introduction

The beta-hydroxy phosphonates are important intermediates for synthesis of pharmaceutical compounds, such as fosfomycin tromethamine - Morunol®, a potent antibiotic.

The bioreduction of beta-ketophosphonates 1a-d by whole cells of Sacharomyces cerevisiae gave the beta-hydroxy correspondent, precursors for fosfomycin and derivatives.

Results and Discussion

The beta-ketophosphonate 1a and 1c was synthesized using chloroacetone or 2-chloro-1-phenylethanone, respectively, trimethylphosphite and potassium iodide in dichloromethane at room temperature. The beta-ketophosphonates 1b and 1d was halogenated by using NH₄Cl and oxone® in dichloromethane at room temperature. Enantioselective reduction of compounds 1a-d mediated by Sacharomyces cerevisiae, Image 2, provided the beta-hydroxy phosphonates 2a-d in excellent isolated yields, and the compounds (R)-2a and (R)-2c in excellent ee, Chart 1.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
<th>[α]D20°</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>(R)-2a</td>
<td>92</td>
<td>-15</td>
<td>&gt;99</td>
</tr>
<tr>
<td>1b</td>
<td>2b</td>
<td>89</td>
<td>-2.7</td>
<td>nd</td>
</tr>
<tr>
<td>1c</td>
<td>(R)-2c</td>
<td>94</td>
<td>-30</td>
<td>&gt;99</td>
</tr>
<tr>
<td>1d</td>
<td>2d</td>
<td>88</td>
<td>+8.2</td>
<td>nd</td>
</tr>
</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 products were purified in chromatographic system Biotage using hexane/aceton gradient. The absolute configuration was compared with literature and the enantiomeric excess was determined using HPLC by chiral column.

Conclusions

The bioreduction process by using Sacharomyces cerevisiae furnished chiral hydroxy phosphonates (R)-2a and (R)-2c in excellent isolated yields and ee. Studies are being conducted to determine the enantiomeric excess (ee) and absolute configuration of beta-hydroxy phosphonates 2b and 2d.

Acknowledgement

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Chart 1. Bioreduction of beta-ketophosphonates 1a-d by Sacharomyces cerevisiae.

Image 1. Fosfomycin tromethamine.

Image 2. Bioreduction of beta-ketophosphonates 1a-d mediated by S. cerevisiae.