

Bioreduction of beta-Ketophosphonates by *Sacharomyces cerevisiae*.

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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 fosfomicin - Morunol®, a potent antibiotic.

Key words:

Sacharomyces cerevisiae, beta-ketophosphonates, fosfomicin, asymmetric synthesis, biocatalysis.

Introduction

The beta-hydroxy phosphonates are important intermediates for synthesis of pharmaceutical compounds, such as fosfomicin tromethamine - Morunol®, a potent antibiotic¹.

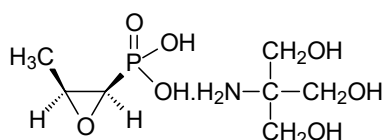
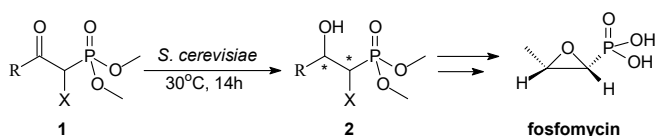


Image 1. Fosfomicin tromethamine.

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

Results and Discussion

The beta-ketophosphonate 1a and 1c was synthesized using chloroacetone or 2-chloro-1-phenylethanol, respectively, trimethylphosphite and potassium iodide in dichloromethane at room temperature². The beta-ketophosphonates 1b and 1d was halogenated by using NH₄Cl and oxone® in dichloromethane at room temperature³. 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.



a: R = CH₃; X = H
 b: R = CH₃; X = Cl
 c: R = Ph; X = H
 d: R = Ph; X = Cl

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

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

Substrate	Product	Yield (%)	[α] _D ²⁰	ee (%)
1a	(R)-2a	92	-15	>99
1b	2b	89	+2,7	nd
1c	(R)-2c	94	-30	>99
1d	2d	88	+8,2	nd

^a 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/acetone gradient. The absolute configuration was compared with literature⁴ 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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