

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.

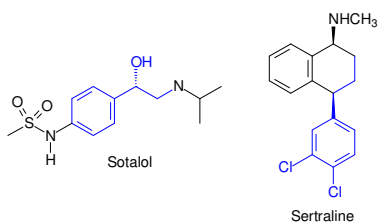


Image 1. Pharmaceuticals products: Sotalol and Sertraline.

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 (\pm)-**3a-b** was synthesized using acetophenones **1a-b**, NH_4Cl and Oxone[®] in dichloromethane at room temperature³ and subsequent reduction using NaBH_4 in methanol, Image 1. The esterification reaction of halohydrins (\pm)-**3a-b** furnished the compounds (\pm)-**4a-b** by using butyric anhydride and DMAP in dichloromethane.

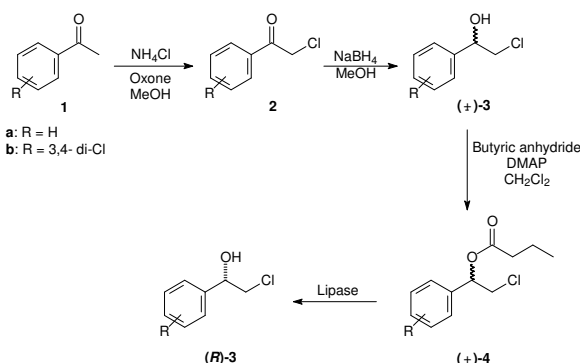


Image 2. Enantioselective synthesis of secondary alcohols mediated by *Burkholderia cepacia* and *Candida rugosa* Lipases.

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 (\pm)-**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 (\pm)-**4a-b** butanoate esters mediated by *Burkholderia cepacia* and *Candida rugosa* Lipases.^a

Substrate	Lipase	Product	Yield (%)	ee (%)	E (%)
1a	<i>B. cepacia</i>	(<i>R</i>)- 3a	80	46	3.6
1a	<i>C. rugosa</i>	(<i>R</i>)- 3a	86	8.1	1.2
1b	<i>B. cepacia</i>	(<i>R</i>)- 3b	78	>99	>200
1b	<i>C. rugosa</i>	3b	91	-	-

^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 MgCl_2 and Lipase, and stirred for 12 h at 30°C. The products were purified in chromatographic system Biotage using hexane/acetone gradiente. The absolute configuration was compare with literature^{2,4} and the enantiomeric excess was performed using HPLC by chiral column.

Conclusions

Enantioselective hydrolysis of compounds (\pm)-**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.

Acknowledgement

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¹ Xu, G.; Yu, H.; Xu, J.. *Chin. J. Chem.* **2013**, *31*, 349.

² Xu, G.-C.; Yu, H.-L.; Zhang, X.-Y.; Xu, J.-H.. *ACS Catal.* **2012**, *2*, 2566.

³ Zhou, Z. S.; Li, L.; He, X. H.. *Chin. Chem. Lett.* **2012**, *23*, 1213.

⁴ Zhu, D.; Mukherjee, C.; Hua, L.. *Tetrahedron: Asymmetry* **2005**, *16*, 3275.