Preliminary study on enzymatic kinetic resolution of isopropylidene glycerol

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ABSTRACT: This work presents a preliminary screening directed to obtaining optically active glycerol derivatives. It was tested six lipases from different sources as a means for kinetic resolution.

Keywords: isopropylidene glycerol, enzymatic resolution, lipase, biocatalysis

Optically active 1,2-O-isopropylidene glycerol (IPG) is an useful starting material for synthesis of important compounds, such as glycerophospholipids, β-blockers, prostaglandins, PAF (platelet aggregation factor) and many others [1, 2]. This compound is usually synthesized from D-mannitol and L-serine or ascorbic acid [1]. An important alternative to prepare chiral glycerol derivatives is using glycerol itself. The differentiation of two enantiotopic groups in the prochiral glycerol molecule would in fact lead to chiral molecules, which could be transformed in both enantiomers of glycerol derivatives by selective functional group manipulation [3]. These desymmetrization methods have long been exploited either in the chemical catalysis as in biocatalysis and offer a valuable tactic for asymmetric induction. In biocatalytic process is often the use of isolated enzymes [4] or whole microorganisms [5], and it has incited much attention from researchers because it’s an environmentally friendly process [6]. Enzymatic resolution of a racemate is also a widely used method to obtain enantiomerically enriched compounds [6, 7].

Hydrolytic enzymes such as lipases, esterases, and proteases have been used

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extensively as catalysts in enantioselective and regioselective synthesis [2, 8, 9]. However, enantioselective esterification of primary alcohol of glycerol derivatives, such as IPG (rac-1) is still a challenge. Thus, screening with different source of lipases is valuable to achieve suitable selectivity. In this work we present a screening made with 6 lipases for kinetic resolution by acetylation of racemic IPG in order to obtain optically active glycerol derivatives (scheme 1).

Scheme 1. Kinetic resolution of IPG

Lipases from porcine pancreas (II), wheat germ and Candida rugosa were purchased from Sigma-Aldrich Co., Penicillium camembertii and Thermomyces lanuginosa lipases from Fluka Co. Lipase from Candida antarctica (Novozym 435) was donated by Novozymes. Glycerol and vinyl acetate were purchased from Acros (Brazil). Hexane was of analytical grade. The enantiomeric excess (ee) was determined by GC using a GC Varian 3800 with chiral adsorbent Astec Chiraldex B-PM. Chromatographic conditions: injector temperature: 250 °C; oven initial temperature 75 °C to 105 °C at 1 °C/min. The flame ionization detector was maintained at 250 °C; carrier gas: helium gas (1 mL/min). $^1$H and $^{13}$C NMR spectra were obtained using a Bruker AVANCE DPX-300 spectrometer and were recorded at 300 and 75 MHz respectively. IPG (rac-1) was prepared from glycerol using a literature procedure [10]. According to work of Kawanami et al. [2], dry hexane was the best choice of solvent among several others for kinetic resolution of cyclic ketales of glycerol. Thus, the solvent was chosen to our reactions.

The compound 1 (30 mg) was subjected to kinetic resolution in dry hexane (6 mL) using 6 different lipases (5 or 1 mg), and the vinyl acetate (1.1 eq.) as the acylating agent, at 30 °C under continuous stirring (150 rpm) in an orbital shaker. The results are presented in Table 1.

According to Table 1, all six lipases showed low selectivity. The results are in accordance to a reported result where enantioselectivity of other lipases toward primary alcohol is much lower than to secondary alcohol [11].

An important outcome is that the use of 2.2 eq. of vinyl acetate causes a dramatic increase in the enantioselectivity promoted by lipase from P. camembertii (ee >99%).
Table 1. Kinetic Resolution of IPG

<table>
<thead>
<tr>
<th>Lipase</th>
<th>Time (min)</th>
<th>ee^s</th>
<th>ee^p</th>
<th>Conv.</th>
<th>E-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. lanuginosa</td>
<td>90</td>
<td>20 (S)</td>
<td>25 (R)</td>
<td>43</td>
<td>2,0</td>
</tr>
<tr>
<td>Novozym 435</td>
<td>15</td>
<td>3 (R)</td>
<td>5 (S)</td>
<td>30</td>
<td>1,1</td>
</tr>
<tr>
<td>P. camembertii</td>
<td>420</td>
<td>-</td>
<td>14 (R)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Porcine Pancreas</td>
<td>420</td>
<td>-</td>
<td>5 (S)</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Candida rugosa</td>
<td>300</td>
<td>10 (S)</td>
<td>31 (R)</td>
<td>27</td>
<td>2,0</td>
</tr>
<tr>
<td>wheat Germ</td>
<td>480</td>
<td>3 (S)</td>
<td>20 (R)</td>
<td>&gt;0,1</td>
<td>-</td>
</tr>
</tbody>
</table>

^aExperimental conditions: Substrate (3 mg); lipase (5 mg/1 mg to T. lanuginosa); vinyl acetate (1.1 eq.); dry hexane (6 mL), at 30 °C under continuous agitation (150 rpm).
^bDetermined by GC (column CHIRALDEX B-PM)
^cCalculated by using the equation: \( E = \ln[(1-\text{ee}_s)(1+\text{ee}_p/\text{ee}_s)]^{-1}/\ln[(1+\text{ee}_s)(1+\text{ee}_s/\text{ee}_p)]^{-1} \) [ref. 5]
^dAbsolute configuration was determined by comparison of the specific optical rotation with literature [ref. 12]
^e\text{ee}_s = substrate enantiomeric excess; \text{ee}_p = product enantiomeric excess

Although it was achieved low E values for this enantioselective kinetic resolution, the results prompted us to take the next step in the research and make a detailed study of these reactions so as to have a better understanding of these results, including the increase of the enantiomeric excess from 14% (1.1 eq. of vinyl acetate) to >99% (2.2 vinyl acetate) promoted by lipase of P. camembertii.

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References and Notes


