Note

Lipase-catalyzed Kinetic Resolution of Racemic Methyl 13-Hydroperoxy-9Z,11E-octadecadienoate in an Organic Solvent

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As reported already by us, 1-phenylethylhydroperoxide in an organic solvent was found to be a good substrate for lipase-catalyzed acylation, the process being highly stereoselective.1 As an application of this enzymatic reaction, we report here the lipase-catalyzed kinetic resolution of racemic methyl 13-hydroperoxy-9Z,11E-octadecadienoate (1). The optical resolution of such a racemic polyunsaturated hydroperoxy fatty acid is of recent interest because both of their enantiomers are important substances for medical studies concerning toxicity and other physiological actions.2

It is generally known that when primary or secondary hydroperoxide is acylated, it can be easily converted to an aldehyde or ketone. In the present system, the acetylated hydroperoxy group could be performed predominantly over this hydrolysis simply by using vinyl acetate alone as a solvent and as an acetylation reagent.

Thus, the reaction was conducted at room temperature, and the reaction progress was checked by TLC. The

![Chemical structure of 13-Hydroperoxy-9Z,11E-octadecadienoate](image)

Table I. Enzymatic Optical Resolution of Racemic Methyl 13-Hydroperoxy-9Z,11E-Octadecadienoate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enzyme</th>
<th>% reaction yield</th>
<th>[α]D (CHCl₃)</th>
<th>%e.e.</th>
<th>Configuration</th>
<th>E-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>64</td>
<td>+2.8</td>
<td>31</td>
<td>S</td>
<td>1.9</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>77</td>
<td>+2.3</td>
<td>25</td>
<td>S</td>
<td>1.4</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>66</td>
<td>+2.2</td>
<td>24</td>
<td>S</td>
<td>1.6</td>
</tr>
<tr>
<td>4</td>
<td>D</td>
<td>77</td>
<td>+3.8</td>
<td>42</td>
<td>S</td>
<td>1.8</td>
</tr>
<tr>
<td>5</td>
<td>E</td>
<td>50</td>
<td>+3.8</td>
<td>42</td>
<td>S</td>
<td>3.6</td>
</tr>
<tr>
<td>6</td>
<td>E</td>
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<td>+4.3</td>
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<td>75</td>
<td>+6.5</td>
<td>72</td>
<td>S</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Enzyme A, cholesterol esterase (Toyo Jozo); B, lipase (Toyobo); C, lipase (Kurita Water Industries); D, Lipase (Nagase Bio-chemicals); E, lipase (Amano Pharmaceutical Co.).
reaction was quenched by filtering the enzyme at a conversion of 50–77%, and the unreacted hydroperoxide was isolated pure. Under the same conditions, one esterase and four lipases from different sources were examined, the results being given in Table I.

For example, when lipase Amano P-catalyzed acetylation (entry 7) was quenched at 75% conversion, the recovered hydroperoxide was found to have 72% optical purity. With other enzymes, the % e.e. ranged over 24–72%, being dependent on the enzyme species as well as the reaction conversion. It was also found that the unreacted hydroperoxide had a predominantly (S)-configuration without exception. This indicates that the R-hydroperoxide was preferentially acetylated by enzymes.

From the foregoing reaction mixture, a ketone (4) was isolated by column chromatography, although complete purification was unsuccessful due to concomitant products with a very close Rf-value.

The E-value, which was defined by Sih,3) was found to be 1.4–1.9 for enzymes A–D and 3.2–3.8 for enzyme E. Thus, as far as the present system has been applied, lipase Amano P was found to have best stereoselectivity.

It should also be noted that, as entries 5–7 show, by increasing the reaction conversion from 50 to 75%, the % e.e. increased from 42 to 72%. This demonstrates that the process involved kinetic resolution from the inherent stereospecificity afforded by each enzyme.

In summary, by using vinyl acetate as a solvent and acetyl donor, the enzymes catalyzed a stereoselective acetylation of the hydroperoxy group. The present study provided a rare but possible route2) to optically active polyunsaturated hydroperoxyfatty acid esters.

**Experimental**

Racemic methyl 13-hydroperoxy-9Z,11E-octadecadienoate (1). This compound was prepared by Corey’s method.4) $[\alpha]_D^{25} = 0^\circ$ (c 2.5, CHCl₃). IR $v_{max}$ (liquid) cm⁻¹: 1745 (C=O), 3400 (OOH). NMR (500 MHz) $\delta_H$ (CDCl₃): 0.88 (t, 3H, $J = 6.6$ Hz, CH₃); 1.2–1.7 (18H, CH₂ × 9); 2.16 (dd, 2H, $J = 7.2$ and 6 Hz, 8-H); 2.3 (t, 2H, $J = 7.2$ Hz, 2-H); 3.66 (s, 3H, OCH₃); 4.37 (ddd, 1H, $J = 8$ and 15 Hz, 13-H); 5.46 (dd, 1H, $J = 7.7$ and 13.8 Hz, 9-H); 5.56 (dd, 1H, $J = 8$ and 15 Hz, 12-H); 6.00 (t, 1H, $J = 11$ Hz, 10-H); 6.57 (dd, 1H, $J = 11$ and 15 Hz, 11-H); 7.90 (dd, 1H, OOH).

General procedure for enzyme-catalyzed acylation of the racemic hydroperoxide (1). Racemic hydroperoxide 1 (0.20 g, 0.6 mmol) was taken into a 5 ml measuring flask and filled up to 5.0 ml with vinyl acetate. The enzyme (0.15 g) was added to the solution, and the mixture stirred at room temperature. The reaction progress was followed by a chromatoscanner at 250 nm and quenched at a conversion yield of 50–75% by filtering out the enzyme. The hydroperoxide (2) left in the solution without acetylation was isolated pure by silica gel chromatography (hexane-ethyl acetate (85:15)), and the optical rotation was measured for this compound, from which the % e.e. was calculated by using the reported maximum rotation $[\alpha]_D^{25} = +9.1^\circ$ (CHCl₃).3)

Ketone 4 was isolated from the corresponding column fraction, IR $v_{max}$ (liquid film) cm⁻¹: 1674 (C=O), 1745 (O=C=O). NMR $\delta_H$ (CDCl₃): 0.89 (3H, t, $J = 6.9$ Hz, CH₃), 1.2–1.5 (16H, m, CH₂), 2.29 (2H, t, $J = 7.2$ Hz, CH₂COO), 5.6–6.0 (3H, m, =CH–CH–CH=), 3.66 (3H, s, OCH₃), 6.53 (1H, d, $J = 12$ Hz, COCH).

**References**