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# Synthesis of optically pure halogenated phenyl 2-hydroxypropanones by lipase-catalyzed enantioselective transesterification

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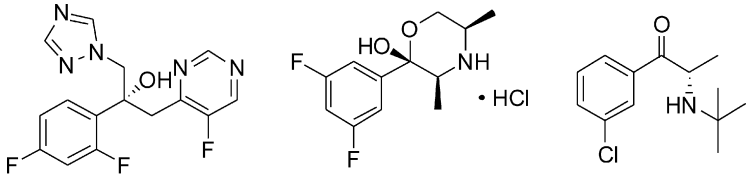
**Abstract**

Lipase-catalyzed enantioselective transesterification has been performed to obtain chiral halogenated phenyl 2-hydroxypropanones, key intermediates of pharmaceuticals. Effects of organic solvents, reaction temperature, and substrate concentration were also investigated in Novozym 435-catalyzed transesterification of 1-(2,4-difluorophenyl)-2-hydroxypropanone with vinyl butanoate. Optically pure halogenated phenyl 2-hydroxypropanones and their esters have been successfully prepared in good yields (>40%) and excellent enantiopurities (>99%) by Novozym 435-catalyzed transesterification at 30 °C in hexane.


*Keywords:* Lipase; Novozym 435; Kinetic resolution; Transesterification; Halogenated phenyl 2-hydroxypropanones

## 1. Introduction

Chiral α-hydroxy ketones (acyloins) are important building blocks due to both carbonyl and hydroxyl groups, which can be easily transformed to various functional groups [1]. Particularly, halogenated phenyl 2-hydroxypropanones are key intermediates for the synthesis of the biologically active compounds. For example, 1-(2,4-difluorophenyl)-2-hydroxypropan-1-one (**1a**) is a starting material for anti-fungal agents such as voriconazole (Vfend®, Pfizer) and posaconazole (Noxafil®, Schering) [2], and 1-(3,5-difluorophenyl)-2-hydroxypropan-1-one (**1b**) is a starting material for manifaxine hydrochloride (an attention deficit hyperactivity disorder and antiobesity drugs) [3]. 1-(3-Chlorophenyl)-2-hydroxypropan-1-one (**1c**) is a key intermediate to synthesize bupropion, which is the active ingredient of Wellbutrin® (an anti-depressant medication, GlaxoSmithKline) and Zyban® (a smoking deterrent, GlaxoSmithKline) [4].




**Voriconazole** **Manifaxine hydrochloride** **Bupropion**

Several chemical and enzymatic methods have been developed for the preparation of optically pure α-hydroxy ketones: asymmetric oxidation of enol phosphates [5], asymmetric dihydroxylation of allenes [6], selective oxidation of asymmetric *sec*-1,2-diols [7], regioselective reduction of α-diketones [8], enantioselective carboligation [9,10], and kinetic resolution [11].

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Lipase-catalyzed kinetic resolution has been widely used as a convenient and efficient method to obtain chiral alcohols and carboxylic acids [12–19]. Recently, we succeeded in obtaining optically pure alkyl lactates in high yields and enantioselectivities by lipase-catalyzed transesterification in organic solvents [20,21]. For optically active halogenated phenyl 2-hydroxypropanones, kinetic resolution has been performed by enzymatic- and fungus-mediated hydrolysis of the corresponding acetates [22,23]. However, from our literature survey, it appears that enzymatic transesterification approach for enantiopure halogenated phenyl 2-hydroxypropanones has not been attempted so far. In this study, we have reported the preparation of pharmacologically interesting chiral halogenated phenyl 2-hydroxypropanones by lipase-catalyzed transesterification with vinyl butanoate in organic solvents.

## 2. Experimental

### 2.1. General methods

All the chemicals were purchased from Aldrich and TCI. The lipases screened were as follows: *Candida antarctica* lipase B, immobilized (Novozym 435, Novozymes), *Rhizomucor miehei* lipase, immobilized (Lipozyme IM, Novozymes), *Candida rugosa* lipase, free (Sigma), porcine pancreatic lipase, free (Sigma), *Aspergillus niger* lipase, free (Lipase A, Amano), *Burkholderia cepacia* lipase, free (Lipase PS, Amano), *B. cepacia* lipase, immobilized on ceramic (Lipase PS-C, Amano), *B. cepacia* lipase, immobilized on diatomite (Lipase PS-D, Amano), *C. rugosa* lipase, free (Lipase AY, Amano), *Mucor javanicus* lipase, free (Lipase M, Amano), *Penicillium camembertii* lipase, free (Lipase G, Amano), *Pseudomonas fluorescence* lipase, free (Lipase AK, Amano), *Rhizopus oryzae* lipase, free (Lipase F-AP 15, Amano). The conversion and ee were determined by HPLC analysis, which was performed with a Young-Lin M930 pump system connected to a Young-Lin M720 absorbance detector. Separations were carried out over a Chiralcel OJ (250 mm × 4.6 mm i.d., 10 μm particle size, Daicel Chemical Industries) at a flow rate of 1.0 mL/min with *n*-hexane: isopropyl alcohol (98.5:1.5, v/v). $^1$H NMR spectra were recorded on a Bruker 300 MHz spectrometer.

### 2.2. Typical procedure for the enzymatic transesterification of rac-**1a** with **2**

To a solution of *rac*-**1a** (14.8 mg, 0.08 mmol) and **2** (0.020 mL, 0.16 mmol) in *n*-hexane (2 mL) was added Novozym 435 (2 mg). The reaction mixture was shaken at 200 rpm at 30 °C. At the pre-determined intervals, the samples were withdrawn, and then subject to HPLC analysis to monitor the reaction.

### 2.3. Preparation of (S)-1 and (R)-3 by Novozym 435-catalyzed transesterification of rac-**1** with **2**

To a solution of *rac*-**1** (0.8 mmol) and **2** (1.6 mmol) in *n*-hexane (0.2 mL) was added Novozym 435 (20 mg). The reaction mixture was shaken at 200 rpm at 30 °C. The solution was monitored by HPLC till a 50% conversion. After a 50% conversion, the mixture was filtered to remove the enzyme, concentrated in vacuum, and then purified by flash chromatography (hexane/ethyl acetate = 9:1).

The syntheses and characterization of (*S*)-1-(2,4-difluorophenyl)-2-hydroxypropan-1-one ((*S*)-**1a**), (*S*)-1-(3,5-difluorophenyl)-2-hydroxypropan-1-one ((*S*)-**1b**), and (*S*)-1-(3-chlorophenyl)-2-hydroxypropan-1-one ((*S*)-**1c**) have been reported elsewhere [22].

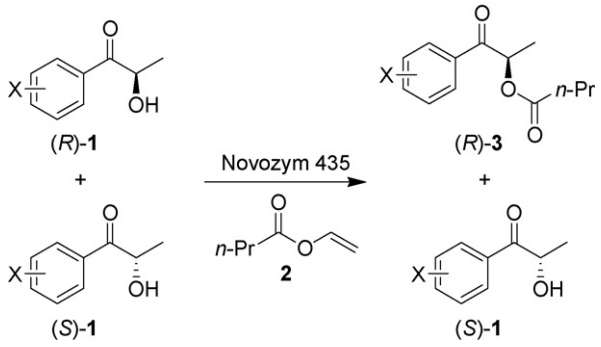
(*R*)-1-(2,4-Difluorophenyl)-1-oxopropan-2-yl butanoate ((*R*)-**3a**) was isolated as a yellow oil. HPLC (Chiralcel OJ): $R_t(R) = 8.7$ min, $R_t(S) = 11.9$ min, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.99–7.91 (q, $J = 8.4$ Hz, 1H), 6.99 (td, $J = 8.1$ Hz, $J = 2.4$ Hz, 1H), 6.89 (t, $J = 8.7$ Hz, 1H), 5.75 (qd, $J = 6.9$ Hz, $J = 1.5$ Hz, 1H), 2.38 (td, $J = 7.4$ Hz, $J = 2.4$ Hz, 2H), 1.74–1.61 (m, 2H), 1.50 (d, $J = 6.9$ Hz, 3H), 0.97 (t, $J = 7.2$ Hz, 3H).

(*R*)-1-(3,5-Difluorophenyl)-1-oxopropan-2-yl butanoate ((*R*)-**3b**) was prepared as a yellow oil. HPLC (Chiralcel OJ): $R_t(R) = 15.4$ min, $R_t(S) = 22.5$ min, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.47–7.43 (m, 2H), 7.04 (tt, $J = 8.4$ Hz, $J = 2.4$ Hz, 1H), 5.79 (q, $J = 6.9$ Hz, 1H), 2.38 (td, $J = 7.4$ Hz, $J = 1.2$ Hz, 2H), 1.70-1.61 (m, 2H), 1.52 (d, $J = 7.2$ Hz, 3H), 0.95 (t, $J = 7.5$ Hz, 3H).

(*R*)-1-(3-Chlorophenyl)-1-oxopropan-2-yl butanoate ((*R*)-**3c**) was isolated as a yellow oil. HPLC (Chiralcel OJ): $R_t(R) = 12.9$ min, $R_t(S) = 18.4$ min, $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.88 (d, $J = 1.2$ Hz, 1H), 7.80 (dd, $J = 7.81$ Hz, $J = 0.9$ Hz, 1H), 7.42 (dt, $J = 7.8$ Hz, $J = 0.9$ Hz, 1H), 7.39 (t, $J = 7.8$ Hz, 1H), 5.85 (q, $J = 6.9$ Hz, 1H), 2.35 (td, $J = 7.4$ Hz, $J = 1.2$ Hz, 2H), 1.64 (sextet, $J = 7.5$ Hz, 2H), 1.46 (d, $J = 9.3$, 3H), 0.92 (t, $J = 7.5$ Hz, 3H).

## 3. Results and discussion

Firstly, commercially available lipases were screened for the transesterification of 1-(2,4-difluorophenyl)-2-hydroxypropanone (*rac*-**1a**) with vinyl butanoate (**2**) in hexane at 30 °C (Scheme 1). In all cases, (*R*)-**1a** was preferentially acylated (Table 1), which was in accord with the Kazlauskas' rule. This empirical rule predicts which enantiomer of a secondary alcohol reacts faster in lipase-catalyzed reactions [24]. Among the lipases tested, Novozym 435, which is an immobilized form of lipase B from *C. antarctica* (CALB),




Scheme 1.

Table 1
Transesterification of *rac*-**1a** with **2** catalyzed by various lipases[a]

| Entry | Lipases | Conversion (%) | | % ee of (*R*)-**3a** |
|---|---|---|---|---|
| | | (*R*)-**3a** | (*S*)-**3a** | |
| 1 | *Candida antarctica* lipase B, immobilized (Novozym 435) | 46 | 0 | >99.9 |
| 2 | *Rhizomucor miehei* lipase, immobilized (Lipozyme IM) | 11 | 0 | >99.9 |
| 3 | *Candida rugosa* lipase, free | 1.5 | 0 | >99.9 |
| 4 | porcine pancreatic lipase, free | 1.6 | 0 | >99.9 |
| 5 | *Aspergillus niger* lipase, free (Lipase A) | 0.7 | 0 | >99.9 |
| 6 | *Burkholderia cepacia* lipase, free (Lipase PS) | 0.8 | 0 | >99.9 |
| 7 | *B. cepacia* lipase, immobilized on ceramic (Lipase PS-C) | 15.4 | 0 | >99.9 |
| 8 | *B. cepacia* lipase, immobilized on diatomite (Lipase PS-D) | 1.1 | 0 | >99.9 |
| 9 | *C. rugosa* lipase, free (Lipase AY) | 0.9 | 0 | >99.9 |
| 10 | *Mucor javanicus* lipase, free (Lipase M) | 0.7 | 0 | >99.9 |
| 11 | *Penicillium camembertii* lipase, free (Lipase G) | 0.6 | 0 | >99.9 |
| 12 | *Pseudomonas fluorescence* lipase, free (Lipase AK) | 0.9 | 0 | >99.9 |
| 13 | *Rhizopus oryzae* lipase, free (Lipase F-AP 15) | 0.7 | 0 | >99.9 |

[a] Reaction conditions: a mixture of *rac*-**1a** (0.08 mmol), **2** (0.16 mmol), and lipase (2 mg) was shaken in hexane (2 mL) at 30 °C for 25 h.

showed the highest reactivity and stereoselectivity when compared to the other lipases as shown in Table 1. Therefore, Novozym 435-catalyzed transesterification of *rac*-**1a** with **2** was conducted in various solvents (Table 2). In hexane and ethers such as *i*-$Pr_2O$, $Et_2O$, *t*-BuOMe, enzymatic transesterification of *rac*-**1a** produced (*R*)-**3a** in excellent yields with excellent ee (entries 1 and 3–5). However, when THF, $CH_2Cl_2$, or dioxane was used as a solvent, the formation of (*R*)-**3a** was very slow (entries 6, 7, and 9). Toluene, $CCl_4$, and acetonitrile afforded a (*R*)-**3a** in moderate yields (entries 2, 8, and 10).

It is known that CALB can be operated at elevated temperature for thousands of hours without any significant activity loss [25]. As expected, the higher reaction temperature resulted in the faster transesterification reaction, when the temperature was raised from 30 to 60 °C using 5 mg of Novozym 435. In contrast, enantioselectivity toward (*R*)-**3a** tended to decrease slightly, and a little amount of (*S*)-**3a** was observed in LC (entries 11–13).

It would be attractive to perform enzymatic reactions without the use of bulk solvents. Vinyl esters can be used as both an acyl donor and a solvent in enzymatic transesterifications [26]. We attempted a solvent-free reaction system maintaining the ratio of *rac*-**1a** (mmol) to the enzyme (mg). Increasing the substrate concentration and decreasing the amount of solvent, the reaction time to reach a 50% conversion was shortened from 22 to 10 h without any enantioselectivity loss (Table 3, entries 1–3). However, when the enzymatic transesterification was carried out in a mixture of *rac*-**1a** and **2** without hexane, the 50% conversion was completed in 24 h (Table 3, entry 4).

Lipase-catalyzed kinetic resolutions of various halogenated phenyl 2-hydroxypropanones (*rac*-**1**) with **2** were conducted at 30 °C in hexane. After about 50% conversion, the remaining substrates and products were separated by column chromatography to provide (*S*)-**1** and (*R*)-**3** with excellent yields (>40%) and enantioselectivities (>99% ee) as shown in Table 4. The reaction rate of 3,5-difluorophenyl 2-hydroxypropanone (**1b**) was slow when compared to the other substrates (**1a** and **1c**), which might be explained by the difference in steric effect resulting from halogenated positions.

Table 2
Novozym 435-catalyzed transesterification of *rac*-**1a** with **2** in various solvents[a]

| Entry | Solvent | Temperature (°C) | Time (h) | Conversion (%) | | % ee of (*R*)-**3a** |
|---|---|---|---|---|---|---|
| | | | | (*R*)-**3a** | (*S*)-**3a** | |
| 1 | Hexane | 30 | 45 | >49 | 0 | >99.9 |
| 2 | Toluene | 30 | 45 | 35 | 0 | >99.9 |
| 3 | $Et_2O$ | 30 | 45 | 42 | 0 | >99.9 |
| 4 | *i*-$Pr_2O$ | 30 | 45 | 47 | 0 | >99.9 |
| 5 | *t*-BuOMe | 30 | 45 | 43 | 0 | >99.9 |
| 6 | THF | 30 | 45 | 5 | 0 | >99.9 |
| 7 | $CH_2Cl_2$ | 30 | 45 | 5 | 0 | >99.9 |
| 8 | $CCl_4$ | 30 | 45 | 23 | 0 | >99.9 |
| 9 | Dioxane | 30 | 45 | 4 | 0 | >99.9 |
| 10 | Acetonitrile | 30 | 45 | 11 | 0 | >99.9 |
| 11 | Hexane[b] | 30 | 22 | 50 | 0 | >99.9 |
| 12 | Hexane[b] | 45 | 14 | 46 | 0.6 | 97 |
| 13 | Hexane[b] | 60 | 13 | 46 | 0.8 | 97 |

[a] Reaction conditions: *rac*-**1a** (0.08 mmol), **2** (0.16 mmol), and Novozym 435 (2 mg) in various solvents were shaken at 200 rpm.
[b] Five milligrams of Novozym 435 was used.

Table 3
The concentration effect on the enzymatic transesterification of *rac*-**1a**[a]

| Entry | *rac*-**1a** (mmol) | **2**[b] (mmol) | Novozym 435 (mg) | Hexane (mL) | Time[c] (h) | % ee of | |
|---|---|---|---|---|---|---|---|
| | | | | | | (*S*)-**1a** | (*R*)-**3a** |
| 1 | 0.08 | 0.16 | 5 | 2 | 22 | 99 | 99 |
| 2 | 0.24 | 0.48 | 15 | 1 | 11 | 99 | 99 |
| 3 | 0.8 | 1.6 | 50 | 0.2 | 10 | 99 | 99 |
| 4 | 0.8 | 16 | 50 | 0 | 24 | 99 | 99 |

[a] The reaction was carried out at 30 °C.
[b] 0.02, 0.06, 0.2, and 2 mL of **2** were used, respectively.
[c] Monitored by LC till a 50% conversion.

Table 4
The transesterification of various halogenated phenyl 2-hydroxypropanones (*rac*-**1**) with **2** catalyzed by Novozym 435[a]

| Entry | X | Time (h)[b] | Yield (%) | | % ee of | |
|---|---|---|---|---|---|---|
| | | | *S*-**1** | *R*-**3** | *S*-**1** | *R*-**3** |
| 1 | 2,4-Difluorophenyl (**1a**) | 10 | 42 | 43 | >99 | >99 |
| 2 | 3,5-Difluorophenyl (**1b**) | 22 | 40 | 43 | >99 | 99 |
| 3 | 3-Chlorophenyl (**1c**) | 7 | 42 | 42 | >99 | 99 |

[a] Reaction conditions: *rac*-**1** (0.8 mmol), **2** (1.6 mmol), and Novozym 435 (20 mg) in hexane (0.2 mL) were shaken at 200 rpm at 30 °C.
[b] Monitored by LC till a 50% conversion.

## 4. Conclusions

The kinetic resolution of racemic halogenated phenyl 2-hydroxypropanones was carried out by lipase-catalyzed transesterification with vinyl butanoate in organic solvents. When the reaction was conducted in hexane at 30 °C using Novozym 435, optically pure halogenated phenyl 2-hydroxypropanones ((*S*)-**1**) and their esters ((*R*)-**3**) were successfully obtained in good yields (>40%) and excellent enantiopurities (>99% ee).

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