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Preparation of (*R*)-2-chloro-1-(*m*-chlorophenyl)ethanol by Lipozyme TL IM-catalyzed second resolution

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Abstract

(*R*)-2-Chloro-1-(*m*-chlorophenyl)ethanol, a precursor of (*R*)-3-chlorostyrene oxide which is the key chiral intermediate for the preparation of several *β*3-adrenergic receptor agonists was prepared in 40% yield and 99% *ee* by the Lipozyme TL IM-catalyzed second resolution of the corresponding racemate in the presence of vinyl acetate.

Keywords: (*R*)-2-Chloro-1-(*m*-chlorophenyl)ethanol; LipozymeTL IM; Enzymatic transesterification; Vinyl acetate; Second resolution

(*R*)-2-Chloro-1-(*m*-chlorophenyl)ethanol (−)-**1** is a precursor of (*R*)-3-chlorostyrene oxide which is the key chiral intermediate for the preparation of several *β*3-adrenergic receptor agonists that show antiobesity, antidiabetic and antidepression activities [1,2] (Scheme 1). To date, several chemical and biological methods for the preparation of (−)-**1** in enantiomerically pure or enriched form have been reported. Chemical reduction suffers from the problem of using expensive chiral catalysts and lower enantioselectivity. Asymmetric reduction of 2-chloro-1-(*m*-chloro-phenyl)ethanone using an oxazaborolidine-based catalyst gave (−)-**1** in 87% yield and 86% *ee* [2]. The microbical synthesis of (−)-**1** was achieved by reduction of the corresponding ketone using an acetone powder of *Geotrichum candidum* in 94% yield and 98% *ee* [3], or using the cell-free extract of *Rhodotorula glutinis* var. *dairenensis* IFO 415 in 75% yield and more than 99% *ee* [4] or using whole cells of *Saccharomyces cerevisiae* CGMCC 2.396 in 90% yield and more than 99% *ee* [5]. The enantiopure (−)-**1** could be obtained from the bioreduction of the corresponding α-chloroketone, while the low productivity of the bioreduction is still a challenge. The kinetic resolution of (±)-**1** is still an attractive method for the preparation of (−)-**1** in case of the (+)-**1** could be racemized efficiently. A practical synthesis of (*R*)-3-chlorostyrene oxide starting from 3-chloroethylbenzene was proposed in which (*R*)-2-bromo-(*m*-chlorophenyl)ethanol was obtained in more than 99% *ee* by the treatment of the corresponding racemate with lipase QL in the presence of propionic anhydride, the propionate was racemized in 92% yield by acid-catalyzed racemization [6].

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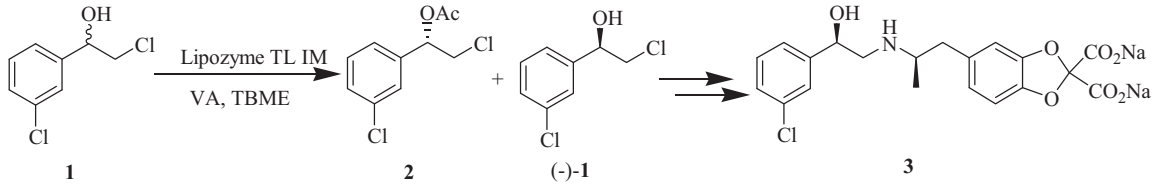

Scheme 1. The resolution of racemic **1** by Lipozyme TL IM.

In the present study, a novel and practical preparation of (−)-**1** was achieved starting from (±)-**1** in 40% yield and 99% *ee* by commercially available Lipozyme TL IM in the presence of vinyl acetate based on the second resolution strategy (Scheme 1).

1. Experimental

Racemic 2-chloro-1-(*m*-chlorophenyl)ethanol was prepared from the reduction of 2-chloro-1-(3-chlorophenyl)-ethanone by $NaBH_4$. Novozyme 435 and Lipozyme TL IM were a gift from Novo-Nordisk Co. Lipase CLL, LBK, HN and DH were purchased from the domestic plants. All other chemicals used in this study were from commercial sources without further purification.

To a 500 mL Erlenmeyer shaking-flask were added 16 g (0.084 mol) (±)-**1**, 1.6 g Lipozyme TL IM, 14.6 g (0.168 mol) vinyl acetate and 400 mL MTBE. The mixture was shaken for 48 h at 40 °C. After the reaction was completed, the enzyme was removed by filtration, and the filtrate was concentrated under certain vacuum. The residue was subjected on silica gel chromatography with *n*-hexane: ethyl acetate (20:1) to give (−)-**1**: yellow oil, 9.4 g, 80% *ee* and (+)-**2**: yellow solid, 7.8 g, 99% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (t, 3H, J = 7.5 Hz), 2.34–2.54 (m, 2H), 3.57 (dd, 1H, J = 5.1 Hz and 10.8 Hz), 3.62 (dd, 1H, J = 7.5 Hz and 10.8 Hz), 5.94 (dd, 1H, J = 5.1 Hz and 7.5 Hz), 7.22−7.31 (m, 1H), 7.32 (m, 3H).

To a 250 mL Erlenmeyer shaking-flask were added 9.4 g (−)-**1** (80% *ee*) obtained above, 0.8 g Lipozyme TL IM, 7.4 g (0.084 mol) vinyl acetate and 200 mL TBME. The mixture was shaken for 12 h at 40 °C. After the reaction was completed, the enzyme was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was subjected on silica gel chromatography with *n*-hexane: ethyl acetate (20:1) to give (−)-**1**: yellow oil, 7.6 g, 48% yield, >99% *ee*. $[\alpha]_D^{22}$ −31.33 (*c* 0.9972, $CHCl_3$) {lit. [6] $[\alpha]_D^{22}$ −33.62 (*c* 1.0, CH_3OH)}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.70 (s, 1H), 3.61 (dd, 1H, J = 11.3 Hz and 8.6 Hz), 3.74 (dd, 1H, J = 11.3 Hz and 3.5 Hz), 4.90 (dd, 1H, J = 8.6 Hz and 3.5 Hz), 7.24–7.32 (m, 3H), 7.40 (s, 1H).

^{1}H NMR spectra were recorded on a Brucker-300 (300/75 MHz) spectrometer in $CDCl_3$. Gas chromatographic analyses were performed using a Fuli GC9790 with a chiral column (CP-Chirasil-DEX CB, Varian, USA) and using a flame ionization detector, nitrogen was used as the carrier gas at 1.5 mL/min, split ratio was 1:50 (v/v), the injector and the detector temperatures were both set at 250 °C, the column temperature was programmed as being kept at 80 °C for 3 min and then upgraded to 220 °C at a rate of 3 °C/min.

2. Results and discussion

We first examined the kinetic resolution of (±)-**1** using different lipases with vinyl acetate at 30 °C and the results are illustrated in Table 1. Among the lipases examined, Lipozyme TL IM was effective for the resolution of (±)-**1** and (+)-**2** was obtained in more than 99% *ee*, but (*R*)-**1** remained moderate enantiomeric purity (56% *ee*).

The enantiomeric excess of (−)-**1** is determined by the yield of (+)-**2** during the kinetic resolution of (±)-**1**. In order to obtain (−)-**1** with high enantiomeric excess, the kinetic resolution conditions, such as organic media, temperature, water content, lipase/substrate ratio and reaction time, were investigated for the resolution of (±)-**1** using Lipozyme TL IM with vinyl acetate. In all cases, the enantioselectivity of (+)-**2** by Lipozyme TL IM was not affected, the variation of resolution conditions affected only the yield of (+)-**2**.

The reaction solvent always affects the enzyme activity and enantioselectivity in the kinetic resolution with lipase. The effects of organic solvents to the kinetic resolution with Lipase TL IM were illustrated in Table 2. Among the solvents examined, the use of ether gave high yield and enantioselectivities. Especially with MTBE as the solvent, the reaction afforded (+)-**2** with 36% yield and >99% *ee* (Table 2, entry 2).

Table 1
Resolution of (±)-**1** using various lipases with vinyl acetate.[a]

Entry	Lipase	(+)-**2** Yield (%)	*ee* (%)
1	Novozyme 435	2	97
2	Lipase CLL	n.r.[b]	n.d.[c]
3	Lipase LBK	n.r.	n.d.
4	Lipozyme TL IM	36	>99
5	Lipase DH	n.r.	n.d.
6	Lipase HB	n.r.	n.d.

[a] 50 mg (±)-**1**, 5 mg lipases, 2 eq. vinyl acetate, 5 mL TBME, 24 h, 30 °C.
[b] Not reacted.
[c] Not detected.

Table 2
The effect of solvents on the resolution of (±)-**1**[a].

Entry	Solvent	(+)-**2** Yield (%)	*ee* (%)
1	Toluene	2	96
2	MTBE	37	>99
3	*i*-Pr_2O	22	>99
4	Isooctane	9	98
5	Hexane	16	98

[a]50 mg (±)-**1**, 5 mg Lipozyme TL IM, 2 eq. vinyl acetate, 5 mL solvents, 48 h, 30 °C.

Resolution of (±)-**1** using Lipozyme TL IM with vinyl acetate in MTBE at different temperatures was carried out for 48 h. The yield of (+)-**2** increased initially with the reaction time at a relatively high rate, reaching 36.5% at 30 °C. Thereafter, the yield increased at a much lower rate, reaching the maximum (38.5%) at 40 °C.

The water content in the reaction system was also discussed. Resolution of (±)-**1** using Lipozyme TL IM with vinyl acetate in MTBE containing different water content (1–100%) was carried out for 48 h at 40 °C. The presence of micro-water in TBME greatly decreased the yield of (+)-**2**, which was decreased to 3% yield in the presence of 1% (v/v) water from 38.5% without additional water.

Mass ratio of the enzyme and substrate affects the enantioselectivity of the kinetic resolution greatly. (+)-**2** was obtained with 24% yield with 1:20 of Lipozyme TI LM/(±)-**1**. When the mass ratio of Lipozyme TI LM/(±)-**1** was 1:10, the yield of (+)-**2** reached 38%. With further increase in mass ratio to 1:2, the yield increased slightly to 40%. Thus, from the economical point of view, the mass ratio of 1:10 would be an appropriate choice for the resolution of (±)-**2**.

The yield of (+)-**2** increased initially with the reaction time at a relatively high rate, reaching 36% at 48 h, Thereafter, the yield increased at a much lower rate, reaching 38% at 96 h incubation.

Under the optimal conditions (Lipozyme TL IM/(±) **1** =1:10, 40 °C, 48 h), the first round kinetic resolution of (±)-**1** using Lipozyme TL IM with vinyl acetate in MTBE was carried out. The reaction afforded the yield and *ee* of (+)-**2** reached 40% and more than 99% respectively, the enantiopurity of the (−)-**1** with 80% *ee*. In order to prepare the enantiopure (−)-**1**, we applied the second round kinetic resolution strategy to resolute (−)-**1** with 80% *ee* from the first round, according the similar procedure to the first resolution. (−)-**1** was obtained in 40% yield and >99% *ee*.

3. Conclusions

In conclusion, (*R*)-2-chloro-1-(*m*-chlorophenyl)ethanol, a precursor of a very important key intermediate for β3-adrenergic receptor agonists was prepared with >99% *ee* using Lipozyme TL IM through second resolution. The usefulness of the resolution system provides an important approach for the preparation of (*R*)-α-halohydrins which are important chiral building blocks of various pharmaceuticals.

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