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Kinetic resolution of 1-chloro-3-(1-naphthyloxy)-2-propanol, an intermediate in the synthesis of β-adrenergic receptor blockers☆

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Abstract

(*R*)- and (*S*)-1-chloro-3-(1-naphthyloxy)-2-propanol are intermediates in the synthesis of β-adrenergic blocking agents and antihypertensive drugs such as propranolol and nadoxolol. Herein, improvement in the preparation of racemic 1-chloro-3-(1-naphthyloxy)-2-propanol generated from 1-naphthol and epichlorohydrin are reported. In addition, kinetic resolution studies have been conducted to obtain both (*R*) and (*S*)-1-chloro-3-(1-naphthyloxy)-2-propanol. These compounds were obtained in highly optically pure form by the stereoselective hydrolysis of its acyl derivatives using whole cell preparations containing enzymes from native sources. The results were compared with those obtained using commercial lipases.

Keywords: Racemic 1-chloro-3-(1-naphthyloxy)-2-propanol; Kinetic resolution; Stereoselective hydrolysis

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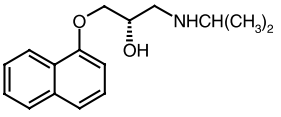
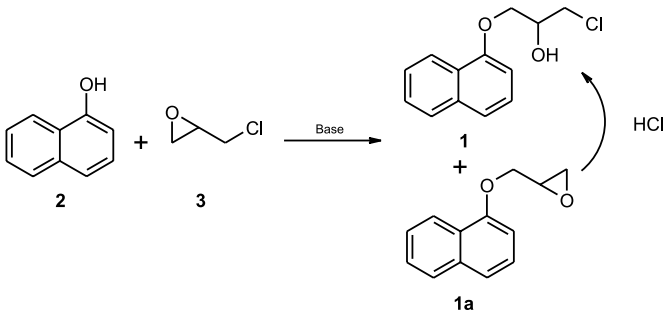
1. Introduction

It is now well established that the biological activities of molecules have close relationships with their chemical structures and that the chirality of the molecule plays an important role in its biological activity. Consequently, in most bioactive substances consisting of one or more optical centers such as drugs, insecticides, flavors, and fragrances, only one of the enantiomers may contribute to the biological activity. In β-adrenergic blocking agents (so called β-blockers) related to aryloxypropylamines (e.g., propranolol and atenolol), the therapeutic effect resides mainly in (*S*)-enantiomer [1–4]. It is reported that the (*S*)-enantiomer of propranolol is 130 times more active than the (*R*)-enantiomer (ER = 130) [5]. Therefore, resolution of the racemic precursors for the preparation of optically enriched (*S*)-enantiomer is important [4].



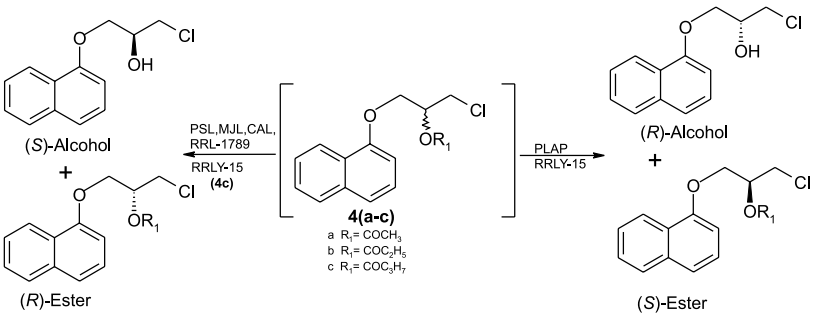
(*S*)-Propranolol

The synthetic approaches for the preparation of (*S*)-propranolol or their precursors are generally based on asymmetric syntheses [6–14] or chemoenzymatic methods [15–41]. Racemic 1-chloro-3-(1-naphthyloxy)-2-propanol (**1,** Scheme 1) is an important and easily preparable precursor of propranolol/nadoxolol, which may be synthesised by the condensation of 1-naphthol (**2**) with epichlorohydrin (**3**). The present studies are directed at the improved preparation of racemic **1** from **2** (Scheme 1). In addition, kinetic resolution studies of racemic **1** were carried out by the stereoselective hydrolysis of its acyl derivatives with crude lipases procured from commercial sources as well as whole cell preparations from native strains of the Institute's repository (Scheme 2). This methodology represents an improvement in the preparation of the enantiomers of **1**.



2 **3** **1** **1a**

Scheme 1.



Scheme 2.

2. Materials and methods

2.1. General methods and materials

^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker (200 MHz) spectrometer using TMS as an internal standard. The enantiomeric excess (ee%) was measured by chiral HPLC (Shimadzu using *R*, *R* -Whelk-O 1 chiral column, mobile phase 3:97:0.1 iso-propanol:*n*-hexane:acetic acid glacial, flow rate 0.55 ml/min.). Lipase PS "Amano" (PSL) (810 U/mg) LPSAZ0951148 was a gift from Amano Pharmaceutical, Japan. *Candida antarctica* lipase (CAL A + B) (3.0 U/g), immobilized on Sol–Gel AK, and *Mucor javanicus* lipase (MJL) (696 U/mg) were purchased from Fluka Biochemical (Switerzland) and Sigma Chemical (Germany), respectively. All the above lipases were used without further purification. Two native strains from the Institute's repository RRLY-15 (52 U/mg), RRL-1789 (650 U/mg), and PLAP (pig liver acetone powder, 1170 U/mg) prepared from fresh pig liver [42], were used in the form of whole cells.

2.2. Cultivation of Trichosporon sp. RRLY-15

The yeast RRLY-15 used in this process has been isolated from locally fermented cottage cheese as per the procedure described by Beech and Davenport [43]. A culture medium comprising of 1.5% glucose, 0.05% potassium dihydrogen phosphate (KH_2PO_4) 1.0% corn steep liquor, and 0.3% urea (pH 6.8 before sterilization and pH 6.5 after sterilization) was prepared and dispensed into shake flasks (200 ml each) and into a 10 L stainless steel (SS 304s) fermenter (working volume 7.5 L) and autoclaved. The preculture of strain *Trichosporon* sp. RRLY-15 was prepared by inoculating a loop full of the culture prepared from solid agar medium and incubating on a shaker at 28±1 °C. The 24 h old preculture thus produced was inoculated into the culture medium and fermentation carried out at 500 rpm, 1.0 vvm aeration rate and at a temperature of 28±1 °C for 15–18 h. After fermentation the wet cell biomass (120 g/L) was centrifuged at 8000*g*. The wet cell biomass (60 g) was lyophilized to a dry powder (15 g) and used directly for the kinetic resolution studies. The yeast strain RRLY-15 has been deposited at Deutsche

Sammlung von Mikroorganismen und Zellekulturen GmbH (DSMZ) Braunchweig, Germany under Accession No. DSM 11829.

2.3. Cultivation of Bacillus sp. RRL-1789

Bacillus sp. RRL-1789 has been isolated from fresh water sources in the hilly areas of Jammu region as per the procedure described by Breed et al. [44]. A culture medium comprising of yeast (1.0 g/L), peptone (10 g/L), glucose (10 g/L), and sodium chloride (5 g/L), (pH 7.0 before sterilization and 6.8 after sterilization) was prepared and dispensed into shake flasks (200 ml each) and into a 10 L stainless steel (SS 304s) fermenter (working volume 10.0 L) and autoclaved. The preculture of strain *Bacillus* sp. RRL-1789 was prepared in the shake flask by inoculating a loop full of the culture prepared from solid agar medium and incubating at 200 rpm at 28±1 °C . The 24 h old preculture thus produced was inoculated into the culture medium and fermentation carried out at 400 rpm, 0.7 vvm aeration rate and at a temperature of 28±1 °C for 15–18 h. After fermentation the wet cell biomass (10 g/L) was centrifuged at 10,000*g*. The wet cell biomass (10 g) was lyophilized to a dry powder (2 g) and used directly for kinetic resolution studies.

2.4. Synthesis of 1-chloro-3-(1-naphthyloxy)-2-propanol (**1**)

A solution of 1-naphthol **2** (14.4 g, 0.1 mol), epichlorohydrin **3** (39 ml, 0.5 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 200 μl) was refluxed on a water bath for 20 min until the TLC showed the completion of the reaction. The excess epichlorohydrin was removed under reduced pressure. The resulting reaction mixture was extracted with dichloromethane (3 × 100 ml). The combined organic layers were washed with water (2 × 30 ml), dried over anhydrous sodium sulphate and the solvent removed under vacuum to give a crude mixture of **1** and **1a** in the ratio of 80:20 (as estimated by GC).

Subsequently, the mixture was dissolved in dichloromethane (60 ml) and conc. hydrochloric acid was added dropwise. The mixture stirred for two hours at 5 °C . After completion of the reaction (monitored by TLC), water (50 ml) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (50 ml) followed by washing of the combined organic layers with water (2 × 30 ml), and drying and removal of solvent under vacuum. The resulting oil (22.5 g) was purified by column chromatography over silica gel using EtOAc:*n*-hexane (1:49) as eluent to yield 22 g of **1** (92.5%).

^{1}H NMR ($CDCl_3$): δ 2.8 (1H, bs, O*H*), 3.9 (2H, d, $J = 4.7$ Hz; CH_2Cl), 4.1–4.4 (3H, m, OCH_2 C*H*OH), 6.8–8.3 (7H, m, Ar–*H*).

2.5. General procedure for the preparation of acyl derivatives of 1-chloro-3-(1-naphthyloxy)-2-propanol (**4a–c**)

A solution of **1** (4.73 g, 20 mmol), alkyl acid anhydride (22mmol) and 4-dimethylaminopyridine (DMAP, in catalytic amount) was stirred at room temperature

for 12 h. Addition of cold water followed by dichloromethane extraction, washing with water, drying, removal of solvent followed by purification on silica gel gave the acyl derivatives **4a–c** in 90–95% yield.

1-Chloro-2-acetoxy-3-(1-naphthyloxy) propane

^{1}H NMR ($CDCl_3$); δ 2.15 (3H, s, CH_3), 3.95 (2H, d, $J = 5.0$ Hz, CH_2Cl), 4.36 (2H, d, $J = 5.0$ Hz, OCH_2), 5.52 (1H, m, C*H*), 6.8-8.3 (7H, m, Ar–*H*).

1-Chloro-2-propanoyloxy-3-(1-naphthyloxy) propane

^{1}H NMR ($CDCl_3$); δ 1.26 (3H, t, $J = 7.5$ Hz, CH_3), 2.45 (2H, q, $J = 7.5$ Hz, $COCH_2$), 3.9 (2H, d, $J = 4.5$ Hz, CH_2Cl), 4.36 (2H, d, $J = 5.0$ Hz, OCH_2), 5.54 (1H, m, C*H*), 6.8–8.3 (7H, m, Ar–*H*).

1-Chloro-2-butanoyloxy-3-(1-naphthyloxy) propane

^{1}H NMR ($CDCl_3$); δ 0.97 (3H, t, $J = 7.45$ Hz, CH_3), 1.68 (2H, m, CH_2), 2.34 (2H, t, $J = 7.4$ Hz, $COCH_2$), 3.92 (2H, d, $J = 5$ Hz, CH_2Cl), 4.36 (2H, d, $J = 5$ Hz, OCH_2), 5.52 (1H, m, C*H*), 6.8–8.3 (7H, m, Ar–*H*).

2.6. General procedure for lipase catalysed kinetic resolution of acyl derivatives of 1-chloro-3-(1-naphthyloxy)-2-propanol

A mixture of substrate **4** (200 mg), crude enzyme preparations in the ratio given in Tables 2 and 3, and sodium phosphate buffer (0.1 M, pH 7, 4 ml) was stirred at 27±1 °C, maintaining pH 7 by the addition of 0.1 N NaOH solution. The course of the reaction was monitored by chiral HPLC. After a certain degree of conversion, the reaction was terminated by centrifugation of the reaction mixture at 10,000*g* to remove cell mass and the suspended particles. The clear solution and the centrifuged cell mass was extracted separately with ethyl acetate (3×10 ml). The organic layers were combined and washed with water, dried and the organic layers concentrated under reduced pressure. The resulting mixture consisted of the alcohol and ester, which were separated by column chromatography over silica gel using EtOAc:*n*-hexane (1:49) as eluent to furnish the optically enriched **1** and **4**.

2.7. Procedure for lipase catalysed kinetic resolution of 1-chloro-2-acetoxy-3-(1-naphthyloxy) propane (4a) by RRLY-15

A mixture of substrate **4a** (200 mg, 0.72 mmol), RRLY-15 (100 mg), and sodium phosphate buffer (0.1 M, pH 7, 4 ml) was stirred at 27±1 °C , maintaining pH 7 by the addition of 0.1 N NaOH solution. The course of the reaction was monitored by chiral HPLC. The reaction was terminated after 47% hydrolysis, by centrifugation of reaction mixture at 10,000*g* to remove cell mass and the suspended particles. The clear solution and the centrifuged cell mass were extracted separately with ethyl acetate (3×10 ml). The organic layers were combined and washed with water, dried and concentrated under reduced pressure. The resulting mixture consisted of the alcohol and ester, which were separated by column chromatography over silica gel using EtOAc:*n*-hexane (1:49) as eluent to furnish optically enriched **1** (70 mg, 0.3 mmol, 35%) (ee > 99%)and **4a** (96 mg, 0.34 mmol, 48%) (ee 88%).

2.8. Procedure for lipase catalysed kinetic resolution of 1-chloro-2-butanoyloxy-3-(1-naphthyloxy) propane (**4c**) by M. javanicus lipase (MJL)

A mixture of substrate **4c** (200 mg, 0.65 mmol), MJL powder (200 mg), and sodium phosphate buffer (0.1 M, pH 7, 4 ml) was stirred at 27±1 °C , maintaining pH 7 by the addition of 0.1 N NaOH solution. The course of the reaction was monitored by chiral HPLC. After 52% hydrolysis, the reaction was worked up as described above and the components were separated by column chromatography over silica gel using EtOAc:*n*-hexane (1:49) as eluent to furnish optically enriched **1** (64 mg, 0.27 mmol, 32%) (ee 91%)and **4c** (88 mg, 0.28 mmol, 44%) (ee > 99%).

3. Results and discussion

1-Chloro-3-(1-naphthyloxy)-2-propanol, **1**, was synthesised by a modification of Stephenson's method [45], consists of a condensation reaction between 1-naphthol **2** and epichlorohydrin **3** in presence of a base (Scheme 1). The results of the condensation reaction in the presence of various bases are presented in Table 1.

Reaction of 1-naphthol **2** with epichlorohydrin **3** in a molar ratio of 1:5, where epichlorohydrin was used as a solvent, in the presence of potassium carbonate [45] in acetone, yielded a mixture of glycidyl-1-naphthyl ether **1a** and chlorohydrin **1** in approximately 40:60 ratio. Optimization of the experimental conditions improved the product ratio to 23:77 in 24 h [15]. However, when the organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used in a catalytic amount the ratio improved to 10:90 in 72 h. By further optimization of the reaction conditions it was possible to obtain a ratio of 20:80 within just 20 min. No further attempts were made to improve the product ratio. However, the 20:80 product mixture could be smoothly converted to a major product **1**, by treatment with conc. hydrochloric acid at 5 °C followed by purification by column chromatography. The racemic chlorohydrin **1** was obtained in an over all yield of 92%. The pure product was then converted to its racemic o-acyl

Table 1
Effect of different bases on the product distribution ratio (**1a**:**1**) in the condensation of 1-naphthol (**2**) with epichlorohydrin (**3**)[a]

Base	Ratio[b]	Temp./exp. conditions	Time	Product ratio[d] (**1a**:**1**)
NaOH	1:1	Reflux	28 h	35:65
K_2CO_3/acetone	1:1	Reflux	24 h	40:60
Piperidine	1:0.05	RT[c]/stirring	48 h	50:50
DBU	1:0.01	RT[c]/stirring	72 h	10:90
DBU	1:0.01	Reflux	20 min	20:80

[a] 1-Naphthol:epichlorohydrin (mole ratio) = 1:5 [Epichlorohydrin used as solvent].
[b] 1-Naphthol:base (mole ratio).
[c] Room temperature (27±1 °C).
[d] Estimated by GC.

derivatives (**4a–c**), which were used as substrates for detailed kinetic resolution studies.

The lipase-catalyzed stereoselective hydrolysis of **4a–c** was studied using three crude lipases procured from commercial sources and whole cell preparations obtained from two native strains of the Institute's repository and one prepared from fresh pig liver. All preparations were used without modification or purification. The hydrolytic reactions were generally carried out in 0.1 M sodium phosphate buffer at pH 7, at concentration of 50 g/L and at a temperature of 27±1 °C (Scheme 2). The results of the experiments using commercial lipases are summarized in Table 2.

From the data in Table 2, it is evident that *M. javanicus* lipase (MJL) showed the greatest selectivity for the *S*-ester ($E > 300$) while PSL showed faster hydrolase activity with moderate enantioselectivity ($E = 18$, ee = 85%, reported ee > 95% [15]). CAL, on the other hand, proved to be the most sluggish and showed moderate selectivity ($E = 22$, ee = 87%). As expected, all the three commercial lipases exhibited a preference for the *S*-enantiomer in the hydrolysis reaction, thus following Kazlauskas's rule of selectivity [47]. Among the acylated derivatives (**4a–c**), MJL showed the greatest selectivity for the butyrate **4c** (ee > 99%). A graph depicting the comparative enantiopurity vs. time course of the reaction using the commercial MJL is presented in Fig. 1.

After screening a large number of microorganisms from the Institute's microbial repository two native strains were selected. Pig liver acetone powder (PLAP) was prepared by a known method from freshly procured pig liver [42]. Table 3 depicts the results of kinetic resolution studies under optimized conditions of the selected

Table 2
Lipase-catalysed kinetic resolution of acyl derivatives of 1-chloro-3-(1-naphthyloxy)-2-propanol using commercial lipases

Enzyme	Subs.[a]	S:E[b]	Time (h)	Conv. (%)[c]	Ester			Alcohol			E[e]
					Isolated yield[d] (%)	Conf.	ee (%)	Isolated yield[d] (%)	Conf.	ee (%)	
MJL	**4a**	1:1	403	32	58	(*R*)	42	25	(*S*)	80.0	13
	4b	1:1	174	34	53	(*R*)	47	23	(*S*)	86.5	21
	4c	1:1	118	52	44	(*R*)	>99	32	(*S*)	91.0	>300
PSL	**4a**	1:0.3	13	35	55	(*R*)	75	23	(*S*)	85.4	18
	4b	1:0.3	20	40	53	(*R*)	68	21	(*S*)	82.8	18
	4c	1:0.3	20	32	61	(*R*)	44	20	(*S*)	85.1	18
CAL	**4a**	1:1	435	33	60	(*R*)	48	24	(*S*)	84.1	17
	4b	1:1	387	31	57	(*R*)	49	22	(*S*)	84.0	17
	4c	1:1	196	31	58	(*R*)	40	40	(*S*)	87.5	22

[a] Subs., Substrate.
[b] S:E, substrate:enzyme ratio (w/w).
[c] Conversions based on HPLC.
[d] Isolated yield in mmol (after column chromatography) based on conversions.
[e] Calculated according to Chen et al. [46]; MJL, *Mucor javanicus* lipase; PSL, Lipase PS "Amano" (*Pseudomonas cepacia*); CAL, *Candida Antarctica* (A + B mixture) lipase.

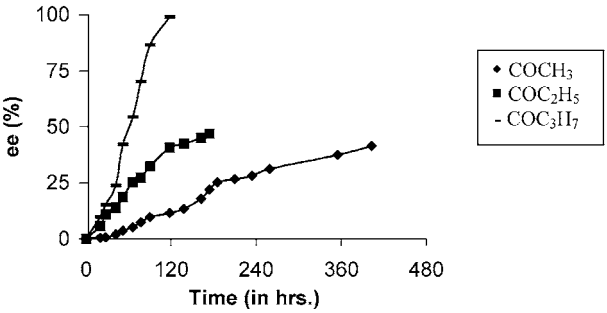


Fig. 1. Study of hydrolase activity of MJL for the acylates of 1-chloro-3-(1-naphthyloxy)-2-propanol **4a–c**.

Table 3
Kinetic resolution of acyl derivatives of 1-chloro-3-(1-naphthyloxy)-2-propanol using whole cell preparations from native strains

Enzyme	Subs.[a]	S:E[b]	Time (h)	Conv.[c]	Ester			Alcohol			E[e]
					Isolated yield[d] (%)	Conf.	ee (%)	Isolated yield[d] (%)	Conf.	ee (%)	
RRLY-15	**4a**	1:0.5	25	47	48	(*S*)	88	35	(*R*)	>99	>550
	4b	1:0.5	18	33	60	(*S*)	29	25	(*R*)	30	14
	4c	1:0.5	35	21	71	(*R*)	4	22	(*S*)	30	2
RRL-1789	**4a**	1:0.1	40	36	53	(*R*)	39	26	(*S*)	64	6
	4b	1:0.1	20	36	54	(*R*)	44	24	(*S*)	62	6
	4c	1:0.1	25	38	51	(*R*)	43	24	(*S*)	47	4
PLAP	**4a**	1:0.08	19	49	34	(*S*)	49	24	(*R*)	35	3
	4b	1:0.08	19	55	32	(*S*)	48	26	(*R*)	24	2
	4c	1:0.08	19	49	35	(*S*)	30	22	(*R*)	23	2

[a] Subs., Substrate.
[b] S:E, substrate:enzyme ratio (w/w).
[c] Conversions based on HPLC.
[d] Isolated yield in mmol (after column chromatography) based on conversions.
[e] Calculated according to Chen et al. [46]; RRLY-15 = *Trichosporon* sp.; RRL-1789 = *Bacillus* sp.; PLAP, pig liver acetone powder.

hydrolases preparations obtained from native strains. In these studies *Trichosporon* sp. (RRLY-15) was found to be the best one, displaying the highest selectivity ($E > 550$). In fact, among all the enzymes studied for the stereoselective hydrolysis, RRLY-15 established its superiority with respect to high enantioselectively and moderate rate of hydrolysis. Furthermore RRLY-15 produced the desired alcohol (*R*-enantiomer) with the highest enantiopurity (ee > 99%). The hydrolases from the other strains [i.e., *Bacillus* sp. (RRL-1789) and PLAP] displayed low to moderate selectivity.

From Table 3 it is evident that both RRLY-15 and PLAP behave like esterases showing reverse selectivity (preference for the *R* enantiomer) compared to results

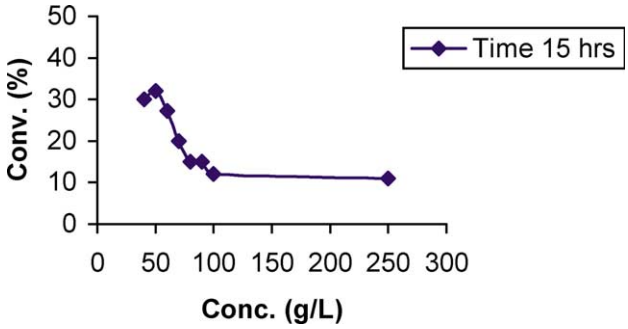


Fig. 2. Effect of the substrate concentration of 1-chloro-2-acetoxy-3-(1-naphthyloxy)propane on the hydrolase activity of RRLY-15.

obtained from commercial lipases (Table 2). Another important characteristic of RRLY-15 is the reversal of selectivity with the increase in the size of the alkyl group from acetyl to butyryl, which is not observed with any other enzyme strain. In order to improve the yield of the product (*R*-alcohol) using RRLY-15, the effect of the increase in concentration (g/L) of substrate (**4a**) was studied keeping the substrate to enzyme ratio constant. The results of these studies are depicted in Fig. 2. It is evident that the substrate concentration of 50 g/L is the optimum one which is easily tolerated by enzyme. Above 50 g/L, conversion is significantly reduced.

RRL-1789 showed moderate selectivity for the substrate. The rate of hydrolysis with PLAP was comparatively high. Using a lower substrate to enzyme ratio resulted in a significant improvement in the enantioselectivity. However, to further improve the enantioselectivity, the effect of lowering the reaction temperature for both RRL-1789 and PLAP was studied. RRL-1789 showed marked improvement in enantioselectivity for **4a** only. The ee of the product was improved to 90%, displaying much lower rates of hydrolysis (conversion 27% after 110 h at 10 °C). On the contrary, PLAP displayed significant reduction in selectivity (ee = 11%) as well as the rate of hydrolysis (conversion 26% after 24 h at 10 °C).

4. Conclusions

The preparation of racemic 1-chloro-3-(1-naphthyloxy)-2-propanol, **1**, the precursor to antihypertensive drug propranolol/nadoxolol (β-blockers) has been successfully modified. The acylates of the above precursor were subjected to kinetic resolution studies using three commercial lipases and hydrolases from two native strains and PLAP. *M. javanicus* lipase (MJL) showed high selectivity for the butyrate furnishing the *S*-alcohol of ee 91% and *R*-ester of ee > 99%. *Trichosporon* sp. RRLY-15, the native yeast strain, proved to be the most suitable one for kinetic resolution of **1** and furnished the desired *R*-alcohol in ee > 99% along with the *S*-ester (ee 88%) demonstrating higher rates of hydrolysis as well as selectivity.

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