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ORIGINAL ARTICLE

# New chemical and chemo-enzymatic synthesis of (*RS*)-, (*R*)-, and (*S*)-esmolol

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**KEYWORDS**

Esmolol;
Biocatalysis;
Lipase;
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Synthesis

**Abstract** One of the β-adrenergic receptor blocking agents, esmolol, is synthesized in its racemic (*RS*) and enantio enriched forms (*R* and *S*) by a new chemical and chemo-enzymatic route. The enantio-pure intermediates (*R*) and (*S*)-methyl 3-(4-(3-chloro-2-hydroxypropoxy)phenyl)propanoate were synthesized from the corresponding racemic alcohol by enzymatic kinetic resolution. The commercially available lipases PCL and CRL showed complementary enantioselectivity in the transesterification reaction of racemic alcohol with vinyl acetate as the acyl donor. The reactions afforded the (*R*)-alcohol along with (*S*)-acetate and the (*S*)-alcohol along with (*R*)-acetate, respectively, indicating the enzymatic switch for reversal of enantioselectivity. Various reaction parameters such as substrate and enzyme concentration, type of reaction medium, duration of conversion and enantioselectivity were optimized. The (*R*)- and (*S*)-alcohols were converted to the (*S*)- and (*R*)-esmolol, respectively, on N-alkylation with isopropanolamine. The enzymatically obtained (*R*)- and (*S*)-acetates were chemically hydrolyzed to the corresponding alcohols and further converted to (*S*)- and (*R*)-esmolol by chemical reactions. These represent the new chemo-enzymatic synthesis of both the enantiomers of the drug. Using chemical routes, the (*RS*)/(*R*)/(*S*)-esmolol were also synthesized from (*RS*)/(*R*)/(*S*)-epichlorohydrin via the corresponding (*RS*)/(*S*)/(*R*)- methyl 3-(4-((oxiran-2-yl)methoxy)phenyl)propanoate and the (*RS*)/(*R*)/(*S*)-methyl 3-(4-(3-chloro-2-hydroxypropoxy)phenyl)propanoate intermediates. This process has given improved overall yield and better enantiomeric excess compared to the reported one.



## 1. Introduction

For the rapid control of heart rate (HR) and/or blood pressure (BP) in the critical care unit for a short period of time, esmolol is a very appropriate drug (Wiest and Haney, 2012). Esmolol is a unique cardioselective $\beta_1$-receptor blocking agent with a fast onset and tiny duration of action (Wiest, 1995). Its efficacy has been established in a variety of patients, including those with myocardial ischemia (Edwards et al., 1994; Hartley and Vaughan, 1993), unstable angina (Anderson et al., 2011;

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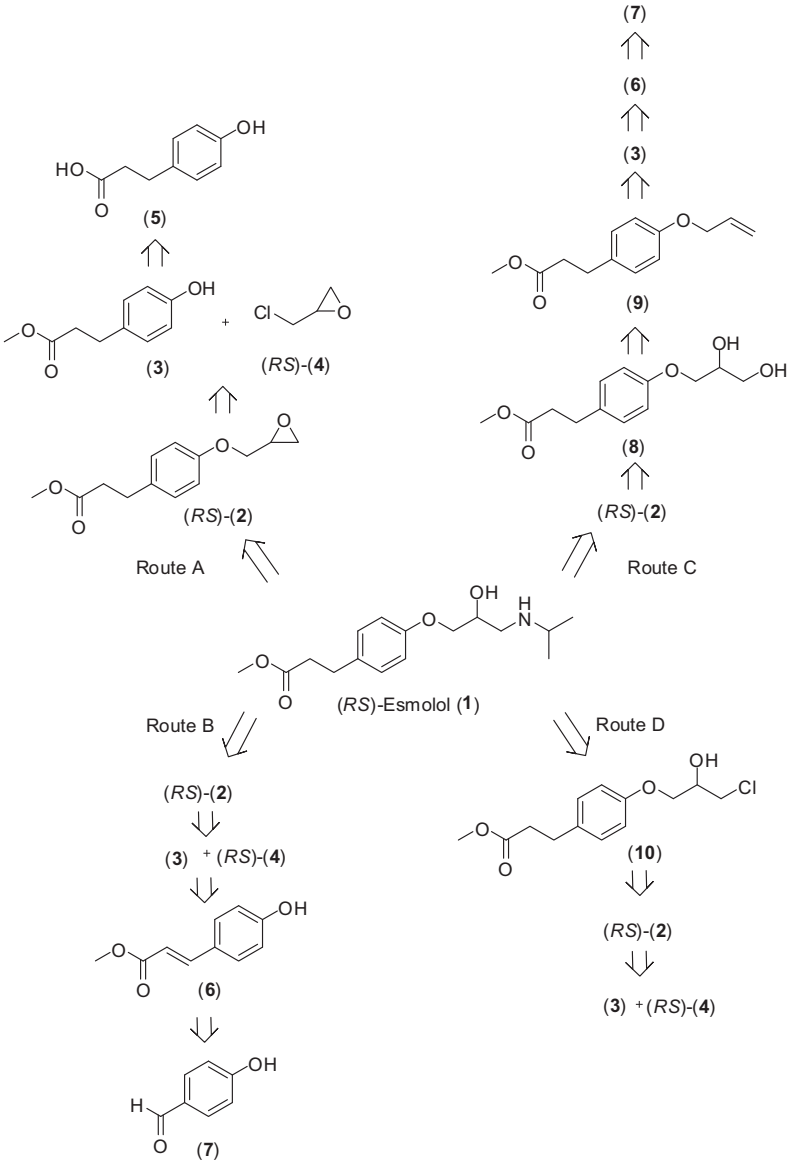
Barth et al., 1991), supraventricular arrhythmias (Adamson et al., 2006; Balser et al., 1998; Garnock-Jones, 2012), peri- and post-operative tachycardia and hypertension (Tempe et al., 1999; Wiest et al., 1998) and electroconvulsive therapy (Van Der Starre et al., 2008; Zvara et al., 1997). Although currently **1** is marketed as the racemic form, (*S*)-enantiomer of esmolol is an eutomer and the (*R*)-enantiomer is a distomer, (*S*)-esmolol as a β-blocker has two times higher potency than that of (*RS*)-esmolol (Quon et al., 1988). The limited reports for the synthesis of **1** are summarized in Scheme 1 (Erhardt et al., 1982) in which one is Sharpless asymmetric dihydroxylation (route C) and the other one is hydrolytic kinetic resolution (route B). The opening of an epoxide ring by amines is the most common strategy for the synthesis of the 1,2-amino alcohol, a class of $\beta_1$-adrenergic blocking agents (Pujala et al., 2011; Shivani et al., 2007). Efforts toward this direction for the synthesis of **1** involve the reaction of isopropylamine with the requisite epoxide 2-phenylglycidyl ether **2** (Erhardt et al., 1982). However, most of these have one or more drawbacks, such as higher cost of chiral transition metal complex catalysts, the toxic nature of catalysts, moisture sensitivity, generation of more by products and tedious separation process. These reported procedures afforded in overall 16–66% chemical yield. Herein, we describe new chemical and chemo-enzymatic synthetic route for (*RS*)-, (*R*)-, and (*S*)-esmolol (route D, Scheme 1) with improved overall chemical yield (61–76%) and higher (92–98%) enantiomeric excess.

## 2. Results and discussion

In the present days context, use of green chemistry tools in the design of a new synthetic route is highly desirable (Alfonsi et al., 2008; Roughley and Jordan, 2011) and integrating biocatalysis in the synthesis is a graceful approach toward green chemistry (Clouthier and Pelletier, 2012). Enzymatic kinetic resolution of various racemic secondary alcohols (Amrutkar




**Scheme 1** Various synthetic strategies for 1.

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et al., 2013; Banoth et al., 2009, 2012a,b) encouraged us to design a new chemo-enzymatic route for (*R*)- and (*S*)-esmolol (Scheme 2).

### 2.1. Synthesis of (RS)-methyl-3-(4-(3-chloro-2-hydroxypropoxy)phenyl)propanoate (10)

The starting racemic epoxide (*RS*)-**2** was prepared (yield, 90%) by the reaction of **3** with (*RS*)-**4** in the presence of $K_2CO_3$ in MeCN under reflux using the reported procedure. The treatment of (*RS*)-**2** with acetyl chloride in DCM and water afforded the desired substrate (*RS*)-**10** for lipase catalyzed kinetic resolution (Scheme 3).

To optimize the experimental condition for the enzymatic kinetic resolution, it is necessary to have authentic samples of (*R*)- and (*S*)-**10** and the corresponding *O*-acylated derivatives (*R*)- and **(*S*)-11**, respectively.

### 2.2. Synthesis of authentic(R)/(S)-methyl-3-(4-(3-chloro-2-hydroxypropoxy)phenyl) propanoate (10) and (RS)/(R)/(S)-methyl-3-(4-(2-acetoxy-3-chloropropoxy)phenyl) propanoate (11)

The starting materials (*S*)- and (*R*)-**2** for the synthesis of the authentic samples of (*R*)- and (*S*)-**10** were prepared by the reaction of **3** with (*R*)- and (*S*)-**4**, respectively, using the modified method. The optical purity was determined by optical rotation value and chiral HPLC. As observed in the previous report, the alkylation using (*R*)-**4** resulted the (*S*)-**2** [89% yield, 95% *ee* and optical rotation $[\alpha]_D^{20}$ +4.46 (*c* 1.0, $CHCl_3$)] and (*S*)-**4** afforded the (*R*)-**2** [87% yield, 94% *ee* and optical rotation $[\alpha]_D^{20}$ +4.42 (*c* 1.0, $CHCl_3$)] (Scheme 4). The formation of (*S*)-**2** from (*R*)-**4** may be due to the nucleophilic ring opening of the epoxide ring at the least substituted carbon atom of the epoxide followed by the nucleophilic displacement of the chlorine atom (Path b, Scheme 4), rather than the direct nucleophilic substitution of the chlorine atom (Path a, Scheme 4). This is responsible for the observed inversion of configuration.

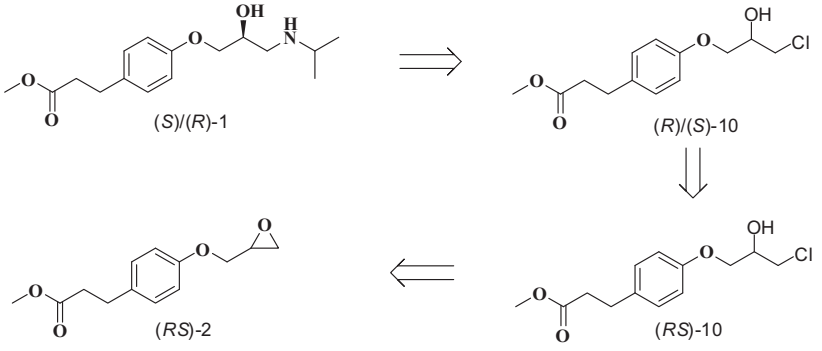
Ring opening of (*S*)-**2** by acetyl chloride and water following the same procedure as used for (*RS*)-**2** afforded (*R*)-**10** (92% yield and 94% *ee*). Similarly, (*S*)-**10** was obtained from (*R*)-**2** in 91% yield and 93% *ee*. The treatment of (*RS*)-**10** with $Ac_2O$ at rt under neat condition in the presence of $ZrCl_4$ (2 mol%) (Chakraborti and Gulhane, 2004) gave the (*RS*)-**11** in 95% yield. Acetylation of (*R*)-**10** and (*S*)-**10** using a similar procedure resulted in the formation of (*R*)-**11** and **(*S*)-11** (93% yield and 94% *ee* and 92% yield and 93% *ee*, respectively).

### 2.3. Lipase-catalyzed kinetic resolution of (RS)-10

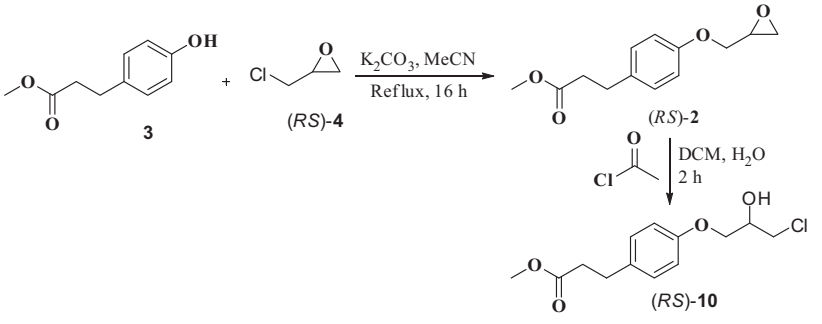
The best operative enzymatic kinetic resolution method using various lipases was found out with the substrates (*RS*)-**10** and the authentic samples of (*R*)/(*S*)-**10** and (*R*)/**(*S*)-11**.

#### 2.3.1. Screening of lipases

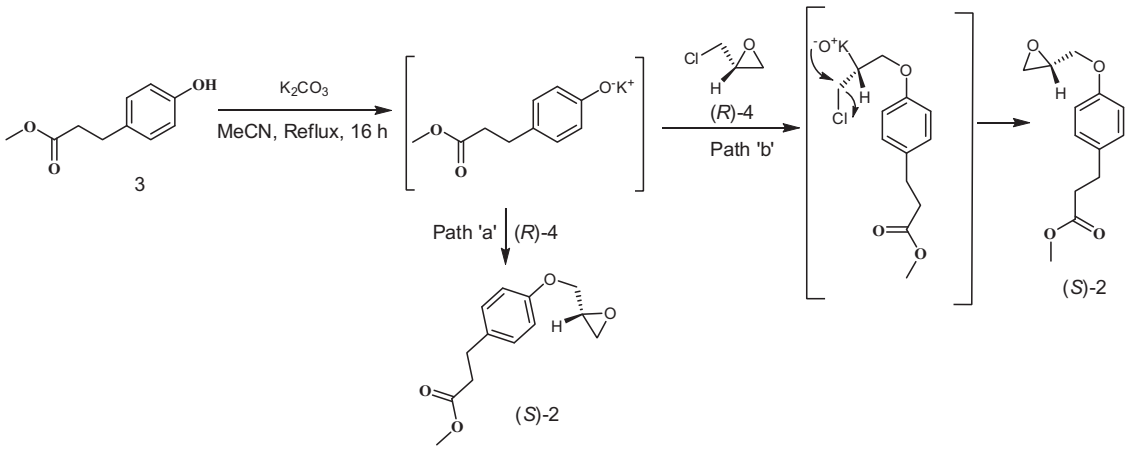
The selection of lipase is the first step to achieve successful kinetic resolution of any transesterification reaction. Initially, lipases from different sources [commercially available immobilized lipase in sol–gel-Ak from *Pseudomonas cepacia* (PCL), immobilized lipozyme from *Mucor miehei* (MML), lipase



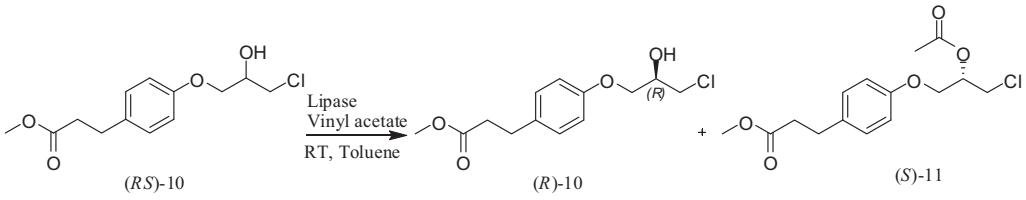

**Scheme 2** New chemo-enzymatic route for (*R*)- and (*S*)-esmolol.




**Scheme 3** Synthesis of (*RS*)-**10**.




**Scheme 4** Formation of (*S*)-**2** from (*R*)-**4**.




**Scheme 5** Enzymatic kinetic resolution of (*RS*)-**10**.

acrylic resin from *Candida antarctica* (CAL), lipase A *C. antarctica* (CAL-A), *Candida rugosa* (CRL L8525), *C. rugosa* (CRL L1754), *Candida cylindracea* (CCL), *Aspergillus niger* (ANL), porcine pancreas lipase (PPL), lipase AY "Amano"30 (CRL) and laboratory strains 5b1, 5b2, 5a1, 1b1 (N), 5d1, 1b1 (Singh et al., 2012)] were screened for the transesterification of (*RS*)-**10** with vinyl acetate in toluene (Scheme 5).

The PCL 62274 exhibited best activity for conversion of (*RS*)-**10** to (*R*)-**10** and **(*S*)-11**, respectively. The CRL 62316 exhibited best activity for conversion of (*RS*)-**10** to (*S*)-**10** and (*R*)-**11**, respectively. Thus, these enzymes show complementary action with respect to enantioselectivity. However, PCL 62274 and CRL 62316 were found to be better in terms of conversion and enantioselectivity (Table 1).

### 2.3.2. Selection of organic solvent

The solvent effect on the enantioselectivity of enzymatic reactions has been reviewed in many literatures (Hudson et al., 2005; Khmelnitsky and Rich, 1999). Lipases have attracted much attention to organic chemists because of their high stability in organic solvents (Dordick, 1989; Khmelnitsky et al., 1988). In the present study several solvents, for instance, t-butyl methyl ether: log $P$ = 1.35, isooctane: log $P$ = 4.5, toluene: log $P$ = 2.5, chloroform: log $P$ = 2.0, dichloromethane: log $P$ = 1.25 etc., were investigated for the resolution of (*RS*)-**10** (Table 2). The effect of solvent on the activity and enantioselectivity of PCL and CRL for kinetic resolution of (*RS*)-**10** was studied using vinyl acetate as acyl donor at 25 °C. It had been observed that both the reaction rate and enantioselectivity were affected largely by the solvent employed (Table 2). Toluene for PCL and cyclohexane for CRL were found to offer maximum enantioselectivity and enantiomeric excess of substrate and product as compared to the other solvents. It has been reported (Laane et al., 1987) in the literature that in polar solvents having a log $P$ < 2, the rates of biocatalytic reactions are less compared to those of apolar solvents having a log $P$ > 4. The moderate rates of reactions are reported in organic solvents with a log $P$ value between 2 and 4 (Laane et al., 1987). It has been reported (Laane et al., 1987) that hydrophobic solvents are unable to strip away the water molecules associated with enzymes and in this process enzymes retain the required degree of hydration to remain catalytically active, whereas hydrophilic solvents, due to its water loving nature strip away water molecules from the enzyme complex which leads to catalytic deactivation. In the case of toluene and cyclohexane as hydrophobic solvents, a positive correlation between the activity of lipase and increased log $P$ values of the solvent could be seen.

### 2.3.3. Effect of reaction time

PCL and CRL catalyzed transesterification reactions of (*RS*)-**10** were separately carried out in toluene and in cyclohexane, respectively. Samples were collected periodically and centrifuged at 10,000*g* for five minutes to remove the enzyme preparation. Conversion and enantiomeric excess were determined using chiral HPLC. In the case of toluene as reaction medium, it was observed that conversion and enantiomeric excess of substrate increased with the reaction time. Maximum conversion ($C$ = 50%) and enantiomeric excess of substrate (97%) were achieved after 36 h of reaction and thereafter no significant change in the rate of conversion and enantiomeric excess was observed. The enantiomeric excess of the product was constant, whereas, the enantiomeric ratio increased up to 36 h ($E$ = 277) and then it decreased with time ($E$ = 100, at 48 h)

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**Table 1** Lipase-catalyzed transesterification of (*RS*)-**10** with vinyl acetate.[a]

| Lipase | Time (h) | *C* (%)[b] | *ee* (%)[c] | *ee* (%)[d] | *E*[e] | Configuration of 11 |
|---|---|---|---|---|---|---|
| CAL 12117 | 48 | 1.02 | 1.03 | 100 | 100 | *S* |
| PCL 62279 | 48 | 51 | 100 | 96.07 | 100 | *S* |
| CAL L4777 | 48 | 33.95 | 49.5 | 96.3 | 86.95 | *S* |
| CRL 62316 | 48 | 55.48 | 85.59 | 68.67 | 14.39 | *R* |
| CRL LY amino | 48 | 54.15 | 74.55 | 63.13 | 9.65 | *R* |
| ANL 62301 | 48 | 86.02 | 21.24 | 3.45 | 1.24 | *RS* |
| CCL 62316 | 48 | 90.76 | 95.84 | 9.76 | 3.25 | *RS* |
| MML 62350 | 48 | 87.50 | 96.67 | 13.81 | 3.91 | *RS* |
| CRL 90860 | 48 | 92.56 | 53 | 4.26 | 1.54 | *RS* |
| CRL L1754 | 48 | 90.79 | 35.13 | 3.56 | 1.35 | *RS* |
| PPL | 48 | 95.45 | 91.79 | 4.37 | 2.29 | *RS* |

[a] Conditions: (*RS*)-**10** (20 mM) in toluene (4 mL) was treated with vinyl acetate (5.4 mmol) at 30 °C in the presence of the enzyme (15 mg/mL).
[b] Conversions were calculated from the enantiomeric excess (*ee*) of (*R*)-**10** (substrate S) and **(*S*)-11** (product P) using the formula: conversion (C) = $ee_S/(ee_S + ee_P)$.
[c] Enantiomeric excess of (*R*)/(*S*)-**10** determined by HPLC analysis (Daicel Chiralcel OD-H column) 90:10; hexane: 2-propanol, 1 mL/min flow rate at 254 nm.
[d] Enantiomeric excess of (*R*)/**(*S*)-11** determined by HPLC analysis (Daicel Chiralcel OD-H column) 90:10; hexane: 2-propanol, 1 mL/min flow rate at 254 nm.
[e] *E* values were calculated using the formula: $E = [\ln (1 - C (1 + ee_P)]/[\ln (1 - C (1\text{-}ee_P)]$ (Straathof and Jongejan, 1997).

**Table 2** The effect of organic solvent on the enantioselectivity in the resolution of (*RS*)-**10** with lipase.[a]

| Solvent | Log *P* | *C*[b] (%) | *ees*[c] (%) | *Epe*[d] (%) | *E*[e] |
|---|---|---|---|---|---|
| *S-selective with PCL* | | | | | |
| Acetonitrile | −0.33 | 37.57 | 46.02 | 76.47 | 11.75 |
| 1,4-Dioxane | −1.1 | 48.2 | 7.82 | 8.4 | 1.27 |
| t-Butyl methyl ether | 1.35 | 52.07 | 100 | 92.04 | 100 |
| Diethyl ether | 0.85 | 49.11 | 83.56 | 86.6 | 36.44 |
| Dichloromethane | 1.25 | 34.19 | 44.69 | 86.01 | 20.62 |
| Benzene | 2 | 61.21 | 100 | 63.36 | 100 |
| Heptane | 4 | 42.75 | 70.52 | 94.42 | 73.68 |
| Toluene | 2.5 | 51 | 100 | 96.07 | 100 |
| Cyclohexane | 3.41 | 54.26 | 100 | 84.29 | 100 |
| Hexane | 3.5 | 49.2 | 90.1 | 93.04 | 85.78 |
| Isooctane | 4.5 | 46.1 | 76.46 | 89.4 | 41.23 |
| *R-selective with CRL 62316* | | | | | |
| Acetonitrile | −0.33 | 36.88 | 20.99 | 35.93 | 2.58 |
| 1,4-Dioxane | −1.1 | 32.16 | 15.76 | 33.23 | 2.31 |
| t-Butyl methyl ether | 1.35 | 51.69 | 71.37 | 66.69 | 10.47 |
| Diethyl ether | 0.85 | 56.09 | 30.34 | 23.76 | 2.12 |
| Dichloromethane | 1.25 | 22.72 | 9.39 | 31.95 | 2.12 |
| Benzene | 2 | 47.98 | 50.21 | 54.43 | 5.48 |
| Heptane | 4 | 84.19 | 71.14 | 13.36 | 2.36 |
| Toluene | 2.5 | 55.48 | 85.59 | 68.67 | 14.39 |
| Cyclohexane | 3.41 | 58.60 | 99.18 | 70.09 | 29.52 |
| Hexane | 3.5 | 77.90 | 75.68 | 21.47 | 3.09 |
| Isooctane | 4.5 | 72.36 | 83.27 | 31.81 | 4.52 |

[a] Conditions: (*RS*)-**10** (20 mM) in organic solvent (4 mL) was treated with vinyl acetate (5.40 mmol) in the presence of lipase (15 mg/mL).
[b] Conversions were calculated from the enantiomeric excess (*ee*) of (*R*)-**10** (substrate S) and **(*S*)-11** (product P) for PCL and enantiomeric excess (*ee*) of (*S*)-**10** (substrate S) and (*R*)-**11** (product P) for CRL using the formula: Conversion (C) = $ee_S/(ee_S + ee_P)$.
[c] Enantiomeric excess of (*R*)-**10** (substrate S) for PCL and (*S*)-**10** (substrate S) for CRL determined by HPLC analysis (Daicel Chiralcel OD-H column) 90:10; hexane/2-propanol, 1 mL/min flow rate at 254 nm.
[d] Enantiomeric excess of (*R*)-**11** (product P) for PCL and **(*S*)-11** (product P) for CRL determined by HPLC analysis (Daicel Chiralcel OD-H column) 90:10; hexane/2-propanol, 1 mL/min flow rate at 254 nm.
[e] *E* values were calculated using the formula: $E = [\ln (1 - C (1 + ee_P)]/[\ln (1 - C (1 - ee_P)]$ (Straathof and Jongejan, 1997).

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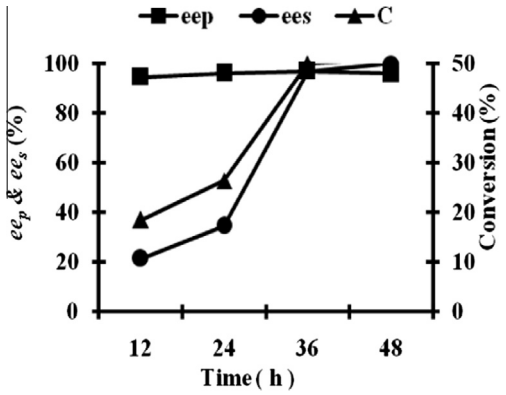


**Figure 1** Course of reaction of PCL catalyzed transesterification of (*RS*)-**10** in toluene.

(Fig. 1). In the case of cyclohexane as reaction medium, it was found that maximum conversion ($C$ = 50.3%) and enantiomeric excess of substrate (99.23) were achieved at 24 h and thereafter, the rate of conversion and enantiomeric excess of substrate increased. On the other hand, the enantiomeric ratio and enantiomeric excess of the product were increased up to 24 h ($E$ = 558.8) and thereafter it decreased with time (at 48 h, $E$ = 29.52, Fig. 2). Prolonging the reaction time further gave the advantage to the slower reacting enantiomer to convert with a less satisfactory enantiomeric excess. Thus, 36 and 24 h were taken as optimum time for further study in toluene and cyclohexane, respectively.

### 2.3.4. Effect of enzyme concentration

Enzyme concentration affects the rate of conversion as well as the enantiomeric excess of the product. To investigate the effect of enzyme concentration on conversion, enantiomeric excess and enantiomeric ratio, resolution was carried out using different concentrations of PCL and CRL preparations (10, 20, 30, 40 and 50 mg/mL) in toluene and cyclohexane, respectively. It was observed that in the case of toluene, with the increase in enzyme concentration, the conversion increased up to a certain level after which there was no significant change in conversion. In toluene as the reaction medium, maximum enantiomeric ratio (807.85) and enantiomeric excesses of the product (98.73) and substrate (98.83) with a conversion of

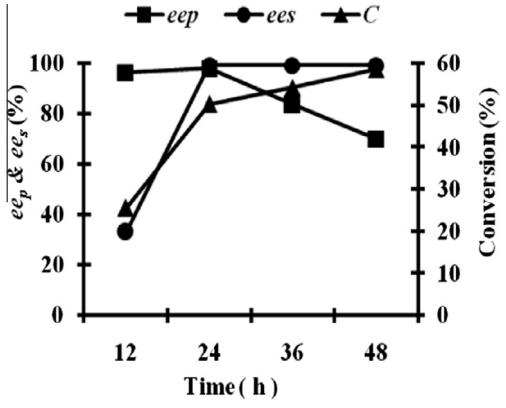


**Figure 2** Course of reaction of CRL catalyzed transesterification of (*RS*)-**10** in cyclohexane.

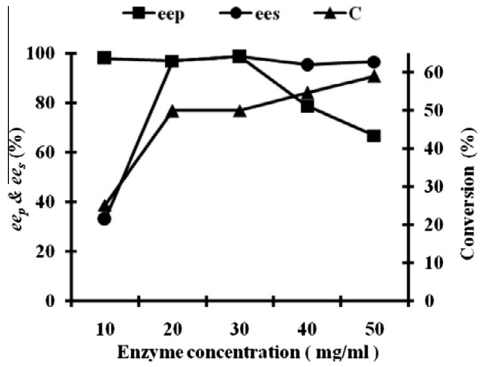


**Figure 3** Effect of enzyme concentration on PCL catalyzed transesterification of (*RS*)-**10** in toluene.

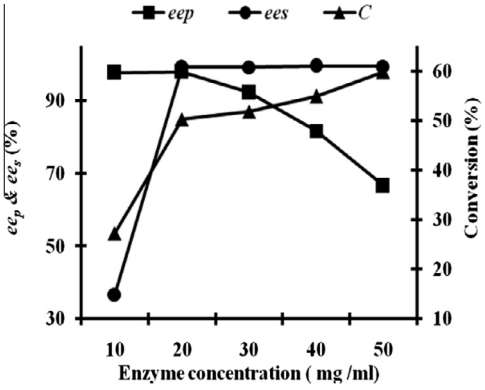


**Figure 4** Effect of enzyme concentration on CRL catalyzed transesterification of (*RS*)-**10** in cyclohexane.

50.02% were obtained with 30 mg/mL PCL enzyme preparation (Fig. 3). In the case of cyclohexane as a reaction medium, the maximum enantiomeric ratio (558.8) and enantiomeric excesses of the product (98.03) and substrate (99.23) with 50.30% conversion were achieved with 20 mg/mL CRL enzyme preparation (Fig. 4). For all the subsequent experiments, enzyme concentrations of 20 and 30 mg/mL of CRL and PCL in cyclohexane and toluene were used, respectively.

### 2.4. Deacylation of (RS)/(R)/(S)-11

The (*RS*)/(*R*)/(*S*)-**10** alcohol from the acetylated intermediate (*RS*)/(*R*)/**(*S*)-11** was formed by deacetylation in aqueous $K_2CO_3$ at rt (Khan et al., 2001) (Scheme 6).

### 2.5. Synthesis of (S)-esmolol 1

(*R*)-**10** [obtained by ring opening of (*S*)-**2** with acetyl chloride and water, deacetyaltion of (*R*)-**11** and the enzymatic kinetic resolution of (*RS*)-**10**] was treated with isopropylamine in methanol under reflux overnight (Zaidlewicz et al., 2005) to afford (*S*)-esmolol **1** (Scheme 7).

(*S*)-**10** [obtained by ring opening of (*R*)-**2** with acetyl chloride, deacetyaltion of **(*S*)-11** and the enzymatic kinetic resolution of (*RS*)-**10**] was treated with isopropylamine in methanol under reflux overnight[23] to afford (*R*)-esmolol 1 (Scheme 8).

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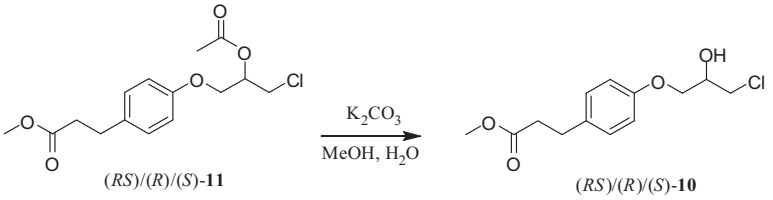
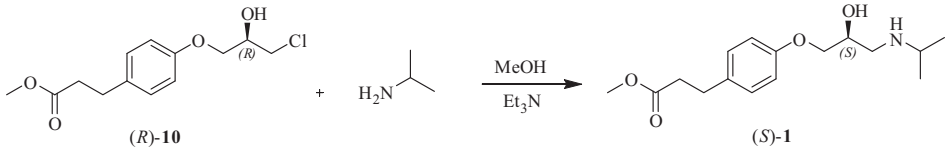
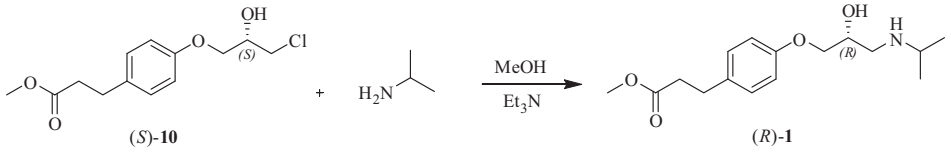



**Scheme 6** Synthesis of (*RS*)/(*R*)/(*S*)-**10**.




**Scheme 7** Synthesis of (*S*)-esmolol **1**.




**Scheme 8** Synthesis of (*R*)-esmolol **1**.

## 3. Conclusion

The efficient chemical and chemoenzymatic synthesis of the highly enantiomerically enriched cardiovascular drug esmolol is reported in this study with an improved overall yield (61–76%) and higher enantiomeric excess (92–98%). Commercial lipases such as PCL and CRL offered complementary selectivity for the transesterification of *RS*-**10** with vinyl acetate to afford the key intermediate (*R*)/(*S*)-**10** for (*R*)/**(*S*)-11** which is required for the synthesis of enantio-pure (*R*)/(*S*)-esmolol. The enzymatic switch toward the synthesis of enantiodivergent esmolol is a good example in the green synthesis. For the efficient chemical synthesis of (*RS*)/(*R*)/(*S*)-esmolol, a new synthetic route is proposed.

## 4. Experimental

### *4.1. General experimental details*

#### *4.1.1. Analysis*

Enzymatic reactions were carried out in an incubator (Kuhner, Switzerland) at 200 rpm. $^{1}$H NMR and $^{13}$C NMR spectra were obtained with Bruker DPX 400 ($^{1}$H 400 MHz and $^{13}$C 100 MHz), chemical shifts were expressed in $\delta$ units relative to the tetramethylsilane (TMS) signal as an internal reference in $CDCl_3$. IR spectra (wave number in $cm^{-1}$) were recorded on Nicolet FT-IR impact 400 instruments as KBr pellets for solid samples or neat for liquid. Merck plates were used for the analytical TLC of all reactions. SRL silica gel (60–120 mesh) was used in column chromatography. LC–MS analysis was carried out on Finninganmat LCQ instrument (USA) using a C-18 hypersil ODS (4.6 mm × 15 mm, 5 m) column. Optical rotation was measured in a Rudolph, Autopol$^{R}$ IV polarimeter. The enantiomeric excesses (*ee*) were determined by HPLC (Shimadzu LC-10AT 'pump', SPD-10A UV–VIS detector) using a Chiralcel OD-H column (0.46 mm × 250 mm; 5 μm, Daicel Chemical Industries, Japan) at 254 nm. The conditions were: mobile phase, hexane: 2-propanol (90:10); flow rate, 1 ml/min; column temperature, 25 °C.

#### *4.1.2. Reagents*

(*RS*)-epichlorohydrin, (*R*)-epichlorohydrin, (*S*)-epichlorohydrin, 2-hydroxy benzonitrile, and the lipase preparations from *C. antarctica* (CAL L4777) *C. rugosa* (CRL 62316) *C. rugosa* (CRL 90860) *C. rugosa* L8525, *C. rugosa* L-1754 (CRL L1754), *C. cylindracea* (CCL 62316), *A. niger* (ANL 62301) and porcine pancreas lipase (PPL) were purchased from SIGMA (USA). The analytical or commercial grade solvents were procured from various commercial sources. HPLC grade solvents were obtained from J.T. Baker, Rankem and Merck Ltd. Immobilized lipase in sol–gel-Ak from *P. cepacia* (PCL 62279), immobilized lipozyme from *M. miehei* (MML 62350), lipase A and *C. antarctica* (CAL 12117) lipase were purchased from Fluka™ and lipase AY "Amano" 30 (CRL LY amino) was purchased from Amano Chem Ltd. They were used without any further treatment. The strains 5b1, 5b2, 5a1, 1b1 (N), 5d1, 1b1 used were previously isolated from soil in our laboratory for the resolution of (*RS*)-3-[5-(4-fluoro-phenyl)-5-hydroxy-pentanoyl]-4-phenyl-oxazolidin-2-one, an intermediate for ezitimibe synthesis (Singh et al., 2012). These isolates were maintained on selective media at 4 °C.

### *4.2. Synthesis of (RS)/(R)/(S)-methyl 3-(4-((oxiran-2-yl)methoxy)phenyl) propanoate (**2**)*

To the mixture of **3** (3.6 g, 20 mmoL) and $K_2CO_3$ (11.04 g, 40 mmoL) in anhydrous MeCN (100 mL) was added (*RS*)-**4** (3.5 mL, 30 mmoL) and the reaction mixture was heated under

reflux for 28 h. The reaction mixture was cooled and filtered and washed with MeCN and the combined organic layer was concentrated under vacuum, and the residue was purified using a silica gel (60–120 mesh) column and eluting with ethyl acetate: hexane (15:85) to afford (*RS*)-**2.** A light yellow liquid (90% yield, 4.24 g); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.55–2.57 (m, 2H) 2.69–2.71 (m, 1H), 2.81–2.91 (m, 3H), 3.26–3.33 (m, 1H), 3.66 (s, 3H), 3.94–3.95 (m, 1H), 4.11–4.15 (dd, 1H), 7.01–7.05 (m, 2H), 7.25–7.29 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 34.5, 35.8, 45.3, 49.8, 52.1, 70.0, 115.2, 128.7, 131.8, 156.8, 172.3; MS (APCI) (*m*/*z*) 237.41.

(*R*)-**2**: a light yellow liquid, (87% yield, 1.02 g); 94% *ee*. $[\alpha]_D^{20}$ −4.42 (*c* 1.0, $CHCl_3$) [lit $[\alpha]_D^{20}$ −4.42 (*c* 1.0, $CHCl_3$), op 94%].

(*S*)-**2**: a light yellow liquid (89% yield, 1.05 g); 95% *ee*. $[\alpha]_D^{20}$ +4.46 (*c* 1.0, $CHCl_3$) [lit $[\alpha]_D^{20}$ +4.46 (*c* 1.0, $CHCl_3$), op 95%].

### *4.3. Synthesis of (RS)/(R/)(S)-methyl-3-(4-(3-chloro-2-hydroxypropoxy)phenyl)propanoate (**10**)*

To a stirred solution of (*RS*)-**2** (4.73 g, 20 mmoL in 100 mL (DCM: water::50:50) containing acetyl chloride (2.35 g, 30 mmoL) was added. The resultant reaction mixture was stirred at room temperature for 2 h and on completion of the reaction (TLC), the mixture was extracted with DCM (50 mL) and washed with water. The organic layer was separated and dried on $Na_2SO_4$ and concentrated under vacuum. The residue was purified by passing through a silica column (60–12 mesh) and eluting with ethyl acetate: hexane (15:85) to obtain (*RS*)-**10**. The (*RS*)-**10** was then subjected to chiral HPLC analysis using chiralcel OD-H column and the two enantiomers were eluted after 23 min and 25 min (90:10 hexane: 2-propanol) respectively and were present in a ratio of 49:51. Following a similar procedure (*R*)-**10** and (*S*)-**10** were prepared from (*S*)-**2** and (*R*)-**2**, respectively.

(*RS*)- **10**: a light yellow liquid (92% yield, 5 g); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.59 (t, $J$ = 7.96 Hz, 2H), 2.89 (t, $J$ = 9.08 Hz, 2H), 3.66 (s, 3H), 3.69–3.79 (m, 2H), 4.02–4.21 (m, 3H), 6.83–6.86 (m, 2H), 7.10–7.13 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 30.1, 35.9, 45.9, 51.6, 68.5, 69.9, 114.6, 129.3, 133.5, 156.7, 173.4. MS (APCI) (*m*/*z*): 273.81;

(*R*)-**10**: a light yellow liquid, (92% yield, 1.25 g); The product was then subjected to chiral HPLC analysis using a chiral OD-H column, the two enantiomers were eluted at $t_S$ = 25 min and $t_R$ = 23 min (90:10::hexane: 2-propanol) with peak areas of 3 and 97%, respectively, (94% *ee*).

(*S*)-**10**: a light yellow liquid, (91% yield, 1.24 g); The product was then subjected to chiral HPLC analysis using a chiral OD-H column, the two enantiomers were eluted at $t_S$ = 25 min and $t_R$ = 23 min (90:10::hexane: 2-propanol) with peak areas of 96.5 and 3.5%, respectively, (93% *ee*).

### *4.4. Synthesis of (RS)/(R/)(S)- methyl-3-(4-(2-acetoxy-3-chloropropoxy)phenyl)propanoate (**11**)*

(*RS*)-**11** was synthesized chemically by treating of (*RS*)-**10** (0.5 g, 2 mmol) with $Ac_2O$ (0.3 g mL, 3 mmoL) in the presence of $ZrCl_4$ (5 mg, 2 mol%) in MeCN at rt withmagnetic stirring. After disappearance of (*RS*)-**10** (TLC, 2 h), water was added into the reaction mixture and washed with $NaHCO_3$. The organic layer was then separated and concentrated under vacuum to afford (*RS*)-**11** as a yellow liquid (95% yield, 0.59 g); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.12–2.16 (s, 3H), 2.59 (t, $J$ = 7.96 Hz, 2H), 2.89 (t, $J$ = 9.08 Hz, 2H), 3.66 (s, 3H), 3.74–3.84 (m, 2H), 4.05–4.26 (m, 3H), 6.86–6.89 (m, 2H), 7.10–7.13 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 21.4, 30.1, 35.9, 45.9, 51.7, 68.6, 69.9, 114.6, 129.4, 133.5, 156.7, 170.2 173.5; MS (APCI) (*m*/*z*): 315.85. (*RS*)-**11** was subjected to chiral HPLC analysis using a chiralcel OD-H column and the two enantiomers were eluted after 32 min and 42 min (90:10 hexane: 2-propanol), respectively and were present in a ratio of 49.9:50.1. Following a similar procedure (*R*)-**11** and **(*S*)-11** were prepared from (*R*)-**10** and (*S*)-**10**, respectively.

(*R*)-**11**: a yellow liquid, (93% yield, 0.58 g); The product was then subjected to chiral HPLC analysis using a chiral OD-H column, the two enantiomers were eluted at $t_R$ = 42 - min and $t_S$ = 32 min (90:10::hexane: 2-propanol) with peak areas of 97% and 3%, respectively, (94% *ee*).

**(*S*)-11**: a yellow liquid (92% yield, 0.57 g); The product was then subjected to chiral HPLC analysis using chiral OD-H column, the two enantiomers were eluted at $t_R$ = 42 min and $t_S$ = 32 min (90:10::hexane: 2-propanol) with peak areas of 3.5% and 96.5%, respectively, (93% *ee*).

### *4.5. Enantioselective transesterification of (RS)-**10***

In a 10 mL round bottomed flask containing magnetic beads, a mixture of (*RS*)-**10** (20 mM) in 4 mL toluene and 5.40 mmoL vinyl acetate was placed. Lipases from different sources (commercial lipase from lipase A, *C. antarctica*, *C. rugosa* L8525, *C. rugosa* L-1754, *C. cylindracea*, *A. niger*, porcine pancreas and AY "Amano" 30 and crude lipase from strains 5b1, 5b2, 5a1, 1b1 (N), 5d1, 1b1 laboratory strains (Singh et al., 2012)) were used to carry out the reaction. The round bottomed flask was capped and placed on a magnetic stirrer which was maintained at room temperature. Immobilized lipase in sol–gel-Ak from *P. cepacia*, immobilized lipozyme from *M. miehei*, lipase acrylic resin from *C. antarctica*, were individually taken into separate 10 mL conical flask, the flasks were capped and placed in shaker which was maintained at 25 °C (200 rpm). Samples (300 μL) were withdrawn from the reaction mixture and conversion and the enantiomeric excess of the reaction were monitored by HPLC.

### *4.6. Optimization of transesterification reaction*

The effect of different organic solvents such as MeCN, 1.4 dioxane, *tert*-butyl methyl ether, diisopropyl ether, diethyl ether, DCM, benzene, heptane, isooctane and toluene on the transesterification of (*RS*)-**10** was observed. The optimum time was determined by carrying out the reaction and collecting the samples at various time intervals. Various enzyme concentrations (10, 20, 30, 40 and 50 mg/mL) were used with a fixed substrate concentration (20 mM). The samples were taken at regular time intervals and analyzed for conversion and enantioselectivity of the transesterification reaction.

### *4.7. Preparative-scale transesterification reaction*

The resolution of (*RS*)-**10** was carried out in preparative scale in optimized condition. The reaction was performed by subjecting 50 mL (20 mmoL substrate, 0.28 g) of the reaction mixture to resolution by PCL and CRL lipase at 30 °C using

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vinyl acetate as acyl donor in toluene and cyclohexane, respectively. When the transformation was ca. 50% (36 h, 50.02% conversion for PCL and 24 h, 50.3% conversion for CRL) the reaction contents were filtered off and the enzyme preparation was washed with solvent. The solvent was evaporated under reduced pressure and the resulting dried residue was subjected to flash chromatography using ethyl acetate:hexane (15:85) (*v*/*v*) as mobile phase. It was observed with PCL that after 36 h the isolated yield of (*R*)-**10** was 46%, 0.128 g, with enantiomeric excess of 98.83% (Chiralcel OD-H) and that of **(*S*)-11** was 47%, 0.151 g with enantiomeric excess of 98.73% (Chiralcel OD-H). It was observed with CCL that after 24 h the isolated yield of (*S*)-**10** was 46.5%, 0.13 g with enantiomeric excess of 99.23%, (Chiralcel OD-H) and that of (*R*)-**11** was 47%, 0.151 g with enantiomeric excess of 98.03%, (Chiralcel OD-H).

#### *4.7.1. For PCL catalyzed reaction*

(*R*)-**10**: a light yellow liquid, (46% yield, 0.128 g); The product was then subjected to chiral HPLC analysis using chiralcel OD-H column, the two enantiomers were eluted at $t_S$ = 25 - min and $t_R$ = 23 min (90:10::hexane: 2-propanol) with peak areas of 0.59% and 99.41%, respectively, (98.83% *ee*).

**(*S*)-11**: a yellow liquid (47% yield, 0.151 g); The product was then subjected to chiral HPLC analysis using a chiralcel OD-H column, the two enantiomers were eluted at $t_R$ = 42 - min and $t_S$ = 32 min (90:10:: hexane: 2-propanol) with peak areas of 0.61% and 99.38%, respectively, (98.73% *ee*).

#### *4.7.2. For CRL catalyzed reaction*

(*S*)-**10**: a light yellow liquid, (46.5% yield, 0.13 g); The product was then subjected to chiral HPLC analysis using chiralcel OD-H column, the two enantiomers were eluted at $t_S$ = 25 - min and $t_R$ = 23 min (90:10::hexane: 2-propanol) with peak areas of 99.6% and 0.4%, respectively, (99.23% *ee*).

(*R*)-**11**: a yellow liquid, (47% yield, 0.151 g); The product was then subjected to chiral HPLC analysis using chiralcel OD-H column, the two enantiomers were eluted at $t_R$ = 42 - min and $t_S$ = 32 min (90:10::hexane: 2-propanol) with peak areas of 99% and 1%, respectively, (98.03% *ee*).

### *4.8. Deacylation of (RS)/(R)/**(S)-11***

A solution of $K_2CO_3$ (0.27 g, 2 mmol) in distilled water (1 ml) 30 was added to a solution of **11** (0.31 g, 1 mmol) in methanol (5 ml) and the resultant reaction mixture was allowed to stir for 2 h at rt. After completion of the reaction the reaction mixture was extracted with EtOAc (3 × 15 ml) and water (10 ml). The combined organic extracts were dried over $Na_2SO_4$ and concentrated under vacuum to obtain the crude which was purified by silica gel column chromatography (100–200 mesh) to obtain the corresponding alcohol.

(*RS*)-**10**: a light yellow liquid (92% yield, 0.251 g);

(*R*)-**10**: a light yellow liquid, (90% yield, 0.245 g); The product was then subjected to chiral HPLC analysis using chiralcel OD-H column, the two enantiomers were eluted at $t_S$ = 25 - min and $t_R$ = 23 min (90:10::hexane: 2-propanol) with peak areas of 1.25% and 98.75%, respectively, (97.5% *ee*).

(*S*)-**10**: a light yellow liquid, (91% yield, 0.248 g); The product was then subjected to chiral HPLC analysis using a chiralcel OD-H column, the two enantiomers were eluted at $t_S$ = 25 min and $t_R$ = 23 min (90:10::hexane: 2-propanol) with peak areas of 99% and 1%, respectively, (98% *ee*).

### *4.9. Synthesis of (RS)-**1***

(*RS*)-**10** (0.27 g, 1 mmoL) was treated with isopropylamine in methanol (10 mL) in the presence of $Et_3N$ (0.1 g, 1 mmoL) under reflux condition for 8 h and on completion of the reaction (TLC), the mixture was diluted with ethyl acetate (15 mL) and washed with water. The organic layer was separated and dried on $Na_2SO_4$ and concentrated under vacuum. The residue was purified by performingcolumn chromatography of silica gel (60–12 mesh) and eluting with ethyl acetate: hexane (15:85) to obtain (*RS*)-**1**.

(*RS*)-**1**: a white solid (92% yield, 0.27 g); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.8 (s, 6H), 2.47 (t, $J$ = 6.4, 2H) 2.62–2.68 (m, 1H), 2.82–2.91 (m, 4H), 3.56 (s, 3H), 3.75–3.93 (m, 3H) 6.78 (d, $J$ = 6.4, 2H), 7.12(d, $J$ = 6.2, 2H): $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 21.24, 27.61, 31.81, 45.21, 46.02, 48.23, 66.56, 69.53, 112.97, 125.76, 129.35, 152.98, 163.87; MS (APCI) (*m*/*z*): 296.49.

### *4.10. Synthesis of (S)/(R)-**1***

(*R*)/(*S*)-**10** (0.27 g, 1 mmoL) was treated with isopropylamine in methanol (10 mL) in the presence of $Et_3N$ (0.1 g, 1 mmoL) under reflux condition for 8 h and on completion of the reaction (TLC), the mixture was diluted with ethyl acetate and washed with water. Ethyl acetate layer was separated and dried on $Na_2SO_4$ and it was concentrated under vacuum. The residue was purified by performing silica gel (60–12 mesh) column chromatography and eluting with ethyl acetate: hexane (15:85) to obtain (*S*)/(*R*)/-**1**.

#### *4.10.1. For enzymatic kinetic resolution directly from enzymatically prepared (R)/(S)-**10***

(*S*)-**1**: a yellow liquid, (90% yield, 0.266 g); The product was then subjected to chiral HPLC analysis using a chiralcel OD-H column, the two enantiomers were eluted at $t_S$ = 26.5 min and $t_R$ = 30.8 min (90:10::hexane: 2-propanol) with peak areas of 99% and 1%, respectively, (98% *ee*).

(*R*)-**1**: a yellow liquid, (89% yield, 0.263 g); The product was then subjected to chiral HPLC analysis using chiralcel OD-H column, the two enantiomers were eluted at $t_S$ = 26.5 min and $t_R$ = 30.8 min (90:10::hexane: 2-propanol) with peak areas of 1% and 99%, respectively, (98% *ee*).

#### *4.10.2. For enzymatic kinetic resolution via by deacylation of enzymatically prepared (R)/**(S)-11***

(*S*)-**1**: a yellow liquid, (91% yield. 0.269 g); The product was then subjected to chiral HPLC analysis using a chiralcel OD-H column, the two enantiomers were eluted at $t_S$ = 26.5 min and $t_R$ = 30.8 min (90:10::hexane: 2-propanol) with peak areas of 98.5% and 1.5%, respectively, (97% *ee*).

(*R*)-**1**: a yellow liquid, (90% yield. 0.266 g); The product was then subjected to chiral HPLC analysis using a chiralcel OD-H column, the two enantiomers were eluted at $t_S$ = 26.5 min and $t_R$ = 30.8 min (90:10::hexane: 2-propanol) with peak areas of 1.25% and 98.75%, respectively, (97.5% *ee*).

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*4.10.3. For all chemical route*

(*S*)-**1**: a yellow liquid, (92% yield, 0.272 g); The product was then subjected to chiral HPLC analysis using chiralcel OD-H column, the two enantiomers were eluted at $t_S$ = 26.5 min and $t_R$ = 30.8 min (90:10::hexane: 2-propanol) with peak areas of 96.5% and 3.5%, respectively, (93% *ee*).

(*R*)-**1**: a yellow liquid, (91% yield, 0.269 g); The product was then subjected to chiral HPLC analysis using a chiralcel OD-H column, the two enantiomers were eluted at $t_S$ = 26.5 -min and $t_R$ = 30.8 min (90:10::hexane: 2-propanol) with peak areas of 4% and 96%, respectively, (92% *ee*).

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## Appendix A. Supplementary data

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