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Lipase catalyzed kinetic resolution of *rac*-2-phenylpropan-1-ol derivatives as building block for phenolic sesquiterpenes

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ABSTRACT

Highly enantioselective and enantiospecific resolution processes were developed for 2-(3-methoxy-4-methyl-phenyl)-propan-1-ol (VI), 2-(2-methoxy-5-methyl-phenyl)-propan-1-ol (VII), 2-(3,4,5-trimethoxy-phenyl)-propan-1-ol (VIII) and 2-(3-hydroxy-4-methyl-phenyl)-propan-1-ol (XII) *via* lipase-catalyzed transesterification and hydrolysis using vinyl propionate as acylating agent. The general procedure for synthesis and kinetic resolution of 2-phenylpropan-1-ol derivatives would be beneficial for getting chiral building block of bisabolane types of natural and unnatural sesquiterpenes. Gallic acid moiety was diversified with a chiral center at the benzylic position and subsequent resolution process gave resolved isomers with higher enantiopurity. Both isomers were separated with *ee* of at least 95%. Enantioselectivity, *E* was even higher up to 316 during the process. These resolved chiral intermediates will facilitate the commercial synthesis of bio-active natural and unnatural xanthorrhizol, elvirol and gallate derivatives.

1. Introduction

Phenolic sesquiterpenes of the bisabolane family were isolated from many different natural sources [1]. Including others xanthorrhizol (I), elvirol (II), curcuphenol (III) and curcuhydroquinone (IV) are bisabolane type natural sesquiterpenes containing a stereogenic center at the benzylic position [2,3]. Gallic acid (V) and its structurally related compounds are found widely distributed in fruits and plants. This is one of the main phenolic components of black and green tea. Although gallic acid is not a member of bisabolane family but it contains tri-hydroxyl phenolic moiety. Diversified biological activity of phenolic sesqueterpenes, like anticancer [4,5], anti-bacterial [6], anti-metastatic [7], anti-oxidant and anti-inflammatory [8] made them promising synthetic target since 30 years. Different strategies were developed for total and enantioselective synthesis of the phenolic sesquiterpenes. Enantioselective synthesis of xanthorrhizol and other bisabolane sesquiterpenes was reported earlier [9]. Elvirol was first synthesized enantioselectively using enzyme [10]. Esters of gallic acid have a diverse range of industrial uses, as antioxidants in food, cosmetics and in the pharmaceutical industry. According to the US Food and Drug Administration list, propyl gallate is used to preserve and stabilize medicinal preparations [11]. However, antioxidants have been proved to exert different degrees of adverse and toxic effects upon consumption [12,13].

Interestingly all those natural products contain phenolic skeleton with or without benzylic chiral center (Fig. 1). We therefore encouraged establishing a universal and convenient method for introducing chiral center at the benzylic position from commercially available benzoates. Similarly gallic acid moiety could be diversified. That might be useful for synthesizing chiral gallate type sesquiterpene and ester for improved biological activity. Moreover lipase-catalyzed kinetic resolution could be an efficient technique [14] for synthesis of optically enriched building block for bisabolane sesquiterpenes from synthesized chiral alcohols.

Lipase-catalyzed enantioselective access to enantiomerically pure secondary alcohols is very efficient tools in organic synthesis. However kinetic resolution of primary alcohols by the same method is difficult to achieve. Enantioselectivity of PCL was studied towards a series of 2-methyl-substituted primary alcohols using vinyl acetate as acyl donor for transesterification in organic solvents [15]. Reported *E* value was extremely low. This is due to the

Abbreviations: CAL-B, *Candida antarctica* lipase B; PCL, *Pseudomonas cepacia* lipase; PPL, *Porcine pancreas* lipase; AOL, *Aspergillus oryzae* lipase; PLE, *Porcine liver* esterase; CRL, *Candida rugosa* lipase; LAN, lipase *Aspergillus niger*; Acylase, *Aspergillus* sp.; PFL, *Pseudomonas fluorescens* lipase; LAH, lipase *Burkholderia cepacia*; LWG, lipase *Wheat germ*; *t*-BuOMe, *tert*-butyl methyl ether; *E*, enantioselectivity; *c*, conversion; *ee*, enantiomeric excess; IU, enzymatic international unit; *C*, concentration.

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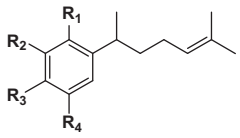
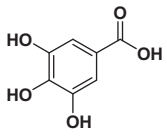




Gallic acid (V)

Where,
Xanthorrhizol (I) : $R_{1\sim2}$ = H, R_3 = CH_3, R_4 = OH
Elvirol (II) : $R_{2\sim3}$ = H, R_4 = CH_3, R_1 = OH
Curcuphenol (III) : $R_{2,4}$ = H, R_3 = CH_3, R_1 = OH
Curcuhydroquinone (IV) : R_2 = H, R_3 = CH_3, $R_{1,4}$ = OH

Fig. 1. Structure of phenolic sesquiterpene and gallic acid.

low enantioselectivity of lipases towards chiral primary alcohols. In fact moving the aryl group closer or further away from the chiral center resulted in low enantioselectivity [16]. To overcome this, we thought to apply simultaneous approach to study transesterification first to separate enantiopure remaining alcohol followed by hydrolysis of enriched ester. This approach worked remarkably well leading to improved *E* value as well as separated enantiomers in optically pure state.

As a part of our research interest we synthesized chiral center containing racemic intermediates, resolved enzymatically and separated chiral pure intermediates. Enantiopure chiral alcohols VI–VIII (Scheme 1) would be valuable for synthesizing xanthorrhizol, elvirol and gallate bisabolane, optically active gallate esters and other derivatives. Additionally enzyme screening, gram scale resolution process, HPLC analytical conditions were also studied. We emphasized on getting enantiopure either product or starting materials during kinetic resolution process [17].

2. Materials and methods

2.1. Materials

Enzymes CAL-B, PCL, PPL, AOL, PLE, CRL, LAN, acylase, PFL, LAH, LWG were used with activity 120, 30, 20, 2, 40, ≥30, 12–15, ≥30, ≥20, 8 and 0.08 IU/mg respectively. Enzymes were collected from Novo Nordisk (CAL-B), Aldrich (PPL), Fluka (AOL, LWG), Chirazyme (PLE) and Amano (PCL, CRL, LAN, acylase, PFL, and LAH). Out of those 11 types of enzymes only CAL-B was immobilized. Vinyl propionate, vinyl acetate, phosphate buffer pH 7.0 and other reagents were purchase from Sigma–Aldrich and TCI with sufficient purity. HPLC analytical grade solvents were collected from J.T. Baker, USA. Shaking incubator was from Vision Scientific Co. Ltd. The methyl protected *rac*-alcohols namely, 2-(3-methoxy-4-methylphenyl)-propan-1-ol (VI), 2-(2-methoxy-5-methyl-phenyl) propan-1-ol (VII), 2-(3,4,5-trimethoxy-phenyl)-propan-1-ol (VIII) and 2-(3-hydroxy-4-methylphenyl)-propan-1-ol (XII) were synthesized according to our patent [18]. Chiral Columns were used: Chiralcel OD-H, Chiralpak AS-H; Manufacturer: Daicel chemical Ind. Ltd. Japan and (R,R)-Whelk-01; Manufacturer: Regis Technologies Inc. USA. ^{1}H and ^{13}C NMR were recorded by 400 and 100 MHz, respectively, with a Bruker Avance 400 instrument using $CDCl_3$ as solvent and TMS as internal standard. Elemental analysis was done with Flash 2000 (Thermo Scientific) and Fisons EA 1108 instruments. Specific optical rotation was measured in $CHCl_3$ using Autopol III polarimeter from Rudolph research analytical.

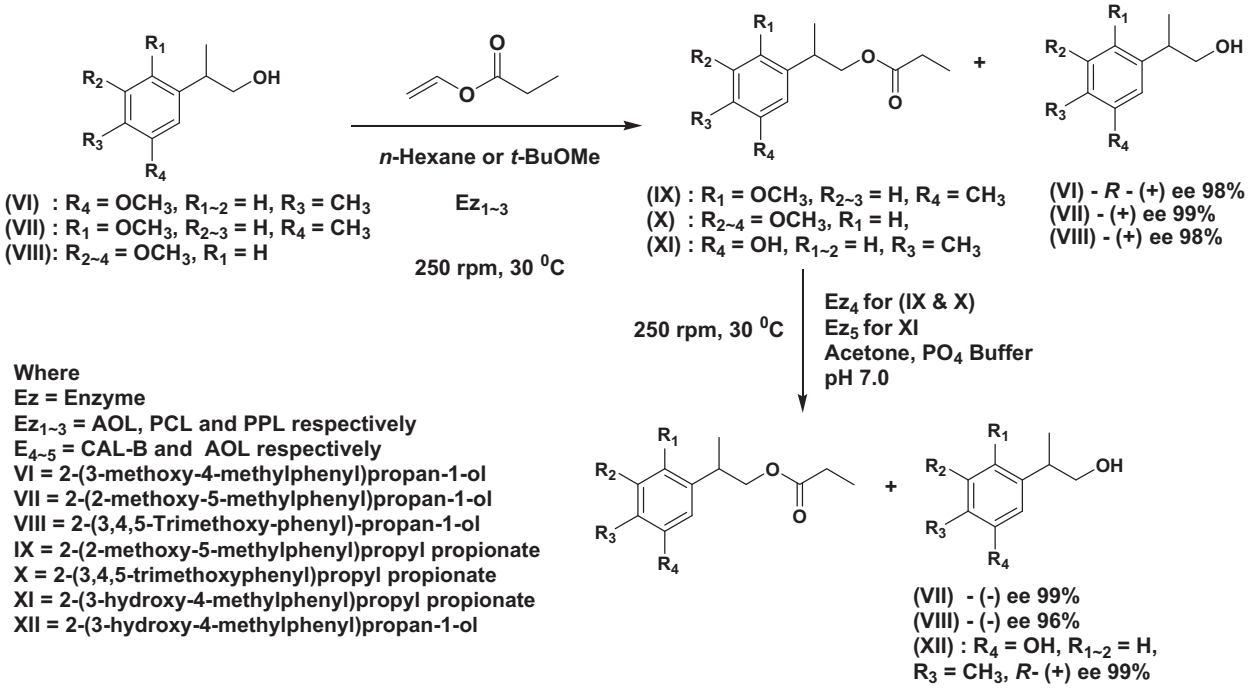
2.2. Enantioselective HPLC analysis

Enantioselectivity was analyzed by Younglin binary gradient HPLC system equipped with UV detector at 230 nm. Analytical condition details are given in (Table 1). For transesterification of racemic alcohol enantioselectivity, *E* and conversion, *c* was calculated from enantiomeric excess of substrate, ee_s and enantiomeric excess of product, ee_p at different time points using the following equation:

$$E = \frac{\ln[(1-c)(1-ee_s)]}{\ln[(1-c)(1+ee_s)]}; \quad c = \frac{ee_s}{ee_s + ee_p}. \tag{1}$$

Similarly for hydrolysis reaction as ee_s was more than zero so the following equation was applied to calculation *E* and *c* [17]:

$$E = \frac{\ln[(1-c)(1+ee_p)]}{\ln[(1-c)(1-ee_p)]}; \quad c = 1 - \frac{c_s}{c_{s0}}, \tag{2}$$



Scheme 1. Kinetic resolution of *rac*-2-phenylpropan-1-ol derivatives using lipase.

Table 1
Chromatographic condition for HPLC analysis of esters and alcohols.

Compound	Column	Dimension	Mobile phase	Flow rate	Retention time (min)			
					(+) Ester	(−) Ester	(−) Alcohol	(+) Alcohol
VI	Chiralpak AS-H	250 mm × 4.6 mm, 5 μm	Hxn:IPA = 95:05	0.4 ml/min	12.0	13.4	15.0	20.1
XI	(R,R) WHELK-01		Hxn:IPA:DEA = 97:03:0.05		22.6	23.2	39.6	42.5
IX, VII			Hxn:IPA = 97:03	0.2 ml/min	19.6	23.3	44.4	47.2
X, VIII	Chiralcel OD-H		Hxn:IPA = 90:10	0.4 ml/min	23.2	26.8	36.0	39.5

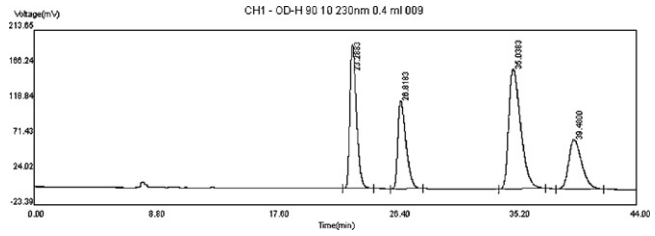


Fig. 2. HPLC chromatogram of ester and alcohol for the compound (VIII) namely 2-(3,4,5-trimethoxy-phenyl)-propan-1-ol.

where C_s is concentration of substrate and C_{s0} is the initial concentration of substrate. A typical HPLC chromatogram of ester and alcohol for the compound (VIII) namely 2-(3,4,5-trimethoxy-phenyl)-propan-1-ol is shown in Fig. 2.

2.3. Screening of lipase catalyzed transesterification reaction for alcohol VI–VIII

10 mg of respective alcohol (VI–VIII) was taken in one-neck flask and dissolved with sufficient amount of *n*-hexane or *t*-BuOMe ether to get a solution of approximately 0.3 g mL^{-1}. 2.5 equiv. of acyl donor was added. Then 10 mg enzyme was added to the reaction mixture and continues reaction in shaking incubator at 30 °C and 250 rpm. 20 μL of samples was drawn at different time points. Collected sample was evaporated under reduced pressure and diluted with 30 μL of respective mobile phase and filtered through 0.45 μm syringe filter. 10 μL of samples was analyzed by HPLC. Screening results are tabulated in Tables 2 and 3, respectively.

2.4. Transesterification of rac-alcohol (VII) and hydrolysis of rac-ester (IX)

rac-2-(2-Methoxy-5-methyl-phenyl)-propan-1-ol (VII) (1 g, 5.583 mM) was taken in a one-neck flask and dissolved in 70 mL of *n*-hexane. Vinyl propionate (1.5 mL, 13.78 mM) and PCL (2 g) were added to the reaction mixture. The flask was placed in shaking incubator and reaction was continued at 30 °C and 250 rpm (Scheme 1). 20 μL of sample was drawn at different time points. Collected sample was evaporated under reduced pressure and diluted with 30 μL of mobile phase and filtered through 0.45 μm syringe filter. 10 μL of the sample was injected to HPLC. After 28 h the reaction mixture was filtered with the suction filter and enzyme was washed with *n*-hexane then evaporated under reduced pressure. Reaction mixture was purified by flash column chromatography using *n*-hexane:ethyl acetate = 10:1 as eluent system. 0.2 g of alcohol with *ee* 99% and 0.86 g of ester was collected. Enantiopure (+)-2-(2-methoxy-5-methyl-phenyl)-propan-1-ol was analyzed by NMR and specific optical rotation was determined by polarimeter. Colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (dd, *J* = 4.0, 1.7 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 1H), 3.79 (s, 3H), 3.74–3.65 (m, 2H), 3.43–3.35 (m, 1H) 2.28 (s, 3H), 1.24 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 131.6, 129.9, 128.1, 127.6, 110.6, 67.9, 55.6, 35.2, 20.7, 16.6. *ee* ≥ 99%; $[\alpha]_D^{20}$: +6.57° (C 1.0%; $CHCl_3$). Anal. calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95; O, 17.75. Found: C, 72.8; H, 9.2; O, 17.5.

2-(2-Methoxy-5-methylphenyl)propyl propionate (IX), *ee* 43% (0.258 g, 1.09 mM) was taken in a one-neck flask. Acetone (2.5 mL) and phosphate buffer pH 7.0 (10 mL) was added to the flask and homogenized for 5 min using vortex mixture. CAL-B (0.5 g) was added to the mixture and placed in shaking incubator at 30 °C and 250 rpm. For every 1 h time interval, 20 μL of sample was collected in a separatory funnel and extracted 2 times with each 2 mL CH_2Cl_2 then filtered through anhydrous $MgSO_4$ and evaporated in rotary evaporator. The sample was diluted with 30 μL of mobile phase and filtered through 0.45 μm syringe filter. 10 μL of the sample was injected to the HPLC system. After 5 h of reaction the mixture was extracted using CH_2Cl_2 and treated with anhydrous $MgSO_4$ and evaporated to dryness. Reaction mixture was then purified to get enantiopure alcohol with *ee* 99% by column chromatography

Table 2
Screening of lipase catalyzed transesterification[a] for *rac*-alcohol (VII).

Enzyme	Time (h)	*c* (%)[b]	ee_p (%)[c]	ee_s (%)[c]	*E*[b]
CAL-B	1	0	3	0	NA
PLE	24	0	0	0	NA
PPL	48	32	68	32	7
CRL	8	24	9	3	1
LAN	48	24	51	16	4
acylase	8	62	7	12	1
PFL	48	67	32	64	3
LWG	48	0	0	0	NA
PCL	48	80	25	100	9
LAH	48	27	59	21	5

E, enantioselectivity; ee_s, enantiomeric excess of starting material; ee_p, enantiomeric excess of product.

[a] Reaction condition: 10 mg *rac*-substrate (VII), *n*-hexane, enzyme 10 mg, vinyl propionate (2.5 equiv.) was shaken at 30 °C and 250 rpm.

[b] Determined from Eq. (1) described in Section 2.3; NA, not applicable as *ee* equal to 0.

[c] Determined by HPLC using (*R*,*R*)-Whelk-01, 250 mm × 4.6 mm, 5 μm column, mobile phase: *n*-hexane:IPA = 97:03 (v/v) with flow rate 0.2 ml/min at RT.

Table 3
Screening of lipase catalyzed transesterification[a] for *rac*-alcohol (VIII).

Enzyme	Time (h)	*c* (%)[b]	ee_p (%)[c]	ee_s (%)[c]	*E*[b]
CAL-B	1	0	0	0	NA
PLE	48	0	0	0	NA
PPL	48	69	46	99.8	16
CRL	24	61	15	23	1
LAN	48	55	45	55	4
acylase	48	11	8	1	1
PFL	48	27	24	9	2
LWG	48	0	0	0	NA
PCL	24	56	40	51	4
LAH	48	62	59	97	15

E, enantioselectivity; ee_s, enantiomeric excess of starting material; ee_p, enantiomeric excess of product.

[a] Reaction condition: 10 mg *rac*-substrate (VIII), *t*-BuOMe, enzyme 10 mg, vinyl propionate (2.5 equiv.) was shaken at 30 °C and 250 rpm.

[b] Determined from Eq. (1) described in Section 2.3; NA, not applicable as *ee* equal to 0.

[c] Determined by HPLC using Chiralcel OD-H, 250 mm × 4.6 mm, 5 μm column, mobile phase: *n*-hexane:IPA = 90:10 (v/v) with flow rate 0.4 ml/min at RT.

using *n*-hexane:ethyl acetate = 10:1 as eluent system. 0.116 g of (−)-2-(2-methoxy-5-methyl-phenyl)-propan-1-ol was obtained.

2.5. Transesterification of rac-alcohol (VIII) and hydrolysis of rac-ester (X)

rac-2-(3,4,5-Trimethoxy-phenyl)-propan-1-ol (VIII) (1 g, 4.42 mM) was taken in a one-neck flask and dissolved in 70 mL of *t*-BuOMe. Vinyl propionate (1.5 mL, 13.7 mM) and PPL (2. 2 g) were added to the reaction mixture. The flask was placed in shaking incubator and reaction was continued at 30 °C and 250 rpm (Scheme 1). 20 μL of sample was drawn at every hour time interval for HPLC analysis. Collected sample was evaporated under reduced pressure and diluted with 30 μL of mobile phase and filtered through 0.45 μm syringe filter. 10 μL of sample was injected to HPLC. After 22 h at 68% conversion the reaction mixture was filtered with the suction filter and enzyme was washed with *t*-BuOMe then evaporated under reduced pressure. Reaction mixture was purified by flash column chromatography using *n*-hexane:ethyl acetate = 4:1 as eluent system. 0.287 g of alcohol with *ee* 98% and 0.823 g of ester was collected. Enantiopure (+)-2-(3,4,5-trimethoxy-phenyl)-propan-1-ol was analyzed by NMR. Specific optical rotation was determined by polarimeter. Colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (s, 2H), 3.85 (s, 6H), 3.81 (s, 3H), 3.72–3.66 (m, 2H), 2.91–2.82 (m, 1H), 1.99 (br s, 1H), 1.25 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 153.3, 139.4, 136.7, 104.2, 68.6, 60.8, 56.1, 42.8, 17.7. *ee* ≥ 98%; $[\alpha]_D^{20}$: +17.8° (C 1.0%; $CHCl_3$). Anal. calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02; O, 28.28. Found: C, 63.0; H, 8.2; O, 27.8.

2-(3,4,5-Trimethoxyphenyl)propyl propionate (X), *ee* 47% (0.823 g, 2.98 mM) was taken in a one-neck flask. Acetone (8.2 mL) and phosphate buffer pH 7.0 (32.8 mL) were added to the flask and homogenized for 5 min using vortex mixture. CAL-B (0.2 g) was added to the mixture and placed in shaking incubator at 30 °C and 250 rpm. For every hour time interval 20 μL of sample was collected in a separatory funnel and extracted 2 times with each 2 mL dichloromethane then filtered through anhydrous $MgSO_4$ and evaporated in rotary evaporator. The sample was diluted with 30 μL of mobile phase and filtered through 0.45 μm syringe filter. 10 μL sample was injected to the HPLC system. After 7 h at 33% conversion of reaction the mixture was extracted using CH_2Cl_2 and treated with anhydrous $MgSO_4$ and evaporated to dryness. Reaction mixture was then purified to get other enantiomer of alcohol than that of transesterification with *ee* 96% by column chromatography using *n*-hexane:ethyl acetate = 10:1 as eluent system. 0.2 g of (−)-2-(3,4,5-trimethoxy-phenyl)-propan-1-ol and 0.233 g of ester with *ee* 1% was separated.

3. Results and discussions

According to our previously reported patent [18] we got common method for introducing chiral center at the benzylic position. We were able to synthesize a number of 2-phenylpropan-1-ol derivatives and studied lipase catalyzed kinetic resolution using those alcohols. Out of 10 different types of lipase for transesterification of compounds VI, VII and VIII enzyme AOL, PCL, PPL and LAH were found selective (Tables 2 and 3). Similarly during hydrolysis reaction CAL-B was selective to compounds IX and X as well as AOL for XI. We resolved the formed ester of transesterification reaction with CAL-B and got other enantiomer during hydrolysis process.

During our previous study [18] we obtained *R*-(+)-2-(3-methoxy-4-methylphenyl)-propan-1-ol (VI) in ≥98% enantiopure state using AOL enzyme for both transesterification and hydrolysis reaction. For compounds (VI and XI), *E* value was 27 (Table 4) and 80 (Table 5), respectively, for transesterification and hydrolysis

Table 4
Transesterification[a] reaction for compounds VI, VII and VIII respectively.

Enzyme	Ez (wt.)	Time (h)	c (%)[b]	ee_p (%)[c]	ee_s (%)[c]	E[b]	Substrate (g)
AOL	30	34	58	72	98	27	10
PCL	2	28	74	36	99	10	1
PPL	2	22	68	47	98	18	1

E, enantioselectivity; ee_s, enantiomeric excess of starting material; ee_p, enantiomeric excess of product; Ez, Enzyme.
[a] Reaction condition: *rac*-substrate, *n*-hexane or *t*-BuOMe, vinyl propionate (2.5 equiv.) was shaken at 30 °C and 250 rpm.
[b] Determined from Eq. (1) described in Section 2.3.
[c] Determined by HPLC using conditions as mentioned in Table 1.

Table 5
Hydrolysis[a] reaction for compounds IX, X and XI.

Enzyme	Ez (wt.)	Time (h)	c (%)[b]	ee_s (%)[c]	ee_p (%)[c]	E[b]	Substrate (g)
AOL	3	23	53	99	87	80	1
CAL-B	0.5	5	40	12	99	316	0.26
CAL-B	0.2	14	48	22	96	175	0.82

E, enantioselectivity; ee_s, enantiomeric excess of starting material; ee_p, enantiomeric excess of product; Ez, Enzyme.
[a] Reaction condition: *rac*-substrate, a mixture of acetone: phosphate buffer (pH 7.0) = 1:4 (v/v), enzyme was shaken at 30 °C and 250 rpm.
[b] Determined from Eq. (2) described in Section 2.3.
[c] Determined by HPLC using conditions as mentioned in Table 1.

reaction. Here we tried lipase catalyzed transesterification followed by hydrolysis using different enzymes. Surprisingly we observed that, for substrate (VII and IX), both enantiomers were successfully separated, where *ee* ≥ 99% and *E* 10 (Table 4) and 316 (Table 5) for transesterification and hydrolysis reaction respectively. PPL was selected to resolve VIII due to its higher selectivity at lower conversion. Similarly for (VIII and X), both enantiomers were separated with *ee* 98 and 96%, where *E* 18 (Table 4) and 175 (Table 5) for transesterification and hydrolysis reaction respectively. *n*-Hexane and *t*-BuOMe solvent was selected for substrate VII and VIII respectively depending on their improved solubility.

Resolution of our substrate was not reported earlier. However 2-phenylpropan-1-ol was studied for transesterification using PCL [15], where *E* value for 2-phenylpropan-1-ol was just 1.8 and *ee* was not reported. Chiral acyl donor was used to resolve the same but *E* was not increased much for that. Reported *E* value was 5.2 and *ee* was 99% towards (*R*) isomer for 2-phenylpropan-1-ol [19,20]. Meanwhile only PCL and PPL are known to efficiently resolve primary alcohols and their esters [21]. Our strategies of using different lipases for transesterification and hydrolysis worked well leading to improvement in *E* as well as *ee* value. PCL shows enantio-preference towards (*S*) isomer so (*R*) becomes slow reacting isomer [22] during kinetic resolution of primary alcohol. That allowed us to separate (*R*) isomer of VI and XI as remaining substrate with high enantiopurity. Similar approach for transesterification towards substrate VII and VIII gave high *ee* for remaining substrate (ee_s). To achieve highest ee_s reaction was required to be extended at appropriate conversion point (≥60%). Similar view was reported by Straathof and Jongejan [17] and Faber [22]. But during hydrolysis of methyl protected propionate ester of substrate VI, some problems arose because of its hydrophobic nature. This made the reaction mixture inhomogeneous and reduced the reaction rate. To overcome these problems, some additives such as surfactants were used to increase solubility in the aqueous phase. However this modification made the enzymes inactive. To facilitate hydrolysis we used deprotected ester XI with improved solubility in aqueous medium. Furthermore solubility and homogeneity was increased using acetone/phosphate buffer instead of aqueous phase alone, which facilitated hydrolysis reaction. Other co-solvent system was also studied but the reported conditions were found to be best

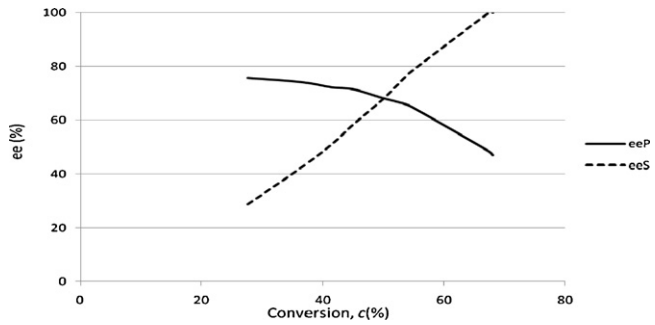


Fig. 3. Dependence of ee_s and ee_p on percent (c) for transesterification of 2-(3,4,5-trimethoxy-phenyl)-propan-1-ol (VIII).

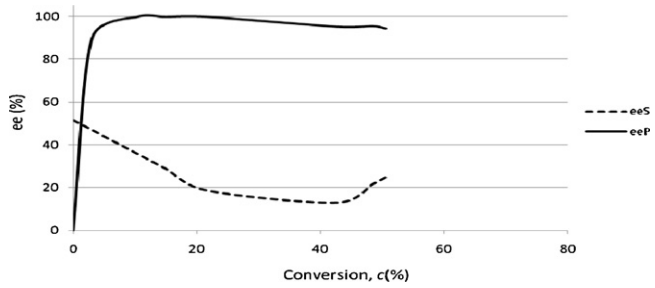


Fig. 4. Dependence of ee_s and ee_p on percent (c) for hydrolysis of 2-(3,4,5-trimethoxy-phenyl)-propyl propionate (X).

that played crucial role for improving E during hydrolysis reactions using AOL and immobilized CAL-B. Increase in E value was reported previously for CAL-B mediated hydrolysis of 3-chloro-1-phenylmetoxy-2-propylbutanoate upon the addition of acetone to the aqueous medium [23]. During hydrolysis of IX and X highest ee for product (ee_p) was achieved at c around 50%, after that ee_p diminished rapidly due to racemization of product. So the reaction was required to stop at $c \leq 50\%$ [22].

E and c was determined using Eq. (2) for hydrolysis reaction for which ee_s was not equal to zero [17]. Relationship of ee_s and ee_p with c for transesterification reaction at different time points was depicted in Fig. 3, similarly for hydrolysis reaction a relationship was depicted in Fig. 4. The graph corresponds as obtained by Chen et al. [24]. This proves the correlation between the mathematical assumption and experimental results of biochemical process. If appropriate enzyme cannot resolve isomers in one reaction then the approach can be applied effectively to get both isomers in pure form. Two selective enzymes can produce opposite isomer *via* transesterification and hydrolysis reaction. Rest of the substrate could be recycled through same process with the next batch until resolved totally. This may be useful for industrial application of biochemical process. Finally chiral xanthorrhizol, elvirol, gallate bisabolane and optically active gallate esters and other derivatives could be synthesized according to the process described in [18] using resolved alcohols. Diversified gallate moiety may open the route for future study of chiral gallate derivatives as potential bio-active molecules.

Absolute stereochemistry of those resolved isomers of (VII and VIII) were not determined immediately as that needs intensive study through X-ray crystallography after getting single crystal. Liquid state of alcohols made the process quite difficult to get single crystal. We will continue our study to determine that from our resolved chiral pure alcohols as well as to synthesize improved biologically active chiral gallate derivatives.

4. Conclusions

General procedure for synthesis and kinetic resolution of 2-phenylpropan-1-ol derivatives are developed to get chiral building block for bisabolane types of natural and unnatural sesquiterpenes. The technique is useful for less enantioselective phenolic primary alcohol towards lipase. Enantiopure chiral intermediates will play an important role for the synthesis of valuable natural and unnatural synthetic sesquiterpenes and their analogues to get more optimized biological properties.

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