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Synthesis of β-adrenergic blockers (*R*)-(−)-nifenalol and (*S*)-(+)-sotalol via a highly efficient resolution of a bromohydrin precursor

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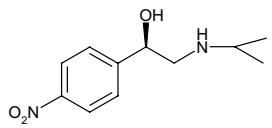
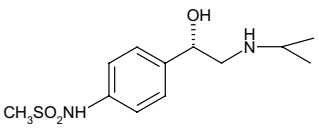
Abstract—(*R*)- and (*S*)-2-bromo-1-(4-nitrophenyl)ethanol are precursors of important β-adrenergic receptor blocking drugs (*R*)-nifenalol and (*S*)-sotalol, respectively. Both were obtained in enantiomeric pure forms via a single highly efficient enzymatic transesterification reaction of (±)-2-bromo-1-(4-nitrophenyl)ethanol using immobilized lipase PS-C-II (E >1000; concn 200 g/L), while PS lipase completely failed to react. On the other hand, the hydrolytic method also produced enantiorich precursors though relatively less efficient (PS-C-II, E = 5.1). Out of all the approaches employed the transesterification method proved to be the most efficient.

1. Introduction

Drugs bearing a structured unit of 2-amino-1-arylethanol such as nifenalol and sotalol are of great importance as β-adrenergic blockers. They are also used in the therapy of asthma, bronchitis and congestive heart failure.[1] Among their enantiomers, only (*R*)-(−)-**1**[2] and (*S*)-(+)-**2**[3] are β-adrenergic blockers and effective in the treatment of cardiovascular diseases. Both **1** and **2** have a common precursor, that is, 2-halo-1-(4-nitrophenyl)ethanol while their final products have opposite configurations at C-1. Therefore an efficient method of resolution of their precursor should simultaneously lead to the preparation of both the drugs in enantiomeric pure form.



(*R*)-**1**



(*S*)-**2**

Asymmetric synthesis of (*R*)-nifenalol, exploiting diverse approaches such as resolution of the racemates through diastereoselective resolution,[4] regioselective aminolysis of chiral epoxides[5] or treatment of the monotosylate of a chiral 1,2-diol with an amine[6] has been described in the literature. There are also reports regarding the preparation of (*S*)-sotalol involving racemate resolution using chiral mandelic acid,[7] or through chiral homogeneous hydrogenation,[8] CBS reduction of aromatic ketone[9] or Sharpless asymmetric dihydroxylation of 4-nitrostyrene.[10] Amongst biocatalytic methods there is only one report of the preparation of (*S*)-sotalol that relates to the use of microbial strain *Geotrichium* sp. 702 in the stereoselective reduction of a keto precursor.[11]

Among the common and easily accessible halo-precursors of these two drugs, 2-bromo-1-(4-nitrophenyl)ethanol appears to be the most suitable substrate due to its higher stability, easy preparation and smooth conversion to the final amino alcohols. Preparation of enantiomerically enriched 2-bromo-1-(4-nitrophenyl)ethanol was reportedly achieved through the chiral reduction of phenacyl bromide, for example, borane-mediated chiral reduction[12] and *cis*-1-amino-2-indanol mediated enantioselective borane reduction of 4-nitrophenacyl bromide.[13] Surprisingly there is no other report regarding a biocatalytic method of preparation of

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2-bromo-1-(4-nitrophenyl)ethanol except a US patent that discloses resolution through transesterification[14] using a panel of lipases with maximum reported enantioselectivity of ~95%.

In pursuance to our programme of kinetic resolution studies of non-racemic drugs and their intermediates,[15] we recently accomplished the resolution of bromo- and iodohydrins of phenylpropanoates wherein out of 22 hydrolases (lipases/esterases) used only one lipase, that is, *Aspergillus niger* was successful in hydrolyzing the acylates and resolving the substrates. This non-acceptability of esters of bromo and iodohydrins displayed by most of the hydrolases was probably due to the presence of bigger atoms such as bromine and iodine in the molecules.[16] However, it was expected that due to its relatively smaller size, 2-bromo-1-(4-nitrophenyl)ethanol **5** would be more acceptable as a substrate to lipases/esterases or other biocatalysts compared to 2-bromo-3-hydroxy phenylpropanoate.[16]

One of our objectives has been to obtain both the precursors in enantiopure form via the simplest possible route possibly by a single lipase/esterase catalyzed transformation. Even though it is more likely to find only one of the two isomers in enantiopure form during lipase/esterase catalyzed hydrolysis or transesterification reactions. It implies that it may be possible to obtain either product or substrate in enantiopure form but at the cost of the other, because in rare cases it is possible to achieve a theoretical 50% conversion (hydrolysis or transesterification) with absolute enantioselectivity. The bioreduction method is another alternative though it would require two different biocatalysts to separately obtain each of the precursors.

Herein, we report the development of the best possible method for preparation of (*R*)- and (*S*)-2-bromo-1-(4-nitrophenyl)ethanol **5** of high enantiopurity via a biocatalytic route taking advantage of three possible strategies, that is, (i) biocatalytic reduction of 4-nitrophenacyl bromide **4**, (ii) kinetic resolution via hydrolysis of acyl derivatives of (±)-2-bromo-1-(4-nitrophenyl)ethanol **6a**–**c** and (iii) transesterification of (±)-**5** using suitable lipases.

2. Results and discussion

2.1. Biocatalytic reduction

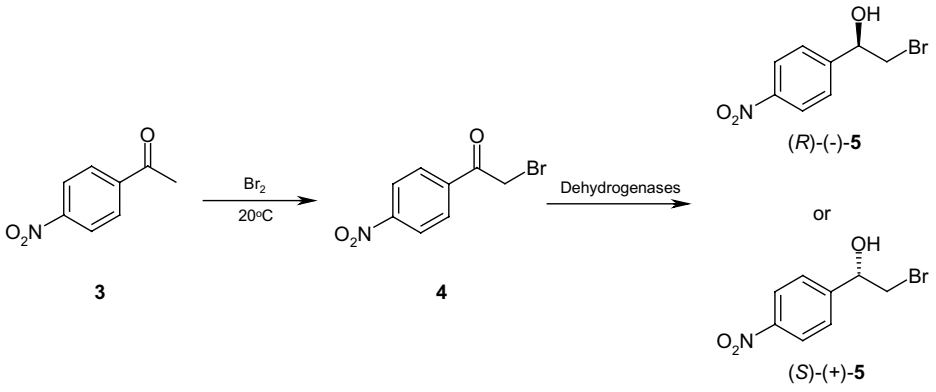
The substrate for bioreduction, that is, 4-nitrophenacyl bromide **4** was easily prepared in the overall yield of 70% by monobromination of readily available 4-nitroacetophenone **3** with bromine (Scheme 1).

Several native strains of dehydrogenases (reductases) were used for affecting the bioreduction of the intermediate **4** under anaerobic conditions. However, it is evident from the results (Table 1) that none of the dehydrogenases was found to be capable of producing 2-bromo-1-(4-nitrophenyl)ethanol **5** in high enantiomeric excess. In many of these experiments bioreduction did not occur at all. In some experiments where bioreduction was observed the enantioselectivity was very poor. Best results were obtained with *Pichia capsulata* where (*S*)-enantiomer **5** with 70% enantiopurity was obtained. *S. cerevisiae* on the other hand produced the (*R*)-enantiomer of 67.8% purity.

After the failure of the bioreductive approach we resorted to kinetic resolution of (±)-2-bromo-1-(4-nitrophenyl)ethanol **5**, that is, the application of hydrolases for the stereoselective hydrolysis or transesterification (Scheme 2).

2.2. Lipase/esterase catalyzed hydrolysis

Experiments for the stereoselective hydrolysis of racemic alkyl acyl esters **6a**–**c** were carried out using a panel of lipases/esterases comprising commercial as well as native strains from institute's repository. Yet again all these experiments failed to show any improvement of the enantiopurity of hydrolyzed products as can be seen from the data presented in Table 2. In terms of activity and selectivity, while commercial enzyme CRL proved to be only partially effective in hydrolyzing the butyl ester **6c** with ee ~60% at 47% conversion; somewhat better selectivity (ee ~75%) was displayed for the acetate by a native strain *Arthrobacter* sp. (RRL-1, MTCC-5225), however it proved to be slow, effecting only 5% hydrolysis after 18 h. In order to further improve the

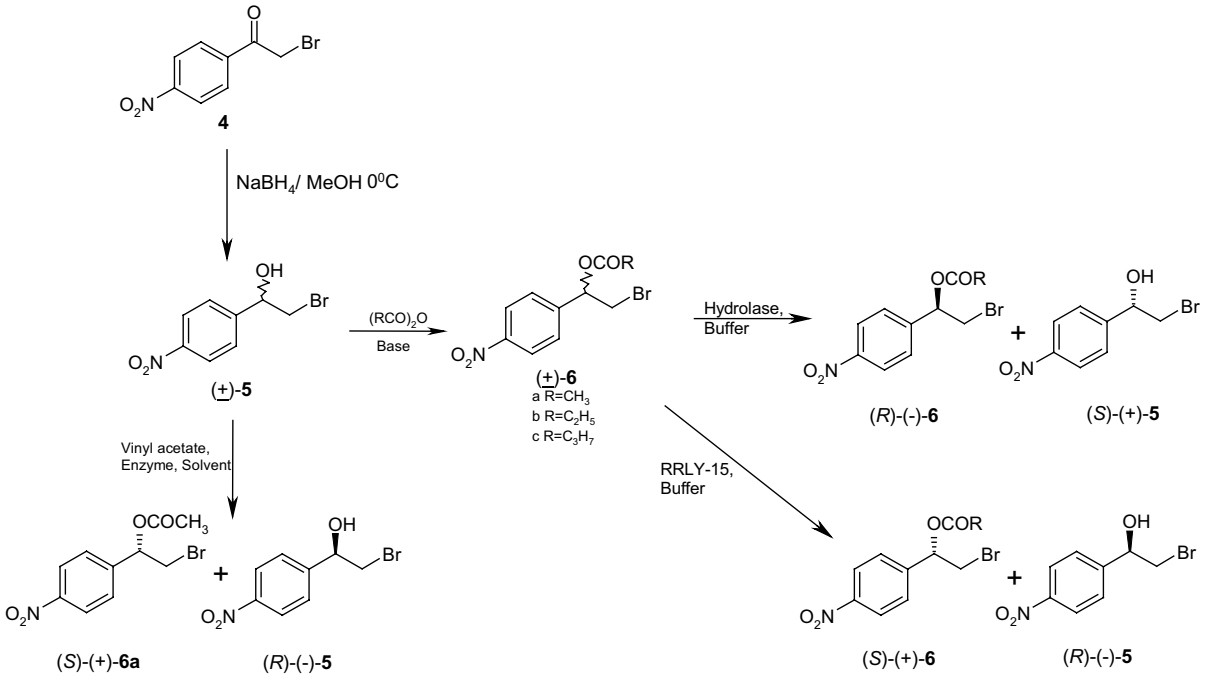


Scheme 1.

Table 1. Bioreduction of 4-nitrophenacyl bromide[a] **4** using dehydrogenases

S.no.	Dehydrogenases	Time (in h)	Reduction (%)	Ee[b] (%)	Conf.[c]	Isolated yield[f] (%)
1	*Bacillus pseudomegatherium*	48	n.r.[d]	—	—	—
2	*B. subtilis*	24	n.r.[d]	—	—	—
3	*Mortierella* sp.	24	41	52.6	(*R*)	57
4	*P. capsulata*	24	100	70.0	(*S*)	70
5	*P. farinosa*	48	n.r.[d]	—	—	—
6	*P. pseudopastoris*	24	90	45.0	(*S*)	72
7	RRL-155[e]	48	n.r.[d]	—	—	—
8	*S. cerevisiae*	24	94	67.8	(*R*)	65
9	*Zygosaccharomyces rouxii*	48	n.r.[d]	—	—	—

[a] Substrate concn 1 g/L.
[b] Ee was determined by Chiral HPLC.
[c] Configuration was determined by the sign of specific rotation compared to that in the literature.[12]
[d] n.r.—no reduction.
[e] Unidentified strain.
[f] Isolated yield (after column chromatography) based on conversions.



Scheme 2.

selectivity of CRL with **6c**, the use of co-solvents was also envisaged. Our efforts in this direction were only partially successful as the enantiopurity of the hydrolyzed product could not be improved beyond 87% in isopropyl alcohol saturated with water as a solvent (Table 3).

2.3. Lipase/esterase catalyzed transesterification

Finally, we followed the transesterification approach in our efforts to obtain both the enantiomers of 2-bromo-1-(4-nitrophenyl)ethanol in enantiomerically pure form. In these experiments transesterification of the substrate was attempted again with a panel of biocatalysts comprising of both commercial as well as lyophilized strains from the institute's repository (Scheme 2). Only three lipases were able to exhibit transesterification and the best results (ee >99.5%, conv. 42%, 48 h) were observed when PS-C-II was used as a catalyst with vinyl acetate as an acetyl donor and solvent (Table 4).

In order to further reduce the reaction time and maximize the efficacy of the transesterification by PS-C-II, we studied these reactions in various organic solvents (Table 5). Most of the solvents improved the reaction rate and toluene was found to be the best, facilitating maximum resolution of enantiomers in a single resolution (Scheme 3). The rate of esterification also improved significantly and almost complete conversion was recorded in 28 h. Effect of substrate concentration on the rate of transesterification was also studied with lipase PS-C-II in the same solvent. The optimum reaction rate was

Table 2. Lipase/esterase catalyzed kinetic resolution of acyl derivatives of (±)-2-bromo-1-(4-nitrophenyl)ethanol **6a–c**

Enzyme	Substrate[a]	Time (h)	Conv.[b] (%)	Ee[c] (%) (P)	Conf.[d] (P)	Isolated yield[e] (%)		E[f]
						S	P	
CRL	**6a**	12	0	—	—	—	Nil	—
	6b	12	48	58	*S*	34	27	6.3
	6c	4	47	60	*S*	32	25	6.7
PLAP	**6a**	6	10	15	*S*	53	4	1.3
	6b	6	49	36	*S*	30	20	2.9
	6c	12	40	33	*S*	35	17	2.4
Lipase PS	**6a**	6	0	—	—	—	Nil	—
	6b	6	30	11	*S*	44	16	1.3
	6c	6	9	65	*S*	68	6	5
RRLBB-1	**6a**	48	5	7	*S*	nd[g]	nd	1.1
	6b	48	33	0	*S*	47	15	0
	6c	24	43	48	*S*	36	21	4
RRL-1 (MTCC 5225)	**6a**	18	5	75	*S*	nd	nd	7.2
	6b	18	56	39	*S*	27	28	3.6
	6c	18	43	53	*S*	38	21	4.7
RRLY-15 (DSM 11829)	**6a**	48	6	54	*R*	nd	nd	3.2
	6b	48	37	46	*R*	45	20	3.4
	6c	48	20	56	*R*	58	11	3.4
RRL-1789	**6a**	12	4	16	*S*	nd	nd	1.5
	6b	12	12	29	*S*	62	7.2	1.9
	6c	12	24	46	*S*	54	14	3.1
PS-C-II	**6a**	12	0	—	—	—	Nil	—
	6b	12	36	58	*S*	42	23	5.1
	6c	12	33	58	*S*	46	21	4.9
S. cerevisiae	**6a**	12	0	—	—	—	Nil	—
	6b	12	6	20	*S*	nd	nd	1.9
	6c	12	3	25	*S*	nd	nd	1.8

CRL = *Candida rugosa* lipase (Sigma); PLAP = pig liver acetone powder (prepared by known method from freshly procured pig liver);[18] lipase PS = *Burkholderia cepacia* (Amano); RRLBB-1 = *B. subtilis*; RRL-1 = *Arthrobacter* sp.; RRLY-15 = *Trichosporon beigilie*; RRL-1789 = *Bacillus* sp.; lipase PS-C-II = *B. cepacia* immobilized on ceramics (Amano).

[a] Substrate:enzyme ratio 1:1 (w/w). All reaction was performed at pH 7, 0.1 M sodium phosphate buffer at concn 40 g/L.

[b] Conversion based on HPLC.

[c] Ee determined by Chiral HPLC.

[d] Configuration determined by the sign of specific rotation compared to the literature.[12]

[e] Isolated yield (after column chromatography) based on conversions.

[f] Calculated according to Chen et al.[17]

[g] Yields for conversions <10% not determined (nd).

recorded at 200 g/L whereas at higher concentrations lower rate of transesterification was observed probably due to low substrate solubility.

A comparison of three different approaches for the preparation of the enantiomers of 2-bromo-1-(4-nitrophenyl)ethanol has been summarized in Figure 1.

3. Conclusion

Highly efficient resolution of racemic 2-bromo-1-(4-nitrophenyl)ethanol, the precursors of two important β-adrenergic receptor blocking drugs (*R*)-nifenalol and (*S*)-sotalol has been achieved in high enantiomeric excess (ee >99.5%; E >1000) by transesterification using immobilized enzyme PS-C-II (Amano) at 200 g/L optimum concentration. Hydrolysis using the same enzyme showed comparatively poor selectivity. Other methods such as bioreduction or stereoselective hydrolysis using lipases were not that effective in achieving the desired enantiomeric excess.

4. Experimental

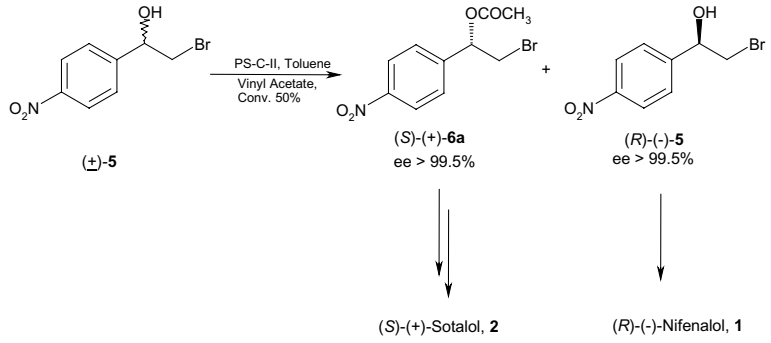
4.1. General

^{1}H and ^{13}C NMR were recorded on a Bruker (200 and 50 MHz) spectrometer in $CDCl_3$ and TMS as internal standard. IR was recorded on a FT-IR Bruker (270-30) spectrophotometer. Mass spectra were recorded on JEOL MSD-300 mass spectrometer. Optical rotations were measured on Perkin–Elmer 241 polarimeter at 25 °C using sodium D light. Enantiomeric excess (ee) was determined on a chiral stationary phase HPLC column. Melting points were determined on Buchi B-542 apparatus by open capillary method and are uncor-

Table 3. Effect of co-solvent on the rate of hydrolysis as well as ee% of the product (alcohol) using (±)-**6c** as substrate and CRL as biocatalyst

Co-solvent (10%)	Time (h)	Conv.[a] (%)	Ee[b] (%) (P)	Conf.[c] (P)	Isolated yield[d] (%)		E[e]
					S	P	
Acetone	4	47	16	*S*	36	24	1.5
Acetonitrile	4	30	24	*S*	48	17	1.7
Benzene	4	30	82	*S*	42	17	14.2
Di-*n*-butyl ether	2	17	65	*S*	59	10	5.3
Diethyl ether	2	13	68	*S*	67	10	5.7
DIPE	4	38	75	*S*	40	22	10.9
DIPE (saturated with water)	16	39	78	*S*	41	21	13.2
DME	2	29	84	*S*	44	22	16
Hexane	4	24	49	*S*	42	10	3.3
IPA (saturated with water)	20	10	87	*S*	66	5	15.8
THF	2	2	73	*S*	nd[f]	nd	7.6
Toluene	4	32	72	*S*	48	17	8.5

DIPE—diisopropylether; IPA—isopropyl alcohol; THF—tetrahydrofuran; DME—1,2-dimethoxyethane.
[a] Conversion based on HPLC.
[b] Ee of the product (alcohol) determined by Chiral HPLC.
[c] Configuration determined by the sign of specific rotation compared to the literature.[12]
[d] Isolated yield (after column chromatography) based on conversions.
[e] Calculated according to Chen et al.[17]
[f] Yields for conversions <10% not determined (nd).



Scheme 3.

Table 4. Lipase catalyzed transesterification of (±)-2-bromo-1-(4-nitrophenyl)ethanol[a] using vinyl acetate as solvent

S.no.	Enzyme	Time (days)	Conv.[b] (%)	Ee[c]	Conf.[d] (P)	Isolated yield[e] (%)		E[f]
						S	P	
1	Lipase PS	9	—	—	—	—	—	—
2	CRL	9	13	79.6	*S*	60	11	9.8
3	PPL	9	—	—	—	—	—	—
4	*Mucor meihei*	9	—	—	—	—	—	—
5	*Pseudomonas fluorescens*	9	—	—	—	—	—	—
6	CAL	9	25	75	*S*	48	20	8.9
7	CCL	9	—	—	—	—	—	—
8	RRL-1	9	—	—	—	—	—	—
9	RRL-191[g]	9	—	—	—	—	—	—
10	NTM-105[h]	9	—	—	—	—	—	—
11	RCCL[h]	9	—	—	—	—	—	—
12	PS-C-II	2	42	>99.5	*S*	43	35	865

[a] Concn of the substrate 40 g/L.
[b] Conversion based on HPLC.
[c] Ee was determined by Chiral HPLC.
[d] Configuration was determined by the sign of specific rotation with that in the literature.[12]
[e] Isolated yield (after column chromatography) based on conversions.
[f] Calculated according to Chen et al.[17]
[g] RRL-191 = *B. pumilus*.
[h] Unidentified strain.

Table 5. Effect of solvent on the rate of transesterification of (±)-2-bromo-1-(4-nitrophenyl)ethanol[a] using PS-C-II

S.no.	Solvent[b]	Conv.[c] (%) (28 h)	Conf. (P)[d]	Isolated yield[e] (%)		E[f]
				S	P	
1	Acetonitrile	6	*S*	nd[g]	nd	425
2	Benzene	4	*S*	nd	nd	415
3	DCM	13	*S*	63	10	461
4	Dioxane	3	*S*	nd	nd	411
5	DME	10	*S*	61	8	445
6	DIPE	23	*S*	52	20	533
7	Diethyl ether	29	*S*	54	25	595
8	Heptane	19	*S*	57	16	501
9	Hexane	0	—	—	Nil	—
10	Methyl cellosolve	0	—	—	Nil	—
11	THF	5	*S*	nd	nd	420
12	Toluene	50	*S*	57	42	>1000

Ee (%) of the product always remains >99.5% in every case. DME—1,2-dimethoxyethane; DCM—dichloromethane; DIPE—diisopropylether; THF—tetrahydrofuran.

[a] Concn of the substrate 40 g/L.

[b] Vinyl acetate as acylating agent.

[c] Conversion based on HPLC.

[d] Configuration determined by the sign of specific rotation with that in the literature.[12]

[e] Isolated yield (after column chromatography) based on conversions.

[f] Calculated according to Chen et al.[17]

[g] Yields for conversions <10% not determined (nd).

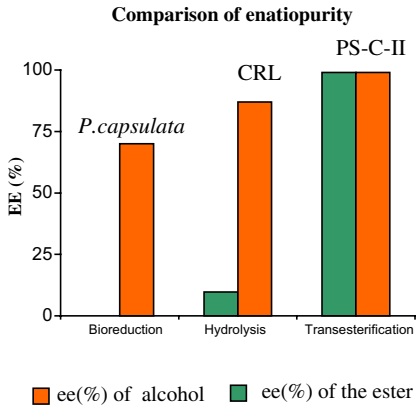


Figure 1.

rected. Lipase PS-C-II was a gift from Amano Enzyme Inc. Co. Japan.

4.2. Synthesis of the 4-nitrophenacyl bromide 4

Bromine 9.6 g (3 mL, 60 mmol) was slowly added over a period of 15 min from a dropping funnel to a stirred solution of 4-nitroacetophenone (10 g, 60 mmol) in glacial acetic acid (40 mL) in a round bottomed flask and temperature of the reaction mixture maintained below 20 °C. After addition of bromine, the contents were allowed to stir overnight. The reaction mixture was diluted by adding 50 mL ice-water and extracted with ethyl acetate (3 × 75 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product that was purified by column chromatography over silica gel (10.3 g, 42 mmol, 70%); mp 89 °C. IR (KBr): 3105, 3047, 2937, 1701, 1600, 1529, 1516, 1343, 1306, 1192, 994, 854, 714 cm^{-1}; ^1H NMR (200 MHz): δ 4.5 (2H, s, CH_2), 8.4 (4H, m, Ar-*H*); ^{13}C NMR (50 MHz): δ 29.3, 123.0, 130.1, 135.8, 138.6, 184.7; MS (*m*/*z*) (%): 245 (11.2), 243 (8.4), 150 (100), 149 (99), 120 (98), 104 (99.2), 92 (87), 89 (73.6), 81 (9.5), 79 (10.6), 76 (100), 74 (34.4); Anal. Calcd for $C_8H_6BrNO_3$: C, 39.37; H, 2.48; N, 5.74. Found: C, 39.21; H, 2.47; N, 5.71.

4.3. Typical method for the biocatalytic reduction of 4-nitrophenacyl bromide

In a typical experiment, ethanolic solution of compound **4** (50 mg, 0.19 mmol in 0.3 mL) was added to a suspension of *P. capsulata* (5 g wet pellet) in 50 mL distilled water containing glucose (2.5 g) and the contents were shaken at 30 °C. After complete reduction as monitored by TLC, the contents were centrifuged and the supernatant liquid and cell pellet was extracted separately with solvent ether (3 × 25 mL each). The combined organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to furnish a crude product that was purified on a silica gel column using ethyl acetate–hexane (10:90) as eluent affording (*S*)-(+)-2-bromo-1-(4-nitrophenyl)-ethanol **5** (35 mg, 0.14 mmol, ~70%), ee 70% (by chiral HPLC).

4.4. Synthesis of (±)-2-bromo-1-(4-nitrophenyl)ethanol 5

Sodium borohydride (550 mg, 14.5 mmol) was added in small installments to a cooled and stirred solution of 4-nitrophenacyl bromide (10.0 g, 41 mmol) in dry methanol (60 mL). The contents were further stirred for 2 h till the reaction was completed (TLC monitored). After completion of the reaction methanol was evaporated and the resulting residue was diluted with water (50 mL), extracted with diethyl ether (4 × 75 mL). The separated organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated under

reduced pressure to yield (±)-**5** as a white solid (9 g, 36.5 mmol, 90%); mp 96.5 °C; IR (KBr): 3549, 1515, 1344, 1068, 850, 707 cm^{-1}; ^1H NMR (200 MHz): δ 3.0 (1H, br s, O*H*), 3.66 (2H, m, CH_2–Br), 5.04 (1H, dd, J = 3.3, 3.3 Hz, CH_2–C*H*OH), 7.59 (2H, d, J = 8.5 Hz, Ar-*H*), 8.25 (2H, d, J = 8.6 Hz, Ar-*H*); ^{13}C NMR (50 MHz): δ 40.6, 73.9, 125.1, 158.2, 148.6, 149.0; MS (*m*/*z*) (%): 247 (2.9), 245 (4.3), 152 (100), 122 (34.1), 94 (48.5), 77 (45.7), 63 (23.7); Anal. Calcd for $C_8H_8BrNO_3$: C, 39.05; H, 3.28; N, 5.69. Found: C, 39.03; H, 3.28; N, 5.69.

4.5. General procedure for the preparation of acyl derivatives of (±)-2-bromo-1-(4-nitrophenyl)ethanol 6a–c

A solution of (±)-2-bromo-1-(4-nitrophenyl)ethanol (2.46 g, 10 mmol), alkanoic anhydride (12 mmol) and catalytic amount of 4-(dimethylamino)pyridine (DMAP) in dry dichloromethane (20 mL) was stirred overnight at room temperature. After completion of the reaction (monitored by TLC), the contents were poured into ice-cold water and extracted with dichloromethane (3 × 50 mL). The organic layer was washed with brine, dried and evaporated at reduced pressure, followed by purification on silica gel column to furnish the product **6a**–**c** in 90–95% yield.

4.5.1. 1-Acetoxy-2-bromo-1-(4-nitrophenyl)ethane 6a. A creamish solid; mp 118.5 °C; IR (KBr): 1748, 1520, 1348, 1233, 1059 cm^{-1}; ^1H NMR (200 MHz): δ 2.23 (3H, s, COCH_3), 3.70 (2H, d, J = 6.0 Hz, –CH_2Br), 5.16 (1H, t, J = 6.0 Hz, C*H*OCOCH_3), 7.66 (2H, d, J = 8.5 Hz, Ar-*H*), 8.41 (2H, d, J = 8.5 Hz, Ar-*H*); ^{13}C NMR (50 MHz): δ 20.8, 33.4, 73.6, 123.9, 127.6, 144.5, 148.0, 169.5; MS (*m*/*z*) (%): 288 (8.3), 286 (9.3), 243 (2.5), 241 (1.8), 226 (50.1), 205 (37.9), 193 (38.5), 178 (22.3), 164 (41.8), 151 (23.5), 147 (100), 102 (100), 91 (86.2), 77 (78); Anal. Calcd for $C_{10}H_{10}BrNO_4$: C, 41.69; H, 3.50; N, 4.86. Found: C, 41.60; H, 3.48; N, 4.81.

4.5.2. 1-Propanoyloxy-2-bromo-1-(4-nitrophenyl)ethane 6b. A viscous liquid; IR (neat): 3113, 3081, 2983, 2943, 1745, 1523, 1349, 1272, 1168, 1082, 855, 708 cm^{-1}; ^1H NMR (200 MHz): δ 1.21 (3H, t, J = 7 Hz, –OCOCH_2–CH_3), 2.48 (2H, q, J = 8 Hz, –OCOCH_2–CH_3), 3.71 (2H, d, J = 6.0 Hz, CH_2Br), 6.16 (1H, t, J = 6.0 Hz, C*H*OCOCH_2–), 7.66 (2H, d, J = 8.5 Hz, Ar-*H*), 8.38 (2H, d, J = 8.5 Hz, Ar-*H*); ^{13}C NMR (50 MHz): δ 10.2, 28.7, 34.7, 67.8, 125.1, 128.8, 146.4, 149.2, 174.3; MS (*m*/*z*) (%): 304 (2.5), 302 (2.6) (M+1), 230 (29.6), 228 (35.6), 222 (36.4), 208 (18.2), 148 (100), 119 (52.8), 102 (89.8), 91 (73.1), 77 (100), 58 (100); Anal. Calcd for $C_{11}H_{12}BrNO_4$: C, 43.73; H, 4.00; N, 4.64. Found: C, 43.65; H, 4.01; N, 4.62.

4.5.3. 1-Butanoyloxy-2-bromo-1-(4-nitrophenyl)ethane 6c. A viscous liquid; IR (neat): 3113, 3081, 2966, 2935, 1743, 1523, 1348, 1251, 1166, 855, 707 cm^{-1}; ^1H NMR (200 MHz): δ 0.96 (3H, t, J = 7.4 Hz, –OCOCH$_2$CH$_2$–CH_3), 1.68 (2H, m, –OCOCH$_2$CH_2–CH$_3$), 2.41 (2H, m, –OCOCH_2CH$_2$–CH$_3$), 3.64 (2H, d, J = 6.0 Hz, –CH_2Br), 6.05 (1H, t, J = 6.0 Hz, C*H*–CH$_2$Br), 7.55 (2H, d, J = 8.7 Hz, Ar-*H*), 8.25 (2H, d, J = 8.7 Hz, Ar-*H*); ^{13}C NMR (50 MHz): δ 13.6, 18.2, 33.5, 36.04, 73.55, 123.8, 127.3, 144.7, 148.0, 172.2; MS (*m*/*z*) (%): 316 (5.6), 314 (4.9), 229 (9.6), 148 (23.3), 119 (15.9), 102 (18.7), 89 (18.1), 71 (100), 57 (51.6); Anal. Calcd for $C_{12}H_{14}BrNO_4$: C, 45.59; H, 4.46; N, 4.43. Found: C, 45.45; H, 4.45; N, 4.39.

4.6. General procedure for lipase/esterase catalyzed hydrolysis of acyl derivatives of (±)-2-bromo-1-(4-nitrophenyl)ethanol 6

A suspension of substrate (±)-**6** (100 mg, 0.35 mmol of **6a**, 0.33 mmol of **6b**, 0.32 mmol of **6c**), crude enzyme powder (100 mg) and sodium phosphate buffer (0.1 M, pH 7, 2.5 mL) was stirred at 28 ± 1 °C, maintaining the pH 7 by addition of 0.1 M NaOH solution. It was essential to monitor the course of reaction by chiral HPLC. After a certain degree of conversion, the reaction was terminated by centrifugation of reaction mixture at 10,000*g*. The clear solution and the centrifuged cell pellet were extracted separately with ethyl acetate (3 × 10 mL). The organic layers were combined and washed with water, dried and the organic layer concentrated under reduced pressure. The resulting mixture consisting of alcohol and ester, was separated by column chromatography over silica gel to furnish enantiorich **5** and **6** (isolated yields 4–68%, Table 2).

4.7. General procedure for lipase/esterase catalyzed hydrolysis of (±)-1-butanoyloxy-2-bromo-1-(4-nitrophenyl)ethane 6c in the presence of co-solvents

A suspension comprising of substrate (±)-**6c** (100 mg, 0.32 mol), crude enzyme powder (100 mg), sodium phosphate buffer (0.1 M, pH 7, 2.25 mL) and solvents (as indicated in Table 3) was stirred at 28 ± 1 °C, maintaining pH 7 by addition of 0.1 M NaOH solution. It was essential to monitor the course of reaction by chiral HPLC. After a certain degree of conversion, the reaction was terminated by centrifugation of reaction mixture at 10,000*g*. The clear solution and the centrifuged cell pellet were extracted separately with ethyl acetate (3 × 10 mL). The organic layers were combined and washed with water, dried and the organic layer concentrated under reduced pressure. The resulting mixture consisting of alcohol and ester, was separated by column chromatography over silica gel to furnish enantiorich **5** and **6c** (isolated yields 5–67%, Table 3).

4.8. General procedure for lipase/esterase catalyzed transesterification of (±)-2-bromo-1-(4-nitrophenyl)ethanol 5

A suspension comprising of substrate (±)-**5** (200 mg, 0.8 mmol), crude or immobilized enzyme (200 mg) in an organic solvent (900 μL) and vinyl acetate (100 μL) was shaken on an orbital shaker at 200 rpm, maintaining the temperature at 28 ± 1 °C. The course of reaction was monitored by chiral HPLC. After a certain degree of conversion, the enzyme was filtered out, washed with organic solvent. The combined solvent was removed under reduced pressure and the resulting dry mass

comprising of enriched alcohol and ester were separated by column chromatography over silica gel to furnish enantiorich (*R*)-(−)-**5** and (*S*)-(+)-**6a**.

4.9. Typical method of transesterification of (±)-2-bromo-1-(4-nitrophenyl)ethanol with PS-C-II

A suspension comprising of (±)-**5** (200 mg, 0.8 mmol), PS-C-II (200 mg), toluene (900 μL) and vinyl acetate (100 μL) was shaken on an orbital shaker at 200 rpm maintaining temperature at 28 ± 1 °C. The course of transesterification reaction was monitored by chiral HPLC. After a 50% conversion that took about 28 h, the enzyme was filtered out, and washed with diethyl ether (3 × 5 mL). The combined solvent mixture was evaporated at reduced pressure. The resulting dry mass comprising of enriched alcohol and ester was separated by column chromatography over silica gel to furnish enantiopure (*R*)-**5** (84 mg, 0.34 mmol, 42%) $[\alpha]_D^{25} = -29.8$ (*c* 1.0, $CHCl_3$) (ee >99.5%) {lit.[14] $[\alpha]_D = -28.3$ (*c* 1.0, $CHCl_3$) (ee >95%)} and (*S*)-**6a** (100 mg, 0.34 mmol, 42.7%) $[\alpha]_D^{25} = +51.2$ (*c* 1.0, $CHCl_3$) (ee >99.5%) {lit.[14] $[\alpha]_D = +49.3$ (*c* 1.0, $CHCl_3$) (ee >95%)}.

4.10. Preparation of (*R*)-nifenalol

A methanolic solution of (*R*)-2-bromo-1-(4-nitrophenyl)ethanol (492 mg, 2 mmol) was slowly added to isopropylamine (850 μL, 10 mmol) in methanol (5 mL) at 35 °C in a round bottomed flask placed in a sonicator and the course of reaction was monitored by TLC. After completion of the reaction (~2 h), methanol was evaporated, the contents diluted by adding cold distilled water (15 mL) followed by extraction with ethyl acetate (3 × 15 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give (*R*)-nifenalol (404 mg, 1.8 mmol, 90%), mp 113.2 °C (lit.[6] 112–114 °C); $[\alpha]_D^{25} = -11.3$ (*c* 1.0, EtOH) {lit.[6] $[\alpha]_D^{20} = -11.4$ (*c* 1.03, EtOH)}; IR (neat): 699, 791, 1073, 1346, 1520, 1604, 2913, 2960 cm^{-1}; ^1H NMR (200 MHz): δ 1.10 and 1.11 (3H each, d, $J = 6.7$ Hz, $CH(CH_3)_2$), 2.60 (1H, dd, $J = 9.3$ and 12.2 Hz, H_A of $-CH_2-NH$), 2.40–2.64 (1H, m, $NH-CH(CH_3)_2$), 2.96 (1H, dd, $J = 3.4$ and 12.2 Hz, H_B of $-CH_2-NH$), 4.82 (1H, dd, $J = 3.2$, 9.2 Hz), 7.50 (2H, d, $J = 8.5$ Hz), 8.17 (2H, d, $J = 8.4$ Hz); ^{13}C NMR (50 MHz): 22.0, 22.1, 49.3, 53.8, 70.53, 123.6, 126.3, 147.3, 150.0; MS (*m*/*z*) (%): 225 (M+1) (4.3), 193 (12.3), 151 (10.1), 130 (3.0), 72 (100.0), 45 (34.1); Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.58; H, 7.10; N, 12.57.

4.11. Preparation of (*S*)-nifenalol and its conversion to (*S*)-sotalol

A solution of isopropylamine (850 μL, 10 mmol) in methanol (5 mL) was slowly added to methanolic solution of acetyl derivative of (*S*)-2-bromo-1-(4-nitrophenyl)ethanol (576 mg, 2 mmol) at 35 °C in a sonicator and progress of the reaction was monitored by TLC. After completion of the reaction, the contents were concentrated and cold distilled water (15 mL) added to the resulting mixture followed by extraction with ethyl acetate (3 × 15 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give (*S*)-nifenalol (394 mg, 1.75 mmol, 88%) $[\alpha]_D^{25} = +11.2$ (*c* 1.0, EtOH); $[\alpha]_D^{25} = +42.7$ (*c* 0.4, 1 N HCl); lit.[10] $[\alpha]_D^{25} = +41.5$ (*c* 0.4, 1 N HCl) (ee 96%). (*S*)-Nifenalol (350 mg, 1.5 mmol) thus obtained was converted to (*S*)-(+)-sotalol by catalytic reduction followed by mesylation of the reduced product by the method reported in the literature.[10] The resulting product after purification and treatment with 1 equiv of 5% HCl furnished (*S*)-sotalol hydrochloride (193 mg, 40%); mp 204 °C (lit.[19] 206.5–207 °C); $[\alpha]_D^{25}(2 \cdot HCl) = +34.4$ (*c* 1.0, H_2O); lit.[20] $[\alpha]_D^{25} = +34.7$ (*c* 1.0, H_2O); IR (KBr): 1043, 1128, 1322, 3400, 3565 cm^{-1}; ^1H NMR (200 MHz, CD_3OD): δ 1.26 (6H, d, $J = 6.6$ Hz, $CH(CH_3)_2$), 3.00 (3H, s, CH_3SO_2), 3.16 (1H, m, $CH(CH_3)_2$), 3.86 (2H, d, $J = 5.1$ Hz, CH_2NH), 4.30 (1H, t, $J = 5.0$ Hz, CHOH), 7.34 (2H, d, $J = 8.7$ Hz, Ar-*H*), 7.46 (2H, d, $J = 8.7$ Hz, Ar-*H*); ^{13}C NMR (50 MHz, $CDCl_3$): 19.38, 20.77, 39.52, 47.70, 50.26, 62.28, 64.60, 121.54, 130.28, 134.18, 140.36; MS (*m*/*z*) (%): 272 (4.3), 193 (12.3), 121 (10.1), 72 (100.0), 43 (34.1), 30 (26.5); Anal. Calcd for $C_{12}H_{20}N_2O_3S{\cdot}HCl$: C, 46.67; H, 6.85; N, 9.07. Found: C, 46.81; H, 6.81; N, 9.02.

4.12. HPLC analysis with chiral stationary phase

Enantiomeric excesses (ee%) were determined by chiral HPLC on (*R*,*R*)-Whelk O1 column (5 μm), Merck, Germany (column temp 22 °C) using a mobile phase hexane–isopropanol–acetic acid = 97:2.9:0.1 at flow rate 0.3 mL/min and detection wavelength 254 nm. Retention times for different chiral compounds are as follows: (*S*)-2-bromo-1-(4-nitrophenyl)ethanol −43.1 min, (*R*)-2-bromo-1-(4-nitrophenyl)ethanol −45.6 min; (*R*)-1-acetoxy-2-bromo-1-(4-nitrophenyl)ethane −24.3 min, (*S*)-1-acetoxy-2-bromo-1-(4-nitrophenyl)ethane −34.8min; (*R*)-1-propanoyloxy-2-bromo-1-(4-nitrophenyl)-ethane −19.1 min, (*S*)-1-propanoyloxy-2-bromo-1-(4-nitrophenyl)ethane −29.4 min; (*R*)-1-butanoyloxy-2-bromo-1-(4-nitrophenyl)ethane −17.7 min and (*S*)-1-butanoyloxy-2-bromo-1-(4-nitrophenyl)ethane −27.5 min.

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