Chemoenzymatic Route for the Synthesis of (*S*)-Moprolol, a Potential β-Blocker

SAPTARSHI GHOSH, JAYEETA BHAUMIK, LINGA BANOTH, SOORAM BANESH, AND UTTAM CHAND BANERJEE*
Department of Pharmaceutical Technology, National Institute of Pharmaceutical Education and Research, Nagar, Punjab, India

ABSTRACT A biocatalytic route for the synthesis of a potential β-blocker, (S)-moprolol is reported here. Enantiopure synthesis of moprolol is mainly dependent on the chiral intermediate, 3-(2-methoxyphenoxy)-propane-1,2-diol. Various commercial lipases were screened for the enantioselective resolution of (RS)-3-(2-methoxyphenoxy)propane-1,2-diol to produce the desired enantiomer. Among them, *Aspergillus niger* lipase (ANL) was selected on the basis of both stereo- and regioselectivity. The optimized values of various reaction parameters were determined such as enzyme (15 mg/mL), substrate concentration (10 mM), organic solvent (toluene), reaction temperature (30 °C), and time (18 h).The optimized conditions led to achieving >49% yield with high enantiomeric excess of (S)-3-(2-methoxyphenoxy)propane-1,2-diol. The lipase-mediated catalysis showed regioselective acylation with dual stereoselectivity. Further, the enantiopure intermediate was used for the synthesis of (S)-moprolol, which afforded the desired β-blocker. *Chirality 28:313–318, 2016.*

KEY WORDS: β-blocker; lipase; stereoselectivity; enantiopure; moprolol

Moprolol (1-(isopropylamino)-3-(O-methoxyphenoxy)-2-propanol), a nonselective β-blocker, is used in the treatment of ocular hypertension, ischemic heart disease, congestive heart failure, and certain arrhythmias. Although currently marketed in the racemic form, the (*S*)-enantiomer of moprolol is a eutomer while the (*R*)-enantiomer is a distomer. (*S*)-moprolol acts as a β-blocker and is more potent than its (*RS*)-form. The literature reveals the presence of quite a good number of publications detailing the synthesis of the enantio-enriched pure form of moprolol. Different synthetic approaches towards the synthesis of moprolol are summarized in Scheme 1. Synthesis of (*S*)-moprolol by proline catalyzed α-aminoxylation of aldehydes with 93% yield was reported by Panchgalle et al. (Route A).[1] The Jacobsen type of hydrolysis for the enantiospecific synthesis of (*S*)-moprolol with 16% yield is also reported (Route B).[2–4] Stereoselective synthesis of (*S*)-moprolol by tetrahydrosalen-Cu(I) complex catalyzed the Henry reaction is reported with 96% yield.[5] Epoxide ring opening with isopropylamine for the enantiospecific synthesis of moprolol was reported by Kamal et al. (Route C).[6,7] Synthesis of (*S*)-moprolol by kinetic resolution of chlorohydrin derivatives using *Pseudomonas* lipase was also discussed by Ader et al. (Route D).[8] Chemical synthesis of enantiopure guaifenesin for the production of (*S*)-moprolol was also reported by Bredikihina et al. (Route E).[9] Moreover, *Pseudomonas cepacia* lipase-mediated enantiopure synthesis of (*S*)-3-hydroxy-4-(4-methoxyphenoxy)- butanenitrile (yield 43%, enantiomeric excess [*ee*] = 99%) and moprolol (88% yield) was also discussed by Kamal et al. (Routes F, G).[10] Interestingly, a 7-step synthesis of moprolol via OsO_4-catalyzed asymmetric dihydroxylation was mentioned in the literature with 76% yield by Sayyed et al. (Route H).[11] Most of the methods described above have several disadvantages, including high cost of chiral metal catalysts, toxicity of the catalysts used, multiple reaction steps, issues associated with moisture sensitivity, removal of major byproducts, and a tedious separation process. The biocatalytic method reported previously (Routes F, G)[10] used a four-step chemical reaction to obtain (*S*)-moprolol from the chiral intermediate. Here we report a new chemo-enzymatic route for the synthesis of (*S*)-moprolol from a different starting material with improved yield and higher *ee*, which does not require costly and toxic chemicals. Lipase, a highly versatile biocatalyst, has been extensively used for the kinetic resolution of racemic alcohols for the synthesis of enantiopure drugs and drug intermediates.[12–14] Due to its high regio- and stereoselectivity, lipase was selected for the biocatalytic resolution of intermediary diol in this study. Here the chemical synthesis of (*S*)-moprolol from the chiral intermediate was reduced to two steps, thus making it a better method.

MATERIALS AND METHODS

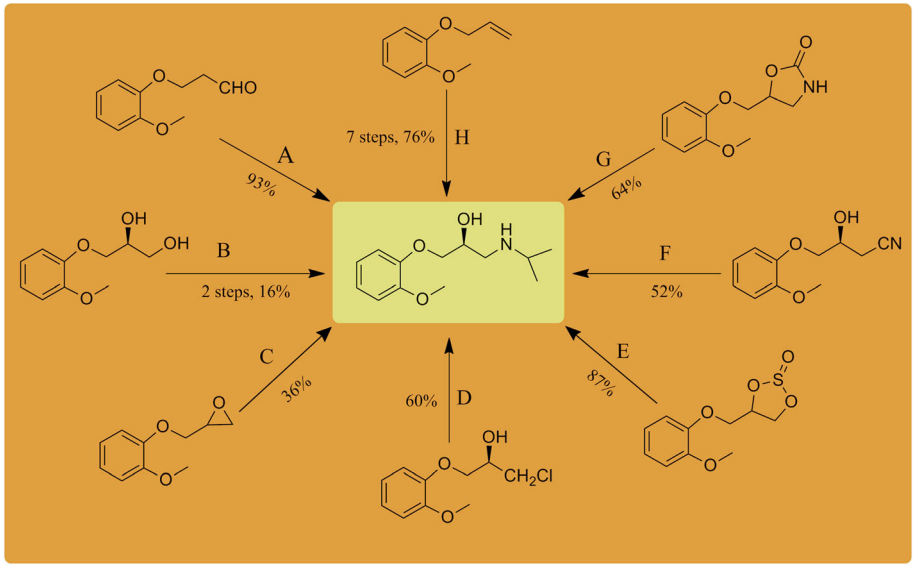
Analytical Methods

Reactions were analyzed by ^{1}H NMR and ^{13}C NMR spectra, obtained with a Bruker (Billerica, MA) DPX 400 (^{1}H 400 MHz and ^{13}C 100 MHz), and chemical shifts are expressed in δ units relative to the tetramethylsilane (TMS) signal as an internal reference in $CDCl_3$. IR spectra (wave number in cm^{-1}) were recorded on a Nicolet (Madison, WI) FT-IR impact 400 instrument. Analytical thin-layer chromatography (TLC) of all the reactions was carried out on Merck (Darmstadt, Germany) plates. SRL silica gel (60–120 mesh) was used in column chromatography. The enantiomeric excesses (*ee*) were determined by HPLC (Shimadzu, Japan, LC-10AT 'pump, SPD-10A UV-VIS detector) using a Chiralcel OD-H column (0.46 × 250 mm; 5 μm, Daicel, Japan) at 254 nm, with mobile phase, hexane:2-propanol (9:1); flow rate, 1 mL/min, and column temperature of 25 °C.

Reagents

(*RS*)/(*R*)/(*S*)-**2**-methoxyphenol, glycidol, isopropylamine, and the lipase preparations from *Candida antarctica* (CAL) in acrylic resin, *C. rugosa* 62316 (CRL 62316), *C. rugosa* 90860 (CRL 90860), *C. rugosa*

*Correspondence to: Uttam Chand Banerjee, Department of Pharmaceutical Technology, National Institute of Pharmaceutical Education and Research, Sec-67, S.A.S. Nagar-160062, Punjab, India. E-mail: ucbanerjee@niper.ac.in
Received for publication 7 September 2015; Accepted 10 December 2015
DOI: 10.1002/chir.22574
Published online 28 January 2016 in Wiley Online Library (wileyonlinelibrary.com).



Scheme 1. Various synthetic strategies for (*S*)-moprolol.

L-1754 (CRL L1754), *C. cylindracea* (CCL), *Aspergillus niger* (ANL), cross-linked enzyme aggregates (CLEA) of *C. antarctica*, lipase from *Pseudomonas cepacia* (PCL), immobilized lipase from *Mucor miehei* (MML), and lipase from porcine pancreas (PPL) were purchased from Sigma (St. Louis, MO), and Fluka (Buchs, Switzerland). Lipase AY "Amano"30 was purchased from Amano Chem (USA). The reagent-grade solvents such as hexane, ethyl acetate, etc., were procured from various commercial sources. Solvents of high-performance liquid chromatography (HPLC)-grade such as hexane and 2-propanol were obtained from J.T. Baker (Phillipsburg, NJ).

Synthesis of (RS)-3-(2-methoxyphenoxy) Propane-1,2-diol 3

(*RS*)-**3** was prepared by the reaction of 2-methoxy-phenol **1** (10 mmol, 1 eq.) with (*RS*)-oxiran-2-yl-methanol **2** (10 mmol, 1 eq.) in the presence of K_2CO_3 (2.07 g, 1.5 eq.) in MeCN (20 mL) at 65–70 °C for 12 h (Scheme 3). The reaction mixture was filtered and the filtrate was dried under vacuum. Further, it was solubilized in ethyl acetate and extracted against water. The organic layer was isolated and dried in rotavapor. The dried fraction was then subjected to column chromatography (silica 60–120, hexane: ethyl acetate:: 9:1) to isolate the pure product.

(*RS*)-3-(2-methoxyphenoxy)propane-1,2-diol **3**, a yellowish white solid (90% yield, 3.76 g); ^{1}H NMR (400 MHz, $CDCl_3$): d 3.72–3.79 (m, 2 H), 3.82 (s, 3 H), 3.98–4.04 (m, 2H), 4.09-4.15 (m, 1H) 6.86–6.94 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.8, 63.8, 69.9, 72.1, 111.8, 120.7, 121.2, 122.2, 147.9, 149.6; MS (*m/z*): 199.28.

Enantioselective Transesterification of (RS)-3

Commercial lipases from different sources such as *Candida antarctica*, *C. rugosa* 90860, *C. rugosa* 62316, *C. rugosa* L-1754, *C. cylindracea*, *Aspergillus niger*, porcine pancreas, AY "Amano"30, and the immobilized lipases like sol-gel-Ak from *Pseudomonas cepacia*, immobilized lipozyme from *Mucor miehei*, lipase acrylic resin from *C. antarctica* CLEA, were individually put into separate 5 mL conical flasks. Substrate (*RS*)-**3** (10 mM) in 0.9 mL toluene along with 0.1 mL vinyl acetate (acyl donor) was added into each flask. The flasks were then capped and placed in an incubator shaker at 37 °C (200 rpm). Reactions were worked up after 24 h and conversion and the *ee* were monitored by HPLC.

Preparative-Scale Transesterification Reaction of (RS)-3

The resolution of (*RS*)-**3** was carried out in preparative scale under the optimized condition. The transesterification was performed with 20 mmol (3.96 g) substrate and ANL lipase at 30 °C using vinyl acetate as the acyl donor in 50 mL toluene. The reaction mixture was filtered and enzyme preparation was washed with toluene when the transformation was ~50% in 18 h (52.4% conversion for (*R*)-**4**; 50% conversion for (*S*)-**5**). The solvent was evaporated under vacuum and the resulting dried residue was subjected to flash chromatography (hexane: ethyl acetate:: 17:3).

(*R*)-3-(2-methoxyphenoxy) propane-1,2-diyl diacetate **4**, a yellow liquid (27% yield, 1.1 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 6H), 3.8 (s, 3H), 4.14–4.18 (m, 2H), 4.28–4.33 (m, 1H), 4.47 (dd, J = 15.8, 12, 1H), 5.35–5.39 (m, 1H), 6.86–6.98 (m, 4H); ^{13}C NMR (100 MHz, CDCl3): δ 20. 9, 55.9, 61.9, 66.8, 69.3, 111.8, 120.6, 121.1, 122.1, 147.9, 149.5, 169.5; MS (APCI) (*m/z*): 283.39. The product was then subjected to chiral HPLC analysis using chiral OD-H column, the (*R*)-enantiomer was eluted at t_R = 7 min (hexane: 2-propanol:: 9:1) with >99% *ee*.

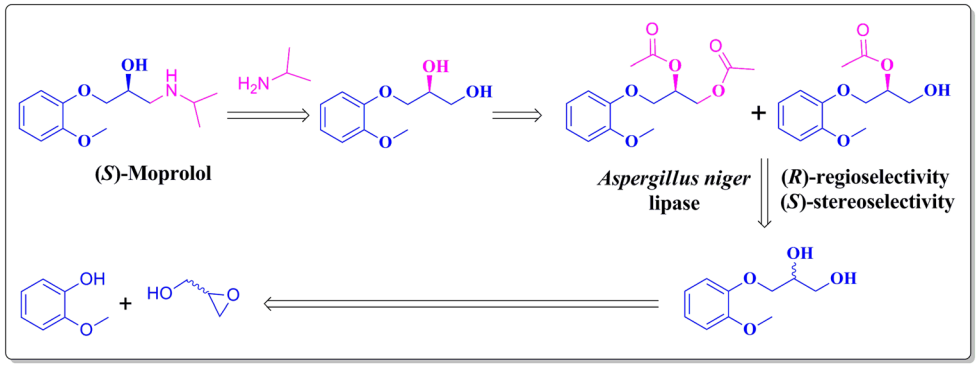
(*S*)-1-hydroxy-3-(2-methoxyphenoxy) propan-2-yl acetate **5**, a colorless liquid (18% yield, 0.7 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 3H), 3.72–3.79 (m, 1 H), 3.82 (s, 3H), 4.14–4.18 (m, 2H), 4.28–4.33 (m, 1H), 4.42–4.47 (m, 1H), 4.55–4.59 (m, 1H), 6.86-6.98 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21. 4, 55.8, 61.5, 66.8, 73.1, 111.8, 120.7, 121.1, 122.1, 147.9, 149.6, 169.5; MS (APCI) (*m/z*): 241.37. The product was then subjected to chiral HPLC analysis using chiral OD-H column, the (*S*)-enantiomer was eluted at t_S = 11 min (hexane: 2-propanol:: 9:1) with >99% *ee*.

Deacylation of (R)-4 and (S)-5

A solution of K_2CO_3 (0.27 g, 2 mmol) in deionized water (1 mL) was added separately to (*R*)-**4** and (*S*)-**5** (1 mmol) in methanol (5 mL) and the reaction mixture was kept under stirring for 2 h at room temperature (25–30 °C). After completion, the reaction mixture was extracted with ethyl acetate (3 × 15 mL) and water (10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum to obtain the crude product, which was purified by column chromatography (hexane: ethyl acetate:: 17:3) on silica gel (100–200 mesh) to obtain the corresponding alcohol.

(*R*)-**3**: a grayish white solid, (90% yield, 0.243 g); 100% *ee*. $[\alpha]_D^{20}$ 9.43 (c 1.0, MeOH).[15] The product was then subjected to chiral HPLC analysis using a Chiralcel OD-H column, the enantiomer was eluted at t_R = 7.6 min (hexane: 2-propanol:: 9:1).

(*S*)-**3**: a light yellow liquid, (91% yield, 0.246 g); 100% *ee*. $[\alpha]_D^{20}$ + 9.16 (c 1.0, MeOH).[16] The product was then subjected to chiral HPLC analysis using a Chiralcel OD-H column, the enantiomer was eluted at t_S = 13.7 min (hexane:2-propanol:: 9:1).



Scheme 2. Retrosynthetic pathway for the chemoenzymatic synthesis of (*S*)-moprolol.

Synthesis of (S)-6

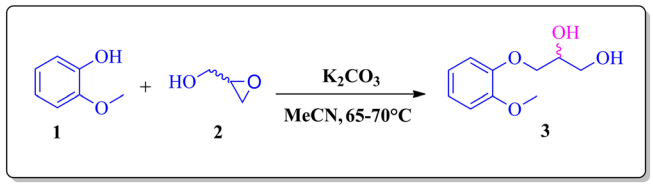
The enantiopure alcohol, (*S*)-**3** (0.3 g, 1.5 mmol, 1 eq.) in 15 mL of CH_2Cl_2 was kept under stirring conditions in an ice bath for 10 min and subsequently DBU (300 µL, 2 mmol, 2 eq.) and p-TsCl (0.38 g, 1 mmol, 2 eq.) was added. After 20 min, the reaction mixture was removed from the ice bath and concentrated under vacuum to afford the desired tosylated derivative. The intermediate was directly used in the next step without further purification and characterization. The tosylated intermediate (1 mmol, 1 eq.) was treated with isopropylamine (1 mmol, 1.5 eq.) in methanol (2 mL) at room temperature (25–30 °C) for 4 h. After completion, the reaction mixture was extracted with ethyl acetate. The combined organic layer was dried with Na_2SO_4 and concentrated under vacuum. The residue was then taken for purification by column chromatography using silica gel (60–120 mesh) and eluted with hexane:ethyl acetate (17:3) to obtain (*S*)-**6**: a white solid (35% yield in two steps, 43 mg); $[\alpha]_D^{20} = -7.5$ (c 0.9, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01–1.09 (s, 6H), 2.66–2.68 (m, 2H), 2.72–2.74 (m, 2H), 3.8 (s, 3H), 3.9–4.04 (m, 2H), 4.07–4.08 (m, 1H) 6.88–6.90 (m, 4H),: ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.23, 53.87, 54.64, 55.95, 68.13, 68.71, 71.75, 112.73, 113.68, 121.30, 148.80, 149.51; MS (APCI) (*m/z*): 239.29.

RESULTS AND DISCUSSION

In the present day's context, the use of green chemistry tools in the design of a new synthetic route is highly desirable.[17,18] Introduction of biocatalysis for the synthesis of drug–drug intermediates is a graceful approach towards green chemistry.[19] Enzymatic kinetic resolution of various racemic secondary alcohols[20–22] encouraged us to design a new chemoenzymatic route for (*S*)-moprolol. Retrosynthetic pathway for the synthesis of (*S*)-moprolol is shown in Scheme 2.

Synthesis of (RS)-3-(2-methoxyphenoxy) Propane-1,2-diol (3)

(*RS*)-3-(2-methoxyphenoxy)propane-1,2-diol (**3**) is a key intermediate for the preparation of enantiopure moprolol. Among the various methods reported in the literature (Scheme 1, Routes A–H), only one group (Route B) used this alcohol as a precursor to moprolol. However, their approach did not involve any biocatalytic pathway. Following a reported procedure with modification,[23] the racemic alcohol (*RS*)-**3** was prepared by the reaction of 2-methoxyphenol **1** with (*RS*)-oxiran-2-yl-methanol **2** in the presence of K_2CO_3 in MeCN at 65–70 °C for 12 h (Scheme 3). The desired racemic product was obtained with 90% yield and was characterized by NMR spectroscopy, mass spectrometry, and chiral HPLC (see Supporting Information for HPLC chromatogram).



Scheme 3. Synthesis of (*RS*)-3-(2-methoxyphenoxy)propane-1,2-diol (**3**).

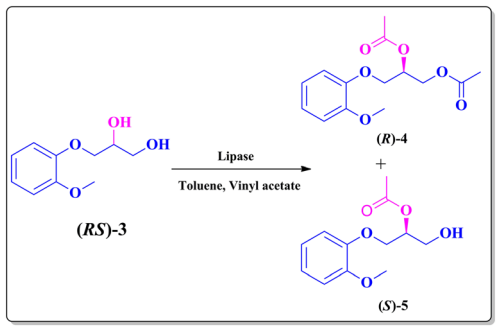
Biocatalytic Route for the Kinetic Resolution of (RS)-3

Biocatalysis is an important methodology for the kinetic resolution of key racemic intermediates. This method gives easy access to enantiopure drugs or drug intermediates that are difficult to synthesize otherwise. Lipase is an important bicatalytic enzyme that can play key role in kinetic resolution of racemic diols. Among various biocatalysts, lipases gained immense popularity for their versatile use in producing enantiopure compounds.

Lipase-Mediated Kinetic Resolution of (RS)-3

Among the various lipases screened, *Aspergillus niger* lipase (ANL) exhibited the best selectivity for the conversion of (*RS*)-**3** to diacylated derivative (*R*)-**4** and monoacylated derivative (*S*)-**5** (Scheme 4) which lead to the kinetic resolution of the racemic diol. A high regioselectivity for the mono- and diacylation along with stereoselectivity was observed. It showed an (*R*)-selective diacylation and (*S*)-selective monoacylation with enantiomeric ratio (E) of 307 (Table 1).

On the basis of better conversion and enantioselectivity of ANL over other lipases, all the subsequent experiments were



Scheme 4. Lipase-mediated kinetic resolution of (RS)-**3**.

TABLE 1. Transesterification of (*RS*)-3 with lipases in toluene[a]

Lipase	ee^{b}_{S}(%)	ee^{c}_{di}(%)	ee^{c}_{mono}(%)	C^{d}_{di}(%)	C^{d}_{mono}(%)	E_{di}
ANL	100	79.7	100	55.6	50.0	307
CAL	13.2	33.0	100	28.5	11.6	2.24
CRL 62316	38.7	12.9	100	74.8	27.9	1.77
CRL 90860	10.0	86.9	34.1	10.3	22.7	15.8
CRL L1754	43.4	14.2	100	75.3	30.3	1.89
CLEA	100	25.3	100	79.8	50	0
MML	26.9	36.1	100	42.7	21.2	2.73
PCL	53.4	79.1	73.8	40.3	41.9	14.5
CCL	7.20	22.7	13.3	24.2	35.3	1.70
Amano	28.5	30.5	48.8	48.3	36.9	2.43
Porcine	8.90	38.2	28.3	19.0	24.1	2.44

[a]Conditions: (*RS*)-**3** (20 mM) in 2 mL toluene was treated with vinyl acetate (5.4 mmol) at 30 °C in the presence of enzyme 15 mg/mL.
[b]Enantiomeric excess of substrate was determined by HPLC analysis (Daicel Chiralcel OD-H column) 90:10; hexane: 2-propanol, 1 mL/min flow rate at 254 nm.
[c]Enantiomeric excess of product was determined by HPLC analysis (Daicel Chiralcel OD-H column) 90:10; hexane: 2-propanol, 1 mL/min flow rate at 254 nm.
[d]Conversions were calculated from enantiomeric excess of substrate (ee_S) and product (ee_{di} and ee_{mono}) using the formula: Conversion (C) = $ee_S/(ee_S + ee_{di})$ and $C = ee_S/(ee_S + ee_{mono})$
[e]Values were calculated using the formula: $E = [\ln (1 - C (1 + ee_P)]/ [\ln (1 - C (1 - ee_P)]$.

carried out with this enzyme preparation (Table 1). In order to optimize the yield of lipase-mediated kinetic resolution, various reaction parameters were screened including: solvent types, reaction time, temperature, and enzyme and substrate concentration (see Supporting Information S1).

Optimization of Physicochemical Parameters for the Lipase-Catalyzed Transesterification of (RS)-3

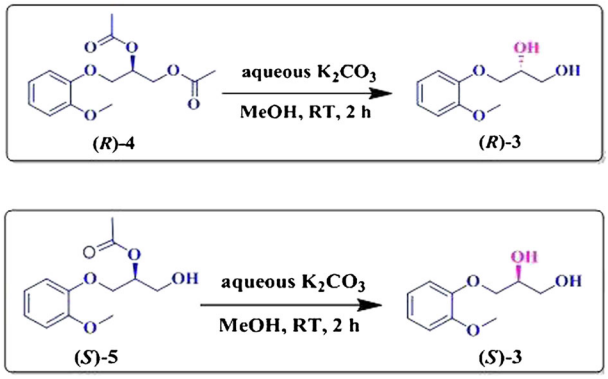
Effect of solvents on transesterification by lipases is one of the crucial parameter because of their versatility and higher stability in organic solvents.[12–14,17–27] The effect of different organic solvents on activity and enantioselectivity of ANL for the kinetic resolution of (*RS*)-**3** was studied. Among them, toluene was selected as the ideal reaction medium due to the higher enantiomeric ratio (E = 215, see Supporting Information S8) and better conversion. The course of reaction was studied and the maximum conversion (C_{di} = 52%; C_{mono} = 50%) and enantiomeric excess (ee_{di} = 91% and ee_{mono} = 100%) was achieved after 18 h of reaction (see Supporting Information S1 Fig. 1a). This result was found to be better than literature methods, which reported 30% and 43% yield, respectively.[10,16] The influence of temperature on the activity and enantioselectivity of ANL catalyzed resolution of (*RS*)-**3** was determined (see Supporting Information S1 Fig. 1b). The best conversion of 49.7% and *ee* of 92.7% was obtained at 30 °C for diacylated product. Although there was no variation in enantiomeric excess for mono-acylated product. It is evident from (see Supporting Information S1 Fig. 1c) that the highest *ee* (91.5%) and conversion (50.7%) for the diacylated product was achieved at enzyme concentration of 15 mg/mL. The best conversion for diacylated product (51%) was obtained with 10 mM substrate with *ee* of 90% see Supporting Information S1 Fig. 1d). Under optimized conditions, the biocatalytic resolution showed ~50% conversion and 90% *ee*.

Deacylation of (R)-4 and (S)-5 to Synthesize Enantiopure Diol

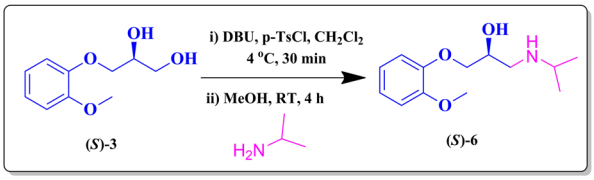
After optimizing important reaction parameters for the preparation of compound (*R*)-**4**/(*S*)-**5** by lipase-mediated selective acylation, we focused on synthesizing the enantiopure diol. Liberation of the parent alcohol [(*R*)/(*S*)-**3**] from the acetylated intermediate (*R*)-**4** and (*S*)-**5** was achieved by deacylation in aqueous K_2CO_3 at room temperature (25–30 °C) for 2 h with 90% yield (Scheme 5).[28]

Synthesis of (S)-moprolol 6 From the Enantiopure Diol

Synthesis of enantiopure moprolol can be easily achieved from compound (*S*)-**3**. Since the primary hydroxyl group of (*S*)-**3** does not react with a secondary amine, a better leaving group (e.g., halide, tosyl, etc.) can be introduced. Following a general procedure with modification,[29,30] the compound (*S*)-**3** was treated with para-toluene sulphonyl chloride (p-TsCl) and DBU in dichloro-methane at 4 °C, which afforded the tosylated intermediate. This reactive intermediate was further treated with iso-propylamine in methanol at room temperature (25–30 °C) for 4 h to produce the desired product (*S*)-moprolol **6** with 35% yield (in two steps, Scheme 6). It should be noted that despite the presence of both primary and secondary alcohols in compound (*S*)-**3**, the tosyl group selectively replaced the primary hydroxyl group. This claim is supported by comparing the ^{1}H NMR data of starting material (*S*)-**3** with the desired product (*S*)-**6**. The chemical shift of the methine bridge proton remained unchanged



Scheme 5. Deacylation of (*R*)-**4** (top panel) and (*S*)-**5** (bottom panel).



Scheme 6. Synthesis of (*S*)-moprolol **6** from the enantiopure diol.

(at ~4.1 ppm) at the final stage, indicating that the secondary alcohol remained intact or unreacted. ^{1}H NMR signal of methylene protons adjacent to primary hydroxyl group appeared at ~3.7 ppm as a multiplate. In final compound (*S*)-**6**, the proton signal shifted upfield (~2.7 ppm) due to the change in the chemical environment due to being adjacent to a secondary amine. This is an improved methodology for the synthesis of enantiopure moprolol, which can be further extended to large-scale production. Here we have significantly reduced the reaction steps (four steps reported by Kamal et al.[10]) from the chiral intermediate to (*S*)-moprolol to two steps, which adds value to this method in terms of process economy.

CONCLUSION

Efficient chemoenzymatic synthesis of the enantiomerically pure (*S*)-moprolol is reported in this study with improved overall yield and high *ee*. Among the various commercial lipases screened, ANL showed both regio- and stereoselectivity for the transesterification of (*RS*)-**3** with vinyl acetate as the acyl donor to afford the key intermediate (*S*)-**3** for the synthesis of (*S*)-moprolol. Various reaction parameters were optimized such as reaction time, solvent, temperature, enzyme, and substrate concentration for the kinetic resolution of (*RS*)-3-(2-methoxy-phenoxy)propane-1,2-diol (**3**). Under the optimized conditions the yield was significantly improved for the diacylated derivative (*R*)-**4** (51%) and monoacylated derivative (*S*)-**5** (50%) with high *ee*. By the deacylation of enantiopure acylated derivative, the chiral diol intermediate was obtained, which was further used for the synthesis of (*S*)-moprolol. Synthesizing the enantiopure diol by enzymatic resolution is comparatively cheaper over the chemical route, which makes the process cost-effective. The enzymatic switch towards the synthesis of (*S*)-moprolol sets an excellent example of green synthesis.

ACKNOWLEDGMENTS

SG acknowledges the financial support by Indian Council of Medical Research, Govt. of India to carry out this research project. LB acknowledges Council of Scientific and Industrial Research, Govt. of India for providing financial support for this work. JB and LB contributed equally to this work.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

LITERATURE CITED

1. Panchgalle SP, Kunte SS, Chavan SP, Kalkote UR. Exploration of L-proline-catalyzed α-aminoxylation of aldehyde to (S)-guaifenesin-related drug molecules. Synth Commun 2011;41:1938–1946.
2. Bredikhin AA, Strunskaya EI, Novikova VG, Azancheev NM, Sharafutdinova DR, Bredikhina ZA. Jacobsen-type enantio-selective hydrolysis of aryl glycidyl ethers. 31 P NMR analysis of the enantiomeric composition of oxiranes. Russ Chem Bull 2004;53:213–218.
3. Wang C, Chen X, Zhu J, Wang Y, Yu K, Sun B, Li Z. Method for synthesizing (S)-moprolol. CN 101759577, 2010.
4. Wang ZY, Wang Y, Sun LW, Zhu JT. Asymmetric synthesis of (R)- and (S)-moprolol. Chem Res Chin U 2008;24:747–751.
5. White JD, Shaw S. A new catalyst for the asymmetric Henry reaction: synthesis of β-nitroethanols in high enantiomeric excess. Org Lett 2012; 14:6270–6273.
6. Kamal A, Rao MV. Enzyme catalyzed stereoselective synthesis of (S)-propanolamines. Tetrahedron: Assymmetry 1994;5:1881–1882.
7. Kamal A, Arifuddin M, Rao MV. Enantioselective ring opening of epoxides with trimethylsilylazide (TMSN3) in the presence of β-cyclodextrin: an efficient route to 1,2-azido alcohols. Tetrahedron: Asymmetry 1999; 10:4261–4264.
8. Ader U, Schneider MP. Enzyme assisted preparation of enantiomerically pure β-adrenergic blockers III. Optically active chlorohydrin derivatives and their conversion. Tetrahedron: Asymmetry 1992;3:521.524.
9. Bredikhina ZA, Novikova VG, Zakharychev DV, Bredikhin AA. Solid state properties and effective resolution procedure for guaifenesin, 3-(2-methoxyphenoxy)-1,2-propanediol. Tetrahedron: Asymmetry 2006; 17:3015–3020.
10. Kamal A, Khanna GBR, Krishnaji T, Tekumalla V, Ramu R. New chemoenzymatic pathway for b-adrenergic blocking agents. Tetrahedron: Asymmetry 2005;16:1485–1494.
11. Sayyed IA, Thakur VV, Nikalje MD, Dewkar GK, Kotkar SP, Sudalai A. Asymmetric synthesis of aryloxypropanolamines via OsO4-catalyzed asymmetric dihydro-xylation. Tetrahedron 2005;61:2831–2838.
12. Gotor-Fernandez V, Brieva R, Gotor V. Lipases: Useful biocatalysts for the preparation of pharmaceuticals. J Mol Catal B: Enzym 2006; 40:111–120.
13. Dwivedee BP, Ghosh S, Bhaumik J, Banoth L, Banerjee UC. Lipase-catalyzed green synthesis of enantiopure atenolol. RSC Adv 2015; 5:15850–15860.
14. Banoth L, Thakur NS, Bhaumik J, Banerjee UC. Biocatalytic approach for the synthesis of enantiopure acebutolol as a β1-selective blocker. Chirality 2015;27:382–391.
15. Bredikhin AA, Bredikhina ZA, Zakharychev DV, Pashagin AV. Chiral drugs related to guaifenesin: synthesis and phase properties of methocarbamol and mephenoxalone. Tetrehedron: Asymmetry 2007; 18:1239–1244.
16. Bala N, Chimni SS, Saini HS, Chadha BS. Bacillus alcalophilus MTCC10234 catalyzed enantioselective kinetic resolution of aryl glycidyl ethers. J Mol Catal B: Enzym 2010;63:128–134.
17. Alfonsi K, Colberg J, Dunn PJ, Fevig T, Jennings S, Johnson TA, Kleine HP, Knight C, Perry MA, Stefaniak M. Green chemistry tools to influence a medicinal chemistry and research chemistry based organization. Green Chem 2008;10:31–36.
18. Roughley SD, Jordan AM. The medicinal chemist's toolbox: an analysis of reactions used in the pursuit of drug candidates. J Med Chem 2011; 54:3451–3479.
19. Clouthier CM, Pelletier JN. Expanding the organic toolbox: a guide to integrating biocatalysis in synthesis. Chem Soc Rev 2012;41:1585–1605.
20. Banoth L, Singh M, Tekewe A, Banerjee UC. Increased enantioselectivity of lipase in the transesterification of DL-(±)-3-phenyllactic acid in ionic liquids. Biocatal Biotransfor 2009;27:263–270.
21. Banoth L, Narayan TK, Banerjee UC. New chemical and chemo-enzymatic routes for the synthesis of (RS)- and (S)-enciprazine. Tetrahedron: Asymmetry 2012;23:1272–1278.
22. Banoth L, Narayan TK, Pujala B, Chakraborti AK, Banerjee UC. New chemo-enzymatic synthesis of (R)-1-chloro-3-(piperidin-1-yl) propan-2-ol. Tetrahedron: Asymmetry 2012;23:1564–1570.
23. Madivada LR, Anumala RR, Gilla G, Kagga M, Bandichhor R. An efficient synthesis of 1-(2-methoxyphenoxy)-2,3-epoxy-propane: key intermediate of β-adrenoblockers. Org Process Res Dev 2012; 16:1660–1664.
24. Khmelnitsky YL, Rich JO. Biocatalysis in nonaqueous solvents. Curr Opin Chem Biol 1999;3:47–53.
25. Hudson EP, Eppler RK, Clark DS. Biocatalysis in semi-aqueous and nearly anhydrous conditions. Curr Opin Biotechnol 2005; 16:637–643.
26. Dordick JS. Enzymatic catalysis in monophasic organic solvents. Enzym Microb Technol 1989;11:194–211.
27. Khmelnitsky YL, Levashov AV, Klyachko NL, Martinek K. Engineering biocatalytic systems in organic media with low water content. Enzym Microb Technol 1988;10:710–724.

28. Khan FA, Dash J, Jain D, Prabhudas B. Rearrangement of 1,4,5,6-tetrahalo-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ones to phenolic derivatives. J Chem Soc Perkin Trans 2001;23:3132–3134.
29. Kim HW, Lee YS, Shetty D, Lee HJ, Lee DS, Chung JK, Lee MC, Chung KH, Jeong JM. Facile chlorination of benzyl alcohols using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and sulfonyl chlorides. Bull Korean Chem Soc 2010;31:3434–3436.
30. Ding R, He Y, Wang X, Xu J, Chen Y, Feng M, Qi C. Treatment of alcohols with tosyl chloride does not always lead to the formation of tosylates. Molecules 2011;16:5665–5673.