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Letter

Lipase-catalyzed resolution of 1-chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazole-3-yl)oxy]propan-2-ol. Synthesis of (*R*)- and (*S*)-timolol

Abstract

Lipase-catalyzed resolution of 1-chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazole-3-yl)oxy]propan-2-ol (**5**) is described using vinyl acetate as acyl donor. The effect of different lipases from various sources in several solvents has been studied. This intermediate **5** is utilized in the preparation of enantiomerically enriched (*R*) and (*S*)-timolol.

Keywords: Lipases; Transesterification; Enantioselectivity; β-Adrenergic blockers; Timolol

1. Introduction

Enantiomerically pure β-amino alcohols are an important class of organic compounds that are present in many biologically significant structures, such as amino sugars [1], antibiotics [2–4], β-adrenergic blocking agents [5–9], etc. They play an increasingly important role in the treatment of a wide variety of human disorders and as chiral auxilaries [10–13] in organic synthesis. β-Adrenergic blocking agents [5–9] have mostly comprising of β-amino alcohols are of pharmaceutical significance and received major attention due to their utility in the management of cardiovascular disorders [14], including hypertension [15], anginapectoris, cardiac arrhythmias and also other disorders [16–20] related to the sympathetic nervous system. After three decades of their evolution, more than 50 different compounds having β-adrenergic blocking activity have been brought to a stage of commercial development and about two dozen of the β-adrenergic blocking agents are being approved for medicinal use. The most important ones are timolol (**1**), propranolol, atenolol, metoprolol and alprenolol. Their therapeutic effect is mostly due to the (*S*)-enantiomer that bears a strong structural resemblance to the adrenergic hormone noradrenaline. The enantiomerically enrich form of (*S*)-timolol is available in the market, which is useful for the treatment of glaucoma and its levorotatory hemimaleate salt shows good beta-blocker activity. Moreover, the (*R*)-enantiomer would probably have been a better choice for this application where reduction of intraocular pressure is the desired effect and beta-blocking activity can be undesired side-effect [21–24].

The eudismic ratios (ER) of the various β-adrenergic blocking agents vary considerably, but in all cases, the (*S*)-enantiomer is the active enantiomer. Due to the high biological importance associated with these compounds, many research groups have carried out extensive research work over a period of three decades for their preparation. Until the early 1980s only a few methods, all non-enzymatic have been described for the preparation of optically active β-adrenergic blocking agents. To date literature reports for the preparation of (*S*)-timolol make use of C_3 synthon via epichlorohydrin, glycidol and related chirons [25–36]. However most of them have limitations. Subsequently, enzyme-mediated processes for chiral intermediates to β-adrenergic blocking agents have been emerging and gaining prominence.

In continuation of our earlier efforts [37–39] towards the preparation of biologically important compounds or their intermediates by employing lipases, we herein wish to report an efficient and flexible preparation of enantiomerically enriched (*R*) and (*S*) enantiomers of timolol (**1**) (Scheme 1).

2. Experimental

2.1. General

^{1}H and ^{13}C NMR spectra were recorded on Gemini Varian-VXR-unity (200 MHz) or Bruker UXNMR/XWIN-NMR (300 MHz) instruments. Chemical shifts (δ) are reported in ppm downfield from internal TMS standard. HRMS mass spectra were recorded on a LSIMS-VG-AUTOSPEC-Micromass spectrometer and ESI on Micromass, Quattro LC using ESI$^+$ software with capillary voltage 3.98 kV. Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254 visualization on

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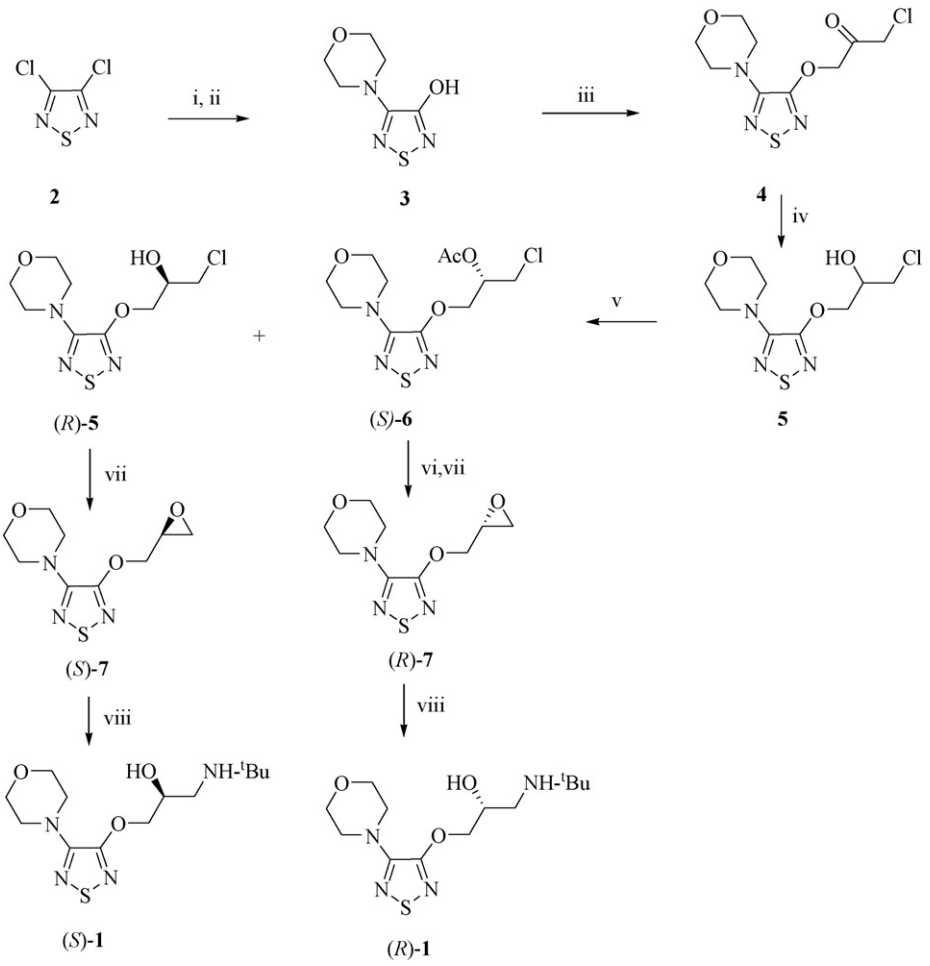

Scheme 1. Reagents and conditions: (i) morpholine, 95%; (ii) 2.5 M NaOH, DMSO, 90%; (iii) dichloroacetone, $NaHCO_3$, DMF, 74%; (iv) $NaBH_4$, MeOH, 90%; (v) lipase, vinyl acetate, hexane; (vi) K_2CO_3, MeOH, 90%; (vii) ^{t}BuOK, THF, 95%; (viii) ^{t}BuNH$_2$, 70%.

TLC were achieved by UV light or iodine indicator. Column chromatography was performed with Merck 60–120 mesh silica gel. Starting materials were either commercially available or purchased from Lancaster and Sigma–Aldrich. All organic solvents were distilled following standard protocols and are dried over molecular sieves prior to use.

2.2. Enzyme source

Pseudomonas cepacia lipase immobilized on diatomite (PS-D), *Pseudomonas cepacia* (PS), *Pseudomonas cepacia* lipase immobilized on modified ceramic particles (PS-C), are obtained from Amano Pharmaceutical Company, Japan. *Pseudomonas fluorescens* lipase immobilized in Sol–Gel-AK on sintered glass (P), lipase immobilized from *Rhizomucor meihei* (RML). *Candida antartica* lipase immobilized in Sol–Gel-AK on sintered glass (CAL-B), AK and Lipozyme are from Fluka and *Candida rugosa* lipase (CRL) is from Sigma.

2.3. HPLC analysis

Acylation reactions were monitored by HPLC analysis on a Chiracel ADH column (4.6 mm id-250 mm; Daicel Chemical Industries) using *n*-hexane/*iso*-propanol as eluent (9:1). The liquid chromatography employed was a Shimadzu LC-10AT instrument with Shimadzu SCL-10A variable wavelength UV monitor. Satisfactory separation of enantiomers of 1-chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazole-3-yl)oxy]propan-2-ol was achieved by choosing an appropriate ratio of *n*-hexane/*iso*-propanol, which allowed the accurate determination of the enantiomeric excess (ee) value of the unreacted alcohol. The peak(s) for acetate and the parent alcohol were separated efficiently on the chiral column for the determination of the extent of conversion. *E*-values were calculated based on the enantiomeric excess of the products (ee_p) and the conversion (*c*) according to Chen and Sih [40] and Chen et al. [41].

2.4. Synthesis of 4-morpholin-4-yl-1,2,5-thiadiazol-3-ol (**3**)

3,4-Dichloro-1,2,5 thiadiazole **2** (1.0 g, 6.5 mmol) was added dropwise over a 30 min period at 105–110 °C to morpholine (2.23 mL, 26 mmol). After addition, the reaction mixture was stirred for 2 h at 105–110 °C, cooled to 15 °C and quenched with 10 mL of water. The mixture was made acidic with 10 mL of conc. HCl. To insoluble oil soon crystallized to a heavy solid,

which was isolated by filtration and washed well with water. After drying in vacuo at 35 °C (1.26 g, 95%) of the morpholine derivative was obtained. Morpholine derivative compound (1.0 g, 4.87 mmol) was added to 8 mL of 2.5 N NaOH and 2 mL of DMSO. The reaction mixture was refluxed with stirring for 3 h. The solution was cooled to 15 °C and rendered acidic with 10 mL of conc. HCl. The precipitated hydroxy compound was filtered at 15 °C, washed well with water and dried yielding of **3** (0.86 g, 95%); mp. 195–200 °C; IR (KBr) ν_{max}: 2857, 1546, 1507, 1442, 1277, 1228, 1116, 955 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.49 (t, 4H, $J = 5.1$ Hz), 3.73 (t, 4H, $J = 4.7$ Hz) ppm; LCMS: 232 $(M+45)^+$.

2.5. Synthesis of 1-chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-one (*4*)

To a stirred solution of hydroxythiadiazole **3** (0.5 g, 2.7 mmol) in dry DMF (10 mL), $NaHCO_3$ (0.27 g, 3.24 mmol) and dichlroacetone (0.67 g, 5.34 mmol) were added sequentially at 0 °C. The reaction mixture was stirred at this temperature for 1 h, and then at room temperature for another 25 h. This was diluted with H_2O (10 mL) and extracted with EtOAc (2×50 mL). The combined organic layers were washed with brine (10 mL), water (10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography to afford **4** as a white solid (0.55 g, 74%); mp. 130–132 °C; IR (KBr) ν_{max}: 2963, 2857, 1745, 1537, 1495, 1406, 1228, 1114, 1019, 923 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.43–3.57 (m, 4H), 3.69–3.85 (m, 4H), 4.12 (s, 2H), 5.22 (s, 2H) ppm; LCMS: 300 $(M+Na)^+$.

2.6. Synthesis of 1-chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (*5*)

To a stirred solution of **4** (0.2 g, 0.72 mmol) in methanol, $NaBH_4$ (0.03 g, 0.72 mmol) was added slowly at 0 °C and stirred at room temperature for 1 h. After completion of the reaction, it was taken into CH_2Cl_2 (1×20 mL), washed with water (1×5 mL), brine (5 mL). The combined organic layer was concentrated, dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography to afford **5** as a white crystalline solid (0.18 g, 90%); mp. 55–58 °C; IR (KBr) ν_{max}: 3287, 2856, 1495, 1228, 1113 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.43–3.45 (m, 4H), 3.59–3.71 (m, 2H), 3.74–3.82 (m, 4H), 4.18–4.28 (m, 1H), 4.47–4.59 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.9, 47.8, 66.4, 69.5, 71.5, 149.7, 153.4 ppm; LCMS: 302 $(M+Na)^+$; HRMS $[M+H]^+$ *m/z* calcd for $C_9H_{15}N_3O_3SCl$ 280.0522, found 280.0517.

2.7. General procedure for the lipase-catalyzed enantioselective acylation of 1-chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (*5*)

To the racemic alcohol **5** (0.5 g, 1.8 mmol) in hexane (50 mL), lipase (0.5 g, w/w) and vinyl acetate (1.0 mL, 10.75 mmol) were added successively, and the mixture was stirred in an orbital shaker at room temperature for 60 h. After conversion to about 50% monitored by HPLC on AD-H chiral column (Daicel), the reaction mixture was filtered and the two compounds (*S*)-**6** and (*R*)-**5** were separated by column chromatography using EtOAc-hexane (85:15) as eluent.

2.8. (R)-1-Chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol [(R)-*5*]

$[\alpha]_D^{25.8}$ +10.5 (*c* 0.8, $CHCl_3$).

2.9. (S)-1-Chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol [(S)-*5*]

To a solution of acetate (*S*)-**6** (0.1 g, 0.31 mmol) in MeOH (15 mL), K_2CO_3 (0.06 g, 0.46 mmol) was added at 0 °C and the suspension was stirred for 15 min at room temperature. After neutralization with AcOH, the solvent was removed and the resulting crude was diluted with H_2O (30 mL), and extracted with EtOAc ($2\,mL \times 50$ mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and concentrated. The crude residue was purified by flash chromatography (10% EtOAc:hexane) to provide (*S*)-**5** (0.08 g, 90%); $[\alpha]_D^{25.8}$ −11.0 (*c* 0.45, $CHCl_3$).

2.10. (S)-1-Chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]methyl acetate [(S)-*6*]

$[\alpha]_D^{25.8}$ +2.0 (*c* 1.32, $CHCl_3$); IR (KBr): 2920, 2852, 1747, 1226, 1118 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.12 (s, 3H), 3.41–3.52 (m, 4H), 3.64–3.84 (m, 6H), 4.48–4.72 (m, 2H), 5.35–5.41 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 42.0, 47.7, 66.2, 68.6, 70.2, 149.5, 152.8, 169.6 ppm; LCMS: 344 $(M+Na)^+$; HRMS: $[M+Na]^+$ *m/z* calcd for $C_{11}H_{16}N_3O_4NaSCl$ 344.0447, found 344.0454.

2.11. (R)-4-{4-[(2R)-Oxiran-2-ylmethoxy]-1,2,5-thiadiazol-3-yl}morpholine [(R)-*7*]

To a stirred solution of (*S*)-**5** (0.1 g, 0.36 mmol), in dry THF (10 mL) potassium *tert*-butoxide (0.08 g, 0.72 mmol) was added at 0 °C for 1 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (25 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography to afford (*R*)-**7** as a white crystalline solid (0.08 g, 95%); $[\alpha]_D^{25.8}$ −18.0 (*c* 1.0, $CHCl_3$); mp. 110–112 °C; IR (KBr): 2921, 2857, 1533, 1495, 1227, 1115, 852 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.64–2.71 (m, 1H), 2.87 (t, 1H, $J = 4.5$ Hz), 3.30–3.39 (m, 1H), 3.50 (t, 4H, $J = 4.5$ Hz), 3.78 (t, 4H, $J = 4.5$ Hz), 4.23 (dd, 1H, $J_1 = J_2 = 6.0$ Hz), 4.71 (dd, 1H, $J_1 = J_2 = 3.0$ Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.6, 47.8, 49.3, 66.4, 71.2, 149.8, 153.3 ppm; LCMS: 266 $(M+Na)^+$; HRMS $[M+Na]^+$ *m/z* calcd for $C_9H_{13}N_3O_3NaS$ 266.0575, found 266.0578.

Table 1
Transesterification of 1-chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (**5**) with various lipases in hexane[a]

Entry	Lipase	Time (h)	Alcohol		Acetate		c (%)	E[d]
			Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)		
1	PS-C	60	45	>99	45	>99	0.5	1060
2	PS-D	100	45	90	40	>99	0.48	598
3	PS	120	60	80	30	95	0.46	98
4	AK	168	44	90	47	94	0.49	100
5	P	168	80	15	12	98	0.13	100
6	Lipozyme	168	88	06	08	89	0.06	19
7	RML	168	69	13	23	80	0.14	10
8	CRL	168	68	14	25	83	0.14	13
9	CAL-B	168	90	03	02	85	0.03	13

[a] Conditions: reactions were carried out in *n*-hexane (15 mL), **5** (0.18 mmol), vinyl acetate (1.08 mmol), and lipase (50 mg, w/w) at 30 °C, 200 rpm.
[b] Isolated yields.
[c] Determined by HPLC (Chiracel AD-H column; Daicel) employing *n*-hexane:*iso*-propanol (9:1) as mobile phase at 0.5 mL/min and monitored at UV (254 nm).
[d] Calculated according to Chen and Sih [40] and Chen et al. [41] using the equation: $E = (\ln[1 - c(1 + ee_p)])/(\ln[1 - c(1 - ee_p)])$.

*2.12. (S)-4-{4-[(2R)-Oxiran-2-ylmethoxy]-1,2,5-thiadiazol-3-yl}morpholine [(S)-**7**]*

$[\alpha]_D^{25.8}$ +20.0 (*c* 0.7, $CHCl_3$).

*2.13. (S)-1-(tert-Butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol [(S)-**1**]*

To a stirred solution of (*S*)-**7** (0.1 g, 0.41 mmol) in *tert*-butylamine (2.1 mL, 20.5 mmol), few crystals of KI were added and the mixture was refluxed for 50 h. Then the solution was cooled to room temperature, the solvent was removed under reduced pressure and the crude residue was purified by column chromatography to afford (*S*)-**1** as a hygroscopic solid (0.1 g, 70%); $[\alpha]_D^{25.8}$ +1.5 (*c* 0.7, $CHCl_3$); IR (KBr): 2920, 2852, 1747, 1226, 1118 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.06 (s, 9H), 2.55 (dd, 1H, $J_1 = J_2 = 8.5$ Hz), 2.73 (dd, 1H, $J_1 = J_2 = 3.5$ Hz), 3.33 (bs, 1H, OH), 3.39–3.52 (m, 4H), 3.67–3.79 (m, 4H), 3.88–4.00 (m, 1H), 4.24–4.43 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.6, 44.4, 47.8, 50.8, 66.4, 67.7, 72.7, 149.8, 153.7 ppm; LCMS: 317 $(M+H)^+$; HRMS $[M+H]^+$ *m/z* calcd for $C_{13}H_{25}N_4O_3S$ 317.1647, found 317.1657.

*2.14. (R)-1-(tert-Butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol [(R)-**1**]*

$[\alpha]_D^{25.8}$ −2.0 (*c* 1.0, $CHCl_3$).

3. Results and discussion

Enantiomerically pure timolol (**1**) was prepared from **3**, which was synthesized from **2** in two steps. Compound **3** was then coupled with dichloroacetone in dry DMF to give haloketone **4**, which was reduced to halo hydrin **5** using $NaBH_4$ in methanol in almost quantitative yields.

The racemic halohydrin (**5**) was subjected to lipase-catalyzed resolution by using different lipases. Among all the lipases screened, lipase from *Pseudomonas cepacia* adsorbed on ceramic particles PS-C (*Burkholderia cepacia*) gave better results in terms of enantioselectivity and yields. This immobilized enzyme showed good conversion compared to crude lipase-PS (Table 1). Further, the effect of different solvents on this substrate has also been studied. It is observed that hydrophobic solvents such as hexane, toluene, diisopropyl ether, and diethyl ether gave remarkable enantioselectivity whereas hydrophilic solvents like acetone, tetrahydrofuran, and 1,4-

Table 2
Effect of solvents on the transesterification of 1-chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (**5**) by lipase PS-C[a]

Entry	Solvent	Log P[b]	Time (h)	Alcohol		Acetate		c (%)	E[e]
				Yield[c] (%)	ee[d] (%)	Yield[c] (%)	ee[d] (%)		
1	*n*-Hexane	3.5	60	44	>99	44	>99	0.5	1060
3	Toluene	2.5	100	45	>99	45	>99	0.5	1060
2	*i*-Pr_2O	1.9	168	72	70	20	95	0.42	86
4	Et_2O	0.85	168	53	85	30	98	0.46	256
5	$CHCl_3$	2.0	168	54	69	38	95	0.42	86
6	Acetone	−0.23	168	86	11	07	>99	0.1	222
7	THF	0.49	168	90	04	03	>99	0.04	21
8	1,4-Dioxane	−1.1	168	91	04	03	>99	0.04	21

[a] Conditions: reactions were carried out in solvent (15 mL), **5** (50 mmol), vinyl acetate (1.08 mmol), and lipase (50 mg, w/w) at 30 °C, 200 rpm.
[b] Source of data: references [42,43].
[c] Isolated yields.
[d] Determined by HPLC (Chiracel AD-H column; Daicel) employing *n*-hexane:*iso*-propanol (9:1) as mobile phase at 0.5 mL/min and monitored at UV (254 nm).
[e] Calculated according to Chen and Sih [40] and Chen et al. [41] using the equation: $E = (\ln[1 - c(1 + ee_p)])/(\ln[1 - c(1 - ee_p)])$.

dioxane provided low conversion rate and the results are discussed in Table 2.

The enantiomeric excess was calculated from the enantiomer ratios obtained by employing a Chiralpak-ADH column. The absolute configuration of the alcohol and the acetate was determined by comparison of their chiroptical and chromatographic properties with those of the corresponding known compounds. In this process, comparison of the specific rotation of the unreacted alcohol (*R*)-**5** with that of the reported alcohol (*R*)-**5** established the (*R*)-configuration of the alcohol and (*S*)-configuration of the acetate. This is further confirmed by conversion of the enantiomerically enriched 1-chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (**5**) to 1-(*tert*-butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (**1**). Comparison of the specific rotation of the derived **1** with that of the reported compound established the (*R*) configuration for the alcohol and the (*S*) configuration for the acetate [35,36].

After enzymatic resolution, alcohol (*R*)-**5** and acetate (*S*)-**6** were separated by column chromatography. Alcohol **5** upon enzymatic resolution gave alcohol (*R*)-**5** in >99% and acetate (*S*)-**6** in >99%, respectively ($E = 1060$). The compound (*R*)-**5** was converted to epoxide (*S*)-**7**, which was then treated with *tert*-butyl amine to give (*S*)-**1**. (*R*)-Timolol-(**1**) was also obtained after hydrolysis of (*S*)-**6** followed by similar sequence of reactions (Scheme 1).

4. Conclusion

In summary, an efficient method for the preparation of (±)-1-chloro-3-(4-morpholin-4-yl-1,2,5-thiadiazole-3-yl) (**5**) and its kinetic resolution employing enzymes has been described. This transesterification process has been optimized with respect to different lipases and solvents. Furthermore, enantiomerically pure **5** has been employed in the preparation of (*R*)-**1** and (*S*)-**1**.

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