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Chemoenzymatic synthesis of (*S*) and (*R*)-propranolol and sotalol employing one-pot lipase resolution protocol

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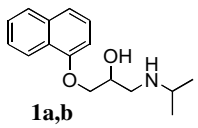
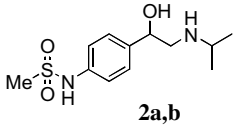
Abstract—Synthesis of both enantiomers of biologically active propranolol and sotalol has been achieved in high optical purity by one-pot reduction of **3** and **7** followed by in situ lipase resolution of the respective chlorohydrins. *Pseudomonas cepacia* lipase immobilized on ceramic particles (PS-C) provided the chlorohydrin and acetate, which on nucleophilic substitution with isopropyl amine afforded the target amino alcohols in high enantioselectivity under mild reaction conditions.

Optically active secondary amino alcohols are important intermediates for asymmetric synthesis of biologically active substances such as adrenergic agents, anthelmintics, antidepressants, class-II β-adrenoceptor blocking agents (β-blockers) and class-III antiarrhythmic agents. Propranolol **1a**,**b** has been used in clinic for the treatment of angina pectoris, various cardiac arrhythmias, phaeochromocytoma and hypertension.[1] Generally, the *S*-enantiomer of the β-blockers are more potent antagonists than the corresponding *R*-enantiomer. It has been demonstrated that (*S*)-propranolol possesses higher binding affinity towards both β_1 and β_2-receptors than *R*-isomer.[2] Sotalol **2a**,**b** belongs to class-III antiarrhythmic compounds. The two enantiomeric forms of sotalol are equiactive in their effect on the cardiac action potential duration (APD), whereas the *l*-enantiomer is about 20 times more potent than the *d*-form as a β-blocker.[3] In the past few decades, considerable progress has been made, in the preparation of *d*-sotalol by chromatographic separation,[4] resolution of racemic sotalol with chiral *l*-mandelic acid[5] chiral homogeneous hydrogenation of 4′-[(isopropyl-amino)acetyl]-methanesulfonanilide hydrochloride,[6] and reduction of 4′-(chloroacetyl)methanesulfonanilide employing CBS (Corey, Bakshi, Shibata) catalyst.[7]



1a,b



2a,b

However, no efforts have been made in the literature so far to prepare both the *R* and *S* forms of sotalol, by the enzymatic resolution. On the contrary enantioselective synthesis of propranolol **1a**,**b** has been extensively studied that includes enzymatic resolution,[8] nitroaldol reaction,[9] asymmetric hydrogenation,[10] and epoxide ring opening with amines and amine equivalents.[11] Some reported methods employ tedious reaction conditions[7] and give product of low enantiopurity.[8a,9] Earlier we have investigated synthesis of various chiral propanolamines by the stereoselective epoxide opening with amines in the presence of rat liver microsomes and various lipases.[12] Moreover, we have also synthesized (*R*)-propranolol from 3-isopropyl-5(1-naphthoxymethyl)oxazolidine with post mitochondrial supernatant from rat liver.[13] We have recently developed a one-pot reduction and in situ lipase resolution protocol, which has been successfully utilized in the enantioselective synthesis of number of biologically important chiral intermediates such as secondary alcohols[14,15] and lactones.[16] In continuation of our efforts, this method has been extended towards the preparation of both the enantiomers of propranolol and sotalol. The present method provides an alternate short synthetic route for the preparation of enantiopure propranolol and sotalol

Keywords: Propranolol; Sotalol; One-pot lipase resolution.
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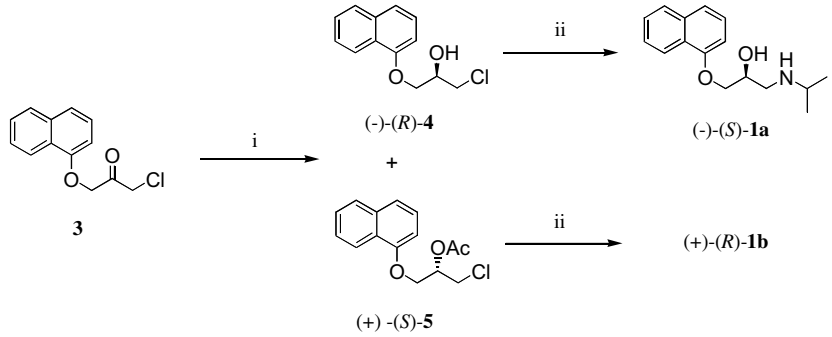
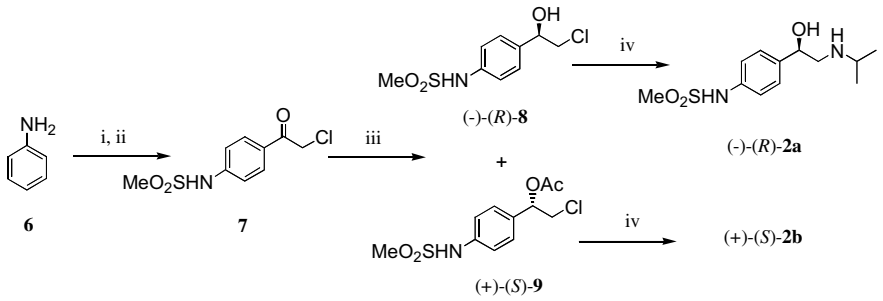


Scheme 1. Reagents and conditions: (i) $NaBH_4$, moist Al_2O_3, diisopropyl ether, lipase PS-C, isopropenyl acetate, 40 °C, 16 h; (ii) 10% aq NaOH, isopropyl amine, *iso*-propanol, rt 1 h, 95%.



Scheme 2. Reagents and conditions: (i) $MeSO_2Cl$, pyridine, CH_2Cl_2, rt, 12 h, 94%; (ii) chloroacetyl chloride, $AlCl_3$, CH_2Cl_2, rt, 6 h, 75%; (iii) $NaBH_4$, moist Al_2O_3, diisopropyl ether, lipase PS–C, isopropenyl acetate, 40 °C, 18 h; (iv) K_2CO_3, MeOH, isopropyl amine, rt, 12 h, 80%.

from their ketone precursors **3**[10,17] and **7**, respectively, under mild reaction conditions. Compound **2b** has been prepared from aniline by employing the modified procedure for N-[4-(2-bromoacetyl)phenyl]-methane sulfonamide.[18] The key step involved in this synthesis is the one-pot reduction of ketone **3** or **7** followed by in situ lipase mediated resolution of the racemic chlorohydrins. The reduction of ketones **3** or **7** has been carried out by sodium borohydride and moist neutral aluminium oxide in diisopropyl ether. The racemic chlorohydrins thus formed have been resolved in situ by transesterification employing immobilized *Pseudomonas cepacia* lipase (PS-C) and isopropenyl acetate as an acyl donor.[19]

The reactions are monitored on HPLC and stopped upon reaching about 50% conversion. The one-pot reduction and resolution of **3** affords alcohol (−)-**4** in 96% ee and acetate (+)**5** in >99% ee. The base catalyzed nucleophilic substitution of chlorine by isopropyl amine gives the corresponding propranolol (−)-**1a** and (+)-**1b** in 95% and 98% ee, respectively (Scheme 1). Whereas, one-pot reduction and resolution of **7** affords the alcohol (−)-**8** and acetate (+)-**9** in 90% and 94% ee, respectively. The nucleophilic substitution of chlorine with isopropyl amine in the presence of K_2CO_3/MeOH gives sotalol (−)-**2a** and (+)-**2b** in 90% and 94% ee, respectively, (Scheme 2). All the compounds have been characterized by NMR, mass and C, H, N analysis.[20,21] The configurations of the compounds have been assigned by the comparison of the sign of optical rotation with the literature values.

In summary, we have developed a new one-pot reduction and in situ lipase resolution protocol for the synthesis of both *R* and *S* enantiomers of propranolol and sotalol in high enantiopurity in short reaction sequence under mild reaction conditions. Moreover, the present method has a potential to explore the synthesis of other various β-amino alcohols and β-blockers.

Acknowledgements

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19. General procedure for one-pot reduction of **3** and **7** and in situ lipase resolution: A solution of **3** or **7** (1 mmol), preactivated neutral aluminium oxide[15a] (1 g), and sodium borohydride (2 mmol) in diisopropyl ether was shaken at 40 °C in an orbital shaker for 3–4 h. After the complete reduction indicated by TLC, PS-C lipase (1 equiv w/w), isopropenyl acetate (6 mmol) were added and the reaction was continued until about 50% conversion by HPLC analysis.[23] The reaction was filtered through the pad of Celite, washed with water and brine and concentrated under reduced pressure. The crude compound was purified on column chromatography to get the corresponding alcohol **4** or **8** and acetate **5** or **9**.
20. Spectral data for compound **4**: 50% yield; 96% ee,[22a] (t_R = 19.11 min); $[\alpha]_D^{25}$ −8.83 (*c* 1.0, EtOH) [lit.[8b] −8.3 (*c* 1, EtOH), 92% ee]; IR (neat) 3410, 1220, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.8 (2H, m), 4.2 (3H, m), 6.7 (1H, d, J = 7.6 Hz), 7.2–7.5 (4H, m), 7.7 (1H, m), 8.2 (1H, m); MS (EI) m/z 236 (M^+), 144 (M^+−92). Anal. Calcd for $C_{13}H_{13}O_2Cl$: C, 65.97; H, 5.54. Found: C, 65.24; H, 5.39%. Spectral data for compound **5**: 47% yield; >99% ee,[23] (t_R = 22.02 min); $[\alpha]_D^{25}$ +19.74 (*c* 1, EtOH) [lit.[8b] +17.5 (*c* 1, EtOH), 88% ee]; IR (KBr) 1744, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.15 (3H, s), 3.83–3.97 (2H, m), 4.34 (2H, d, J = 5.28 Hz), 5.47 (1H, m), 6.8 (1H, d, J = 7.17 Hz), 7.3–7.5 (4H, m), 7.75 (1H, m), 8.15 (1H, m); MS (EI) m/z 278 (M^+). Anal. Calcd for $C_{15}H_{15}O_3Cl$: C, 68.57; H, 5.75. Found: C, 68.13; H, 5.43%. Spectral data for compound **8**: white solid, mp 96–98 °C; 52% yield; 90% ee,[22b] (t_R = 45.30 min); $[\alpha]_D^{25}$ −19.09 (*c* 1.03, EtOH); IR (KBr) 3400, 1325 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.67 (1H, br s), 3.02 (3H, s), 3.58–3.67 (1H, dd, J = 8.68, 11.33 Hz), 3.69–3.77 (1H, dd, J = 3.4, 11.33 Hz), 4.9 (1H, dd, J = 8.68, 3.4 Hz), 7.26 (2H, d, J = 8.6 Hz), 7.4 (2H, d, J = 8.6 Hz); MS (EI) m/z 215 (M^+−34). Anal. Calcd for $C_9H_{12}NO_3ClS$: C, 43.29; H, 4.84; N, 5.61; S, 12.84. Found: C, 43.12; H, 4.38; N, 5.54; S, 12.45%. Spectral data for compound **9**: white solid mp 138–140 °C; 49% yield; 94% ee,[22b] (t_R = 34.15 min); $[\alpha]_D^{25}$ +84.07 (*c* 0.9, EtOH); IR (KBr) 1728 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.07 (3H, s), 2.9 (3H, s), 3.48–3.78 (2H, m), 5.8 (1H, dd, J = 5.2, 7.43 Hz), 7–7.3 (4H, m); MS (EI) m/z 291 (M^+). Anal. Calcd for $C_{11}H_{14}NO_4ClS$: C, 49.74; H, 5.57; N, 4.83; S, 11.06. Found: C, 49.22; H, 5.46; N, 4.67; S, 11.04%.
21. Spectral data for compound **1a**: white solid mp 70 °C; 95% ee[23], (t_R = 11.96 min); $[\alpha]_D^{25}$ −8.83 (*c* 1, EtOH) [lit.[8b]−9.7 (*c* 1.5, EtOH)]; IR (KBr) 3260, 3030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (6H, d, J = 6.42 Hz), 2.83–3.08 (3H, m), 3.2 (2H, br s), 4–4.3 (3H, m), 6.77 (1H, d, J = 6.79 Hz), 7.24–7.5 (4H, m), 7.75 (1H, m), 8.2 (1H, m); ^{13}C NMR (200 MHz, $CDCl_3$) δ 154.33, 134.48, 127.44, 126.32, 125.74, 125.58, 125.14, 121.79, 120.54, 104.97, 70.82, 68.58, 49.58, 48.93, 23.12, 22.99; MS (FAB) m/z 260 (M^+ + 1); HRMS data: Calcd for $C_{16}H_{21}NO_2$ 260.165054, found 260.165902. Spectral data for compound **1b**: white solid mp 69–70 °C; 98% ee[23], (t_R = 20.50 min); $[\alpha]_D^{25}$ +10.5 (*c* 1, EtOH) [lit.[8b] +9.8 (*c* 1.6, EtOH)]. Spectral data for compound **2a**: 90% ee [from the HPLC analysis of the precursor (*R*)-**8**][22b]; $[\alpha]_D^{25}$ (**2a**·HCl) −30.6 (*c* 1, water) [lit.[4d] −34.7 (*c* 1, water)]; IR (KBr) 3570, 3410, 1325 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 1.24 (6H, d, J = 6.59 Hz), 3.0 (3H, s), 3.14 (1H, m), 3.83 (2H, d, J = 5.12 Hz), 4.3 (1H, t, J = 5.12 Hz), 7.3 (2H, d, J = 8.78 Hz), 7.45 (2H, d, J = 8.78 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 140.32, 134.13, 130.28, 121.54, 64.61, 62.28, 50.28, 47.72, 39.52, 20.78, 19.40; MS (FAB) m/z 273 (M^+ + 1). Anal. Calcd for $C_{12}H_{20}N_2O_3ClS$: C, 52.92; H, 7.40; N, 10.29; S, 11.77. Found: C, 52.86%; H, 7.35%; N, 10.20%; S, 11.62%. Spectral data for compound **2b**: 94% ee [from the HPLC analysis of the precursor (*S*)-**9**][22b]; $[\alpha]_D^{25}$ (**2b**·HCl) +30.4 (*c* 1, water) [lit.[4d] +35.8 (*c* 1, water)].
22. (a) Enantioselectivity was determined by HPLC (CHIRACEL, AD-H column, Daicel). (a) Employing hexane/isopropanol = 90/10 as a mobile phase, with 0.5 mL/min flow rate and monitored at 254 nm wavelength; (b) Employing hexane/isopropanol/diethylamine = 90/10/0.1 as a mobile phase, with 0.5 mL/min flow rate and monitored at 254 nm wavelength.
23. Enantioselectivity was determined by HPLC (CHIRACEL, OD column, Daicel) by employing hexane/isopropanol/diethylamine = 90/10/0.1 as a mobile phase, with 0.5 mL/min flow rate and monitored at 254 nm wavelength.