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An efficient asymmetric synthesis of (*S*)-atenolol: using hydrolytic kinetic resolution☆

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Abstract—Enantiomerically pure (*S*)-atenolol was prepared by using (*R*,*R*) salen Co(III) complex for the resolution of terminal epoxide. This process was carried out at room temperature in excellent enantio selectivity. The method can be applied for large-scale preparation of (*S*)-atenolol without any problem.

1. Introduction

β-Adrenoreceptor antagonists are a group of compounds that competitively inhibit, the effects of catecholamines at β-adrenergic receptors.[1] These agents are widely used in clinical medicine for the treatment of various conditions. As the β-adrenoreceptor antagonists (β-blockers) have such a diverse range of clinical applications, the mode of delivery of these drugs becomes crucial. In particular there has been great interest in the percutaneous transport of β-blockers for hypertension and ocular delivery for glaucoma.[2] Since the biological activity in a racemic drug often resides in a single enantiomer, synthesizing such drugs in their optically pure form is becoming important.[3] For instance, racemic atenolol is one of the top five best-selling drugs in the world today,[3b] for the treatment of hypertension, angina and also in the treatment of post-myocardial infarction, yet the *S* isomer has found to avoid the occasional side effect of a lowered heart rate encountered with racemate.[4]

There are few reports in the literature for chiral synthesis of atenolol using expensive chiral epichlorohydrin[5] in presence of alkali metal hydroxide, which was an highly basic condition and another case involves the use of biological catalyst enzyme,[6] which was also a lengthy process. Herein we wish to report a better process for the asymmetric synthesis of (*S*)-atenolol by using hydrolytic kinetic resolution (HKR) method, which was introduced by Jacobsen and co-workers.[7] This technique provides high enantioselectivity and extremely simple compared to other approaches. The reasons to select this route are (1) the ready availability of the catalyst, (2) the catalyst would be used in small quantities (0.5 mol%) and (3) the recyclability of the catalyst and 0.55 equiv amount of water only the solvent as well as reactant (Fig. 1, Schemes 1 and 2).

2. Results and discussion

The synthetic approach started from the commercially available 4-hydroxy acetophenone, which was treated with sulfur and morpholine at 100 °C for well-known Willgerodt[8] reaction to obtain the thioacetomorpholide in 85% yield. The resulted thioacetomorpholide was hydrolyzed with 10% ethanolic NaOH solution under reflux condition for 10 h to obtain the 4-hydroxy phenyl acetic acid. The acid compound was dissolved in methanol and added catalytic amount of thionylchloride at ice cooling, later it was refluxed to get the methyl ester. The phenolic hydroxy group was reacted with allylbromide in acetone using K_2CO_3 as base to obtain the allyloxy compound, the resulted compound was subjected with *meta*-chloroperbenzoic acid (*m*CPBA) in dichloro methane (DCM) for epoxidation at room temperature. The methyl ester functional group was maintained unto the final stage. Because of the ester function it was a free-floating liquid and was convenient to apply hydrolytic kinetic resolution method.

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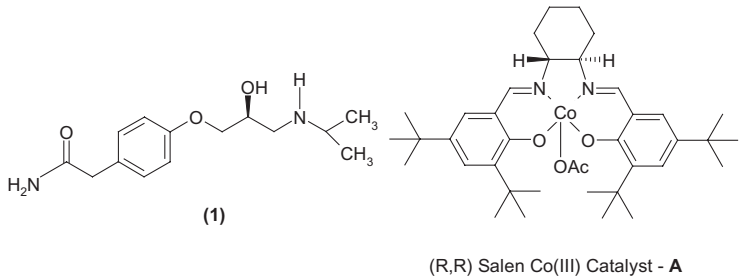
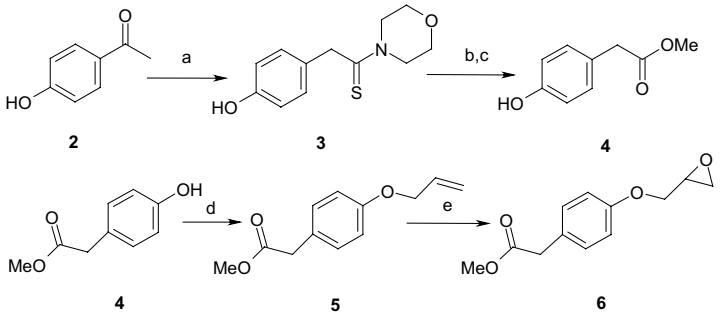
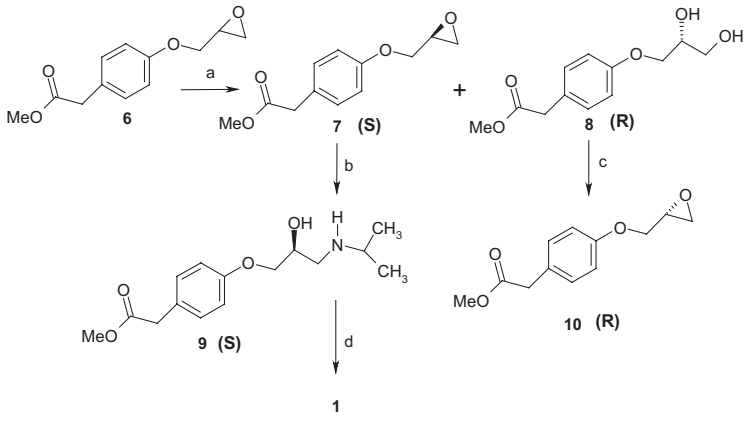


Figure 1.



Scheme 1. Reagents and conditions: (a) sulfur, morpholine, 100 °C; (b) ethanolic-NaOH solution, reflux; (c) methanol–thionyl chloride; (d) allyl bromide, acetone, K_2CO_3; (e) *m*CPBA–DCM.



Scheme 2. Reagents and conditions: (a) (*R*,*R*)-salen Co(III)-**A**; (b) isopropylamine, water, reflux; (c) TPP–DEAD, C_6H_6; (d) NH_4OH–methanol.

The treatment of racemic epoxide with Jacobsen catalyst (*R*,*R*) (salen Co(III)OAc) (0.5 mol%) and water (0.55 equiv) at room temperature for 8 h and monitored by HPLC (ODS-Column) UV: 225 nm, 60% CH_3CN in H_2O. The reaction mixture was chromatographed on silica gel to give the selective epoxide *S*, from the racemic mixture in 46% yield and 94% ee. The optical rotation of **7** shows that $[\alpha]_D^{21}$ 5.7 (*c* 1, $CHCl_3$) and on further elution by increasing the polarity of mobile phase gave the (*R*)-diol **8** in 48% yield and 98% of ee, the optical rotation $[\alpha]_D^{21}$ −7.0 (*c* 1, $CHCl_3$).

The enantiomerically rich *R* diol **8** was treated with triphenyl phosphine (TPP) and diethylazo dicarboxylate (DEAD) in benzene by Mitsunobu reaction in one step to get optically active (*R*) epoxide **10** (83.7% yield, 98% ee) the optical rotation $[\alpha]_D^{21}$ −6.00 (*c* 1, $CHCl_3$). The enantiomer excess of all the chiral compounds was determined by HPLC using chiral column. The first separated enantioselective (*s*) epoxide **7** was treated an excess amount of *N*-isopropylamine in presence of water at reflux for 5 h to obtain the hydroxy amine compound **9** was confirmed by its ^1H NMR, IR and mass spectroscopy. Then, the hydroxy amine compound was treated with aqueous ammonium hydroxide solution in methanol at low temperature (0–5 °C) to afford the target molecule (*S*)-atenolol **1** in excellent enantio selectivity.

3. Conclusion

In summary, we have described here, the total synthesis of *S*-atenolol in high enantioselection fashion. The key

intermediate was terminal epoxide from which selectively using Jacobsen catalyst for hydrolytic kinetic resolution protocol separated *S*-isomer. This method can cater the needs of pharmaceutical demand.

4. Experimental

4.1. Chemistry

Melting points were recorded in a Buchi capillary melting point (R-535) apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR 240C spectrophotometer. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer with TMS as the internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 ev. All chemicals or reagents were purchased from standard commercial suppliers.

4.1.1. 4-Hydroxy phenyl thioacetomorpholide (3). A mixture of 4-hydroxy acetophenone (10 g, 0.0735 mol), powdered sulfur (3.5 g, 0.109 mol) and morpholine (10 g) were refluxed at 100 °C for 10 h. The starting material disappearance was confirmed by thin layer chromatography (TLC). Then reaction mixture was cooled to room temperature and poured in water, followed by extraction with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated to yield crude product of thioacetomorpholide, which was purified by column chromatography to yield 15 g (86%). ^{1}H NMR ($CDCl_3$): δ 3.35–3.48 (m, 2H), 3.60–3.65 (m, 2H), 3.70–3.78 (m, 2H), 4.20 (s, 2H), 4.30–4.40 (m, 2H), 5.85 (br s, 1H, OH), 6.78 (d, 2H, J = 7.5 Hz), 7.15 (d, 2H, J = 7.5 Hz).

4.1.2. 4-Hydroxy phenylacetic acid methyl ester (4). The above thioacetomorpholide compound (10 g, 0.042 mol) was dissolved in 10% ethanolic-NaOH solution (40 mL, 15 mL, EtOH, 25 mL H_2O) and refluxed for 10 h. The complete hydrolysis was confirmed by TLC. The solvent was removed completely under reduced pressure. The residue was acidified with dil HCl and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated to get crude product (5.4 g). The obtained compound was dissolved in methanol (50 mL) and added thionylchloride (2 mL) slowly at ice cooling. After complete addition of thionylchloride cooling was removed and refluxed for 6 h. Starting material absence was confirmed by TLC. The solvent from the reaction mixture was removed under reduced pressure and the residue was poured in ice and neutralized with triethylamine followed by extraction with ethyl acetate. The organic layer was dried over Na_2SO_4 concentrated and the obtained crude compound was purified by column chromatography by eluting with a mixture of ethyl acetate and hexane in 2:8 ratio to yield, 5.81 g (83%). Mp 55–56 °C. IR (KBr): ν 3496, 3087, 2963, 2841, 1708, 1618, 1878, 1347, 1269, 1135, 1063, 957, 874, 753 cm^{-1}; 1H NMR ($CDCl_3$): δ 3.52 (s, 2H), 3.73 (s, 3H), 6.65 (d, 2H, J = 8.0 Hz), 7.05 (d, 2H, J = 8.0 Hz). EIMS *m*/*z* (%): 166 (M^+, 48), 151(12), 132(28), 107(100), 90(10), 78(59), 52(26).

4.1.3. 4-Allyloxy phenyl acetic acid methyl ester (5). A mixture of the methyl ester compound **4** (5.0 g, 0.030 mol), potassium carbonate (6.5 g, 0.047 mol) in acetone (50 mL) was stirred for some time and added allylbromide (5.5 g, 0.045 mol). The resulting mixture was stirred at reflux condition for 7 h. Then the solvent was removed under reduced pressure. The residue was dissolved in water and extracted with ethyl acetate. The organic layer was dried and concentrated to obtain the crude product, which was purified by column chromatography to yield 5.4 g (87%). IR (Neat): ν 3100–2850, 1735, 1600, 1569, 1407, 1256, 1184, 1022, 978, 843 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.55 (s, 2H), 3.69 (s, 3H), 4.48–4.55 (m, 2H), 5.20–5.50 (m, 2H), 5.90–6.15(m, 1H), 6.85 (d, 2H, J = 8.0 Hz), 7.15 (d, 2H, J = 8.0 Hz); ^{13}C NMR: δ 171.7, 157.8, 133.4, 130.2, 126.2, 117.3, 114.8, 68.7, 51.7, 40.2; EIMS, *m*/*z* (%): 206(M^+, 38) 147(79), 107(18), 78(27), 41(100).

4.1.4. 1-[4[(Methoxycarbonyl) methyl] phenoxy]-2,3-epoxy propane (racemic) (6). To a stirred mixture of allyloxy compound **5** (5.0 g, 0.024 mol) in dry dichloromethane (50 mL) was added *meta*-chloroperbenzoic acid (6.5 g, 0.037 mol) in portions for a period of 30 min at ice cooling. After the addition of *m*CPBA, cooling was removed and continued stirring for 15 h at room temperature. The completion of the reaction was confirmed by TLC. Then the reaction mixture was diluted by adding dichloromethane (50 mL) and washed with dilute 5% $NaHCO_3$, followed by water wash. The organic layer was dried over Na_2SO_4 and concentrated to get crude product, which was purified by column chromatography to yield 4.5 g (84%). ^{1}H NMR ($CDCl_3$): δ 2.70–2.75 (m, 1H), 2.85–2.93 (m, 1H), 3.28–3.36 (m, 1H), 3.55 (s, 2H), 3.70 (s, 3H), 3.90 (q, 1H, J = 7.5 Hz), 4.15 (dd, 1H, J = 9.5, 2.5 Hz), 6.88 (d, 2H, J = 8.0 Hz), 7.20 (d, 2H, J = 8.0 Hz).

4.1.5. (*S*) 1-[4[(Methoxycarbonyl) methyl] phenoxy]-2,3-epoxy propane (7). A mixture of racemic epoxide **6** (10 g, 0.045 mol) and (*R*,*R*) salen Co(III)OAc complex **A** (0.144 g, 0.225 mmol) were vigorously stirred for 15 min. Then cooled to 0 °C, and added water (0.45 mL, 0.025 mol) over a period of 1 h, through syringe pump. The reaction mixture was stirred at room temperature and monitored by HPLC (ODS-column) UV: 225 nm, 60% CH_3CN in H_2O. The reaction mixture was diluted with ethyl acetate, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate and petroleum ether 1:9 ratio. The less polar epoxide **7** eluted first as colourless liquid, $[\alpha]_D^{21}$ 5.7 (*c* 1, $CHCl_3$). Later the ethyl acetate and petroleum ether ratio was raised to 3:7 to elute the diol **8**, $[\alpha]_D^{25}$ −7.0 (*c* 1, $CHCl_3$). ^{1}H NMR: ($CDCl_3$): 2.70–2.75 (m, 1H), 2.85–2.93 (m, 1H), 3.28–3.36 (m, 1H), 3.55 (s, 2H), 3.70 (s, 3H), 3.98 (q,1H, J = 7.5 Hz), 4.15 (dd, 1H, J = 9.5, 2.5 Hz), 6.88 (d, 2H, J = 8.0 Hz), 7.20 (d, 2H, J = 8.0 Hz).

4.1.6. (*R*) 1-[4[(Methoxycarbonyl) methyl] phenoxy]-2,3-epoxy propane (10). A mixture of the 1,2 diol compound **8** (4 g, 0.0166 mol) Ph_3P (6.55 g, 0.025 mol) and diethylazo dicarboxylate (4.35 g, 0.025 mol) in benzene

(40 mL) was refluxed for 18 h. Then the solvent was removed under reduced pressure and the residue was diluted with ether to precipitate Ph_3PO, which was removed by filtration. The filtrate was concentrated and the residue was chromatographed to afford a colourless liquid of *R*-epoxide, yield, 3.1 g (83.7%) and $[\alpha]_D^{21}$ −6.0 (*c* 1, $CHCl_3$).

4.1.7. (*S*) 1-[4[(Methoxycarbonyl) methyl] phenoxy]-3-(isopropyl amino) propan-2-ol (9). A mixture of *S*-epoxide **7** (4 g, 0.018 mol), isopropyl amine (15 mL, 0.180 mmol) and water (0.5 mL) was refluxed for 5 h and the isopropyl amine was removed under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography to afford the pure product amino alcohol (3.8 g, 78%). $[\alpha]_D^{21}$ −4.0 (*c* 1, $CHCl_3$); IR (neat): *v* 3406, 3196, 3064, 2947, 2859, 1600, 1563, 1508, 1412, 1357, 1263, 1122, 1069, 953, 876 cm^{-1}; ^1H NMR: ($CDCl_3$): δ 1.10 (d, 6H, J = 7.0 Hz), 2.80–2.90 (m, 1H), 3.00–3.10 (m, 2H), 3.45 (s, 2H) 3.75 (s, 3H), 3.85–4.00 (m, 2H), 4.15–4.25 (m, 1H), 6.80–6.90 (m, 2H), 7.15 (t, 2H, J = 6.5 Hz); EIMS *m*/*z* (%): 281 (M^+, 29), 250(19), 222(12), 164(32), 106(67), 78(100), 52(43).

4.1.8. Preparation of (*S*)-atenolol (1). A cold solution (0–5 °C) of optically active ester compound **9** (2.0 g, 7.2 mmol), methanol (20 mL) and NH_4OH (8 mL) were mixed, stoppered and allowed to attain room temperature and stirred for 1 day and monitored by TLC. The solvent was removed and the crude product was recrystallized with ethyl acetate to get pure product (*S*)-atenolol (1.4 g, ~72%). $[\alpha]_D^{21}$ −17.0 (*c* 1, 1 N HCl); mp 148–150 °C; IR (KBr): *v* 3325, 3170, 2950, 2839, 1687, 1596, 1506, 1329, 1263, 1139, 1054, 968, 835 cm^{-1}. ^1H NMR: (DMSO-d_6): δ 1.05 (d, 6H, J = 7.0 Hz), 2.70–2.90 (m, 1H), 3.25 (d, 2H, J = 6.0 Hz), 3.42 (s, 2H) 3.90–4.10 (m, 2H), 6.18 (br s, 2H), 6.85 (d, 2H, J = 7.2 Hz), 7.15 (d, 2H, J = 7.2 Hz), 7.55 (br s, 1H); EIMS: *m*/*z* (%): 266(M^+, 45), 248(21), 208(11), 190(10), 150(22), 132(100), 104(31), 78(16), 52(31).

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