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A convenient synthesis of the enantiomerically pure β-blocker (*S*)-betaxolol using hydrolytic kinetic resolution

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Abstract—Enantiopure (*S*)-betaxolol was prepared in an extremely simple and practical way using hydrolytic kinetic resolution of a terminal epoxide by Jacobsen's catalyst. High enantiomeric purity (99% ee) has been achieved and the method is amenable to industrial scale-up.

1. Introduction

β-Adrenergic antagonists (β-blockers)[1] are an important class of drugs due to their prevalent use in the treatment of cardiovascular disorders such as hypertension, cardiac arrhythmia, angina pectoris and open angle glaucoma.[2] The principle effect of the β-adrenoreceptor blocker is to reduce cardiac activity by diminishing or preventing β-adrenoreceptor stimulation. The aryloxypropanol amine[3] class of drugs have a specific action on the cardiovascular receptor sites and most of the drugs in this series contain one stereogenic carbon centre, but are generally administered as racemates. The biological activity in a racemic drug often resides one single enantiomer. For instance betaxolol,[4] an important drug falling in this category whose (*S*)-isomer is associated with β-blocking activity while the (*R*)-isomer is responsible for side effects.[5] The synthesis of drugs in their enantiomerically pure form becomes very important for the pharmaceutical industries,[6] due to increased demand for more effective, safer single isomers.

To the best of our knowledge, there are only two reports on the asymmetric synthesis of (*S*)-betaxolol **1**, one is a lipase catalysed chemoenzymatic route[7] and the other involves asymmetric synthesis starting from oxazolidinone derivative.[8a] In the chemoenzymatic method, the enantiomeric excess of (*S*)-betaxolol was 82%, which was further improved to 91% ee after crystallising its hydrochloride salt. On the other hand, asymmetric synthesis using an oxazolidinone derivative has limited utility as the oxazolidinone derivative preparation itself is cumbersome and involves multi steps.[8b] In continuation of our work on improving the process for the preparation of (*S*)-betaxolol hydrochloride for industrial applications,[9] herein, we report a simple and practical process for the asymmetric synthesis of (*S*)-betaxolol (Fig. 1, Schemes 1 and 2) using hydrolytic kinetic resolution (HKR) method,[10] which was introduced by Jacobsen et al.[11] This approach provides high enantioselectivity and is extremely simple compared to other approaches.

2. Results and discussion

The synthesis commenced from the commercially available 2-(4-hydroxyphenyl) ethanol **2**. 2-(4-Hydroxyphenyl) ethanol **2** was treated with benzyl bromide in THF using KOH as a base and a catalytic amount of phase transfer catalyst at ambient temperature to obtain the regioselective *O*-alkylated 2-(4-benzyloxyphenyl) ethanol **3** in 90% yield. The resulted benzylated compound **3** was condensed with allyl bromide in the presence of KO^{t}Bu in DMSO to provide 1-(2-allyloxyethyl)-4-benzyloxy benzene **4** in 98% yield. Cyclopropanation of the terminal olefin of compound **4** was achieved by the Furukawa modification[12] of Simmon–Smith reaction,[13] that is, compound **4** on treatment with 15% hexane solution of diethyl zinc and diiodomethane at 0 °C gave compound **5** in 95% yield. Subsequently,

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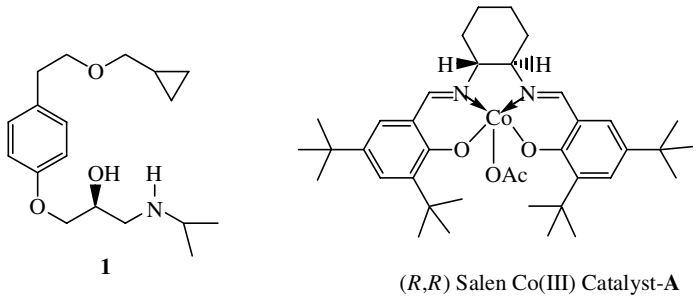
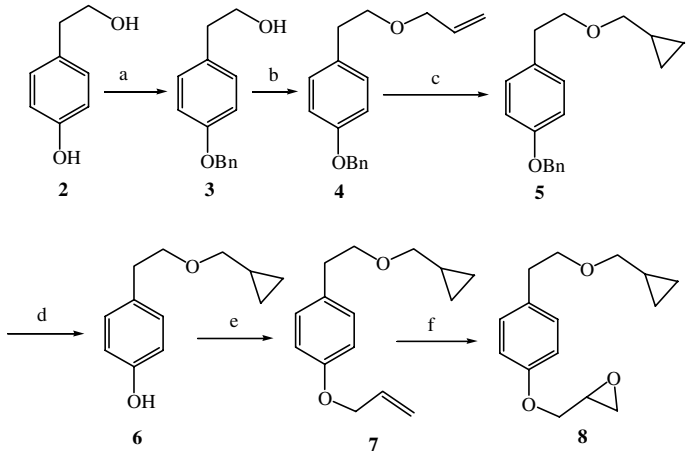
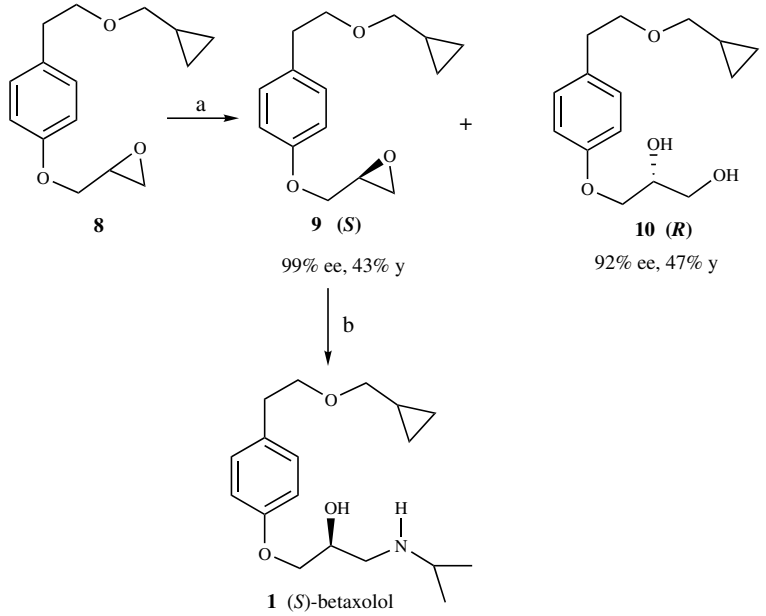


Figure 1.



Scheme 1. Reagents and conditions: (a) benzyl bromide, KOH, THF, 90%; (b) allyl bromide, KO^{t}Bu, DMSO, 40 °C, 98%; (c) diethyl zinc, diiodomethane, hexane, 0 °C, 95%; (d) Raney nickel, MeOH, H_2, 65 psi, 86%; (e) allyl bromide, KOH, THF, 95%; (f) *m*CPBA–DCM, 75%.



Scheme 2. Reagents and conditions: (a) (*R*,*R*)-salen Co(III)-**A**; (b) isopropylamine, DCM, 76%.

debenzylation of compound **5** was carried out by hydrogenation over Raney-Nickel catalyst in methanol to afford debenzylated compound **6** in 86% yield. The phenolic hydroxyl group of compound **6** was allylated with allyl bromide in THF using KOH as base to give compound **7**, which was further treated with *meta*-chloroperbenzoic acid (*m*CPBA) in dichloromethane at ambient condition to afford epoxide **8**. The epoxide **8** was a

free-floating liquid and was suitable to apply to the hydrolytic kinetic resolution method.

The hydrolytic kinetic resolution of racemic epoxide **8** was performed with Jacobsen catalyst (*R*,*R*) (salen Co(III)OAc) (0.5 mol %) and water (0.55 equiv) at room temperature for 16 h and the reaction was monitored by HPLC (SS-Wakosil; UV: 225 nm, 90% MeOH in H_2O). After completion of the reaction, the reaction mixture was chromatographed over silica gel column to give the selective (*S*)-epoxide **9** from the racemic mixture in 43% yield and 99% ee {$[\alpha]_D = +2.05$ (*c* 1, $CHCl_3$)} and (*R*)-diol **10** in 47% yield and 92% ee. The enantiomeric excess of all the chiral compounds was determined by HPLC using chiral column Chiralcel OD.

Subsequently, (*S*)-epoxide **9** was treated with an excess amount of *N*-isopropyl amine in dichloromethane at ambient temperature for 30 h afforded crude (*S*)-betaxolol which was further purified over silica gel column chromatography afforded pure (*S*)-betaxolol in excellent enantioselectivity (99% ee) $[\alpha]_D = -7.13$ (*c* 1, $CHCl_3$) {lit.[7] $[\alpha]_D = -5.4$ (*c* 1, $CHCl_3$)}. The structure of (*S*)-betaxolol was confirmed by its IR, ^{1}H NMR, ^{13}C NMR, HPLC, elemental analysis and mass spectroscopy. Alternatively, the crude (*S*)-betaxolol can be purified by making its maleate salt $[\alpha]_D = -14.1$ (*c* 2.4, MeOH) {lit.[8a] $[\alpha]_D = -14.9$ (*c* 2.4, MeOH)} and hydrochloride salt $[\alpha]_D = -13.5$ (*c* 2, $CHCl_3$).

3. Conclusion

In summary, the asymmetric synthesis of (*S*)-betaxolol with high enantioselectivity has been achieved. The main advantages of the process being high enantioselectivity, the ready availability of the catalyst and use of water (0.55 equiv) as the medium and reactant. Moreover, the Jacobsen catalyst can be regenerated by treating with acetic acid and recycled.[10a] We envisage that this simple and efficient process may find application in the pharmaceutical industry for the large scale production of (*S*)-betaxolol. Application of this simple protocol to asymmetric synthesis of other β-blockers is currently ongoing in our group.

4. Experimental

4.1. General

Melting points were measured on a BUCHI Melting Point B-540 melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a BRUKER 200 and 500 MHz NMR spectrometer. Chemical shifts were given in parts per million (ppm). Spectra were obtained in $CDCl_3$. Elemental analysis was recorded using Karlo–Erba elemental analyser. Monitoring of reactions was carried out using TLC plates Merck Silica gel 60 F_{254} and visualisation with UV light (254 and 365 nm), I_2 and anisaldehyde in ethanol as development reagents. Optical rotations were measured with a JASCO DIP 370 digital polarimeter. IR spectra were obtained from Perkin–Elmer 68515 PC-FTIR spectrophotometer. GCMS analysis was carried out using SHIMADZU-QP5050 system. HPLC analysis were performed on 'SHIMADZU SCL-10A. unit' system controller and UV monitor as detector. Chiral compounds were analysed on Daicel Chiralcel OD column and reaction monitoring was performed on SS-Wakosil column. All reagents and solvents were obtained from commercial suppliers and were used as such without further purification.

4.2. 2-(4-Benzyloxyphenyl) ethanol 3

To a solution of 2-(4-hydroxyphenyl) ethanol **2** (10 g, 0.073 mol) in tetrahydrofuran (65 ml) were successively added potassium hydroxide (6.1 g, 0.109 mol) and catalytic amount of tetrabutylammonium bromide (0.15 g) and the reaction mixture was stirred at room temperature under N_2 atmosphere for 1.5 h. Benzyl bromide (8.6 ml, 0.073 mol) was added dropwise to the reaction mixture and continued the stirring for 5 h. Filtered the solid, washed the solid with THF and concentrated the filtrate under reduced pressure. The residue was diluted with EtOAc, washed with water, dried over Na_2SO_4 and evaporated to obtain crude product, which was recrystallised from petroleum ether to yield **3** (14.9 g, 90%). Mp 85–86 °C; IR (Neat): *v* 3294, 3187, 2924, 2855, 1609, 1580, 1514, 1453, 1382, 1239, 1054, 1012, 829 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.80 (t, $J = 6.5$ Hz, 2H), 3.81 (t, $J = 6.5$ Hz, 2H), 5.04 (s, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 7.15 (d, $J = 8.7$ Hz, 2H), 7.30–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 157.38, 136.99, 130.69, 129.91, 128.48, 127.80, 127.36, 114.87, 69.92, 63.66, 38.17; MS *m*/*z*: 228 (M^+). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.14; H, 7.32.

4.3. 1-(2-Allyloxyethyl)-4-benzyloxy benzene 4

A solution of 2-(4-benzyloxyphenyl) ethanol **3** (12 g, 0.052 mol), KO^{t}Bu (8.84 g, 0.079 mol) in DMSO (50 ml) was stirred at 40 °C under N_2 for 30 min. Allyl bromide (6.7 ml, 0.079 mol) was added dropwise to the reaction mixture at temperature about 20–25 °C. The mixture was then stirred at 40 °C for 2 h. The reaction mixture was subsequently quenched by the addition of water (150 ml) and extracted with toluene. The toluene layer was washed with water, dried over Na_2SO_4, evaporated and the residue was purified by column chromatography (silica gel, pet. ether/EtOAc = 98/2) to provide **4** (13.8 g, 98%). IR (Neat): *v* 3064, 2933, 2860, 1611, 1511, 1454, 1240, 1176, 1099, 1025, 923, 827 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.87 (t, $J = 7.3$ Hz, 2H), 3.64 (t, $J = 7.3$ Hz, 2H), 4.02 (d, $J = 5.6$ Hz, 2H), 5.06 (s, 2H), 5.20 (dd, $J = 10.4$, 1.3 Hz, 1H), 5.30 (dd, $J = 17.2$, 1.8 Hz, 1H), 5.95 (m, 1 H), 6.84 (d, $J = 8.7$ Hz, 2H), 7.05 (d, $J = 8.7$ Hz, 2H), 7.33 (t, $J = 7.3$ Hz, 1H), 7.40 (t, $J = 7.3$ Hz, 2H), 7.44 (d, $J = 7.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 157.21, 137.07, 134.77, 131.18, 129.77, 128.46, 127.80, 127.37, 116.76, 114.65, 71.76, 71.36, 69.89, 35.38; MS *m*/*z*: 268 (M^+). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.34; H, 7.71.

4.4. 1-Benzyloxy-4-(2-cyclopropylmethoxyethyl) benzene 5

To a stirred solution of compound **4** (12 g, 0.045 mol) in dry hexane (50 ml), diethyl zinc (1.1 M solution in hexane, 185 ml) was added at 0 °C under N_2 followed by diiodomethane (18 ml, 0.224 mol). The reaction mixture was stirred at 0 °C for 6 h and poured over cold aqueous solution of ammonium chloride. The organic layer was separated and the aqueous layer was extracted repeatedly with diethyl ether. The combined organic layer was washed with aq solution of sodium thiosulfate, dried over Na_2SO_4, evaporated and the residue was purified by column chromatography (silica gel, pet. ether/EtOAc = 99/1) to afford compound **5** (12 g, 95%). IR (Neat): ν 3065, 2931, 2859, 1611, 1583, 1511, 1454, 1380, 1336, 1240, 1176, 1096, 1020, 929, 829 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.20 (m, 2H), 0.51 (m, 2H), 1.05 (m, 1H), 2.84 (t, $J = 7.5$ Hz, 2H), 3.27 (d, $J = 7$ Hz, 2H), 3.62 (t, $J = 7.5$ Hz, 2H), 5.04 (s, 2H), 6.89 (d, $J = 8.6$ Hz, 2H), 7.13 (d, $J = 8.6$ Hz, 2H), 7.31 (t, $J = 7.3$ Hz, 1H), 7.37 (t, $J = 7.3$ Hz, 2H), 7.42 (d, $J = 7.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 157.24, 137.15, 131.36, 129.68, 128.36, 127.66, 127.24, 114.69, 75.35, 71.63, 69.92, 35.40, 10.53, 2.84; MS m/z: 282 (M^+). Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.64; H, 7.55.

4.5. 4-(2-Cyclopropylmethoxy ethyl) phenol 6

A solution of compound **5** (12 g, 0.062 mol) in methanol (100 ml) was stirred over Raney-Nickel (10 ml slurry) under H_2 pressure (Parr Shaker; 65-psi pressure) for 5 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated. The crude product was purified by column chromatography (silica gel, dichloromethane) to yield compound **6** (7 g, 86%). IR (Neat): ν 3329, 3081, 2934, 2864, 1614, 1595, 1516, 1447, 1379, 1265, 1230, 1083, 930, 829 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.21 (m, 2H), 0.54 (m, 2H), 1.05 (m, 1H), 2.83 (t, $J = 7.3$ Hz, 2H), 3.31 (d, $J = 7$ Hz, 2H), 3.64 (t, $J = 7.3$ Hz, 2H), 6.75 (d, $J = 8.6$, 2H), 7.06 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 154.31, 130.27, 129.85, 115.26, 75.72, 71.84, 35.20, 10.44, 3.06; MS m/z: 192 (M^+). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.99; H, 8.54.

4.6. 1-Allyloxy-4-(2-cyclopropylmethoxy ethyl) benzene 7

To a solution of 4-(2-cyclopropylmethoxyethyl) phenol **6** (10 g, 0.052 mol) in tetrahydrofuran (65 ml) were successively added potassium hydroxide (3.8 g, 0.067 mol) and catalytic amount tetra butyl ammonium bromide (0.15 g) and the reaction mixture was stirred at room temperature under N_2 for 1.5 h. Allyl bromide (6.8 ml, 0.078 mol) was added dropwise to the reaction mixture and continued the stirring for 6 h. Filtered the solid, washed the solid with THF and concentrated the filtrate under reduced pressure. The residue was diluted with EtOAc, washed with water, dried over Na_2SO_4 and evaporated to obtain crude product, which was purified by column chromatography (silica gel, pet. ether/EtOAc = 90/10) to yield compound **7** (11.5 g, 95%). IR (Neat): ν 3080, 2934, 2859, 1648, 1611, 1583, 1511, 1425, 1378, 1241, 1177, 1097, 1021, 927, 827 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.20 (m, 2H), 0.54 (m, 2H), 1.05 (m, 1H), 2.83 (t, $J = 7.5$ Hz, 2H), 3.31 (d, $J = 6.8$ Hz, 2H), 3.64 (t, $J = 7.5$ Hz, 2H), 4.50 (d, $J = 5.3$ Hz, 2H), 5.25 (d, $J = 10.4$ Hz, 1H), 5.50 (d, $J = 17.3$ Hz, 1H), 6.05 (m, 1H), 6.75 (d, $J = 8.7$ Hz, 2H), 7.06 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 156.96, 133.36, 131.10, 129.70, 117.42, 114.52, 75.52, 71.75, 68.71, 35.39, 10.54, 2.90; MS m/z: 232 (M^+). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.83; H, 8.90.

4.7. 2-[4-(2-Cyclopropylmethoxy ethyl) phenoxymethyl] oxirane 8

To an ice-cooled solution of allyloxy compound **7** (10 g, 0.043 mol) in dry CH_2Cl_2 (50 ml) *meta*-chloroperbenzoic acid (11.48 g, 0.065 mol) was added in portions for a period of 30 min. After the addition of *m*CPBA, cooling was removed and continued stirring at room temperature for 24 h. The reaction mixture was diluted by adding dichloromethane (50 ml) and washed with dilute 5% $NaHCO_3$, followed by water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, pet. ether/EtOAc = 90/10) to yield compound **8** (8 g, 75%). IR (Neat): ν 3078, 3004, 2928, 2861, 1723, 1612, 1583, 1512, 1454, 1378, 1297, 1243, 1179, 1096, 1037, 937, 828 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.20 (m, 2H), 0.54 (m, 2H), 1.06 (m, 1H), 2.70–2.75 (m, 1H), 2.83 (t, $J = 7.3$ Hz, 2H), 2.88–2.93 (m, 1H), 3.26 (d, $J = 6.8$ Hz, 2H), 3.28–3.36 (m, 1H), 3.61 (t, $J = 7.3$ Hz, 2H), 3.95 (dd, $J = 11.1$, 5.5 Hz, 1H), 4.15 (dd, $J = 11.1$, 3.2 Hz, 1H), 6.87 (d, $J = 8.2$ Hz, 2H), 7.16 (d, $J = 8.2$, 2H); ^{13}C NMR ($CDCl_3$): δ 156.84, 131.53, 129.76, 114.42, 75.50, 71.63, 68.65, 50.09, 44.59, 35.32, 10.48, 2.88; MS m/z: 248 (M^+). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.70; H, 8.42.

4.8. (*S*)-2 [4-(2-Cyclopropylmethoxy ethyl) phenoxymethyl] oxirane 9

A mixture of racemic epoxide **8** (10 g, 0.04 mol) and (*R*,*R*) salen Co(III)OAc complex-A (0.130 g, 0.00022 mol) were vigorously stirred for 15 min. Then cooled to 0 °C, and added water (0.4 ml, 0.022 mol) over a period of 1 h, through syringe. The reaction mixture was stirred at room temperature and monitored by HPLC (SS Wakosil-column) UV: 225 nm, 90% MeOH in H_2O. The reaction mixture was diluted with EtOAc, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, pet. ether/EtOAc = 70/30). The less polar epoxide **9** eluted first as colourless liquid, $[\alpha]_D = +2.05$ (*c* 1, $CHCl_3$); ee >99% [chiral HPLC analysis; DAICEL CHIRALCEL OD (0.46 × 25 cm) column; eluent: hexane/isopropanol = 97.5/2.5; flow rate: 1.0 ml/min; detector: 254 nm ($t_R = 9.25$ min), ($t_S = 10.25$ min)]; followed by the diol **10**, ee 92% [chiral HPLC analysis; DAICEL CHIRALCEL OD (0.46 × 25 cm) column; eluent: hexane/isopropanol = 97.5/2.5; flow rate:

0.5 ml/min; detector: 254 nm ($t_R = 18.52$ min), ($t_S = 21.55$ min)]; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.21 (m, 2H), 0.54 (m, 2H), 1.06 (m, 1H), 2.70–2.75 (m, 1H), 2.83 (t, $J = 7.3$ Hz, 2H), 2.88–2.93 (m, 1H), 3.26 (d, $J = 6.8$ Hz, 2H), 3.28–3.36 (m, 1H), 3.64 (t, $J = 7.3$ Hz, 2H), 3.95 (m, 1H), 4.12 (m,1H), 6.87 (d, $J = 8.4$ Hz, 2H), 7.16 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 156.79, 131.3, 129.68, 114.28, 75.43, 71.55, 70.38, 68.88, 63.47, 35.20, 10.41, 2.85; MS *m/z*: 266 (M^+). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.27; H, 8.51.

4.9. Preparation of (*S*)-betaxolol 1

To a solution of (*S*)-epoxide **9** (3 g, 0.012 mol) in dichloromethane (5 ml) isopropyl amine (10.3 ml, 0.12 mol) was added slowly. The reaction mixture was stirred for 30 h at room temperature 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 (silica gel, dichloromethane/MeOH = 95/5) to afford the pure (*S*)-betaxolol **1** (2.82 g, 76%); $[\alpha]_D = -7.13$ (*c* 1, $CHCl_3$) {lit.[7] $[\alpha]_D = -5.4$ (*c* 1, $CHCl_3$)}; ee >99% [chiral HPLC analysis; DAICEL CHIRALCEL OD (0.46 × 25 cm) column; eluent: hexane/isopropanol/diethylamine = 60/40/0.1; flow rate: 0.5 ml/min; detector: 228 nm ($t_R = 8.53$ min), ($t_S = 10.61$ min)]; IR (Neat): *v* 3327, 3045, 2981, 2866, 1611, 1585, 1512, 1472, 1383, 1298, 1243, 1216, 1178, 1092, 930, 828, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.20 (m, 2H), 0.52 (m, 2H), 1.06 (m, 8H), 2.70–2.75 (m, 1H), 2.83–2.93 (m, 3H), 3.27 (d, $J = 7.2$ Hz, 2H), 3.61 (t, $J = 7.3$ Hz, 2H,), 3.90 (d, $J = 5.6$ Hz, 3H), 3.98–4.02 (m, 1H), 6.84 (d, $J = 8.7$ Hz, 2H), 7.13 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 156.93, 131.03, 129.54, 114.17, 75.31, 71.53, 70.59, 68.16, 49.49, 48.68, 35.0, 22.66, 10.36, 2.75; MS *m/z*: 307 (M^+). Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 69.91; H, 9.74 N, 4.15.

4.10. Preparation of (*S*)-betaxolol hydrochloride

To an ice cooled solution of crude (*S*)-betaxolol **1** (2.5 g) in toluene (15 ml) HCl in isopropanol (10%, 5 ml) was added dropwise under N_2 atmosphere and stirred the reaction mixture for 1.5 h. Concentrated the reaction mixture under reduced pressure and fresh toluene (5 ml) was added and stirred for 15 min. This process was repeated twice. Finally, evaporated the solvent completely and (*S*)-betaxolol hydrochloride was precipitated by the addition of diethyl ether. The precipitated (*S*)-betaxolol hydrochloride was filtered under N_2 atmosphere (1.96 g, 70%) mp 92–93 °C (lit.[7] mp 115 °C), $[\alpha]_D = -13.5$ (*c* 2, $CHCl_3$). Anal. Calcd for $C_{18}H_{30}ClNO_3$: C, 62.87; H, 8.79; Cl, 10.31; N, 4.07. Found: C, 62.56; H, 8.65; Cl, 10.20; N, 3.97.

4.11. Preparation of maleate salt of (*S*)-betaxolol

To a solution of crude (*S*)-betaxolol (2 g, 0.007 mol) in diethyl ether (15 ml) maleic acid (0.6 g, 0.005 mol) was added under N_2 atmosphere. Stirred for 2 h. The maleate salt was isolated by filtration (1.96 g, 71%) mp 96–97 °C (lit.[8] mp 96–97 °C); $[\alpha]_D = -14.1$ (*c* 2.4, CH_3OH) {lit.[8] $[\alpha]_D = -14.9$ (*c* 2.4, CH_3OH)}. Anal. Calcd for $C_{22}H_{33}NO_7$: C, 62.39; H, 7.85; N, 3.31. Found: C, 62.18; H, 7.64; N, 3.72.

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