# Application of Kinetic Resolution Using HCS as Chiral Auxiliary: Novel Synthesis of β-Blockers (*S*)-Betaxolol and (*S*)-Metoprolol

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*ABSTRACT* Optically pure (*S*)-betaxolol and (*S*)-metoprolol were prepared with an extremely facile and practical method using kinetic resolution of β-amino alcohols employing HCS as chiral auxiliary. High enantiomeric purity (ee > 99%) was achieved and the synthetic strategy is amenable to industrial scale-up. *Chirality 21:745–750, 2009.* 

*KEY WORDS:* resolution; synthesis; (*S*)-betaxolol; (*S*)-metoprolol

## INTRODUCTION

The first trials of β-adrenergic receptor blockers (beta-blockers) were performed involving relatively small populations of adults with heart failure in the 1980s[1–4] and early 1990s.[5,6] β-Adrenergic receptor blockers[7,8] now play an important role in the management of cardiovascular disease, including hypertension, cardiac arrhythmia, and angina pectoris.[9–12] Most β-blocking drugs are aryloxypropanolamine derivatives containing chiral centers. The *S*-enantiomers are generally 50–500 times more effective compared to the *R*-enantiomers.[13] Only a few of them (for example timolol and moprolol) are administered in optically pure form; however, the others are used as racemates. The β-blockers show stereoselectivity in absorption, interaction with proteins or receptors and metabolism. The biological activity of racemic β-blocking drugs resides in the S-enantiomer, while the other isomer may be responsible for side effects.[14] Therefore, the synthesis of β-blockers in their enantiomerically pure form becomes very important.

Metoprolol (**1**) and betaxolol (**2**) (Fig. 1), widely used for the treatment of angina, hypertension,[15,16] and open angle glaucoma,[17] are very important drugs in this series. Although both of them possess one stereogenic carbon center, they are generally administered as racemates. It is extremely important for the pharmaceutical industry[18,19] to produce drugs in optically pure form to meet the increased demand for more effective, safe single isomers. Many procedures have been reported in the literatures for the asymmetric synthesis of (*S*)-metoprolol[20–26] and (*S*)-betaxolol.[27–30] However, most of these methods require either lengthy reaction sequences or give product in low yield and enantioselectivity. Therefore, synthetic efforts now need to be directed at short, practical routes that are amenable to scale-up for drug preparation.

In our previous work, we have reported the NKR (nonenzymatic kinetic resolution) of β-amino alcohols using nonmetallic C-12 higher carbon sugar (HCS) (Fig. 2) as chiral auxiliary (Scheme 1).[31] In continuation of these efforts, it was considered of interest to investigate the application of the kinetic resolution for the chiral preparation of optically pure β-blockers. Herein, we report the facile and practical synthetic methodology of (*S*)-metoprolol and (*S*)-betaxolol in the large scale.



## EXPERIMENTAL SECTION

### *General Methods*

All chemicals were used as received unless otherwise noted. Reagent grade solvents were distilled prior to use. All reported NMR spectra were collected on a Bruker DPX 400 NMR spectrometer with TMS as internal reference. Infrared spectra were recorded on Nicolet IR200 instrument using KBr disks in the 400–4000 $cm^{-1}$ regions. High resolution mass spectra (HRMS) were obtained on a Waters Micromass Q-Tof Micro$^{TM}$ instrument using the ESI technique. Melting points were determined using a XT5A apparatus and were uncorrected. Optical rotations were determined on a Perkin Elmer 341 polarimeter. Single crystal structure was determined with Rigaku R-AXIS-IV area detector. Enantiomeric excess was determined by chiral HPLC at room temperature using Syltech 500 pump equipped with a UV 500 version 4.1 ultra-violet detector and a Chiralcel OD-H (4.6 mm × 250 mm) column (see Supporting Information).

### *C12 Higher Carbon Sugar*

C12 higher carbon sugar (HCS) was synthesized as described in the literature[32] and identified by $^{1}$H-NMR and $^{13}$C-NMR spectroscopy (Scheme 1).

Additional Supporting Information may be found in the online version of this article.

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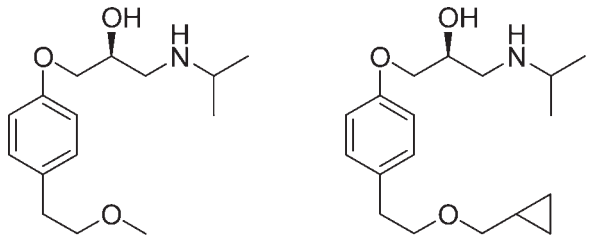



**Fig. 1.** Chemical structure of (*S*)-metoprolol and (*S*)-betaxolol.

### *General Procedure for the Synthesis of Racemic Epoxypropane 4*

To a stirred solution of **3** (4.00 mol) and $K_2CO_3$ (828 g, 6.00 mol) in anhydrous acetone (2.00 l), (±)-epichlorohydrin was added (0.620 l, 8.00 mol), and the reaction mixture was stirred under reflux until all of the **3** had been consumed (8 h; TLC). The reaction mixture was filtered, solvent was removed under vacuum, and the residue was purified by recrystallization from petroleum ether to yield **4a** and **4b** as a white solid.

**1-[4-(2-hydroxyethyl)phenoxy]-2,3-epoxypropane (racemic) (4a).** Yield: 760 g (98.0%). White solid. m.p. 56–57°C. IR (KBr): 3396, 2928, 2876, 1612, 1514, 1244, 1047, 1023, 908, 831 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.12(d, $J$ = 8.4 Hz, 2H, H-3 and H-5, Ph), 6.84 (d, $J$ = 8.5 Hz, 2H, H-2 and H-6, Ph), 4.17–4.21(dd, $J$ = 11.0 and 3.0 Hz, 1H, C$H_a$H$_b$O-Ph), 3.87–3.92 (dd, $J$ = 11.0 and 5.7 Hz, 1H, CH$_a$$H_b$O-Ph), 3.74–3.78 (m, 2H, HOC$H_2$CH$_2$Ph), 3.33–3.35 (m, 1H, C$H$CH$_2$O-Ph), 2.88–2.90 (m, 1H, C$H_a$H$_b$CH-CH$_2$O-Ph), 2.74 (dd, $J$ = 13.2 and 6.6 Hz, 2H, C$H_2$Ph), 2.73–2.75 (m, 1H, CH$_a$$H_b$CHCH$_2$O-Ph); $^{13}C$ NMR ($CDCl_3$): δ 156.9(C-1 Ph), 131.0(C-4 Ph), 129.8(C-3,5 Ph), 114.5(C-2,6 Ph), 68.6(*C*H$_2$O-Ph), 63.5(HO*C*H$_2$CH$_2$Ph), 50.1(*C*H CH$_2$O-Ph), 44.5(*C*H$_2$CHCH$_2$O-Ph), 38.1(*C*H$_2$Ph); HRMS: Calcd for $C_{11}H_{14}O_3$: 194.0943, Found: 195.1042 $[M+H]^+$.

**1-[4-(2-methoxyethyl)phenoxy]-2,3-epoxypropane (racemic) (4b).** Yield: 807 g (97.0%). White solid. m.p. 67–68°C. IR (KBr): 3396, 2928, 2875, 1612, 1515, 1251, 1114,1035, 914, 836 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.16 (d, $J$ = 8.3 Hz, 2H, H-3, and H-5, Ph), 6.87 (d, $J$ = 8.4 Hz, 2H, H-2, and H-6, Ph), 4.18–4.22 (dd, 1H, $J$ = 11.0 and 2.3 Hz, C$H_a$H$_b$O-Ph), 3.88–3.93 (dd, 1H, $J$ = 11.0 and 5.6 Hz, CH$_a$$H_b$O-Ph), 3.56–3.60 (t, 2H, $J$ = 7.0 Hz, C$H_2$ CH$_2$Ph), 3.36 (s, 3H, C$H_3$OCH$_2$CH$_2$Ph), 3.34 (m, 1H, C$H$CH$_2$O-Ph), 2.82–2.88 (m, 3H, C$H_2$Ph and C$H_a$H$_b$CH-CH$_2$O-Ph), 2.74 (m, 1H, CH$_a$$H_b$CHCH$_2$O-Ph); $^{13}C$ NMR ($CDCl_3$): δ156.7(C-1 Ph), 131.3(C-4 Ph), 129.5(C-3,5 Ph), 114.2(C-2,6 Ph), 73.5(*C*H$_2$CH$_2$Ph), 68.5(*C*H$_2$O-Ph), 58.3 (*C*H$_3$OCH$_2$CH$_2$Ph), 49.8(*C*HCH$_2$O-Ph), 44.3(*C*H$_2$CHCH$_2$ O-Ph), 35.0(*C*H$_2$Ph); HRMS: Calcd for $C_{12}H_{16}O_3$: 208. 1099, Found: 209.1183 $[M+H]^+$.

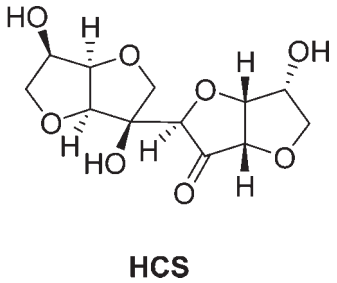
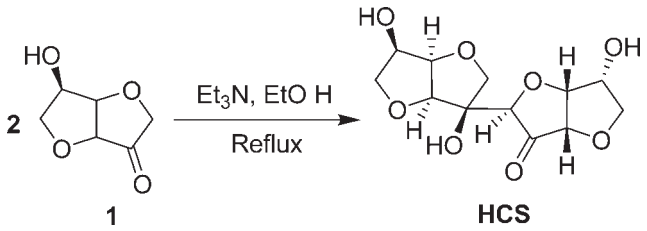



**Fig. 2.** Chemical structure of synthetic C12 higher carbon sugar.




**Scheme 1.** Synthesis of C12 higher carbon sugar (HCS).

### *General Procedure for the Synthesis of Racemic β-Amino Alcohols 5*

Racemic epoxypropane **4a** and **4b** (3.92 mol) were mixed with excess 25–28% $NH_3$ aq. and stirred for 15 h at 0–10°C. Then water and excess $NH_3$ were removed under vacuum. The residue was dissolved with ethanol to which water was added giving white deposit. The mixture was filtered and pure racemic amino alcohols were obtained by recrystallization from ethanol to afford white solids **5a** and **5b**.

**1-amino-3-(4-(2-hydroxyethyl)phenoxy)propan-2-ol (racemic) (5a).** Yield: 794 g (96.0%). White solid. m.p. 102–103°C IR (KBr): 3325, 3041, 2938, 2881, 1610, 1512, 1425, 1046 $cm^{-1}$; $^1H$ NMR(400 MHz, $D_2O$): δ 7.18(d, 2H, $J$ = 8.6 Hz, H-3 and H-5, Ph), δ6.92(d, 2H, $J$ = 8.6 Hz, H-2 and H-6, Ph), 4.21(m, 1H, NH$_2$CH$_2$C$H$CH$_2$), 4.08(dd, 1H, $J$ = 3.9, 10.3 Hz, CH$_a$$H_b$O-Ph), 4.03(dd, 1H, $J$ = 5.5, 10.2 Hz, C$H_a$H$_b$O-Ph), 3.73(t, 2H, $J$ = 6.6 Hz, HOC$H_2$CH$_2$Ph), 3.23(dd, 1H, $J$ = 3.8, 13.2 Hz, NH$_2$CH$_a$$H_b$CH), 3.11(dd, 1H, $J$ = 8.3, 13.2 Hz, NH$_2$C$H_a$H$_b$CH), 2.74(t, $J$ = 6.6 Hz, HOCH$_2$C$H_2$Ph) $^{13}C$ NMR(100.6 MHz, $D_2O$): δ 156.8(C-1 Ph), 132.6(C-4 Ph), 130.6(C-3,5 Ph), 115.2(C-2,6 Ph), 70.1(*C*H$_2$O-Ph), 66.6(NH$_2$CH$_2$*C*HCH$_2$), 63.0(HO*C*H$_2$CH$_2$ Ph), 42.2(CH*C*H$_2$NH), 37.3(HOCH$_2$*C*H$_2$Ph); HRMS: Calcd for $C_{11}H_{17}NO_3$ : 211.1208, Found: 212.1265 $[M+H]^+$.

**1-amino-3-(4-(2-methoxyethyl)phenoxy)propan-2-ol (racemic) (5b).** Yield: 821 g (94.0%). White solid. m.p. 98–99°C. IR (KBr): 3355, 2926, 2871, 1582, 1513, 1119 $cm^{-1}$; $^1H$ NMR(400 MHz, DMSO-$d_6$): δ 7.12(d, 2H, $J$ = 8.3 Hz, H-3 and H-5, Ph), δ6.84(d, 2H, $J$ = 8.4 Hz, H-2 and H-6, Ph), 3.91(dd, 1H, $J$ = 3.9, 10.3 Hz, CH$_a$$H_b$O-Ph), 3.84(dd, 1H, $J$ = 5.5, 10.2 Hz, C$H_a$H$_b$O-Ph), 3.73(m, 1H, NH$_2$CH$_2$C$H$CH$_2$), 3.47(t, 2H, $J$ = 6.9 Hz, HOC$H_2$CH$_2$Ph), 3.23(s, 1H, CH$_2$OC$H_3$), 3.17(m 2H, NH$_2$C$H_2$CH), 2.72(t, $J$ = 6.8 Hz, HOCH$_2$C$H_2$Ph) $^{13}C$NMR(100.6 MHz, DMSO-$d_6$): δ 158.0(C-1 Ph), 131.7(C-4 Ph), 130.5(C-3,5 Ph), 115.1(C-2,6 Ph), 73.9(*C*H$_2$O-Ph), 71.2(NH$_2$CH$_2$*C*HCH$_2$),

71.1($HOCH_2CH_2Ph$), 58.6($CH_3OCH_2$), 45.6($CHCH_2NH$), 35.3($HOCH_2CH_2Ph$); HRMS: Calcd for $C_{12}H_{19}NO_3$: 225.1365, Found: 226.2942 $[M+H]^+$.

### *Synthesis of* S-*5a,*S-*5b, 6a and 6b*

To a solution of HCS (294 g, 1.02 mol) in methanol (2.00 l), racemic **5a** and **5b** (2.00 mol) was added (a catalytic amount of *p*-TsOH was added). The mixture was stirred at 5°C for 20 h, followed by concentration and purification by crystallization from ethyl acetate, giving **6a** and **6b** as white solids. Then, the filtrate was concentrated to dryness and recrystallized from methanol to afford *S*-**5a** and *S*-**5b**.

**(*S*)-1-amino-3-(4-(2-hydroxyethyl)phenoxy)propan-2-ol(*S*-5a).** Yield: 202 g (47.8%, determined based on racemic **5a**) m.p. 102–103°C, $[\alpha]_D^{25} = -4.0$ (*c* 1.00, $CH_3OH$); ee >99%; [chiral HPLC analysis; Daicel Chiralcel OD-H (4.6 mm × 250 mm) column; eluent:hexane:isopropanol: diethylamine = 60: 40: 0.05; flow rate: 0.5 ml/min; detector: 254 nm($t_S$ = 19.13 min)].

**(*S*)-1-amino-3-(4-(2-methoxyethyl)phenoxy)propan-2-ol(*S*-5b).** Yield 212 g (47.1%, determined based on racemic **5b**). m.p. 98–99°C, $[\alpha]_D^{25} = -6.8$ (*c* 1.00, $CH_3OH$); ee >99%; [chiral HPLC analysis; Daicel Chiralcel OD-H (4.6 mm ×250 mm) column; eluent: hexane:isopropanol:-diethylamine = 60: 40: 0.05; flow rate: 0.5 ml/min; detector: 254 nm($t_S$ = 16.59 min)].

**(2*R*,3*R*,3a*S*,6*R*,6a*R*,3′*R*,3′a*S*,6′*R*,6′a*R*,5″*R*)-Spiro-[6,3′,6′-trihydroxyoctahydro [2,3′]bi[furo[3,2-b]furan]-3,2″-[5″-[4‴-[2⁗-hydroxyethyl]]phenoxymethyl-1″,3″-oxazolidine] (6a).** Yield: 481 g (98.0%). white solid. m.p. 156–157°C, $[\alpha]_D^{20} = +67.3$ (c 1.00, $CH_3OH$); IR(KBr): 3469, 3408, 3287, 2934, 2874, 1614, 1512, 1421, 1235, 1083, 1043 $cm^{-1}$; $^1H$ NMR(400 MHz, $D_2O$):δ 7.13(d, 2H, *J* = 8.5 Hz, H-3 and H-5, Ph), 6.83(d, 2H, *J* = 8.5 Hz, H-2 and H-6, Ph), 4.60(d, 1H, *J* = 5.4 Hz, H-9), 4.54 (t, 1H, *J* = 4.5 Hz, H-4), 4.35(m, 1H, $HNCH_2CHCH_2$), 4.26(m, 2H, H-3, H-10), 4.25(dd, 1H, H-5, *J* = 5.2, 9.3 Hz), 4.11(m, 1H, H-11), 3.99(dd, 1H, *J* = 3.4, 10.2 Hz, $CH_aH_bO$-Ph), 3.97(s, 1H, H-7), 3.90(dd, 1H, *J* = 3.4, 10.2 Hz, $CH_aH_bO$-Ph), 3.89(d, 1H, *J* = 8.5 Hz, H-1b), 3.87(m, 1H, H-6b) 3.84(d, 1H, *J* = 8.5 Hz, H-1a), 3.81(dd, 1H, *J* = 6.0, 8.5 Hz, H-12b), 3.65(t, 2H, *J* = 6.6 Hz, $HOCH_2CH_2Ph$), 3.42(dd, 1H, *J* = 6.0, 8.5 Hz, H-12b), 3.41(m, 1H, H-6a), 3.09(dd, 1H, *J* = 7.4, 12.4 Hz, $HNCH_aH_bCH$), 3.03(dd, 1H, *J* = 4.2, 12.4 Hz, $HNCH_aH_bCH$), 2.66(t, *J* = 6.6 Hz, $HOCH_2CH_2Ph$); $^{13}C$ NMR(100 MHz, $D_2O$): δ 156.3(C-1 Ph), 131.9(C-4 Ph), 130.1(C-3,5 Ph), 114.7(C-2,6 Ph), 104.6(C-8), 85.5(C-9), 83.6(C-10), 81.0(C-3), 80.8(C-2), 80.7(C-7), 80.6(C-4), 75.3($CHCH_2OPh$), 74.6(C-1), 72.0(C-5), 71.2(C-6), 70.8(C-12), 70.5(C-11), 69.2($CH_2OPh$), 62.5($HOCH_2CH_2Ph$), 45.6($CHCH_2NH$), 36.8($HOCH_2CH_2Ph$); HRMS: Calcd for $C_{23}H_{31}NO_{10}$: 481.1948, Found: 482.2026 $[M+H]^+$.

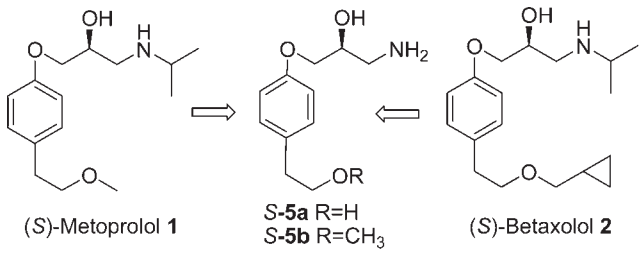
**(2*R*,3*R*,3a*S*,6*R*,6a*R*,3′*R*,3′a*S*,6′*R*,6′a*R*,5″*R*)-Spiro-[6,3′,6′-trihydroxyoctahydro [2,3′]bi[furo[3,2-b]furan]-3,2″-[5″-[4‴-[2⁗-methoxyethyl]]phenoxymethyl-1″,3″-oxazolidine] (6b).** Yield white solid. Mp 135–136°C, $[\alpha]_D^{20}$ = +25.6 (c 0.8, $CH_3OH$); IR(KBr): 3417, 2932, 2878, 1611, 1512, 1243, 1114, 1050 $cm^{-1}$; $^1H$ NMR(400 MHz, $D_2O$):δ 7.15(d, 2H, *J* = 8.4 Hz, H-3, and H-5, Ph), 6.88(d, 2H, *J* = 8.5 Hz, H-2, and H-6, Ph), 4.65(d, 1H, *J* = 4.2 Hz, H-9), 4.59 (t, 1H, *J* = 4.5 Hz, H-4), 4.35(m, 1H, $HNCH_2CHCH_2$), 4.30(m, 2H, H-3, H-10), 4.29(m, 1H, H-5), 4.15(m, 1H, H-11), 4.00(s, 1H, H-7), 3.99(m, 1H, $CH_aH_bO$-Ph), 3.96(d, 1H, *J* = 8.5 Hz, H-1b), 3.95(m, 1H, H-6b), 3.93(dd, 1H, *J* = 4.3, 6.9 Hz, $CH_aH_bO$-Ph), 3.91(d, 1H, *J* = 8.5 Hz, H-1a), 3.85(dd, 1H, *J* = 6.6, 8.4 Hz, H-12b), 3.59(t, 2H, *J* = 6.6 Hz, $HOCH_2CH_2Ph$), 3.50 (dd, 1H, *J* = 6.6, 8.4 Hz, H-12b), 3.49(m, 1H, H-6a), 3.23(s, 3H, $CH_2OCH_3$), 3.13(dd, 1H, *J* = 7.3, 12.3 Hz, $HNCH_aH_bCH$), 3.08(dd, 1H, *J* = 4.2, 12.3 Hz, $HNCH_aH_bCH$), 2.74(t, *J* = 6.5 Hz, $HOCH_2CH_2Ph$); $^{13}C$ NMR(100 MHz, $D_2O$): δ 156.9(C-1 Ph), 132.3(C-4 Ph), 130.4(C-3,5 Ph), 115.2(C-2,6 Ph), 105.0(C-8), 86.0(C-9), 84.1(C-10), 81.6(C-3), 81.5(C-2), 81.3(C-7), 81.1(C-4), 75.7($CHCH_2OPh$), 75.2(C-1), 73.5($CH_2OCH_3$), 72.4(C-5), 71.7(C-6), 71.3(C-12), 71.0(C-11), 69.6(-$CH_2OPh$), 58.1($HOCH_2CH_2Ph$), 46.2($CHCH_2$ NH), 34.4($HOCH_2CH_2Ph$); HRMS: Calcd for $C_{24}H_{33}NO_{10}$: 495.2104, Found: 518.2002 $[M+Na]^+$.

### *Synthesis of (S)-1-(4-(2-hydroxyethyl)phenoxy)-3-(isopropylamino)propan-2-ol(S-7)*

A solution of (*S*)-**5a** (200 g, 0.948 mol) in acetone, isopropyl bromide (232 g, 1.90 mol), and $K_2CO_3$ (262 g, 1.90 mol) was stirred at 50°C until TLC showed the reaction had gone to completion (6 h). Filtration and removal of the solvent yielded S-7 as a white solid (235 g, 98.0%). m.p. 85°C, $[\alpha]_D^{25} = -1.1$(c 1.00, $CH_3OH$); ee >99% [chiral HPLC analysis; Daicel Chiralcel OD-H(0.46 × 25 cm)column; eluent: hexane/isopropanol/diethylamine = 60/40/0.05; flow rate: 0.5 ml/min; detector: 254 nm ($t_S$ = 9.27 min)]; IR(KBr): 3448, 3279, 2964, 2923, 2866, 1609, 1512, 1239, 1110, 1046, 1023, 898, 866, 815 $cm^{-1}$; $^1H$ NMR (400 MHz, $D_2O$): δ 7.12 (d, 2H, *J* = 8.5 Hz, H-3 and H-5, Ph), 6.86 (d, 2H, *J* = 8.5 Hz, H-2 and H-6, Ph), 3.93–3.96(m, 2H, $CH_aH_bOPh$, $CHCH_2OPh$), 3.82–3.85(dd, 1H, *J* = 7.1 Hz, $CH_aH_bOPh$), 3.65(t, 2H, *J* = 6.6 Hz, $HOCH_2CH_2Ph$), 2.64–2.73(m, 4H, $CH_2Ph$, $HOCH_aH_bCHCH_2OPh$, $NHCH$ $CH_3CH_3$), 2.55–2.64(dd, 1H, *J* = 8.3 Hz, $HOCH_aH_b$ CH $CH_2OPh$), 0.91–0.93(m, 6H, $NHCHCH_3CH_3$); $^{13}C$ NMR (100.6 MHz, $D_2O$): δ 156.57(C-1 Ph), 131.82(C-4 Ph), 130.08(C-3,5 Ph), 114.75(C-2,6 Ph), 70.45($CH_2OPh$), 68.48 ($CHCH_2OPh$), 62.54($CH_2CH_2Ph$), 48.14($CH_2NH$), 48.01 (CHNH), 36.76($CH_2Ph$), 20.97($CH_3$), 20.87($CH_3$); HRMS: Calcd for $C_{14}H_{23}NO_3$: 253.1678, Found: 254.1756 $[M+H]^+$.

### *Synthesis of (S)-Betaxolol (2)*

To a solution of (*S*)-1-(4-(2-hydroxyethyl)phenoxy)-3-(isopropylamino)propan-2-ol S-**7** (200 g, 0.791 mol) in toluene (0.650 l) were added successively benzaldehyde (100 g, 0.949 mol) and catalytic amount of *p*-TsOH. The reaction mixture was heated and stirred at refluxing temperature under $N_2$ atmosphere for 6–10 h followed by concentration under vacuumed pressure to dryness to yield pale yellow oil. Then, To an ice-cooled solution of the oil in dry DMF (0.800 l), cyclopropylmethyl bromide (212 g, 1.58 mol) was added dropwise to the reaction mixture stirring




**Scheme 2.** Retrosynthetic route for Metoprolol and Betaxolol.

for 6 h at −10°C. Subsequently, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was acided with 10% HCl and extracted with EtOAc(100 ml ×3), then the water layer was treated with 10% NaOH(0.380 l) at room temperature for 0.5 h and then extracted with toluene (100 ml ×3). The organic layer was washed with water, dried over $Na_2SO_4$ and evaporated to yield crude (*S*)-betaxolol **1** as a free base, which was purified by recrystallization (231 g, 95.0%), white solid; mp 71–72°C $[\alpha]_D^{25} = -7.40$ (*c* = 1.0, $CHCl_3$) {lit.[26] $[\alpha]_D = -7.13$ (*c* = 1, $CHCl_3$)}; ee >99% [chiral HPLC analysis; Daicel Chiralcel OD-H (4.6 mm ×250 mm) column; eluent: hexane/isopropanol/diethylamine = 60/40/0.05; flow rate: 0.5 ml/min; detector: 254 nm ($t_S$ = 9.19 min)]; IR (neat): 3297, 3040, 2929, 2864, 1612, 1511, 1466, 1379, 1246, 1174, 1099, 913, 874, 820 $cm^{-1}$; $^1H$ NMR (400 MHz, $D_2O$): δ 0.02 (dd, 2H, *J* = 4.6, 10.2 Hz), 0.35 (dd, 2H, *J* = 3.7, 5.7 Hz), 0.81 (m, 1H), 1.20 (m, 6H), 2.64 (t, 3H, *J* = 6.8 Hz), 3.03–3.15 (m, 4H), 3.31–3.34 (m, 1H), 3.51 (t, 2H, *J* = 5.6), 3.89–3.93 (m, 2H), 4.13–4.68(m, 1H), 6.80 (d, 2H *J* = 8.5 Hz,), 7.05 (d, 2H, *J* = 8.5 Hz); $^{13}C$ NMR ($D_2O$): δ 156.4, 131.9, 130.1, 114.7, 75.4, 70.9, 69.5, 65.5, 51.0, 46.6, 34.0, 18.2, 17.8, 9.5, 2.4; HRMS: Calcd for $C_{18}H_{29}NO_3$: 307.2147, Found: 308.2236 $[M+H]^+$.

### *(S)-Metoprolol (1)*

A solution of (*S*)-**5b** (200 g, 0.890 mol) in acetone, isopropyl bromide (217 g, 1.78 mol) and $K_2CO_3$ (246 g, 1.78 mol) was stired at 50°C until TLC showed the reaction had gone to completion (6 h). Filteration and removal of the solvent yielded crude (*S*)-metoprolol. The crude (*S*)-metoprolol **1** free base was purified by recrystallization (227 g; 96.0%), white solid; $[\alpha]_D^{25} = -8.80$ (c 10.0, $CHCl_3$) {lit.[23] $[\alpha]_D = -8.70$ (c 10.0, $CHCl_3$)}; ee >99% [chiral HPLC analysis; Daicel Chiralcel OD-H (0.46 × 25 cm) column; eluent: hexane/ethylalcohol/diethylamine = 70/30/0.05; flow rate: 0.5 ml/min; detector: 254 nm ($t_S$ = 12.70 min)]; IR (neat): 3327, 3045, 2981, 2866, 1611, 1585, 1512, 1472, 1383, 1298, 1243, 1216, 1178, 1092, 930, 828, 756 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 1.08 (d, *J* = 6 Hz, 6H), 2.68(m, 2H), 2.72–2.88 (m, 4H), 3.35 (s, 3H), 3.55 (t, *J* = 8 Hz, 2H), 3.91–3.95 (m, 2H), 3.99–4.03 (m, 1H), 6.84 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H); $^{13}C$ NMR ($CDCl_3$): δ 157.1, 131.2, 129.7, 114.4, 73.8, 68.4, 58.6, 49.4, 48.8, 35.2, 22.9; HRMS: Calcd for $C_{15}H_{25}NO_3$: 267.1834, Found: 268.1927 $[M+H]^+$.

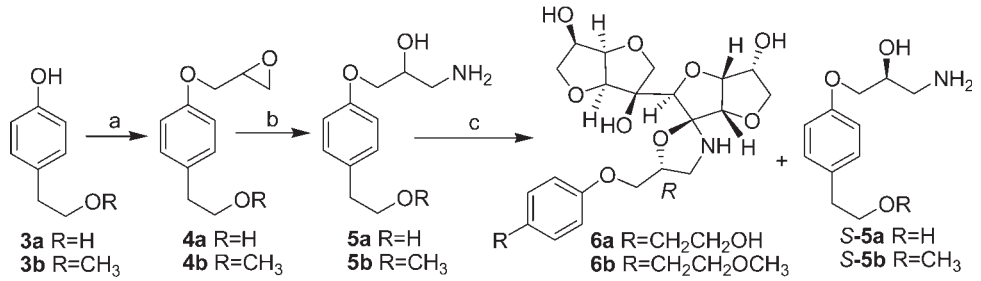
### *Recovery and Reuse of Resolving Agent (HCS)*

General procedure: 1 mol of the crystals of oxazolidine derivatives obtained was dissolved in 2.0 l of methanol after which 2.0 mol *c*. HCl aq. was added. After the evaporation of methanol, 1.0 l of water was added and the mixture was stirred for 30 min, then HCS was recovered by extraction using toluene or ethyl acetate and reused in the resolution of the amino alcohols (**5a**, **5b**).

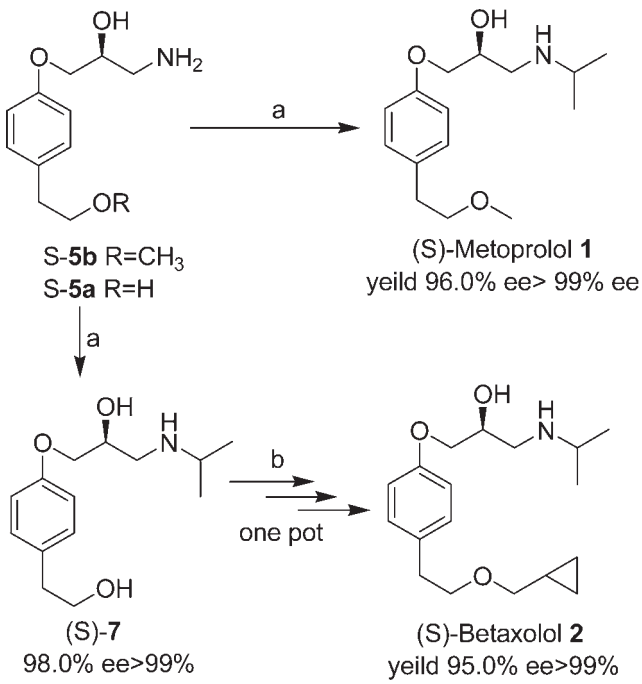
## RESULTS AND DISCUSSION

As part of our broader program to explore the application of C-12 higher carbon sugar, we describe here, a novel practical synthetic route for (*S*)-betaxolol and (*S*)-metoprolol. According to the retrosynthetic disconnection (Scheme 2), we considered that (*S*)-1-amino-3-(4-(2-hydroxyethyl)phenoxy)propan-2-ol (*S*-**5a**) and (*S*)-1-amino-3-(4-(2-methoxyethyl)phenoxy) propan-2-ol (*S*-**5b**) were substrates of special interest because they serve as the intermediates for (*S*)-metoprolol and (*S*)-betaxolol and can be easily converted to compounds **1** and **2** by a simple reaction sequence in high enantiopurity and good yield (Scheme 3 and Scheme 4).

The racemic epoxides 2-(4-(oxiran-2-ylmethoxy)phenyl) ethanol (**4a**) and 2-((4-(2-methoxyethyl)phenoxy)methyl) oxirane (**4b**) were obtained from alkylation of 4-(2-hydroxyethyl)phenol (**3a**) and 4-(2-methoxyethyl)phenol (**3b**) with (±)-epichlorohydrin in anhydrous acetone in the presence of $K_2CO_3$ under reflux temperature for 8 h in 98.0% and 97.0% yields, respectively (Schemes 3). Subsequently, the epoxides **4a** and **4b** were, respectively, treated with excess ammonia for 12–15 h at 0–10°C to yield racemic amino alcohols **5a** (96.0%) and **5b** (94.0%). After that, the NKR of racemic amino alcohols **5a** and **5b** was performed with HCS (0.51 equiv) in methanol at 5°C




**Scheme 3.** Synthesis of *S*-**5a and** *S*-**5b**. Reagents and conditions: **(a)** (±)-epichlorohydrin, $K_2CO_3$, acetone **(b)** ammonia (25–28%); 0–10°C **(c)** HCS, methanol, TsOH. 5°C.




**Scheme 4.** Synthesis of (*S*)-metoprolol and (*S*)-betaxolol. Reagents and conditions: (**a**) isopropyl bromide; $K_2CO_3$, acetone, reflux (**b**) i> toluene, phenyl aldehyde, TsOH; ii> DMF, NaH, cyclopropylmethyl bromide; iii >10%HCl, isopropanol; iv >10%NaOH, $H_2O$, toluene.

for 30 h and the reactions were monitored by TLC. The mixtures were concentrated and purified by crystallization from ethyl acetate, giving compound **6a** (98.0%) and **6b** (97.8%) as white solids. The filtrate was concentrated to obtain the S-isomers of amino alcohols *S*-**5a** (47.8% yield and ee >99%) and *S*-**5b** (47.1% yield and ee >99%).

Subsequently, *S*-**5a** and *S*-**5b** were treated, respectively with an excess amount of isopropyl bromide at 50°C for 6–8 h in the presence of $K_2CO_3$ to afford (*S*)-metoprolol free base (**1**) and the amino alcohol *S*-**7** (Scheme 4). After protection of amino group of (*S*)-**7** using benzaldehyde, O-alkylation of the hydroxyl group was carried out with bromomethylcyclopropane in the presence of NaH in DMF at −10°C for 8 h to provide pale yellow oil. Then, the oil was treated with 10%HCl followed by extraction with ethyl acetate to afford (*S*)-betaxolol as the hydrochloride salt. After that, (*S*)-betaxolol hydrochloride was treated with 10%NaOH followed by extraction with toluene to yield (*S*)-betaxolol free base. The crude (*S*)-metoprolol (**1**) and (*S*)-betaxolol (**2**) were further purified by recrystallization from ether to afford pure (*S*)-metoprolol in 96% yield with excellent enantioselectivity (ee > 99%) $[\alpha]_D^{25} = -8.80$ (c 10, $CHCl_3$) {lit.[23] $[\alpha]_D = -8.70$ (c 10, $CHCl_3$)} and (*S*)-betaxolol in 95.0% yield with excellent enantioselectivity (ee >99%) $[\alpha]_D^{25} = -7.35$ (c 1.0, $CHCl_3$) {lit.[26] $[\alpha]_D = -7.13$ (c 1.0, $CHCl_3$)}.

## CONCLUSION

In summary, a facile asymmetric synthesis of (*S*)-metoprolol and (*S*)-betaxolol with high enantioselectivity has been achieved using kinetic resolution as the key step and source of chirality. The main advantage of the procedure is its high enantioselectivity and the recoverable nonmetallic resolving reagent. More importantly, most of the intermediates and products were obtained by recrystallization, which makes possible the large scale production of (*S*)-betaxolol and (*S*)-metoprolol.

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