Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 2831–2838

Asymmetric synthesis of aryloxypropanolamines via OsO_4-catalyzed asymmetric dihydroxylation

Iliyas A. Sayyed, Vinay V. Thakur, Milind D. Nikalje, Gajanan K. Dewkar, S. P. Kotkar and A. Sudalai*

Chemical Engineering and Process Development Division, National Chemical Laboratory, Pashan Road, Pune 411 008, India

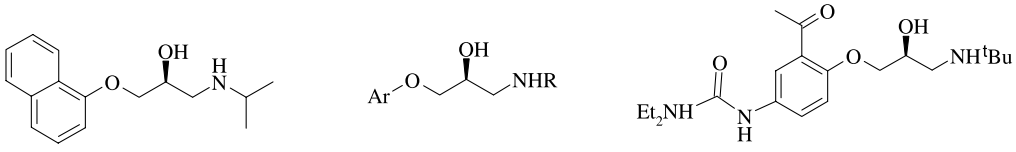
Received 18 October 2004; revised 4 January 2005; accepted 20 January 2005

Abstract—A simple and effective procedure for the enantioselective synthesis of several β-adrenergic blocking agents incorporating the first asymmetric synthesis of celiprolol, is described. The key steps are (i) sharpless asymmetric dihydroxylation of aryl allyl ethers to introduce chirality into the molecules and (ii) conversion of cyclic sulfates into the corresponding epoxides using a three-step procedure.

1. Introduction

β-Adrenergic blocking agents (β-blockers) are important drugs widely used for the treatment of hypertension, angina pectoris, glaucoma, anxiety and obesity. The discovery of propranolol (**1a**), the first successful drug having antianginal and antihypertensive effects, prompted the synthesis of many thousands of compounds containing an aryloxypropanolamine moiety.[1] The three fundamental goals of cardiovascular drugs are: lowering of blood pressure (antihypertensive), return of the heart to rhythmic beating (antiarrhythmics) and the general improvement of the heart muscle tone (cardiotonics).[2] Biochemically, the mechanism of action involves the adrenergic system in which the hormonal system provides the communication link between the sympathetic nervous system and involuntary muscle.[3] Blocking of the β-receptor system reduces the overall activity of the sympathetic nervous system. β-Blockers are thus used to increase life expectancy after heart attack. Biological systems, in most cases, recognize the members of a pair of enantiomers as different substances, and the two enantiomers will exhibit different responses. It has been shown for many pharmaceuticals that only one enantiomer contains all the desired activity, and the other is either totally inactive or highly toxic. Although (*S*)-isomers are known to be much more effective (100–500-fold) than the (*R*)-isomer,[4] these antihypertensive drugs are presently sold as racemic mixtures. To avoid unnecessary stress or in some cases toxicity to an organism caused by the (*R*)-isomers, the administration of optically pure (*S*)-isomer is desirable.

In the literature, there are several reports available for the synthesis of β-blockers (**1a–g**)[5] (Fig. 1) which include classical resolution via diastereomers, chromatographic



1a : (S)-Propranolol

1b: Ar = 2-methoxyphenyl, R=^{i}Pr, (S)-Moprolol
1c: Ar = 3-methylphenyl, R=^{i}Pr, (S)-Toliprolol
1d: Ar = 2-cyanophenyl, R=^{t}Bu, (S)-Bunitrolol
1e: Ar = 4-acetamidophenyl, R=^{i}Pr, (S)-Practolol
1f: Ar = 2,3-dimethylphenyl, R=^{t}Bu,(S)-Xibenolol

1g : (S)-Celiprolol

Figure 1.

Keywords: Antihypertensive; Asymmetric dihydroxylation; Epoxides; Cyclic sulfates.
* Corresponding author. Tel.: +91 20 25893300; fax: +91 20 25893359; e-mail: sudalai@dalton.ncl.res.in

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.01.074

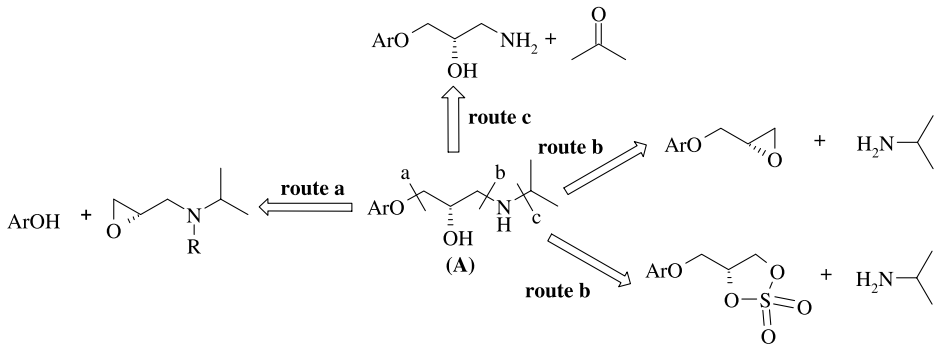


Figure 2. Retrosynthetic analysis of β-adrenergic blocking agents (**A**).

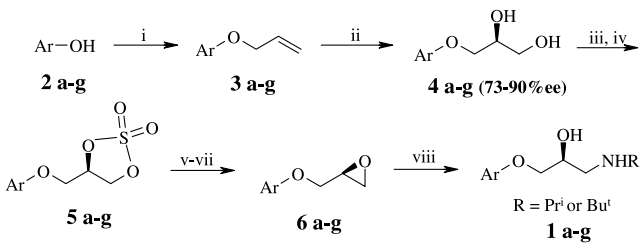
separation of enantiomers, enzymatic resolution, kinetic resolution and asymmetric synthesis via chiral pool strategy. Furthermore, many of these methods suffer from disadvantages such as low overall yields, use of expensive enzymes and resolving agents, low optical purity, the need for separation of diastereomers and the use of expensive chiral catalysts. In order to develop a new general route for the asymmetric synthesis of β-adrenergic blockers with good optical purity and yield, we decided to make use of sharpless asymmetric dihydroxylation (AD) and chemistry of chiral 1,2- cyclic sulfates.[6] Herein, we report catalytic enantioselective synthesis of seven such β-blockers (**1a–g**) from readily available starting materials (Fig. 1).

2. Results and discussion

Retrosynthetic analysis of these β-adrenergic blocking agents (**A**) is shown in Figure 2. There are three possible disconnections at the a, b and c bonds. Most of the previous synthetic routes are based on the disconnection of bonds at either a or b.

The general synthetic scheme we have employed for the synthesis of (*S*)-propranolol (**1a**), (*S*)-moprolol (**1b**), (*S*)-toliprolol (**1c**), (*S*)-bunitrolol (**1d**), (*S*)-practolol (**1e**), (*S*)-xibenolol (**1f**) and (*S*)-celiprolol (**1g**) is presented in Scheme 1.

Allylation of phenols **2a–g** (**2a**=α-naphthol, **2b**=2-methoxyphenol, **2c**=3-methylphenol, **2d**=2-cyanophenol, **2e**=4-acetamidophenol, **2f**=2,3-dimethylphenol, **2g**=2-hydroxy, 4-nitro- acetophenone) with allyl bromide gave allyl ethers **3a–g** in >97% yield.



Scheme 1. (i) K_2CO_3, $CH_2{=}CHCH_2Br$, acetone, reflux, 12 h, 97–99%; (ii) cat. OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O, 0 °C, 12 h, 94–98%, 73–90% ee; (iii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 40 min. 96–99%; (iv) cat. $RuCl_3$ $3H_2O$, $NaIO_4$, CH_3CN:H_2O, 0 °C, 30 min. 94–98%; (v) LiBr, THF 25 °C, 2–3 h; (vi) 20% H_2SO_4, Et_2O, 25 °C, 10 h; (vii) K_2CO_3, MeOH, 0 °C, 2 h, 80–85% overall in three steps; (viii) R-NH_2, H_2O (cat.), reflux, 2 h, 99%.

These allylic ethers **3a–g** were then subjected for the Os-catalyzed sharpless asymmetric dihydroxylation (AD) using $(DHQD)_2$-PHAL (hydroquinidine 1,4-phthalazinediyl diether) as chiral ligand in the presence of $K_3Fe(CN)_6$/K_2CO_3 as co-oxidant to give the enantiomerically enriched diols **4a–g**. The diols **4a–g** were then treated with freshly distilled $SOCl_2$, Et_3N in CH_2Cl_2 at 0 °C to afford cyclic sulfites in 96–99% yield as 1:1 diastereomeric mixture. The formation of cyclic sulfite was clearly evident from the appearance of multiplets at δ 4.00–5.50 in its ^1H NMR spectrum. The cyclic sulfites of the corresponding diols were then converted into cyclic sulfates **5a–g** in 94–98% yield using $RuCl_3$-catalyzed oxidation. The ^1H NMR spectrum of cyclic sulfates **5a–g** showed the disappearance of several multiplets at δ 4.25–4.32, 4.72–4.86 and at 5.22–5.26 due to diastereomeric mixtures of cyclic sulfites. Finally, the cyclic sulfates **5a–g** were subjected to nucleophilic displacement with appropriate amine nucleophiles followed by hydrolysis of the resulting salts to afford the corresponding β-blockers **1**(**a–g**), respectively. However, these reactions resulted in very low yields of the final β-blockers (yields were often less than 30%). Hydrolysis of the salts of cyclic sulfates using various reaction conditions such as 20% H_2SO_4 in ether, 50% H_2SO_4 in ether, concd HCl, 20% aq NaOH and 50% aq NaOH was conducted but all of them failed to improve the yields of the final products. Hence, we decided to convert these cyclic sulfates **5a–g** into the corresponding epoxides **6a–g** using a three-step procedure. Thus, cyclic sulfates **5a–g** were first treated with anhydrous LiBr, followed by treatment with 20% aq H_2SO_4 in ether to give the corresponding bromoalcohols. These were then treated with anhydrous K_2CO_3 in MeOH at 0 °C to afford the corresponding epoxides **6a–g** in high overall yields (80–85% in three steps).[7]

Finally the epoxides **6a–g** were then subjected to regiospecific nucleophilic opening with the respective amines to furnish the corresponding β-blockers **1**(**a–g**) in excellent yields and enantiomeric excess (up to 99%). In case of celiprolol, the nitro group was hydrogenated at 20 psi H_2 pressure with 10% Pd/C as catalyst at room temperature to get the amine which was condensed with diethyl carbomyl chloride (DECC) to afford the corrosponding (*S*)-celiprolol.

3. Conclusion

In conclusion, we have developed a simple and efficient protocol for the asymmetric synthesis of seven β-blockers namely (*S*)-propranolol (**1a**) (67% overall yield, 90% ee), (*S*)-moprolol (**1b**) (74% overall yield, 68% ee), (*S*)-toliprolol (**1c**) (77% overall yield, 78% ee), (*S*)-bunitrolol (**1d**) (35% overall yield, 60% ee), (*S*)-practolol (**1e**) (31% overall yield, 82% ee), (*S*)-xibenolol (**1f**) (35% overall yield, 67% ee), and (*S*)-celiprolol (**1g**) (33% overall yield, 97% ee) in eight steps starting from the corresponding phenols **2a–g**. The asymmetric synthesis of celiprolol has been achieved for the first time.

4. Experimental

4.1. General information

Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60–80 °C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. Infrared spectra were recorded on Shimadzu FTIR-8400 spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AC-200 and MSL-300 NMR spectrometers, respectively. Mass spectra were obtained with a Finnigan MAT-1020 B-70 eV mass spectrometer. Elemental analysis was carried out on a Carlo Erba CHNS-O analyzer. Enantiomeric excess was determined by chiral HPLC or by using chiral shift reagent Eu-(hfc)$_3$.

4.2. Preparation of allyl phenyl ethers 3a–g

A mixture of one of the phenols **2a–g** (10 mmol), allylbromide (12 mmol) and anhydrous K_2CO_3 (15 mmol) in dry acetone (20 mL) was refluxed under N_2 for 20 h (reactions monitored by TLC). The reaction mixture then cooled to room temperature, filtered through sintered funnel to remove solid residue and the filtrate was evaporated to dryness. The residue was purified by column chromatography using pet. ether/EtOAc (9:1) as eluent to get pure allyl phenyl ethers **3a–g** in 85–99% yield.

4.2.1. Allyl 1-naphthyl ether (3a). Yield: 1.78 g, 97%; gum; IR (neat, cm^{-1}): 744, 927, 999, 1012, 1028, 1125, 1200, 1260, 1458, 1520, 2829, 2930; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=4.68$ (2H, d, $J=4.0$ Hz), 5.29–5.54 (2H, m), 6.08–6.24 (1H, m), 6.78 (1H, d, $J=8.1$ Hz), 7.34–7.49 (4H, m), 7.76–7.81 (1H, m), 8.29–8.34 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=68.6$, 104.9, 117.0, 120.2, 122.0, 125.0, 125.7, 126.2, 127.3, 133.2, 134.4, 154.2; Analysis: $C_{13}H_{12}O$ requires C, 84.75; H, 6.57; found C, 84.69; H, 6.51%.

4.2.2. Allyl 2-methoxyphenyl ether (3b). Yield: 1.62 g, 99%; gum; IR (neat, cm^{-1}): 742, 927, 997, 1026, 1124, 1224, 1251, 1454, 1504, 1593, 2835, 2935; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=3.85$ (3H, s), 4.57–4.67 (2H, m), 5.24–5.45 (2H, m), 6.00–6.24 (1H, m), 6.87–6.90 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=55.5$, 69.5, 111.5, 113.4, 117.5, 120.4, 121.0, 133.2, 147.8, 149.2; MS *m/z* (% rel intensity): 164 (M^+, 80), 149 (10), 123 (94), 109 (25), 95 (100), 80 (30), 77 (95), 65 (25); Analysis: $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.37; found C, 73.28; H, 7.34%.

4.2.3. Allyl 3-methylphenyl ether (3c). Yield: 1.43 g, 97%; gum; IR (neat, cm^{-1}): 670, 738, 780, 927, 1020, 1127, 1224, 1260, 1458, 1490, 1510, 1594, 2859, 2945; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=2.36$ (3H, s), 4.49–4.55 (2H, m), 5.25–5.48 (2H, m), 5.97–6.21 (1H, m), 6.75–6.79 (3H, m), 7.16 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=21.3$, 68.5, 111.4, 115.4, 117.2, 121.5, 129.0, 133.4, 139.2, 158.5; MS *m/z* (% rel intensity): 148 (M^+, 50), 133 (60), 119 (65), 105 (70), 91 (100), 77 (50); Analysis: $C_{10}H_{12}O$ requires C, 81.04; H, 8.16; found C, 81.12; H, 8.21%.

4.2.4. Allyl 2-cyanophenyl ether (3d). Yield: 1.54 g, 97%; gum; IR ($CHCl_3$, cm^{-1}): 3082, 2925, 2227, 1598, 1579, 1490, 1450, 1425, 1290, 1259, 1234, 1166, 1110, 995, 933, 788, 756, 732; ^{1}H NMR (200 MHz, $CDCl_3$)): $\delta=4.66$ (2H, d, $J=2.0$ Hz), 5.31–5.36 (1H, m), 5.44–5.53 (1H, m), 5.90–6.20 (1H, m), 6.90–7.10 (2H, m), 7.45–7.65 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=69.1$, 101.8, 112.5, 116.0, 117.7, 120.6, 131.6, 133.3, 134.0, 159.9; MS (*m/z*, RI): 159 (M^+, 100), 158 (98), 143 (5), 130 (14), 119 (20), 118 (18), 104 (7), 92 (21), 90 (22), 82 (6), 76 (12), 69 (7), 64 (16), 58 (8); Analysis: $C_{10}H_9NO$ requires C, 75.45; H, 5.69; N, 8.79; found C, 75.41; H, 5.79; N, 8.78%.

4.2.5. Allyl 4-acetamidophenoxy ether (3e). Yield: 1.81 g, 95%; crystalline solid; mp: 100–102 °C (EtOAc and hexane); IR ($CHCl_3$, cm^{-1}): 3298, 3020, 2962, 1685, 1605, 1589, 1514, 1435, 1280, 1217, 1118, 850; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=2.14$ (3H, s), 4.51 (2H, d, $J=4.0$ Hz), 5.20 (1H, d, $J=12.0$ Hz), 5.35 (1H, d, $J=16.0$ Hz), 5.95–6.20 (1H, m), 6.80 (2H, d, $J=8.0$ Hz), 7.30 (2H, d, $J=8.0$ Hz), 7.50 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=33.0$, 72.3, 79.1, 79.4, 123.7, 130.2, 141.8, 164.1, 177.2; Mass (*m/z*, RI): 191 (M^+, 18), 190 (6), 150 (12), 149 (5), 109 (11), 108 (100), 95 (3), 80 (12), 65 (4), 57 (5); Analysis: $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.85; N, 7.34; found 69.13; H, 6.87; N, 7.32%.

4.2.6. Allyl 2,3-dimethylphenyl ether (3f). Yield: 1.37 g, 85%; gum; IR ($CHCl_3$, cm^{-1}): 2935, 1593, 1503, 1454, 1251, 1224, 1178, 1026, 997, 927, 1593, 1503, 1454, 1251, 1224, 1178, 1026, 997, 927, 742; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=2.17$ (3H, s), 2.26 (3H, s), 4.49–4.51 (2H, m), 5.22 (1H, d, $J=10.0$ Hz), 5.40 (1H, d, $J=16.0$ Hz), 5.99–6.13 (1H, m), 6.66 (1H, d, $J=8.0$ Hz), 6.7(1H, d, $J=16.0$ Hz), 6.98–7.02 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=11.6$, 19.9, 68.9, 109.2, 116.6, 122.3, 125.3, 125.6, 133.8, 137.8, 156.5; Mass (*m/z*, RI): 162 (M^+, 32), 147 (35), 119 (54), 103 (22), 91 (100), 77 (88), 65 (15); Analysis: $C_{11}H_{14}O$ requires C, 81.44; H, 8.70%; found: C, 81.31; H, 8.48%.

4.2.7. Allyl-2-acetyl-4-nitrophenyl ether (3g). Yield: 2 g, 95%; white solid; mp: 78–80 °C; IR ($CHCl_3$, cm^{-1}): 3020, 2405, 1690, 1523, 1345, 1275, 1215, 1117, 756, 667; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=2.66$ (3H, s), 4.78 (2H, d, $J=4.0$ Hz), 5.38–5.52 (2H, m), 6.00–6.19 (1H, m), 8.31–8.42 (2H, m), 8.61 (1H, d, $J=2.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=31.4$, 70.1, 112.9, 119.2, 126.0, 128.3, 131.0, 141.0, 159.5, 161.9, 196.9; Analysis: $C_{11}H_{11}NO_4$ requires

C, 59.72; H, 5.011, N, 6.33; found: C, 59.79; H, 5.43; N, 6.48%.

4.3. Preparation of 1-(aryloxy)-2,3-dihydroxypropane 4a–g

A 100 mL RB flask was charged with $K_3Fe(CN)_6$ (18.0 mmol), K_2CO_3 (18.0 mmol), $(DHQD)_2$-PHAL (0.24 mmol) and *t*-BuOH/H_2O (1:1, 60 mL) and the resulting mixture was stirred for 10 min at 25 °C. It was then cooled to 0 °C and a solution of OsO_4 (256 μL, 0.124 mmol, 0.5 M solution in toluene) was added. The resulting reaction mixture was stirred at 0 °C for 5 min and then one of the olefins **3a–g** (6 mmol) was added. The reaction mixture was stirred at 0 °C for 20–22 h (monitored by TLC). It was quenched with sodium sulfite (4.0 g) and extracted with ethyl acetate (4×25 mL). Combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using 50% EtOAc in pet. ether as eluent to yield pure diols **4a–g** as white solids in 84–98% yield.

4.3.1. (2*S*)-1-(1-Naphthoxy)-2,3-propanediol (4a). Yield: 1.25 g, 96%; white solid; mp: 113–114 °C; $[\alpha]^{25}_D$: +6.10 (*c* 1.1, MeOH), (lit.[8] +4.01 (*c* 1.1, MeOH), 60% ee); HPLC: 91% ee, Chiralcel OD-H, 5% EtOH/hexane, 1 mL/min. Retention time: (*R*): 13.23 min, (*S*): 16.55 min; IR ($CHCl_3$, cm^{-1}): 740, 780, 845, 993, 1020, 1130, 1257, 1379, 1390, 1458, 1515, 1598, 2845, 2910, 3280; ^1H NMR (200 MHz, $CDCl_3$): δ=3.55 (1H, br s), 3.80–3.95 (3H, m), 4.10–4.25 (3H, m), 6.83 (1H, d, *J*=6.1 Hz), 7.32–7.49 (4H, m), 7.77–7.81 (1H, m), 8.24–8.29 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ=63.7, 69.1, 70.4, 104.8, 120.3, 121.7, 124.9, 125.4, 125.6, 126.2, 127.2, 134.3, 154.2; MS *m/z* (% rel intensity): 218 (M^+, 70), 144 (100), 127 (10), 115 (43), 89 (7), 77 (5); Analysis: $C_{13}H_{14}O_3$ requires C, 71.54; H, 6.47; found C, 71.52; H, 6.49%.

4.3.2. (2*S*)-1-(2-Methoxyphenyl)-2,3-propanediol (4b). Yield: 1.1 g, 94%; white solid; mp: 101–102 °C; $[\alpha]^{25}_D$: +6.70 (*c* 1.1, MeOH), 73% ee (lit.[9] +5.8 (*c* 1.1, MeOH), 63% ee); HPLC: 73% ee, Chiralcel OD-H, 5% EtOH/hexane, 1 mL/min. Retention time: (*R*): 11.18 min, (*S*): 15.21 min; IR ($CHCl_3$, cm^{-1}): 744, 837, 993, 1022, 1128, 1257, 1377, 1456, 1510, 1593, 2854, 2953, 3234; ^1H NMR (200 MHz, $CDCl_3$): δ=3.75–3.84 (2H, m), 3.86 (3H, s), 4.04–4.17 (3H, m), 6.90–6.97 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ=55.9, 63.2, 69.8, 70.6, 111.5, 113.6, 120.6, 121.1, 147.7, 148.9, 159.4; MS *m/z* (% rel intensity): 198 (M^+, 28), 149 (10), 124 (100), 109 (80), 77 (13); Analysis: $C_{10}H_{14}O_4$ requires C, 60.60; H, 7.12; found C, 60.56; H, 7.14%.

4.3.3. (2*S*)-1-(3-Methylphenyl)-2,3-propanediol (4c). Yield: 1.06 g, 98%; white solid; mp: 61–62 °C; $[\alpha]^{25}_D$: +7.86 (*c* 1, EtOH) 80% ee (lit.[10] +9.5 (*c* 1, EtOH) 97% ee); HPLC: 80% ee, Chiralcel OD-H, 5% EtOH/hexane, 1 mL/min. Retention time: (*R*): 19.18 min, (*S*): 24.15 min; IR ($CHCl_3$, cm^{-1}): 690, 775, 933, 1055, 1159, 1259, 1290, 1453, 1490, 1585, 1602, 2877, 2927, 3390; ^1H NMR (200 MHz, $CDCl_3$): δ=2.30 (3H, s), 3.65–3.80 (2H, m), 4.00–4.25 (3H, m), 6.66–6.85 (3H, m), 7.20–7.30 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ=21.2, 63.4, 68.8, 70.4, 111.2, 115.1, 121.7, 129.0, 139.2, 158.2; MS *m/z* (% rel intensity): 182 (M^+, 30), 133 (12), 121 (18), 109 (100), 92 (23), 77 (20); Analysis: $C_{10}H_{14}O_3$ requires C, 65.92; H, 7.74; found C, 65.86; H, 7.79%.

4.3.4. (2*S*)-1-(2-Cyanophenoxy)-2,3-propanediol (4d). Yield: 960 mg, 84%; white solid; mp: 140–142 °C (hexane and EtOAc); $[\alpha]^{25}_D$: +21.8 (*c* 0.5, EtOH); 65% ee, (lit.[11] $[\alpha]^{25}_D$ +9.4 (*c* 0.49, EtOH) for 28% ee); IR ($CHCl_3$, cm^{-1}): 3421, 3018, 2229, 1598, 1492, 1450, 1290, 1215; ^1H NMR (200 MHz, $CDCl_3$)): δ=3.50–3.90 (4H, m), 4.10–4.25 (3H, m), 7.90–7.05 (2H, m), 7.45 (1H, d, *J*=8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ=63.2, 69.8, 70.0, 101.4, 112.4, 116.5, 120.9, 133.3, 134.5, 160.2; MS (*m/z*, RI): 193 (M^+, 10), 162 (12), 149 (4), 133 (38), 119 (100), 104 (42), 91 (80), 85 (4), 75 (16), 64 (22), 57 (12); Analysis: $C_{10}H_{11}NO_3$ requires C, 62.17; H, 5.73; N, 7.25; found C, 62.10; H, 5.75; N, 7.25%.

4.3.5. (2*S*)-1-(4-Acetamidophenoxy)-2,3-propanediol (4e). Yield: 1.14 g, 85%; white solid; mp: 142–144 °C (EtOAc); $[\alpha]^{25}_D$ +7.0 (*c* 1.0, EtOH); HPLC; 80% ee, Chiralcel OD-H, λ=254 nm, 10% 2-propanol/hexane, 1 mL/min. Retention time: (*S*) 11.464. (*R*) 17.358 min; IR ($CHCl_3$, cm^{-1}): 3321, 3240, 3138, 3077, 2941, 2882, 1663, 1604, 1554, 1514, 1414, 1284, 1254, 1113, 1050; ^1H NMR (200 MHz, DMSO-d_6): δ=2.10 (3H, s), 3.60–3.75 (2H, m), 3.90–4.05 (3H, m), 4.24 (1H, br s), 4.45 (1H, br s), 6.84 (2H, d, *J*=8.0 Hz), 7.46 (2H, d, *J*=8.0 Hz), 9.35 (1H, br s); ^{13}C NMR (50 MHz): δ=23.4, 62.7, 69.8, 69.8, 114.1, 120.6, 132.1, 154.5; Mass (*m/z*, RI): 225 (M^+, 10), 183 (4), 151 (16), 135 (4), 117 (5), 110 (8), 109 (100), 108 (15), 93 (7), 74 (4), 65 (8), 60 (6), 57 (15); Analysis: $C_{11}H_{15}NO_4$ requires C, 58.63; H, 6.71; N, 6.22; found C, 58.63; H, 6.79; N, 6.26%.

4.3.6. (2*S*)-1-(2,3-Dimethylphenoxy)-2,3-dihydroxypropane (4f). Yield: 1.1 g, 94%; colourless solid; mp: 104–105 °C (EtOH); $[\alpha]^{25}_D$ +4.25 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3431–3414, 3019, 2400, 1639, 1215, 751; ^1H NMR (200 MHz, $CDCl_3$): δ=2.14 (3H, s), 2.27 (3H, s), 2.55 (OH, br s), 3.0 (OH, br s), 3.77–3.90 (2H, m), 3.99 (2H, d, *J*=6.0 Hz), 4.05–4.2 (1H, m), 6.68 (1H, d, *J*=8.0 Hz), 6.78 (1H, d, *J*=8.0 Hz), 7.00 (1H, t, *J*=8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ=11.5, 19.9, 63.8, 69.2, 70.6, 109.1, 122.7, 125.0, 125.8, 137.9, 156.2; Mass (*m/z*, RI):196 (M^+, 18), 165 (0.2), 147 (8), 123 (100), 107 (40), 91 (12), 77 (8), 65 (0.2); Analysis: $C_{11}H_{16}O_3$ requires C, 67.32; H, 8.22%; found: C, 67.21; H, 8.16%.

4.3.7. (2*S*)-1-(2-Acetyl-4-nitrophenyl)-2,3-propanediol (4g). Yield: 1.46 g, 96%; yellow gum; $[\alpha]^{25}_D$: −5.31 (*c* 1.1, EtOH); HPLC: 97% ee, Chiracel-OD (25 cm) λ_{max}: 254 nm, 70:30 pet. ether/isopropanol, 1 mL/min. Retention time: (*S*): 7.08 min, (*R*): 8.26 min; IR: ($CHCl_3$, cm^{-1}): 740, 780, 845, 993, 1020, 1130, 1257, 1379, 1390, 1458, 1515, 1598, 2845, 2910, 3280; ^1H NMR (200 MHz, acetone-d_6): δ=2.66 (3H, s), 3.83–3.87 (2H, m), 4.16–4.34 (3H, m), 7.10 (1H, d, *J*=9.3 Hz), 8.33 (1H, dd, *J*=2.9, 9.0 Hz), 8.58 (1H, d, *J*=4.0 Hz); ^{13}C NMR (50 MHz, acetone-d_6): δ=31.0, 62.8, 69.8, 70.4, 112.7, 125.6, 127.6, 128.2, 140.5, 162.1,

196.9; Analysis: $C_{11}H_{13}NO_6$ requires C, 51.76; H, 5.13; N, 5.48; found C, 51.52; H, 5.08; N, 5.45%

4.4. Preparation of cyclic sulfates 5a–g

A. To a solution of one of the diols **4a–g** (4 mmol) and triethylamine (2.21 mL, 16 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added freshly distilled thionyl chloride (0.44 mL, 6 mmol) drop-wise under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 30–45 min (monitored by TLC). The reaction mixture was quenched by the addition of cold water (10 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3×15 mL). The combined organic extracts were washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent under reduced pressure yielded pale yellow colored liquid, which was purified by the column chromatography using 10% EtOAc in pet. ether as a eluent to afford the corresponding cyclic sulfite as viscous yellow liquid in 96–99% yield.

B. To a solution of one of the cyclic sulfites (3 mmol) in CH_3CN: H_2O mixture (9:1, 8 mL) at 0 °C was added solid $NaIO_4$ (0.963 g, 4.5 mmol) and $RuCl_3 \cdot 3H_2O$ (0.012 g, 0.06 mmol). The reaction mixture was stirred for 30–40 min at 0 °C (monitored by TLC). After the reaction was completed, it was filtered through a pad of celite. Solvent evaporated under reduced pressure to give the crude product, which was purified by column chromatography using pet. ether/EtOAc (8:2) as eluent to afford cyclic sulfates **5a–g** in 86–98% yield.

4.4.1. (4*S*)-4-(1-Naphthoxymethyl)-1,3,2-dioxathiolane-2,2-dioxide (5a). Yield: 789 mg, 94%; gum; $[\alpha]^{25}_D$: +17.4 (*c* 0.5, EtOH); IR ($CHCl_3$, cm^{-1}): 651, 753, 984, 1024, 1130, 1190, 2113, 1255, 1398, 1460, 1510, 1600, 2854, 2940; ^{1}H NMR (200 MHz, $CDCl_3$): δ=4.25–4.29 (2H, m), 4.60–4.67 (1H, m), 4.88–4.96 (1H, m), 5.36–5.41 (1H, m), 6.79 (1H, d, *J*=8.1 Hz), 7.26–7.53 (4H, m), 7.70–7.84 (1H, m), 8.16–8.21 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ=66.5, 68.3, 77.9, 104.7, 121.1, 121.4, 125.0, 125.4, 126.5, 127.3, 134.3, 153.3; MS *m/z* (% rel intensity): 280 (M^+, 100), 157 (55), 144 (56), 137 (25), 123 (28), 118 (10), 91 (8); Analysis: $C_{13}H_{12}SO_5$ requires C, 55.71; H, 4.32; S, 11.44; found C, 55.56; H, 4.29; S, 11.42%.

4.4.2. (4*S*)-4-[(2-Methoxyphenyl)methyl]-1,3,2-dioxathiolane-2,2-dioxide (5b). Yield: 756 mg, 97%; gum; $[\alpha]^{25}_D$: +20.12 (*c* 1, EtOH); IR ($CHCl_3$, cm^{-1}): 651, 754, 819, 981, 1026, 1126, 1178, 1213, 1255, 1392, 1456, 1506, 1595, 2839, 2935, 3018; ^{1}H NMR (200 MHz, $CDCl_3$): δ=3.85 (3H, m), 4.31 (2H, t, *J*=6.2 Hz), 4.81 (1H, d, *J*=6.2 Hz), 4.85 (1H, d, *J*=2.1 Hz), 5.22–5.28 (1H, m), 6.94–7.10 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ=55.6, 68.0, 69.7, 79.2, 112.4, 116.9, 120.9, 123.6, 146.9, 150.2; MS *m/z* (% rel intensity): 260 (M^+, 100), 216 (5), 137 (45), 123 (65), 109 (58), 95 (46), 77 (50); Analysis: $C_{10}H_{12}SO_6$ requires C, 46.15; H, 4.65; S, 12.32; found C, 46.21; H, 4.63; S, 12.26%.

4.4.3. (4*S*)-4-[(3-Methylphenyl)methyl]-1,3,2-dioxathiolane-2,2-dioxide (5c). Yield: 717 mg, 98%; gum; $[\alpha]^{25}_D$: +21.39 (*c* 1, EtOH); IR ($CHCl_3$, cm^{-1}): 652, 750, 819, 944, 1097, 1208, 1291, 1347, 1444, 1584, 2431, 2926, 3020; ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.33 (3H, s), 4.01–4.14 (2H, m), 4.45–4.51 (1H, m), 4.78–4.86 (1H, m), 5.23–5.28 (1H, m), 6.68–6.84 (3H, m), 7.14–7.26 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ=21.2, 65.5, 69.5, 79.1, 111.3, 115.4, 122.8, 129.3, 139.8, 157.4; MS *m/z* (% rel intensity): 244 (M^+, 23), 228 (16), 147 (10), 121 (96), 108 (92), 91 (100), 77 (15); Analysis: $C_{10}H_{12}SO_5$ requires C, 49.17; H, 4.95; S, 13.13; found C, 49.21; H, 4.86; S, 13.06%.

4.4.4. (2*R*)-1-(2-Cyanophenoxy)-1,3,2-dioxathiolane-2,2-dioxide (5d). Yield: 657 mg, 86%; gum; $[\alpha]^{25}_D$ +8.6 (*c* 2.0, EtOH); IR ($CHCl_3$, cm^{-1}): 3082, 2873, 2227, 1649, 1598, 1579, 1492, 1450, 1425, 1411, 1365, 1290, 1259, 1234, 1166, 1110, 1043, 995, 933, 839, 756, 590, 497; ^{1}H NMR (200 MHz, $CDCl_3$): δ=4.35–4.55 (1H, m), 4.90 (1H, d, *J*=2.0 Hz) 5.05 (1H, d, *J*=6.0 Hz), 5.25–5.45 (1H, m), 6.95–7.20 (2H, m), 7.50–7.70 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ=96.9, 70.0, 78.8, 102.0, 112.6, 115.6, 122.1, 133.6, 134.5, 158.7; MS (*m/z*, RI): 255 (M^+, 6), 232 (3), 218 (4), 204 (4), 193 (11), 176 (4), 162 (15), 146 (6), 134 (15), 133 (56), 119 (100), 104 (45), 102 (15), 91 (72), 80 (27), 75 (24), 64 (45), 57 (26); Analysis: $C_{10}H_9NSO_5$ requires C, 47.05; H, 3.55; N, 5.48; found C, 47.01; H, 3.66; N, 5.49%.

4.4.5. (4*R*)-4-(4-Acetamidophenoxy)-1,3,2-dioxathiolane-2,2-dioxide (5e). Yield: 740 mg, 86%; gum; IR ($CHCl_3$, cm^{-1}): 3409, 3018, 1652, 1627, 1419, 1215, 1053, 1029, 757; ^{1}H NMR (200 MHz, DMSO-d_6): δ=2.13 (3H, s), 4.28 (2H, d, *J*=4.0 Hz), 4.70 (1H, dd, *J*=2.0, 6.0 Hz), 4.86 (1H, dd, *J*=2.0, 6.0 Hz), 5.20–5.40 (1H, m), 6.84 (1H, d, *J*=8.0 Hz), 7.50 (2H, d, *J*=8.0 Hz), 9.10 (1H, s); ^{13}C NMR (50 MHz): δ=23.6, 67.8, 70.9, 81.9, 116.1, 123.0, 156.1, 158.7, 171.5; Analysis: $C_{11}H_{13}NSO_6$ requires C, 45.79; H, 4.57; N, 4.89; S, 11.16; found C, 51.93; H, 4.47; N, 4.82; S, 11.13%.

4.4.6. (4*S*)-4-[(2,3-Dimethyl) methyl]-1,2,3-dioxathiolane-2,2-dioxide (5f). Yield: 665 mg, 86%; colourless solid; mp: 230–231 °C; $[\alpha]^{25}_D$ −8.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3020, 2926, 2431, 1584, 1444, 1347, 1291, 1208, 1097, 944, 819, 750, 652; ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.15 (3H, s), 2.28 (3H, s), 4.26 (2H, d, *J*=4.0 Hz), 4.78–4.88 (2H, m), 5.2–5.35 (1H, m), 6.65 (1H, d, *J*=6.0 Hz), 6.84 (1H, d, *J*=6.0 Hz), 7.0 (1H, t, *J*=8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.5, 19.9, 63.8, 68.6, 78.1, 108.9, 123.3, 125.3, 125.8, 138.3, 155.7; Mass (*m/z*, RI): 258 (M^+, 32), 162 (12), 159 (20), 145 (30), 135 (78), 122 (72), 105 (65), 91 (60), 77 (100), 65 (0.5); Analysis: $C_{11}H_{14}O_5S$ requires: C, 51.15; H, 5.46, S, 12.41%; found: C, 51.19; H, 5.39, S, 12.61%.

4.4.7. (4*S*)-4-[(2-Acetyl-4-nitrophenyl) methyl]-1,3,2-dioxathiolane-2,2-dioxide (5g). Yield: 932 mg, 98%; solid; mp: 138–140 °C; $[\alpha]^{25}_D$: −2.97 (*c* 0.4, EtOH); IR: ($CHCl_3$, cm^{-1}): 651, 753, 984, 1024, 1130, 1213, 1255, 1460, 1510, 1600, 1688, 2854, 2940; ^{1}H NMR (200 MHz, acetonitrile-d_3): δ=2.36 (3H, s), 4.39–4.54 (2H, m), 4.59 (1H, dd, *J*=4.1, 9.0 Hz), 4.74 (1H, dd, *J*=4.2, 9.0 Hz), 5.29–5.35 (1H, m), 7.00 (1H, d, *J*=9.3 Hz), 8.05 (1H, dd, *J*=2.9, 9.0 Hz), 8.26 (1H, d, *J*=4.1 Hz); ^{13}C NMR (50 MHz, acetonitrile-d_3): δ 32.5, 69.0, 71.5, 81.7, 115.4,

127.3, 130.2, 143.66, 162.7, 199.0; Analysis: $C_{11}H_{11}NSO_8$ requires C, 41.64; H, 3.49; N, 4.41; S, 10.10; found C, 41.62; H, 3.45; N, 4.46; S, 9.78%.

4.5. Preparation of epoxides 6a–g

A. To a solution of one of the cyclic sulfates **5a–g** (2.5 mmol) in dry THF (15 mL) was added anhydrous LiBr (1.04 g, 12 mmol) and the resulting reaction mixture was stirred for 40–50 min (monitored by TLC for the disappearance of cyclic sulfate) at 25 °C. After completion of the reaction the solvent was removed under reduced pressure. In the resulting residue diethyl ether (25 mL) and 20% H_2SO_4 (25 mL) were added and stirred at 25 °C for 4–5 h (monitored by TLC). After completion of the reaction the two layers were separated, the aqueous layer extracted with diethyl ether (3×15 mL), combined organic extracts were washed with saturated $NaHCO_3$, water and brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the corresponding bromoalcohols.

B. The above crude bromoalcohol (2 mmol) was dissolved in MeOH (20 mL) and treated with anhydrous K_2CO_3 (1.10 g, 8 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 2 h (monitored by TLC). After completion the reaction was quenched by the addition of saturated NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (4× 15 mL), washed with water and brine, dried over anhydrous Na_2SO_4, evaporated under reduced pressure to give crude product. It was then purified by column chromatography using pet. ether/EtOAc (8:2) as eluents to give pure epoxides **6(a–g)** as oil in 80–85% yield.

4.5.1. (2*S*)-3-(1-Naphthyloxy)-1,2-epoxypropane (6a). Yield: 400 mg, 80% overall in two steps; gum; $[\alpha]^{25}_D$: +10.91 (*c* 1.3, EtOH); IR (neat, cm^{-1}): 748, 790, 916, 1021, 1123, 1190, 1240, 1260, 1454, 1510, 1590, 2890, 2990; ^1H NMR (200 MHz, $CDCl_3$): δ=2.75–2.79 (1H, m), 2.86–2.95 (1H, m), 3.39–3.44 (1H, m), 3.89 (1H, dd, *J*= 12.1, 6.2 Hz), 4.28 (1H, dd, *J*=12.1, 2.1 Hz), 6.73 (1H, d, *J*=8.14 Hz), 7.28–7.48 (4H, m), 7.74–7.79 (1H, m), 8.26–8.31 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ=44.5, 50.0, 68.8, 104.9, 120.7, 121.9, 125.2, 125.6, 126.4, 127.3, 134.4, 154.1; MS *m/z* (% rel intensity): 200 (M^+, 100), 157 (28), 144 (65), 127 (18), 115 (53), 89 (10); Analysis: $C_{13}H_{12}O_2$ requires C, 77.98; H, 6.04; found C, 77.96; H, 6.04%.

4.5.2. (2*S*)-3-(2-Methoxyphenyl)-1,2-epoxypropane (6b). Yield: 382 mg, 85% overall in two steps; gum; $[\alpha]^{25}_D$: +9.83 (*c* 1.2, EtOH); IR (neat, cm^{-1}): 746, 779, 916, 1027, 1124, 1180, 1224, 1255, 1454, 1504, 1593, 2837, 2929, 3001; ^1H NMR (200 MHz, $CDCl_3$): δ=2.72 (1H, dd, *J*= 6.1, 4.0 Hz), 2.89 (1H, t, *J*=4.0 Hz), 3.35–3.44 (1H, m), 3.87 (3H, s), 3.99 (1H, dd, *J*=12.1, 6.1 Hz), 4.20 (1H, dd, *J*=12.1, 4.0 Hz), 6.90–6.93 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ=44.7, 50.1, 55.9, 70.3, 112.5, 115.5, 120.9, 122.1, 148.3, 150.0; MS *m/z* (% rel intensity): 180 (M^+, 98), 150 (13), 137 (20), 124 (100), 109 (80), 95 (37), 81 (30), 77 (43), 65 (21); Analysis: $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71; found C, 66.67; H, 6.81%.

4.5.3. (2*S*)-3-(3-Methylphenyl)-1,2-epoxypropane (6c). Yield: 344 mg, 84% overall in two steps; gum; $[\alpha]^{25}_D$: +13.43 (*c* 2.2, EtOH); IR (neat, cm^{-1}): 690, 775, 860, 900, 1041, 1053, 1161, 1261, 1290, 1454, 1488, 1585, 1602, 2871, 2923, 2999; ^1H NMR (200 MHz, $CDCl_3$): δ=2.33 (3H, s), 2.73–2.76 (1H, m), 2.87–2.92 (1H, m), 3.32–3.36 (1H, m), 3.91 (1H, dd, *J*=12.1, 3.1 Hz), 4.15 (1H, dd, *J*= 12.1, 4.1 Hz), 6.71–6.80 (3H, m), 7.13–7.25 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ=21.4, 44.6, 50.1, 68.6, 111.5, 115.5, 112.0, 129.2, 139.5, 158.5; MS *m/z* (% rel intensity): 164 (M^+, 100), 134 (13), 119 (30), 108 (98), 91 (93), 77 (91), 65 (31), 57 (30); Analysis: $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.37; found C, 73.21; H, 7.42%.

4.5.4. (2*S*)-1-(2-Cyanophenoxy)-1,2-epoxypropane (6d). Yield: 393 mg, 90%; gum; $[\alpha]^{25}_D$ +2.3 (*c* 2.3, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 4217, 3614, 3020, 2399, 2231, 1600, 1514, 1505, 1450, 1290, 1261, 1210, 1045, 1026, 908, 760, 669; ^1H NMR (200 MHz, $CDCl_3$)): δ=2.80–2.95 (2H, m), 3.35–3.45 (1H, m), 4.05 (1H, dd, *J*=6.0 Hz each), 4.30 (1H, dd, *J*=4.0, 8.0 Hz), 6.95 (2H, dd, *J*=8.0 Hz), 7.45–7. 65 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ=44.2, 49.6, 69.2, 102.0, 112.5, 116.1, 121.2, 133.6, 134.3, 159.9; MS (*m/z*, RI): 175 (M^+, 8), 162 (10), 149 (10), 133 (28), 119 (45), 104 (36), 102 (32), 91 (80), 90 (32), 77 (20), 76 (18), 75 (28), 64 (52), 63 (45), 57 (100), 77 (72); Analysis: $C_{10}H_9NO_2$ requires C, 68.56; H, 5.17; N, 7.99; found C, 68.59; H, 5.17; N, 7.98%.

4.5.5. (2*S*)-3-(4-Acetamidophenoxy)-1,2-epoxypropane (6e). Yield: 414 mg, 80%; crystalline solid; mp: 104 °C (EtOAc and hexane); $[\alpha]^{25}_D$ +14.0 (*c* 2.0, EtOH); IR ($CHCl_3$, cm^{-1}): 3299, 2931, 1664, 1604, 1540, 1510, 1411, 1240, 1038, 828; ^1H NMR (200 MHz, $CDCl_3$)): δ=2.15 (3H, s), 2.76 (1H, dd, *J*=5.0, 3.0 Hz), 2.89 (1H, dd, *J*=5.0, 3.0 Hz), 3.25–3.45 (1H, m), 3.85 (1H, dd, *J*=8.0, 5.0 Hz), 4.15 (1H, dd, *J*=8.0, 5.0 Hz), 6.85 (2H, d, *J*=8.0 Hz), 7.40 (2H, d, *J*=8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ=24.0, 44.5, 50.1, 68.9, 114.8, 121.9, 131.5, 154.7, 168.7; Analysis: $C_{11}H_{13}NO_3$ requires C, 63.75; H, 6.32; N, 6.75; found C, 63.77; H, 6.35; N, 6.66%.

4.5.6. (2*S*)-3-(2,3-Dimethylphenyl)-1,2-epoxypropane (6f). Yield: 240 mg, 53.3%; gum; $[\alpha]^{25}_D$ −6.52 (*c* 2.3, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3020, 2926, 2431, 1584, 1444, 1347, 1291, 1208, 1097, 944, 819, 750, 652; ^1H NMR (200 MHz, $CDCl_3$): δ=2.17 (3H, s), 2.27 (3H, s), 2.75 (1H, dd, *J*=2.0 Hz each), 2.87 (1H, t, *J*=6.0 Hz), 3.34–3.39 (1H, m), 3.91 (1H, dd, *J*=4.0, 6.0 Hz), 4.16 (1H, dd, *J*= 4.0 Hz each), 6.66 (1H, d, *J*=10.0 Hz), 6.78 (1H, d, *J*= 8.0 Hz), 7.0 (1H, t, *J*=8.0 Hz);^{13}C NMR (50 MHz, $CDCl_3$): δ=11.5, 19.9, 44.6, 50.3, 69.2, 109.6, 122.9, 125.8, 138.0, 156.5, 159.7; Analysis: $C_{11}H_{14}O_2$ requires: C, 74.13; H, 7.92%; found C, 74.41; H, 7.69%.

4.5.7. (2*S*)-3-(2-Acetyl-4-nitrophenyl)-1,2-epoxypropane (6g). Yield: 503 mg, 85%; solid; mp: 80–83 °C; $[\alpha]^{25}_D$: −10.7 (*c* 0.9, EtOH); IR: ($CHCl_3$, cm^{-1}): 413, 430, 440, 459, 471, 487, 756, 1017, 1116, 1216, 1277, 1345, 1485, 1523, 1586, 1610, 1685, 2930, 3020; ^1H NMR (200 MHz, $CDCl_3$): δ=2.70 (3H, s), 2.28 (1H, dd, *J*=2.1, 9.0 Hz), 3.00 (1H, dd, *J*=2.0, 9.0 Hz), 3.43–3.49 (1H, m), 4.57 (1H, dd, *J*=2.0, 10.0 Hz), 7.09 (1H, d, *J*=9.3 Hz), 8.34 (1H, dd, *J*= 2.9, 9.0 Hz), 8.63 (1H, d, *J*=4.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ=31.5, 44.3, 49.3, 70.3, 112.9, 126.4, 128.5, 141.6, 159.6, 161.7, 196.9; MS *m/z* (% rel intensity): 237

(M^+, 20), 192 (8), 178 (40), 164 (18), 148 (10), 132 (60), 118 (30), 99 (35), 89 (10), 77 (20), 63 (35), 43 (100); Analysis: $C_{11}H_{11}NO_5$ requires C, 55.69; H, 4.67; N, 5.90; found C, 55.52; H, 4.61; N, 5.82%.

4.6. Preparation of (*S*)-propranolol (1a), (*S*)-moprolol (1b), (*S*)-toliprolol (1c), (*S*)-bunitrolol (1d), (*S*)-practolol (1e), (*S*)-xibenolol (1f) and (*S*)-celiprolol (1g) via opening of epoxides 6a–g

One of the epoxides **6a–g** (1.5 mmol) was dissolved in appropriate amines (10 mL) and refluxed in presence of water (0.5 mL) for 1 h. Excess of amine was removed under reduced pressure to afford **1(a–g)**.

In case of toliprolol, the resulting gum after evaporation of isopropylamine was dissolved in ether and dry HCl gas was passed through it for 15 min, the solvent was removed under reduced pressure and resulting solid recrystallized from MeOH+EtOAc afford (*S*)-toliprolol (**1c**) as its hydrochloride salt.

In case of celiprolol, the nitro group was hydrogenated at 20 psi H_2 pressure with 10% Pd/C as catalyst at room temperature to get the amine which was condensed with diethyl carbomyl chloride (DECC) to afford the corrosponding (*S*)-celiprolol.

4.6.1. (*S*)-(−)-Propranolol (1a). Yield: 384 mg, 99%; colourless solid; mp: 73–74 °C, (lit.[12] 72–73 °C); $[\alpha]^{25}_D$: −9.00 (*c* 0.5, EtOH), 90% ee (lit.[12] −9.9 (*c* 0.5, EtOH)); IR ($CHCl_3$, cm^{-1}): 570, 667, 750, 1029, 1120, 1175, 1210, 1240, 1450, 1500, 1594, 2930, 2960, 3300, 3432; ^1H NMR (200 MHz, $CDCl_3$): δ=1.09 (6H, d, *J*=6.1 Hz), 2.76–3.01 (5H, m), 4.08–4.19 (3H, m), 6.79 (1H, d, *J*=8.1 Hz), 7.34–7.51 (4H, m), 7.76–7.81 (1H, m), 8.22–8.27 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ=22.8, 48.7, 49.6, 68.4, 70.7, 104.8, 120.4, 121.7, 125.0, 125.4, 125.7, 126.2, 127.3, 134.4, 154.3; MS *m/z* (% rel intensity): 259 (M^+, 3), 144 (13), 115 (20), 84 (100), 72 (50), 69 (23), 56 (33); Analysis: $C_{16}H_{21}NO_2$ requires C, 74.10; H, 8.16; N, 5.40; found C, 74.25; H, 8.16; N, 5.30%.

4.6.2. (*S*)-(−)-Moprolol (1b). Yield: 351 mg, 98%; solid; mp: 84–85 °C, (lit.[12] 82–83 °C); $[\alpha]^{25}_D$: −3.90 (*c* 4.5, EtOH), 68% ee (lit.[11] −5.6 (*c* 4.5, EtOH)]; IR ($CHCl_3$, cm^{-1}): 667, 757, 1029, 1124, 1178, 1217, 1253, 1454, 1506, 1593, 2933, 2966, 3313, 3400; ^1H NMR (200 MHz, $CDCl_3$): δ=1.07 (6H, d, *J*=6.0 Hz), 2.69–2.90 (5H, m), 3.85 (3H, s), 3.97–4.07 (3H, m), 6.86–6.97 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ=23.0, 48.8, 49.3, 55.9, 68.6, 73.1, 112.4, 115.3, 121.1, 121.9, 148.6, 150.1; MS *m/z* (% rel intensity): 239 (M^+, 5), 224 (10), 195 (52), 124 (7), 109 (6), 77 (12), 72 (100), 56 (12); Analysis: $C_{13}H_{21}NO_3$ requires C, 65.25; H, 8.84; N, 5.85; found C, 65.11; H, 8.64; N, 5.75%.

4.6.3. (*S*)-(−)-Toliprolol (1c) hydrochloride. Yield: 383 mg, 99%; gum; mp: 117–118 °C, (lit.[5k] 119 °C); $[\alpha]^{25}_D$: −21.54 (*c* 1.01, EtOH) 78% ee; (lit.[5k] −27.4 (*c* 1.01, EtOH)); IR ($CHCl_3$, cm^{-1}): 694, 775, 968, 1062, 1110, 1257, 1294, 1379, 1461, 1488, 1585, 1612, 2711, 2852, 2933, 3257, 3303; ^1H NMR (200 MHz, $CDCl_3$): δ=1.48 (6H, s), 2.30 (3H, s), 3.19–3.48 (3H, m), 3.94–4.15 (2H, m), 4.55–4.63 (1H, m), 6.71–6.79 (3H, m), 7.10–7.18 (1H, m), 8.50 (1H, br s), 8.57 (1H, br s); ^{13}C NMR (50 MHz, $CDCl_3$): δ=18.6, 18.8, 21.2, 47.8, 51.2, 65.5, 69.3, 111.2, 115.1, 121.8, 129.0, 139.3, 158.0; MS *m/z* (% rel intensity): 259 (M^+, 2), 236 (30), 223 (9), 208 (13), 179 (19), 108 (7), 91 (10), 72 (100); Analysis: $C_{13}H_{22}ClNO_2$ requires C, 60.11; H, 8.54; Cl, 13.65; N, 5.39; found C, 60.20; H, 8.55; Cl, 13.75; N, 5.41%.

4.6.4. (*S*)-Bunitrolol (1d). Yield: 279 mg, 75%; white solid; mp: 162 °C (EtOH) (lit.[11] 163–165 °C); $[\alpha]^{25}_D$ −10.0 (*c* 1.4, H_2O); HPLC: 60% ee, ChiraSpher NT, λ=254 nm, (*n*-hexane/EtOH/MeOH (60:20:20)/0.05% NH_3 (25%)), 0.5 mL/min. Retention time: (*S*) 9.359 min, (*R*) 12.354 min; IR ($CHCl_3$, cm^{-1}): 3400, 3019, 2995, 1485, 1410, 2227, 1554, 1490, 1215, 756; ^1H NMR (200 MHz, $CDCl_3$): δ=1.14 (9H, s), 2.37 (1H, br s), 2.70 (1H, dd, *J*=4.0, 6.0 Hz), 2.86 (1H, dd, *J*=4.0, 6.0 Hz), 3.80–4.15 (3H, m), 6.90 (2H, d, *J*=8.0 Hz), 7.45 (2H, d, *J*=8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ=28.6, 44.4, 50.6, 67.7, 71.6, 101.8, 112.4, 116.2, 120.8, 133.4, 134.2, 160.3; Analysis: $C_{14}H_{20}N_2O_2$ requires C, 67.71; H, 8.11; N, 11.28; found C, 67.75; H, 8.16; N, 11.25%.

4.6.5. (*S*)-Practolol (1e). Yield: 280 mg, 70%; white solid; mp: 125 °C (dioxane); lit.[5n] 128–129 °C; $[\alpha]^{25}_D$ −2.6 (*c* 1.0, EtOH); 82%ee (lit.[5n] $[\alpha]^{25}_D$ +3.5 (*c* 1.0, EtOH) for (*R*)-Practolol]; IR ($CHCl_3$, cm^{-1}): 3314, 3284, 2975, 2359, 1715, 1665, 1511, 1398, 1220, 1040, 769; ^1H NMR (200 MHz, $CDCl_3$): δ=0.95 (6H, d, *J*=6.0 Hz), 1.93 (3H, s), 3.30–3.50 (2H, m), 3.55–3.70 (1H, m), 3.80–4.10 (4H, m), 6.75 (2H, d, *J*=8.0 Hz), 7.44 (2H, d, *J*=8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ=23.7, 45.0, 49.9, 52.1, 69.0, 73.5, 115.9, 123.0, 133.7, 156.3, 171.4; Mass (*m/z*, RI): 248 (4), 222)3), 178 (5), 151 (40), 136 (20), 109 (100), 98 (15), 91 (10), 80 (32), 64 (60); Analysis: $C_{14}H_{22}N_2O_3$ requires C, 63.14; H, 8.31; N, 10.51; found C, 63.10; H, 8.25; N, 11.02%.

4.6.6. (*S*)-Xibenolol (1f). Yield: 214 mg, 57%; gum; $[\alpha]^{25}_D$ −17.58 (*c* 1.0, $CHCl_3$); 67% ee (lit.[5o] −25.4 (*c* 1.0, $CHCl_3$)]; IR ($CHCl_3$, cm^{-1}): 3421–3501, 2926, 2928, 2856, 1649, 1580, 1458, 1375, 1263, 1194 ^1H NMR (200 MHz, $CDCl_3$): δ=1.49 (9H, s), 2.12 (3H, s), 2.23 (3H, s), 3.07–3.36 (3H, m), 3.90–4.11 (2H, m), 4.66 (1H, br s), 6.62 (1H, d, *J*=8.0 Hz), 6.75–6.78 (1H, d, *J*=6.0 Hz), 6.96–7.03 (1H, t, *J*=8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ=11.4, 19.6, 25.6, 45.5, 57.4, 65.7, 69.9, 109.1, 122.6, 124.9, 125.7, 137.6, 156.0; Mass (*m/z*, RI): 233 (M^+–H_2O, 40), 218 (65), 161 (100), 147 (20), 122 (55), 112 (70), 91 (10), 77 (5); Analysis: $C_{15}H_{25}NO_2$ requires: C, 71.67; H, 10.02; N, 5.57%; found: C, 71.51; H, 9.89%; N, 5.51%.

4.6.7. (*S*)-(−) Celiprolol (1g). Yield: 511 mg, 90%; solid; mp 116–118 °C; lit.[5p] mp 117–118 °C; $[\alpha]^{25}_D$: −12.5 (*c* 1.76, EtOH), HPLC: 97% ee, Chiracel-OD 10% diethylamine/2-propanol, 1 mL/min. Retention time: (*S*): 10.35 min, (*R*): 12.67 min; IR: ($CHCl_3$, cm^{-1}): 673, 759, 824, 1044, 1076, 1162, 1221, 1307, 1382, 1430, 1500, 1651, 1677, 2794, 2966, 3320; ^1H NMR (200 MHz, $CDCl_3$): δ=1.39 (6H, t, *J*=10.0 Hz), 1.48 (9H, s), 2.57 (3H, s), 2.99 (1H, br s) 3.11–3.13 (3H, m), 3.38 (8H, m), 4.01–4.05 (2H, m), 6.84 (1H, d, *J*=10.0 Hz), 7.53 (1H, d, *J*=10.0 Hz), 7.70

(1H, s); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 8.5$, 13.8, 25.6, 31.0, 41.4, 46.0, 57.6, 65.2, 71.0, 113.5, 123.4, 126.9, 127.4, 133.1, 153.2, 155.4, 159.6, 199.8; Analysis: $C_{20}H_{33}N_3O_4$ requires C, 63.30; H, 8.76; N, 11.07; found C, 63.29; H, 8.81; N, 11.10.

Acknowledgements

IAS, VVT, MDN, GKD and SPK thank CSIR, New Delhi for the award of research fellowship. We also thank Dr. B. D. Kulkarni, Head, CEPD, for his constant encouragement. Financial support from DST, New Delhi is gratefully acknowledged.

References and notes

1. Stinson, S. C. *Chem. Eng. News* **1998**, *21*(September 21), 83.
2. Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437.
3. Taylor, S. H.; Grimm, R. H. J. *Am. Heart J.* **1990**, *119*, 655.
4. (a) Howe, S. *Nature* **1966**, *210*, 1336. (b) Leftheris, K.; Goodman, M. J. *J. Med. Chem.* **1990**, *33*, 216. (c) Shiratsuchi, M.; Kawamura, K.; Akashi, T.; Ishihama, H.; Nakamura, M.; Takenaka, F. *Chem. Pharm. Bull.* **1987**, *35*, 3691.
5. **Propranolol**: (a) Dukes, M.; Smith, L. H. *J. Med. Chem.* **1971**, *14*, 326. (b) Tsuda, Y.; Yoshimoto, K.; Nishikawa, T.; *Chem. Pharm. Bull.* **1981**, *29*, 3593. (c) Iriuchijima, S.; Kojima, N. *Agric. Biol. Chem.* **1982**, *46*, 1153. (d) Katsuki, T. *Tetrahedron Lett.* **1984**, *25*, 2821. (e) Matsuo, N.; Ohno, N. *Tetrahedron Lett.* **1985**, *26*, 5533. (f) Kiunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295. (g) Sakabura, S.; Takahashi, H.; Takeda, H.; Achiwa, K. *Chem. Pharm. Bull.* **1995**, *43*, 738. (h) Sessai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Appl. Organomet. Chem.* **1995**, *9*, 421. **Moprolol**: (i) Kazunori, K.; Akimasa, M.; Shigeki, H.; Takehisa, O.; Kiyoshi, W. *Agri. Biol. Chem.* **1985**, *49*, 207. (j) Ferrari, G., Vecchietti, V. US. 4683245 **1980**. **Toliprolol**: (k) Howe, R.; Rao, B. S. *J. Med. Chem.* **1968**, *11*, 1118. **Bunitrolol**: (l) Zhenya, H. *Gongye, Y.* **1987** *18*, 339 (Chinese). **Practolol**: (m) Thakkar, N. V.; Banerji, A. A.; Berinakatti; Hanumanthsa, S. *Biotechnology Lett.* **1995**, *17*, 217 (n) Danilewicz, J. C.; Kemp, J. E. G. *J. Med. Chem.* **1973**, *16*, 168. **Xibenolol**: (o) Hunma, S.; Ito, T.; Kambekawa, A. *Chem. Pharm. Bull.* **1985**, *33*, 760. **Celiprolol**: (p) Zoelss, G. *Arzneim-forsch.* **1983**, *33(1A)*, 2*(German)*. (q) Joshi, R. A.; Gurjar, M. K.; Tripathy, N. K. *Org. Proc. Res. Dev.* **2001**, *5*, 176.
6. (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis Ojima I*; Ojima, I., Ed.; VCH Publishers: New York, 1993; Chapter 4, pp 227–270.
7. Linli, He; Hoe-Sup, Byun; Robert, Bittman *J. Org. Chem.* **1998**, *16*, 5696.
8. Rao, A. V. R.; Gurjar, M. K.; Joshi, S. V. *Tetrahedron: Asymmetry* **1990**, *1*, 697.
9. Wang, Z. M.; Zhang, X. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2267.
10. Theil, F.; Weidner, J.; Ballaschuh, S.; Kunath, A.; Schick, H. *J. Org. Chem.* **1994**, *59*, 388.
11. The Merck Index, 13th Ed. Merck and Co., Inc. Whitehouse Station, NJ.
12. Hou, X. L.; Li, B. F.; Dai, L. X. *Tetrahedron: Asymmetry* **1999**, *10*, 2319.