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Enantioselective synthesis of (*S*)-timolol via kinetic resolution of terminal epoxides and dihydroxylation of allylamines

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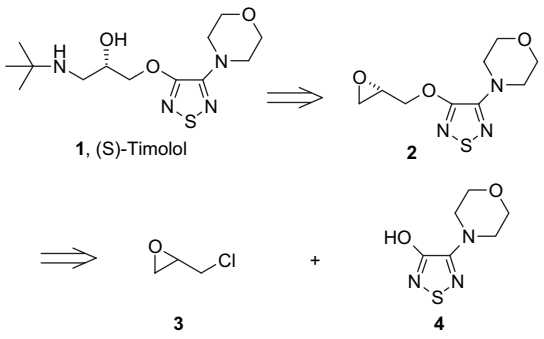
Abstract—An efficient enantioselective synthesis of (*S*)-timolol has been described using chiral Co–salen-catalyzed kinetic resolution of less expensive (±)-epichlorohydrin with 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole in good overall yield (55%) and excellent enantioselectivity (98%). Synthesis of (*S*)-timolol has also been achieved using hydrolytic kinetic resolution as well as asymmetric dihydroxylation routes in 90% ee and 56% ee, respectively.

1. Introduction

The β-adrenergic antagonist drug timolol, [(*S*)-(−)-3-(3-*tert*-butylamino-2-hydroxypropoxy)-4-(*N*-morpholino)-1,2,5-thiadiazole, **1**], like propranolol and a number of other β-blockers, has been shown to be effective in humans for the treatment of hypertension and angina pectoris.[1] In addition, timolol has been marketed recently for the treatment of glaucoma, based on its ability to lower intraocular pressure when administered directly into the eye.[2] The absolute configurations of (*S*)-timolol hemihydrate and (*S*)-timolol *O,O*-diacetyl-(*R,R*)-tartaric acid monoester were determined by single crystal X-ray diffraction.[3] The β-blocker activity of **1** resides mainly in one of the enantiomers, the levorotatory hemimaleate salt.[4] All of the syntheses described in the literature for (*S*)-timolol make use of a C_3-synthon via epichlorohydrin, glycidol, and related chirons[1b,5] and chemo-enzymatic approaches.[6] The main drawback of these synthetic methods is the loss of one-half of the expensive 1,2,5-thiadiazole unit during the resolution step, coupled with the low enantiomeric excess of (*S*)-timolol obtained. In this communication, we describe our results on the enantioselective synthesis of (*S*)-timolol (**1**) from readily available starting materials and employing two reliable asymmetric catalytic methods i.e., asymmetric dihydroxylation (SAD)[7] of allyl amines and kinetic resolution of terminal epoxides with phenolic compounds[8] as the chirality inducing steps (Schemes 2 and 3).

2. Results and discussion

Retrosynthetic analysis of timolol (**1**) reveals that chiral epoxide **2** could be visualized as a key intermediate, which is readily obtained by the O-alkylation of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (**4**) with epichlorohydrin (Scheme 1). The Sharpless asymmetric dihydroxylation (SAD) of nitrogen bearing olefins such as amides, azides, and *N*-protected allylic/homoallylic amines has emerged as one of the most promising methods for the preparation of optically pure amino alcohols.[9] For the synthesis of (*S*)-timolol, the starting material, *N*-*tert*-butyl allylamine (**5**) was readily prepared in 90% overall yield via protection of *tert*-butylamine with $(Boc)_2O$, followed by allylation with allylbromide in the presence of NaH. Allyl amine **5** was then subjected to Os-catalyzed asymmetric dihydroxylation using $(DHQ)_2$-PHAL as ligand to produce the corresponding chiral diol **6** in 93% yield {$[\alpha]_D^{25}$ −2.90 (*c* 2, EtOH)}. Several



Scheme 1. Retrosynthetic analysis of (*S*)-timolol.

Keywords: Asymmetric reactions; Diols; Kinetic resolution; Epoxides; Oxazolidinone.
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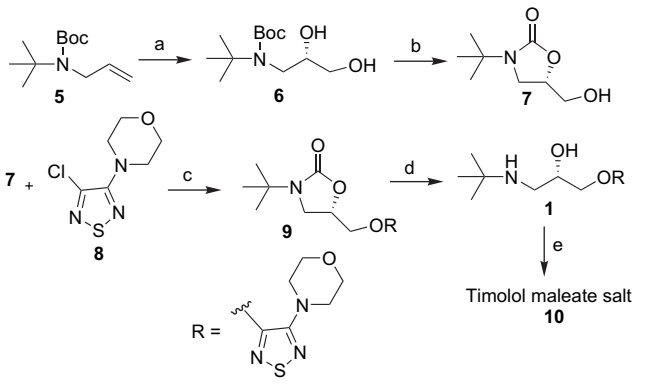
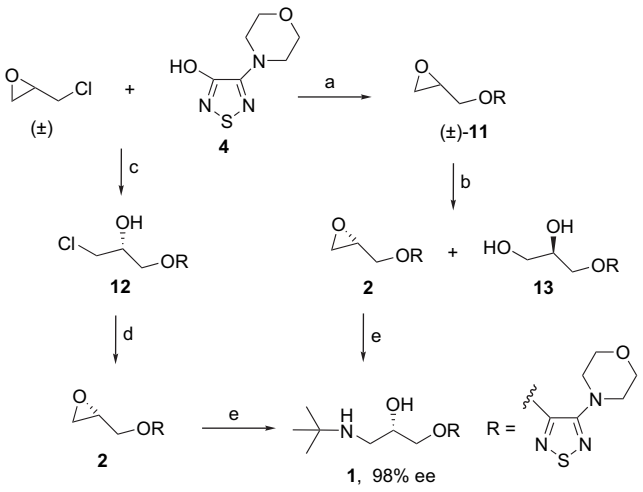


Scheme 2. Reagents and conditions: (a) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 0–25 °C, 24 h, 93%, 56% ee; (b) K_2CO_3, MeOH, reflux, 5 h, 95%; (c) *t*-BuOK, *t*-BuOH, 25 °C, 12 h, 75%; (d) 1 N NaOH, MeOH, 90%; (e) maleic acid, THF, 25 °C, 1 h, 85%.



Scheme 3. Reagents and conditions: (a) *t*-BuOK, THF, 5 h, 95%; (b) (*S,S*)-salen–cobalt(II) (0.5 mol %), AcOH (2 mol %), THF, H_2O (0.55 equiv), 0 °C, 14 h (46%, 90% ee for **2** and 45% for **13**); (c) (*R,R*)-(salen)-$Co[OC(CF_3)_3]$ (0.044 equiv), epichlorohydrin (2.5 equiv), *tert*-butyl methyl ether, 12 h, 86%, 98% ee; (d) *t*-BuOK, THF, 0–25 °C, 1 h, 97%; (e) *t*-$BuNH_2$, reflux, 30 h, 66%.

attempts to prepare the cyclic sulfate[10] from the diol **6** had failed probably due to its unstable nature. However, when the diol **6** was subjected to treatment with K_2CO_3 in MeOH under reflux, 2-oxazolidinone **7**[9a] was obtained in 95% yield and 56% ee (determined by ^{1}H NMR analysis of its Mosher's ester **14**). Oxazolidinone **9** was obtained by O-alkylation of the hydroxy compound **7** with 3-chloro-4-(*N*-morpholino)-1,2,5-thiadiazole (**8**).[5g] It was then hydrolyzed using 1 N NaOH in methanol[12] to furnish timolol (**1**), which was isolated as its maleate salt **10**[5g] in 85% yield and 56% ee (determined by chiral HPLC using OD-H column) {$[\alpha]_D$ −6.45 (*c* 4, 1 N aq HCl); lit.[5g] $[\alpha]_D$ −11.52 (*c* 4, 1 N aq HCl)} (Scheme 2).

Although the asymmetric dihydroxylation route to (*S*)-timolol was facile and high yielding, it suffers from low enantioselectivity. Hence, we focused on a new strategy, which involves preparing the racemic epoxide **11**, followed by Jacobsen's hydrolytic kinetic resolution (HKR).[13] Thus, the racemic epoxide **11**, prepared by the O-alkylation of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (**4**) with epichlorohydrin in excellent yield, was subjected to hydrolytic kinetic resolution[13] [(*S,S*)-salen–cobalt(II) (0.5 mol %), AcOH (2 mol %), THF, distilled H_2O (0.55 equiv), 0 °C, 14 h] to afford chiral epoxide **2** in 46% yield and 90% ee {$[\alpha]_D$ +23.0 (*c* 1, $CHCl_3$); lit.[6,5f] $[\alpha]_D$ +25.6 (*c* 1, $CHCl_3$)} along with its diol **13** in 45% yield. The chiral epoxide **2** was readily separated from its diol **13** by simple column chromatographic purification. Finally, the regiospecific ring opening of the epoxide **2** with *tert*-butylamine[5b] afforded (*S*)-timolol **1**, which was isolated as its maleate salt **10** in 85% yield and 90% ee (determined by chiral HPLC using an OD-H column) {$[\alpha]_D$ −10.36 (*c* 4, 1 N aq HCl); lit.[5g] $[\alpha]_D$ −11.52 (*c* 4, 1 N aq HCl)} (Scheme 3).

Although the optical purity of (*S*)-timolol increased considerably in HKR route, the methodology has the disadvantage of losing half of the valuable epoxide **11**. Hence, the recent methodology of kinetic resolution of terminal epoxides via enantioselective ring opening with phenolic substrates[8] was attempted. The cheaper and readily accessible (±)-epichlorohydrin renders kinetic resolution of its epoxide with phenolic substrates as a potentially attractive route for the preparation of chiral epoxide **2** using active Co(salen) complex as the chiral catalyst. Thus, the reaction of 2.5 equiv of (±)-epichlorohydrin with 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (**4**) in the presence of (*R,R*)-(salen)$Co[OC(CF_3)_3]$ complex (0.044 equiv) in *tert*-butyl methyl ether at 25 °C led to isolation of (2*R*)-1-chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (**12**) in 86% yield based on hydroxy thiadiazole **4** and 98% enantiomeric excess {$[\alpha]_D$ +6.88 (*c* 1, $CHCl_3$); lit.[6] $[\alpha]_D$ −6.1 (*c* 1, $CHCl_3$) for the (*S*)-isomer}. The chlorohydrin **12** was then converted to epoxide **2** in 97% yield (*t*-BuOK, THF, 0 °C). Finally, the chiral epoxide **2** was subjected to regiospecific ring opening with *tert*-butylamine to afford (*S*)-timolol, which was isolated as its maleate salt **10** in 85% yield and 98% ee (determined by chiral HPLC using an OD-H column) {$[\alpha]_D$ −11.3 (*c* 4, 1 N aq HCl); lit.[5g] $[\alpha]_D$ −11.52 (*c* 4, 1 N aq HCl)} (Scheme 3). The physical and spectroscopic data of maleate salt of **1** were in complete agreement with the reported values.[5g]

3. Conclusion

In conclusion, the asymmetric synthesis of (*S*)-timolol, an important drug for the treatment of *glaucoma* and *ocular hypertension*, has been achieved in a lesser number of steps with excellent overall yield (55%) and high enantiomeric excess (98%) using kinetic resolution of cheap and readily available (±)-epichlorohydrin with 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (**4**) catalyzed by the (*R,R*)-(salen)-$Co[OC(CF_3)_3]$ complex.

4. Experimental

4.1. General

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 a Shimadzu FTIR-8400 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 spectrometer. Elemental analysis was carried out on a Carlo Erba CHNS-O analyzer. Enantiomeric excess was determined by chiral HPLC.

4.1.1. (*S*)-(−)-*N*-Boc-3-*tert*-butylamino-1,2-propane diol (6). A mixture of $K_3Fe(CN)_6$ (2.1 g, 6.4 mmol), K_2CO_3 (0.89 g, 6.4 mmol), and $(DHQ)_2$-PHAL (0.038 g, 0.04 mmol) in *t*-BuOH/H_2O (1:1, 40 mL) was stirred for 10 min at 25 °C. It was then cooled to 0 °C and a solution of OsO_4 (50 μL, 0.02 mmol, 0.5 M solution in toluene) was added. The resulting reaction mixture was stirred at 0 °C for 5 min and then the olefin **5** (0.450 g, 2.1 mmol) was added. The reaction mixture was stirred at 25 °C for 18–24 h (monitored by TLC). It was quenched with sodium sulfite (2.0 g) and extracted with ethyl acetate (4×20 mL). Combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo to give the crude product, which was purified by column chromatography (30% EtOAc/petroleum ether) to give pure diol **6** (0.482 g, 93%) as a colorless thick syrup. $[\alpha]_D^{25}$ −2.90 (*c* 2, EtOH); R_f (30% EtOAc/petroleum ether) 0.43; IR: ($CHCl_3$) ν_{max}: 443, 749, 861, 920, 953, 1285, 1393, 1452, 1688, 1710, 2902, 2977, 3396; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.81–3.32 (m, 5H), 2.99–2.75 (br s, 2H), 1.48 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.7, 80.6, 72.4, 63.3, 55.8, 46.9, 29.9, 28.5. Anal. Calcd for $C_{12}H_{25}NO_4$ (247.33): C, 58.27; H, 10.19; N, 5.66%. Found: C, 58.20; H, 10.26; N, 5.70%.

4.1.2. (*S*)-3-*tert*-Butyl-5-(hydroxymethyl)oxazolidin-2-one (7). A mixture of diol **6** (0.988 g, 4 mmol) and K_2CO_3 (0.828 g, 6 mmol) in dry MeOH (10 mL) was refluxed for 5 h. The resulting reaction mixture was cooled to room temperature and the solvent was evaporated in vacuo. Work-up (extraction with 30 mL of EtOAc) and purification by column chromatography (30% EtOAc/petroleum ether) gave 2-oxazolidinone **7** (0.657 g, 95%) as a colorless oil. $[\alpha]_D^{25}$ −2.5 (*c* 2, EtOH); R_f (30% EtOAc/petroleum ether) 0.46; IR: ($CHCl_3$) ν_{max}: 491, 677, 919, 1066, 1227, 740, 3026 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.50–4.39 (m, 1H), 3.85–3.50 (m, 4H), 3.40–3.31 (br s, 1H), 1.36 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.0, 72.4, 62.4, 53.2, 44.5, 27.2. Anal. Calcd for $C_8H_{15}NO_3$ (173.2): C, 55.47; H, 8.73; N, 8.09%. Found: C, 55.54; H, 8.60; N, 8.14%.

4.1.3. Preparation of Mosher's ester of (*S*)-3-*tert*-butyl-5-(hydroxymethyl)oxazolidin-2-one (14). A two-neck 10 mL flask with septum was charged with *N,N′*-dicyclohexylcarbodiimide (DCC) (44 mg, 0.21 mmol), catalytic amount of 4-dimethylaminopyridine (DMAP), and CH_2Cl_2 (2 mL) under argon atmosphere. The flask was allowed to cool at 0 °C for 10 min and a solution of alcohol **7** (31 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was introduced through a syringe. It was allowed to stir for additional 10 min, followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 (2 mL). This reaction mixture was then stirred at 0 °C for additional 1 h and then at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated sodium bicarbonate solution (50 mL), dried over Na_2SO_4, and then concentrated in vacuo to give Mosher's ester of the alcohol **7** (53 mg, 70%) as a colorless thick syrup. $[\alpha]_D^{25}$ −4.8 (*c* 0.8, MeOH); ^{1}H NMR ($CDCl_3$) δ: 7.32–7.49 (m, 5H), 4.65–4.45 (m, 1H), 3.98–3.55 (m, 4H), 3.52 (s, 3H), 1.38 (s, 9H).

4.1.4. (*S*)-5-((4-Morpholino-1,2,5-thiadiazol-3-yloxy)-methyl)-3-*tert*-butyloxazolidin-2-one (9). To a mixture of 2-oxazolidinone **7** (0.432 g, 2.5 mmol) and 3-chloro-4-morpholino-1,2,5-thiadiazole[11] (0.512 g, 2.5 mmol) in *tert*-butyl alcohol (5 mL) at 25 °C was added potassium *tert*-butoxide (0.336 g, 3 mmol). The mixture was stirred for 12 h. The solvent was evaporated in vacuo and the residue was neutralized by 6 N HCl. Work-up (extraction with 30 mL of EtOAc) and purification by column chromatography (40% EtOAc/petroleum ether) gave oxazolidinone **9** (0.641 g, 75%) as a white solid. Mp 86–87 °C; $[\alpha]_D^{25}$ −3.4 (*c* 2, EtOH); R_f (40% EtOAc/petroleum ether) 0.39; IR: ($CHCl_3$) ν_{max}: 472, 685, 782, 1227, 1760, 3046 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.80–4.65 (m, 1H), 4.54 (br s, 2H), 3.91–3.40 (m, 10H), 1.36 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.8, 152.9, 149.7, 70.3, 69.2, 66.3, 53.5, 47.8, 44.9, 27.3. Anal. Calcd for $C_{14}H_{22}N_4O_4S$ (342.41): C, 49.11; H, 6.48; N, 16.36; S, 9.36%. Found: C, 49.25; H, 6.31; N, 16.42; S, 9.31%.

4.1.5. (2*S*)-1-(*tert*-Butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (1, (*S*)-timolol). To a stirred solution of oxazolidinone **9** (0.684 g, 2 mmol) in methanol (20 mL) was added 1 N NaOH (10 mL). The reaction mixture was stirred for 8 h, the residue filtered off, and the solvent removed in vacuo to give the crude product, which was purified by column chromatography (20% MeOH/Et_2O) to give timolol **1** (0.569 g, 90%) as a colorless thick syrup. $[\alpha]_D^{25}$ −1.93 (*c* 1, $CHCl_3$); R_f (30% MeOH/Et_2O) 0.52; IR (neat) ν_{max}: 768, 957, 1122, 1228, 1311, 1497, 2855, 2964, 3295 (br), 3412 (br) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.48 (dd, *J*=11.1, 4.1 Hz, 1H), 4.37 (dd, *J*=11.1, 5.6 Hz, 1H), 3.94 (m, 1H), 3.79–3.83 (t, *J*=4.9 Hz, 4H), 3.50–3.55 (t, *J*=5.4 Hz, 4H), 2.82 (dd, *J*=4.0, 12.1 Hz, 1H), 2.59 (dd, *J*=7.9, 12.1 Hz, 1H), 2.09 (br s, 1H), 1.10 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.7, 150.0, 72.7, 68.0, 66.3, 50.3, 47.8, 44.3, 28.9. Anal. Calcd for $C_{13}H_{24}N_4O_3S$ (316.41): C, 49.35; H, 7.65; N, 17.71; S, 10.13%. Found: C, 49.48; H, 7.53; N, 17.79; S, 10.01%.

4.1.6. (*S*)-(−)-3-(3-*tert*-Butylamino-2-hydroxypropoxy)-4-(*N*-morpholino)-1,2,5-thiadiazole ((*S*)-1 hemimaleate salt, 10). To a stirred solution of timolol **1** (0.418 g, 1.3 mmol) in THF (5 mL) was added a solution of maleic acid (0.151 g, 1.3 mmol) in THF (3 mL). The mixture was seeded and aged for 1 h at 25 °C. The resulting salt was filtered, washed with THF (3 mL), and dried at 50 °C in vacuo to give hemimaleate salt **10** (0.477 g, 85%) as a white solid. Mp 198–201 °C {lit.[5g] mp 201–202 °C}; $[\alpha]_D^{25}$ −6.45 (*c* 4, 1 N aq HCl), 56% ee {lit.[5g] $[\alpha]_D^{25}$ −11.52 (*c* 4, 1 N aq HCl)}; HPLC: 56% ee, Chiracel OD-H, λ=297 nm, diethyl amine/2-propanol/hexane (1:40:960), 1 mL/min, retention time: (*R*)-enantiomer 9.07 min, (*S*)-enantiomer 11.33 min; IR (neat) ν_{max}: 443, 749, 861, 920, 953, 1285, 1393, 1452, 1562, 1688, 1710, 2902, 2977, 3396 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.36 (br s, 1H), 6.01 (s, 2H,

CH=CH), 4.38 (m, 2H), 4.19 (m, 1H), 3.69 (t, J=4.2 Hz, 4H), 3.44 (t, J=5.0 Hz, 4H), 3.09–3.16 (m, 1H), 2.82–2.92 (m, 1H), 2.49 (m, 1H), 1.27 (s, 9H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 167.5, 153.4, 149.9, 136.1, 72.1, 65.7, 65.1, 56.5, 47.6, 43.7, 25. Anal. Calcd for $C_{17}H_{28}N_4O_7S$ (432.49): C, 47.21; H, 6.53; N, 12.95; S, 7.41%. Found: C, 47.31; H, 6.54; N, 12.89; S, 7.35%.

4.1.7. 4-{4-[Oxiran-2-ylmethoxy]-1,2,5-thiadiazol-3-yl}-morpholine (11). To a stirred solution of epichlorohydrin (2 g, 21.7 mmol) and 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole **4** (4 g, 21.7 mmol) in anhydrous THF (70 mL) at 0 °C was added potassium *tert*-butoxide (4.8 g, 43.4 mmol). The reaction mixture was stirred at 25 °C for 5 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with Et_2O (3×10 mL). The collected organic phases were washed with brine (50 mL) and dried (Na_2SO_4). The organic layer was concentrated and purified by chromatography (10% EtOAc/petroleum ether) to give **11** (5 g, 95%) as a white solid. Mp 112–114 °C {lit.[5f] mp 113–114 °C}; R_f (10% EtOAc/petroleum ether) 0.48; IR (KBr) ν_{max}: 537, 643, 855, 906, 1117, 1497, 2865, 2925, 2980 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.70 (dd, J=11.7, 3.1 Hz, 1H), 4.22 (dd, J=11.7, 6.2 Hz, 1H), 3.77 (t, J=5.1 Hz, 4H), 3.48 (t, J=5.1 Hz, 4H), 3.37–3.29 (m, 1H), 2.86 (t, J=4.7 Hz, 1H), 2.67 (dd, J=4.7, 2.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.2, 149.6, 71.3, 66.2, 49.2, 47.8, 45.8. Anal. Calcd for $C_9H_{13}N_3O_3S$ (243.28): C, 44.43; H, 5.39; N, 17.27; S, 13.18%. Found: C, 44.59; H, 5.50; N, 17.15; S, 13.09%.

4.1.8. 4-{4-[(2*S*)-Oxiran-2-ylmethoxy]-1,2,5-thiadiazol-3-yl}morpholine (2). A mixture of (*S*,*S*)-salen–cobalt(II) catalyst (57 mg, 0.09 mmol), epoxide **11** (4.6 g, 19 mmol), and acetic acid (0.022 g, 0.38 mmol) was stirred under air at room temperature. After the red reaction mixture turned to a dark brown solution, the flask was cooled to 0 °C and dry THF (0.2 mL) and H_2O (0.2 mL) were added. After 2 h the reaction was allowed to warm to room temperature and stirred for 6 h. The solution of crude products was purified by column chromatography (10% EtOAc/petroleum ether) to give chiral epoxide **2** (2.12 g, 46%); $[\alpha]_D^{25}$ +23.0 (c 1, $CHCl_3$) {lit.[6,5f] $[\alpha]_D$ +25.6 (c 1, $CHCl_3$)}; R_f (10% EtOAc/petroleum ether) 0.48.

4.1.9. (2*S*)-1-(*tert*-Butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (1, (*S*)-timolol). To a stirred solution of chiral epoxide **2** (0.972 g, 4 mmol) in *tert*-butylamine (10 mL, 95 mmol) was added KI (0.08 g, 0.5 mmol). The reaction mixture was refluxed for 72 h. Thereafter, the solution was cooled, the solvent removed in vacuo to give crude product, which was purified by column chromatography (20% MeOH/Et_2O) to afford (*S*)-timolol **1** (0.834 g, 66%) as a colorless thick syrup.

4.1.10. (*S*)-(−)-3-(3-*tert*-Butylamino-2-hydroxypropoxy)-4-(*N*-morpholino)-1,2,5-thiadiazole ((*S*)-1 hemimaleate salt, 10). Following the procedure described in Section 4.1.6, **10** was obtained. $[\alpha]_D^{25}$ −10.36 (c 4, 1 N aq HCl) {lit.[5g] $[\alpha]_D^{25}$ −11.52 (c 4, 1 N aq HCl)}; HPLC: 90% ee, Chiracel OD-H, λ=297 nm, diethyl amine/2-propanol/hexane (1:40:960), 1 mL/min, retention time: (*R*)-enantiomer 9.07 min, (*S*)-enantiomer 11.33 min.

4.1.11. (2*R*)-1-Chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (12). To a mixture of (*R,R*)-(salen)Co[OC(CF_3)$_3$] complex (86 mg, 0.100 mmol), epichlorohydrin (0.462 g, 5.00 mmol), TBME (0.15 mL), and 3 Å MS (100 mg) at room temperature was added phenol **4** (0.374 g, 2.00 mmol). The reaction was stirred at room temperature until GC analysis indicated complete conversion of phenol, at which time pyridinium *p*-toluenesulfonate (75 mg, 0.30 mmol) was added. The reaction mixture was filtered through a pad of silica and washed with 50% EtOAc/hexanes (15 mL). The filtrate was concentrated in vacuo to give the crude product, which was purified by chromatography (20% EtOAc/petroleum ether) to give **12** (0.480 g, 86%) as a pale yellow solid. Mp 59–61 °C {lit.[6] mp 58–61 °C}; $[\alpha]_D^{25}$ +6.88 (c 1, $CHCl_3$) {lit.[6] $[\alpha]_D$ −6.1 (c 1, $CHCl_3$) for the (*S*)-enantiomer}; R_f (20% EtOAc/petroleum ether) 0.41; IR ($CHCl_3$) ν_{max}: 953, 1113, 1298, 1493, 2854, 2923, 2964, 3563 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.54 (d, J=4.54 Hz, 2H), 4.17–4.28 (m, 1H), 3.79 (t, J=4.53 Hz, 4H), 3.63–3.67 (m, 2H), 3.49 (t, J=5.03 Hz, 4H), 2.83 (d, J=5.44 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.4, 149.8, 71.5, 69.5, 66.4, 47.9, 46.0. Anal. Calcd for $C_9H_{14}ClN_3O_3S$ (279.74): C, 38.64; H, 5.04; N, 15.02; S, 11.46%. Found: C, 38.53; H, 5.15; N, 15.14; S, 11.38%.

4.1.12. 4-{4-[(2*S*)-Oxiran-2-ylmethoxy]-1,2,5-thiadiazol-3-yl}morpholine (2). To a stirred solution of **12** (230 mg, 0.82 mmol) in anhydrous THF (5 mL) at 0 °C was added potassium *tert*-butoxide (184 mg, 1.64 mmol). The reaction mixture was stirred for 1 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3×10 mL). The collected organic phases were washed with brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated in vacuo to afford chiral epoxide **2** (194 mg, 97%) as a white solid, which was used without further purification. $[\alpha]_D^{25}$ 28.9 (c 1, $CHCl_3$) {lit.[6,5f] $[\alpha]_D$ +25.6 (c 1, $CHCl_3$)}.

4.1.13. (2*S*)-1-(*tert*-Butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (1, (*S*)-timolol). Following the procedure described in Section 4.1.9, **1** was obtained. $[\alpha]_D^{25}$ −3.38 (c 1, $CHCl_3$).

4.1.14. (*S*)-(−)-3-(3-*tert*-Butylamino-2-hydroxypropoxy)-4-(*N*-morpholino)-1,2,5-thiadiazole ((*S*)-1 hemimaleate salt, 10). Following the procedure described in Section 4.1.6, **10** was obtained. $[\alpha]_D^{25}$ −11.3 (c 4, 1 N aq HCl) {lit.[5g] $[\alpha]_D^{25}$ −11.52 (c 4, 1 N aq HCl)}; HPLC: 98% ee, Chiracel OD-H, λ=297 nm, diethyl amine/2-propanol/hexane (1:40:960), 1 mL/min, retention time: (*R*)-enantiomer 9.07 min, (*S*)-enantiomer 11.33 min.

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