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Organocatalytic enantioselective synthesis of β-blockers: (*S*)-propranolol and (*S*)-naftopidil

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ABSTRACT

An efficient enantioselective synthesis of β-adrenergic blockers (*S*)-propranolol and (*S*)-naftopidil with >98% ee using an L-proline-catalyzed α-aminoxylation of an aldehyde as a key step is described.

1. Introduction

The synthesis of enantiomerically pure bioactive molecules was explored in recent years because (i) biological activity is often associated with only one enantiomer; and (ii) enantiomers may exhibit very different types of activity, both of which may be beneficial or one may be beneficial and the other undesirable.[1] Due to this, the aim for enantiomerically pure molecules has intensified during recent years.

1,2-Diols are versatile staring materials for the synthesis of bioactive molecules.[2] Different methods for the synthesis of enantiopure 1,2-diols have been investigated[3] which include chemical kinetic resolution via diastereomer formation, enzymatic resolution, and asymmetric synthesis.

In recent years, organocatalytic asymmetric synthesis has rapidly grown in organic chemistry and has provided several new methods for obtaining chiral building blocks.[4] Organocatalytic asymmetric α-aminoxylation of aldehydes has emerged as a powerful method for the preparation of enantiopure 1,2-diols with good yields.[5] The reaction has several advantages from a practical point of view, which include inexpensive and commercially available proline as the catalyst, the commercial availability of both forms of proline, low catalyst loadings (10–20 mol %), and the good to excellent yield of enantiomerically enriched 1,2-diols.

Many routes have been developed for the synthesis of 3-aryloxy-1,2-propanediol but the organocatalytic asymmetric α-aminoxylation of aldehydes has not yet been utilized. In this context we wish to demonstrate a practical enantioselective synthesis of 3-aryloxy-1,2-propanediol using a proline-catalyzed α-aminoxylation of an aldehyde. The generality of this strategy is illustrated in enantioselective synthesis of the β-blockers (*S*)-propranolol **1**[6,7] and (*S*)-naftopidil **2**[6,7] (Fig. 1). β-Adrenergic blocking agents of the 3-(aryloxy)-2-hydroxy-(*N*-isopropyl)-propylamine type, for example, (*S*)-propranolol **1**, are such a group of drugs whose biological activity is associated with only the (*S*)-enantiomer, that is, (*S*)-propranolol **1** is 100-fold more potent than the (*R*)-isomer.[8]

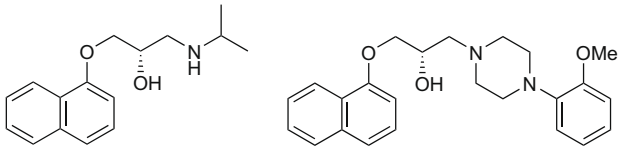

Figure 1.

2. Results and discussion

According to our proposed retrosynthetic analysis (Scheme 1), we envisaged that the aforementioned β-blockers can be easily synthesized from α-naphthol by synthetic manipulations with L-proline-catalyzed asymmetric α-aminoxylation of aldehydes as the key step.

As per the retrosynthetic analysis, we envisaged the L-proline-catalyzed α-aminoxylation of aldehyde strategy for introduction of chirality in the molecule. Thus, we initiated the synthesis of (*S*)-propranolol **1** and (*S*)-naftopidil **2** from commercially available α-naphthol and 3-bromopropanol. α-Naphthol and 3-bromopropanol in aqueous NaOH solution were refluxed for 6 h to furnish alcohol **4** in 67% yield. Oxidation of alcohol **4** was carried out with IBX[9] to afford aldehyde **5** in 89% yield. Aldehyde **5** was subjected to L-proline (20 mol %)-catalyzed asymmetric α-aminoxylation[5a] with nitrosobenzene at −20 °C for 24 h and the subsequent reduction was carried out with $NaBH_4$ in methanol in one pot. The crude aminoxy intermediate was subjected to Pd/C-catalyzed hydrogenolysis[5b] without purification to obtain diol **6** in 79% yield over two steps and >98% enantiomeric purity. The enantiomeric purity was determined by chiral HPLC analysis. Diol **6** was then converted to

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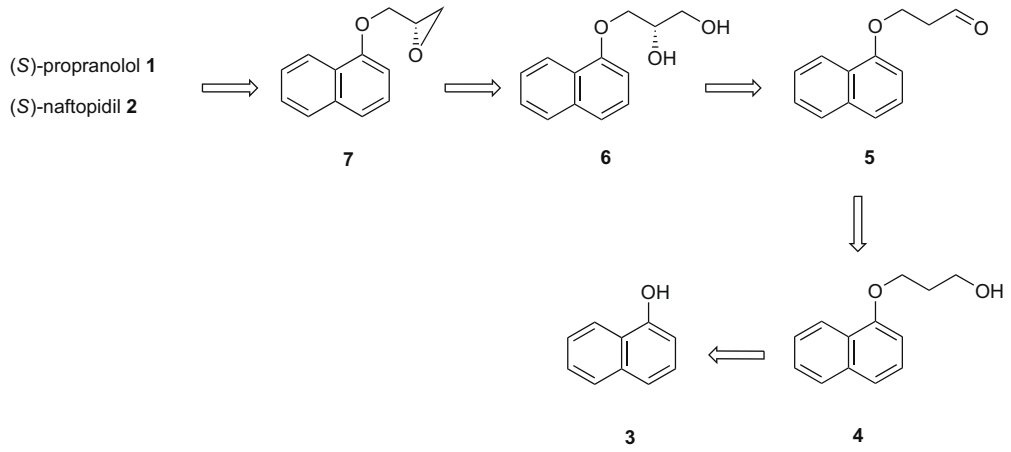
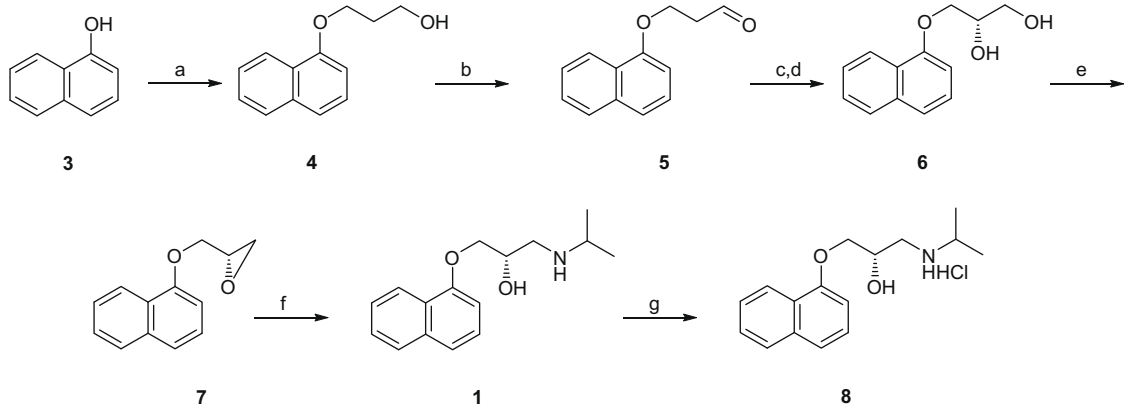


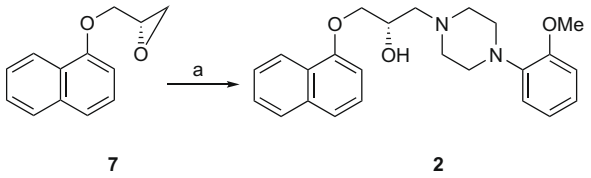
Scheme 1. Retrosynthetic analysis of (*S*)-propranolol and (*S*)-naftopidil.



Scheme 2. Reagents and conditions: (a) 3-bromopropanol, 10% aq NaOH, reflux, 6 h, 67%; (b) IBX, DMSO, rt, 2 h, 89%; (c) PhNO, L-proline, CH_3CN, −20 °C, 24 h then $NaBH_4$, MeOH, −20 °C, 0.5 h; (d) 10% Pd/C, MeOH, H_2, rt, 6 h, for two steps 79%; (e) PPh_3, DIAD, reflux, 6 h, 67%; (f) isopropylamine, CH_2Cl_2, rt, 12 h, 83%; (g) Et_2O, HCl gas, 1 h, 86%.

epoxide **7** using Mitsunobu reaction[10] conditions using PPh_3 and DIAD in one step in 67% yield. Epoxide **7** was then stirred with isopropylamine in CH_2Cl_2 at room temperature for 12 h to afford (*S*)-propranolol **1** in 83% yield and >98% ee. (*S*)-Propranolol **1** on treatment with anhydrous HCl gas afforded (*S*)-propranolol hydrochloride **8** (Scheme 2).

Finally, synthesis of (*S*)-naftopidil **2** was accomplished from epoxide **7**. Epoxide **7** and 1-(2-methoxyphenyl)-piperazine were refluxed in 2-propanol for 32 h, to afford (*S*)-naftopidil **2** in 85% yield and >98% ee (Scheme 3).



Scheme 3. Reagents and conditions: (a) 1-(2-methoxyphenyl)-piperazine, CH_2Cl_2, rt, 32 h, 85%.

3. Conclusion

In conclusion, we have achieved a highly enantioselective, efficient synthesis of the β-adrenergic blockers: (*S*)-(−)-propranolol (overall yield 26%) and (*S*)-(+)-naftopidil (overall yield 26%) employing the proline-catalyzed asymmetric α-aminoxylation of aldehyde as a key step and source of chirality. Excellent yields, simple and environmentally friendly procedures, and the easy availability of starting materials are some of the salient features of this approach.

4. Experimental

4.1. General information

Reagents and solvents were of analytical grade or were purified by standard procedures prior to use. IR spectra were recorded on a Perkin–Elmer 68B or a Perkin–Elmer 1615 FT infrared spectrophotometer. ^1H (200 MHz/400 MHz) and ^{13}C (50 MHz/100 MHz) NMR spectra were recorded on a Bruker AC-200/AC-400 spectrometer. The carbon resonances were assigned by use of DEPT experiments. Mass spectra were recorded at an ionization energy 70 eV on API Q STARPULSAR spectrometer using electrospray ionization. Microanalytical data were obtained on a Carlo-Erba CHNS–O EA 1108 elemental analyzer. Optical rotations were measured on Jasco P-1020 polarimeter. Progress of the reactions was monitored by TLC on Merck Silica Gel 60 F254 precoated plates, and compounds were visualized by fluorescence quenching, by use of I_2, or by charring after treatment with a *p*-anisaldehyde–AcOH–H_2SO_4 mixture in EtOH. Column chromatography was performed on flash silica gel (230–400 mesh size).

4.2. 3-(1′-Naphthoxy)propanol 4

To a stirring solution of α-naphthol **3** (2.880 g, 20 mmol) in 10% aqueous NaOH solution (20 mL) was added 3-bromopropanol (3.056 g, 22 mmol). After refluxing for 6 h, the reaction mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with water (1 × 50 mL), brine, dried over anhydrous Na_2SO_4, filtered, and concentrated on a rotary evaporator under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel) using EtOAc–petroleum ether (15:85) as an eluent, to afford alcohol **4**. Yield: 2.706 g (67%); yellow oil; IR ($CHCl_3$) ν_{max} 3461, 3059, 3011, 2889, 2580, 1657, 1641, 1589, 735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.64 (br s, 1H), 2.13–2.25 (m, 2H), 3.97 (t, J = 5.94 Hz, 2H), 4.30 (t, J = 5.94 Hz, 2H), 6.83 (d, J = 8.46 Hz, 1H), 7.32–7.52 (m, 4H), 7.76–7.84 (m, 1H), 8.18–8.26 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.8, 59.7, 64.9, 104.5, 120.1, 121.6, 125.0, 125.3, 125.7, 126.2, 127.3, 134.3, 154.3 ppm.

4.3. 3-(1′-Naphthoxy)propanal 5

To solution of alcohol **4** (2.500 g, 12.37 mmol) in anhydrous dimethyl sulfoxide (16 mL) was added IBX (5.343 g, 18.55 mmol, 1.5 equiv). After stirring at room temperature for 2 h, the reaction mixture was diluted with water (10 mL), and then with diethyl ether (100 mL). The diethyl ether layer was filtered through bed of Celite. The filtrate was washed with water (50 mL), brine, dried over anhydrous Na_2SO_4, filtered, and concentrated on rotary evaporator under reduced pressure to afford aldehyde **5**. Yield: 2.202 g (89%); yellow oil; IR ($CHCl_3$) ν_{max} 3061, 3011, 2957, 2837, 2356, 2045, 1721, 1587, 1511, 1257, 749 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.99–3.06 (m, 2H), 4.48 (t, J = 6.07 Hz, 2H), 6.84 (d, J = 8.47 Hz, 1H), 7.33–7.53 (m, 4H), 7.76–7.84 (m, 1H), 8.14–8.22 (m, 1H), 9.94 (t, J = 1.64 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.0, 61.7, 104.6, 120.6, 121.7, 125.2, 125.3, 125.6, 126.4, 127.3, 134.3, 153.9, 200.1 ppm.

4.4. (*S*)-3-(1′-Naphthoxy)propane-1,2-diol 6

To a solution of aldehyde **5** (2.0 g, 10 mmol) and nitrosobenzene (1.070 g, 10 mmol) in CH_3CN (50 mL) was added L-proline (0.230 g, 2 mmol, 20 mol %) at −20 °C. The reaction mixture was allowed to stir at the same temperature for 24 h followed by addition of MeOH (25 mL) and $NaBH_4$ (0.570 g, 15 mmol) to the reaction mixture, which was stirred for 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (3 × 50 mL) and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator under reduced pressure to afford crude aminoxy alcohol. To a solution of crude aminoxy alcohol in MeOH was added 10% Pd/C (100 mg) carefully. The reaction mixture was then stirred under a hydrogen atmosphere (1 atm of H_2) for 6 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a Celite pad and then concentrated to near dryness. Purification by flash column chromatography (silica gel) using EtOAc–petroleum ether (40:60) as an eluent afforded diol **6**. Yield: 1.722 g (79%); white solid; mp 113–115 °C {Lit.[7p] mp 113–114 °C}; $[\alpha]_D^{25}$ = +6.7 (c 1.05 MeOH). {Lit.[7g] $[\alpha]_D$ = +6.7 (c 1.1 MeOH)}; ee >98% [Chiral HPLC analysis: Kromasil 5-Cellucoat (250 × 4.6 mm) column; eluent: ethanol–hexane 20:80; flow rate: 0.5 mL/min, detector: 254 nm t_R = 15.13 min, t_S = 16.85 min]; IR ($CHCl_3$) ν_{max} 3443, 3024, 2887, 2589, 1647, 1635, 1597, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.34 (br s, 2H), 3.84–3.97 (m, 2H), 4.22–4.24 (m, 2H), 4.26–4.31 (m, 1H), 6.83 (d, J = 7.53 Hz, 1H), 7.36–7.40 (m, 1H), 7.46–7.53 (m, 4H), 7.81–7.83 (m, 1H), 8.21–8.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.8, 69.2, 70.5, 105.0, 120.9, 121.5, 125.3, 125.4, 125.7, 126.5, 127.6, 134.5, 154.0 ppm. Elemental Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.47; H, 6.39.

4.5. (*S*)-2-((1′-Naphthoxy)-methyl)oxirane 7

To a stirred solution of diol **6** (1.500 g, 6.88 mmol) in anhydrous 1,4-dioxane (25 mL) was added PPh_3 (2.703 g, 10.32 mmol, 1.5 equiv) at 70 °C for 10 min. Diisopropyl azodicarboxylate (2.084 g, 10.32 mmol, 1.5 equiv) diluted in 20 mL of anhydrous 1,4-dioxane was added dropwise and the reaction mixture was stirred at the same temperature for further 40 min. The reaction mixture was cooled to room temperature, washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated on a rotary evaporator under reduced pressure. Purification by flash column chromatography (silica gel) using EtOAc–petroleum ether (15:85) as an eluent afforded epoxide **7**. Yield: 0.921 g (67%); yellow oil; $[\alpha]_D^{25}$ = −34.0 (c 1.52, MeOH) {Lit.[7i] $[\alpha]_D^{25}$ = −33.9 (c 1.55, MeOH)}; IR ($CHCl_3$) ν_{max} 3443, 3420, 3031, 1265 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.84–2.88 (dd, J = 2.6, 4.9 Hz, 1H), 2.95–2.99 (m, 1H), 3.46–3.54 (m, 1H), 4.10–4.18 (dd, J = 5.5, 11.1 Hz, 1H), 4.37–4.44 (dd, J = 3.1, 10.9 Hz, 1H), 6.80 (d, J = 7.3 Hz, 1H), 7.32–7.53 (m, 4H), 7.76–7.84 (m, 1H), 8.26–8.34 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 44.4, 50.0, 68.7, 104.8, 120.6, 121.9, 125.1, 125.4, 125.6, 126.3, 127.3, 134.3, 154.0 ppm.

4.6. (*S*)-(−)-Propranolol 1

To a stirred solution of epoxide **7** (0.500 g, 2.5 mmol) in 10 mL dichloromethane was added slowly isopropylamine (1.475 g, 25 mmol). The reaction mixture was stirred for 30 h at room temperature, and then excess isopropylamine was removed under reduced pressure. The residue was diluted with water and extracted with EtOAc (2 × 25 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated on rotary evaporator under reduced pressure. Purification by flash column chromatography (silica gel) using EtOAc–petroleum ether (75:25) as an eluent afforded (*S*)-propranolol **1**. Yield: 0.537 g (83%), white solid; mp 71–72 °C {Lit.[7p] mp 72–73 °C}; $[\alpha]_D^{25}$ = −9.8 (c 0.55, EtOH) {Lit.[7p] $[\alpha]_D^{25}$ = −9.9 (c 0.5, EtOH)}; IR ($CHCl_3$) ν_{max} 3410, 3281, 3011, 2989, 1271 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.23 (d, J = 6.2 Hz, 6 H), 2.90–3.13 (m, 3H), 4.05–4.21 (m, 2H), 4.35–4.46 (m, 1H), 5.14 (br s, 2H), 6.73 (d, J = 7.2 Hz, 1H), 7.25–7.50 (m, 4H), 7.74–7.81 (m, 1H), 8.20–8.26 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.4, 49.0, 49.5, 67.4, 70.3, 104.8, 120.4, 121.7, 125.1, 125.3, 125.6, 126.2, 127.3, 134.2, 154.0 ppm; LC–MS: m/z = 260.17 (M^++1), 282.20 (M^++Na).

4.7. (*S*)-(−)-Propranolol hydrochloride 8

(*S*)-Propranolol **1** (0.500 g, 1.93 mmol) was dissolved in diethyl ether (20 mL) and treated with HCl gas. The resultant solid was filtered and recrystallization from methanol–ether afforded (*S*)-propranolol hydrochloride **8**. Yield: 0.490 g (86%), white crystals; mp 192–193 °C {Lit.[7f] mp 192–193.5 °C}; $[\alpha]_D^{25}$ = −25.8 (c 1.25, EtOH) {Lit.[7f] $[\alpha]_D^{25}$ = −25.7 (c 1.23, EtOH)}; ^1H NMR (200 MHz, D_2O): δ = 1.35 (d, J = 6.2 Hz, 6H), 3.29–3.42 (m, 2H), 3.45–3.55 (dd, J = 6.2, 12.2 Hz, 1H), 4.21–4.36 (m, 2H), 4.41–4.50 (m, 1H), 7.01 (d, J = 7.4 Hz, 1H), 7.47 (m, 1H), 7.52–7.63 (m, 3H), 7.92 (d, J = 7.4 Hz, 1H), 8.28 (d, J = 7.4 Hz, 1H); ^{13}C NMR (50 MHz, D_2O): δ = 22.9, 48.9, 49.6, 68.7, 70.7, 104.8, 120.5, 121.8, 125.1, 125.5, 126.3, 126.8, 127.4, 134.5, 154.2 ppm. Elemental Anal. Calcd for $C_{16}H_{22}ClNO_2$: C, 64.96; H, 7.50; N, 4.74. Found: C, 64.71; H, 7.66; N, 4.61.

4.8. (*S*)-(+)-Naftopidil 2

To a solution of epoxide **7** (0.400 g, 2 mmol) in anhydrous 2-propanol (10 mL) was added 1-(2-methoxyphenyl) piperazine (0.384 g, 2 mmol, 1 equiv) and the reaction mixture was refluxed for 32 h. After completion of the reaction, the solvent was removed

under reduced pressure and purification by flash column chromatography (silica gel) using EtOAc–petroleum ether (60:40) as an eluent afforded (*S*)-(+)-naftopidil **2**. Yield: 0.666 g (85%); yellow solid; mp 126–127 °C {Lit.[7o] mp 126–129 °C (dec)}; $[\alpha]_D^{25} = +4.7$ (*c* 1.55, MeOH) {Lit.[7o] $[\alpha]_D = +4.5$ (*c* 1.5, MeOH)}; IR ($CHCl_3$) ν_{max} 3403, 3031, 2977, 2907, 1261, 1225 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.70–2.79$ (m, 4H), 2.94 (t, $J = 5.2$ Hz, 2H), 3.10–3.18 (m, 4H), 3.87 (s, 3H), 4.15–4.19 (dd, $J = 5.0$, 9.5 Hz, 1H), 4.21–4.25 (dd, $J = 5.0$, 9.5 Hz, 1H), 4.28–4.34 (m, 1H), 6.84–6.89 (m, 2H), 6.92–6.97 (m, 2H), 7.01–7.04 (m, 1H), 7.36–7.40 (m, 1H), 7.44–7.50 (m, 3H), 7.80–7.82 (m, 1H), 8.29 (d, $J = 4.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 50.6$, 53.5, 55.3, 60.8, 65.5, 70.4, 104.8, 111.1, 118.1, 120.5, 120.9, 121.8, 122.9, 125.1, 125.5, 125.7, 126.3, 127.4, 134.4, 141.0, 152.1, 154.3 ppm. LC–MS: *m*/*z* = 393.36 (M^++1), 415.36 (M^++Na). Elemental Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found: C, 73.41; H, 7.14; N, 7.18.

Acknowledgments

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