# Convenient Synthesis of Enantiopure β-Adrenergic Blockers: (*R*)-Nifenalol, (*R*)-Denopamine, (*R*)-Dichloroisoproterenol and (*R*)-Pronethalol†

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Recently much attention on chiral drugs has been growing rapidly,[1] since the US Food and Drug Administration (FDA) first raised the topic of stereochemical regulation in its 1987 Drug Substance Guidelines.[2] It has been reported that single enantiomers of chiral drugs are often more potent or have less side effects compared to their racemates.[3] Pharmaceuticals bearing a structure unit of 2-amino-1-arylethanol such as nifenalol (**1**), denopamine (**2a**), dichloroisoproterenol (**3**) and pronethalol (**4**) are of great importance as β-adrenergic agonists in the therapy of asthma, bronchitis and congestive heart failure (Figure 1).[4] Among them, only (*R*)-isomers of **1** and **2** act as β-adrenergic blockers which are effective in the treatment of cardiovascular disease.[5] Also, (*R*)-isomers of **3** and **4** showed more potent pharmacological activity than their racemates.[6a] Asymmetric syntheses of these chiral drugs have been reported earlier with several approaches such as classical resolution of the racemates with resolving agents,[6] and regioselective aminolysis of the corresponding chiral epoxides,[7] direct amination of chiral iodohydrin,[8] and reductive amination[9] or reduction[10] of optically active α-hydroxy aldehyde or amides. However, these procedures have disadvantages such as low yields due to the intrinsic 50% limitation implied in a resolution process,[7] control of regioselectivity,[7a,11] and lengthy reaction steps.[9-10] Herein we wish to report a concise, convenient synthesis of the β-adrenergic chiral drugs **1-4** by the direct treatment of the corresponding (*R*)-1,2-diol monotosylates **6** with amines (Scheme 1).

To obtain (*R*)-**6**, the reduction of α-sulfonyloxy ketones **5** was carried out with *N*-ethyl-*N*-isopropylaniline-borane

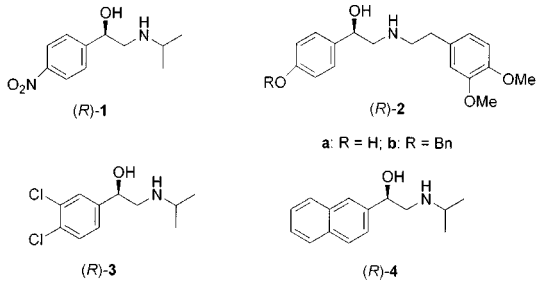
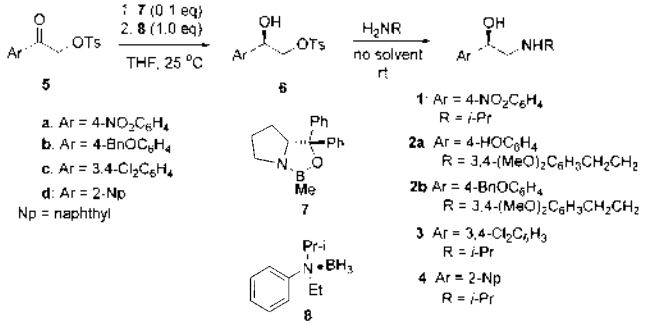



**Figure 1**




**Scheme 1**

complex (**8**) in the presence of 0.1 equiv. of (*R*)-methyl-CBS-oxazaborolidine **7** in THF at 25 °C according to our previous procedure.[12] All the reductions were complete within 10 min to give (*R*)-**6** with very high enantioselectivity in almost quantitative yields. (*R*)-**6** obtained was directly treated with excess amines (5 equiv.) under solvent-free condition at room temperature to afford 2-amino-1-arylethanols **1-4**. The optical purities and absolute configurations of **1-4** were determined by HPLC analyses using chiral columns and/or by comparing optical rotation values of the known compounds. As shown in Table 1, all the products **1-4** were obtained in high yields with optical purities approaching 100% ee.

In summary, we have established a concise and convenient synthesis of enantiopure β-adrenergic chiral drugs, such as nifenalol (**1**), denopamine (**2a**), dichloroisoproterenol (**3**) and pronethalol (**4**) with (*R*)-configurations by direct treatment of the corresponding 1,2-diol monotosylates **6** with amines under solvent-free conditions. The present method is of great advantages over the known methods for providing

**Table 1.** Preparation of (*R*)-Nifenalol (**1**), (*R*)-Denopamine (**2a**), (*R*)-Dichloroisoproterenol (**3**) and (*R*)-Pronethalol (**4**)

| Compd | Yield (%) | Mp (°C) | $[\alpha]_D^{20}$ (*c*, solvent) | % ee |
|---|---|---|---|---|
| (*R*)-**1** | 93 | 112-114 | -11.4 (1.03, EtOH) | >99[a] |
| (*R*)-**1**·HCl | 93 | 200-202 | -40.2 (0.94, $H_2O$) | >99[b] |
| (*R*)-**2a** | 92 | 162-164 | -28.5 (0.98, MeOH) | >99[b] |
| (*R*)-**3** | 94 | 99-101 | -24.3 (1.05, EtOH) | >99[c] |
| (*R*)-**4** | 96 | 107-109 | -22.8 (1.0, EtOH) | >99[a] |

[a]Determined by HPLC analysis using a Chiralcel OB column. [b]Compared by optical rotation value of the known compound. [c]Determined by HPLC analysis using a Whelk-O1 column.

†This paper is dedicated to the late Professor Sang Chul Shim for his distinguished achievements in chemistry.

the efficiency of reaction, short reaction time, mild reaction conditions and high yields of the products with very high optical purity.

## Experimental Section

**General**. All operations with air-sensitive materials were carried out under a nitrogen atmosphere with oven-dried glassware. Liquid materials were transferred with a double-ended needle. The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (Merck; 230-400 mesh). NMR spectra were recorded at 200 or 400 MHz for $^1$H and 50 or 100 MHz for $^{13}$C using $Me_4Si$ as the internal standard in $CDCl_3$ unless otherwise noted. Optical rotations were measured with a high resolution digital polarimeter. Melting points were uncorrected.

**Preparation of (*R*)-2-(*p*-Toluenesulfonyloxy)-1-aryl-ethanols 6**.

**General procedure**: According to the known procedure,[12] asymmetric reduction of **5** using (*R*)-methyl-CBS-oxaza-borolidine **7** as catalyst was carried out to give **6** in 94-99% yields. IR, $^1$H and $^{13}$C NMR data of **6a** and **6c-d** were identical with those of the corresponding (*S*)-isomers.

**(*R*)-(−)-1-(*p*-Nitrophenyl)-2-(*p*-toluenesulfonyloxy)ethanol (*R*)-6a**: Yield 94%; mp 167-168 °C (acetone) (lit.[12] 168-169 °C); $[\alpha]_D^{20}$ -24.06 (*c* 0.97, acetone).

**(*R*)-(−)-1-(*p*-Benzyloxyphenyl)-2-(*p*-toluenesulfonyloxy)-ethanol (*R*)-6b**: Yield 98%; mp 76-77 °C; $[\alpha]_D^{20}$ -41.9 (*c* 1.08, $CHCl_3$); IR (KBr, cm$^{-1}$): 3344, 1613, 1514, 1453, 1386, 1348, 1240, 1173, 1096, 1017, 814; $^1$H NMR (400 MHz) $\delta$ 2.44 (s, 3H), 2.50 (brs, 1H), 4.02 (dd, 1H, $J$ = 8.58, 10.38 Hz), 4.10 (dd, 1H, $J$ = 3.42, 10.41 Hz), 4.91 (dd, 1H, $J$ = 3.31, 8.53 Hz), 5.05 (s, 2H), 6.93 (d, 2H, $J$ = 8.76 Hz), 7.20-7.43 (m, 9H), 7.77 (d, 2H, $J$ = 8.32 Hz); $^{13}$C NMR (100 MHz) $\delta$ 21.7, 70.0, 71.5, 74.3, 115.0, 127.4, 127.5, 127.9, 128.0, 128.6, 129.9, 130.6, 132.7, 136.7, 145.1, 159.0. Anal. Calcd for $C_{22}H_{22}O_5S$: C, 66.31; H, 5.56; S, 8.05; Found: C, 66.43; H, 5.67; S, 8.12.

**(*R*)-(−)-1-(3,4-Dichlorophenyl)-2-(*p*-toluenesulfonyloxy)-ethanol (*R*)-6c**: Yield 92%; mp 88-89 °C (chloroform) (lit.[12] 87-88 °C); $[\alpha]_D^{20}$ -39.22 (*c* 1.0, $CHCl_3$).

**(*R*)-(−)-1-(2-Naphthyl)-2-(*p*-toluenesulfonyloxy)ethanol (*R*)-6d**: Yield 99%; mp 114-116 °C (chloroform) (lit.[12] 113-115 °C); $[\alpha]_D^{20}$ -52.3 (*c* 1.1, $CHCl_3$).

**Preparation of 1-4**.

**General Procedure**: **6** (2 mmol) was treated with isopropylamine (or 3,4-dimethoxyphenylethylamine) (10 mmol) at room temperature for 5 h. To the reaction mixture was added 1 N NaOH (15 mL) and extracted with ether (3 × 15 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was further purified by recrystallization from ethyl acetate or by flash column chromatography on silica gel using methanol/ethyl acetate (4 : 1) to give products **1-4**.

**(*R*)-Nifenalol (*R*)-1**: Yield 93%; mp 112-114 °C (lit.[7b] 118-121 °C); $[\alpha]_D^{20}$ -11.4 (*c* 1.03, EtOH); IR (KBr, cm$^{-1}$): 3097, 2987, 2856, 1604, 1520, 1347, 1096; $^1$H NMR (400 MHz) $\delta$ 1.08 (d, 3H, $J$ = 6.04 Hz), 1.10 (d, 3H, $J$ = 6.17 Hz), 2.58 (dd, 1H, $J$ = 8.74, 12.34 Hz), 2.84 (m, 1H), 3.00 (dd, 1H, $J$ = 3.77, 12.26 Hz), 4.73 (dd, 1H, $J$ = 3.63, 8.91 Hz), 7.55 (d, 2H, $J$ = 8.71 Hz), 8.21 (d, 2H, $J$ = 8.82 Hz); $^{13}$C NMR (100 MHz) $\delta$ 23.0, 23.3, 48.7, 54.2, 71.0, 123.6, 126.5, 147.3, 150.3. HPLC analysis using a Chiralcel OB showed it to be >99% ee [hexane-EtOH-$Et_2NH$ 99.8 : 0.2 : 0.1, flow rate = 1.0 mL/min, $t_R$ (*S*) 155.82 min and $t_R$ (*R*) 189.05 min]. **(*R*)-1·HCl** was obtained in a quantitative yield by bubbling HCl gas into the solution of **1** in ether; mp 200-202 °C (lit.[7b] 208-211 °C, lit.[6b] 217-218 °C); $[\alpha]_D^{20}$ -40.2 (*c* 0.94, $H_2O$) {lit.[7b] $[\alpha]_D^{20}$ -40.3 (*c* 1.07, $H_2O$), *R*; lit.[6b] $[\alpha]_D^{20}$ -41 (*c* 2.0, $H_2O$)}.

**(*R*)-(−)-(*p*-Benzyloxyphenyl)-2-(3,4-dimethoxyphenyl-ethylamino)ethanol (*R*)-2b**: Yield 92%; mp 108-110 °C; $[\alpha]_D^{20}$ -17.5 (*c* 1.09, MeOH); IR (KBr, cm$^{-1}$): 3286, 3042, 2935, 2762, 1612, 1516, 1262, 1023; $^1$H NMR (400 MHz) $\delta$ 2.18 (brs, 2H), 2.68-2.80 (m, 3H), 2.84-2.98 (m, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.63 (dd, 1H, $J$ = 3.50, 9.07 Hz), 5.05 (s, 2H), 6.72-6.80 (m, 3H), 6.94 (d, 2H, $J$ = 8.68 Hz), 7.27-7.43 (m, 7H); $^{13}$C NMR (100 MHz) $\delta$ 36.0, 50.8, 55.8, 55.9, 57.0, 70.0, 71.3, 111.3, 111.9, 114.8, 120.6, 127.1, 127.5, 128.0, 128.6, 132.3, 134.8, 137.0, 147.5, 148.9, 158.3. Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17; N, 3.44. Found: C, 73.53; H, 7.27; N, 3.25.

**(*R*)-(−)-Denopamine (*R*)-2a**: This was obtained in a quantitative yield by catalytic hydrogenolysis of **(*R*)-2b** on 20 wt. % $Pd(OH)_2$-C at 60 psi; mp 162-164 °C (lit.[8] 163-164 °C); lit.[9] 165-165.5 °C; lit.[10] 164-165 °C; $[\alpha]_D^{20}$ -28.5 (*c* 0.98, MeOH) {lit.[8] $[\alpha]_D^{21}$ -27.5 (*c* 0.95, MeOH), *R*; lit.[9] $[\alpha]_D$ -28.8 (*c* 1.3, MeOH), *R*; lit.[10] $[\alpha]_D^{20}$ -28.3 (*c* 1.1, MeOH), *R*}; IR (KBr, cm$^{-1}$): 3275, 3066, 2932, 1616, 1515, 1452, 1278, 1234, 1158, 1028; $^1$H NMR (400 MHz, MeOH-$d_4$) $\delta$ 2.18 (brs, 2H), 2.78-2.85 (m, 6H), 3.30-3.31 (m, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 4.64 (dd, 1H, $J$ = 4.82, 8.32 Hz), 6.72-6.73 (m, 3H), 6.79 (d, 1H, $J$ = 1.85 Hz), 6.84 (d, 1H, $J$ = 8.10 Hz), 7.11-7.14 (m, 2H); $^{13}$C NMR (100 MHz, MeOH-$d_4$) $\delta$ 36.1, 51.7, 56.4, 56.6, 57.7, 73.1, 113.3, 113.7, 116.2, 122.0, 128.3, 133.7, 135.0, 149.1, 150.6, 158.2.

**(*R*)-(−)-Dichloroisoproterenol (*R*)-3**: Yield 94%; mp 99-101 °C (lit.[6c] 101 °C); $[\alpha]_D^{20}$ -24.3 (*c* 1.05, EtOH) {lit.[6c] $[\alpha]_D^{21}$ -24.1 (*c* 0.97, EtOH); lit.[7a] $[\alpha]_D$ -24.1 (*c* 1.2, EtOH), *R*}; IR (KBr, cm$^{-1}$): 3291, 3061, 2918, 2749, 1463, 1074; $^1$H NMR (400 MHz) $\delta$ 1.07 (d, 3H, $J$ = 6.25 Hz), 1.08 (d, 3H, $J$ = 6.25 Hz), 2.48 (brs, 2H), 2.57 (dd, 1H, $J$ = 8.87, 12.23 Hz), 2.82 (m, 1H), 2.93 (dd, 1H, $J$ = 3.71, 12.21 Hz), 4.59 (dd, 1H, $J$ = 3.67, 8.86 Hz), 7.19 (m, 1H), 7.40 (d, 1H, $J$ = 8.33 Hz), 7.48 (d, 1H, $J$ = 1.93 Hz); $^{13}$C NMR (100 MHz) $\delta$ 23.0, 23.3, 48.7, 54.3, 70.7, 125.1, 127.8, 130.3, 131.2, 132.5, 143.2. HPLC analysis using a Chiralcel OB showed it to be >99% ee [hexane-EtOH-$Et_2NH$ 99.5 : 0.5 : 0.1, flow rate = 0.3 mL/min, $t_R$ (*S*) 66.35 min and $t_R$ (*R*) 72.26 min].

**(*R*)-(−)-Pronethalol (*R*)-4**: Yield 96%; mp 107-109 °C (lit.[6c] 108-109 °C); $[\alpha]_D^{20}$ -22.8 (*c* 1.0, EtOH) {lit.[6c] $[\alpha]_D$ -29.0 (*c* 1.3, EtOH); lit.[7a] $[\alpha]_D$ -22.1 (*c* 1.0, EtOH), *R*}; IR (KBr, cm$^{-1}$): 3136, 2966, 2833, 1451, 1382, 1081; $^1$H NMR

(400 MHz) $\delta$ 1.09 (d, 3H, $J$ = 6.18 Hz), 1.10 (d, 3H, $J$ = 6.29 Hz), 2.40 (brs, 2H), 2.76 (dd, 1H, $J$ = 8.66, 12.08 Hz), 2.87 (m, 1H), 3.04 (dd, 1H, $J$ = 3.67, 12.11 Hz), 4.85 (dd, 1H, $J$ = 3.66, 8.70 Hz), 7.45-7.49 (m, 3H), 7.82-7.85 (m, 4H); $^{13}$C NMR (100 MHz) $\delta$ 23.0, 23.2, 48.6, 54.4, 72.0, 124.0, 124.5, 125.7, 126.1, 127.7, 127.9, 128.1, 133.0, 133.3, 140.1. HPLC analysis using a Whelk-O1 showed it to be >99% ee [hexane-EtOH-$Et_2NH$ 99 : 1 : 0.1, flow rate = 0.9 mL/min, $t_R$ (*S*) 36.88 min and $t_R$ (*R*) 42.66 min].

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