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Stereospecific Synthesis of Specifically Deuterated Metoprolol Enantiomers from Chiral Starting Materials

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ABSTRACT

Enantiomers of metoprolol (**1**) containing six deuterium atoms in the isopropyl methyl groups [(2*R*-**2**], two deuterium atoms at C-2 and C-6 of the aromatic ring [(2*S*)-**3**], and two deuterium atoms at C-3 of the propanolamine side chain [(2*S*)-**4**] were prepared. Chiral 2,2-dimethyl-1,3-dioxolane-4-methanols [(4*R*)-**5** and (4*S*)-**5**] were key synthons. Sources of deuterium were [$^2H_6$]-isopropylamine, 4-(2-methoxyethyl)-2,6-[$^2H_2$]-phenol (**12**), prepared by $^2HCl/^2H_2O$ exchange, and (4*S*)-2,2-dimethyl-1,3-dioxolane-4-[$^2H_2$]-4-methanol (**19**), prepared by $LiAl^2H_4$ reduction of (4*S*)-methyl 2,2-dimethyl-1,3-dioxolane-4-carboxylate. Enantiomeric excess was greater than 94% for each of the prepared enantiomers, as determined independently by ^1H NMR spectroscopy on diastereomeric derivatives and by chiral column HPLC.

Key words: metoprolol enantiomers, stereospecific synthesis, deuterium labelling, optical purity.

INTRODUCTION

Metoprolol (**1**) is a β_1-selective adrenergic antagonist of the aryloxypropanolamine type used extensively in the treatment of a variety of cardiovascular disorders. The (2*S*)-enantiomer has significantly greater β_1-adrenergic receptor affinity by >25 fold,[1] and there is evidence that the enantiomers are oxidatively metabolized at different rates.[2-6] Its oxidative metabolism has been shown to be genetically linked to debrisoquine and bufurolol hydroxylation,[7-14] and the α-hydroxylation pathway shows a high degree of product stereoselectivity in the presence of rat liver microsomes.[15] In order to explore enantioselective and stereoselective aspects of its metabolism by GC-MS, sources of specifically deuterated metoprolol enantiomers were needed in which the deuterium atoms were located at metabolically stable sites. In this paper we report synthesis of enantiomers of **1** labeled in several ways: with six deuterium atoms in the *N*-isopropylmethyl groups

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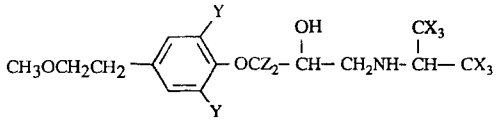
(2), two deuterium atoms at the 2- and 6-positions in the aromatic ring (3), and with two deuterium atoms at the 3-position in the propanolamine side chain (4).



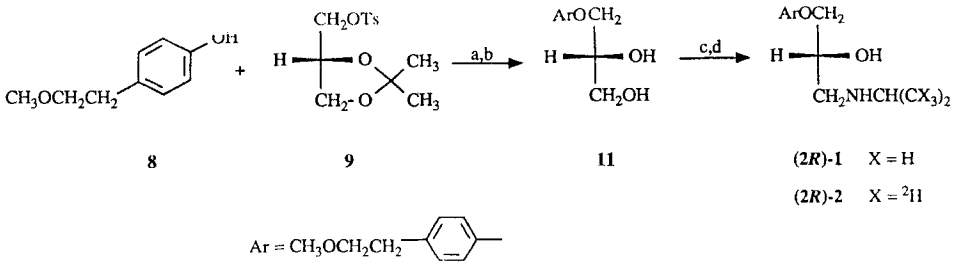
1 X = Y = Z = H
2 X = ^{2}H Y = Z = H
3 X = H Y = ^{2}H Z = H
4 X = Y = H Z = ^{2}H

RESULTS AND DISCUSSION

In initial efforts to synthesize the metoprolol enantiomers, we attempted to utilize the available enantiomeric glycidol tosylates previously used by Sharpless in the synthesis of the propranolol enantiomers.[16] (2*S*)-Propranolol was obtained in >98% ee by this procedure. Unfortunately, we obtained (2*S*)-metoprolol in only 80% ee, and further we failed to enrich its optical purity by recrystallization of its tartrate salt. The low optical purity is the result of apparently decreased selectivity for displacement of tosyl group *vs.* competing opening of the epoxide of glycidyl tosylate by the 4-(2-methoxyethyl)phenoxide ion compared to the 1-naphthoxide ion in the reported preparation of (2*S*)-propranolol.[16]

Efforts were then directed to the use of enantiomers of 2,2-dimethyl-1,3-dioxolane-4-methanol [(4*R*)-**5** and (4*S*)-**5**], similar to reports of synthesis of other β-adrenergic blockers utilizing these chiral precursors.[17-19] We obtained the (2*R*)-enantiomers of metoprolol and metoprolol-$^2H_6$ [(2*R*)-**1** and (2*R*)-**2**] in >94% ee using (4*S*)-**5** (Scheme I). The required starting material, 4-(2-methoxyethyl)-phenol (**8**),[20-22] was prepared by methoxide ion displacement of corresponding phenethyl bromide (**7**), which was prepared from 4-methoxyphenethyl alcohol (**6**) by treatment with HBr. Significant changes from the reported reaction conditions were required to optimize the yield and purity of **8**.

SCHEME I.



8 **9** **11** (2*R*)-**1** X = H (2*R*)-**2** X = ^{2}H

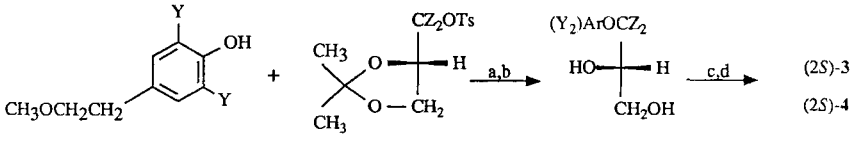
Ar = $CH_3OCH_2CH_2$

Reagents: a, NaOH; b, H_3O^+; c, TsCl, C_5H_5N; d, $H_2NCH(CX_3)_2$.

(4*S*)-(+)-2,2-Dimethyl-1,3-dioxolane-4-methanol [(4*S*)-**5**] was tosylated[17] affording **9**, which when treated with **8** yielded acetonide **10**. This crude acetonide was hydrolyzed under very mild conditions to the resulting glycol **11**. The side chain was elaborated further *via* tosylation and displacement with isopropylamine, affording (2*R*)-metoprolol [(2*R*)-**1**] in 37% overall yield from **8**. The free base was converted efficiently into its neutral (+)-tartrate salt. Use of isopropylamine-$^2H_6$, prepared by the method of Andresen and Davis,[23] in the final step afforded (2*R*)-**2**.

Preparation of (2*S*)-**3** and (2*S*)-**4** followed similar lines (Scheme II). Incorporation of deuterium atoms into the aromatic ring was accomplished by acid catalyzed exchange on phenol **8**. Almost complete deuteration at positions 2 and 6 of the aromatic ring occurred when **8** was refluxed in 5% ^2HCl in ^2H_2O, the ^2HCl being conveniently generated by hydrolysis of $SOCl_2$ in ^2H_2O. The deuterium exchange was incomplete at a lower ^2HCl concentrations, and demethylation of **8** was noted at higher concentrations of ^2HCl. The extent of deuteration (>99% ^2H) was determined by ^1H NMR, and the specificity of deuteration was verified by ^2H NMR. No deuterium incorporation at positions 3 and 5 occurred under these conditions. Deuterated phenol **12** was carried through the series of steps noted in Scheme II using (4*R*)-(-)-2,2-dimethyl-1,3-dioxolane-4-methanol [(4*R*)-**5**] as the chiral building block to obtain (2*S*)-**3**. The deuterium atoms in the aromatic ring were not lost in any of the synthetic steps.

SCHEME II.



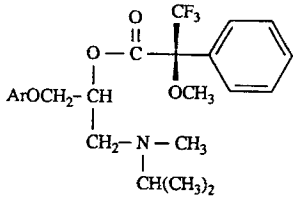
12 Y = ^2H **14** Z = H **16** Y = ^2H Z = H

8 Y = H **20** Z = ^2H **21** Y = H Z = ^2H

Reagents: a, NaOH; b, H_3O^+; c, TsCl, C_5H_5N; d, $H_2NCH(CH_3)_2$.

For synthesis of (2*S*)-**4**, where the deuterium atoms were located in the side chain, (4*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-[$^2H_2$]-4-methanol (**19**) prepared by $LiAl^2H_4$ reduction of (4*S*)-(-)-methyl 2,2-dimethyl-1,3-dioxolane-4-carboxylate was used. Phenol **8** was condensed with tosylate **20** yielding a crude acetonide, which was hydrolysed under acidic conditions to give deuterated glycol **21**. Its conversion to (2*S*)-**4** was effected by tosylation to **22** and subsequent reaction with isopropylamine in 40% overall yield.

The synthesized enantiomers were analyzed for optical purity both by ^{1}H NMR and chiral column HPLC methods. For ^{1}H NMR determination, racemic metoprolol or one of the enantiomers was first *N*-methylated[24] and then esterified with (2*R*)-2-methoxy-2-(trifluoromethyl)phenylacetyl chloride.[25] The ^{1}H NMR signals of the diastereomeric *N*-CH3 groups of **24** were well resolved from each other and were used for determination of enantiomeric excess (ee). (2*R*)-Metoprolol [(2*R*)-**1**] was found to be in 97% ee (98.5:1.5) and (2*S*)-**3** in 94% ee (97:3). We also determined optical purity independently by chiral column HPLC analysis using a Chiralcel OD column.[26,27] The neutral tartrate salts of enantiomers of metoprolol were also checked for enantiomeric excess and no enrichment upon crystallization occurred. For (2*R*)-**1**, the enantiomeric excess was 96.4% by this method, 96.2% ee for (2*R*)-**2**, 94.0% ee for (2*S*)-**3**, and 94.0% ee for (2*S*)-**4**.



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Metabolic experiments using pseudoracemic metoprolol will be reported elsewhere.

EXPERIMENTAL SECTION

High-field ^{1}H NMR and ^{2}H NMR spectra were recorded at 300 MHz on a Varian VXR-300 spectrometer. Chemical shifts are expressed in δ, relative to the position of the internal standard, TMS (δ 0.0). Notations used to describe the splitting patterns are s = singlet, d = doublet, t = triplet and m = multiplet. Analytical thin layer chromatography (TLC) was performed on Analtech silica gel HLF TLC plates (0.25 mm thickness), and the spots were detected by a UV lamp (254 nm). Kieselgel 60 (230-400 mesh ASTM) was used for flash chromatography.[28] Electron impact mass spectra were obtained on a VG 7070 H mass spectrometer equipped with a VG 2050 data system. Gas chromatography/electron impact mass spectrometric analysis was carried out on the same setup, which was interfaced with a Hewlett-Packard 5710 gas chromatograph with a splitless inlet system. The column was a J & W DB-5 fused silica capillary column of 30 m x 0.32 mm i.d. and 0.25 μm film thickness. Chromatographic parameters were: carrier gas, helium, flow (total) rate 60 mL/min, septum purge flow 6 mL/min, column head pressure 15 psi, injector temperature 250°C, detector temperature 280°C and temperature program 200°C for 1 min and then increased to 280°C at 10°C per min. The septum purge flow and vent flow valves were activated 30 sec after injection. Mass spectral conditions were: source temperature 200°C and ionizing voltage 70 eV. HPLC

analysis was performed on a Micromeretics model 700 liquid chromatograph equipped with a variable wavelength UV detector (226 nm) and a Spectra Physics SP 4100 computing integrator. Deuterium incorporation was determined by selected ion monitoring of parent ions of oxazolidinone derivatives according to the method of Hoffmann.[29]

Tetrahydrofuran (THF) was distilled under argon from sodium metal with benzophenone as an indicator. Methylene chloride and *n*-propanol were dried over molecular sieves (3 Å). Triethylamine and pyridine were dried over KOH pellets and then distilled over NaH. Benzene was dried by distilling over $LiAlH_4$. Argon was dried by passing it through columns of Drierite and KOH in series. All reactions were carried out under an argon atmosphere.

4-(2-Methoxyethyl)phenol (8).[20-22] A mixture of 4-methoxyphenethyl alcohol (**6**), (15.2 g, 100 mmol) and 48% aqueous HBr (150 mL) was refluxed for 1.5 h, cooled, poured into cold H_2O (100 mL), and the mixture was extracted with ethyl acetate (150 mL). The organic layer was washed with water (20 mL), dried (Na_2SO_4) and the solvent was evaporated, affording a brown oil (**7**), 18.6 g (93%), which was used without further purification. TLC ($CHCl_3$:ethyl acetate::8:2) showed no starting material. To sodium methoxide (10.8 g, 200 mmol), absolute CH_3OH (100 mL) was added gradually with stirring at 0°C. When a clear solution resulted, crude **7** (4.02 g, 20 mmol) in CH_3OH (5 mL) was added dropwise *via* syringe. The reaction mixture was stirred at room temperature for 2 h, and the solvent was evaporated. The residue was dissolved in water (50 mL) and washed with ether (20 mL). The aqueous layer was made acidic (aqueous HCl) and extracted with CH_2Cl_2 (3 x 50 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4), evaporated and the resulting oil was vacuum distilled, bp 115-116 °/0.15 mm (lit.[22] 110-112 °/0.5 mm), affording **8** as a colorless oil, 2.06 g (68%); ^1H NMR ($CDCl_3$) δ 2.83 (t, J = 7.0 Hz, 2, $ArCH_2$), 3.39 (s, 3, OCH_3), 3.61 (t, J = 7.0 Hz, 2, CH_2OCH_3), 6.72 (d, J = 8.7 Hz, 2, ArH-2 and H-6) and 7.05 (d, J = 8.7 Hz, 2, ArH-3 and H-5).

(4*R*)-2,2-Dimethyl-4-tosyloxymethyl-1,3-dioxolane (9).[17] A solution containing a mixture of (4*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol [(4*S*)-**5**] (1.98 g, 15 mmol), and triethylamine (3.04 g, 30 mmol) in CH_2Cl_2 (20 mL) was cooled to 0°C. A solution of *p*-toluenesulfonyl chloride (3.15 g, 16.5 mmol) in CH_2Cl_2 (5 mL) was then added dropwise with continuous stirring, and after the addition was completed, the mixture was maintained at 0°C for 10 h. The reaction mixture was then diluted with CH_2Cl_2 (25 mL), washed with H_2O (2 x 25 mL), and the CH_2Cl_2 layer was dried ($MgSO_4$). Evaporation followed by flash chromatography, eluting with CH_2Cl_2 containing 0.1% triethylamine on a 3 x 30 cm column afforded **9** as a colorless oil, 4.16 g (97%): ^1H NMR ($CDCl_3$) δ 1.32 and 1.34 [2s, 6, $C(CH_3)_2$], 2.45 (s, 3, $ArCH_3$), 3.77 (dd, J = 5.1, 8.8 Hz, 1, $TsOCH_2CHCH_2$),

3.94-4.06 (m, 3, TsOC*H*$_2$CHC*H*$_2$), 4.28 (quintet, J = 5.3 Hz, 1, CH), 7.35 (d, J = 7.9 Hz, 2, ArH-3 and H-5), and 7.80 (d, J = 8.4 Hz, 2, ArH-2 and H-6).

(2*R*)-3-[4-(2-Methoxyethyl)phenoxy]-1,2-propanediol (11). A mixture of KOH (0.951 g, 16.9 mmol), phenol **8** (2.34 g, 15.4 mmol) and tosylate **9** (4.01 g, 14.0 mmol), in 50 mL of 90% ethanol was refluxed for 24 h. The cooled reaction mixture was evaporated and the oily residue was partitioned between ether (50 mL) and H_2O (25 mL). The aqueous layer was discarded and the organic layer was washed successively with 1N NaOH solution (10 mL) and H_2O (10 mL), dried ($MgSO_4$) and evaporated affording dioxolane **10** as a colorless oil, 3.59 g (13.5 mmol): ^{1}H NMR ($CDCl_3$) δ 1.42 and 1.48 [2s, 6, C(CH_3)$_2$], 2.83 (t, J = 7.2 Hz, 2, ArCH_2), 3.36 (s, 3, OCH_3), 3.57 (t, J = 7.2 Hz, 2, C*H*$_2$OCH$_3$), 3.91-4.17 (m, 4, ArOC*H*$_2$CHC*H*$_2$), 4.48 (quintet, J = 5.9 Hz, 1, CH), 6.85 (d, J = 8.6 Hz, 2, ArH-2 and H-6), 7.14 (d, J = 8.6 Hz, 2, ArH-3 and H-5).

The crude dioxolane **10** was stirred in a mixture of ethanol (25 mL) and 1N HCl (5 mL) for 6 h at room temperature. Solid Na_2CO_3 was then added to neutralize the reaction mixture, and following the addition of absolute ethanol (20 mL), the reaction mixture was evaporated to dryness. The residual oil was dissolved in ethyl acetate (50 mL), filtered and evaporated affording **11** as a pale yellow oil, which after flash chromatography on a 2.5 x 30 cm column eluting with ethyl acetate afforded a colorless oil, 2.21 g (73%) which solidified upon cooling: ^{1}H NMR ($CDCl_3$) δ 2.84 (t, J = 7.0 Hz, 2, ArCH_2), 3.36 (s, 3, OCH_3), 3.58 (t, J = 7.0 Hz, 2, C*H*$_2$OCH$_3$), 3.74 (dd, J = 11.4, 5.4 Hz, 1, C*H*$_2$OH), 3.84 (dd, J = 11.4, 3.8 Hz, 1, C*H*$_2$OH), 4.03 (m, 2, ArOCH_2), 4.09 (m, 1, CH), 6.86 (d, J = 8.6 Hz, 2, ArH-2 and H-6) and 7.15 (d, J = 8.6 Hz, 2, ArH-3 and H-5).

(2*S*)-3-[4-(2-Methoxyethyl)phenoxy]-1-tosyloxy-2-propanol (13). A solution of **11** (2.15 g, 9.5 mmol) in CH_2Cl_2 (20 mL) and pyridine (1.50 g, 19 mmol) was cooled in a dry ice bath. Then *p*-toluenesulfonyl chloride (1.81 g, 9.5 mmol) in CH_2Cl_2 (4 mL) was added dropwise with stirring and the bath temperature was raised to 0°C, and the reaction mixture maintained at 0°C overnight. The mixture was then diluted with CH_2Cl_2 (50 mL), washed with 0.5N HCl (20 mL) and then with H_2O (20 mL), dried ($MgSO_4$) and evaporated. After flash chromatography on a 2.5 x 35 cm column, eluting with CH_2Cl_2:CH_3OH::98:2, **13** was obtained as a colorless oil, 2.29 g (63%): ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3, ArCH_3), 2.82 (t, J = 7.0 Hz, 2, ArCH_2), 3.35 (s, 3, OCH_3), 3.56 (t, J = 7.0 Hz, 2, C*H*$_2$OCH$_3$), 3.96 (m, 2, C*H*$_2$OTs), 4.20 (m, 3, ArOC*H*$_2$C*H*OH), 6.75 (d, J = 8.6 Hz, 2, ArH-2 and H-6), 7.12 (d, J = 8.6 Hz, 2, ArH-3 and H-5), 7.31 (d, J = 7.9 Hz, 2, TsArH-3 and H-5) and 7.79 (d, J = 8.4 Hz, 2, TsArH-2 and H-6).

(2*R*)-3-[4-(2-Methoxyethyl)phenoxy]-1-isopropylamino-2-propanol [(2*R*)-Metoprolol] [(2*R*)-1]. A mixture of tosylate **13** (2.28 g, 6.0 mmol) and isopropylamine (5 mL) was refluxed in acetonitrile (50 mL) for 6 h. Upon evaporation of the solvent, the residue was partitioned between ether (50 mL) and 1N NaOH solution (10 mL). The alkaline layer was removed, re-extracted with ether (10 mL), and the ether layers were combined and then washed with saturated NaCl solution (10 mL). The combined ether extract was dried ($MgSO_4$), the solvent was evaporated and the crude product was flash chromatographed, eluting with ethyl acetate:CH_3OH:triethylamine:: 95:5:0.5 on a 2 x 20 cm column. Evaporation of the solvent afforded (2*R*)-**1** as a white, waxy solid, 1.30 g (81%): ^1H NMR ($CDCl_3$) δ 1.10 [d, J = 6.3 Hz, 6, $CH(CH_3)_2$], 2.68-2.94 (m, 5, CH_2NHCH and $ArCH_2$), 3.36 (s, 3, OCH_3), 3.57 (t, J = 7.0 Hz, 2, CH_2OCH_3), 3.98 (m, 3, OCH_2CHOH), 6.86 (d, J = 8.6 Hz, 2, ArH-2 and H-6) and 7.14 (d, J = 8.6 Hz, 2, ArH-3 and H-5).

The neutral (+) tartrate salt of (2*R*)-**1** was prepared. A solution of (+)-tartaric acid (300 mg, 2.0 mmol) in *n*-propanol (10 mL) was added to a solution of (2*R*)-**1** (700 mg, 4.0 mmol) in *n*-propanol (10 mL) and mixed. The mixture was stored at 0°C, and when crystallization ceased, *n*-hexane (5 mL) was added dropwise, and the mixture was stored overnight at 0°C. After filtration and drying (P_2O_5 - vacuum), fine, white crystals 1.17 g (86%), mp 102-103°C, were obtained; $[\alpha]_D^{20}$ = +22.6° (c = 1.0, CH_3OH).

(2*R*)-3-[4-(2-Methoxyethyl)phenoxy]-1-([$^2H_6$]-isopropylamino)-2-propanol [(2*R*)-2]. Tosylate **13** (0.89 g, 2.33 mmol), [$^2H_6$]-isopropylamine HCl[23] (2.00 g, 19.7 mmol) and NaOH (1.57 g, 39.3 mmol) dissolved in H_2O (10 mL) were added to acetonitrile (50 mL), and the mixture was refluxed for 15 h. The reaction mixture was cooled, filtered and concentrated by evaporating. The residue was dissolved in ether (100 mL) and the ether layer washed with H_2O (25 mL), dried ($MgSO_4$) and evaporated to dryness. The crude product was flash chromatographed on a 2.5 x 10 cm column eluting with ethyl acetate:CH_3OH:triethylamine::90:10:0.5 to yield (2*R*)-**2** as a white, waxy solid, 0.35 g (50%): ^1H NMR ($CDCl_3$) δ 2.60-2.96 (m, 5, CH_2NHCH and $ArCH_2$), 3.40 (s, 3, OCH_3), 3.60 (t, J = 7.2 Hz, 2, CH_2OCH_3), 3.95-4.10 (m, 3, OCH_2CHOH), 6.88 (d, J = 8.5 Hz, 2, ArH-2 and ArH-6), 7.16 (d, J = 8.5 Hz, 2, ArH-3 and H-5). The neutral (+)-tartrate salt of (2*R*)-**2** was prepared by the procedure described for preparation of the salt of (2*R*)-metoprolol [(2*R*)-**1**]. From 820 mg (3.0 mmol) of (2*R*)-**2**, 400 mg (40%) of its (+)-tartrate salt was obtained as white, fluffy crystals, mp 108°C, $[\alpha]_D^{20}$ = +20.5° (c = 1.0, CH_3OH); deuterium content 78.0% $^2H_6$, 17.6% $^2H_5$, 3.6% $^2H_4$, 0.8% = $^2H_3$.

4-(2-Methoxyethyl)-2,6-[$^2H_2$]-phenol (12). Phenol **8** (2.28 g, 15 mmol) was placed in a flask, stirred with ^2H_2O (5 mL) for 5 min and the contents were evaporated at room temperature. Separately, thionyl chloride (4.77 g, 4.0 mmol) was added dropwise to ^2H_2O (60 mL), with stirring. The resulting solution was transferred to the flask containing **8**, and the mixture was refluxed (bath temperature 105°C) for 3.5 h, cooled, and the phenol was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with saturated NaCl solution (20 mL) dried (Na_2SO_4), evaporated and the crude product was flash chromatographed on a 2.5 x 15 cm column eluting with CH_2Cl_2:ethyl acetate::95:5. Deuterated phenol **12** was obtained as a colorless oil, 2.18 g (94%): ^1H NMR ($CDCl_3$) δ 2.83 (t, J = 7.1 Hz, 2, $ArCH_2$), 3.39 (s, 3, OCH_3), 3.61 (t, J = 7.1 Hz, 2, CH_2OCH_3) and 7.07 (s, 2, ArH-3 and H-5). ^2H NMR ($CHCl_3$) δ 6.79 (s, 2, Ar^2H-2 and ^2H-6).

(4*S*)-2,2-Dimethyl-4-tosyloxymethyl-1,3-dioxolane (14). (4*R*)-(-)-2,2-Dimethyl-1,3-dioxolane-4-methanol [(4*R*)-**5**], (1.66 g, 12.6 mmol) was tosylated by the procedure described for preparation of **9**, yielding 3.41 g (95%) of **14** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.34 and 1.36 [2s, 6, $C(CH_3)_2$], 2.47 (s, 3, $ArCH_3$), 3.79 (dd, J = 8.8, 5.0 Hz, 1, $TsOCH_2CHCH_2$), 3.96-4.10 (m, 3, $TsOCH_2CHCH_2$), 4.30 (quintet, J = 5.3 Hz, 1, CH), 7.38 (d, J = 7.9 Hz, 2, ArH-3 and H-5) and 7.82 (d, J = 7.9 Hz, 2, ArH-2 and H-6).

(2*S*)-3-[4-(2-Methoxyethyl)-2,6-[$^2H_2$]-phenoxy]-1,2-propanediol (16). Acetonide **15** was obtained from deuterated phenol **12** (2.01 g, 13 mmol) and acetonide **14** (3.72 g, 13 mmol) as a pale yellow oil (3.08 g, 11.5 mmol) using the procedure described for preparation of **10**: ^1H NMR ($CDCl_3$) δ 1.42 and 1.48 [2s, 6, $C(CH_3)_2$], 2.83 (t, J = 7.0 Hz, 2, $ArCH_2$), 3.36 (s, 3, OCH_3), 3.57 (t, J = 7.2 Hz, 2, CH_2OCH_3), 3.89-4.21 (m, 4, $ArOCH_2CHCH_2$), 4.48 (quintet, J = 5.9 Hz, 1, CH), 7.14 (s, 2, ArH-3 and H-5). Acetonide **15** was hydrolyzed and the resulting diol **16** was purified in the same way as described for preparation of **11**. Compound **16** was obtained as a white amorphous powder, 1.65 g (63%): ^1H NMR ($CDCl_3$) δ 2.84 (t, J = 7.0 Hz, 2, $ArCH_2$), 3.36 (s, 3, OCH_3), 3.58 (t, J = 7.0 Hz, 2, CH_2OCH_3), 3.75 (dd, J = 11.4, 5.4 Hz, 1, CH_2OH), 3.84 (dd, J = 11.4, 3.8 Hz, 1, CH_2OH), 4.03 (m, 2, $ArOCH_2$), 4.09 (m, 1, CHOH), 7.15 (s, 2, ArH-3 and H-5).

(2*R*)-3-[4-(2-Methoxyethyl)-2,6-[$^2H_2$]-phenoxy]-1-tosyloxy-2-propanol (17). Tosylation of **16** (1.60 g, 7.0 mmol) was carried out by the procedure described for preparation of **13**, yielding **17** as a colorless, viscous oil, 1.71 g (64%): ^1H NMR ($CDCl_3$) δ 2.45 (s, 3, $ArCH_3$), 2.85 (t, J = 7.0 Hz, 2, $ArCH_2$), 3.38 (s, 3, OCH_3), 3.59 (t, J = 7.0 Hz, 2, CH_2OCH_3), 3.98 (m, 2, CH_2OTs), 4.22 (m, 3, $ArOCH_2CHOH$), 7.15 (s, 2, ArH-3 and H-5), 7.33 (d, J = 7.9 Hz, 2, TsArH-3 and H-5) and 7.81 (d, J = 8.4 Hz, 2, TsArH-2 and H-6).

(2*S*)-3-[4-(2-Methoxyethyl)-2,6-[$^2H_2$]-phenoxy]-1-isopropylamino-2-propanol [(2*S*)-3]. Tosylate **17** (1.68 g, 4.39 mmol) was converted to (2*S*)-**3** in the same way as described for the conversion of **13** to (2*R*)-**1**. (2*S*)-**3** was obtained as a waxy solid, 0.900 g (77%): ^1H NMR ($CDCl_3$) δ 1.10 [d, J = 6.2 Hz, 6, $CH(CH_3)_2$], 2.69-2.95 (m, 5, CH_2NHCH and $ArCH_2$), 3.36 (s, 3, OCH_3), 3.57 (t, J = 7.1 Hz, 2, CH_2OCH_3), 3.98 (m, 3, OCH_2CHOH), and 7.14 (s, 2, ArH-3 and H-5). The (+)-tartrate salt of (2*S*)-**3** was prepared by the procedure described for preparation of the salt of (2*R*)-metoprolol [(2*R*)-**1**]. From 1.08 g (4.0 mmol) of (2*S*)-**3**, 1.17 g (85%) of its (+)-tartrate was obtained as white, fluffy crystals, m.p. 104-105°C, $[\alpha]_D^{20}$ = -8.1° (c = 1.0, CH_3OH); deuterium content 96.9% $^2H_2$, 3.1% $^2H_1$.

(4*S*)-2,2-Dimethyl-1,3-dioxolane-4-[$^2H_2$]-4-methanol (19). Lithium aluminum deuteride (2.10 g, 50 mmol) was added slowly to 100 mL of ether (sodium dried and distilled) to form a suspension and stirred at 0°C. Methyl (4*S*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (8.68 g, 54.2 mmol) dissolved in ether (10 mL) was added dropwise to the reaction mixture *via* syringe. After refluxing for 3 h, (the reaction mixture was diluted with ether (25 mL), decomposed with H_2O (3.0 mL, 166 mmol) and filtered. The solid material was washed thoroughly with ether (200 mL) and then extracted (Soxhlet apparatus) with ethanol (175 mL). The filtrate and the extracts were combined, concentrated and distilled to give **19** as a colorless liquid (6.37 g, 87%), bp 40-41°C/0.4 mm: ^1H NMR ($CDCl_3$) δ 1.38 and 1.45 [2s, 6, $C(CH_3)_2$], 3.80 (dd, 1, J = 8.5, 5.2 Hz, 1, CH_2O), 4.05 (dd, J = 8.5, 5.1 Hz, 1, CH_2O) and 4.25 (t, J = 6.7 Hz, 1, CH).

(4*S*)-2,2-Dimethyl-4-[$^2H_2$]-4-tosyloxymethyl-1,3-dioxolane (20). (4*S*)-2,2-Dimethyl-1,3-dioxolane-4-[$^2H_2$]-methanol (**19**) (2.50 g, 18.6 mmol) was tosylated according to the procedure described for preparation of **9** to yield 4.87 g (90%) of **20** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.32 and 1.34 [2s, 6, $C(CH_3)_2$], 2.46 (s, 3, $ArCH_3$), 3.75 (dd, J = 8.6, 5.2 Hz, 1, CH_2O), 4.05 (dd, J = 8.6, 6.35 Hz, 1, CH_2O), 4.28 (t, J = 6.80 Hz, 1, CH), 7.35 (d, J = 8.3 Hz, 2, ArH-3 and H-5) and 7.80 (d, J = 8.3 Hz, 2, ArH-2 and H-6).

(2*S*)-3-[$^2H_2$]-3-[4-(2-Methoxyethyl)phenoxy]-1,2-propanediol (21). Diol **21** was obtained from **20** (4.84 g, 16.7 mmol) by a procedure similar to that for preparation of **11** as a waxy white solid, 1.87 g (60%): ^1H NMR ($CDCl_3$) δ 2.84 (t, J = 7.0 Hz, 2, $ArCH_2$), 3.36 (s, 3, OCH_3), 3.58 (t, J = 7.0 Hz, 2, CH_2OCH_3), 3.85 (dd, J = 10.8, 5.4 Hz, 1, CH_2OH), 3.85 (dd, J = 10.8, 5.2 Hz, 1, CH_2OH), 4.10 (t, J = 6.4 Hz, 1, CHOH), 6.86 (d, J = 8.6 Hz, 2, ArH-2 and H-6) and 7.15 (d, J = 8.6 Hz, 2, ArH-3 and H-5).

(2S)-3-[$^2H_2$]-3-[4-(2-Methoxyethyl)phenoxy]-1-tosyloxy-2-propanol (22). Tosylation of **21** (1.87 g, 8.19 mmol) was accomplished by the procedure described for preparation of **13** to obtain **22** as a colorless oil, 1.94 g (62%): ^1H NMR ($CDCl_3$) δ 2.43 (s, 3, $ArCH_3$), 2.83 (t, J = 7.0 Hz, 2, $ArCH_2$), 3.35 (s, 3, OCH_3), 3.57 (t, J = 6.95 Hz, 2, CH_2OCH_3), 4.20 (m, 3, $CHOHCH_2OTs$), 6.75 (d, J = 8.4 Hz, 2, ArH-2 and H-6), 7.12 (d, J = 8.6 Hz, 2, ArH-3 and H-5), 7.31 (d, J = 7.9 Hz, 2, TsArH-3 and H-5) and 7.79 (d, J = 8.3 Hz, 2, TsArH-2 and H-6).

(2S)-3-[$^2H_2$]-3-[4-(2-Methoxyethyl)phenoxy]-1-isopropylamino-2-propanol [(2S)-4]. Tosylate **22** (1.94 g, 5.0 mmol) was allowed to react with isopropylamine as described for preparation of (2*R*)-**1** to yield 1.03 g (76%) of (2*S*)-**4** as a waxy solid: ^1H NMR ($CDCl_3$) δ 1.10 [d, J = 6.2 Hz, 6, $CH(CH_3)_2$], 2.68 - 2.94 (m, 5, CH_2NHCH and $ArCH_2$), 3.36 (s, 3, OCH_3), 3.57 (t, J = 7.0 Hz, 2, CH_2OCH_3), 3.98 (dd, J = 7.0, 4.1 Hz, 1, CHOH), 6.86 (d, J = 8.6 Hz, 2, ArH-2 and H-6) and 7.14 (d, J = 8.6 Hz, 2, ArH-3 and H-5).

The neutral (+)-tartrate salt of (2*S*)-**4** was prepared using a procedure similar to that used for preparation of (2*R*)-**1** tartrate. From 1.03 g of (2*S*)-**4** 1.10 g (68%) of (2*S*)-**4** (+)-tartrate was obtained as white, fluffy crystals, mp 105°C, $[\alpha]_D^{20}$ = -8.1° (c = 1.0, CH_3OH); deuterium content 96.6% $^2H_2$, 3.4% $^2H_1$.

Determination of % ee. ^1H NMR method. To racemic metoprolol (**1**) (134 mg, 0.50 mmol) in 1.5 mL of acetonitrile, was added formaldehyde solution (37%, 203 μL, 2.5 mmol). Sodium cyanoborohydride (63 mg, 1.0 mmols) was added in portions, with stirring, over 15 min. The reaction mixture was adjusted to approximately pH 6, with glacial acetic acid. After stirring the mixture for an additional 4 h, the mixture was diluted with ether (10 mL) and washed with 1N NaOH solution (5 mL). The ether layer was washed with H_2O (2 x 5 mL), dried ($MgSO_4$) and evaporated yielding **23** as a colorless oil, 139 mg (99%). GC analysis indicated no starting material: ^1H NMR ($CDCl_3$) δ 1.04 and 1.08 [2d, J = 6.6 Hz, 6, $CH(CH_3)_2$], 2.29 (s, 3, NCH_3), 2.55 (m, 2, CH_2N), 2.84 (t, J = 7.2 Hz, 2, $ArCH_2$), 2.93 [septet, J = 6.6 Hz, 1, $CH(CH_3)_2$], 3.37 (s, 1, OCH_3), 3.58 (t, J = 7.1 Hz, 2, CH_2OCH_3), 4.00 (m, 3, OCH_2CHOH), 6.88 (d, J = 8.7 Hz, 2, ArH-2 and H-6) and 7.15 (d, J = 8.6 Hz, 2, ArH-3 and H-5).

The above *N*-methylated (±)-metoprolol (**23**) (20 mg) was dissolved in benzene (200 μL), and triethylamine (10 μL) and (2*R*)-2-methoxy-2-(trifluoromethyl)phenylacetyl chloride (30 μL) were added in succession. After vortex mixing, the reaction mixture was allowed to stand at room temperature for 1 h. The mixture was then diluted with ether (10 mL), washed with 5% $NaHCO_3$ solution (2 x 5 mL) and dried ($MgSO_4$). After removal of the solvent, the crude residue was flash

chromatographed on a 1 x 20 cm column eluting with CH_2Cl_2:methanol::95:5 mixture to yield **24** as a colorless oil, 32 mg: ^1H NMR ($CDCl_3$) δ 0.99 [m, 6, $CH(CH_3)_2$], 2.24 and 2.28 (2s, 3, NCH_3), 2.57 to 2.94 (m, 5, CH_2NCH and $ArCH_2$), 3.36 (s, 3, CH_2OCH_3), 3.57 (m, 5, CH_2OCH_3 and CF_3COCH_3), 3.99 to 4.28 (m, 2, $ArOCH_2$) 5.57 (m, 1, $ArOCH_2CH$), 6.76 and 6.82 (2d, J = 8.6 Hz each, 2, ArH-2 and H-6) 7.10 and 7.14 (2d, J = 9.0 Hz each, 2, ArH-3 and H-5), 7.35 (m, 3, $CF_3C(OMe)$ArH-2 and H-6).

Both (2*R*)-**1** and (2*S*)-**3** were *N*-methylated and then esterified with (2*R*)-2-methoxy-2-(trifluoromethyl)phenylacetyl chloride as described above, and the esters were subjected to ^1H NMR analysis. 2*R*-Metoprolol [(2*R*)-**1**] was in 97% ee, and (2*S*)-metoprolol-d_2 [(2*S*)-**3**] was in 94% ee as determined by the integration of the *N*-CH_3 signals.

Chiral HPLC method. An HPLC system consisting of a Chiralcel OD 4.6 mm x 250 mm column (Daicel Chemical Industries Limited, Tokyo) and an UV detector (254 nm) operated with mobile phase, *n*-hexane:2-propanol:diethylamine::80:20:0.4 at a flow rate of 0.5 mL/min and 140 psi column head pressure was used for the analyses. Solutions containing 125 ng/μL of each of the (±)-metoprolol (**1**), (2*R*)-**1**, (2*R*)-**2**, (2*S*)-**3** and (2*S*)-**4** in the mobile phase were prepared and 10-20 μL quantities of each were analyzed. (±)-Metoprolol was resolved into enantiomers with retention times 10.19 and 16.73 min for (2*R*)- and (2*S*)-enantiomers, respectively. (2*R*)-**1** was found to be in 96.4% ee, (2*R*)-**2** in 96.2% ee, (2*S*)-**3** in 94.2% ee, and (2*S*)-**4** in 94.0% ee.

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