

Enantioselective Preparation of Metoprolol and Its Major Metabolites

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(Received March 21, 2000)

To obtain the standard compounds of metoprolol for a pharmacokinetic study, a convenient synthetic procedure to prepare enantiomers of metoprolol (**3a**) and its major metabolites, 2-4-(2-hydroxy-3-isopropylamino)propoxyphenylethanol (**3b**) and 4-(2-hydroxy-3-isopropylamino)pro-poxyphenylacetic acid (**4**), was developed from their respective starting materials, 4-(2-methoxyethyl)phenol (**1a**), 4-(2-hydroxyethyl)phenol (**1b**) and methyl 4-hydroxyphenylacetate (**1c**). These phenolic compounds (**1a, b, c**) were converted *in situ* to their corresponding phenoxides with sodium hydroxide treatment followed by (R)- or (S)-epichlorohydrin treatment. The resulting epoxides **2** were transformed to **3** through reaction with isopropylamine. Ester **3c** was hydrolyzed to the metabolite **4**. Measured using the HPLC method on chiral column without any derivatization, the optical purity of enantiomers of metoprolol and *o*-demethylated metabolite **3b** ranged between 96-99% ee and that of enantiomers of carboxylic acid metabolite **4** ranged 91% ee.

Key words: Enantioselective synthesis, Metoprolol, Metabolites of metoprolol

INTRODUCTION

Metoprolol is a β -selective adrenoceptor antagonist used for the treatment of angina and hypertension. The (S)-enantiomer of this agent exhibits 33-times more potency than its (R)-enantiomer in the heart (Nathansson, 1998). Metoprolol is eliminated through hepatic metabolism (Chiu *et al.*, 1997) mainly by oxidative deamination and *O*-dealkylation and further oxidation and aliphatic hydroxylation (Borg *et al.*, 1975 and Johnsson *et al.*, 1976). It has been known that its enantiomers are metabolized at different rates (Murphy *et al.*, 1990). Since metoprolol is metabolized extensively in humans, it is important to determine its enantiomers and their major metabolites in measuring the pharmacokinetic profile of metoprolol (Li *et al.*, 1995).

Enantiomers of metoprolol and its metabolites are not commercially available at present, and preparative HPLC (Kim *et al.*, 1999) and some other processes to produce them are time consuming. In this paper, a simple and highly enantioselective method for the preparation of enantiomers of metoprolol (**3a**) and its major metabolites

3b and **4** from commercially available materials is described.

MATERIALS AND METHODS

4-Hydroxyphenethyl alcohol, 4-hydroxyphenylacetic acid, (RS)-, (R)- and (S)-epichlorohydrin (97% ee) were obtained from Aldrich Chemical (St. Louis, MO, USA), and 4-(2-methoxyethyl)phenol was obtained from TCA Co. (Tokyo, Japan). All solvents were distilled prior to use. Unless noted, other commercially available reagents were used as received. Chiral columns used for the measurement of enantiomeric excess (ee) are Chiracel OD (4.6 \times 250 mm, 5 μ m) from Daicel Chem. (Tokyo, Japan) and Sumichiral OA-4900 (4.6 \times 250 mm, 5 μ m) from Sumika Chem. (Osaka, Japan). Melting points (m.p.) were determined on Electrothermal 1A 9100 MK2 apparatus and were uncorrected. IR spectra were recorded with Jasco IR-Report-100 IR spectrometer in cm^{-1} and corrected against peak at 1601 cm^{-1} of polystyrene. NMR spectra were measured in δ against the peak of tetramethylsilane by JEOL JNM-EX90 NMR (89.45 MHz) spectrometers. Mass spectra (Ms) were obtained by JEOL MS SX-102A mass spectrometer. Elemental analysis was performed with the EA1110 elemental analyzer (CE Instrument).

Preparation of (S)- and (R)-3a (metoprolol)

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To a solution of **1a** (0.5 g, 3.3 mmol) in methanol (5 mL), sodium hydroxide (0.14 g, 3.4 mmol) was added, and the mixture was stirred at room temperature for 20 minutes. (R)-Epichlorohydrin (0.26 mL, 3.3 mmol) was then added. The reaction mixture was stirred overnight at room temperature and poured into water (20 mL). After extraction of the mixture with chloroform (3 × 20 mL), the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The obtained residue was subjected to column chromatography on silica gel (dichloromethane:methanol=20:1) to give 3-[4-(2-methoxyethyl)phenoxy]-1,2-epoxypropane (**2a**, 0.36 g, 51.5 % yield) as pale brown liquid. ¹H-NMR (CDCl₃) δ 2.74 (4H, m), 3.35 (3H, s), 3.56 (2H, t, J=7.2 Hz), 3.90 (3H, m), 6.87 (2H, d, J=9.0 Hz), 7.18 (2H, d, J=9.0 Hz).

Isopropylamine (2 mL) was added to a solution of **2a** (0.2 g, 0.96 mmol) in methanol (5 mL) and stirred at 60–65°C for 20 min. The solvent was then evaporated under vacuum, and the residue was dried *in vacuo* to give (S)-1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethylamino)-2-propanol] (**S-3a**, 0.25 g, 98% yield) as white solid. m.p. 39–40°C [35°C *lit.* (Kai *et al.*, 1992)]; ee=97.2%, [α]_D²⁶ = -8.70 (c, 10.0, CHCl₃); IR (KBr) 3270, 3100 cm⁻¹; ¹H-NMR (CDCl₃) 1.08 (6H, d, J=6.3 Hz), 2.80 (5H, m), 3.35 (3H, s), 3.56 (2H, t, J=7.2 Hz), 3.99 (3H, m), 6.87 (2H, d, J=9.0 Hz), 7.18 (2H, d, J=9.0 Hz); MS *m/z* (rel. intensity) 267 (M⁺, 30), 252 (41), 223 (100), 107 (45); Anal. Calcd. for C₁₅H₂₅NO₃ C 67.38, H 9.42, N 5.24; Found C 68.11, H 9.98, N 5.11.

The same procedure used to prepare (S)-**3a** was employed to prepare (R)-**3a** using (S)-epichlorohydrin. (R)-**3a**: ee 94.4%, [α]_D²⁶ = +8.70 (c, 10.0, CHCl₃).

Preparation of (S)- and (R)-3b (o-demethylmetoprolol)

To a solution of **1b** (0.5 g, 3.6 mmol) in methanol (5 mL), sodium hydroxide (145 mg, 3.6 mmol) was added, and the solution was stirred at room temperature for 20 minutes. Then (R)-epichlorohydrin (0.28 mL, 3.6 mmol) was added, and the mixture was stirred at 60–65°C for 45 min. The reaction mixture was diluted with water (20 mL) and extracted with chloroform (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The obtained residue was subjected to column chromatography on silica gel (hexane:ethyl acetate=2:1) to give 2-4-(2,3-epoxy)propoxyphenylethanol (**2b**, 0.32 g, 47.2 % yield) as white solid. ¹H-NMR (CDCl₃) δ 2.74 (4H, m), 3.90 (5H, m), 6.87 (2H, d, J=9.0 Hz), 7.18 (2H, d, J=9.0 Hz).

Isopropylamine (1.5 mL) was added to a solution of **2b** (0.1 g, 0.5 mmol) in methanol (5 mL) and stirred at 60–65°C for 20 min. The solvent was removed under vacuum to give pure (S)-2-[4-(2-hydroxy-3-isopropylamino)propoxyphenyl]ethanol (o-demethylmetoprolol, (S)- **3b** (0.12 g, 94% yield) as white solid. mp 91–93°C; ee=

93.5%, [α]_D²⁵ = -7.80 (c, 10.0, CHCl₃); IR (KBr) 3400, 2950 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.08 (6H, d, J=6.3 Hz), 2.80 (5H, m), 3.99 (5H, m), 6.87 (2H, d, J=9.0 Hz), 7.18 (2H, d, J=9.0 Hz); MS *m/z* (rel. intensity) 253(M⁺, 19), 209(15), 107(100); Anal. Calcd. for C₁₄H₂₃NO₃: C 66.37, H 9.15, N 5.53; Found C 66.51, H 9.60, N 5.33.

The same procedure used to prepare (S)-**3b** was employed to prepare (R)-**3b** using (S)-epichlorohydrin. (R)-**3b**: ee=93.6%, [α]_D²⁵ = +7.80 (c, 10.0, CHCl₃).

Preparation of (S)- and (R)-4

To a solution of **1c** (1.03 g, 6.2 mmol) prepared from esterification of 4-hydroxyphenylacetic acid in methanol (5 mL), sodium hydroxide (0.245 g, 6.1 mmol) was added, and the solution was stirred at room temperature for 20 minutes. (R)-Epichlorohydrin (0.485 mL, 6.2 mmol) was added and refluxed for 90 min. After the solvent evaporated under vacuum, the residue was diluted with water (20 mL) and extracted with chloroform (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The obtained residue was subjected to column chromatography on silica gel (dichloromethane:methanol=20:1) to give methyl 4-(2,3-epoxy)propoxyphenylacetate (**2c**, 0.64 g, 46.5% yield) as liquid. ¹H-NMR (CDCl₃) δ 2.78 (2H, m), 3.59 (2H, s), 3.64 (3H, s), 4.02 (3H, m), 6.85 (2H, d, J=9.0 Hz), 7.14 (2H, d, J=9.0 Hz).

Isopropylamine (1.5 mL) was added to a solution of **2c** (0.64 g, 2.88 mmol) in methanol (5 mL) and stirred at 60–65°C for 20 min. The solvent was removed under vacuum, and the residue was separated by column chromatography on silica gel (dichloromethane:methanol=20:1) to give methyl 4-(2-hydroxy-3-isopropylamino)propoxyphenylacetate (**3c**, 0.7 g, 86.5% yield) as yellow liquid. ¹H-NMR (CDCl₃) δ 1.19 (6H, d, J=6.3 Hz), 2.94 (3H, m), 3.56 (2H, s), 3.68 (3H, s), 4.06 (3H, m), 6.87 (2H, d, J=9.0 Hz), 7.18 (2H, d, J=9.0 Hz).

Potassium hydroxide (0.138 g, 2.46 mmol) was added to a solution of **3c** (0.7 g, 2.49 mmol) in methanol-water (1:1) and stirred for 2 h. The solution was filtrated, and the filtrate was evaporated under vacuum. The residue was purified by column chromatography on silica gel (methanol:water=10:1, 5:1, 100:0) to give potassium (S)-4-(2-hydroxy-3-isopropylamino)propoxyphenylacetate (**4**, 0.64 g, 85.4 % yield) as white solid. m.p. 182–184°C; ee=91.1%, [α]_D²³ = -13.3 (c, 2.0, CH₃OH:H₂O=1:1); IR (KBr) 3400, 3210, 1550 cm⁻¹; ¹H-NMR (CD₃OD) δ 1.05 (6H, d, J=6.3 Hz), 2.75 (3H, m), 3.36 (2H, s), 4.00 (3H, m), 6.87 (2H, d, J=9.0 Hz), 7.18 (2H, d, J=9.0 Hz); 4-(2-hydroxy-3-isopropylamino)propoxyphenylacetic acid: MS *m/z* (rel. intensity) 267(M⁺, 15), 223(100), 107(98), Anal. Calcd. for C₁₄H₂₀NO₄K: C 55.06, H 6.60, N 4.59; Found C 55.84, H 6.60, N 4.59.

The same procedure used to prepare (S)-**4** was employed

to prepare (R)-**4** using (S)-epichlorohydrin. (R)-**4**: ee = 91.1%, $[\alpha]_D^{23} = +13.3$ (c, 2.0, CH₃OH:H₂O = 1:1).

Measurement of optical purity

The optical purities of enantiomers of **3a**, **3b**, and **4** prepared were measured by HPLC method with chiral column without any derivatization. The products were dissolved in methanol (0.1 mg/mL). To separate the enantiomers of **3a** and **3b**, *n*-hexane:ethanol:2-propanol :diethylamine (88:6:6:0.25, v/v) on Chiracel OD (4.6 × 250 mm, 5 μm) was used. To separate the enantiomers of **4**, *n*-hexane:dichloromethane:trifluoroacetic acid (24:60:2: 0.1, v/v) on Sumichiral OA-4900 (4.6 × 250 mm, 5 μm) was used. Eluent flow rate was 1.0 mL/min., and detection was carried out at UV 276 nm. Optical purity was calculated using the area of each peak.

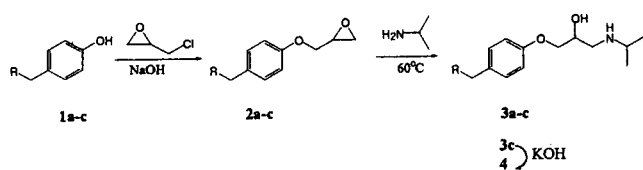
RESULTS AND DISCUSSION

Several protocols have been developed for the asymmetric synthesis of metoprolol (Gurjar *et al.*, 1998), α-hydroxy metabolite (Shetty *et al.*, 1988), and fluorinated metoprolol (Iseki *et al.*, 1997). Most of these methods require more than five steps, and therefore overall yield and enantiomeric excess are relatively low. Several patents exist on the synthesis of (S)-metoprolol through stereoselective epoxidation of 4-(2-methoxyethyl)phenyl allyl ether into 4-(2-methoxyethyl)phenyl glycidyl ether using microorganism (Phillips *et al.*, 1990) and through the intermediate produced by reacting 4-(2-methoxyethyl)phenol with (S)-5-hydroxymethyl-3-isopropylloxazolidin-2-one (Keding *et al.*,

1991). Sasai *et al.* (1995) established a catalytic asymmetric synthesis of (S)-**3a** starting with **1a** in four steps (overall yield 63%, ee 85%). These processes are somewhat complicated. Therefore, new synthetic procedure for the preparation of enantiomer of metoprolol and its metabolites was developed, as shown in Scheme 1, to perform a pharmacokinetic study of metoprolol.

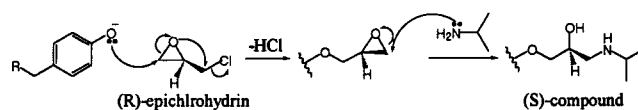
Phenolic compounds **1** was initially converted to the corresponding phenoxides *in situ* using one equivalent sodium hydroxide in methanol. The reaction mixture was then treated with epichlorohydrin to give 2,3-epoxypropoxy compound **2**. On treatment with isopropylamine, **2** transformed into the desired compound (**3**) in a satisfactory yield. To prepare **4**, **3c** was hydrolyzed using potassium hydroxide in aqueous methanol (1:1). Upon neutralization of **4** with hydrochloric acid or acetic acid, it formed hygroscopic salt due to its inherent amino acid property. Therefore, **4** as a potassium salt form was isolated and characterized.

For the preparation of enantiomers of **3**, (R)- or (S)-epichlorohydrin was used to synthesize S- or R-enantiomers of **2**, respectively. Scheme 2 explains the stereochemical conversion of epichlorohydrin in this procedure. The optical purities of the enantiomers of **3a**, **3b**, and **4** were measured by HPLC (Fig. 1) and are listed in Table I. The enantiomeric excesses of the enantiomers of **3a** and **3b** well reflect the optical purity of epichlorohydrin (97% ee) used in the first step. The optical purities (91.1% ee) of the enantiomers of **4** is slightly less compared to those of the isomers of **3a** and **3b**, though the purities still indicate that these products could be used as standards for the pharmacokinetic study. However, enantiomers of **4**, obtained from the reaction of **1c** with the enantiomers of epichlorohydrin in the presence of excessive amount of triethylamine instead of sodium hydroxide, exhibit mark-



R for a: CH₂OCH₃ b: CH₂OH c: COOCH₃
R for 4: COOK

Scheme 1. Synthesis of metoprolol and its metabolites



Scheme 2. Mechanism for stereochemical conversion of (R)-epichlorohydrin to (S)-compound

Table I. Specific rotations and optical purities of compounds **3a**, **3b**, and **4**

entry No.	compounds	$[\alpha]_D^{23}$ ^{a)}		% ee ^{b)}	
		S	R	S	R
1	3a	-8.70	+8.70	99.8	97.2
2	3b	-7.80	+7.80	96.8	96.8
3	4 ^{c)}	ND ^{d)}	ND ^{d)}	38.2	47.1
4	4	-13.30	+13.30	91.1	91.1

^{a)} $[\alpha]_D^{23}$ for enantiomers of **3a**, $[\alpha]_D^{25}$ for enantiomers of **3b**, and $[\alpha]_D^{23}$ for enantiomers of **4** are mean values of three measurements. ^{b)}Optical purities (enantiomeric excess, % ee) of enantiomers of **3a**, **3b**, and **4** were measured by HPLC method. ^{c)}During the synthesis of **4**, triethylamine was used as a base when **1c** condensed with (S)- or (R)-epichlorohydrin. ^{d)}ND: not determined.

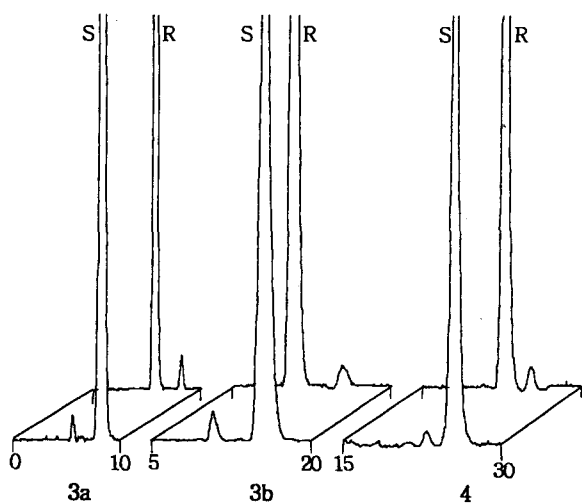


Fig. 1. Chromatogram for enantiomers of 3a, 3b and 4

edly decreased optical purities (Table I, entry 3). This reaction condition has been used generally for the condensation of phenolic compounds with epichlorohydrin (Matsuki *et al.*, 1982). This result indicates that triethylamine epimerizes the epichlorohydrin before reacting with phenolic compounds **1** and forms corresponding phenoxides from **1** using the strong base. The addition of epichlorohydrin to phenoxide of **1** is critical to secure the high optical purities of the products obtained from this procedure.

In comparison with other methods previously reported, our method of preparing metoprolol and its enantiomers is very convenient and results higher enantiomeric purity (overall yield 50%, 97.2% ee). This procedure can be easily applied in the preparation of enantiomers of the corresponding various metabolites. These features make this method more desirable than others in obtaining standard materials for the pharmacokinetic study of metoprolol and its enantiomers.

ACKNOWLEDGEMENTS

This work was supported by the Institute of Drug Research and Development at the College of Pharmacy of the Chungnam National University.

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