A Facile Stereospecific Synthesis of the [$^2H_6$]-Isopropyl-labelled Metoprolol Enantiomers from (2*R*)- and (2*S*)-Glycidyl 3-Nitrobenzenesulfonate

Satya S. Murthy and Wendel L. Nelson

Department of Medicinal Chemistry, School of Pharmacy,

University of Washington, Seattle, WA 98195

SUMMARY

Enantiomers of metoprolol containing six deuterium atoms in the isopropyl methyl groups were prepared in two steps from the sodium salt of 4-(2-methoxyethyl)phenol (**3**) and the commercially available (2*R*)- and (2*S*)-glycidyl 3-nitrobenzenesulfonates [(2*R*)-**2** and (2*S*)-**2**]. The resulting (2*R*)- and (2*S*)-epoxides were opened using [$^2H_6$]-isopropylamine. The enantiomeric excesses were 93 and 95% for the deuterated (2*R*)- and (2*S*)-enantiomers of metoprolol [(2*R*)-**1** and (2*S*)-**1**], respectively, as determined by chiral column HPLC.

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

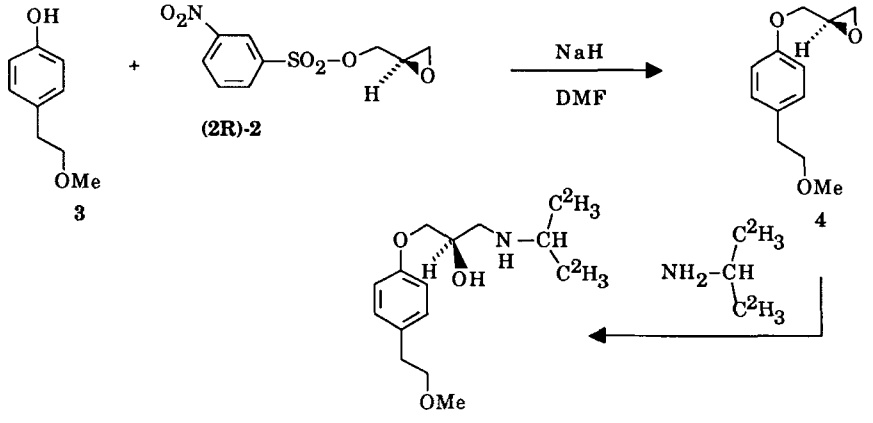
Metoprolol, a β_1-selective aryloxypropanolamine adrenergic antagonist, has been shown to be effective in the treatment of a variety of cardiovascular disorders.[1] Like many other agents of this structural type, the (2*S*)-enantiomer has significantly greater ß-adrenergic receptor affinity,[2] and there is evidence that metoprolol enantiomers are oxidatively metabolized at different rates.[3,4] The α-hydroxylation pathway shows significant product stereoselectivity in humans.[5] The oxidative metabolism of metoprolol has been shown to display genetic polymorphism of the debrisoquine type.[6,7] Concomitant therapy of metoprolol with other drugs, e.g. verapamil, has led to adverse side effects, at least in part due to inhibition of metoprolol

0362–4803/90/121411–06$05.00

Received May 9, 1990
Revised July 30, 1990

oxidation by verapamil.[8-10] In order to carefully examine the stereochemical features of metoprolol metabolism utilizing GC-MS methodology, we needed large amounts of deuterium-labelled enantiomers of metoprolol.

Although we recently reported the synthesis of deuterated enantiomers of metoprolol from the diastereomeric 2,2-dimethyl-1,3-dioxolane-4-methanols as chiral precursors, this synthesis is a somewhat tedious five-step procedure with an overall yield of 30-40%.[11] Similar processes have been used in the synthesis of enantiomers of aryloxypropanolamine ß-adrenergic antagonists. The obvious alternative synthesis from the enantiomeric glycidyl tosylates was unsatisfactory, because the metoprolol enantiomers were obtained in only 80% ee, apparently due to low selectivity in the displacement of the tosyl group *vs.* the competing opening of the epoxide ring of glycidyl tosylate. The vagaries of the regiochemistry of displacement and ring opening reactions in chiral three carbon epoxides with terminal leaving groups has been shown to be dependent upon the leaving group, the nucleophile and subtleties of the reaction conditions.[12] Whereas glycidyl triflate underwent displacement of the triflate leaving group by substituted phenoxide anions, glycidyl methanesulfonate and epichlorohydrin underwent attack at both termini. The recent availability of (2*R*)- and (2*S*)-glycidyl 3-nitrobenzenesulfonate enantiomers that show increased selectivity for the displacement of the 3-nitrobenzenesulfonate group[13] suggested reevaluation of the use of chiral glycidyl derivatives for the process.



Scheme I. Synthesis of (2*R*)-[$^2H_6$]-metoprolol [(2*R*)-1].

The synthetic procedure used was a modification of the reported procedure by Klunder, et al.[14] The starting phenol (3)[11] was allowed to react with the enantiomeric glycidyl 3-nitrobenzenesulfonates (2) to obtain the enantiomeric epoxides (4) (Scheme I). The epoxide was treated with excess [$^2H_6$]-isopropylamine, prepared by the method of Andresen and Davis,[15] to afford the [$^2H_6$]-labelled metoprolol enantiomers [(2*R*)-1 and (2*S*)-1] in 60-70% yield in two steps.

The synthesized metoprolol enantiomers were analyzed for optical purity by a chiral column HPLC system using a Chiralcel OD column[16,17] [silica-based cellulose tris-(3,5-dimethylphenylcarbamate]. For (2*R*)-1, the enantiomeric excess was 93% (96.5:3.5) and for (2*S*)-1, 95% (97.5:2.5). This facile two-step synthetic procedure appears adaptable to other labelled and unlabelled enantiomers of aryloxypropanolamines.

EXPERIMENTAL SECTION

High-field ^1H 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 E. Merck 60 silica gel F_{254} 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.[18] Gas chromatography/electron impact mass spectrometric analysis was carried out using a GC-MS system consisting of a Hewlett-Packard 5710 gas chromatograph interfaced with the 5970 series mass selective detector. 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, column head pressure 15 psi, injector temperature 250°C, and temperature program 170°C for 1 min and then increased to 250°C at 10°C per min. Deuterium incorporation was determined by selected ion monitoring of parent ions of oxazolidinone derivatives, prepared with phosgene by the method of Hoffmann, et al.,[19] *m/z* 299 [$^2H_6$], 298 [$^2H_5$], 297 [$^2H_4$] and 296 [$^2H_3$]. HPLC analysis was performed on a liquid chromatographic system consisting of a LKB 2150 pump equipped with a Waters tunable wavelength UV detector (226 nm) and a Spectra Physics SP 4100 computing integrator.

Tetrahydrofuran (THF) was distilled under argon from sodium metal with benzophenone as an indicator. Dimethylformamide (DMF) was dried over molecular sieves (3Å). All reactions were carried out under an argon atmosphere.

(2*R*)-3-[4-(2-Methoxyethyl)phenoxy]-1,2-epoxypropane [(2*R*)-4]. Sodium hydride (oil free, 0.60 g, 25.0 mmol) was suspended in DMF (8 mL, stored over 3Å sieves) at room temperature under an atmosphere of nitrogen. A solution of 4-(2-methoxyethyl)phenol (**3**)[11] (3.1 g, 20.0 mmol) in DMF (8.0 mL) was added slowly from a syringe to produce a foamy green reaction mixture. After 20 min, a solution of (2*R*)-(-)-glycidyl 3-nitrobenzenesulfonate [(2*R*)-**2**] (4.0 g, 15.4 mmol) in DMF (10.0 mL) was added dropwise by syringe resulting in a deep brown solution. The reaction mixture was stirred for 4 hr and then diluted with water (100 mL). The resulting mixture was extracted with ether (2 x 60 mL). The combined ether extracts were washed with aqueous 1N NaOH (100 mL), dried ($MgSO_4$) and evaporated to give 3.05 g (95% crude yield) of epoxide **3** as a colorless oil. The crude product was flash chromatographed on silica gel eluting with CH_2Cl_2 to afford 2.89 g of (2*R*)-**4** (90% yield). ^1H NMR ($CDCl_3$) δ 2.75 (dd, J = 4.6 and 2.7 Hz, 1, epoxide CH_2), 2.85 (t, J = 7.1 Hz, 2, ArCH_2), 2.90 (dd, J = 4.6 and 4.5 Hz, 1, epoxide CH_2), 3.35 (s, 3, OCH_3), 3.58 (t, J = 7.1 Hz, 2, CH_2OCH_3), 3.95 (dd, J = 11.0 and 5.6 Hz, 1, ArOCH_2), 4.20 (dd, J = 11.0 and 3.3 Hz, 1, ArOCH_2), 6.85 (d, J = 8.6 Hz, 2, ArH-2 and H-6), 7.15 (d, J = 8.6 Hz, 2, ArH-3 and H-5).

(2*R*)-3-[4-(2-Methoxyethyl)phenoxy]-1-([$^2H_6$]-isopropylamino)-2-propanol [(2*R*)-1]. A solution of sodium hydroxide (5.91 g, 147.8 mmol) dissolved in water (20 mL) was added slowly from a glass pipet to [$^2H_6$]-isopropylamine HCl[15] (13.37 g, 134.4 mmol) in a 200 mL round bottomed flask cooled in ice. The ice bath was removed from the stirred mixture after 5 min and the flask closed with a serum cap. Epoxide (2*R*)-**4** (2.89 g, 13.8 mmol) dissolved in acetonitrile (10 mL) was added by syringe, and the mixture was stirred overnight. The reaction mixture was evaporated to remove acetonitrile and made acidic with aqueous 1N HCl (50 mL). The acidic mixture was washed with ether (2 x 35 mL) and then made alkaline (pH 10.0) by the addition of solid NaOH and extracted with ether (2 x 70 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated to give 3.40 g of the crude (2*R*)-**1**. The product was flash chromatographed on silica gel eluting with ethyl acetate:methanol:triethylamine::90:10:0.5 to yield 2.54 g (67%) of (2*R*)-**1** as a colorless oil. ^1H NMR ($CDCl_3$) δ 2.65 - 2.90 (m, 5, CH_2NHCH and ArCH_2), 3.35 (s, 3, OCH_3), 3.55 (t, J = 7.0 Hz, 2, CH_2OCH_3), 3.90 - 4.05 (m, 3, ArOCH_2CHOH), 6.85 (d, J = 8.7 Hz, 2, ArH-2 and H-6), 7.12 (d, J = 8.7 Hz, 2, ArH-3 and H-5).

The neutral (+)-tartrate salt of (2*R*)-**1** was prepared. A solution of (2*R*,3*R*)-(+)-tartaric acid (0.70 g, 4.6 mmol) in dry acetone (10 mL) was added to a solution of (2*R*)-**1** (2.54 g, 9.2 mmol) in acetone (10 mL) and mixed. The mixture was allowed to crystallize at 0°C. After filtration, 1.6 g (40%) of light yellow crystals, mp 95°C were obtained, $[\alpha]_D^{25}$ = +29.4° (c = 1.0, CH_3OH). Mass

spectrum (oxazolidinone derivative): *m/z* 299 [$^2H_6$-79.7%], 298[$^2H_5$-16.4%], 297 [$^2H_4$-3.1%] and 296 [$^2H_3$-0.8%].

(2*S*)-3-[4-(2-Methoxyethyl)phenoxy]-1-([$^2H_6$]-isopropylamino)-2-propanol [(2*S*)-1]. Compound (2*S*)-1 was synthesized in 62% overall yield starting from (2*S*)-(+)-glycidyl 3-nitrobenzenesulfonate [(2*S*)-2] using the same procedure described above for the preparation of (2*R*)-1. ^1H NMR ($CDCl_3$) δ 2.65 - 2.90 (m, 5, CH_2NHCH and $ArCH_2$), 3.35 (s, 3, OCH_3), 3.55 (t, J = 7.2 Hz, 2, CH_2OCH_3), 3.90 - 4.05 (m, 3, $ArOCH_2CHOH$), 6.85 (d, J = 8.5 Hz, 2, ArH-2 and H-6), 7.10 (d, J = 8.5 Hz, 2, ArH-3 and H-5). The neutral (2*R*,3*R*)-tartrate salt of (2*S*)-1 was prepared by the procedure described for the preparation of the salt of (2*R*)-1. From 2.6 g (9.5 mmol) of (2*S*)-1, 1.5 g (37%) of its (2*R*,3*R*)-tartrate salt, mp 95-97°C was obtained, $[\alpha]_D^{25}$ = -4.0° (c = 1.0, CH_3OH). Mass spectrum (oxazolidinone derivative): *m/z* 299 [$^2H_6$-76.5%], 298 [$^2H_5$-18.1%], 297 [$^2H_4$-4.1%] and 296 [$^2H_3$-1.3%].

Determination of % ee by Chiral Column HPLC. 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 and (2*S*)-1 in the mobile phase were prepared and 10-20 μL quantities of each were analyzed. (±)-Metoprolol (1) was resolved into enantiomers with retention times of 10.19 and 16.73 min for (2*R*)- and (2S)-enantiomers, respectively. Compound (2*R*)-1 was found to be in 93% ee (96.5:3.5) and (2*S*)-1 in 95% ee (97.5:2.5).

ACKNOWLEDGEMENT

The authors acknowledge support of this work from grants GM 25,373 and GM 32,165 from the National Institute of General Medical Sciences.

REFERENCES

1. *Clinical Pharmacology of the β-Adrenoceptor Blocking Drugs*, 2nd edition, W. H. Frishman, ed., Appleton-Century-Croft, Norwalk, Conn., 1984.

2. Baldwin J. J. and Abrams W. B. In *Drug Stereochemistry*, Chapter 13, J. W. Wainer and D. E. Drayer, eds., Marcel-Dekker, New York, 1988, p. 319.

3. Lennard M. S., Crewe H. K., Tucker G. T. and Woods H. F. — *Biochem. Pharmacol.* **35**: 2757 (1986).

4. Gengo F. M., Ulatowski J. A. and McHugh W. B. — *Clin. Pharmacol. Ther.* **36**: 320 (1984).

5. Murthy S. S., Shetty H. U., Nelson W. L., Jackson P. R. and Lennard M. S. — *Biochem. Pharmacol.* (in press).

6. Lennard M. S., Silas J. H., Freestone S., Ramsay L. E., Tucker G. T. and Woods H. F. — *N. Engl. J. Med.* **307**: 1558 (1982).

7. McGourty J. C., Silas J. H., Lennard M. S., Tucker G. T. and Woods H. F. — *Br. J. Clin. Pharmacol.* **20**: 555 (1985).

8. Keech A. C., Harper R. W., Harrison P. M., Pitt A. and McLean A. J. — *Am. J. Cardiol.* **58**: 551 (1986).

9. McLean A. J., Knight R., Harrison P. M. and Harper R. W. — *Am. J. Cardiol.* **55**: 1628 (1985).

10. Renton K. W. — *Biochem. Pharmacol.* **34**: 2549 (1985).

11. Shetty H. U., Murthy S. S. and Nelson W. L. — *J. Labelled. Compd. Radiopharm.* **XXVII**: 1215 (1989).

12. McClure D. E., Arison B. H. and Baldwin J. J. — *J. Am. Chem. Soc.* **101**: 3666 (1979).

13. *Aldrichimica Acta* **21**: 54 (1988).

14. Klunder J. M., Ko S. Y. and Sharpless K. B. — *J. Org. Chem.* **51**: 3710 (1986).

15. Andresen B. D. and Davis F. T. — *Drug. Metab. Dispos.* **7**: 360 (1979).

16. Okamoto Y., Kawashima M. and Hatada K. — *J. Am. Chem. Soc.* **106**: 5357 (1984).

17. Okamoto Y., Kawashima M. and Hatada K. — *J. Chromatogr.* **363**: 173 (1986).

18. Still W. C., Kahn M. and Mitra A. — *J. Org. Chem.* **43**: 2923 (1978).

19. Hoffmann K. J., Gyllenhaal O. and Vessman J. — *Biomed. Environ. Mass Spectrom.* **14**: 543 (1987).