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A Practical Synthesis of (*R*)-(−)-Phenylephrine Hydrochloride

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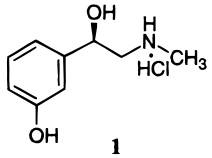
Abstract:

(*R*)-(−)-Phenylephrine hydrochloride is a clinically potent adrenergic agent and β-receptor sympathomimetic drug, exclusively marketed in the optically active form. An asymmetric synthesis has been developed with high enantiomeric excess based on hydrolytic kinetic resolution of a styrene oxide derivative using (*R,R*)-SalenCo^{III}OAc complex.

Introduction

The growing awareness of chirality in the context of biological activity has led to the discovery of many new asymmetric reactions in order to produce drugs and drug intermediates in enantiomerically pure forms. Catalytic asymmetric reactions have distinct advantages over stoichiometric versions for economic and environmental reasons. Due to growing concern about chiral drugs being sold as racemates, many pharmaceutical industries are switching over to producing enantiomerically pure forms of the chiral drugs. Since its discovery, phenylephrine hydrochloride,[1] a potent adrenergic agent and β-receptor sympathomimetic drug, has been marketed in the optical (*R*)-form. Although many nonchiral syntheses of phenylephrine hydrochloride (**1**) have been reported,[2−5] the asymmetric synthesis of (*R*)−**1** has been largely neglected.[6] Presently, (*R*)-phenylephrine hydrochloride is produced by a resolution process.[3] This paper describes a practical synthesis of (*R*)-phenylephrine hydrochloride ((*R*)**1**) using hydrolytic kinetic resolution[7,8] of a styrene oxide derivative.



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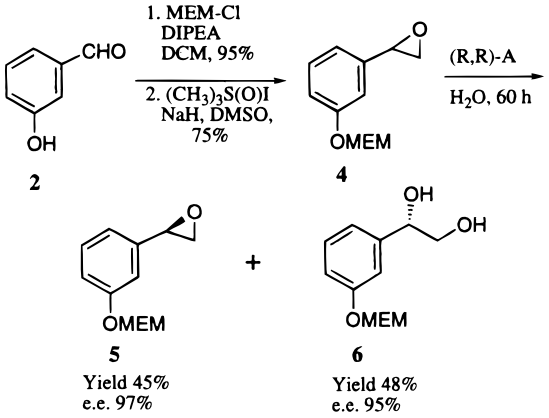
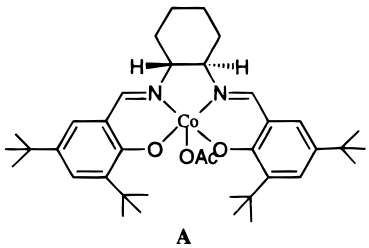
Scheme 1



Results and Discussion

Synthesis of (*R*)-(−)-phenylephrine hydrochloride (**1**) was initiated from *m*-hydroxybenzaldehyde (**2**), which was protected as the methoxyethoxymethyl ether derivative (**3**) (Scheme 1), by treatment with methoxyethoxymethyl chloride in the presence of *N,N*-diisopropylethylamine (DIPEA) and CH_2Cl_2 at room temperature for 3 h in 95% yield. Reaction of **3** with trimethylsulfoxonium iodide in the presence of NaH/DMSO at ambient temperature for 30 min yielded the racemic epoxide **4** in 75% yield.

The epoxide (±)-**4** was resolved by hydrolytic kinetic resolution by mixing with (*R,R*)-(−)-*N,N*^{1}-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt (III) acetate complex (A) (0.8 mol %) and water (0.55 equiv) at 0 °C with vigorous stirring. The reaction was monitored by HPLC



A

with an ODS column (flow rate 1.0 mL/min, UV, 225 nm) using 60% acetonitrile in water as a mobile phase. The reaction was worked up and chromatographed on silica gel to afford (*R*)-styrene oxide **5** (45% yield) and (*S*)-diol **6** (48% yield). The 95% enantiomeric excess of the diol **6** was determined by ^{1}H and ^{19}F NMR spectral studies of the

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(1) Roth, H. J.; Kleemann, A. *Pharmaceutical Chemistry*; Ellis Horwood: Chichester, 1988; Vol 1, p 41.
(2) Bergmann, E. D.; Sulzbacher, M. *J. Org. Chem.* **1951**, *16*, 84.
(3) Ravdel, G. A.; Sergievskaya, S. E. *J. Gen. Chem*. **1952**, 359.
(4) Britten, A. Z.*Chem. Ind.* **1968**, 771.
(5) Russel, P. B.; Childers, S. T. *J. Pharm. Sci*. **1961**, *50*, 713.
(6) Takeda, H.; Tachninami, T.; Aburatuni, M. *Tetrahedron Lett*. **1989**, *30*, 367.
(7) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.
(8) Brandes, B. D.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **1997**, *8*, 3927.

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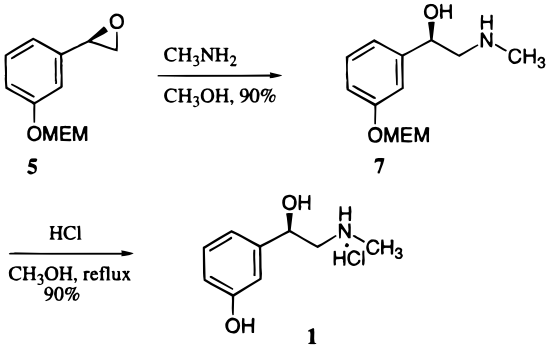
Scheme 2



corresponding (*R*)-methoxy(trifluoromethyl)phenylacetic ester (*R*-MTPA) derivative.

The (*R*)-epoxide **5** was treated with methylamine in methanol at room temperature to give the *N*-methylamino alcohol derivative **7** with 97% ee and in 90% yield[9] (Scheme 2). Removal of the methoxyethoxymethyl (MEM) group with concomitant hydrochloride formation occurred in one step when compound **7** was heated under reflux in methanolic HCl for 1 h to give **1**, (mp 141 °C; lit.[3] mp 141−144 °C). The ^{1}H NMR spectrum in D_2O and the optical rotation data were comparable to the literature values.[6]

Conclusion

An efficient and practical method for the synthesis of (*R*)-(−)-phenylephrine hydrochloride (**1**) involving hydrolytic kinetic resolution technique has been described.

Experimental Section

Optical rotations were measured on a JASCO DIP-370 digital polarimeter at 22 °C. NMR spectra were recorded on a Varian Gemini 200 MHz and a Varian Unity 400 MHz in $CDCl_3$ and D_2O. Chemical shifts are expressed in parts per million downfield from TMS. Mass spectra were recorded on VG Micro Mass 7070H (LRHS) and VG Autospec M (HRMS) spectrometers. Melting point was determined on a Buchi 535 apparatus.

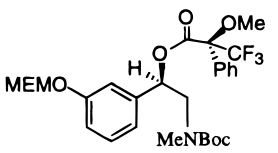
(3-Methoxyethoxymethyloxy)benzaldehyde (3). To a stirred solution of the *m*-hydroxybenzaldehyde (**2**) (20.0 g, 163.9 mmol) in dry dichloromethane (200 mL) at 0 °C were added diisopropylethylamine (42. 4 mL, 327.8 mmol) and MEM-Cl (22.4 mL, 196.6 mmol). After 3 h, the reaction mixture was washed with water (100 mL). The organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified on silica gel by eluting with EtOAc−light petroleum (1:9) to furnish compound **3** (31.0 g, 90% yield). ^{1}H NMR ($CDCl_3$): δ 3.27 (s, 3H, OCH_3), 3.47 (t, 1H, J = 4.5 Hz, OCH_2CH$_2$OCH$_3$), 3.75 (t, 1H, J = 4.5 Hz, OCH$_2$CH_2OCH$_3$), 5.25 (s, 2H, OCH_2O), 7.20−7.50 (m, 4H, *Ph*), 9.89 (s, 1H, C*H*O).

1-(3-Methoxyethoxymethyloxy)phenylethylene Oxide (4). To a stirred suspension of NaH (60% dispersion in oil, 5.7 g, 142.8 mmol) in dry DMSO (40 mL) at 0 °C was added trimethylsulfoxonium iodide (31.4 g, 142.8 mmol). After 15 min, compound **3** (25.0 g, 119.0 mmol) in DMSO (50 mL) was introduced. The reaction was stirred for 30 min at room temperature, diluted with water (100 mL), and extracted with ethyl acetate (2 × 200 mL). The ethyl acetate layer was washed with brine (100 mL), dried (Na_2SO_4), and concentrated, and the residue was filtered through a pad of silica gel and washed with EtOAc−light petroleum (1:9), followed by concentration to give **4** (20.0 g, 75% yield). ^{1}H NMR ($CDCl_3$): δ 2.72 (dd, 1H, J = 2.1 Hz, 6.4 Hz, *H*-2a), 3.09 (dd, 1H, J = 4.3 Hz, 6.4 Hz, *H*-2b), 3.36 (s, 3H, OCH_3), 3.53 (t, 2H, J = 4.2 Hz, OCH$_2$CH_2O), 3.78 (m, 3H, *H*-1 and OCH_2CH$_2$O), 5.23 (s, 2H, OCH_2O), 6.89−7.27 (m, 4H, *Ph*).

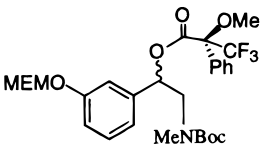
(*R*)-1-(3-Methoxyethoxymethyloxy)phenylethylene Oxide (5) and (*S*)-1-(3-Methoxyethoxymethyloxy)phenyl-1,2-ethanediol (6). A stirred solution of the epoxide (±)-**4** (18.0 g, 80.3 mmol) and (*R,R*)-SalenCo^{III}OAc complex (**A**) (0.43 g, 0.64 mmol) was cooled to 0 °C. Water (0.8 mL, 44.2 mmol) was added dropwise over a period of 1 h. The reaction mixture was then stirred at room temperature for 60 h, diluted with ethyl acetate (100 mL), dried (Na_2SO_4), and concentrated. [TLC ethyl acetate−light petroleum (3:2), R_f = 0.8 for compound **5** and R_f = 0.2 for compound **6**.] The brown syrup residue was chromatographed on silica gel using ethyl acetate−light petroleum (1:9) as eluent. The first fraction to be eluted gave (*R*)-epoxide **5** (8.1 g, 45%), $[\alpha]_D$ = −13.14° (c = 1.34, $CHCl_3$). The second fraction to be eluted afforded (*S*)-diol **6** (9.3 g, 48%), $[\alpha]_D$ = +34.44° (c = 1.49, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.38 (bs, 1H, O*H*), 2.90 (bs, 1H, O*H*), 3.36 (s, 3H, OCH_3), 3.55 (t, 2H, J = 4.5 Hz, OCH$_2$CH_2OCH$_3$), 3.60−3.77 (m, 2H, 2 × *H*-2), 3.81 (t, 2H, J = 4.5 Hz, OCH_2CH$_2$OCH$_3$), 4.77 (dd, 1H, J = 3.4, 6.8 Hz, *H*-1), 5.27 (s, 2H, OCH_2O), 6.93−7.30 (m, 4H, *Ph*). HRMS: (MH$^+$) found 243.1243, calcd for $C_{12}H_{19}O_5$ (MH$^+$) 243.1232.

(*R*)-Phenylephrine Hydrochloride (1). A solution of **5** (8.0 g, 35.7 mmol) in dry methanol (60 mL) saturated with methylamine gas was stirred at room temperature for 2 h. The reaction mixture was concentrated to give **7** (8.1 g, 90% yield). ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 3H, NCH_3), 2.76 (m, 1H, *H*-2a), 2.88 (m, 1H, *H*-2b), 3.36 (s, 3H, OCH_3), 3.58 (t, 2H, J = 4.5 Hz, OCH$_2$CH_2OCH$_3$), 3.80 (t, 2H, J = 4.5 Hz, OCH_2CH$_2$OCH$_3$), 4.79 (m, 1H, *H*-1), 5.29 (s, 2H, OCH_2O), 6.98−7.25 (m, 4H, *Ph*). HRMS: (M$^+$) found 255.1478, calcd for $C_{13}H_{21}NO_4$ (M$^+$) 255.1470.

(9) (*R*)-**7** was converted into optically pure (*R,R*)-*N*-Boc-MTPA ester **8** in two steps. Likewise, (±)-**7** was transformed into (*RS,R*)-*N*-Boc-MTPA ester **9**. Comparison of ^{1}H and ^{19}F NMR spectra of **8** and **9** conclusively confirmed 97% ee for the parent compound (*R*)−**7**.



(R,R)-8



(RS,R)-9

To a solution of **7** (8.0 g, 31.4 mmol) in methanol (80 mL) was added concentrated HCl (2 mL), and the solution was heated under reflux for 1 h. The reaction mixture was concentrated and the residue crystallized with 2-propanol to afford (*R*)-phenylephrine (**1**) (5.7 g, 90% yield; (mp 141 °C, lit.[3] mp 141−145 °C), $[\alpha]_D = -44.0°$ ($c = 2.16$, H_2O), lit.[6] $[\alpha]_D = -45.2°$ ($c = 2.0$, H_2O). ^{1}H NMR (D_2O): δ 2.78 (s, 3H, NCH_3), 3.28 (m, 2H, *H*-2), 5.03 (m, 1H, *H*-1), 6.92−7.35 (m, 4H, *Ph*).

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