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Enantioselective synthesis of (*R*)-phenylephrine hydrochloride

Rajesh Kumar Pandey, Puspesh Kumar Upadhyay and Pradeep Kumar*

Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune 411008, India

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Abstract—An efficient method for the synthesis of enantiomerically pure (*R*)-phenylephrine hydrochloride **1** is described using a Sharpless asymmetric dihydroxylation as the key step.

(*R*)-Phenylephrine hydrochloride[1] **1** (Fig. 1) is a clinically potent adrenergic agent and β-receptor sympathomimetic drug, exclusively marketed in the optically active form. Various methods for the synthesis of phenylephrine hydrochloride have been documented in the literature. Most of these approaches are nonchiral involving the use of a Curtius rearrangement of a β-hydroxy acid azide,[2] the ring opening of 3-benzyloxystyrene epoxide[3] and reduction of a mandelamide.[4] Presently (*R*)-phenylephrine hydrochloride is produced by a resolution process.[5] The asymmetric synthesis reported in the literature utilises the asymmetric hydrogenation of an aminoacetophenone derivative employing a MCCPM-rhodium complex as a chiral catalyst.[6] Another interesting synthetic strategy is based on hydrolytic kinetic resolution of a styrene oxide derivative using a (*R*,*R*)-SalenCo^{III}OAc complex.[7] However, there has been no report in the literature about the asymmetric synthesis of phenylephrine hydrochloride employing the Sharpless asymmetric dihydroxylation procedure.

As part of our research program aimed at developing enantioselective syntheses of naturally occurring amino alcohols,[8] the Sharpless asymmetric dihydroxylation[9] was envisaged as a powerful tool to chiral dihydroxy compounds offering considerable opportunities for synthetic manipulations. We have now developed a new and highly enantioselective synthesis of (*R*)-phenylephrine hydrochloride employing a Sharpless asymmetric dihydroxylation as the key step (Scheme 1).

The synthesis of (*R*)-phenylephrine hydrochloride commenced from *m*-hydroxybenzaldehyde **2**, a readily available starting material, as illustrated in Scheme 1.

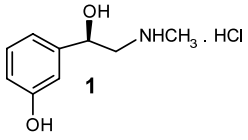
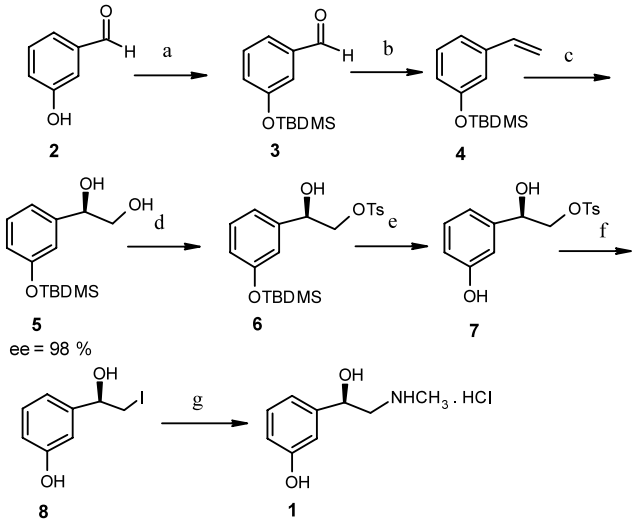


Figure 1.



Scheme 1. *Reagents and conditions*: (a) TBDMSCl, imidazole, DCM, 0°C–rt, 5 h, 90%; (b) $Ph_3P{=}CH_2$, THF, rt, 6 h, 90%; (c) $(DHQD)_2PHAL$, $K_3Fe(CH)_6$, K_2CO_3, *t*-BuOH:H_2O, OsO_4, 0°C, 24 h, 97%; (d) dibutyltin oxide (0.2, mol%), TsCl, NEt_3, DCM, rt, 45 min, 98%; (e) AcOH:H_2O:THF, 60°C, 10 h, 90%; (f) NaI, acetone, reflux, 6 h, 98%; (g) i. aq. $MeNH_2$, THF, rt, 3 h; ii. methanolic HCl, rt, 90%.

* Corresponding author. Tel.: +91-20-5893300 ext. 2050; fax:+91-20-5893614; e-mail: tripathi@dalton.ncl.res.in

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Thus treatment of **2** with *t*-butyldimethylsilyl chloride (TBDMS-Cl) in the presence of imidazole gave the silyl compound **3** in 90% yield. The subsequent Wittig olefination of **3** with methylenetriphenylphosphorane generated by the reaction of triphenylmethylphosphonium iodide and *n*-BuLi furnished styrene **4** in 90% yield. The dihydroxylation of **4** with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQD)_2PHAL$ as the chiral ligand under Sharpless asymmetric dihydroxylation conditions[9] gave the diol **5**[10] in 97% yield with 98% ee,[11] $[\alpha]_D^{25} = -34.33$ (*c* 1.2, $CHCl_3$). Selective conversion of the primary hydroxyl group of **5** into a tosylate was carried out using tosyl chloride in the presence of a catalytic amount of dibutyltin oxide to give **6** in 98% yield. Our initial attempt to synthesize **1** by the direct nucleophilic displacement of tosylate **6** with methylamine was not very satisfactory. Hence, we attempted the following sequence of reactions. Deprotection of the TBDMS group was carried out by treatment of tosylate **6** with acetic acid in THF and water (3:1:1) at 60°C to afford **7** in 90% yield. The nucleophilic displacement of tosylate **7** with sodium iodide in acetone under reflux furnished the iodo compound **8** in essentially quantitative yield, $[\alpha]_D^{25} = -16.0$ (*c* 0.16, $CHCl_3$). Compound **8** was reacted with 40% aqueous methylamine in THF at room temperature followed by subsequent treatment with methanolic HCl to furnish (*R*)-phenylephrine hydrochloride in 90% yield as a white solid, m.p. 141–142°C (lit[5] 141–145°C); $[\alpha]_D^{25} = -45.0$ (*c* 0.75, H_2O) [lit[7] −44.0 (*c* 2, H_2O)]. The physical and spectroscopic data were in full agreement with the literature.[5–7]

In conclusion, a practical and highly enantioselective synthesis of (*R*)-phenylephrine hydrochloride has been achieved employing the Sharpless asymmetric dihydroxylation as the key step. The synthetic strategy can be extended to the enantiomer and related analogs. Currently, further studies are underway in our laboratories.

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10. Compound **5**: Viscous liquid; $[\alpha]_D^{25} = -34.33$ (*c* 1.2, $CHCl_3$). IR (neat): cm^{-1} 3401, 2924, 2818, 1604, 1586, 1451, 1248. ^1H NMR (200 MHz, $CDCl_3$): δ 0.20 (s, 6H), 0.99 (s, 9H), 2.26 (bs, 2H), 3.60–3.80 (m, 2H), 4.75 (dd, $J = 4.5$, 8.5 Hz, 1H), 6.96–7.25 (m, 4H). ^{13}C NMR (200 MHz, $CDCl_3$): δ −4.67, 17.88, 25.45, 67.78, 74.25, 117.62, 118.84, 118.93, 129.04, 142.31, 155.44.
11. The enantiomeric excess was determined by HPLC. HPLC model: Merck-Hitachi Lachrom PDA system D-7000 series; Column: Lichrospher RP-18 (4 mm ID×125 mm); mobile phase: methanol: water: (65:35); flow: 1 ml/min.