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An asymmetric dihydroxylation route to enantiomerically pure norfluoxetine and fluoxetine

Rajesh Kumar Pandey, Rodney A. Fernandes and Pradeep Kumar*

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

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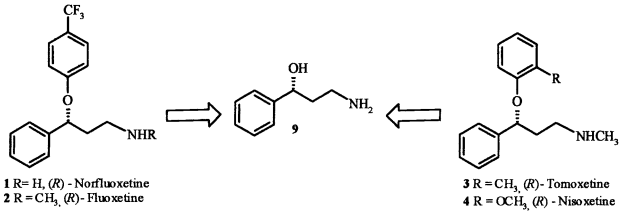
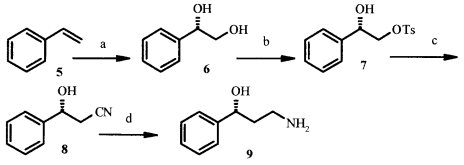
Abstract—An efficient, practical asymmetric synthesis of (*R*)-norfluoxetine **1** and (*R*)-fluoxetine **2** has been achieved. The synthetic strategy features a Sharpless asymmetric dihydroxylation (SAD) route to the common building block 1,3-amino alcohol **9**, from which (*R*)-norfluoxetine, (*R*)-fluoxetine and other related analogs can be synthesized.

Fluoxetine, tomoxetine and nisoxetine (**2**–**4**) are among the most important pharmaceuticals for the treatment of psychiatric disorders (depression, anxiety, alcoholism) and also metabolic problems (obesity and bulimia).[1] In view of different pharmacological activities displayed by the individual enantiomers and differences in metabolic behavior, the asymmetric synthesis of both enantiomers of fluoxetine and related compounds has received growing interest in recent years. Most of these approaches start with a three-carbon-chain segment and establish the chirality by enzymatic resolution,[2] asymmetric reduction,[3] asymmetric epoxidation,[4] chemical resolution[5] and an asymmetric carbonyl-ene reaction.[6] Recently a four-carbon-chain segment has been employed to make fluoxetine and its analogs by incorporating asymmetric reduction and Hofmann rearrangement.[7] Surprisingly there has been no report in the literature about the asymmetric synthesis of fluoxetine and its analogs employing the Sharpless asymmetric dihydroxylation procedure. As part of our research program aimed at developing enantioselective syntheses of naturally occurring lactones,[8a,8b] amino alcohols,[8c–e] and diolmycins,[8f] the Sharpless asymmetric dihydroxylation[9] was envisaged as a powerful tool to chiral dihydroxy compounds offering considerable opportunities for synthetic manipulations. Herein we report a new and highly enantioselective synthesis of (*R*)-fluoxetine and (*R*)-norfluoxetine through a common intermediate **9** by employing the Sharpless asymmetric dihydroxylation.

The 1,3-amino alcohol **9** is envisaged as a common building block from which (*R*)-fluoxetine and related analogs can be synthesized (Scheme 1). The synthesis of intermediate **9** starts from styrene **5**, a readily available starting material as illustrated in Scheme 2. We planned to incorporate the amine functionality early in the synthesis via cyanide addition. Towards this end, the asymmetric dihydroxylation of styrene using osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of 1,4-bis(dihydroquinin-9-*O*-yl)-phthalazine [$(DHQ)_2$–PHAL] gave the diol **6** essentially in quantitative yield with 97% ee having $[\alpha]_D^{20}$ +54.93 (*c* 1, $CHCl_3$) [lit.[10] $[\alpha]_D^{21}$ +38.1 (*c* 1.25, EtOH)].



Scheme 1.



Scheme 2. *Reagents and conditions*: (a) $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2$-PHAL, OsO_4 (cat), *t*-BuOH:H_2O (1:1), 0°C, 24 h, 100%; (b) *p*-TsCl, pyridine, CH_2Cl_2, −15°C, 24 h, 78%; (c) NaCN, EtOH:H_2O (4:1), rt, 24 h, 90%; (d) $BH_3{\cdot}SMe_2$, THF, reflux, 2 h, 96%.

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

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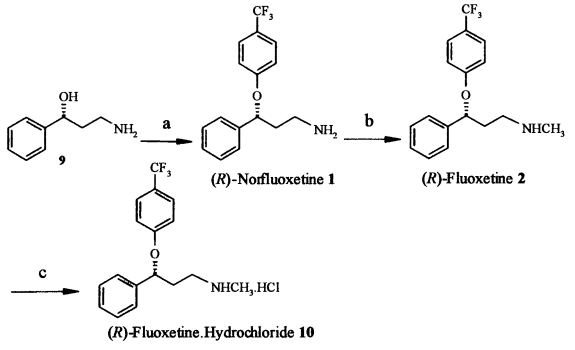
Selective conversion of the primary hydroxyl group of **6** into a tosylate was carried out using tosyl chloride in pyridine at −15°C to give **7** in 78% yield. The nucleophilic displacement of tosylate **7** with sodium cyanide in aqueous ethanol furnished cyano compound **8** in 90% yield. While the reduction of nitrile **8** with lithium aluminum hydride was not very satisfactory, the reaction proceeded smoothly with the use of borane–dimethyl sulfide as reducing agent providing the 1,3-amino alcohol **9** in 96% yield having $[\alpha]_D^{20}$ +40.5 (*c* 1, $CHCl_3$) [lit. $[\alpha]_D^{25}$ −43.65 (*c* 1, MeOH) for (*S*)-enantiomer].[4b] This key intermediate was then used to prepare the optically active (*R*)-norfluoxetine and (*R*)-fluoxetine (Scheme 3). Thus, the arylation of **9** was carried out by nucleophilic aromatic substitution employing NaH as a base and 4-chlorobenzotrifluoride as an electrophile in DMSO to afford (*R*)-norfluoxetine **1** in 90% yield. Conversion of (*R*)-norfluoxetine **1** to (*R*)-fluoxetine **2** was achieved via carbamate formation. Thus, the treatment of (*R*)-norfluoxetine **1** with methylchloroformate in aq. K_2CO_3 afforded the carbamate which on subsequent reduction with lithium aluminum hydride furnished (*R*)-fluoxetine **2** which was treated with hydrogen chloride to form the colorless, crystalline hydrochloride of **2** in 95% yield. $[\alpha]_D^{20}$ −13.6 (*c* 1, $CHCl_3$) [lit.[3a] $[\alpha]_D$ −13.8 (*c* 1, $CHCl_3$)]. The physical and spectroscopic data of **10** are in full agreement with the literature data.[3d,4a]

In summary, a practical and highly enantioselective synthesis of (*R*)-norfluoxetine **1** and (*R*)-fluoxetine **2** has been achieved for the first time using the Sharpless asymmetric dihydroxylation as the source of chirality. Thus, the results described herein constitute a short and efficient route to (*R*)-norfluoxetine and (*R*)-fluoxetine. The synthesis of other analogs, tomoxetine **3** and nisoxetine **4** can be achieved by arylation of the intermediate **9** with *o*-chlorotoluene and *o*-chloroanisole, respectively. The synthetic strategy described here has significant potential for further extension to (*S*)-enantiomers via β-dihydroxylation of **5** and following the reaction sequence as shown in Schemes 2 and 3. Currently studies are in progress in this direction.



Scheme 3. *Reagents and conditions*: (a) NaH, DMSO, 55°C, 30 min, then 4-chlorobenzotrifluoride, 90°C, 1 h, 90%; (b) (i) $ClCO_2Me$, CH_2Cl_2, aq. K_2CO_3, 30 min, (ii) $LiAlH_4$, THF, 65°C, 2 h, 90%; (c) HCl gas, ether, 95%.

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