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Chemoenzymatic Synthesis of Both Enantiomers of Fluoxetine

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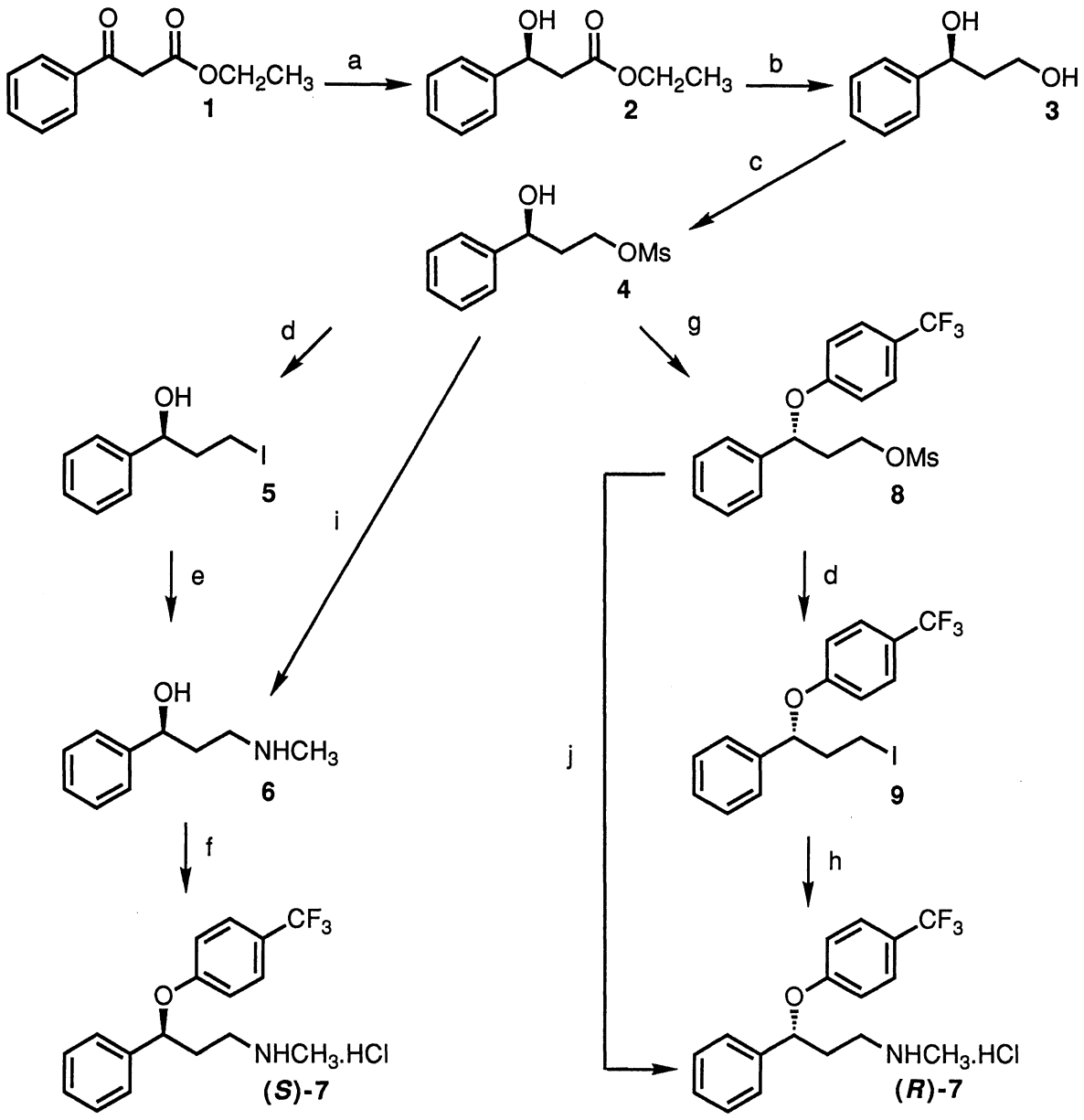
Both enantiomers of fluoxetine have been synthesized from ethyl benzoylacetate. The key step is the enantioselective reduction of the starting material by baker's yeast.

Fluoxetine **7** is one of the first selective serotonin uptake inhibitors with little effect on noradrenergic or dopaminergic systems.[1,2] Although fluoxetine is used therapeutically as a racemate, there is some stereospecificity associated with its biological action.[3,4] Three enantioselective syntheses of **7** have been reported recently. The key step of these syntheses is the preparation of an enantiomerically pure benzyl alcohol group (Ph-CHOH-). Sharpless et al.[5] reported a synthesis of fluoxetine from cinnamyl alcohol by a catalytic asymmetric epoxidation and a regioselective reduction of the epoxide. Robertson et al.[4] used a borane-mediated asymmetric reduction developed by Brown et al.,[6] whereas Corey et al.[7] used a chiral, enzyme-like catalyst or chemzyme to establish the stereocenter. We report here a novel synthesis based on the baker's yeast reduction of ethyl benzoylacetate **1**.[8]

Active fermenting baker's yeast[9,10] reduced ethyl benzoylacetate **1** to give ethyl (*S*)-3-hydroxy-3-phenyl propionate **2** in 60% yield (Scheme 1). This bioreduction has been reported[11,12] but apparently no attempt has been made to determine accurately the optical purity of the product. We established the enantiomeric purity of **2** by ^{1}H NMR analysis (200 MHz) of the MTPA derivative[13,14] (ester of α–methoxy–α–trifluoromethylphenylacetic acid, Mosher's reagent). Racemic



a) Baker's yeast (Sigma, Type I), 60% ; b) $LiAlH_4$, ether, 80% ; c) MsCl, Et_3N, ether , -10 to 0°C, 85% ; d) NaI, acetone, 96% ; e) 40% aqueous CH_3NH_2, THF, rt, 86 % ; f) (1) NaH, DMAC, 90 °C ; *p*-chlorobenzotrifluoride, 100-105 °C, 80% ; (2) $HCl_{(gas)}$, ether, 70% ; g) trifluoro-*p*-cresol, Ph_3P, DEAD, ether, -23 °C, 70% ; h) (1) 40% aqueous CH_3NH_2, THF, rt, 85% ; (2) $HCl_{(gas)}$, ether, 80% ; i) 40% aqueous CH_3NH_2, THF, 70°C, pressure tube, 93% ; j) (1) same as i), 90% ; (2) $HCl_{(gas)}$, ether, 75%.

Scheme 1.

2 obtained by reduction of **1** with $NaBH_4$ was employed as a reference compound in the NMR experiments. The values were further confirmed by ^{19}F NMR analysis of the MTPA ester. The enantiomeric purity of **2** was 90 ± 3% ee (95% *S* , 5% *R* , several runs).

Reduction of **2** with $LiAlH_4$ gave diol **3**. Treatment of the crude diol **3** with one equivalent of methanesulfonyl chloride in ether led to the monomesylate **4** in 85% yield after chromatographic purification. Treatment of **4** with an excess of 40% aqueous CH_3NH_2 in THF under reflux according to the method reported by Sharpless[5] failed to give hydroxy amine **6** in good yield. However the latter reaction gave high yield when performed in a pressure tube. In an alternative two-step procedure, **4** was treated with NaI in acetone under reflux to give **5** and then with 40% aqueous CH_3NH_2 in THF at room temperature to give **6**. Generation of the sodium alkoxide of **6** in the presence of NaH in *N*,*N*-dimethylacetamide and reaction with *p*-chlorobenzotrifluoride, followed by acidification with gaseous HCl led to the hydrochloride salt of (*S*)-fluoxetine **7**.

The monomesylate **4** was converted to (*R*)-fluoxetine in the following way: reaction with trifluoro-*p*-cresol under Mitsunobu conditions[15] (triphenylphosphine, diethyl azodicarboxylate) produced **8.** This compound was then treated with an excess of 40% aqueous CH_3NH_2 in THF in a pressure tube at 70°C followed by acidification with gaseous HCl to give the hydrochloride salt of (*R*)-fluoxetine. The two-step procedure mentioned above has also been used: transformation of mesylate **8** into the iodo intermediate **9** followed by substitution with CH_3NH_2 and acidification to give (*R*)-fluoxetine **7**.

Both enantiomers were recrystallized in hexane-ether and then samples were derivatized with (*S*)-(+)-(1-naphthyl)ethyl isocyanate, and the resulting ureas were assayed by ^1H NMR to determine optical purities according to the method developed by Robertson.[4] (*S*)-fluoxetine hydrochloride: ee ≥ 95%, $[\alpha]^{25}_D$ +6.92° (c 1.5, H_2O); lit.[5] $[\alpha]^{25}_D$ +7.08° (c 1.3, H_2O). (*R*)-fluoxetine hydrochloride: ee ≥ 95%, $[\alpha]^{25}_D$ -7.00° (c 1.50, H_2O); lit.[5] $[\alpha]^{25}_D$ -7.12° (c 1.53, H_2O).

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