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 ¹H 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) LiAlH₄, ether, 80%; c) MsCl, Et₃N, ether, -10 to 0°C, 85%; d) Nal, acetone, 96%; e) 40% aqueous CH₃NH₂, THF, rt, 86 %; f) (1) NaH, DMAC, 90 °C; p-chlorobenzotrifluoride, 100-105 °C, 80%; (2) HCl_(gas), ether, 70%; g) trifluoro-p-cresol, Ph₃P, DEAD, ether, -23 °C, 70%; h) (1) 40% aqueous CH₃NH₂, THF, rt, 85%; (2) HCl_(gas), ether, 80%; i) 40% aqueous CH₃NH₂, 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 NaBH₄ 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 \pm 3% ee (95% S, 5% R, several runs).

Reduction of 2 with LiAlH₄ 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 Sharpless⁵) 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 HCI 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 conditions¹⁵⁾ (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 $70^{\circ}C$ 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 \geq 95%, $[\alpha]^{25}_D$ +6.92° (c 1.5, H₂O); lit.⁵) $[\alpha]^{25}_D$ +7.08° (c 1.3, H₂O). (R)-fluoxetine hydrochloride: ee \geq 95%, $[\alpha]^{25}_D$ -7.00° (c 1.50, H₂O); lit.⁵) $[\alpha]^{25}_D$ -7.12° (c 1.53, H₂O).

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