Tetrahedron Letters,Vol.30 No.39,pp 5207-5210,1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Pergamon Press plc

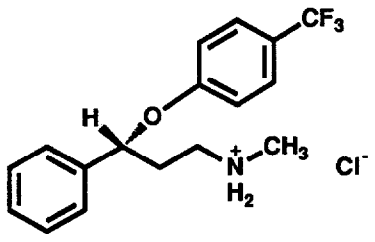
ENANTIOSELECTIVE AND PRACTICAL SYNTHESES OF *R*- AND *S*-FLUOXETINES

E. J. Corey and Gregory A. Reichard

Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138

Summary: An efficient synthetic route to either *R*- or *S*-fluoxetine is described which depends on the use of a chiral, enzyme-like catalyst (chemzyme) to establish the stereocenter and which makes these important therapeutic agents readily available in enantiomerically pure form.

One of the most exciting new therapeutic agents is the serotonin-uptake inhibitor fluoxetine, sales of which have risen beyond the 100 million dollar per annum level within a year of its introduction. Fluoxetine shows promise not only as an antidepressant (its presently indicated use) but also for treatment of anxiety, alcoholism, chronic pain, and eating disorders such as obesity and bulimia.[1] Fluoxetine hydrochloride is sold at present as the racemate ((±) - **1**) (Prozac,® Eli Lilly Co.), despite the current preference for use of enantiomerically pure medicines and the differing activities and rates of metabolism of *R* and *S* forms of **1**.[2,3] A chemically selective and enantioselective synthesis of the chiral forms of fluoxetine is obviously desirable. One enantioselective route to fluoxetines has recently been described by Gao and Sharpless[4] (5 steps, 49% overall yield, one chromatography). This note outlines a four-step synthesis of enantiomerically pure fluoxetines from commercial β-chloropropiophenone (**2**) which proceeds in 77-82% overall yield and which does not involve chromatography. The key step in the synthesis involves the recently described CBS enantioselective catalytic reduction process.[5]



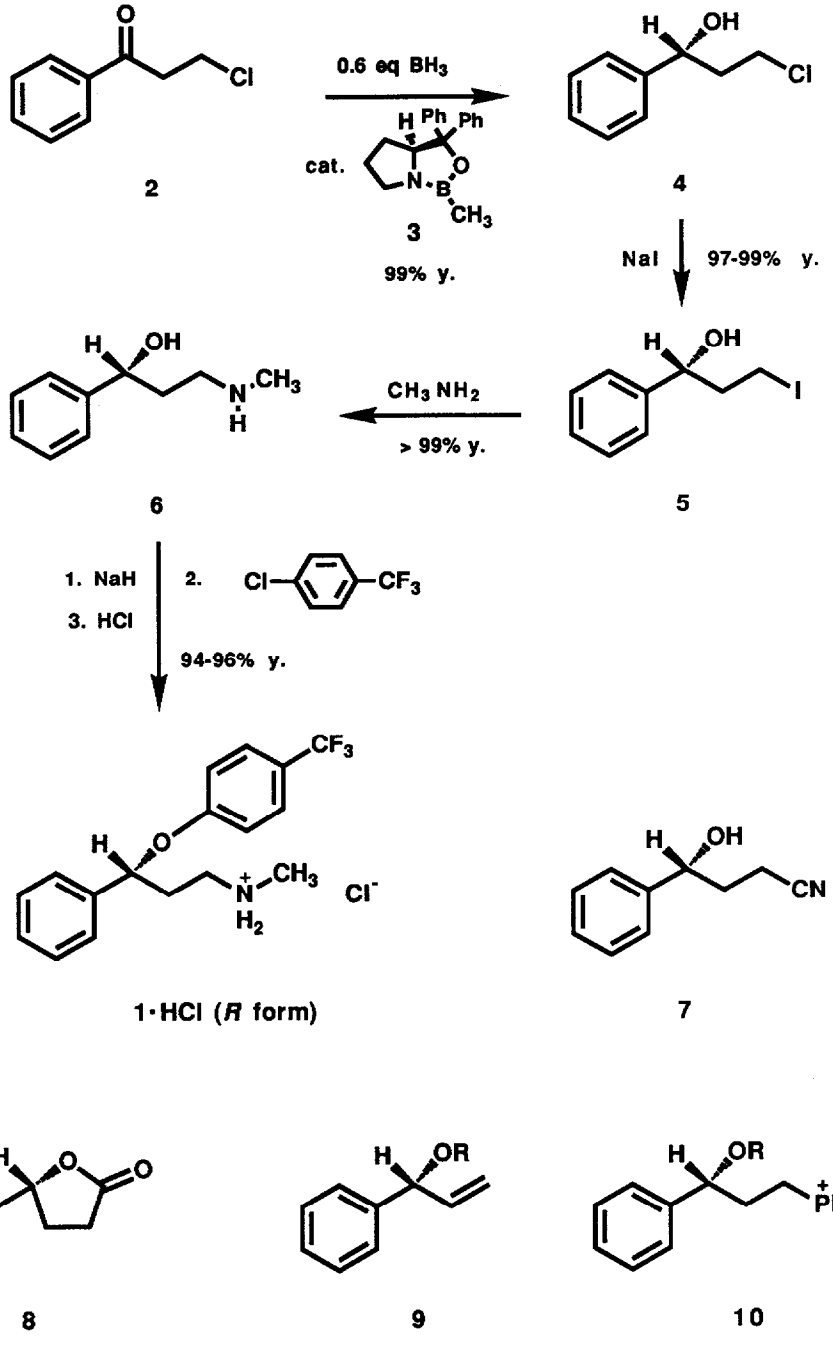
1·HCl (*R* form)

Addition of a solution of β-chloropropiophenone (**2**) in dry tetrahydrofuran (THF) to a solution of 0.6 equiv of borane as reductant and 0.1 equiv of the *S*-oxazaborolidine **3**[5b,5c] as catalyst in THF at 0°C over 20 min followed by an additional reaction period of 30 min resulted in complete and clean reduction of ketone **2** to secondary alcohol **4**. Addition of methanol and 1.2 equiv of ethereal HCl, removal of volatile components, and addition of toluene afforded the crystalline hydrochloride salt of *S*-diphenylprolinol (which could be recycled to catalyst **3**[5c]) and a solution which yielded after concentration in vacuo *R*-(+)-3-chloro-1-phenyl-1-propanol (**4**) as a crystalline solid in >99% yield and 94% ee.[6] Recrystallization from hexane afforded enantiomerically pure **4** (82%, first crop), mp 57-58°C, $[\alpha]^{23}_D$ +24.0° (c=1, $CHCl_3$). Treatment of **4** with saturated sodium iodide in acetone at reflux for 16 h provided iodo alcohol **5** (>99%), mp 53-53.5°C, $[\alpha]^{23}_D$ -4.1° (c=1.0, $CHCl_3$). Reaction of **5** in THF and 40% aqueous methylamine (50 equiv, vol. ratio 1 : 2) at 23°C for 2 h produced after concentration in vacuo and extractive isolation amino alcohol **6** as a yellow oil (>99%) which was used directly in the next step.

The amino alcohol **6** was converted to *R*-(+)-fluoxetine (**1**) in the following way. The sodium alkoxide of **6** was generated in N,N-dimethylacetamide solution using 1.1 equiv of sodium hydride by reaction at 0°C initially and then, after warming, at 70°C for 30 min. p-Chlorobenzotrifluoride was added and the mixture was heated for 2.5 h at 100°C and cooled. Extractive isolation afforded the free base form of **1** which was treated in ether with hydrogen chloride to form the colorless, crystalline hydrochloride of **1** (96%), $[\alpha]^{23}_D$ -13.8° (c=1, $CHCl_3$), shown by gas chromatographic analysis of the Mosher amide[6] to be >99.8% enantiomerically pure.

By use of the process outlined above for the synthesis of *R*-fluoxetine with substitution of the *R* enantiomer of catalyst **3** in the reduction of β-chloropropiophenone, the *S* enantiomer of **4** and, thence, the *S* enantiomer of fluoxetine were obtained. Thus, either enantiomer of fluoxetine is now easily available by a sequence which is appropriate for large scale operations, since both reaction and isolation procedures are simple and inexpensive. There is no need for chromatography or distillation. The chiral controller group used for the catalyst **3** is efficiently recoverable and can be used repeatedly.

The synthesis of fluoxetine by enantioselective, enzyme-like reduction, using the CBS catalyst **3**[5], which belongs to a new class of non-transition metal catalysts which we describe as chemzymes, provides another illustration of the value of this newly introduced methodology. Other recent applications which are noteworthy include the enantioselective synthesis of ginkgolides A and B,[7,8] forskolin,[9] and anti-PAF 2,5-diarylfurans.[10] It should also be mentioned that compounds such as chiral chloro alcohol **4** are extremely useful in synthesis. For example standard procedures convert **4** to products **7** - **10** which can serve as reagents for numerous construction reactions.[11]


0.6 eq BH3
cat.
99% y.
NaI
97-99% y.
CH3 NH2
> 99% y.
1. NaH
2.
3. HCl
94-96% y.
2
3
4
5
6
1·HCl (R form)
7
8
9
10

References and Notes

1. D. L. Murphy, E. A. Mueller, N. A. Garrick, and C. S. Aulakh, *J. Clin. Psychiatry*, **47**, (4, Suppl.), 9 (1986).

2. See D. W. Robertson, J. H. Krushinski, R. W. Fuller, and J. D. Leander, *J. Med. Chem.*, **31**, 1412 (1988) and refs. cited therein.

3. D. W. Robertson, N. D. Jones, J. K. Swartzendruber, K. S. Yang, and D. T. Wong, *J. Med. Chem.*, **31**, 185 (1988).

4. Y. Gao and K. B. Sharpless, *J. Org. Chem.*, **53**, 4081 (1988).

5. (a) E. J. Corey, R. K. Bakshi, and S. Shibata, *J. Am. Chem. Soc.*, **109**, 5551 (1987); (b) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, and V. K. Singh, *J. Am. Chem. Soc.*, **109**, 7925 (1987); (c) E. J. Corey, S. Shibata, and R. K. Bakshi, *J. Org. Chem.*, **53**, 2861 (1988).

6. Enantiomeric purity was established by ^{1}H NMR analysis of the MTPA (Mosher) ester; J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).

7. E. J. Corey, *Chem. Soc. Rev.*, **17**, 111 (1988).

8. E. J. Corey and A. V. Gavai, *Tetrahedron Letters*, **29**, 3201 (1988).

9. E. J. Corey, P. D. S. Jardine, and T. Mohri, *Tetrahedron Letters*, **29**, 6409 (1988).

10. E. J. Corey, C.-P. Chen, and M. J. Parry, *Tetrahedron Letters*, **29**, 2899 (1988).

11. This research was assisted financially by the National Institutes of Health and the National Science Foundation.

(Received in USA 7 July 1989)