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A practical asymmetric synthesis of (*R*)-fluoxetine and its major metabolite (*R*)-norfluoxetine†

James W. Hilborn,[b] Zhi-Hui Lu,[a,*] Alex R. Jurgens,[b] Q. Kevin Fang,[a] Paul Byers,[a] Stephen A. Wald[a] and Chris H. Senanayake[a,*]

[a]*Sepracor, Inc., Chemical Process R&D, 111 Locke Dr., Marlborough, MA 01752, USA*
[b]*Sepracor Canada Ltd., 24 Ivey Lane, Windsor, N.S. Canada B0N 2T0*

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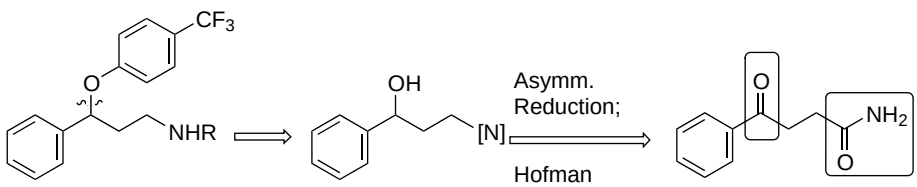
Abstract—A convenient and chromatography-free synthesis for the enantiomers of fluoxetine and norfluoxetine is described. The synthesis relied on the use of the CBS reduction, and Hofman rearrangement to establish the key common intermediate **5**, and enrichment of optical purity of the final product by crystallization as the tartrate salt.

Fluoxetine (Prozac®), marketed as a racemate, is a potent and selective inhibitor of neural serotonin-reuptake, and is used for the treatment of depression and anxiety.[1] Although both enantiomers are reportedly equal in pharmacological activity, marked differences have been observed between the two major metabolites (*R*)- and (*S*)-norfluoxetine in regard to their inhibition of 5-HT re-uptake.[2] (*R*)-Norfluoxetine is 10- to 20-fold less active than the (*S*)-enantiomer. Due to the lengthy half-life of (*S*)-norfluoxetine (16–19 days), pure (*R*)-fluoxetine is expected to reduce the time for elimination of the functional drug from the body.[3] In view of their pharmaceutical potential, it is not surprising that much effort has been expanded in devising asymmetric syntheses of both enantiomers of fluoxetine and its major active metabolites.[4–19] Most of these approaches start with a three-carbon-chain segment and establish the chirality by enzymatic resolution,[4–12] asymmetric reduction,[13–16] asymmetric epoxidation,[17,18] or resolution.[19] Among the most effective route is Corey's procedure for the preparation of the enantiomers of fluoxetine, which involves the asymmetric reduction of 3-chloropropiophenone,[13] and this method might be adaptable to the synthesis of (*R*)-norfluoxetine. We felt that it might offer certain advantages over previous methodologies, if the chiral aminoalcohol **I** could be derived from readily accessible four-carbon-chain ketoamide **II** by incorporating asymmetric reduction and Hofman rearrangement (Scheme 1). Such a strategy could circumvent the enolization problem frequently associated with previous 3-carbon strategies in the reduction of β-ketoesters, and the amide functionality of 4-carbon fragment **II** could be envisaged as a protected amine equivalent, which can be directly manipulated to either (*R*)-fluoxetine or (*R*)-norfluoxetine. Herein, we describe the first entry utilizing inexpensive methyl benzylpropi-



Scheme 1.

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* Corresponding authors. Tel.: +1-508-357-7575; fax: +1-508-357-7808; e-mail: zlu@sepracor.com; csenanay@sepracor.com
† This paper is dedicated to Professor Carl R. Johnson on the occasion of his retirement.

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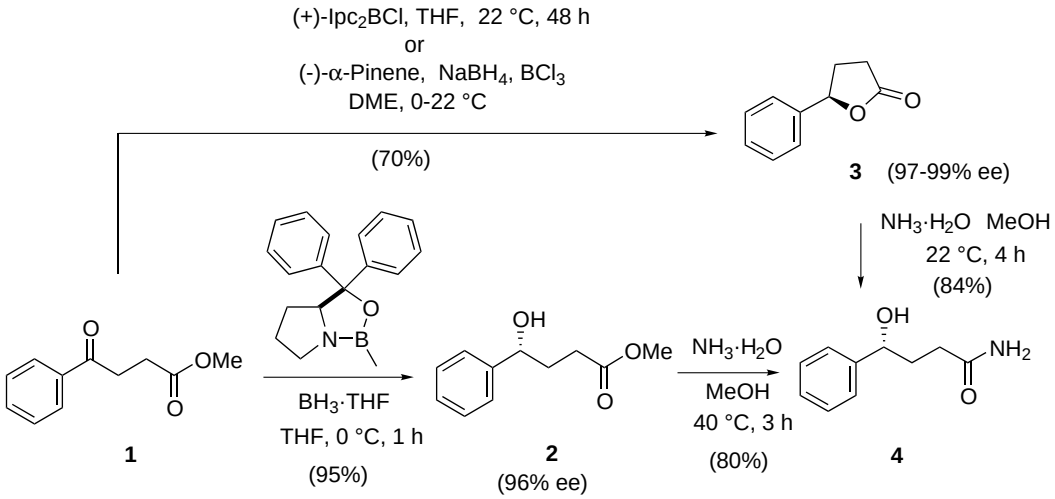
onate to synthesize (*R*)-fluoxetine and norfluoxetine via optically pure strategic cyclic carbamate **5**.

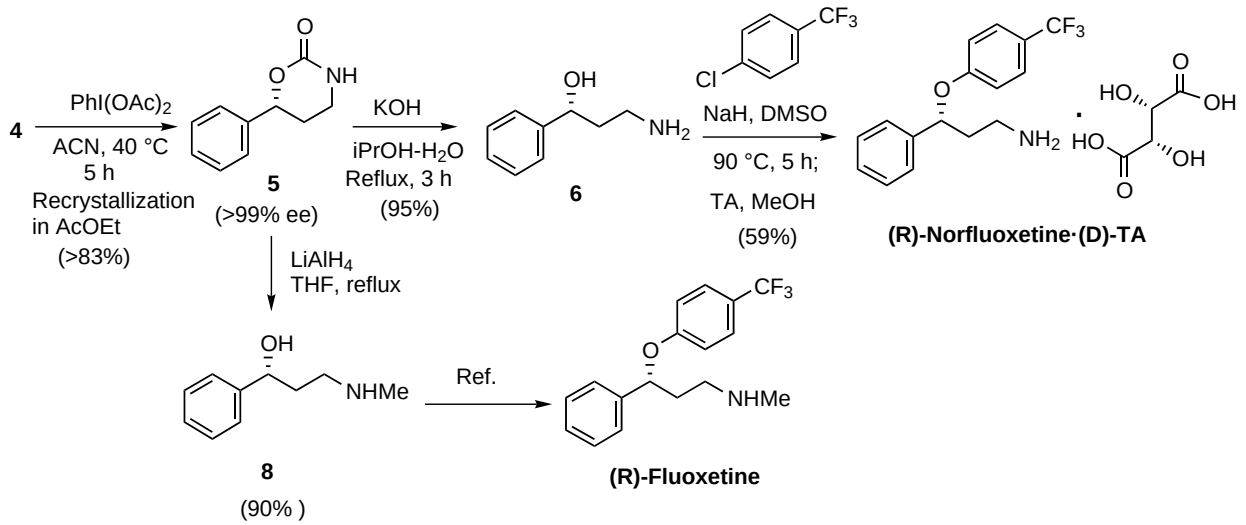
Our approach began with the conversion of methyl 3-benzoylpropionate (**1**) into (*R*)-4-hydroxy-4-phenylbutyramide (**4**) in two steps (Scheme 2). The first key-step involved the asymmetric reduction of ketoester **1** to afford methyl 4-(*R*)-hydroxy-4-phenylbutyrate (**2**), or (*R*)-χ-phenyl-χ-butyrolactone (**3**). Two approaches have been reported previously for this purpose, by using oxazaborolidine–borane reduction,[20] and BINAP–Ru(II)-catalyzed hydrogenation,[21] respectively. The latter procedure involved a rigorous reaction condition (1500 psi, 35°C) and was inefficient (258 h, 30% conversion). Therefore, the former method using Me–CBS reagent was examined. It was found that excellent enantioselectivity (96% e.e.) and high yield (95%) were achieved when the reaction was performed by simultaneous slow addition of borane and ketoester **1** to the solution of (*S*)-Me–CBS catalyst in THF.[22]

As an alternative method, asymmetric reduction of **1** with (+)-Ipc_2BCl[23] directly afforded the lactone **2** in excellent enantiomeric excess (99% e.e.). Although (+)-Ipc_2BCl is expensive, and operationally inconvenient on large-scale, the reagent could be generated in situ by treatment of α-pinene (87% e.e.) with $NaBH_4$, boron trichloride in DME.[24] The reagent generated by such a process could effectively reduce the ketoester **1** and allow formation of lactone **3** in 97% e.e. Aminolysis of either hydroxy ester **2** or lactone **3** by treatment with ammonium hydroxide in MeOH at 40°C or room temperature afforded (*R*)-4-hydroxy-4-phenylbutyramide (**4**) in 84 or 80% yield, respectively (Scheme 2).[25]

To complete the synthesis of (*R*)-fluoxetine and (*R*)-norfluoxetine, amide **4** was converted into optically pure cyclic carbamate **5** in 83% yield by Hofman rearrangement using 1 equiv. of iodobenzene diacetate in acetonitrile at 40°C, followed by recrystallization in AcOEt (Scheme 3). Hydrolysis of cyclic carbamate **5** by refluxing with KOH in aqueous isopropyl alcohol for



Scheme 2.



Scheme 3.

3 h afforded aminoalcohol **6** in 84% yield.[26] It is worth noting that isopropyl alcohol was determined to be the proper solvent for efficient extraction of this highly polar product from the aqueous phase. Contrary to intuition, isopropanol is not miscible with aqueous phase when the pH is adjusted to above 10, and has a clear phase-cut for easy separation. Arylation of the aminoalcohol **6** was carried out according to literature procedure by treatment with sodium hydride, and 4-chlorobenzotrifluoride in DMSO at 90°C.[19] Isolation of the desired product in the form of a pharmacologically useful salt from the crude mixture without using chromatography is crucial to the practicability of this process. Although formation of the HCl salt of norfluoxetine has been reported,[27] the stability of the HCl salt was poor. We found that (*R*)-norfluoxetine was readily isolated as the D-tartrate salt, by treatment of the crude product with D-tartaric acid in methanol. Furthermore, formation of the D-tartrate salt allowed for easy enrichment of the optical purity of the final product by recrystallization in methanol, in case the precursor is not optically pure. By this procedure, (*R*)-norfluoxetine·D-tartrate was obtained as a white solid in 59% overall yield for two steps, and in 99.6% e.e., as well as 99.2% chemical purity.

On the other hand, reduction of the key optically pure carbamate **5** with lithium aluminum hydride in THF, afforded *N*-methyl aminoalcohol **8** in 90% yield, which could be converted into the corresponding (*R*)-fluoxetine by the same method mentioned above.[19]

In conclusion, an economical and operationally simple process for the asymmetric synthesis of (*R*)-fluoxetine and (*R*)-norfluoxetine·tartrate has been developed via novel optically pure cyclic carbamate **5**. The process uses low-cost raw materials and conventional reagents, thereby providing (*R*)-fluoxetine and (*R*)-norfluoxetine·tartrate with >99% chemical purity and >99% e.e. without resorting to chromatography or distillation. This novel strategy is applicable to other medicinally important chiral 1,3-aminoalcohol building blocks.

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    Experimental procedure: To a dry 2.5 L round bottom flask were added (*S*)-Me–CBS (50 mL, 1.0 M in toluene, 50 mmol) and 500 mL of THF under argon. The solution was cooled to −5°C. To this solution were added simultaneously BH_3·THF (500 mL, 1.0 M in THF, 500 mmol) and ketoester **1** in neat (96 g, 500 mmol) via syringe pump. The reaction mixture was stirred at the same temperature for another 30 min and worked up by addition of 2N K_2CO_3 aqueous solution. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine and dried (Na_2SO_4). Removal of the solvents gave a pale yellow oil containing (*R*)-**2** and the catalyst. The crude product was used for next reaction without further purification. Solution yield of (*R*)-**2** was determined by HPLC (>95%). E.e. was measured by HPLC on lactone (*R*)-**3** derived from (*R*)-**2** [Column: Chiralcel AS; Mobil phase: hexane–isopropanol (90:10); wavelength: 254 nm; rate: 1.0 mL/min].
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