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Asymmetric synthesis of (–)-paroxetine using PLE hydrolysis

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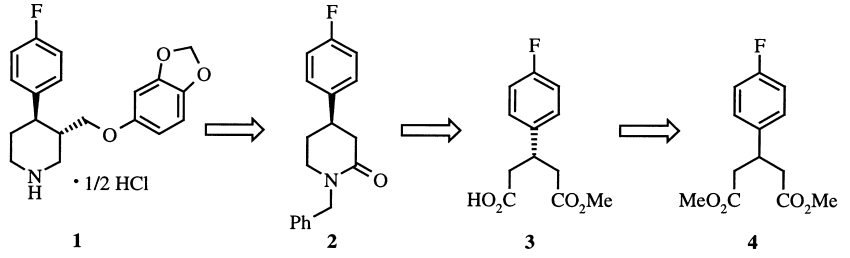
Abstract

(–)-Paroxetine hydrochloride was produced asymmetrically in seven steps starting from 4-fluorobenzaldehyde. The stereocenter at C-4 was initially set through desymmetrization of glutaric acid bis methyl ester **4** by PLE hydrolysis. A unique one-pot reduction–alkylation procedure was then developed to provide entry to lactam **2** with the appropriate absolute stereochemistry. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: enzymes and enzyme reactions; piperidines; stereochemistry.

(–)-Paroxetine hydrochloride, **1**, marketed as Paxil/Seroxat, is a selective serotonin reuptake inhibitor used in the treatment of depression, obsessive compulsive disorder, and panic which currently generates sales in excess of $1.5 billion/year. In our role as process chemists we desired a new asymmetric synthesis[1] which would be amenable to large-scale preparation. We report herein a new synthesis of **1**, whose key feature is a porcine liver esterase mediated asymmetric desymmetrization[2] followed by a novel reduction–alkylation sequence to provide the required stereochemistry at the benzylic center of the piperidine. The retrosynthetic analysis shown in Scheme 1, envisions paroxetine arising from optically pure lactam **2**, which would be derived from monomethyl glutaric acid **3**. Enzymic hydrolysis of **4** would give optically enriched **3**.



Scheme 1.

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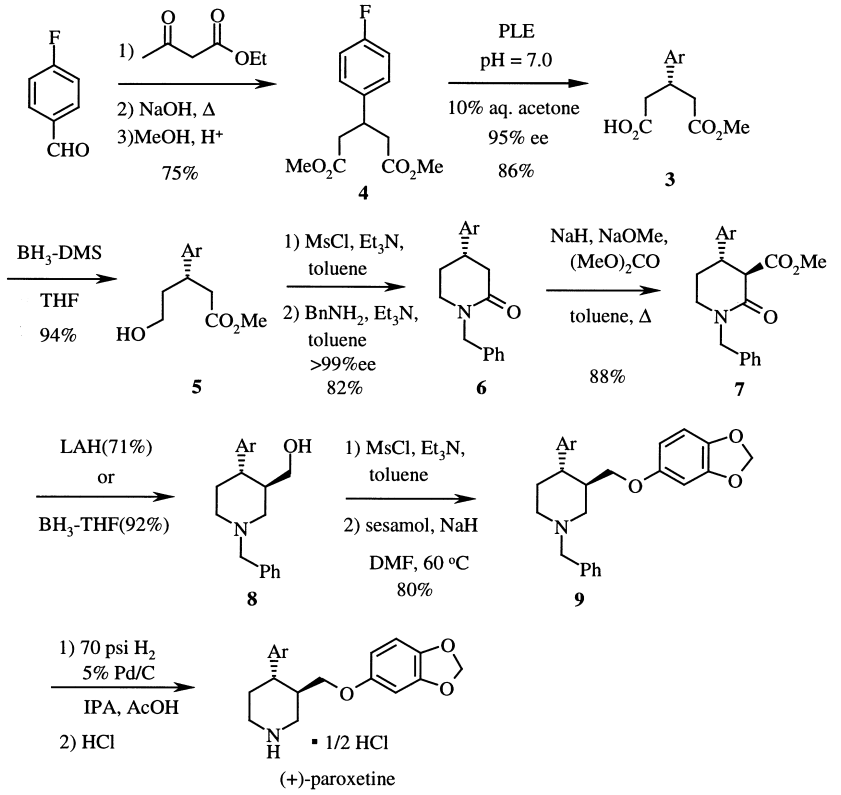
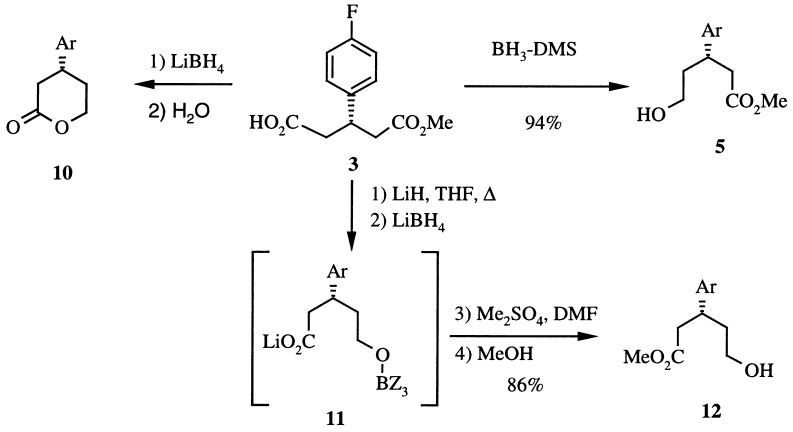
The synthesis (Scheme 2) begins with the preparation of bis ester **4** in 75% yield by reaction of *p*-fluorobenzaldehyde with ethyl acetoacetate and NaOH, followed by esterification.[3] An extensive study of numerous variables eventually found that hydrolysis of **4** with pig liver esterase (600U/gram **4**, room temperature, 10% aqueous acetone buffered to pH = 7.0) consistently afforded optically active acid ester **3** in 86% yield and 95% ee.[4] The absolute stereochemistry of **3** was initially not determined, since using borane or $LiBH_4$ could selectively reduce either the acid or the ester, respectively.[5] Therefore, regardless of the absolute stereochemical outcome of **3**, the desired enantiomer of paroxetine could, in theory, be obtained, and the optical rotation of the material produced would then be compared to authentic drug substance. Reduction of the acid functionality of **3** with borane provided **5** in 94% yield. Alcohol **5** was mesylated and treated with benzylamine to provide lactam **6** in 82% yield. The crystalline lactam **6** obtained was found to be > 99% ee.[6] Acylation afforded **7** (88%). The relative stereochemistry of the aryl group and the C-3 side chain was determined by examination of the ^1H NMR coupling constants between the C-3 and C-4 protons ($J = 11.0$ Hz). Reduction of **7** with either LAH (71%) or BH_3·THF in refluxing THF (92%) gave aminoalcohol **8**. Etherification with sesamol (80%) and hydrogenolysis of the benzyl group (93%) completed the synthesis of paroxetine. Analysis of the final product by circular dichroism, however, revealed that undesired (+)-paroxetine was obtained. This work, however, demonstrated that **3** was a useful intermediate to paroxetine and inversion of the stereochemistry by reduction of the ester would provide the proper absolute stereochemistry.



Scheme 2.

The reduction of the ester functionality of **3** was not, however, as straightforward as reduction of the acid for several reasons. First, in the case of glutaric acid derivatives spontaneous lactonization of the resultant δ-hydroxy acid occurs. Jones, in fact, reports that they were unable to find conditions that afforded the acid alcohol exclusively.[5c] Although lactone **10** could be converted to the desired lactam, the yields were unacceptably low and the transformation added to the length of the synthesis. We also found that **10** suffered from instability making it unsuitable for large-scale work. A third problem was that the chemoselectivity of the reduction was exceptionally sensitive to the quality of the $LiBH_4$. Undesired reduction of the acid was often seen when using previously opened bottles of $LiBH_4$, presumably due to the presence of borane from decomposition of the reagent. These problems were circumvented, however, by a novel deprotonation–reduction–alkylation sequence.

As shown in Scheme 3, the conversion of acid ester **3** to δ-hydroxy ester **12** begins with deprotonation using LiH in refluxing THF in order to protect the carboxylic acid as its carboxylate. Reaction with $LiBH_4$ then selectively reduced the ester with no reaction at the lithium carboxylate, even with samples of $LiBH_4$ which previously gave mixtures, to provide a boronate intermediate of general structure **11**. DMF was added to aid solubility followed by 1.6 equiv. of dimethyl sulfate to alkylate the carboxylate. After 4 h at room temperature, the reaction was quenched with MeOH resulting in an 86% yield of **12** from acid ester **3**.[7] Less than 1% of lactone could be detected in the product by HPLC and ^1H NMR. Deprotonation of **3** with LiH, therefore, not only protects the acid from undesired reduction, but also allows for methylation of the carboxylate avoiding lactone formation. The overall result is net inversion of the C-3 stereocenter and provides a true complement to the borane reduction of the acid. This was converted to desired (–)-paroxetine, which was identical to that of an authentic sample by all spectral and physical characterization methods, by the route described previously. Subsequent experimentation found that far less expensive $NaBH_4$ could be used in place of $LiBH_4$. After deprotonation with LiH, addition of $NaBH_4$ resulted in reduction of the ester as effectively, and in the same rate, as using $LiBH_4$. Since $NaBH_4$ does not reduce esters under normal conditions,[8] it is assumed that a cation exchange between the borohydride and the carboxylate takes place, forming $LiBH_4$ in situ.[9]



Scheme 3.

In summary, we have described a new asymmetric synthesis of (–)-paroxetine through the enzymatic desymmetrization of a *meso*-diester. In addition, a novel method for the transformation

of glutaric acid monoesters to δ-hydroxy esters with opposite stereoconfiguration to that obtained from borane reduction has been developed. This one-pot reaction sequence should be applicable to other monoester dicarboxylates where unwanted lactonization needs to be minimized or for the formation of esters which would otherwise be inappropriate substrates for PLE. With this new method, the desymmetrization may be optimized for enzyme and substrate without regard to stereochemical outcome, since either δ-hydroxy ester can be realized without the involvement of other chemical intermediates. Future activities in these areas are planned and will be disclosed in due course.

Acknowledgements

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7. Procedure for synthesis of **12**: Acid ester **3** (5.0 g, 20.8 mmol) was dissolved in 50 mL THF in a 250 mL round-bottomed flask equipped with spinbar and condenser. LiH (200 mg, 25 mmol, 1.2 equiv.) was added and the mixture heated at reflux and stirred for 1 h. $LiBH_4$ (300 mg, 13.5 mmol, 0.65 equiv.) was added and stirring at reflux continued for 10 h. The mixture was cooled to ambient temperature and 25 mL DMF added followed by dimethylsulfate (3.30 mL, 34.5 mmol, 1.6 equiv.). After 4 h at ambient temperature the mixture had turned into a clear pale yellow and reaction was complete as monitored by HPLC. MeOH (5 mL) and SiO_2 (5 g) were added. After 45 min the mixture was filtered and filtrate taken up in 100 mL *t*-butyl methyl ether and washed twice with 10% aq. NH_4Cl. The organic layer was rotary evaporated and dried in vacuo to give 4.65 g of **12** as a pale yellow oil, which was used without further purification. Crude yield = 99%. HPLC assay of this material showed it to be 86% by weight. ^1H NMR (300 MHz, $CDCl_3$, TMS/ppm) δ 7.15 (dd, 2H, J = 2.8, 3.3 Hz), 7.02 (apparent t, 2H, J = 2.8, 6.3 Hz), 3.56 (s, 3H), 3.50 (m, 2H), 3.31 (m, 1H), 2.61 (m, 2H), 1.86 (m, 2H), 1.62 (br s, 1H).
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