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Asymmetric Synthesis of Both Enantiomers of α-(4-Fluorophenyl)-4-(2-pyrimidinyl)-1-piperazinebutanol: Potential Antipsychotic Agents

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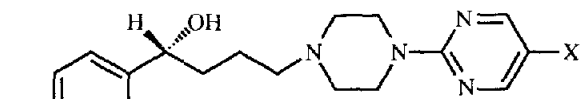
Abstract: Asymmetric syntheses of both enantiomers of the potential antipsychotic agent, α-(4-fluorophenyl)-4-(2-pyrimidynyl)-1-piperazinebutanol, have been achieved *via* the chiral reduction of 4-chloro-4'-fluorobutyrophenone with (+)- and (–)-DIP-Chloride as the key step.

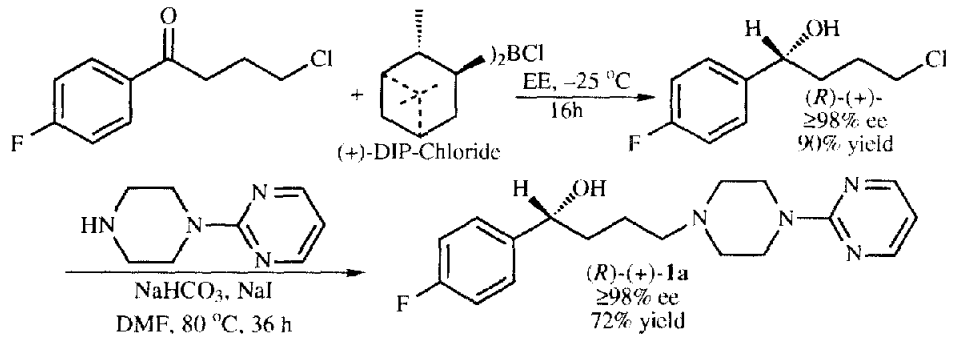
Synthesis of optically pure products as candidates for drug development is becoming a norm unless justifications are made based on differential activity, disposition and therapeutic need.[1] Drug designers are synthesizing single enantiomer products at the discovery stage itself to obtain 'cleaner drugs'. Recently, the Bristol-Myers Squibb group developed several novel and safer antipsychotic agents bearing the 1-(pyrimidin-2-yl)piperazine (1-PP) pharmacophore and selected the most successful candidate, α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanol (BMS 181100, **1b**), for clinical evaluation.[2]



(*R*)-(+)-**1a**, X = H
(*R*)-(+)-**1b**, X = F (BMS 181100)

Unfortunately, the published multistep synthesis of optically pure BMS 181100 is very lengthy and cumbersome. This procedure involves a chiral resolution using α-methylbenzyl isocyanate, providing ~10% overall yield of **1b**. We have been involved in the development of several efficient chiral reagents for the reduction of prochiral ketones.[3] From these, *B*-chlorodiisopinocampheylborane (Aldrich: DIP-Chloride™) has emerged as one of the best reagents for the chiral reduction of aralkyl and α-hindered ketones.[4] Since its introduction, DIP-Chloride has found applications for key steps in the syntheses of important pharmaceuticals and natural products. We applied DIP-Chloride for the syntheses of both enantiomers of Tomoxetine, Fluoxetine and Nisoxetine.[5] The Merck group described the use of DIP-Chloride for the syntheses of PAF-antagonists L-659,989[6a] and MK-287[6b] and an LTD_4 antagonist L-699,392.[6c] Yamamura synthesized Aplysiatoxins[7] and the Abbott group synthesized (1*R*,3*S*)-1-aminomethyl)-3,4-dihydroxy-3-phenyl-1H-2-benzopyran, a potent and selective D1 agonist.[8] Jaen and coworkers applied DIP-Chloride for the synthesis of reduced haloperidol.[9]

In this communication, we describe an efficient asymmetric synthesis of an analog of BMS 181100 *via* chiral reduction, as shown in the Scheme. Thus, the asymmetric reduction of 4-chloro-4'-fluorobutyrophenone with (+)- or (–)-DIP-Chloride[9,10] provides the corresponding (*R*)- or (*S*)-alcohol, respectively, in 90% yield. A gas chromatographic analysis of its MTPA ester[11] on a SPB-5 capillary column revealed an ee of 98%. Coupling this with 2-(1-piperazinyl)pyrimidine, prepared as described in the literature,[2] yields 72% of **1a**.



Scheme. Asymmetric synthesis of an analog of BMS 181100

The above synthesis utilizing DIP-Chloride has several advantages. Both enantiomers of the drug can be synthesized efficiently, in few steps with high chemical and optical yields. The reagent is readily available from an economical chiral auxiliary, α-pinene. Most importantly, the synthesis is quite general. The synthesis of BMS 181100 itself should be straightforward from coupling α-3-chloropropyl-4-fluorobenzene-methanol and 5-fluoro-2-(1-piperazinyl)pyrimidine.

(*R*)-α-(3-chloropropyl)-4-fluorobenzenemethanol (2.63 g, 13 mmol), prepared by the reduction of the corresponding ketone with (+)-DIP-chloride[4,9], 2-(1-piperazinyl)pyrimidine[2] (1.64 g, 10 mmol), $NaHCO_3$ (2.2 g), and NaI (0.3 g) in 100 mL DMF, were heated at 80 °C for 36 h. The solvent was removed under vacuum, the residue dissolved in water, extracted with ether (4x30 mL) and dried over $MgSO_4$. Purification of this crude product by filtration through silica gel (eluent: ether-acetone) provides (*R*)-(+)-**1a** (2.4 g, 72%) as a white solid, mp 98-100 °C, $[\alpha]_D^{21}$ = +52.6 (*c* 1.1, $CHCl_3$). Crystallization from hexane gave the product, mp 100-101 °C, $[\alpha]_D^{21}$ = +52.8 (*c* 1.1, $CHCl_3$). Elemental analysis, ^1H NMR, ^{13}C NMR, i.r., and mass spectra confirmed the structure.

A similar reaction with (*S*)-α-(3-chloropropyl)-4-fluorobenzenemethanol yielded (*S*)-(–)-**1a**: mp 100-101 °C, $[\alpha]_D^{21}$ = –52.6 (*c* 1.1, $CHCl_3$). Elemental analysis confirmed the structure.

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