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Chemoenzymatic Synthesis of *(R)*-(+)-α-(4-Fluorophenyl)-4-(2-pyrimidinyl)-1-piperazinebutanol and *(R)*-(+)-α-(4-Fluorophenyl)-4-methyl-1-piperidinebutanol as Potential Antipsychotic Agents

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Abstract: A chemoenzymatic straightforward synthesis of (*R*)-(+)-α-(4-fluorophenyl)-4-methyl-1-piperidinebutanol (**2**) and (*R*)-(+)-α-(4-fluorophenyl)-4-(2-pyrimidinyl)-1-piperazinebutanol (**3**), two potential antipsychotic agents, has been developed by two different approaches involving lipase-mediated resolution of the racemic compounds or through asymmetrization of the precursor alcohol **4**. A second enzymatic resolution followed by condensation of (*R*)-**4** with 4-methylpiperidine (**6**) or 1-(2-pyrimidinyl)piperazine (**7**) leads to (*R*)-**2** and (*R*)-**3** in good chemical and excellent optical yields (>99% ee).

Antipsychotic activity of neuroleptics, particularly derivatives of butyrophenones, is exerted by blockade of cerebral dopamine receptors[1,2]. Among them, melperone (**1**) has been effective in the treatment of anxiety, agitation and confusion, especially in geriatric patients[3]. One of its urinary metabolites (4-fluorophenyl)-4-methyl-1-piperidinebutanol (**2**) showed similar potency as melperone in increasing serum levels of prolactin, another characteristic effect of antipsychotic agents[4]. Many dopamine antagonists, however, are responsible for serious extrapyramidal effects, and therefore other neuroleptics have been synthesized to avoid such drawbacks. In this regard, Yevich and coworkers[5] have found that compounds containing the 1-(pyrimidinyl)piperazine pharmacophore, like compound **3**, displayed psycotherapeutic activity without promoting undesired effects (Figure 1).

Synthesis of enantiomerically pure molecules through enzyme-catalyzed kinetic resolution of the racemic precursors or by asymmetric induction of prochiral substrates is at present a well-defined area of research[6-10]. However, to our knowledge, no report has been found on the enantioselective synthesis of either enantiomer of **2** and only one of the two enantiomers of **3**. This involved in the key step the asymmetric reduction of 4-chloro-4'-fluorobutyrophenone with (+) or (-)-*B*-chlorodiisopinocampheylborane[11]. Continuing our efforts directed to the enzyme-mediated chiral resolution of secondary alcohols[12,13], we present herein enantioselective syntheses of compounds (*R*)-**2** and (*R*)-**3** by two different approaches involving asymmetrization of the precursor alcohol **4** followed by condensation with the appropriate amines (approach A) and lipase-mediated resolution of the racemic compounds (approach B).

1: R = O

2 : R = H, OH

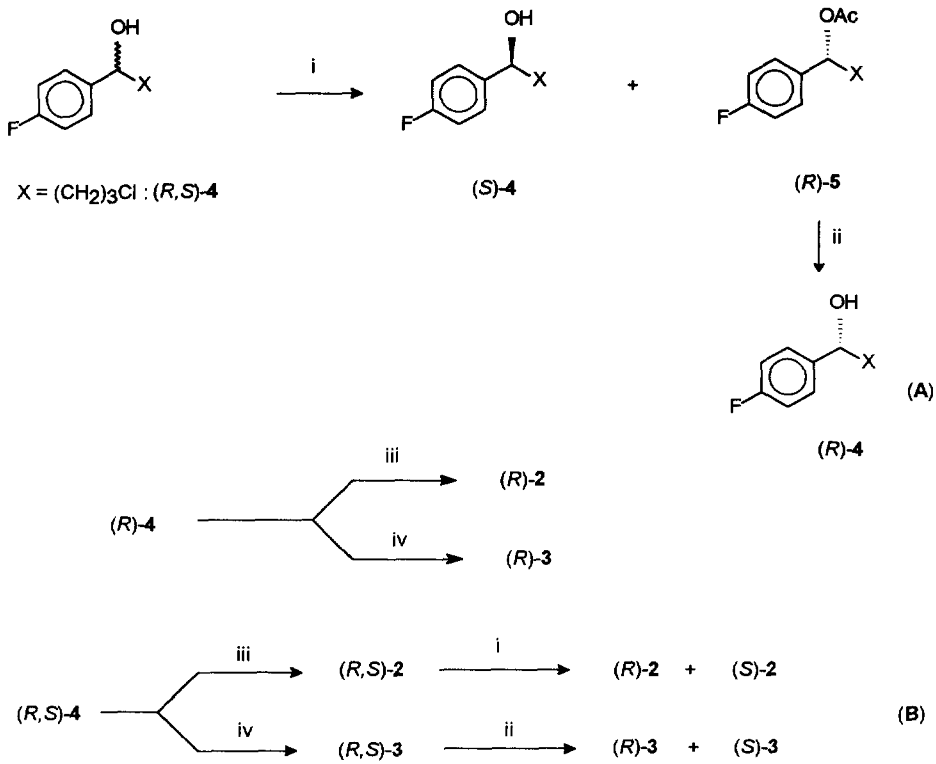
3

Figure 1

Results and Discussion

The two approaches required preparation of chloroalcohol **4**. This compound was obtained by $NaBH_4$ (1.9 equiv.) reduction of the corresponding ketone at 0°C for 7 h in 95% isolated yield. The process was optimized in order to minimize the undesired concomitant formation of the corresponding cyclized product, 2-(4-fluorophenyl)tetrahydrofuran.

Although resolution of **4** has been recently reported, very few experimental details were given[14] (approach A). In our hands and among several enzymes tested (*Pseudomonas cepacia* or lipase PS, AP6, AY, and *Rhizopus arrhizus*), best results were obtained with Celite-immobilized[15] lipase PS. Immobilization of the enzyme allowed us to dramatically reduce the 1:2 substrate:lipase ratio used by Bianchi and coworkers[14] to 1:0.1. A variety of solvents with different hydrophobicity, i.e. n-dodecane (log P 6.6), n-hexane (log P 3.5), benzene (log P 2.0), diethyl ether (log P 0.85) and acetone (log P -0.23) was also screened to examine the effect of the solvent on the degree of conversion and enantioselectivity[12,16]. In contrast to the previous report wherein the authors used diisopropyl ether as solvent, we have found that the enzyme showed highest activity in non-polar solvents, like hexane and n-dodecane, being only moderate in benzene and diethyl ether and practically inactive in highly polar solvents, such as acetone. The non-polar and more volatile solvent, i.e. hexane, was therefore used to obtain the chiral alcohol **4** in a multigram scale. When the desired conversion (ca. 50%) was achieved, the mixture was filtered off and the non-reactive alcohol (*S*)-**4** was separated from the corresponding acetate (*R*)-**5** by conventional column chromatography. The acetate was hydrolyzed under basic conditions to furnish the expected (*R*)-**4** enantiomer (Figure 2). The enantiomeric purity was determined by ^{19}F NMR or GC analysis of the corresponding Mosher esters[17]. In our hands, only the immobilized form of the enzyme provided an excellent E value (179) of the resolution process, with a 97% ee of (*R*)-**4** (44% overall yield from racemic **4**) and 85% ee of (*S*)-**4** (48% yield) (Table 1). Although the enantiomeric purity of thus obtained (*R*)-**4** is sufficiently high for many purposes, we have increased the ee value to >99% through a new enzymatic resolution of the latter alcohol in order to prepare the enantiomerically pure compounds (*R*)-**2** and (*R*)-**3**.



i: lipase PS, vinyl acetate/hexane; ii:K_2CO_3/MeOH, iii: **6**, $NaHCO_3$, NaI cat./ CH_3CN (73%)
iv: **7**, $NaHCO_3$, NaI cat./ CH_3CN (65%)

Figure 2

Coupling reaction of enantiomerically pure (*R*)-**4** with 4-methylpiperidine (**6**) or 1-(2-pyrimidinyl)piperazine (**7**), in the presence of $NaHCO_3$ and NaI as catalyst in CH_3CN at reflux for 8-13 h, provided (*R*)-**2** and (*R*)-**3** in 73% and 65% isolated yields, respectively. The ee of both compounds was >99% (Figure 2). The coupling reaction for (*R*)-**3** has been reported using DMF as solvent under longer reaction time (36 h)[11].

In approach B, racemic compounds (*R,S*)-**2** and (*R,S*)-**3**[18], resulting from racemic alcohol **4** under similar conditions than those used to obtain the chiral compounds, were subjected to a new enzymatic resolution with lipase PS. In this case, the reactions were sluggish using the free enzyme, while the immobilized form gave better results, particularly on substrate **3**. In this case and after 59 h reaction, the chemical yields of (*S*)-**3** and (*R*)-**3** were 46% and 36% overall from the racemic material and the ee values of 72% and 84%, respectively. The enantiomeric ratio (E) was 25 (Table 1). When compound **2** was tested, neither form of the enzyme efficiently enantiodifferentiated the substrate, the highest E value being only 9.

Table 1. Enzymatic resolution of alcohols 2, 3 and 4.

Comp.	Lipase	Ratio[a]	Time (h)	Conv. (%)	Yield[b] (*S*) (%)	ee[d] (*S*)	Yield[b,c] (*R*) (%)	ee[d] (*R*)	E[e]
4	PS	1:2:10	25	48	49	76	43	82	23
4	PS imm.	1:0.1:10	100	50	48	85	44	97[f]	179
2	PS	1:2:10	288	37	52	31	31	48	4
2	PS imm.	1:2:10	120	41	45	46	34	69	9
3	PS	1:2:10	126	--	--	--	--	--	--
3	PS imm.[g]	1:0.8:10	59	41	46	72	36	84	25

[a]Substrate:lipase:vinyl acetate ratio.
[b]Yields refer to pure isolated products after column chromatography purification.
[c]Overall yield of alcohol resulting from hydrolysis of the initially formed chiral acetate.
[d]Based on ^{19}F NMR or GC analysis of the diastereomeric Mosher esters[17]. Attempts to determine the ee of the chiral compounds by HPLC analysis using cellulose 3,5-dichlorobenzoate, cellulose benzoate, cellulose 3,5-dimethylphenylcarbamate, amylose 3,5-dimethylphenylcarbamate and amylose 4-chlorophenylcarbamate as chiral phases were unsuccessful.
[e]Enantiomeric ratio (E) values were determined from the ee of the residual substrate and the extent of conversion[19].
[f]A second enzymatic resolution of this alcohol afforded (*R*)-4 in enantiomerically pure form (>99%)
[g]Hexane:diethyl ether 30:70 was used as solvent.

It is known that high enantioselection in lipase-mediated kinetic resolutions requires a large difference in size of the substituents attached to the stereogenic centre, provided they fit onto the active site of the enzyme[20]. We have carried out molecular mechanics optimization of the conformational geometries of molecules **2-4** as well as those of the substituents adjacent to the carbinol group on Hyperchem™ (1994), and found that while compound **4** would need a minimum space of 107.2 Å^3 to accommodate onto the active site of the enzyme, compound **2** would require 302.8 Å^3 and compound **3** a minimum of 341.0 Å^3. The same trend was observed, i.e. **3**>**2**>**4**, when the relative volume of the substituents around the chiral carbon was considered. However, since the order of enantiopreference for the substrate is **4**>**3**>**2**, it is likely that other type of interactions, like hydrogen bondings involving the nitrogen atom(s) within the active site of the enzyme, may be responsible for the observed "abnormal" reactivities. A similar unexpected result was reported by Theil and coworkers[21], when the diisopropylaminomethyl group was one of the substituents of the carbinol in the enzymatic resolution of 3-(aryloxy)-1,2-propanediol derivatives, wherein no enantioselectivity was observed.

In summary, a chemoenzymatic synthesis of the enantiomers of the two potential antipsychotic agents **2** and **3** has been developed. The process is straightforward and allows preparation of the more reactive *R* enantiomer in excellent ee. If desired, enantiomerically pure compounds can be obtained by a second enzymatic resolution of the enriched precursor (*R*)-**4**. The procedure should be also useful for the preparation of other

butyrophenone-type chiral antidepressants, particularly BMS 181100, a fluorinated analogue of 3, which was originally prepared in a lengthy low-yield process by chiral resolution using α-methylbenzyl isocyanate[5].

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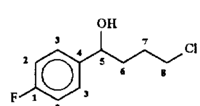
Experimental

Melting points were determined on a Koffler apparatus and are uncorrected. Elemental analyses were carried out on Carlo Erba models 1106, 1107 and 1500. IR spectra were recorded on a FT-IR Bomem MB-120 instrument. [^{1}H] and [^{13}C]NMR spectra were obtained in $CDCl_3$ solutions on a Varian XL-200 and Unity 300 spectrometers, operating at 200 and 300 MHz for [^{1}H] and 25 and 75 MHz for [^{13}C]. The values are expressed in δ scale relative to internal Me_4Si. [^{19}F]NMR spectra were recorded on a Varian Unity 300 or a Varian 500 instrument operating at 282 and 470 MHz, respectively, and the values are reported in δ scale relative to $CFCl_3$ as internal standard. Mass spectra were run on a Fisons MD 800 using a HP-5 25 m x 0,20 μm ID capillary column. GC analyses of the diastereomeric Mosher esters were performed using a BPX 35 (SGE) 25m x 0.25 μm ID capillary column. Optical rotations were measured on a Perkin Elmer 141 polarimeter. *Rhizopus arrhizus* was purchased from Fluka. Analytical-grade reagents were obtained commercially and used directly without further purification.

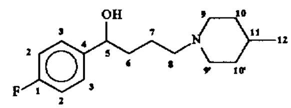
4-Chloro-α-(4-fluorophenyl)-1-butanol (4). A mixture of 2.88 g (14.35 mmole) of freshly distilled 4-chloro-*p*-fluorobutyrophenone, 0.26 g (6.90 mmole) of $NaBH_4$ and 30 ml of absolute ethanol was stirred at 0°C for 7 h. The reaction was quenched by addition of 40 ml of water. The solvent was stripped off, the resulting suspension was neutralized with 0.1N HCl and extracted with CH_2Cl_2 (3 x 40 ml). The organic phase was washed with brine and dried ($MgSO_4$). Evaporation of the solvent afforded a crude, which was purified by column chromatography on silica gel, eluting with hexane:ethyl acetate 98:2, to yield 2.77 g (95%) of alcohol 4.



IR υ: 3383, 1604, 1508, 1222, 1157, 1070, cm^{-1}. ^{1}H NMR δ: 7.34-7.25 (m, 2H, arom. $2CH_{(3)}$), 7.07-6.96 (m, 2H, arom. $2CH_{(2)}$), 4.69 (m, 1H, C<u>H</u>OH), 3.60-3.45 (m, 2H, C<u>H</u>$_2$Cl), 1.92-1.40 (m, 4H, C<u>H</u>$_2$C<u>H</u>$_2$). ^{13}C NMR δ: 162.2 (d, J=246 Hz, C-1), 140.0 (d, J=3 Hz, C-4), 127.4 (d, J=8 Hz, C-3), 115.4 (d, J=21 Hz, C-2), 73.2 (C-5), 44.9 (C-8), 36.2 (C-6), 28.8 (C-7). ^{19}F NMR δ: -115.25 (m). Elem. Anal.: Calcd. for $C_{10}H_{12}OClF$: C: 59.27; H: 5.97; Cl: 17.49; F: 9.37. Found: C: 59.18; H: 5.99; Cl: 17.67%; F: 9.28.

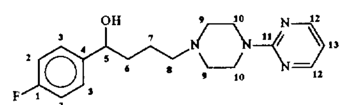
(*R,S*)-α-(4-Fluorophenyl)-4-methyl-1-piperidinebutanol (2). To a solution of 0.31 g (1.53 mmole) of alcohol 4 in 5 ml of anh. CH_3CN was added 0.26 g (3.09 mmole) of $NaHCO_3$, 12 mg (0.08 mmole) of NaI and 1.50 g (15.2 mmole) of 4-methylpiperidine. The mixture was heated to reflux for 8 h, cooled to room temperature and

the solvent evaporated off. The residue was treated with CH_2Cl_2 (3 x 25 ml) and washed with 0.1N HCl, water and brine and dried ($MgSO_4$). Evaporation of the solvent left a residue, which was purified by column chromatography on silica gel, eluting with $CHCl_3$:MeOH 99:1 mixture, to yield 0.30 g (73%) of racemic 2.



M.p.: 88-90°C. IR υ: 3109, 1606, 1508, 1222, 1153, 1076, cm^{-1}. ^1H NMR (500 MHz) δ: 7.96 (bs, 1H, CHO$\underline{H}$), 7.35-7.29 (m, 2H, arom. $2CH_{(3)}$), 7.00-6.93 (m, 2H, arom. $2CH_{(2)}$), 4.70-4.50 (m, 1H, C$\underline{H}$OH), 3.09 (d, J=11 Hz, 1H, $CH_{(9a)}$), 2.87 (d, J=11.4 Hz, 1H, $CH_{(9'a)}$), 2.50-2.30 (m, 2H, $CH_{(8a)}$ and $CH_{(8b)}$), 2.14-2.00 (m, 1H, $CH_{(9'b)}$), 2.00-1.84 (m, 2H, $CH_{(6a)}$ and $CH_{(9b)}$), 1.82-1.52 (m, 5H, $CH_{(6b)}$, $CH_{(7a)}$, $CH_{(7b)}$, $CH_{(10a)}$ and $CH_{(10'a)}$), 1.50-1.20 (m, 3H, $CH_{(10b)}$, $CH_{(10'b)}$ and $CH_{(11)}$), 0.93 (d, J=5.7 Hz, 3H, $-CH_3$). ^{13}C NMR δ: 161.6 (d, J=244 Hz, C-1), 141.8 (d, J=3 Hz, C-4), 127.1 (d, J=8 Hz, C-3), 114.7 (d, J=21 Hz, C-2), 73.1 (C-5), 59.0 (C-8), 54.7 (C-9'), 53.0 (C-9), 40.4 (C-6), 33.7 (C-10), 33.5 (C-10'), 30.7 (C-11), 24.2 (C-7), 21.6 (C-12). ^{19}F NMR δ: -117.48 (m). MS (EI) m/z (%): 265 (M^+, 2), 112 (100). Elem. Anal.: Calcd. for $C_{16}H_{24}OFN$: C: 72.42; H: 9.12; N: 5.28; F: 7.16. Found: C: 72.05; H: 9.02; N: 5.33; F: 7.44.

(*R,S*)-α-(4-Fluorophenyl)-4-(2-pyrimidinyl)-1-piperazinebutanol (3). The same procedure as for compound 2 was applied. Thus, starting from 0.84 g (10.0 mmole) of $NaHCO_3$, 39 mg (0.26 mmole) of NaI, 1.01 g (4.98 mmole) of alcohol 4 and 8.18 g (49.81 mmole) of 1-(2-pyrimidinyl)piperazine, after 13 h of reflux, were obtained 1.10 g (67%) of the expected compound 3, after purification on silica gel eluting with $CHCl_3$:MeOH 99.5:0.5 mixture.



M.p.: 98-99°C (Lit.: 100-101°C[11]). IR υ: 3361, 1602, 1585, 1548, 1508, 1261, 1220, 983 cm^{-1}. ^1H NMR δ: 8.29 (d, J=4.5 Hz, 2H, $2CH_{(12)}$), 7.38-7.28 (m, 2H, arom. $2CH_{(3)}$), 7.04-6.94 (m, 2H, arom. $2CH_{(2)}$), 6.48 (t, J=4.5 Hz, 1H, $CH_{(13)}$), 4.68 (m, 1H, C$\underline{H}$OH), 3.89 (t, J=5.1 Hz, 4H, $2CH_{(10a)}$ and $2CH_{(10b)}$), 2.70-2.58 (m, 2H, $CH_{(8a)}$ and $CH_{(8b)}$), 2.55-2.42 (m, 4H, $2CH_{(9a)}$ and $2CH_{(9b)}$), 2.20-1.88 (m, 2H, $CH_{(6a)}$ and $CH_{(6b)}$), 1.88-1.60 (m, 2H, $CH_{(7a)}$ and $CH_{(7b)}$). ^{13}C NMR δ: 161.8 (d, J=244 Hz, C-1), 161.5 (C-11), 157.7 (2C-12), 141.4 (d, J=3 Hz, C-4), 127.2 (d, J=8 Hz, 2C-3), 114.9 (d, J=21 Hz, 2C-2), 110.1 (C-13), 73.0 (d, J=1 Hz, C-5), 58.9 (C-8), 52.9 (2C-9), 43.2 (2C-10), 39.8 (C-6), 23.7 (C-7). ^{19}F NMR δ: -117.08 (m). MS (EI) m/z (%): 330 (M^+, 21), 108 (40), MS (CI, CH_4) m/z (%): 331 (M^++1, 100), 313 (42), 311 (39). Exact Mass: Calc. for $C_{18}H_{23}OFN_4$: 330.185589. Found: 330.185630.

Acylation of (*R,S*)-4-chloro-α-(4-fluorophenyl)-1-butanol (4) with *Pseudomonas cepacia* lipase. Synthesis of (*R*)-(+)-4 and (*S*)-(-)-4. In a 250 ml erlenmeyer-flask was placed a mixture of 15 g (74 mmole) of (*R,S*)-4 in

60 ml of n-hexane, 1.5 g of immobilized lipase PS and 68 ml (736 mmole) of vinyl acetate. The erlenmeyer-flask was capped, placed in a thermostatized bath at 37°C and shaken at 82 U/min. The reaction was monitored by TLC and when the transformation was ca. 50% (100 h), the mixture was filtered off and the enzyme washed with $CHCl_3$. The solvent was stripped off and the resulting crude purified by column chromatography on silica gel, eluting with hexane:ethyl acetate mixtures, to furnish 9.5 g (49%) of the corresponding acetate (*R*)-**5** and 7.2 g (48%) of unreactive alcohol (*S*)-(-)-**4**, $[\alpha]_D^{20}$= -33.5° (c 3.2, $CHCl_3$), 85% ee. The acetate was hydrolyzed to the corresponding alcohol (*R*)-(+)-(**4**) by treatment with K_2CO_3 in MeOH/H_2O for 4 h at room temperature, to yield 6.6 g (44% overall from racemic **4**) of (*R*)-(**4**), $[\alpha]_D^{20}$= +41.4° (c 2.3, $CHCl_3$), 97% ee. A second enzymatic resolution lead to enantiomerically pure (*R*)-(**4**). Thus, from 4.7 g of the latter alcohol, 30 ml of hexane, 0.15 g of lipase PS and 22 ml of vinyl acetate were obtained 3.9 g of the corresponding acetate, which after hydrolysis and purification yielded (*R*)-(**4**) in enantiomerically pure form, $[\alpha]_D^{24}$ = +42.5° (c 3.4, $CHCl_3$), >99% ee.

***(R)*-α-(4-Fluorophenyl)-4-methyl-1-piperidinebutanol (*(R)*-2).** Following the same procedure as described for the racemic compound, (*R*)-**2** was obtained from enantiomerically pure (*R*)-(**4**) in 73% isolated yield, $[\alpha]_D^{24}$ = +59.4° (c 2.5, $CHCl_3$), >99% ee. Enzymatic resolution of the racemic compound (*R,S*)-**2** with immobilized lipase PS, following a similar procedure than for alcohol **4**, yielded the *R* enantiomer in 34% isolated overall yield (69% ee) and the *S* enantiomer in 45% isolated yield (46% ee).

***(R)*-α-(4-Fluorophenyl)-4-(2-pyrimidinyl)-1-piperazinebutanol (*(R)*-3).** Following the same procedure as described for the racemic compound, *(R)*-**3** was obtained from enantiomerically pure (*R*)-(**4**) in 65% isolated yield, $[\alpha]_D^{24}$ = +41.0° (c 2.9, $CHCl_3$), >99% ee. Enzymatic resolution of the racemic compound (*R,S*)-**3** with immobilized lipase PS, following a similar procedure than for alcohol **4**, afforded the *R* enantiomer in 36% isolated overall yield (84% ee) and the *S* enantiomer in 46% isolated yield (72% ee).

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