Tetrahedron: Asymmetry Vol. 3, No. 4, pp. 525-528, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

An efficient route to enantiomerically pure antidepressants: Tomoxetine, Nisoxetine and Fluoxetine

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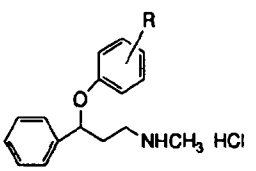
(*Received* 24 *February* 1992)

Abstracts: *Both enantiomers (R)- and (S)- 3-chloro- 1-phenyl- 1-propanol can be obtained conveniently by an efficient enzymatic resolution process. They can be converted via enantioconvergent routes into all enantiomers of the important antidepressants (R)- and (S)- Tomoxetine, Fluoxetine and Nisoxetine.*

Highly selective norephinephrine or serotonin reuptake inhibitors with aryloxyphenylpropylamin substructure like Tomoxetine **1**, Fluoxetine **2**, and Nisoxetine **3** are among the most important pharmaceuticals for the treatment of psychiatric disorders (depression, anxiety, alcoholism) and also metabolic problems (obesity, bulimia).



1 R= 2- CH_3 Tomoxetine

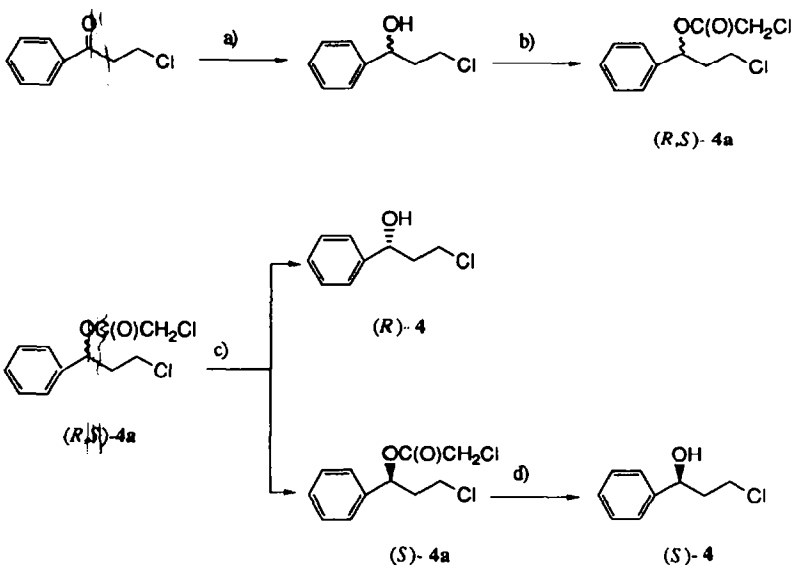
2 R= 4- CF_3 Fluoxetine

3 R= 2- OCH_3 Nisoxetine

In view of the different pharmacological activities displayed by individual enantiomers of the above racemates [1], differences in metabolic behaviour [2] and also a general trend to provide enantiomerically pure drugs, the preparation of these antidepressants in enantiomerically pure form is highly desirable. Consequently several groups have recently be engaged in the preparation of enantiomerically pure building blocks for these compounds, e.g. via enantioselective epoxidation [3] or chemical [4,5,6,7] and chemoenzymatic [8,9] reduction of suitable precursors. Since, depending on the structure in question the dominating biological activities reside in different absolute configurations of the above molecules, we felt that the facile resolution of a suitable intermediate may provide an attractive, alternative route to these pharmaceuticals in enantiomerically pure form.

We wish to report here such a simple route to all enantiomers (*R*)- and (*S*)- **1**- **3** based on the enzymatic resolution of the key intermediate (*R*)- and (*S*)- 3- chloro- 1- phenyl- 1-propanol (*R*)- and (*S*)- **4.**

Scheme 1: Synthesis and enzymatic resolution of (*R,S*)- **4a**



a) $LiAlH_4$, Et_2O; b) $(ClCH_2CO)_2O$, pyridine, CH_2Cl_2; c) lipase SAM-2, buffer pH 7; d) K_2CO_3 /MeOH

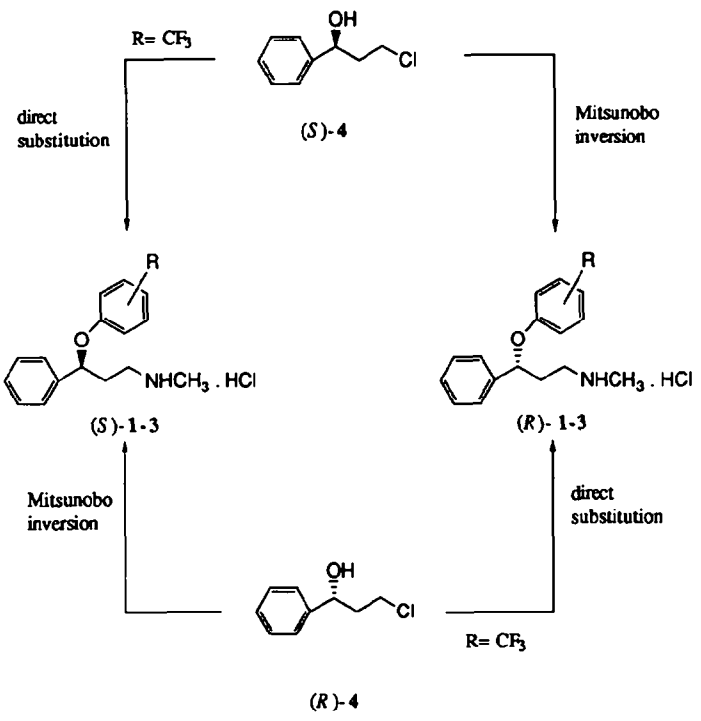
The success and practical usefulness of an enzymatic resolution depends on a) a highly selective enzyme; b) a reasonable rate of transformation; c) a facile, non chromatographic separation of the products.

Based on our previous experience in this area [10] we found that all these requirements are ideally fulfilled by the enzymatic hydrolysis of the racemic chloroacetate (*R,S*)- **4a** in presence of a lipase from *Pseudomonas fluorescens*. For this (*R,S*)- **4**, easily accessible by reduction of comercially available 4- chloroacetophenone [12] was converted first into the corresponding chloroacetates (*R,S*)- **4a**.

The enzymatic hydrolysis was carried out in presence of a lipase from *Pseudomonas fluorescens* [11] under pH control in phosphate buffer. The reaction terminated after ca. 50 % conversion leading to compound (*R*)- **4** and (*S*)- **4a**. Due to the substantial differences in the boiling points the two products can be separated by simple vacuum distillation. No further purification was required. Saponification (K_2CO_3/MeOH) of the chloroacetate (*S*)- **4a** ($[\alpha]_D^{20}$ -64.2 (c=0.75 $CHCl_3$)) led to the corresponding alcohol (*S*)- **4** in quantitative yield. The optical purities, as determined by HPLC (Chiracel OB, hexane, 2-propanol 95 : 5, 1 ml / min) were 97.3 % ee for (*R*)- **4** ($[\alpha]_D^{20}$ +23.8 (c=1.06 $CHCl_3$)) and >99 % ee for (*S*)- **4**.($[\alpha]_D^{20}$ -24.1 (c=1.12 $CHCl_3$))

From scheme 2 it is clear, that following the indicated reaction sequences, (*R*)- **4** and (*S*)- **4** are useful intermediates for the synthesis of all six enantiomers (*R*)- and (*S*)- **1**- **3**. No recycling of an undesired enantiomer is required. Obviously, by a combination of direct substitution and Mitsunobo inversion the method can led in an enantiocovergent way to any of these pharmaceuticals in enantiomerically pure form.

Scheme 2 : Synthesis of (*R*)- and (*S*)- Tomoxetine **1**, Fluoxetine **2** and Nisoxetine **3**



Thus, synthesizing (*S*)- Fluoxetine employing the direct substitution route enatiomerically pure chloroalcohol (*S*)- **4** is first converted into the corresponding aminoalcohol by reaction with aqueous methylamine via a NaI assisted nucleophilic substitution. Transformation of this material into the alkoxide (NaH/DMA), followed by reaction with 4- chlorotrifuoromethylbenzene produces (*S*)- Fluoxetine as free base. Finally (*S*)- Fluoxetine hydrochloride (*S*)- **2** is obtained by the reaction of the free base with gaseous HCl, followed by recrystallisation (hexane / ethylacetate).

For the synthesis of (*S*)- Fluoxetine by the "Mitsunobo inversion" method (*R*)- **4** is reacted under the usual conditions (Ph_3P, diethylazodicarboxylate) with 4- trifluoromethylphenol to generate the (*S*)- enantiomer of the corresponding chloroether, which is converted into (*S*)- Fluoxetine hydrochloride (*S*)- **2** by the method described above. During this inversion step no detectable racemisation occurs as was shown by chiral HPLC.

It is obvious, that by using the same methodology, using 2- methylphenol or 2- methoxyphenol all enantiomers of Tomoxetine or Nisoxetine can be prepared from (*R*)- or (*S*)- **4**.

This way all enantiomers (*R*)-and (*S*)- **1- 3** were prepared in enantiomerically pure form with their specific rotations summarized in table 1.

compound	$[\alpha]_D^{20}$	c (solvent)	literature $[\alpha]_D$ (c)	ref.
(*R*)- **1**	-41.8	1.78 (MeOH)	-41.4 (1.0)	3
(*S*)- **1**	+42.0	1.56 (MeOH)	+43.2 (0.8)	3
(*R*)- **2**	-13.8	1.02 ($CHCl_3$)	-13.8 (1)	5
(*S*)- **2**	+13.9	1.01 ($CHCl_3$)		
(*R*)- **3**	+51.2	1.66 (MeOH)	+51.9 (4.8)	3
(*S*)- **3**	-51.1	1.40 (MeOH)	-52 (5)	3

Table 1

We thank the Fonds der chemischen Industrie for financial support.

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