Tetrahedron Letters, Vol.32, No.16, pp 1901-1904, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

A NEW CHEMOENZYMATIC ENANTIOSELECTIVE SYNTHESIS OF R-(-)-TOMOXETINE, (R)- AND (S)-FLUOXETINE.

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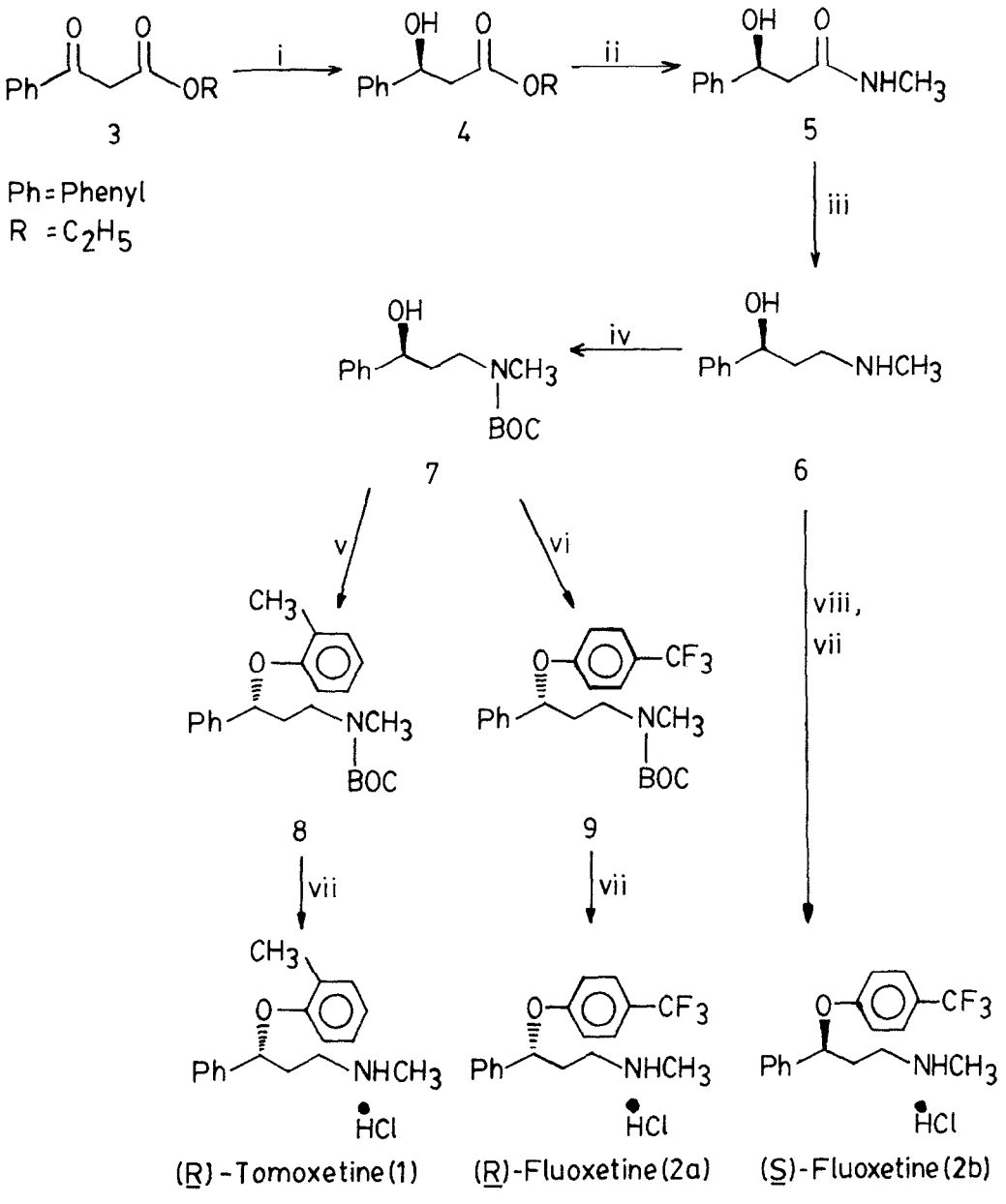
Abstract : A new chemoenzymatic synthesis of optically pure (R)-Tomoxetine and both the enantiomers of Fluoxetine starting from (S)-ethyl-3-hydroxy-3-phenyl propionate obtained by enzymatic methods, is described.

Tomoxetine (1) is the first norepinephrine (NE) reuptake inhibiting anti-depressant without strong affinity for α- or β-adrenergic receptors with R-(-) isomer being nine times more potent than its antipode.[1] Similarly Fluoxetine (2) (Prozac^{TM}, Eli Lilly Co.) is also a potent clinically effective anti-depressant. In addition, 2 has been active against wide range of symptoms like anxiety, alcoholism, chronic pain, obesity and bulimia.[2] 2 is being currently sold as racemate even though current preference is for the use of enantiomerically pure medicines. Since the classical resolution method[3] to get pure 1 and 2 is not desirable asymmetric synthesis of these molecules has been subject of current interest.[4] These syntheses relied on the chemical reduction of appropriate ketone[4a,c] and the Sharpless epoxidation method.[4b]

Herein, we wish to report a different and new flexible chemo-enzymatic approach to the synthesis of (R)-1 and both the enantiomers of 2 starting from commercially available inexpensive ethyl benzoyl acetate (3). Baker's yeast reduction of 3 to yield ethyl 3-hydroxy-3-phenyl propionate (4) has been reported[5] to give not more than 66% ee. Using modified conditions we have been able to obtain 4 in 85% ee. The latter was reacted with aqueous methyl amine to get the corresponding 5 in optically pure form in 78% chemical yield after crystallisation[6] from chloroform. ($[\alpha]_D^{25}$ - 25.5°, MeOH, C=1.25). We have now found out that 5 of the same optical purity could also be obtained from 4 of 99% ee produced by enzymatic hydrolysis of acetate of racemic 4. These findings will be the subject of separate communication. Lithium aluminium hydride reduction of 5 yielded (-)-N-methyl-3-phenyl-3-hydroxy propylamine (6)



Ph = Phenyl
R = C_2H_5

(i) Baker's yeast, glucose, water; (ii) aq $MeNH_2$; (iii) LAH, ether;
(iv) di-t-butyldicarbonate, CH_2Cl_2 (v) O-Cresol, Ph_3P, DEAD, ether;
⟶ (vi) p-trifluromethyl phenol, Ph_3P, DEAD, ether; ⟶
(vii) HCl (gas) ethanol; (viii) NaH, DMAC, p-chlorobenzotrifluoride.

SCHEME

in 98% yield ($[\alpha]_D^{25}$ -38.2°, $CHCl_3$, C=1.07; lit. $[\alpha]_D^{25}$ - 37.37°, $CHCl_3$, C=1.0). Treatment of 6 with di-t-butyl dicarbonate followed by chromatography (Silica gel : Hexane : Ethyl acetate; 95 : 5) provided N-Boc derivative[6] 7 ($[\alpha]_D^{25}$ -7.33°, $CHCl_3$, C=1.032) in 95% yield. The latter on reaction with o-cresol under Mitsunobu coupling[7] reaction afforded N-methyl-3-phenyl-3-(2-methyl phenoxy) propaneamide 8[6], ($[\alpha]_D^{25}$ - 14.83°, $CHCl_3$, C=1.04). The latter on treatment with ethanolic HCl gave (R)-tomoxetine hydrochloride in 89% yield ($[\alpha]_D^{25}$ -41.35° , MeOH, C=1.4); lit.[4b] $[\alpha]_D^{25}$ - 41.37°, MeOH, C=1.02), m.p. 164-66°C.

Synthesis of (R)-Fluoxetine was straightforward. Thus 7 on reaction with 4-trifluoromethyl phenol under Mitsunobu conditions followed by treatment with ethanolic HCl provided (R)-Fluoxetine hydrochloride[8] in 86% yield ($[\alpha]_D^{25}$ -14.8°, $CHCl_3$, C=5.13; lit.[4c] $[\alpha]_D^{25}$ - 13.8°, $CHCl_3$, C=1), m.p. 140-1° C. Similarly (S)-Fluoxetine was synthesized as depicted in the scheme.

In conclusion, a simple and new chemoenzymatic synthesis of (R)-Tomoxetine as well as both the enantiomers of Fluoxetine in optically pure form has been accomplished.

Acknowledgements : The authors wish to thank ICI India Limited for financial support and Dr M Chakraborty for NMR analyses.

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6. New compounds were characterized by their IR, ^{1}H NMR and elemental analysis. The data for selected compounds is :

5 : IR (KBr) cm^{-1}: 3380, 3320 (NH & OH), 1645 (C=O), 1560 (ar). ^{1}H NMR ($CDCl_3$) δ : 2.54 (d, 2H, CH_2), 2.8 (d, 3H, $NHCH_3$), 4.08 (br.S, 1H, OH), 5.1 (m, 1H, CHOH), 5.8 (br.S, 1H, NH), 7.32 (br.S, 5H, ar). Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.03: H, 7.26; N, 7.82. Found : C, 67.21; H, 7.35; N, 8.00.

7 : IR (neat) cm^{-1}: 3420 (OH): 1690, 1675 (C=O); ^{1}H NMR ($CDCl_3$) δ : 1.46 (S, 9H, t-butyl), 1.8 (m, 2H, CH), 2.86 (S, 3H, N-CH_3), 3.8 (br.S, 1H, OH), 4.6 (m, 1H, O-CH), 7.32 (m, 5H, ar). Anal. Calcd. for $C_{15}H_{23}O_3N$: C, 67.92; H, 8.68; N, 5.28. Found : C, 68.02; H, 8.81; N, 5.20.

8 : IR (neat) cm^{-1}: 1695 (C=O), 1600, 1590 (ar); ^{1}H NMR ($CDCl_3$) δ: 1.38 (S, 9H, t-butyl), 1.95 2.30 (m, 2H, CH), 2.32 (S, 3H, Ar-CH) 2.83 (S, 3H, NCH_3), 3.42 (m, 2H, N-CH), 5.2 (m, 1H, O-CH), 6.5-7.2 (m, 4H, ar), 7.29 (m, 5H, ar). Anal. Calcd. for $C_{22}H_{29}O_3N$: C, 74.37; H, 8.17; N, 3.94. Found : C, 74.45; H, 8.20; N, 4.01.

9 : IR (neat) cm^{-1}: 1660 (C=O), 1620 (ar); ^{1}H NMR ($CDCl_3$) δ : 1.37 (S, 9H, t-butyl); 1.90-2.38 (m, 2H, CH_2), 2.88 (S, 3H, N-CH_3), 3.22-3.6 (m, 2H, N-CH_2), 5.15 (m, 1H, OCH), 6.85 (d, 2H, ArH, J=8.0 Hz), 7.28 (m, 5H), 7.42 (d, 2H, ArH, J=8.0 Hz).

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8. IR and NMR data is identical with the reported one.

(Received in UK 12 February 1991)