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An Efficient Chemoenzymatic Route to the Antidepressants (*R*)-Fluoxetine and (*R*)-Tomoxetine†

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Abstract—(*S*)-1-Phenyl-3-buten-1-ol (**1**), prepared in high optical purity by enzymatic resolution of the racemate, is a convenient building block for the synthesis of (*R*)-fluoxetine (**7a**) and (*R*)-tomoxetine (**7b**). Compound **1** was converted to the title drugs by etherification with appropriate phenols under Mitsunobu conditions, ozonolysis of the terminal double bond, mesylation of the resulting alcohol and substitution with methylamine. Copyright © 1996 Elsevier Science Ltd

Introduction

The two enantiomers of a chiral drug can display dramatically different biological activities. Consequently, the introduction of pure enantiomers is desirable. Therefore, there is a need for the development of efficient methodologies for the synthesis of optically pure drugs. Over the last several years, enzymes have found growing application in the preparation of pure enantiomers.[1] Among the wide variety of commercially available enzymes, esterases and lipases have found widest application in drug synthesis, since they are able to discriminate between enantiotopic groups and between enantiomers of a racemate, accept a broad range of substrates, do not require expensive co-factors and are stable even toward organic solvents.[2,3]

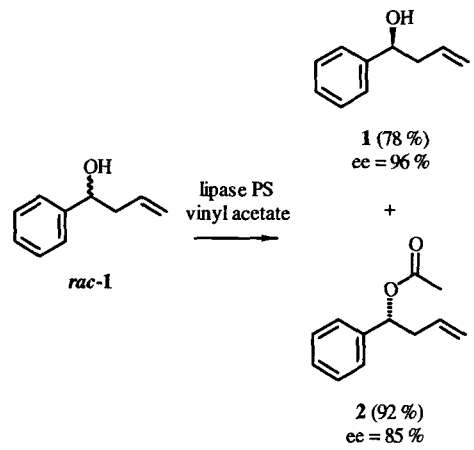
In this paper we report on the application of a lipase-catalysed resolution of a racemate to the synthesis of the drugs (*R*)-fluoxetine (**7a**) and (*R*)-tomoxetine (**7b**). Fluoxetine is a potent and highly selective inhibitor of the neural serotonin-reuptake and is among the most important drugs for the treatment of diseases such as depression and anxiety. Although fluoxetine is marketed as a racemate, there is a stereospecificity associated with its biological activities and the (*R*)-enantiomer **7a** was found to be ca. twice as effective than the (*S*)-enantiomer.[4] The structurally related antidepressant tomoxetine shows comparable stereospecificity.[5] Due to the importance of these drugs, several enantioselective syntheses using chemical,[4,6] enzymatic[7] and microbiological[8] methods have been described in the last few years. We intended to work out new syntheses of the (*R*)-enantiomers **7a** and **b** that should compare favourably with the known methods with regard to operational simplicity, overall number of steps, and costs.

†Dedicated to Professor Dr G. Seitz, Marburg, on the occasion of his 60th birthday.

Results and Discussion

As a starting material we selected racemic 1-phenyl-3-buten-1-ol (*rac*-**1**), which is available in almost quantitative yield by a Barbier-type reaction of benzaldehyde with allyl bromide and zinc in THF/aqueous NH_4Cl.[9] For the resolution of *rac*-**1**, we used a lipase-catalyzed enantioselective transesterification in an organic solvent. Previous attempts of other authors[10] to resolve this racemate via enantioselective hydrolysis of the corresponding acetate by crude enzymes in aqueous media gave only poor optical yields. In contrast, we found that Amano lipase PS-catalyzed reaction of *rac*-**1** with vinyl acetate in a mixture of anhydrous *tert*-butyl methylether and dodecane[11] gives the (*R*)-configurated acetate **2** and (*S*)-alcohol **1** in high optical purity (Scheme 1). However, the reaction proceeded very slowly at room temperature. The reaction rate could be enhanced significantly by running the transesterification at reflux temperature. The boiling point of *tert*-butyl methylether (55 °C) is near the optimum temperature of the enzyme (50 °C).[12] By this way, after a conversion of 53%, the (*S*)-alcohol **1** (ee = 96%) was obtained in 78% yield, whereas the (*R*)-acetate **2** was formed with 85% ee. The enzyme was separated by filtration and could be used at least three times for the same reaction without significant loss of activity.

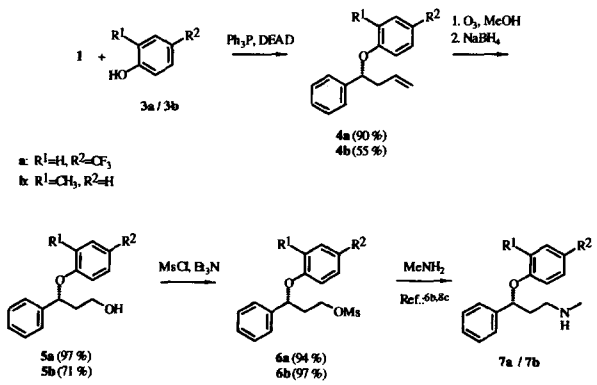
Alcohol **1** was converted to the (*R*)-configurated aryl ethers **4a** and **b** by reaction with 4-trifluoromethylphenol (**3a**) and 2-methylphenol (**3b**), respectively, under Mitsunobu conditions[13] with complete inversion of the chiral centre. The yields of the coupling reactions were significantly higher, when anhydrous toluene was used as a solvent instead of diethyl ether.[8c] For the synthesis of the title drugs, the side chains of the homoallyl alcohols **4a** and **b** had to be degraded by oxidative cleavage of the double bonds. In a first experiment we tried to convert the olefin **4b** into an



Scheme 1.

aldehyde by oxidation with $NaIO_4/OsO_4$.[14] However, the desired aldehyde was accompanied by equimolar amounts of cinnamic aldehyde and phenol **3b** and the amounts of the unwanted by-products increased upon storage. Obviously, the β-aryloxy aldehyde formed by the oxidative cleavage of the olefin decomposed in a retro-Michael reaction to give the unsaturated aldehyde and the phenol. Therefore, we used another degradation method that avoids the isolation of unstable aldehydes. Ozonolysis of the olefins **4a** and **b** in methanol followed by reductive work up with $NaBH_4$[15] gave the primary alcohols **5a** and **b** in high to excellent yields. The enantiomeric excess of **5a** was determined by HPLC and found to be 95%. Thus, no racemization had occurred during Mitsunobu reaction and ozonolysis. The alcohols **5a** and **b** were converted into the mesilates **6a** and **b** in almost quantitative yields. Further conversions of these mesilates to the desired drugs (*R*)-fluoxetine (**7a**) and (*R*)-tomoxetine (**7b**) are known processes.[6b,8c] Racemic compounds were prepared for the determination of the enantiomeric excesses under the same conditions from *rac*-**1** (see Scheme 2).

In conclusion, we have elaborated new, short approaches to the drugs **7a** and **b** in high optical purities using cheap starting materials and reagents.



Scheme 2.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Solvents were purified and dried by standard methods. Melting points were determined with a Reichert Heiztischmikroskop and are uncorrected. Elemental analyses were prepared on a Carlo Erba CHNO elemental analyzer 1106 and were within ±0.4%. Optical rotations were determined on a Perkin–Elmer 241. HPLC was performed on a Merck–Hitachi L-6200 and 655-A (λ = 254 nm), column: Chiralcel OD-R® (25 cm, 0.46 cm, 10 μm, Baker/Daicel). IR spectra were obtained on a Philips PU 9800 FTIR spectrometer. NMR spectra were obtained on a Bruker AM 400, TMS as internal standard. Mass spectra were obtained on a Finnigan MAT 8430. Kieselgel 60 (230–400 mesh), Merck, was used for flash column chromatography (FCC).

Enzymatic resolution of (±)-1-phenyl-3-buten-1-ol (*rac*-1)

rac-**1** (3.00 g, 20.3 mmol) was dissolved in a mixture of anhydrous *tert*-butyl methyl ether (25 mL), dodecane (6 mL) and vinyl acetate (3.22 g, 40.3 mmol). Then lipase PS (1.50 g, Amano) was added and the mixture was refluxed for 21 h. After filtration and washing with *tert*-butyl methyl ether (4 × 10 mL) the filtrate was concentrated in vacuo. Purification by FCC (petroleum ether:ethyl acetate 19:1 to 14:6) gave two fractions.

Fraction 1: *(R)*-1-phenyl-3-buten-1-yl acetate (**2**). 1.77 g (92%), colourless liquid; $[\alpha]_D^{20}$ +41.6° (*c* 1.5, $CHCl_3$), ee = 85% (determined by HPLC; eluent: $CH_3CN:H_2O$ 40:60, T = 35 °C, u = 0.9 mL/min; (*R*)-enantiomer: t_R 22.78 min, (*S*)-enantiomer: t_R 24.59 min); IR (film, NaCl): ν 3074, 3034, 1741, 1372, 1237, 1024, 974, 920, 760, 701 cm^{-1}; MS (EI, 70 eV) *m/z* 190 (0.5) $[M]^+$, 150 (14), 149 (100), 107 (13); ^1H NMR ($CDCl_3$): δ 2.07 (s, 3H, CH_3), 2.52–2.69 (m, 2H, CH_2), 5.03–5.10 (m, 2H, CH=C$\underline{H}_2$), 5.65–5.75 (m, 1H, C$\underline{H}$=CH_2), 5.81 (dd, J = 7.7 and 6.0 Hz, 1H, Ar-C$\underline{H}$), 7.26–7.37 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 21.21 (CH_3), 40.76 (CH_2), 75.15 (Ar-$\underline{C}$H), 118.01 (CH=$\underline{C}H_2$), 126.56 (2C, aromatic CH), 127.96 (aromatic CH), 128.42 (2C, aromatic CH), 133.34 ($\underline{C}$H=CH_2), 140.09 (quart. aromatic C), 170.24 (CO), anal. ($C_{12}H_{14}O_2$) C, H.

Fraction 2: (*S*)-1-phenyl-3-buten-1-ol (**1**). 1.16 g (78%), colourless liquid; $[\alpha]_D^{20}$ −73.5° (*c* 1.4, $CHCl_3$), ee = 96% (determined by HPLC; eluent: $CH_3CN:H_2O$ 28:72, T = 40 °C, u = 0.9 mL/min; (*R*)-enantiomer: t_R = 19.36 min, (*S*)-enantiomer: t_R = 20.92 min); IR (film, NaCl): ν 3390, 3075, 1453, 1048, 1000, 916, 757, 701 cm^{-1}; MS (EI, 70 eV): *m/z* 148 (0.2) $[M]^+$, 107 (100); ^1H NMR ($CDCl_3$): δ 2.26 (br s, 1H, OH), 2.43–2.53 (m, 2H, CH_2), 4.69 (dd, J = 7.2 and 5.7 Hz, 1H, C$\underline{H}$OH), 5.10–5.16 (m, 2H, CH=C$\underline{H}_2$), 5.73–5.83 (m, 1H, C$\underline{H}$=CH_2), 7.23–7.35 (m, 5H, aromatic CH); ^{13}C NMR ($CDCl_3$): δ 43.79 (CH_2), 73.30 (CHOH), 118.32 (CH=$\underline{C}H_2$), 125.82 (2C, aromatic CH), 127.51

(aromatic CH), 128.39 (2C, aromatic CH), 134.48 (CH=CH_2), 143.89 (quart. aromatic C), anal. ($C_{10}H_{12}O$) C, H.

General procedure for the preparation of the ethers 4a and b

To an ice-cooled stirred solution of (*S*)-1-phenyl-3-buten-1-ol (**1**), (0.59 g, 4.0 mmol), the phenols **3a** or **b** (4.5 mmol) and Ph_3P (1.18 g, 4.5 mmol) in dry toluene (20 mL) under nitrogen atmosphere were added dropwise to a DEAD-solution (40% in toluene, 2.1 mL, 4.5 mmol). The mixture was stirred for 1 day at room temperature and then filtered. The filtrate was washed with H_2O, the aqueous layer extracted with ethyl acetate and the combined organic phases were dried over K_2CO_3 and concentrated in vacuo. The residue was purified by FCC (petroleum ether:ethyl acetate 9:1) to yield the ethers **4a** or **b**.

(*R*)-1-(4-Trifluoromethylphenoxy)-1-phenyl-3-butene (4a). 1.05 g (90%), colourless liquid; $[\alpha]_D^{20} -7.4°$ (*c* 1.0, $CHCl_3$). IR (film, NaCl): ν 3078, 2913, 1615, 1516, 1328, 1251, 1162, 1115, 836, 701 cm^{-1}; MS (EI, 70 eV): *m/z* 292 (0.6) $[M]^+$, 251 (22), 183 (17), 132 (13), 131 (100), 130 (24), 129 (21), 115 (16), 91 (40), 77 (15); ^1H NMR ($CDCl_3$): δ 2.57–2.63 (m, 1H, CH^AH^B), 2.73–2.81 (m, 1H, CH^AH^B), 5.07–5.19 (m, 3H, CH=CH_2, Ph—CH), 5.79–5.89 (m, 1H, CH=CH_2), 6.89 (m, 2H, aromatic $H^AH^{A'}$), 7.22–7.34 (m, 5H, aromatic H), 7.42 (m, 2H, aromatic $H^XH^{X'}$); ^{13}C NMR ($CDCl_3$): δ 42.82 (CH_2), 80.15 (Ph—CH), 115.85 (2C, aromatic CH), 117.92 (CH=CH_2), 122.88 (q, J=33 Hz, quart. aromatic C), 124.45 (q, J=271 Hz, CF_3), 125.99 (2C, aromatic CH), 126.78 (q, J=3.7 Hz, 2C, aromatic CH), 127.93 (aromatic CH), 128.74 (2C, aromatic CH), 133.72 (CH=CH_2), 140.59 (quart. aromatic C), 160.59 (quart. aromatic C), anal. ($C_{17}H_{15}F_3O$) C, H.

(*R*)-1-(2-Methylphenoxy)-1-phenyl-3-butene (4b). 0.52 g (55%), colourless liquid; $[\alpha]_D^{20}$ 0° (*c* 1.4, $CHCl_3$); IR (film, NaCl): ν 3069, 3027, 2917, 1492, 1239, 1120, 1048, 993, 916, 751, 701 cm^{-1}, MS (EI, 70 eV): *m/z* 238 (6) $[M]^+$, 132 (10), 131 (93), 130 (100), 129 (27), 115 (14), 91 (41), 77 (10); ^1H NMR ($CDCl_3$): δ 2.31 (s, 3H, CH_3), 2.57–2.64 (m, 1H, CH^AH^B), 2.71–2.79 (m, 1H, CH^AH^B), 5.04–5.17 (m, 3H, CH=CH_2, Ph—CH), 5.82–5.93 (m, 1H, CH=CH_2), 6.59 (m, 1H, aromatic H), 6.76 (m, 1H, aromatic H), 6.94 (m, 1H, aromatic H), 7.11 (m, 1H, aromatic H), 7.19–7.35 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.50 (CH_3), 43.07 (CH_2), 79.49 (Ph—CH), 112.82 (aromatic CH), 117.48 (CH=CH_2), 120.23 (aromatic CH), 125.92 (2C, aromatic CH), 126.49 (aromatic CH), 127.21 (quart. aromatic C), 127.48 (aromatic CH), 128.48 (2C, aromatic CH), 130.59 (aromatic CH), 134.29 (CH=CH_2), 141.67 (quart. aromatic C), 156.04 (quart. aromatic C), anal. ($C_{17}H_{18}O$) C, H.

General procedure for the ozonolysis of the olefins 4a and 4b and reductive work up

The olefins **4a** (0.91 g, 3.1 mmol) or **b** (0.47 g, 1.4 mmol) were dissolved in methanol (5 mL). An ozone–oxygen mixture (Fischer Ozongenerator OZ I, 1 bar, 15 L/h, 2 g O_3/h) was bubbled through the solution for 10 min at −78 °C. After addition of 5 g $NaBH_4$ methanol (40 mL) was added and the solution was allowed to warm up to room temperature with stirring. Then the solution was diluted with water and extracted with ethyl acetate. The organic layer was dried over K_2CO_3 and concentrated in vacuo. The residue was purified by FCC (petroleum ether:ethyl acetate 8:2 to 7:3) to yield the alcohols **5a** or **b**.

(*R*)-3-(4-Trifluoromethylphenoxy)-3-phenylpropan-1-ol (5a). 0.89 g (97%), colourless liquid; $[\alpha]_D^{20} +17.7°$ (*c* 0.8, $CHCl_3$), ee=95% (determined by HPLC; eluent: CH_3CN:H_2O 87:13, T=20 °C, u=0.5 mL/min; (*R*)-enantiomer (phenylurethane derivate): t_R=14.07 min, (*S*)-enantiomer (phenylurethane derivate): t_R=16.22 min); IR (film, NaCl): ν 3352, 2954, 2890, 1615, 1329, 1251, 1176, 1162, 1113, 1967, 1052, 836 cm^{-1}; MS (EI, 70 eV): *m/z* 296 (2) $[M]^+$, 135 (53), 106 (10), 105 (100), 104 (20), 91 (52); ^1H NMR ($CDCl_3$): δ 1.70 (br s, 1H, OH), 2.04–2.31 (m, 2H, CH_2), 3.74–3.89 (m, 2H, CH_2OH), 5.43 (dd, J=8.6 and 4.6 Hz, 1H, Ph—CH), 6.91 (m, 2H, aromatic $H^AH^{A'}$), 7.25–7.37 (m, 5H, aromatic H), 7.43 (m, 2H, aromatic $H^XH^{X'}$); ^{13}C NMR ($CDCl_3$): δ 41.17 (CH_2), 59.41 (CH_2OH), 77.89 (Ph—CH), 115.82 (2C, aromatic CH), 123.03 (q, J=32.7 Hz, quart. aromatic C), 124.38 (q, J=271 Hz, CF_3), 125.79 (2C, aromatic CH), 126.82 (q, J=3.7 Hz, 2C, aromatic CH), 127.97 (aromatic CH), 128.89 (2C, aromatic CH), 140.74 (quart. aromatic C), 160.38 (quart. aromatic C), anal. ($C_{16}H_{15}F_3O_2$) C, H.

(*R*)-3-(2-Methylphenoxy)-3-phenylpropan-1-ol (5b). 0.34 g (71%), white crystalline solid; mp 74 °C, $[\alpha]_D^{20} -2.8°$ (*c* 1.1, $CHCl_3$); IR (film, NaCl): ν 3343, 2950, 1560, 1492, 1453, 1239, 1193, 1120, 1050 cm^{-1}; MS (EI, 70 eV): *m/z* 242 (5) $[M]^+$, 135 (13), 134 (12), 108 (100), 107 (41) 105 (78), 91 (50), 79 (46), 77 (32); ^1H NMR ($CDCl_3$): δ 1.93 (br s, 1H, OH), 2.08–2.30 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 3.78–3.92 (m, 2H, CH_2OH), 5.40 (dd, J=8.6 and 4.2 Hz, 1H, Ph—CH), 6.63 (m, 1H, aromatic H), 6.78 (m, 1H, aromatic H), 6.96 (m, 1H, aromatic H), 7.11 (m, 1H, aromatic H), 7.22–7.37 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.62 (CH_3), 41.27 (CH_2), 59.94 (CH_2OH), 77.77 (Ph-CH), 112.87 (aromatic CH), 120.50 (aromatic CH), 125.73 (2C, aromatic CH), 126.64 (aromatic CH), 126.83 (quart. aromatic C), 127.59 (aromatic CH), 128.69 (2C, aromatic CH), 130.71 (aromatic CH), 141.60 (quart. aromatic C), 155.73 (quart. aromatic C), anal. ($C_{16}H_{18}O_2$) C, H.

General procedure for the formation of the mesilates

The alcohols **5a** (0.16 g, 0.54 mmol) or **b** (0.18 g, 0.75 mmol) were dissolved in a mixture of THF (5 mL) and

triethylamine (0.8 g). A solution of mesyl chloride (0.1 mL, 1.3 mmol) in THF (2 mL) was added dropwise to the stirred mixture under nitrogen atmosphere at 0 °C. After 1 day diethyl ether was added and the organic layer was washed with cold H_2SO_4 (20%) and cold saturated $NaHCO_3$ solution. Then the organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by FCC (petroleum ether: ethyl acetate 9:1 to 8:2) to yield the mesilates **6a** or **b**.

(*R*)-3-(4-Trifluoromethylphenoxy)-3-phenylprop-1-yl methanesulfonate (6a). 0.19 g (94%), colourless syrup; $[\alpha]_D^{20}+5.3°$ (*c* 2.0, $CHCl_3$),[8c] $[\alpha]_D^{25}+3.5°$ (*c* 1.2, $CHCl_3$); IR (film, NaCl): ν 3031, 2940, 1614, 1517, 1249, 1174, 1114, 1067, 971, 929, 838, 703 cm^{-1}; MS (EI, 70 eV): *m/z* 374 (1) $[M]^+$, 136 (37), 118 (17), 117 (100), 91 (17), 72 (23); ^1H NMR ($CDCl_3$): δ 2.25–2.45 (m, 2H, CH_2), 2.94 (s, 3H, SO_2CH_3), 4.31–4.51 (m, 2H, CH_2—O), 5.36 (dd, $J=8.8$ and 4.5 Hz, 1H, Ph—CH), 6.91 (m, 2H, aromatic $H^AH^{A'}$), 7.26–7.37 (m, 5H, aromatic H), 7.43 (m, 2H, aromatic $H^XH^{X'}$); ^{13}C NMR ($CDCl_3$): δ 37.26 (SO_2CH_3), 38.14 (CH_2), 66.38 (CH_2—O), 76.78 (Ph—CH), 115.85 (2C, aromatic CH), 123.19 (q, $J=32.7$ Hz, quart. aromatic C), 124.28 (q, $J=271$ Hz, CF_3), 125.80 (2C, aromatic CH), 126.84 (q, $J=3.7$ Hz, 2C, aromatic CH), 128.38 (aromatic CH), 129.08 (2C, aromatic CH), 139.73 (quart. aromatic C), 160.12 (quart. aromatic C), anal. ($C_{17}H_{17}F_3O_4S$) C, H.

(*R*)-3-(2-Methylphenoxy)-3-phenylprop-1-yl methanesulfonate (6b). 0.23 g (97%), colourless syrup; $[\alpha]_D^{20}-10.7°$ (*c* 1.2, $CHCl_3$); IR (film, NaCl): ν 3028, 2936, 1600, 1492, 1355, 1239, 1176, 970, 753, 703 cm^{-1}; MS (EI, 70 eV): *m/z* 320 (0.4) $[M]^+$, 151 (10), 150 (100), 107 (28), 91 (36), 72 (45); ^1H NMR ($CDCl_3$): δ 2.32 (s, 3H, Ar—CH_3), 2.27–2.45 (m, 2H, CH_2), 2.89 (s, 3H, SO_2CH_3), 4.34–4.52 (m, 2H, CH_2—O), 5.33 (dd, $J=8.8$ and 4.4 Hz, 1H, Ph—CH), 6.60 (m, 1H, aromatic H), 6.78 (m, 1H, aromatic H), 6.95 (m, 1H, aromatic H), 7.11 (m, 1H, aromatic H), 7.25–7.35 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 16.50 (Ar—CH_3), 37.17 (SO_2CH_3), 38.24 (CH_2), 66.70 (CH_2—O), 75.44 (Ph—CH), 112.73 (aromatic CH), 120.70 (aromatic CH), 125.73 (2C, aromatic CH), 126.69 (aromatic CH), 126.86 (quart. aromatic C), 127.98 (aromatic CH), 128.86 (2C, aromatic CH), 130.78 (aromatic CH), 140.71 (quart. aromatic C), 155.54 (quart. aromatic C), anal. ($C_{17}H_{20}O_4S$) C, H.

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