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Lipase mediated resolution of γ-azidoalcohols in aqueous and organic media: Synthesis of (*R*)- and (*S*)-fluoxetine and duloxetine

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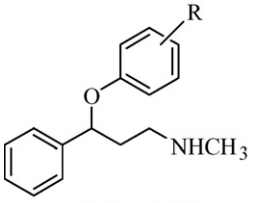
ABSTRACT

A simple and efficient method for the synthesis of optically active γ-azidoalcohols is described. The lipase catalyzed kinetic resolutions of acetates of γ-azidoalcohols in aqueous as well as organic media have been studied. The enantiomerically pure γ-azidoalcohols obtained by the kinetic resolution in high enantiopurity have been utilized towards the synthesis of enantiomeric pairs of anti-depressant drugs, fluoxetine and duloxetine.

1. Introduction

One of the important structural units in many biologically active compounds and chiral catalyst are enantiomerically pure chiral aminoalcohols [1,2]. Amongst them, the chiral γ-aminoalcohol unit is present in many natural products, pharmacologically useful drugs and chiral ligands or auxiliaries that are useful in stereoselective synthesis [3–7]. Notably, the anti-depressant drugs being used in clinic like fluoxetine (**1**), tomoxetine (**2**), nisoxetine (**3**) and duloxetine (**4**) contain the γ-aminoalcohol unit [8–14]. It is also present in the novel glycine transport blocker (*R*)-N-[3-(4′-fluorophenyl)-3-(4′-phenylphenoxy)propyl]-sarcosine (**5**) which is potentially useful in treating psychosis [15]. The chiral γ-azidoalcohols are immediate precursors of γ-aminoalcohols and are found to be useful in the ring expansion of symmetrical cyclohexanones in the asymmetric Schmidt reaction [16]. A number of chiral β-azidoalcohols have been prepared by kinetic resolution using hydrolytic enzymes [17–19], however the resolution of γ-azidoalcohols has been investigated in this laboratory [20].



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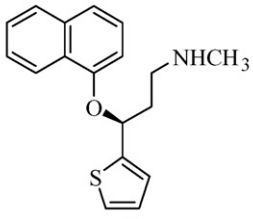

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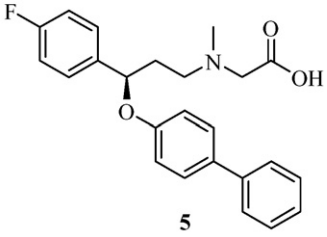

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Fluoxetine is a selective serotonin reuptake inhibitor and is approved for the treatment of major depression, obsessive-compulsive disorder, bulimia nervosa, and anorexia nervosa [21,22]. The serotonin–norepinephrine reuptake inhibitor duloxetine is used for treating stress urinary incontinence and anxiety disorder in addition to depression [23–25]. It is well known that the

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pharmacological potencies and metabolic behavior of individual enantiomers of racemic fluoxetine and duloxetine differ considerably, e.g., the (*S*)-enantiomer of the duloxetine is more active than the *R* enantiomer [9–11,14]. Moreover in recent years, drugs in enantiomerically pure form are strongly recommended underlining the importance of preparation of enantiopure form of the above mentioned drugs. In literature, approaches based on stereoselective opening, asymmetric reduction, microbial reductions and enzymatic or chemical resolutions have been described [26–31].

In continuation of our interest in the development of chemoenzymatic methodologies [32–36] and moreover as an extension of our previous study on the lipase mediated resolution of γ-azidoalcohols, we herein describe the studies relating to the resolution of their acetates. Further, their application towards the synthesis of enantiomerically pure anti-depressant drugs like fluoxetine and duloxetine have been investigated.

2. Experimental

2.1. General

^{1}H and ^{13}C NMR spectra were recorded on Gemini Varian-VXR-unity (200 MHz) or Bruker UXNMR/XWINNMR (300 MHz) instruments. Chemical shifts (δ) are reported in ppm downfield from internal TMS standard. Infrared spectra were recorded on Perkin-Elmer model 683 or 1310 spectrometers and are reported in wave numbers (cm^{-1}). ESI mass spectra were recorded on a Micromass instrument. Optical rotations were measured on a SEPA-300 (Horiba) digital polarimeter. Analytical TLC of all reactions was performed on Merck prepared plates (silica gel 60F-254 on glass). Column chromatography was performed using Acme silica gel (100–200 mesh). All organic solvents were distilled following standard protocols and are dried over molecular sieves prior to use.

2.2. Enzyme source and HPLC analysis

Pseudomonas cepacia lipase immobilized on diatomaceous earth (PS-D), *P. cepacia* (PS), *P. cepacia* lipase immobilized on modified ceramic particles (PS-C) and *Pseudomonas fluorescens* (AK-20) are obtained from Amano Pharmaceutical Company, Japan. *Candida antartica* lipase immobilized in Sol–Gel-AK on sintered glass (CAL-B), is obtained from Sigma. The hydrolytic reactions were monitored by HPLC analysis on a Chiracel OD-H column (4.6 mm id—250 mm; Daicel Chemical Industries) using *n*-hexane/*iso*-propanol as eluent (9:1) for compound **11a** and Chiralcel OB-H column (4.6 mm id—250 mm; Daicel Chemical Industries) using *n*-hexane/*iso*-propanol as eluent (9:1) for compound **11b**. The liquid chromatography employed was a Shimadzu LC-10AT instrument with Shimadzu SCL-10A variable wavelength UV monitor. Satisfactory separation of enantiomers were achieved by choosing an appropriate ratio of *n*-hexane/*iso*-propanol, which allowed the accurate determination of the enantiomeric excess (ee) value of the both acetates and alcohols.

2.3. 3-Chloro-1-phenyl-1-propanone (**8a**)

To a solution of aluminium chloride (6.15 g, 46.1 mmol) in 35 mL of dry CH_2Cl_2, 3-chloropropionyl chloride (4.04 mL, 42.2 mmol) was added dropwise at 0 °C, followed by benzene **6** (3.41 mL, 38.4 mmol). The reaction was warmed to room temperature, stirred overnight and quenched by adding ice pieces at 0 °C. After aqueous workup and purification by column chromatography on silica gel 5.96 g of acylated product **8a** was obtained. Yield: 92%; IR (neat): 1685, 1236, 750, 634 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.43 (2H, t, J = 7.5 Hz, J = 6.8 Hz), 3.89 (2H, t, J = 7.5 Hz, J = 6.8 Hz), 7.46 (2H, t, J = 7.5 Hz), 7.53–7.60 (1H, m), 7.91–7.98 (2H, m); EIMS (m/z): 168 (M^+); Anal. Calcd for C_9H_9ClO: C, 64.11%; H, 5.38%. Found: C, 64.08%; H, 5.35%.

2.4. 3-Chloro-1-(2-thienyl)-1-propanone (**8b**)

Thiophene **7** (2.83 mL, 35.7 mmol) was subjected to Friedel-Craft acylation in the presence of aluminium chloride (5.71 g, 42.8 mmol) and 3-chloropropionyl chloride (3.77 mL, 39.2 mmol) in 40 mL of dry CH_2Cl_2 as described in the above procedure to afford 5.8 g of **8b**. Yield: 93%; IR (neat): 1660, 1451, 1242, 851 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (2H, t, J = 6.8 Hz), 3.87 (2H, d, J = 6.8 Hz), 7.14 (1H, t, J = 3.7 Hz, J = 4.5 Hz), 7.65 (1H, d, J = 4.5 Hz), 7.71 (1H, d, J = 3.7 Hz); EIMS (m/z): 174 (M^+); Anal. Calcd for C_7H_7ClOS: C, 48.14%; H, 4.04%. Found: C, 48.12%; H, 4.01%.

2.5. 3-Azido-1-phenyl-1-propanone (**9a**)

To a stirred solution of ketochloride **8a** (5.0 g, 29.6 mmol) in 35 mL of dry CH_2Cl_2 was added sodium azide (2.80 g, 44.4 mmol) followed by 18-crown-6 (0.78 g, 2.96 mmol) and stirred for 6–7 h. After aqueous workup, the crude **9a** obtained was used for next step without purification on silica gel. For analytical purpose, a small quantity was purified by column chromatography on silica gel. Yield: 78%; IR (neat): 2104, 1685, 1212, 751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.21 (2H, t, J = 6.6 Hz), 3.72 (2H, t, J = 6.6 Hz), 7.43–7.50 (2H, m), 7.53–7.60 (1H, m), 7.92–7.97 (2H, m); EIMS (m/z): 175 (M^+); Anal. Calcd for $C_9H_9N_3O$: C, 61.70%; H, 5.18%. Found: C, 61.67%; H, 5.19%.

2.6. 3-Azido-1-(2-thienyl)-1-propanone (**9b**)

Prepared from ketochloride **8b** (5.0 g, 28.7 mmol) by azidation with sodium azide (2.80 g, 44.4 mmol) in the presence of 18-crown-6 (0.75 g, 2.87 mmol) by following the above procedure. Yield: 75%; IR (neat): 2101, 1660, 1242, 853 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.18 (2H, t, J = 6.8 Hz), 3.74 (2H, t, J = 6.8 Hz), 7.16 (1H, t, J = 3.7 Hz, J = 4.5 Hz), 7.68 (1H, d, J = 4.5 Hz), 7.75 (1H, d, J = 3.7 Hz); EIMS (m/z): 181 (M^+); Anal. Calcd for $C_7H_7N_3OS$: C, 46.40%; H, 3.89%. Found: C, 46.36%; H, 3.93%.

2.7. 3-Azido-1-phenyl-1-propanol (**10a**)

To a stirred solution of ketoazide **9a** (3.50 g, 19.9 mmol) in methanol (30 mL) was added $NaBH_4$ (0.83 g, 21.9 mmol) in portions at 0 °C and stirred at room temperature for 1 h. The solvent was evaporated, water was added followed by extraction with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue obtained was purified by column chromatography on silica gel to provide 3.36 g of γ-azidoalcohol **10a**. Yield: 95%; IR (neat): 3408, 2097, 1261, 761 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (1H, s), 1.83–2.07 (2H, m), 3.31–3.55 (2H, m), 4.77–4.84 (1H, m), 7.22–7.38 (5H, m); EIMS (m/z): 177 (M^+); Anal. Calcd for $C_9H_{11}N_3O$: C, 61.00%; H, 6.26%. Found: C, 61.03%; H, 6.23%.

2.8. 3-Azido-1-(2-thienyl)-1-propanol (**10b**)

Prepared from ketoazide **9b** (3.50 g, 19.4 mmol) by reduction with $NaBH_4$ (0.81 g, 21.3 mmol) in methanol by following the above procedure to provide 3.33 g of γ-azidoalcohol **10b**. Yield: 94%; IR (neat): 3407, 2098, 1263, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96–2.15 (2H, m), 3.32–3.58 (2H, m), 5.01–5.12 (1H, m), 6.91–6.99 (2H, m), 7.19–7.24 (1H, m); EIMS (m/z): 183 (M^+); Anal. Calcd for $C_7H_9N_3OS$: C, 45.89%; H, 4.95%. Found: C, 45.85%; H, 4.96%.

2.9. 3-Azido-1-phenylpropyl acetate (**11a**)

A solution of azidoalcohol **10a** (0.30 g, 1.7 mmol) in CH_2Cl_2 (8 mL) was treated with triethylamine (0.60 mL, 4.2 mmol) and acetic anhydride (0.31 mL, 3.3 mmol) at 0 °C in catalytic presence of DMAP. The reaction mixture was stirred at room temperature for 3 h and quenched with addition of water and after aqueous workup and column purification gave 0.33 g of pure azidoacetate **11a**. Yield: 91%; IR (neat): 2096, 1737, 1231, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.93–2.24 (2H, m), 2.06 (3H, s), 3.17–3.36 (2H, m), 5.77–5.83 (1H, m), 7.23–7.36 (5H, m); EIMS (*m*/*z*): 219 (M^+); Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26%; H, 5.98%. Found: C, 60.22%; H, 5.94%.

2.10. 3-Azido-1-(2-thienyl)propyl acetate (**11b**)

Prepared from azidoalcohol **10b** (0.30 g, 1.6 mmol) and acetic anhydride (0.30 mL, 3.2 mmol) in the presence of triethylamine (0.56 mL, 4.0 mmol) and DMAP by following the above procedure to provide 0.34 g of pure azidoacetate **11b**. Yield: 93%; IR (neat): 2929, 2099, 1739, 1229 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.06 (3H, s), 2.07–2.33 (2H, m), 3.24–3.42 (2H, m), 6.09–6.15 (1H, m), 6.93–6.97 (1H, m), 7.04 (1H, d, J = 3.0 Hz), 7.25 (1H, d, J = 3.0 Hz); EIMS (*m*/*z*): 225 (M^+); Anal. Calcd for $C_9H_{11}N_3O_2S$: C, 47.99%; H, 4.92%. Found: C, 47.95%; H, 4.90%.

2.11. General procedure for lipase mediated kinetic resolution of 3-azido-1-phenyl-1-propanol (**10a**)

To the racemic γ-azidoalcohol **10a** (3.0 g, 16.9 mmol) dissolved in *n*-hexane (40 mL) under ultrasonication, was added lipase (2.25 g) and isopropenyl acetate (11.05 mL, 101.4 mmol) and the reaction mixture was shaken at 42 °C in an orbital shaker. The progress of the reaction was monitored by HPLC using chiral column and after about 50% conversion (ca. 48 h), the reaction mixture was filtered and the residue washed with ethyl acetate. The two enantiomers were separated by column chromatography to afford 1.64 g of azidoacetate (*R*)-**11a** $[\alpha]^{27}_D$ = +56.4 (*c* 3.0, $CHCl_3$) and 1.37 g of unreacted alcohol (*S*)-**10a** $[\alpha]^{27}_D$ = −33.5 (*c* 6.0, $CHCl_3$). The enantiomeric excess of acetate (*R*)-**11a** and alcohol (*S*)-**10a** has been determined by HPLC (chiral column OD-H; Daicel) employing hexane–*iso*-propanol (90:10) as a mobile phase at 0.5 mL/min and monitored at UV (220 nm). Retention times for acetate (*R*)-**11a** and alcohol (*S*)-**10a** were 10.65 and 14.87 min, respectively.

2.12. General procedure for lipase mediated kinetic resolution of 3-azido-1-(2-thienyl)-1-propanol (**10b**)

To the racemic γ-azidoalcohol **10b** (3.0 g, 16.3 mmol) dissolved in *n*-hexane (40 mL) under ultrasonication, was added lipase (2.25 g) and isopropenyl acetate (10.66 mL, 97.8 mmol) and the reaction mixture was shaken at 42 °C in an orbital shaker. The progress of the reaction was monitored by HPLC using chiral column and after about 50% conversion (ca. 17 h) the reaction mixture was filtered and the residue washed with ethyl acetate. The two enantiomers were separated by column chromatography to afford 1.70 g of azidoacetate (*R*)-**11b** $[\alpha]^{27}_D$ = +67.3 (*c* 1.1, $CHCl_3$) and 1.24 g of unreacted alcohol (*S*)-**10b** $[\alpha]^{27}_D$ = −17.8 (*c* 1.7, $CHCl_3$). The enantiomeric excess of acetate (*R*)-**11b** and alcohol (*S*)-**10b** have been determined by HPLC (chiral column OB-H; Daicel) employing hexane–*iso*-propanol (90:10) as a mobile phase at 0.5 mL/min and monitored at UV (230 nm). Retention times for acetate (*R*)-**11a** and alcohol (*S*)-**10a** were 16.75 and 21.58 min, respectively.

2.13. (R)-3-Azido-1-phenyl-1-propanol (**10a**)

To (*R*)-**11a** (1.60 g, 7.3 mmol) in methanol (20 mL), anhydrous K_2CO_3 (3.02 g, 21.9 mmol) was added and stirred at room temperature for 2 h. Potassium carbonate was removed by filtration through Celite pad and the solvent evaporated under reduced pressure. 1.27 g of (*R*)-**10a** was obtained after purification by column chromatography. Yield: 98%; $[\alpha]^{27}_D$ = +32.7 (*c* 1.0, $CHCl_3$).

2.14. (R)-3-Azido-1-(2-thienyl)-1-propanol (**10b**)

Prepared from (*R*)-**11b** by following the above procedure to give 1.25 g of (*R*)-**10b**. Yield: 96%; $[\alpha]^{27}_D$ = +12.2 (*c* 2.0, $CHCl_3$).

2.15. (S)-Ethyl N-(3-hydroxy-3-phenylpropyl)carbamate (**12a**)

The azidoalcohol (*S*)-**10a** (1.0 g, 5.6 mmol) was dissolved in methanol (15 mL) and stirred under a hydrogen atmosphere (1 atm) in the presence of 10% Pd/C (0.2 g) for 5 h. The catalyst was filtered on Celite pad and the solvent was concentrated to provide a residue of amino alcohol. The residue was dissolved in 20 mL of CH_2Cl_2 and to it was added ethyl chloroformate (0.55 mL, 5.8 mmol) and stirred vigorously. To this mixture was added potassium carbonate (2.19 g, 15.9 mmol) in 8 mL of water and stirred for an hour. After aqueous workup and purification by column chromatography 1.06 g of carbamate (*S*)-**12a** was obtained. Yield: 82%; $[\alpha]^{27}_D$ = −24.0 (*c* 1.0, $CHCl_3$); IR (neat): 3347, 1695, 1263, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (3H, t, J = 7.5 Hz), 1.77–1.93 (2H, m), 3.16–3.28 (1H, m), 3.41–3.58 (1H, m), 4.09 (2H, q, J = 7.5 Hz), 4.73 (1H, dd, J = 7.5 Hz, J = 5.3 Hz), 5.05 (1H, br s), 7.18–7.34 (5H, m); EIMS (*m*/*z*): 223 (M^+); Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.56%; H, 7.67%. Found: C, 64.51%; H, 7.62%.

2.16. (R)-Ethyl N-(3-hydroxy-3-phenylpropyl)carbamate (**12a**)

$[\alpha]^{27}_D$ = +23.2 (*c* 1.0, $CHCl_3$).

2.17. (S)-Ethyl N-[3-hydroxy-3-(2-thiophenyl)propyl]carbamate (**12b**)

Prepared from azidoalcohol (*S*)-**10b** by following the procedure described for (*S*)-**12a** to give 1.02 g of carbamate (*S*)-**12b**. Yield: 81%; $[\alpha]^{27}_D$ = −8.7 (*c* 2.1, $CHCl_3$); IR (neat): 3342, 3291, 1693, 1537 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (3H, t, J = 6.8 Hz), 1.89–2.04 (2H, m), 3.16–3.33 (2H, m), 3.44–3.60 (1H, m), 4.10 (2H, q, J = 6.8 Hz), 4.93–5.03 (2H, m), 6.90–6.95 (2H, m), 7.16–7.22 (1H, m); EIMS (*m*/*z*): 229 (M^+); Anal. Calcd for $C_{10}H_{15}NO_3S$: C, 52.38%; H, 6.59%. Found: C, 52.32%; H, 6.55%.

2.18. (R)-Ethyl N-[3-hydroxy-3-(2-thiophenyl)propyl]carbamate (**12b**)

$[\alpha]^{27}_D$ = +3.8 (*c* 1.0, $CHCl_3$).

2.19. (S)-3-(Methylamino)-1-phenyl-1-propanol (**13a**)

To a stirred suspension of LAH (0.34 g, 8.9 mmol) in dry THF (10 mL) at 0 °C was added a solution of (*S*)-**12a** (1.0 g, 4.45 mmol) in 10 mL of THF dropwise under nitrogen atmosphere and refluxed for 1 h. The reaction was quenched with slow addition of ethyl acetate and the slurry formed was removed by filtration and after aqueous workup 0.61 g of (*S*)-**13a** was obtained. Yield: 84%; $[\alpha]^{27}_D$ = −35.7 (*c* 1.0, $CHCl_3$); IR (neat): 3310, 3058, 2940, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.75–1.93 (2H, m) 2.45 (3H, s), 2.82–2.94 (2H, m), 4.89 (1H, dd, J = 3.3 Hz, J = 7.2 Hz), 7.27–7.38 (5H, m); EIMS (*m*/*z*):

165 (M^+); Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69%; H, 9.15%. Found: C, 72.65%; H, 9.19%.

2.20. (R)-3-(Methylamino)-1-phenyl-1-propanol (**13a**)

$[\alpha]^{27}_D$ = +35.0 (*c* 1.0, $CHCl_3$).

2.21. (S)-3-(Methylamino)-1-(thiophen-2-yl)propan-1-ol (**13b**)

Prepared from (*S*)-**12b** by following the above reaction procedure to afford 0.62 g of (*S*)-**13b**. Yield: 83%; $[\alpha]^{27}_D$ = −13.4 (*c* 1.0, MeOH); IR (neat): 3300, 3106, 2937, 1470 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.12–2.18 (3H, m), 2.50 (3H, s), 3.02–3.11 (2H, m), 5.09–5.18 (1H, m), 6.92–6.95 (2H, m), 7.18–7.21 (1H, m); EIMS (*m*/*z*): 171 (M^+); Anal. Calcd for $C_8H_{13}NOS$: C, 56.11%; H, 7.65%. Found: C, 56.08%; H, 7.63%.

2.22. (R)-3-(Methylamino)-1-(thiophen-2-yl)propan-1-ol (**13b**)

$[\alpha]^{27}_D$ = +8.5 (*c* 1.5, MeOH).

2.23. (S)-Fluoxetine (**1**)

To a solution of (*S*)-**13a** (0.50 g, 3.0 mmol) in dry DMSO (5 mL) was added NaH (0.18 g (60%), 4.5 mmol) and heated at 55 °C for 45 min. To the resulting mixture was added 4-chlorobenzotrifluoride (0.50 mL, 3.3 mmol) dissolved in DMSO (3 mL) and heated at 90–100 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with cold water and extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4, evaporated and the residue obtained was purified by column chromatography to provide 0.63 g of (*S*)-**1**. Yield: 68%; $[\alpha]^{27}_D$ = −3.9 (*c* 1.0, $CHCl_3$); IR (neat): 3362, 3018, 2950, 1605, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.99–2.33 (2H, m), 2.44 (3H, s), 2.72–2.86 (2H, m), 5.33 (1H, dd, *J* = 5.2 Hz, *J* = 7.8 Hz), 6.88 (2H, d, *J* = 7.8 Hz), 7.23–7.35 (5H, m), 7.41 (2H, d, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.45, 35.23, 47.86, 78.10, 115.68, 123.62, 125.68, 126.65, 126.68, 128.21, 128.93, 139.44, 160.20; EIMS (*m*/*z*): 309 (M^+); Anal. Calcd for $C_{17}H_{18}F_3NO$: C, 66.01%; H, 5.86%. Found: C, 65.96%; H, 5.82%.

2.24. (R)-Fluoxetine (**1**)

$[\alpha]^{27}_D$ = +3.7 (*c* 1.2, $CHCl_3$).

2.25. (S)-Duloxetine (**4**)

Prepared from (*S*)-**13b** (0.50 g, 2.9 mmol) and 1-fluoro napthalene (0.34 mL, 3.1 mmol) in the presence of NaH (0.17 g (60%), 4.3 mmol) by following the above procedure to provide 0.67 g of (*S*)-**4**. Yield: 78%; $[\alpha]^{27}_D$ = −111.4 (*c* 1.2, MeOH); IR (neat) 3434, 3064, 2963, 1577, 1264 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.16-2.32 (1H, m), 2.42 (3H, s), 2.42–2.51 (1H, m), 2.80 (2H, t, *J* = 7.9 Hz) 5.72 (1H, t, *J* = 6.7 Hz), 6.78–6.87 (2H, m), 6.98 (1H, d, *J* = 3.4 Hz), 7.06 (1H, d, *J* = 5.6 Hz), 7.19 (1H, t, *J* = 7.9 Hz), 7.31 (1H, d, *J* = 7.9 Hz), 7.40 (2H, p, *J* = 6.7 Hz, *J* = 9.0 Hz), 7.68 (1H, d, *J* = 7.9 Hz), 8.36 (1H, d, *J* = 7.9 Hz); EIMS (*m*/*z*): 297 (M^+); Anal. Calcd for $C_{18}H_{19}NOS$: C, 72.69%; H, 6.44%. Found: C, 72.65%; H, 6.41%.

2.26. (R)-Duloxetine (**4**)

$[\alpha]^{27}_D$ = +95.2 (*c* 1.0, MeOH).

3. Results and discussion

3.1. Preparation of racemic acetates of γ-azidoalcohols

The γ-azidoalcohols (**10a**, **10b**), the precursor of γ-aminoalcohols, were studied for the lipase-catalyzed kinetic resolutions with their corresponding acetates. The racemic azidoacetates (**11a**, **11b**) were prepared starting with Friedel-Crafts acylation on benzene **6** and thiophene **7** by 3-chloropropionyl chloride to provide the ketochlorides **8a** and **8b**, respectively. The nucleophilic displacement of **8a** and **8b** by sodium azide in the presence of 18-crown-6 provided γ-ketoazides **9a** and **9b**, respectively, which were reduced by sodium borohydride to provide γ-azidoalcohols **10a** and **10b**. The acetylation of azidoalcohols with acetic anhydride provided the azidoacetates (**11a**, **11b**) that were required as intermediates for the lipase mediated kinetic resolution (Scheme 1).

3.2. Lipase mediated resolution of acetates of γ-azidoalcohols

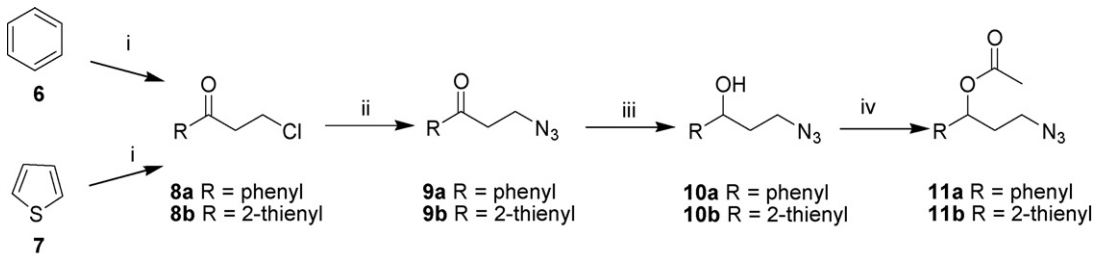
The racemic azidoacetates **11a** and **11b** were subjected to lipase mediated hydrolytic resolution using different lipases in phosphate buffer at pH 7. Amongst them, lipase from *P. cepacia* immobilized on ceramic particle PS-C (*Burkholderia cepacia*) showed high enantioselectivity and conversion for the substrate **11a**. The crude and diatomaceous immobilized form of lipase *P. cepacia* (PS, PS-D) also showed good enantioselectivity. However for azidoacetate **11b**, the rate of hydrolysis was faster compared to **11a** but the lipases showed comparatively lower enantioselectivity. The lipase PS-C furnished the acetate in good enantiomeric excess (Table 1).

On the basis of the hydrolysis of azidoacetate in aqueous medium, the immobilized lipase from *P. cepacia* PS-C and PS-D were used for kinetic resolution of the azidoacetates **11a** and **11b** in organic medium. The alcoholysis process was carried in three different solvents and *n*-butanol. The lipases (PS-C, PS-D) provided good enantioselectivity for the alcohol and the rate of alcoholysis was faster for azidoacetate **11b** (Table 2). The hydrophobic solvents *n*-pentane and *n*-hexane furnished the alcohol in good enantioselectivity compared to diisopropyl ether. In the alcoholysis process, the use of methanol, ethanol and propanol provided poor enantioselectivity compared to *n*-butanol.

In continuation to our previously reported lipase mediated resolution of γ-azidoalcohol by transesterification, it was considered worthwhile to carry out the process on preparative scale for the preparation of anti-depressant drugs utilizing the enantiopure γ-azidoalcohol. The lipase-catalyzed transesterification of the racemic γ-azidoalcohols **10a** and **10b** was performed on preparative scale with lipase from *P. cepacia* (PS-D) in *n*-hexane with diisopropenyl acetate as the acyl donor. The conversion and enantiopurity of alcohols as well as acetates were analyzed on HPLC using chiral column at regular intervals and the reactions were stopped at around 50% conversion. The required alcohols (*S*)-**10a** and (*S*)-**10b** were thus obtained in high enantiopurity (>99% ee and 95% ee, respectively) and the acetates (*R*)-**11a** and (*R*)-**11b** in 93% ee and 75% ee, respectively. The deacetylation of acetates gave alcohols (*R*)-**10a** and (*R*)-**10b** with retention of configuration and enantiopurity (Scheme 2).

3.3. Synthesis of R and S enantiomers of fluoxetine and duloxetine

The enantiomerically enriched key intermediates, γ-azidoalcohols (*S*)-**10a** and (*S*)-**10b** were reduced by catalytic hydrogenation to γ-aminoalcohols, which without isolation were converted to their corresponding ethyl carbamates (*S*)-**12a** and (*S*)-**12b** in good yields. These carbamates were then transformed to the required target compounds by following the reported



Scheme 1. Reagents: (i) 3-chloropropionyl chloride, $AlCl_3$, CH_2Cl_2; (ii) NaN_3, 18-crown-6, CH_2Cl_2; (iii) $NaBH_4$, MeOH; (iv) Ac_2O, TEA, DMAP, CH_2Cl_2.

Table 1
Lipase mediated hydrolysis of acetate (±)-**11a** and (±)-**11b**[a].

Entry	Lipase	Time[b]	ee %[c]		c[d]	E[e]	Time (h)	ee %[f]		c[d]	E[e]
			Acetate (*S*)-**11a**	Alcohol (*R*)-**10a**				Acetate (*S*)-**11b**	Alcohol (*R*)-**10b**		
1	PS	8	95	82	0.53	<10	20	74	63	0.54	<10
2	PS-C	8	97	94	0.51	147 (153)[g]	20	94	62	0.60	<15 (26)[g]
3	PS-D	8	91	93	0.49	83	40	52	40	0.56	<10
4	AK-20	8	77	55	0.58	<10	40	78	49	0.61	<10
5	CAL	8	24	58	0.29	<10	40	81	42	0.65	<10

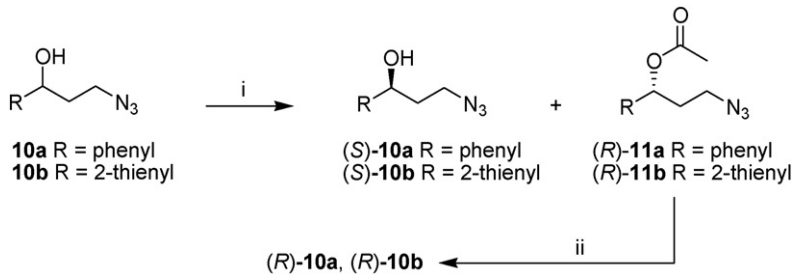
[a] Conditions: 30 mg of (±)-**11a** or (±)-**11b**, 15 mg of lipase (50%, w/w), 4 mL of 0.1 M phosphate buffer NaH_2PO_4–Na_2HPO_4 (pH 7), temperature 35 °C.
[b] Time taken for the acetate hydrolysis in days.
[c] Determined by HPLC analysis employing Daicel Chiralcel OD-H column (0.46 cm × 25 cm); eluent: hexane:2-propanol = 90:10; flow rate: 0.5 mL/min; detector: 220 nm.
[d] Conversion (c) is calculated from enantiomeric excess of substrate acetates **11a**, **11b** (ee_s) and product alcohols **10a**, **10b** (ee_p) using the formula: $c = ee_s/(ee_s + ee_p)$.
[e] Enantiomeric ratio calculated with the formula $E = \{\ln[1 - c(1 + ee_p)]\}/\{\ln[1 - c(1 - ee_p)]\}$
[f] Determined by HPLC analysis employing Daicel Chiralcel OB-H column (0.46 cm × 25 cm); eluent: hexane:2-propanol = 90:10; flow rate: 0.5 mL/min; detector: 230 nm.
[g] Enantiomeric ratio obtained by transesterification process (Ref. [20]).

Table 2
Lipase mediated alcoholysis of (±)-**11a** and (±)-**11b**[a].

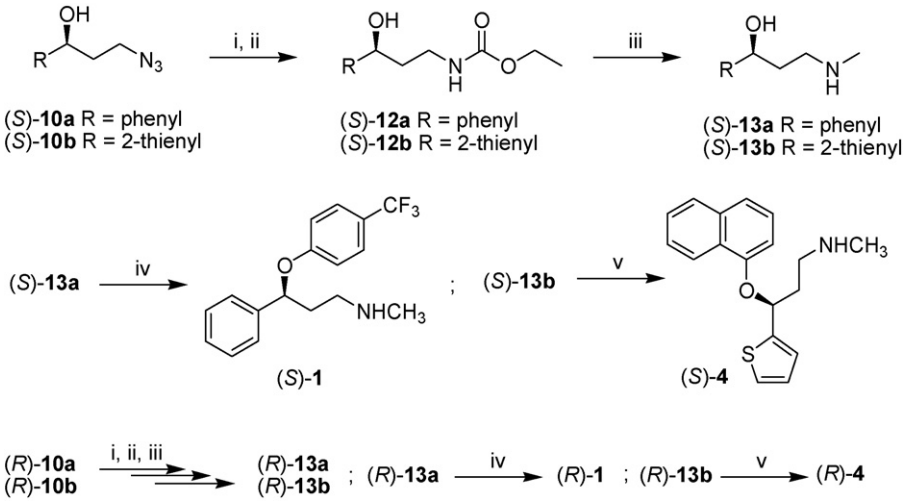
Entry	Lipase	Time[b]	ee %		c	E	Time[b]	ee %		c	E
			Acetate (*S*)-**11a**	Alcohol (*R*)-**10a**				Acetate (*S*)-**11b**	Alcohol (*R*)-**10b**		
1	PS-C[c]	10	90	99	0.47	>200	3	84	90	0.48	50
2	PS-C[d]	10	82	99	0.45	>200	3	98	57	0.63	<15
3	PS-C[e]	10	69	93	0.43	58	3	41	91	0.31	32
4	PS-D[c]	10	66	98	0.40	196	3	32	93	0.25	38
5	PS-D[d]	10	62	97	0.39	125	3	66	94	0.41	64
6	PS-D[e]	10	22	99	0.20	253	3	24	92	0.21	30

[a] Conditions: 25 mg of (±)-**11a** or (±)-**11b**, 25 mg of lipase (50%, w/w), 0.26 mL of *n*-butanol, 3 mL solvent (washed with water), temperature 30 °C.
[b] Time taken for the acetate hydrolysis in days.
[c] *n*-Hexane used as solvent.
[d] *n*-Pentane used as solvent.
[e] Diisopropyl ether used as solvent.

procedures. Lithium aluminium hydride assisted reduction of these carbamates provided the *N*-monomethylated amino alcohols (*S*)-**13a** and (*S*)-**13b**. The ether formation by arylation of (*S*)-**13a** by 4-chlorobenzotrifluoride afforded the enantiomerically pure (*S*)-fluoxetine. Under similar conditions the *O*-arylation of *N*-monomethylated aminoalcohol (*S*)-**13b** with 1-fluoro naphthalene provided (*S*)-duloxetine. The other enantiomers of the anti-depressants (*R*)-**1** and (*R*)-**4** were also synthesized from



Scheme 2. Reagents: (i) lipase PS-D, isopropenyl acetate, *n*-hexane; (ii) K_2CO_3, MeOH.



Scheme 3. Reagents: (i) H_2, 10% Pd-C, MeOH; (ii) ethyl chloroformate, K_2CO_3, CH_2Cl_2; (iii) LAH, THF; (iv) 4-chlorobenzotrifluoride, NaH, DMSO; (v) 1-fluoronaphthalene, NaH, DMSO.

(*R*)-**10a** and (*R*)-**10b** following a similar sequence of reactions (Scheme 3).

4. Conclusion

In summary, lipase catalyzed resolutions of acetates of γ-azidoalcohols by hydrolysis and alcoholysis have been studied. The enantiomerically pure γ-azidoalcohols obtained by the kinetic resolution have been utilized towards the synthesis of enantiomeric pairs of anti-depressant drugs fluoxetine and duloxetine. Moreover, the present method provides an alternate and practically useful protocol for the preparation of target compounds under mild and environmentally friendly conditions.

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