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Chemoenzymatic synthesis of duloxetine and its enantiomer: lipase-catalyzed resolution of 3-hydroxy-3-(2-thienyl) propanenitrile

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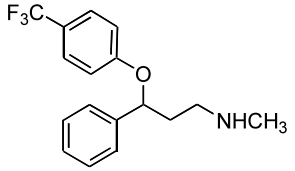
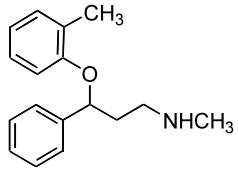
Abstract—An efficient and facile chemoenzymatic synthesis of duloxetine by lipase mediated resolution of 3-hydroxy-3-(2-thienyl)propanenitrile has been achieved. This process also describes an enantioconvergent synthesis of duloxetine via a Mitsunobu reaction. © 2003 Elsevier Science Ltd. All rights reserved.

Antidepressants (serotonin reuptake inhibitors, norepinephrine reuptake inhibitors) with 3-aryloxy-3-aryl propylamine sub-structures such as fluoxetine,[1] tomoxetine,[2] nisoxetine and duloxetine[3] are among the most important pharmaceuticals for the treatment of psychiatric and metabolic disorders. Fluoxetine[4] is a selective inhibitor of serotonin in serotonergic neurons, tomoxetine[5] and nisoxetine[6] are selective inhibitors of norepinephrine in noradrenergic neurons while duloxetine[3] is a dual inhibitor of serotonin and norepinephrine reuptake and has a better pharmacological profile for an antidepressant drug. Serotonin and norepinephrine neurotransmitters are intimately involved in a number of physiological and behavioral processes, suggesting that duloxetine (ability to produce a robust increase of extracellular serotonin and norepinephrine levels) is not only a highly efficient antidepressant agent for treating psychiatric disorders,[7] but also can be used for treating other symptoms[8–13] such as urinary incontinence,[7b,8] obsessive compulsive disorder[7b,11] etc. Improved efficacy, tolerability, safety, faster recovery, fewer side effects, low affinity for neuronal receptors and dual inhibiting nature gives duloxetine an edge over other existing antidepressants such as fluoxetine and it is anticipated that duloxetine may reach its peak sales of over US $ 1 billion in 2003.

Fluoxetine and tomoxetine are marketed in their racemic form whereas duloxetine (Cymbalta: (*S*)-*N*-methyl-3-(1-naphthyloxy)-3-(2-thienyl)-1-propanamine) is marketed in its *S* enantiomeric form. In the literature, there are only a few reports of the synthesis of duloxetine, particularly its enantioselective preparation. One of the methods employs an asymmetric reduction of a Mannich base[3c] with an LAH complex while another method employs the reduction of 3-chloro-1-(2-thienyl)-1-propanone with BH_3 in the presence of oxazaborolidine.[14] Some methods are based on resolution processes involving classical resolution of 3-chloro-1-(2-thienyl)-1-propanol employing mandelic acid,[15] and an enzymatic resolution of 3-chloro-1-(2-thienyl)-1-propanol employing *Candida antartica* lipase.[3d] These chiral intermediates obtained by employing the above processes have been subsequently used for the synthesis of duloxetine.



Fluoxetine



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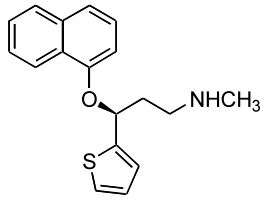

Duloxetine

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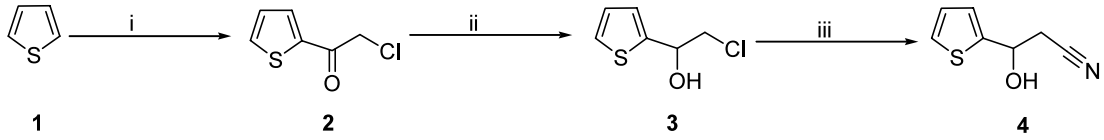
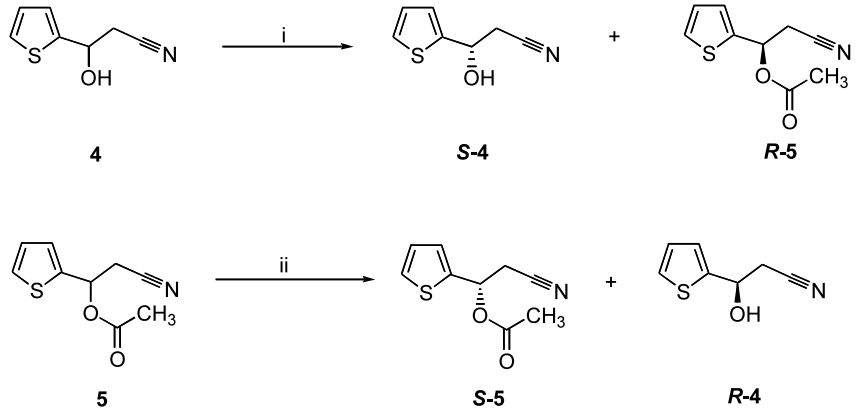
In continuation of our earlier efforts towards the preparation of biologically important compounds or their intermediates by the application of enzymes[16] we herein wish to report an efficient and facile synthesis of duloxetine. Based on a retrosynthetic strategy optically pure 3-hydroxy-3-(2-thienyl)propanenitrile is considered as a potential building block for the total synthesis of duloxetine.[16f] Therefore, the corresponding β-hydroxynitrile has been resolved enzymatically by employing various lipases for transesterification as well as hydrolysis. The starting material, 3-hydroxy-3-(2-thienyl) propanenitrile, required for the enzymatic resolution was prepared by acylation of thiophene followed by reduction and nucleophilic displacement of chlorine by cyanide as depicted in Scheme 1.[17]

The lipase-catalyzed kinetic resolution of hydroxynitrile **4** was carried out by transesterification of 3-hydroxy-3-(2-thienyl)propanenitrile with vinyl acetate to afford (*S*)-3-hydroxy-3-(2-thienyl)propanenitrile[18] (*S*-**4**) $[\alpha]_D^{30} = -33.5$ (*c* 1, $CHCl_3$) in 42% yield and (*R*)-3-acetyloxy-3-(2-thienyl)propanenitrile[18] (*R*-**5**) $[\alpha]_D^{30} = +94.0$ (*c* 1, $CHCl_3$) in 43% yield (Scheme 2).

Various lipases were screened for this resolution process in diisopropyl ether and the results are discussed in Table 1. It is interesting to note that the immobilized lipase from *Pseudomonas cepacia* (PS-D) provided not only high enantioselectivity but also good yields. The role played by different solvents has also been investigated and the results are illustrated in Table 2. It was



Scheme 1. *Reagents and conditions*: (i) $AlCl_3$, $ClC(O)CH_2Cl$, CS_2, rt, 24 h, 85%; (ii) $NaBH_4$, MeOH, rt, 30 min, 90%; (iii) NaCN, $MeOH/H_2O$ (3:1), rt, 4 h 77% yield.



Scheme 2. *Reagents and conditions*: (i) lipase (PS-D), vinyl acetate; (ii) lipase (PS-D), phosphate buffer (pH 7.2)

Table 1. Transesterification of 3-hydroxy-3-(2-thienyl)propanenitrile with various lipases in diisopropyl ether

S. No.	Lipases[a]	Time (h)	Alcohol (*S*-**4**)		Acetate (*R*-**5**)	
			Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)
1	PS-D	14	42	>99	43	>99
2	PS-C	3.5	40	84.3	45	83.2
3	PS	70	68	44.4	22	>99
4	Lipozyme	240	80	11.9	12	>99
5	CRL	240	88	6.2	5	>99
6	CCL	240	85	7.4	6	>99
7	PPL	240	98	–	–	–

[a] *Pseudomonas cepacia* lipase immobilized on modified ceramic particles (PS-C), *Pseudomonas cepacia* lipase immobilized on diatomite (PS-D), *Pseudomonas cepacia* (PS), Porcine pancreas lipase (PPL), *Candida cylindracea* lipase (CCL), *Candida rugosa* lipase (CRL), lipase immobilized from Mucor meihei (Lipozyme).

[b] Isolated yields.

[c] Determined by chiral HPLC (chiral OJ-H column; Diacel) employing hexane–isopropanol (85:15) as mobile phase at 0.75 mL/min and monitored by UV (254 nm).

Table 2. Effects of different solvents on the transesterification of 3-hydroxy-3-(2-thienyl)-propanenitrile by lipase PS-D 'Amano' II

S. No.	Solvent	Time (h)	Alcohol (*R*-**4**)		Acetate (*S*-**5**)	
			Yield[a] (%)	ee[b] (%)	Yield[a] (%)	ee[b] (%)
1	Diisopropyl ether	14	42	>99	43	>99
2	Toluene	15	43	>99	42	>99
3	Hexane	11.5	40	>99	46	91.3
4	Dioxane	67	65	42.4	35	>99
5	Chloroform	39	60	65.2	33	84.5
6	Tetrahydrofuran	63	80	24.8	14	>99
7	Acetonitrile	63	88	7.0	5	>99
8	Acetone	70	90	–	–	–

[a] Isolated yields.
[b] Determined by chiral HPLC (chiral OJ-H column; Diacel) employing hexane–isopropanol (85:15) as mobile phase at 0.75 mL/min and monitored by UV (254 nm).

observed that a number of hydrophobic solvents such as diisopropyl ether, toluene and hexane gave excellent results when compared with hydrophilic solvents.

The lipase-mediated hydrolysis of 3-acetyloxy-3-(2-thienyl)propanenitrile **5** has also been investigated (Scheme 2). Hydrolysis of 3-acetyloxy-3-(2-thienyl)propanenitrile with lipase in phosphate buffer (pH 7.2) and acetone afforded (*R*)-3-hydroxy-3-(2-thienyl)propanenitrile (*R*-**4**) $[\alpha]_D^{30}=+32.0$ (*c* 1, $CHCl_3$) in 41% yield and (*S*)-3-acetoxy-3-(2-thienyl)propanenitrile (*S*-**5**) $[\alpha]_D^{30}=-92.1$ (*c* 1, $CHCl_3$) in 40% yield as described in Table 3.

The optically pure enantiomers thus obtained were used in an enantioconvergent synthesis of duloxetine (Scheme 3).

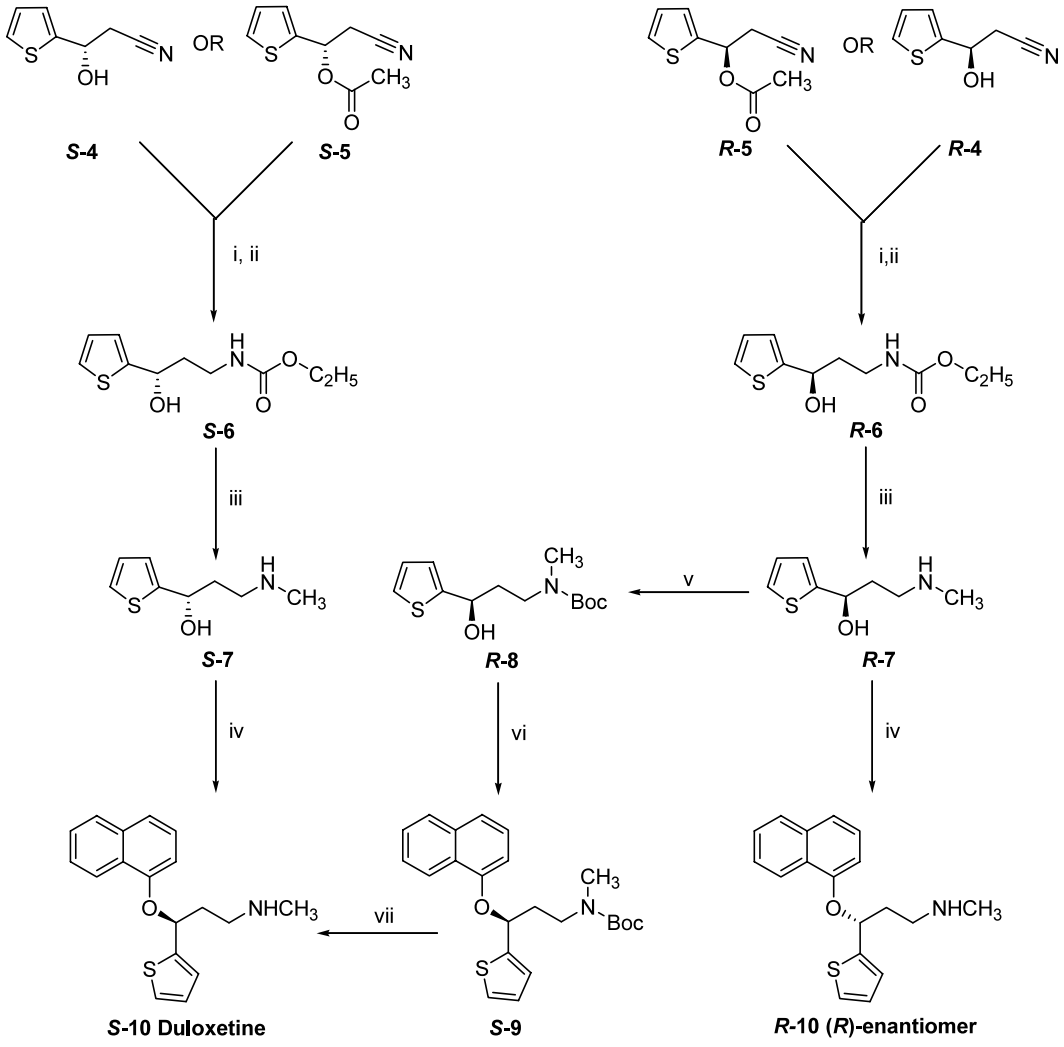
The key chiral intermediates (*S*)-3-hydroxy-3-(2-thienyl)propanenitrile (*S*-**4**) or (*R*)-3-hydroxy-3-(2-thineyl)propanenitrile (*R*-**4**) and their acetates *S*-**5** or *R*-**5** were then transformed to the respective 3-amino-1-(2-thienyl)-1-propanol by employing $BH_3{\cdot}Me_2S$.[19] These amino alcohols without isolation were converted to their corresponding ethyl carbamates, (*S*)-*N*-(ethoxycarbonyl)-3-amino-1-(2-thienyl)-1-propanol (*S*-**6**) [18] $[\alpha]_D^{34}=-9.1$ (*c* 1.36, $CHCl_3$) and (*R*)-*N*-(ethoxycarbonyl)-3-amino-1-(2-thienyl)-1-propanol (*R*-**6**)[18] $[\alpha]_D^{30}=+8.3$ (*c* 1.15, $CHCl_3$) upon treatment with ethyl chloroformate in aqueous K_2CO_3 and CH_2Cl_2 in 80–86% yields. These carbamates were subjected to LAH reduction to give the *N*-monomethylated amino alcohols, *N*-methyl-3-amino-1-(2-thienyl)-1-propanol (*S*-**7**) and (*R*-**7**) $[\alpha]_D^{34}=+13.9$ (*c* 2.4, MeOH) (for the *R* isomer) lit.[3d] $[\alpha]_D^{22}=+9.74$ (*c* 3.8, MeOH) in excellent yields. *O*-Arylation of the monomethylated amino alcohols was carried out using 1-fluoronaphthalene in dry DMSO employing NaH as the base to afford duloxetine (*S*-**10**) and its *R*-enantiomer (*R*-**10**) in 80–82% yield $[\alpha]_D^{30}=+114$ (*c* 1, MeOH) (for duloxetine) lit.[3c] $[\alpha]_D^{22}=+117$ (*c* 1, MeOH). Furthermore, an enantioconvergent synthesis of duloxetine has also been carried out by Boc protection of *R*-**7** to give *N*-Boc-*N*-methyl-(3-hydroxy)-3-(2-thienyl)-1-propanamine (*R*-**8**) $[\alpha]_D^{30}=-8.2$ (*c* 1.4, $CHCl_3$) followed by Mitsunobu coupling to afford Boc protected duloxetine (*S*-**9**) $[\alpha]_D^{30}=+10.0$ (*c* 0.95, $CHCl_3$) and this upon deprotection gave duloxetine.

In summary, a simple, practical and highly enantioselective synthesis of duloxetine has been accomplished by employing lipase catalyzed resolution of 3-hydroxy-3-(2-thienyl)propanenitrile. Moreover, this methodology also describes an enantioconvergent route towards the synthesis of duloxetine.

Table 3. Enzymatic hydrolysis of 3-acetyloxy-3-(2-thienyl)propanenitrile in phosphate buffer

S. No.	Lipases[a]	Time (h)	Alcohol		Acetate	
			Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)
1	PS-D	14	41	>99	40	>99
2	PS-C	3.5	44	84.6	38	97.5

[a] *Pseudomonas cepacia* lipase immobilized on modified ceramic particles (PS-C), *Pseudomonas cepacia* lipase immobilized on diatomite (PS-D).
[b] Isolated yields.
[c] Determined by chiral HPLC (chiral OJ-H column; Diacel) employing hexane–isopropanol (90:15) as mobile phase at 0.75 mL/min and monitored by UV (254 nm).



Scheme 3. *Reagents and conditions*: (i) $BH_3{\cdot}Me_2S$, THF, reflux, 2 h; (ii) $ClCO_2C_2H_5$, K_2CO_3, CH_2Cl_2, rt, 30 min, 78% (overall); (iii) LAH, THF, reflux 1.5 h, 88%; (iv) NaH, dry DMSO, 1-fluoronaphthalene, 8 h, 81%; (v) Boc anhydride, Et_3N, CH_2Cl_2, rt, 2 h, 88%; (vi) PPh_3, DIAD, 1-naphthol, THF, 24 h, 51%; (vii) TFA, $CHCl_3$, 70%.

Acknowledgements

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17. (a) Thiophene was slowly added to an equimolar solution of $AlCl_3$ and chloroacetyl chloride in CS_2 at 0°C and allowed to warm to room temperature over a period of 12 h; (b) $NaBH_4$ in methanol at room temperature for 30 min gave the corresponding alcohol; (c) 2 equiv. of NaCN was added to a solution of chlorohydrin in $MeOH/H_2O$ (3:1) at room temperature and stirred for 4 h.
18. **4**: IR (neat) 3475, 3075, 2878, 2251, 1105, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.82 (dd, 2H, $J=3.0$ Hz, $J=6.6$ Hz), 3.00 (s, 1H), 5.25 (t, 1H, $J=5.5$ Hz), 6.98 (t, 1H, $J=4.9$ Hz), 7.05 (d, 1H, $J=3.7$ Hz), 7.28 (d, 1H, $J=4.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 66.0, 117.0, 124.6, 125.6, 127.0, 144.4; mass (EI) 153 (M^+), 127, 113, 85. **5**: IR (neat) 3114, 2910, 2800, 2243, 1734, 1216 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.94 (d, 2H, $J=6.7$ Hz), 6.20 (t, 1H, $J=6.7$ Hz), 6.97 (t, 1H, $J=3.8$ Hz), 7.10 (d, 1H, $J=3.0$ Hz), 7.30 (d, 1H, $J=5.9$ Hz); mass (EI) 195 (M^+), 154, 137, 114, 85, 43. **6**: IR (neat) 3325, 3294, 2934, 2886, 2839, 1678, 1255, 1129, 1066, 1012 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.24 (t, 3H, $J=7.3$ Hz), 1.88–2.02 (m, 2H), 3.13–3.32 (m, 1H), 3.40–3.60 (m, 1H), 4.09 (q, 2H, $J=7.32$ Hz), 4.89–5.05 (m, 1H), 6.85–6.96 (m, 2H), 7.13–7.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 37.7, 39.2, 61.0, 67.7, 123.3, 124.3, 126.6, 148.1, 157.4; mass (EI) 229 (M^+), 183, 166, 140, 113, 85. **7**: IR (neat) 3325, 3196, 2949, 2910, 1553, 1396, 1051 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.15–2.18 (m, 2H), 2.55 (s, 3H), 3.04–3.09 (m, 2H), 5.16 (t, 1H, $J=5.95$ Hz), 6.93–6.95 (m, 2H), 7.20 (dd, 1H, $J=2.3$ Hz, $J=4.5$ Hz); mass (EI) 171 (M^+), 128, 110, 85, 44. ***R*-8**: mp 80–83°C ^1H NMR (200 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.78–2.12 (m, 2H), 2.88 (s, 3H), 3.02–3.10 (m, 1H), 3.85–3.89 (m, 1H), 4.79–4.83 (br d, 1H, $J=7.3$ Hz), 6.90–6.92 (m, 2H), 7.18–7.26 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.4, 34.4, 37.1, 45.2, 66.6, 80.1, 123.0, 124.1, 126.5, 148.2. ***S*-9**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 9H), 2.25–2.34 (m, 1H), 2.40–2.45 (m, 1H), 2.85 (s, 3H), 3.42–3.53 (m, 2H), 5.63–5.65 (m, 1H), 6.76 (d, 1H, $J=7.5$ Hz), 6.90 (dd, 1H, $J=3.4$, $J=5$ Hz), 7.03–7.04 (m, 1H), 7.17–7.19 (m, 1H), 7.23 (d, 1H, $J=8.3$ Hz), 7.35 (d, 1H, $J=8.2$ Hz), 7.42–7.47 (m, 2H), 7.73 (dd, 1H, $J=3.1$, $J=6.2$ Hz), 8.30 (dd, 1H, $J=3.4$, $J=6.3$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.4, 34.7, 37.3, 45.8, 74.0, 79.5, 106.9, 120.7, 122.0, 124.7, 125.2, 125.6, 126.3, 126.4, 126.6, 127.5, 128.8, 134.6, 144.8, 153.2, 155.7. ***S*-10**: IR (neat) 3404, 3059, 2965, 2925, 2855, 2785, 1567, 1396, 1263, 1247, 1082 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.18–2.42 (m, 1H), 2.52 (s, 3H), 2.57–2.59 (m, 1H), 3.02 (t, 2H, $J=7.0$ Hz) 5.81 (m, 1H), 6.83 (d, 1H, $J=7.5$ Hz), 6.88–6.91 (m, 1H), 7.05 (d, 1H, $J=3$ Hz), 7.18 (d, 1H, $J=4.9$ Hz), 7.22–7.27 (m, 1H), 7.37–7.40 (m, 1H), 7.46–7.49 (m, 2H), 7.75–7.78 (m, 1H), 8.27–8.31 (m, 1H).
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