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Chemoenzymatic synthesis2 of both enantiomers of fluoxetine, tomoxetine and nisoxetine: lipase-catalyzed resolution of 3-aryl-3-hydroxypropanenitriles

Ahmed Kamal,* G. B. Ramesh Khanna and R. Ramu

Biotransformation Laboratory, Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—A facile preparation of (±)-3-hydroxy-3-phenylpropanenitrile has been carried out by ring-opening of styrene oxide with NaCN in aqueous ethanol. Subsequent kinetic resolution of this material via lipase-mediated transesterification gave the *S*-alcohol and *R*-acetate in excellent yields and high enantioselectivities, particularly with lipase PS-C 'Amano' II. The effect of solvents and immobilization of the lipase has also been investigated. It is interesting to note that the use of immobilized lipase for this transesterification process in hydrophobic solvents (diisopropyl ether, toluene and hexane) enhanced the reaction rate drastically and gave optimal yields with high enantioselectivity (>99%). Moreover, enantiopure 3-hydroxy-3-phenylpropanenitrile products have been converted via enantioconvergent routes into the (*R*)- and (*S*)-enantiomers of the important anti-depressants fluoxetine, tomoxetine, nisoxetine and norfluoxetine.

1. Introduction

The anti-depressants (selective serotonin reuptake inhibitors/norepinephrine reuptake inhibitors) with a 3-aryloxy-3-phenylpropylamine sub-structure, e.g. fluoxetine[1] **12**, tomoxetine[2] **16** and nisoxetine **18** are among the most important pharmaceuticals for the treatment of psychiatric disorders and metabolic problems.

Fluoxetine offers the potential for treatment of additional indications such as anxiety, alcoholism, chronic pain, migraine headache, obsessive compulsive disorders, memory disorders, sleep disorders and bulimia. Fluoxetine in its racemic form (prozac) is the worlds leading anti-depressant with the sales of approximately US $3 billions per annum. In view of the different pharmacological activities displayed by the individual enantiomers of the above racemates,[3] differences in metabolic behavior and also in recent years the importance of preparing drugs in enantiomerically pure form, the preparation of these anti-depressants in enantiomerically pure form is highly desirable. The unique pharmacology of (*R*)-fluoxetine offers the potential for more rapid onset of relief, greater efficacy in the treatment of depression and fewer side effects such as sexual dysfunction. (*R*)-Fluoxetine also offers the potential for the treatment of additional indications, including anxiety. Improvement in pharmacokinetic profile of such compounds allows shorter washout and reduced drug–drug interactions. Presently, (*R*)-fluoxetine, an 'improved chemical entity' version of the drug, is in phase III clinical trials under a collaborative program between Eli Lilly and Company and Sepracor. However, many differences have been reported in the literature with regard to the pharmacological potencies of the isomers of fluoxetine.[3c] Some studies suggest that the (*S*)-isomer is more potent than the (*R*)-isomer, while some suggest that the (*R*)-isomer is more potent and some studies suggest that the eudismic ratio for the isomers is unity.[3b] In the case of tomoxetine, the (*R*)-enantiomer is twice more potent than the racemate and nine times more potent than the (*S*)-form. This has led many research groups to explore the preparation of enantiomerically pure building blocks for these compounds via enantioselective epoxidation followed by stereoselective opening, asymmetric reduction, microbial reductions and enzymatic resolutions (Fig. 1).

* Corresponding author. Fax: +91-40-7160512, +91-40-7160757; e-mail: ahmedkamal@iict.ap.nic.in

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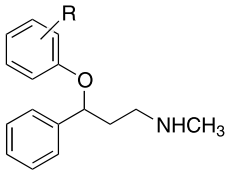


12 R = 4-CF_3 Fluoxetine

16 R = 2-CH_3 Tomoxetine

18 R = 2-OCH_3 Nisoxetine

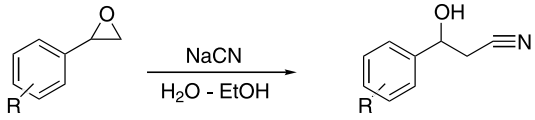
Figure 1.

History shows that β-hydroxy nitriles have importance both as reagents and as technical products in organic chemistry. These have been extensively investigated and employed[4] in the preparation of various intermediates for naturally occurring bioactive compounds.[5] Moreover, as the cyano group can be readily transformed into different functional groups by simple methods, chiral β-hydroxy nitriles have enormous synthetic potential for the preparation of optically active β-hydroxy amides,[6] β-hydroxy acids,[7] β-hydroxy esters,[7c,8] diols,[7c,9] and amino alcohols.[10] These compounds, derived from optically active β-hydroxy nitriles, are synthetically interesting highly functionalized chiral synthons and versatile intermediates in both asymmetric synthesis and medicinal chemistry. Moreover, the stereogenicity at the hydroxyl group in these compounds can be used to control the generation of new stereocenters thus offering a potential diastereoselective route to 1,3-diols[11] and 1,3-amino alcohols,[12] intermediates for a large number of natural products, antibiotics[13] and chiral auxillaries.[14] In view of the need for development of practical efficient methodologies for the preparation of enantiomerically pure anti-depressant drugs such as fluoxetine, tomoxetine and nisoxetine, we have considered enantiomerically pure β-hydroxy nitriles as suitable precursors for the synthesis of these compounds. In continuation of our earlier efforts towards the synthesis of biologically important compounds employing enzymes,[15] we wish to report herein a successful enzymatic resolution of β-hydroxy nitriles and their application in the synthesis of optically active antipsychic drugs, viz. fluoxetine, tomoxetine, and nisoxetine.

2. Results and discussion

2.1. Preparation of β-hydroxy nitriles, 1–2

In the literature, β-hydroxy nitriles have been prepared by the ring-opening of styrene oxide with HCN,[16] alkali metal cyanides in the presence of perchlorates,[17] $Yb(CN)_3$,[17,18] acetone cyanohydrin,[19] alkylaluminum cyanides,[20] $Ce(OTf)_4$,[21] TMSCN.[18,20b,22] Most of these methods have some limitations such as poor chemoselectivity, and the use of volatile toxic substances and expensive reagents. In order to overcome these problems, a new practical method for the preparation of β-hydroxy nitriles has been developed by the regioselective ring-opening of styrene oxide with NaCN in aqueous–alcoholic medium. The presence of water in the reaction media not only facilitates the availability of the cyanide nucleophile but also assists complete regioselective opening in good yields (Eq. (1)).



(1)

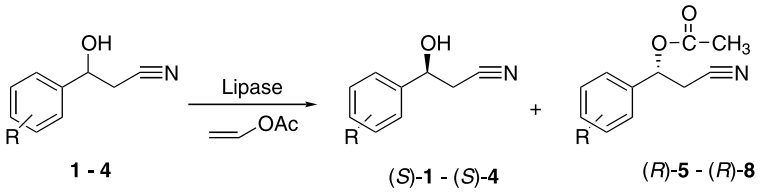
1 : R = H
2 : R = 3-Cl

2.2. Lipase-catalyzed resolution of β-hydroxy nitriles, 1–4

A number of biologically important compounds contain chiral β-hydroxy nitrile components in their structures. However, there are very few reports on the preparation of optically active β-hydroxy nitriles, and most of them are based on enzymatic approaches. Earlier attempts to reduce 3-oxo-3-phenylpropanenitrile by employing bakers' yeast[23] gave the required (*S*)-3-hydroxy-3-phenylpropanenitrile in very low yields (10%), while the major product formed was the alkylated compound (±)-2-ethyl-3-oxo-3-phenylpropanenitrile. Recently, it has been demonstrated[24] that on performing this reaction at low temperature (*S*)-3-hydroxy-3-phenylpropanenitrile is formed exclusively in moderate yield. However, this bakers' yeast-mediated reaction had to be carried out at 4°C for 7 days to give the desired reduction product. Another recent enantioselective bioreduction of β-ketonitriles has been carried out with fungus *Curvularia lunata*[25] and even this organism produced the ethylated β-hydroxy nitrile on employing ethanol as well as DMF as co-solvent. However, use of methanol as a co-solvent improved the yield (55%) and ee of the β-hydroxy nitrile product. Lipase-catalyzed hydrolysis has been extensively utilized for the resolution of various optically active hydroxy substituted substrates and this has also been applied to the resolution of β-hydroxy nitriles. As most of the enzymatic hydrolytic processes are substrate specific, the enantioselectivity depends on both the acid and the ester components. However, enzymatic hydrolysis by employing lipases failed to resolve the β-hydroxy nitriles. With a view to improving the enantioselectivity of the resolution process, sulphur-containing bulky esters[26] have been hydrolyzed with various lipases. It is further observed from the literature[26e,f] that not much attention has been given to the resolution of 3-hydroxy-3-phenylpropanenitrile **1** by lipase-catalyzed transesterification. Therefore, we became interested in the transesterification of these substrates (**1**–**4**) (Eq. (2)) employing various lipases to prepare optically active 3-aryl-3-hydroxy propanenitriles and these results are discussed in Table 2. Although the maximum yield of this resolution process is only 50%, the reaction holds high importance if certain criteria are met with: if both isomers obtained after resolution are easily separable and have high enantiomeric purities, the lipase used can be recovered

and reused, and the substrate for the resolution process can be readily obtained. In this context, we investigated the potential of different lipases for the transesterification of 3-hydroxy-3-phenylpropanenitrile.[27]

It was observed from the results (Table 1) that lipase PS-C 'Amano' II gave excellent yields and high enantioselectivity. Moreover, this led us to examine the effect of immobilization (Table 2) and solvent effects in this transesterification process (Table 3). It is interesting to observe that in the transesterification of **1** with immobilized PS lipase (Table 1, entry 1) is 14 times faster than when the non-immobilized form is used (Table 1, entry 3). In this investigation the effect of solvents on the rate of conversion and enantioselectivity has been examined. It was also observed that diisopropyl ether, toluene and hexane are the solvents of choice, offering remarkable enantioselectivities (Table 3, entries 1, 2 and 3). Whereas in hydrophilic solvents like acetone, THF and acetonitrile the reaction did not proceed, or proceeded with negligible formation of the product and no significant enantioselectivity (Table 3, entries 5, 6, and 7). The generality of the process has been extended to various aryl substituted 3-aryl-3-



1 - 4 (*S*)-**1** - (*S*)-**4** (*R*)-**5** - (*R*)-**8** (2)

Table 1. Transesterification of 3-hydroxy-3-phenylpropanenitrile with various lipases in diisopropyl ether at 40°C

Entry	Lipases[a]	Time (h)	Alcohol		Acetate	
			Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)
1	PS-C	13	46	>99	46	>99
2	PS-D	75	45	>99	46	>99
3	PS	180	46	>99	44	>99
4	PPL	240	98	–	–	–
5	CCL	216	81	21	15	>99
6	CRL	139	65	33	28	78
7	Lipozyme	216	80	16	14	>99
8	CAL	220	90	–	5	–
9	P	216	60	55	32	>99

[a] *Pseudomonas cepacia* lipase immobilized on modified ceramic particals (PS-C) (Amano Pharmaceutical company), *Pseudomonas cepacia* lipase immobilized on diatomite (PS-D) (Amano Pharmaceutical company), *Psedomonas cepacia* (PS) (Amano Pharmaceutical company), Porcine pancreas lipase (PPL) (Sigma), *Candida cylindracea* lipase (CCL) (Sigma), *Candida rugosa* lipase (CRL) (Sigma), lipase immobilized from Mucor meihei (Lipozyme) (Fluka), *Candida antartica* lipase immobilized in Sol-Gel-AK on sintered glass (CAL) (Fluka), *Pseudomonas fluorescens* lipase immobilized in Sol-Gel-AK on sintered glass(P) (Fluka).

[b] Isolated yields.

[c] Determined by chiral HPLC (chiral OJ-H column; Diacel) employing hexane–isopropanol (90:10) as the mobile phase at 0.5 mL/min and monitored by UV (254 nm).

Table 2. Transesterification of various substrates using both immobilized (PS-C) and non-immobilized lipase (PS) in diisopropyl ether

Entry	Substrate (R)	Lipase	Time (h)	Alcohol		Acetate	
				Yield[a] (%)	ee[b] (%)	Yield[a] (%)	ee[b] (%)
1	H	PS-C[c]	16	46	>99	46	>99
2	H	PS[d]	180	46	>99	44	>99
3	3-Cl	PS-C[c]	8	45	>99	46	>99
4	3-Cl	PS[d]	93	59	74	35	>99
5	4-Cl	PS-C[c]	7.5	46	>99	47	>99
6	4-Cl	PS[d]	72	60	74	34	>99
7	4-CH_3	PS-C[c]	10	45	>99	46	>99
8	4-CH_3	PS[d]	170	55	78	34	>99

[a] Isolated yields.

[b] Determined by chiral HPLC (chiral OJ-H column; Diacel) employing hexane–isopropanol (90:10) as mobile phase at 0.5 mL/min and monitored by UV (254 nm).

[c] Reaction carried out at 27°C.

[d] Reaction carried out at 40°C.

Table 3. Effects of solvents on the transesterification of 3-hydroxy-3-phenylpropanenitrile by lipase PS-C 'Amano' II

Entry	Solvent	Time (h)	Alcohol		Acetate	
			Yield[a] (%)	ee[b] (%)	Yield[a] (%)	ee[b] (%)
1	Diisopropyl ether	16	46	>99	46	>99
2	Toluene	18	44	>99	44	>99
3	Hexane	17	45	>99	46	>99
4	Chloroform	24	70	30	24	>99
5	Acetonitrile	25	80	17	14	<10
6	Acetone	24	95	–	–	–
7	Tetrahydrofuran	30	96	–	–	–
8	*t*-Butyl methyl ether	20	96	–	–	–

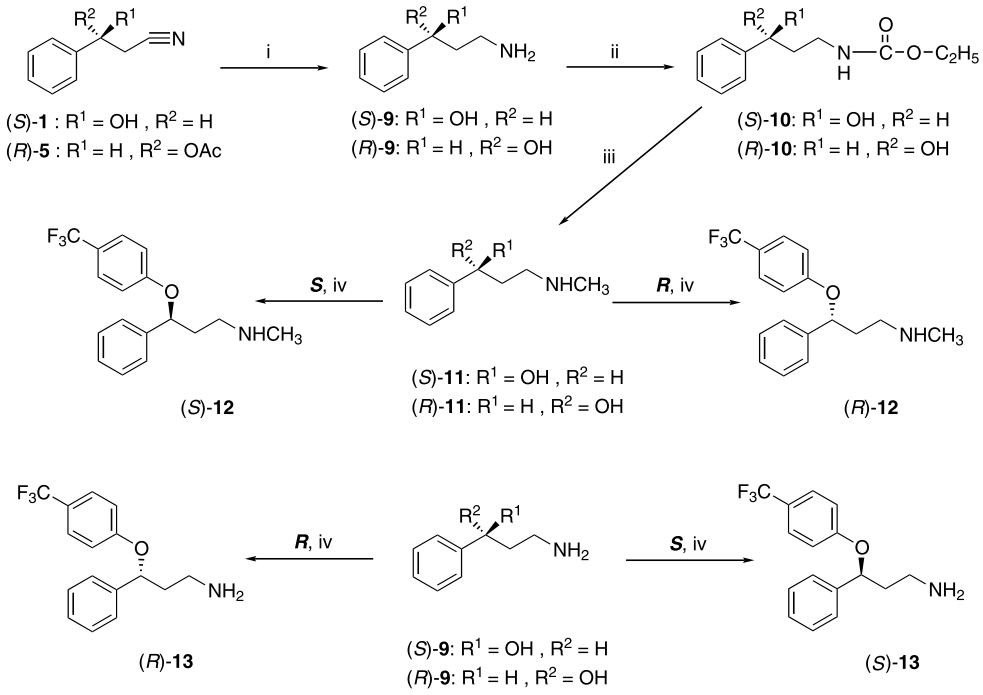
[a] Isolated yields.
[b] Determined by chiral HPLC (chiral OJ-H column; Diacel) employing hexane–isopropanol (90:10) as mobile phase at 0.5 mL/min and monitored by UV (254 nm).

hydroxypropanenitriles, as illustrated in Table 2. The absolute configuration of these compounds has been assigned by the comparison of the specific rotation value for the authentic (*S*)-3-hydroxy-3-phenylpropanenitrile[24] (*S*)-**1**. From our earlier experience[15a] with *Pseudomonas cepacia* lipase and by the empirical rule for the enantiopreference of this lipase the absolute configuration of acetates (*R*)-**6**-(*R*)-**8** has been assumed to be *R*.

2.3. Synthesis of both enantiomers of fluoxetine, tomoxetine, nisoxetine and norfluoxetine

Introduction of chirality in these non-tricyclic antidepressants fluoxetine, tomoxetine, nisoxetine has been described in the literature by employing different methods and various substrates. One of the methods involves Sharpless epoxidation[28] of cinnamyl alcohol followed by regioselective reduction (Red-Al) to produce the corresponding (*S*)- or (*R*)-1-phenyl-1,3-propanediol which were subsequently utilized for the preparation of enantioselective forms of fluoxetine and tomoxetine. Another method deals with the ring-opening of optically active styrene oxide[29] with acetone cyanohydrin to provide chiral 3-hydroxy-3-phenylpropanenitrile which has been utilized as the key intermediate in the preparation of optically active fluoxetine and norfluoxetine. Optically active 3-chloro-1-phenyl-1-propanol has been extensively used as the key intermediate for the preparation of these drugs. This intermediate was either prepared by enzymatic kinetic resolution[30] of the chlorohydrin or by asymmetric reduction of the corresponding ketone with diisopinocamphenylchloroborane,[31] borane in the presence of chiral oxazaborolidine[32] and baker' yeast.[33] Ethyl benzoylacetate[34] is another substrate which has been subjected to asymmetric reduction by bakers' yeast and later employed for the preparation of enantiomeric fluoxetine and tomoxetine. Similarly, asymmetric hydrogenation of benzoylamide in the presence of chiral BINAP-ruthenium(II)[35] catalyst under 200 psi pressure of hydrogen afforded hydroxyamide which has been used in the preparation of chiral fluoxetine. Another substrate is allyl alcohol,[36] which has been resolved by lipase and employed in the preparation of enantiomerically pure fluoxetine and tomoxetine. It was observed that most of the methods reported in the literature have either employed expensive chiral reagents or the yields and enantioselectivities of the desired precursors are not very high. Therefore, in the present investigation we have employed both enantiomeric forms of 3-hydroxy-3-phenylpropanenitrile, (*S*)-**1** and (*R*)-**5**, which have been obtained in very good yields and high enantioselectivity by lipase-mediated transesterification, for the synthesis of fluoxetine, tomoxetine and nisoxetine.

Attempts to couple (*S*)-**1** with aryl halides in the presence of a base and Mitsunobu coupling with phenols did not afford the desired ether (in the Mitsunobu coupling cinnamonitrile is formed as a major product as a result of dehydration of (*S*)-**1**). Therefore, to overcome this problem the nitrile functionality of (*S*)-**1** was reduced to an amine by employing borane–methyl sulphide[37] without any loss in enantiomeric purity. It has been observed that during the workup of this reaction using conc. HCl and aqueous NaOH, most of the reduced product decomposed. Therefore, treatment of the reaction mixture with methanol upon completion provides the required (*S*)-3-amino-1-phenyl-1-propanol, (*S*)-**9** in high yields. In contrast (*R*)-3-amino-1-phenyl-1-propanol, (*R*)-**9** was obtained by the simultaneous reduction of the nitrile functionality and hydrolysis of the acetate of (*R*)-3-acetyloxy-3-phenylpropanenitrile (*R*)-**5** on treatment with borane–methyl sulphide. Again, the Mitsunobu coupling of (*S*)-**9** or (*R*)-**9** did not give satisfactory results, as such (*S*)-**9** and (*R*)-**9** were converted to their carbamates (*S*)-*N*-(ethoxycarbonyl)-3-amino-1-phenyl-1-propanol ((*S*)-**10**) and (*R*)-*N*-(ethoxycarbonyl)-3-amino-1-phenyl-1-propanol ((*R*)-**10**), respectively, by their reaction with ethyl chloroformate in the presence of K_2CO_3. Importantly, these carbamates provide the monomethylated product (*S*)-*N*-methyl-3-amino-1-phenyl-1-propanol ((*S*)-**11**) and (*R*)-*N*-methyl-3-amino-1-phenyl-1-propanol ((*R*)-**11**) upon reduction with LAH. Upon treatment with NaH and 4-chlorobenzotrifluoride in DMSO (*R*)-**11** and (*S*)-**11** gave the corresponding (*R*)-fluoxetine ((*R*)-**12**) and (*S*)-fluoxetine ((*S*)-**12**) (Scheme 1). In a similar manner, both enantiomers of norfluoxetine, (*R*)-**13** and (*S*)-**13**



Scheme 1. *Reagents*: (i) BH_3-Me_2S, THF; (ii) ethyl chloroformate, K_2CO_3, DCM; (iii) LAH, THF; (iv) 4-chlorobenzotrifluoride, NaH, dry DMSO.

have been prepared by etherification of (*S*)-**9** and (*R*)-**9** with 4-chlorobenzotrifluoride/NaH in DMSO.

This approach was not successful in etherification reactions with 2-chlorotoluene and 2-chloroanisole to obtain tomoxetine and nisoxetine. Therefore, another approach was investigated for the preparation of both the enantiomers of these drugs. Mitsunobu coupling of the carbamate with phenols such as 4-hydroxy benzotrifluoride, 2-methylphenol, and 2-methoxyphenol gave the corresponding products with inversion at the stereogenic center, as depicted in Scheme 2. Reduction of these ethers with LAH then afforded both isomers of fluoxetine, tomoxetine and nisoxetine.

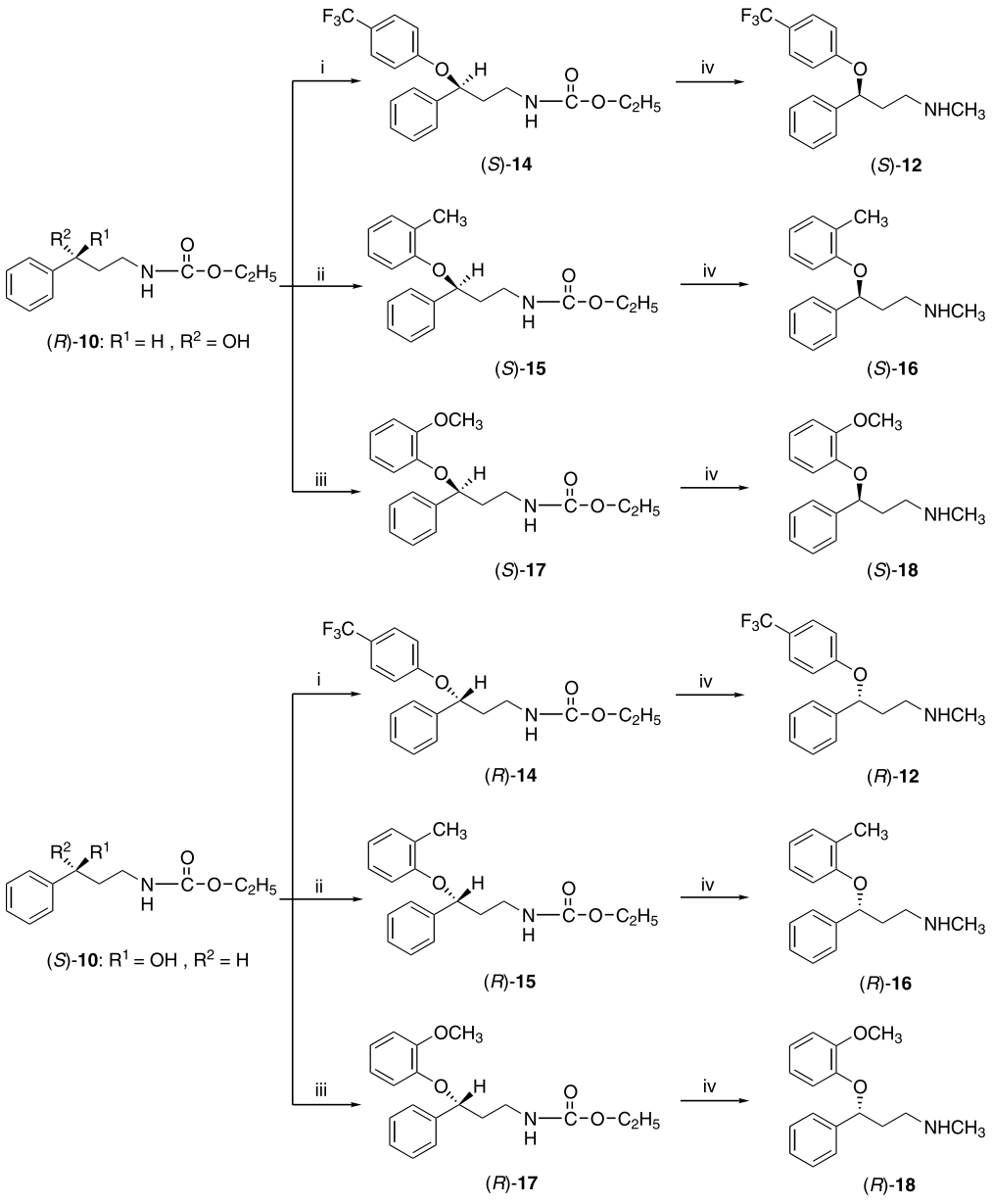
The carbamate appears to be a versatile intermediate in this process: etherification with various phenols to provide the required products such as (*S*)-*N*-(ethoxycarbonyl)-3-(4-(trifluoromethyl)phenoxy)-3-phenyl-1-propanamine ((*S*) - **14**), (*S*) - *N* - (ethoxycarbonyl) - 3-(2-(methyl)-phenoxy)-3-phenyl-1-propanamine ((*S*)-**15**) and (*S*)-*N*-(ethoxycarbonyl)-3-(2-(methoxy)-phenoxy)-3-phenyl-1-propanamine ((*S*)-**17**) and, importantly, to afford the monomethylated product selectively upon hydride reduction.

2.4. Transformation of (*S*)-3-hydroxy-3-phenylpropanenitrile to useful chiral intermediates

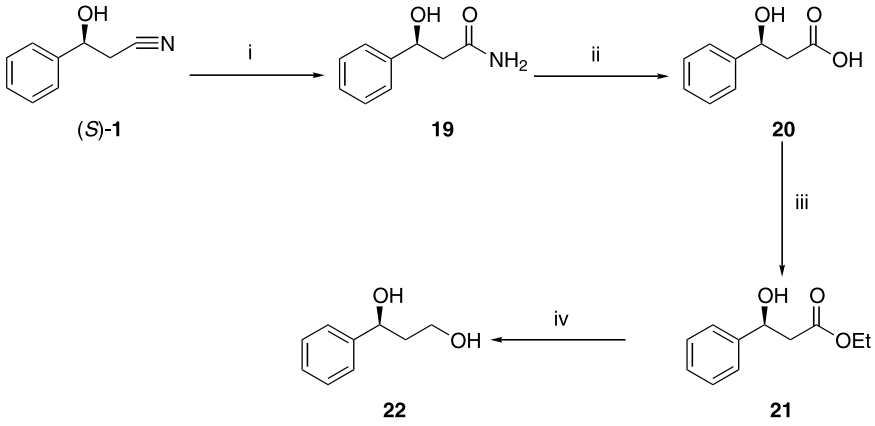
(*S*)-3-Hydroxy-3-phenylpropanenitrile provides an entry to a wide range of chiral synthons. Therefore, (*S*)-**1** has been transformed to its amide **19** followed by its acid **20**, ester[34] **21** and 1,3-diol[28,36] **22**. Interestingly, all of these intermediates have not only been employed in the enantioselective preparation of fluoxetine and tomoxetine but are also useful building blocks for the construction of chiral organic frameworks. Various attempts to perform this hydrolysis with a large number of literature methods produced undesired products. Alkaline or acid hydrolysis of (*S*)-**1**, at elevated temperature and room temperature, produced cinnamic acid and cinnamamide, respectively. To overcome this problem, hydrolysis of (*S*)-**1** has been carried out using K_2CO_3/H_2O_2 in DMSO and the corresponding acid, ester and diol have been prepared in the usual manner as shown in Scheme 3.

3. Conclusion

We have developed an efficient method for the preparation of β-hydroxy nitriles and their resolution in good yields and with high enantioselectivities employing lipase-catalyzed transesterifications. Further, we have utilized these β-hydroxy nitriles for practical preparation of both enantiomers of fluoxetine, tomoxetine, nisoxetine and norfluoxetine. The transformation of (*S*)-3-hydroxy-3-phenylpropanenitrile to its corresponding acid, ester, and 1,3-diol has also been investigated. In conclusion, efficient chemoenzymatic syntheses of the important anti-depressants fluoxetine, tomoxetine and nisoxetine have been carried out starting from simple racemic styrene oxide.



Scheme 2. *Reagents*: (i) PPh_3, DIAD, 4-hydroxy benzotrifluoride, diethyl ether; (ii) PPh_3, DIAD, 2-methyl phenol, diethyl ether; (iii) PPh_3, DIAD, 2-methoxy phenol, diethyl ether; (iv) LAH, THF.



Scheme 3. *Reagents*: (i) H_2O_2, DMSO, K_2CO_3; (ii) dil. HCl; (iii) ethyl iodide, K_2CO_3, acetone; (iv) LAH, THF.

4. Experimental

4.1. General

Unless specified all solvents and reagents were reagent grade and used without purification. THF and ether were dried and distilled from sodium benzophenone ketyl under nitrogen while DMSO was vacuum distilled and dried on 4 Å molecular sieves. Reactions involving moisture-sensitive reagents were performed under an inert atmosphere of nitrogen in glassware that has been oven dried. Melting points have been recorded on an electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin–Elmer model 683 or 1310 spectrometers and are reported in wave numbers (cm^{-1}). ^1H NMR spectra were recorded as solutions in $CDCl_3$, CD_3OD or DMSO (d_6) and chemical shifts are reported in parts per million (PPM, δ) on Gemini 200 MHz, AV 300 MHz, Unity 400 MHz instrument using tetramethylsilane (TMS) as an internal standard. Spectral patterns are designated as s, singlet; d, doublet; dd, double doublet; t, triplet; br, broad; m, multiplet. ^{13}C NMR spectra were recorded as solutions in $CDCl_3$ at an operational frequency of 50 MHz. Coupling constants are reported in hertz (Hz). Low resolution mass spectra were recorded on CEC-21-100B Finnigan Mat 1210 or VG 7070H Micromass mass spectrometers. Analytical TLC of all reactions was performed on Merck prepared plates (silica gel 60 F-254 on glass). Column chromatography was performed using Acme silica gel (100–200 mesh). Percentage yields are given for compounds. HPLC analysis was performed on an instrument that consisted of a Shimadzu LC-6A system controller, SPD-6A fixed wavelength UV monitor as detector, FCV-100B fraction collector and chromatopac C-R4A data processor as a recording integrator.

4.2. Preparation of 3-aryl-3-hydroxypropanenitriles

4.2.1. (±)-3-Hydroxy-3-phenylpropanenitrile, 1. To a solution of styrene oxide (12.00 g, 100.00 mmol) in ethanol (100 mL) was added water (300 mL). After stirring for 5 min sodium cyanide (7.35 g, 150.00 mmol) was added and stirring was continued overnight at room temperature. On completion of the reaction, as indicated by TLC, the reaction mixture was concentrated to about 25% of the total volume under reduced pressure. The residue was extracted with ethyl acetate (3×150 mL) washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by column chromatography employing EtOAc–hexane (25:75) as eluent afforded **1** in 80% yield. IR (Neat) 3438, 3046, 3015, 2954, 2923, 2892, 2238, 1115, 1092 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.67 (d, 2H, $J=7.23$ Hz), 3.15 (br s, 1H), 4.94 (t, 1H, $J=5.78$), 7.35 (s, 5H); mass (EI) 147, 121, 107, 105, 91, 79, 77.

4.2.2. (±)-3-(3-Chlorophenyl)-3-hydroxypropanenitrile, 2. To a solution of 3-chlorostyrene oxide (1.54 g, 10.00 mmol) in ethanol (20 mL) was added water (60 mL). After stirring for 5 min, sodium cyanide (0.74 g, 15.10 mmol) was added and stirring was continued overnight at room temperature. On completion of the reaction, as indicated by the TLC, the reaction mixture was concentrated to about 25% of the total volume under reduced pressure. The residue was extracted with ethyl acetate (3×30 mL), the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by column chromatography employing EtOAc–hexane (25:75) as eluent afforded the required product in 82% yield. IR (Neat) 3441, 3085, 3000, 2256, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.72 (d, 2H, $J=6.23$ Hz), 2.97 (s, 1H), 5.00 (t, 1H, $J=6.23$ Hz), 7.26–7.38 (m, 4H); mass (EI) 161, 141, 113, 77, 50; anal. calcd for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found C, 59.71; H, 4.38; N, 7.63%.

4.2.3. (±)-3-(4-Chlorophenyl)-3-hydroxypropanenitrile, 3. A solution of 2-chloro-1-(4-chlorophenyl)-1-ethanol (1.24 g, 6.50 mmol) in methanol (24 mL) was added dropwise to NaCN (0.95 g, 19.50 mmol) in water (8 mL) at room temperature. After complete addition the reaction mixture was heated under reflux for 6 h while monitoring the progress of the reaction by TLC. On completion of the reaction the reaction mixture was allowed to reach room temperature and the reaction mixture was concentrated to about 25% of the total volume. The residue was extracted with ethyl acetate (3×20 mL) and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by column chromatography employing EtOAc–hexane (25:75) as the eluent afforded the product in 71% yield. Mp 58–60°C; IR (KBr) 3444, 3074, 2936, 2904, 2234, 1069 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.73 (d, 2H, $J=5.85$ Hz), 2.86 (s, 1H), 5.00 (t, 1H, $J=5.85$ Hz), 7.32–7.39 (m, 4H); mass (EI) 181, 141, 113, 77, 51; anal. calcd for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found C, 59.80; H, 4.43; N, 7.68%.

4.2.4. (±)-3-Hydroxy-3-(4-methylphenyl)propanenitrile, 4. To a solution of 4-methylstyrene (1.77 g, 15.00 mmol) in THF (30 mL) was added water (6 mL) and NBS (4.00 g (recrystallized), 22.50 mmol) at room temperature and stirred for 30 min. After completion of the reaction as indicated by TLC, THF was evaporated under reduced pressure and the residue was extracted twice with DCM (15 mL). The organic layer was washed with hypo and then with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to leave a residue which on purification afforded 2-bromo-1-(4-methylphenyl)-1-ethanol in 70% yield.

The above obtained bromohydrin was dissolved in methanol (25 mL) and added dropwise to NaCN (1.50 g, 31.35 mmol) in water (8 mL) at room temperature. After complete addition the reaction mixture was heated under reflux for 4 h, cooled to room temperature and the reaction mixture was concentrated to about 25% of the total volume. The residue was extracted with ethyl acetate (3×20 mL), washed with brine, dried over Na_2SO_4 and concentrated. The residue

was subjected to purification by column chromatography employing EtOAc–hexane (25:75) as eluent to afford the required product in 76% yield. Mp 62–64°C; IR (KBr) 3443, 3011, 2924, 2253, 1063 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.72 (d, 2H, $J=8.60$ Hz), 4.97 (t, 1H, $J=8.60$ Hz), 7.13–7.30 (m, 4H); mass (EI) 161, 121, 91, 77, 65, 41; anal. calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found C, 74.34; H, 6.81; N, 8.71%.

4.3. General procedure for preparation of 3-acetyloxy-3-arylpropanenitriles 5–8

To 3-aryl-3-hydroxy propanenitrile (5.00 mmol) under N_2 was added acetic anhydride (20.00 mmol) and pyridine (5.50 mmol) and the resultant mixture was stirred at room temperature overnight. After completion of the reaction (TLC) the reaction mixture was diluted with ethyl acetate (25 mL) and treated with 1N HCl (20 mL). The organic layer was separated, washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography employing EtOAc–hexane (15:85) as eluent to afford the required 3-acetyloxy-3-aryl propanenitrile in nearly quantitative yield.

4.3.1. (±)-3-Acetyloxy-3-phenylpropanenitrile, 5. **1** (0.73 g) was acetylated using the above general procedure to obtain the product as white solid in 92% yield. Mp 97–100°C; IR (KBr) 3054, 3008, 2961, 2923, 2254, 1738, 1238, 1200, 1046 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.86 (d, 2H, $J=5.52$ Hz), 5.94 (t, 1H, $J=5.52$ Hz), 7.35 (s, 5H); mass (EI) 189, 162, 149, 130, 120, 107, 77.

4.3.2. (±)-3-Acetyloxy-3-(3-chlorophenyl)propanenitrile, 6. **2** (0.20 g) was acetylated using the above general procedure to obtain the product as a white solid in 95% yield. Mp 76–78°C; IR (KBr) 3065, 3021, 2933, 2250, 1746, 1052 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.87 (d, 2H, $J=6.67$ Hz), 5.90 (t, 1H, $J=6.67$ Hz), 7.23–7.40 (m, 4H); mass (EI) 223, 183, 181, 164, 154, 141, 111, 77, 51, 43; anal. calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found C, 59.12; H, 4.47; N, 6.28%.

4.3.3. (±)-3-Acetyloxy-3-(4-chlorophenyl)propanenitrile 7. **3** (0.20 g) was acetylated using the above general procedure to obtain the product as a white solid in 90% yield. Mp 95–98°C; IR (KBr) 2967, 2945, 2252, 1750, 1094, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.75–2.94 (m, 2H), 5.90 (t, 1H, $J=5.76$ Hz), 7.30–7.40 (m, 4H); mass (EI) 223, 196, 183, 154, 141, 77, 43; anal. calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found C, 58.92; H, 4.49; N, 6.28%.

4.3.4. (±)-3-Acetyloxy-3-(4-methylphenyl)propanenitrile, 8. **4** (0.10 g) was acetylated using the above general procedure to obtain the product as a white solid in 95% yield. Mp 72–74°C; IR (KBr) 2979, 2940, 2250, 1744, 1051 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.38 (s, 3H), 2.87 (d, 2H, $J=8.79$ Hz), 5.92 (t, 1H, $J=8.79$ Hz), 7.15–7.34 (m, 4H); mass (EI) 203, 163, 143, 121, 93, 91, 77, 43; anal. calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found C, 70.98; H, 6.41; N, 6.69%.

4.4. General procedure for resolution of 3-aryl-3-hydroxypropanenitriles 1–4

To a solution of the β-hydroxy nitrile (0.20 g) in diisopropyl ether (20 mL) were successively added lipase (0.15 g) and vinyl acetate (6 equiv.) and the mixture was shaken at 40°C in an orbital shaker. After about 50% completion of the reaction as indicated by the HPLC analysis, the reaction mixture was filtered and the residue was washed three times with diisopropyl ether. The combined organic layers were evaporated under reduced pressure and purification was accomplished by column chromatography employing EtOAc–hexane (20:80) as eluent to afford the corresponding (*R*)-acetate followed by (*S*)-alcohol.

4.4.1. (*R*)-3-Acetyloxy-3-phenylpropanenitrile, (*R*)-5. Mp 121–124°C; $[\alpha]_D^{30}=+71.9$ (*c* 1.0, $CHCl_3$); NMR, IR, and mass spectral data are identical to **5**.

4.4.2. (*S*)-3-Hydroxy-3-phenylpropanenitrile, (*S*)-1. $[\alpha]_D^{30}=-60.5$ (*c* 1.0, $CHCl_3$), lit.[26b] $[\alpha]_D^{20}=+58.0$ (*c* 1.0, EtOH) (*R* enantiomer); NMR, IR, and mass spectral data are identical to **1**.

4.4.3. (*R*)-3-Acetyloxy-3-(3-chlorophenyl)propanenitrile, (*R*)-6. Mp 77–79°C; $[\alpha]_D^{30}=+68.0$ (*c* 1.0, $CHCl_3$); NMR, IR, and mass spectral data are identical to **6**.

4.4.4. (*S*)-3-(3-Chlorophenyl)-3-hydroxypropanenitrile, (*S*)-2. $[\alpha]_D^{30}=-50.5$ (*c* 2.0, $CHCl_3$); NMR, IR, and mass spectral data are identical to **2**.

4.4.5. (*R*)-3-Acetyloxy-3-(4-chlorophenyl)propanenitrile, (*R*)-7. Mp 99–103°C; $[\alpha]_D^{30}=+80.5$ (*c* 1.0, $CHCl_3$); NMR, IR, and mass spectral data are identical to **7**.

4.4.6. (*S*)-3-(4-Chlorophenyl)-3-hydroxypropanenitrile, (*S*)-3. $[\alpha]_D^{30}=-54.5$ (*c* 2.0, $CHCl_3$); NMR, IR, and mass spectral data are identical to **3**.

4.4.7. (*R*)-3-Acetyloxy-3-(4-methylphenyl)propanenitrile, (*R*)-8. Mp 88–91°C; $[\alpha]_D^{30}=+106.5$ (*c* 1.0, $CHCl_3$); NMR, IR, and mass spectral data are identical to **8**.

4.4.8. (*S*)-3-Hydroxy-3-(4-methylphenyl)propanenitrile, (*S*)-4. $[\alpha]_D^{30}=-52.6$ (*c* 2.0, $CHCl_3$); NMR, IR, and mass spectral data are identical to **4**.

4.5. Preparation of enantiomers of 3-amino-1-phenyl-1-propanol, (*S*)- and (*R*)-9

4.5.1. (*S*)-3-Amino-1-phenyl-1-propanol, (*S*)-9. Borane–methyl sulphide complex (1.34 g, 17.68 mmol) was slowly added to a solution of (*S*)-**1** (2.00 g, 13.60 mmol) in dry THF (20 mL) at room temperature. After completion of the addition, the reaction mixture was heated under reflux and the progress of the reaction was monitored by TLC. On completion of the reaction (2 h reflux) the reaction mixture was cooled and methanol was slowly added at 0°C to decompose the unreacted

borane complex. The organic solvents were evaporated and the purification of the residue by column chromatography employing NH_4OH–MeOH–EtOAc (1:9:90) afforded (*S*)-amino alcohol, (*S*)-**9** in 85% yield. $[\alpha]_D^{30} = -42.8$ (*c* 1.0, MeOH); IR (Neat) 3346, 3277, 3169, 3054, 3015, 2923, 2869, 1554, 1477, 1438, 1315, 1046 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.64–1.85 (m, 2H), 2.60 (br s, 3H), 2.86–3.12 (m, 2H), 4.91 (dd, 1H, $J_1 = 5.00$ Hz, $J_2 = 10.00$ Hz), 7.15–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.24, 39.50, 73.54, 125.50, 126.87, 128.08, 144.84; mass (EI) 134, 107, 104, 91, 77; FABMS 152, 151, 134, 107, 91, 77.

4.5.2. (*R*)-3-Amino-1-phenyl-1-propanol, (*R*)-9. Prepared from (*R*)-**5** (2.00 g, 10.60 mmol) using borane–methyl sulphide complex (1.61 g, 21.20 mmol) by employing a similar procedure to that used in the preparation of (*S*)-**9** (88%). $[\alpha]_D^{30} = +41.8$ (*c* 1.0, MeOH); NMR, IR, and mass spectral data are identical to (*S*)-**9**.

4.6. Preparation of enantiomers of *N*-(ethoxycarbonyl)-3-amino-1-phenyl-1-propanol, (*S*)- and (*R*)-10

4.6.1. (*S*)-*N*-(Ethoxycarbonyl)-3-amino-1-phenyl-1-propanol ((*S*)-carbamate), (*S*)-10. Ethyl chloroformate (0.56 g, 5.16 mmol) was added to a solution of (*S*)-amino alcohol ((*S*)-**9**) (0.60 g, 3.97 mmol) in DCM (8 mL) at room temperature and stirred vigorously. To this vigorously stirred mixture was added K_2CO_3 (2.74 g, 19.85 mmol) in H_2O (8 mL) over a period of 5 min and stirring was then continued for 30 min. After completion of the reaction as indicated by the TLC, the reaction mixture was extracted with DCM. The solvent was evaporated and the residue was purified by column chromatography employing EtOAc–hexane (10:90) as the eluent to afford the (*S*)-carbamate, (*S*)-**10** in 90% yield. Mp 67–69°C; $[\alpha]_D^{30} = -25.0$ (*c* 1.0, $CHCl_3$); IR (KBr) 3423, 3300, 3254, 3046, 3015, 2961, 2923, 2877, 1692, 1546, 1269, 1007 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, 3H, $J = 7.33$ Hz), 1.81–1.91 (m, 2H), 3.17–3.27 (m, 1H), 3.45–3.65 (m, 1H), 4.10 (q, 2H, $J = 7.33$ Hz), 4.74 (t, 1H, $J = 7.33$ Hz), 5.05 (br s, 1H), 7.20–7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.47, 37.89, 38.99, 60.76, 71.78, 76.68, 76.99, 77.31, 125.53, 127.53, 128.28, 144.21, 157.27; mass (EI) 223, 133, 117, 107, 102, 91, 77.

4.6.2. (*R*)-*N*-(Ethoxycarbonyl)-3-amino-1-phenyl-1-propanol, ((*R*)-carbamate), (*R*)-10. Prepared in 88% yield from (*R*)-amino alcohol (*R*)-**9** by employing a similar procedure to that used for the preparation of (*S*)-**10**. Mp 67–69°C; $[\alpha]_D^{30} = +24.1$ (*c* 1.0, $CHCl_3$); NMR, IR, and mass spectral data are identical to (*S*)-**10**.

4.7. Preparation of enantiomers of *N*-Methyl-3-amino-1-phenyl-1-propanol, (*S*)- and (*R*)-11

4.7.1. (*S*)-*N*-Methyl-3-amino-1-phenyl-1-propanol, (*S*)-11. To a solution of LAH (0.17 g, 4.48 mmol) in dry THF (15 mL) under N_2 at room temperature was added dropwise a solution of (*S*)-**10** (0.50 g, 2.24 mmol) in dry THF (3 mL) and the resultant reaction mixture was heated under reflux for 1 h. After completion of the reaction the mixture was cooled to room temperature and ethyl acetate was slowly added. The resultant reaction mixture was filtered, the residue was treated with ethyl acetate and filtered three times. The filtrates were combined and evaporated under reduced pressure to leave a residue which was purified by column chromatography employing NH_4OH–MeOH–EtOAc (1:9:90) as eluent to afford the product in 88% yield. $[\alpha]_D^{30} = -36.2$ (*c* 0.85, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.74–1.86 (m, 1H), 1.90–1.95 (m, 1H), 2.50 (s, 3H), 2.86–2.93 (m, 2H), 4.92 (dd, 1H, $J_1 = 3.33$ Hz, $J_2 = 7.14$ Hz), 7.27–7.36 (m, 5H); mass (EI) 165, 133, 117, 104, 91, 77, 43.

4.7.2. (*R*)-*N*-Methyl-3-amino-1-phenyl-1-propanol, (*R*)-11. Prepared from (*R*)-**10** in 89% yield using a procedure analogous to that used for (*S*)-**11**. $[\alpha]_D^{30} = +37.1$ (*c* 1, $CHCl_3$); NMR, and mass spectral data are identical to (*S*)-**11**.

4.8. Preparation of enantiomers of norfluoxetine, (*S*)- and (*R*)-13

4.8.1. (*S*)-3-Phenyl-3-(4-trifluoromethylphenoxy)-1-propanamine, ((*S*)-norfluoxetine), (*S*)-13. To a solution of (*S*)-**9** (0.45 g, 2.98 mmol) in dry DMSO (8 mL) at room temperature was added NaH (0.18 g (60%), 4.50 mmol) and heated at 55°C for 45 min to form a sodium alkoxide of the amino alcohol. To the above-formed alkoxide was added 4-chlorobenzotrifluoride (0.81 g, 4.48 mmol) taken in DMSO (2 mL) and the resultant mixture was heated for 1 h at 90–100°C. After completion of the reaction as indicated by the TLC, the reaction mixture was allowed to reach room temperature, diluted with cool water (10 mL) and then extracted with diethyl ether (3×25 mL). The combined ether layers were concentrated to leave a residue, which was purified by column chromatography to afford the required product **13*S*** in 65% yield. $[\alpha]_D^{30} = -3.5$ (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, DMSO) δ 2.05–2.36 (m, 2H), 2.93–3.05 (m, 2H), 5.38–5.55 (m, 1H), 6.88–7.00 (d, 2H, $J = 4.76$ Hz), 7.12–7.50 (m, 7H).

4.8.2. (*R*)-3-Phenyl-3-(4-trifluoromethylphenoxy)-1-propanamine, ((*R*)-norfluoxetine), (*R*)-13. Prepared from (*R*)-**9** in 68% yield using the procedure described for (*S*)-norfluoxetine. $[\alpha]_D^{30} = +3.0$ (*c* 1, $CHCl_3$); NMR spectral data is identical to (*S*)-**13**.

4.9. Preparation of enantiomers of *N*-(ethoxycarbonyl)-3-(4-(trifluoromethyl)-phenoxy)-3-phenyl-1-propanamine, (*S*)- and (*R*)-14

4.9.1. (*S*)-*N*-(Ethoxycarbonyl)-3-(4-(trifluoromethyl)-phenoxy)-3-phenyl-1-propanamine, (*S*)-14. Diisopropyl azodicarboxylate (0.41 g, 2.03 mmol) in dry ether (1 mL) was slowly added to a solution of triphenyl phosphine (0.79 g, 3.01 mmol) in dry ether (6 mL) at 0°C to form a betaine complex, after 20 min at 0°C 4-hydroxy benzotrifluoride (0.39 g, 2.41 mmol) taken in dry ether (2 mL) was added. To this resultant mixture was added (*R*)-**10** (0.45 g, 2.02 mmol) in dry ether (5 mL) and

allowed to warm to room temperature. After completion of the reaction as indicated by the TLC (2 h), the ether solvent was evaporated from the reaction mixture and the residue was purified by column chromatography employing EtOAc–hexane (5:95) as eluent to afford the required product in 71% yield. $[\alpha]_D^{30}=-7.1$ (*c* 1.0, $CHCl_3$); IR (Neat) 3420, 3310, 3059, 3027, 2964, 2918, 1694, 1498, 1318, 1231, 1161, 1114 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.24 (t, 3H, $J=7.32$ Hz), 2.15–2.20 (m, 2H), 3.37 (q, 2H, $J=5.86$ Hz), 4.09 (q, 2H, $J=7.32$ Hz), 4.76 (br s, 1H), 5.22 (dd, 1H, $J_1=4.39$ Hz, $J_2=8.06$ Hz), 6.87 (d, 2H, $J=8.79$ Hz), 7.26–7.35 (m, 5H), 7.44 (d, 2H, $J=8.79$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.54, 37.83, 38.67, 60.74, 78.44, 115.69, 123.00, 125.62, 126.70, 126.74, 127.95, 128.83, 140.39, 156.67, 160.20; mass (EI) 209, 164, 145, 104, 44; FABMS 390 (M^++Na), 366 (M^+–1), 206, 117, 102, 91.

4.9.2. (*R*)-*N*-(Ethoxycarbonyl)-3-(4-(trifluoromethyl)-phenoxy)-3-phenyl-1-propanamine, (*R*)-14. Prepared from (*S*)-**10** using the same procedure as for (*S*)-**14** in 78% yield with inversion at the stereogenic center. $[\alpha]_D^{30}=+7.4$ (*c* 1.0, $CHCl_3$); NMR, IR, and mass spectral data are identical to (*S*)-**14**.

4.10. Preparation of enantiomers of fluoxetine, (*S*)- and (*R*)-12

4.10.1. (*S*)-*N*-Methyl-3-phenyl-3-(4-trifluoromethylphenoxy)-1-propanamine ((*S*)-fluoxetine) (*S*)-12. **Method A**: To a solution of LAH (0.08 g, 2.18 mmol) in dry THF (8 mL) under N_2 at room temperature was added dropwise a solution of (*S*)-**14** (0.40 g, 1.09 mmol) in dry THF (4 mL) and the resultant reaction mixture was heated under reflux for 1 h. After completion of the reaction the mixture was cooled to room temperature and ethyl acetate was slowly added. The mixture was filtered, the residue was thrice treated with ethyl acetate and filtered. The filtrates were combined and evaporated under reduced pressure to leave a residue, which was purified by column chromatography employing NH_4OH–MeOH–EtOAc (1:9:90) as eluent to afford the product in 85% yield.

Method B: To a solution of (*S*)-**11** (0.20 g, 1.21 mmol) in dry DMSO (5 mL) at room temperature was added NaH (0.08 g (60%), 2.00 mmol) and heated at 55°C for 45 min to form the sodium alkoxide of the amino alcohol. To the above formed alkoxide was added 4-chlorobenzotrifluoride (0.33 g, 1.82 mmol) taken in DMSO (3 mL) and the resultant mixture was heated for 1 h at 90–100°C. After completion of the reaction as indicated by the TLC, the reaction mixture was allowed to come to room temperature, diluted with cool water (8 mL) and then extracted with diethyl ether (3×20 mL). The combined ether layers were concentrated to leave a residue, which was purified by column chromatography to afford the required product (*S*)-fluoxetine (*S*)-**12** in 71% yield. $[\alpha]_D^{30}=-4.1$ (*c* 1.0, $CHCl_3$); IR (Neat) 3369, 3031, 2954, 2931, 2731, 1600, 1323, 1254, 1108 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.00–2.32 (m, 2H), 2.46 (s, 3H), 2.73–2.88 (m, 2H), 5.32 (dd, 1H, $J_1=5.19$ Hz, $J_2=7.79$ Hz), 6.86 (d, 2H, $J=7.79$ Hz), 7.20–7.33 (m, 5H), 7.40 (d, 2H, $J=7.79$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.97, 34.76, 45.87, 76.99, 115.68, 123.14, 125.54, 126.63, 126.66, 128.19, 128.91, 139.41, 159.74; mass (EI) 309 (M^+), 164, 162, 148, 104, 91, 77, 44.

4.10.2. (*R*)-*N*-Methyl-3-phenyl-3-(4-trifluoromethylphenoxy)-1-propanamine, (*R*)-fluoxetine, (*R*)-12. Using method (A) described for the preparation of (*S*)-fluoxetine, (*R*)-fluoxetine (*R*)-**12** was prepared from (*R*)-**14** in 85% yield and also using procedure (B) (*R*)-fluoxetine (*R*)-**12** was prepared from (*R*)-**11** in 70% yield. $[\alpha]_D^{30}=+4.3$ (*c* 0.7, $CHCl_3$); NMR, IR, and mass spectral data are identical to (*S*)-**12**.

4.11. Preparation of enantiomers of *N*-(ethoxycarbonyl)-3-(2-(methyl)-phenoxy)-3-phenyl-1-propanamine, (*S*)- and (*R*)-15

4.11.1. (*S*)-*N*-(Ethoxycarbonyl)-3-(2-(methyl)-phenoxy)-3-phenyl-1-propanamine, (*S*)-15. Diisopropyl azodicarboxylate (0.41 g, 2.03 mmol) in dry ether (1 mL) was slowly added to a solution of triphenylphosphine (0.79 g, 3.01 mmol) in dry ether (6 mL) at 0°C to form a betaine complex, after 20 min at 0°C a solution of 2-methyl phenol (0.26 g, 2.41 mmol) in dry ether (2 mL) was added. To this resultant mixture was added (*R*)-**10** (0.45 g, 2.02 mmol) in dry ether (5 mL) and allowed to reach to room temperature. After completion of the reaction as indicated by the TLC (2 h), the ether solvent was evaporated from the reaction mixture and the residue was purified by column chromatography employing EtOAc–hexane as eluent to afford the required product in 76% yield. $[\alpha]_D^{30}=+10.2$ (*c* 1.0, $CHCl_3$); IR (Neat) 3443, 3333, 3059, 3012, 2965, 2918, 1686, 1600, 1506, 1475, 1223, 1027 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.22 (t, 3H, $J=6.40$ Hz), 2.14 (q, 2H, $J=5.33$), 2.30 (s, 3H), 3.34 (q, 2H, $J=5.33$ Hz), 4.06 (q, 2H, $J=6.40$ Hz), 4.85 (br s, 1H), 5.20 (t, 1H, $J=5.50$ Hz), 6.49 (d, 1H, $J=8.00$ Hz), 6.72 (t, 1H, $J=6.40$ Hz), 6.90 (t, 1H, $J=8.00$ Hz), 7.06 (d, 1H, $J=6.40$ Hz), 7.20–7.32 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.51, 16.48, 38.01, 38.56, 60.58, 77.91, 112.63, 120.36, 125.56, 126.25, 126.48, 127.51, 128.56, 130.60, 141.26, 155.61, 156.58; mass (EI) 205, 115, 43; FABMS 312 (M^+–1), 206, 197, 117, 102, 91.

4.11.2. (*R*)-*N*-(Ethoxycarbonyl)-3-(2-(methyl)-phenoxy)-3-phenyl-1-propanamine, (*R*)-15. Prepared from (*S*)-**10** in 70% yield with inversion at the stereogenic center analogous to (*S*)-**15**. $[\alpha]_D^{30}=-10.7$ (*c* 1.0, $CHCl_3$); NMR, IR, and mass spectral data are identical to (*S*)-**15**.

4.12. Preparation of enantiomers of tomoxetine, (*S*)- and (*R*)-16

4.12.1. (*S*)-*N*-Methyl-3-(2-methylphenoxy)-3-phenyl-1-propanamine ((*S*)-tomoxetine), (*S*)-16. To a solution of LAH (0.07 g, 1.92 mmol) in dry THF (8 mL) under N_2 at room temperature was added dropwise a solution of **15*S*** (0.30 g, 0.96 mmol) taken in dry THF (2 mL) and

the resultant reaction mixture was heated under reflux for 1 h. After completion of the reaction the reaction mixture was cooled to room temperature and ethyl acetate was slowly added. The resultant reaction mixture was filtered, residue was thrice treated with ethyl acetate and filtered. Solvent in all the combined filtrates was evaporated under reduced pressure to leave a residue, which was purified by column chromatography employing NH_4OH–MeOH–EtOAc (1:9:90) as eluent to afford the product in 88% yield. $[\alpha]_D^{30}=+42.2$ (*c* 0.56, MeOH); IR (Neat) 3341, 3004, 2925, 2886, 1584, 1561, 1474, 1388, 1224, 1108, 1038 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.07–2.17 (m, 1H), 2.23–2.29 (m, 1H), 2.33 (s, 3H), 2.49 (s, 3H), 2.80–2.89 (m, 2H), 5.24–5.31 (m, 1H), 6.57 (d, 1H, $J=5.70$ Hz), 6.75 (t, 1H, $J=4.70$ Hz), 6.92 (t, 1H, $J=5.70$ Hz), 7.07 (d, 1H, $J=4.70$ Hz), 7.30–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.42, 32.86, 34.76, 46.02, 76.47, 112.65, 120.60, 125.566, 126.568, 126.73, 127.88, 128.75, 130.65, 140.32, 155.22; mass (EI) 255 (M^+), 148, 104, 91, 77, 44.

4.12.2. (*R*)-*N*-Methyl-3-(2-methylphenoxy)-3-phenyl-1-propanamine ((*R*)-tomoxetine), (*R*)-16. (*R*)-Tomoxetine was prepared in 84% yield by subjecting (*R*)-**15** to LAH reduction, similar to the preparation of (*S*)-tomoxetine. $[\alpha]_D^{30}=-43.0$ (*c* 0.8, MeOH); NMR, IR, and mass spectral data are identical to (*S*)-**16**.

4.13. Preparation of enantiomers of *N*-(ethoxycarbonyl)-3-(2-(methoxy)phenoxy)-3-phenyl-1-propanamine, (*S*)- and (*R*)-17

4.13.1. (*S*)-*N*-(Ethoxycarbonyl)-3-(2-(methoxy)-phenoxy)-3-phenyl-1-propanamine, (*S*)-17. Diisopropyl azodiarboxylate (0.41 g, 2.03 mmol) in dry ether (1 mL) was slowly added to a solution of triphenyl phosphine (0.79 g, 3.01 mmol) in dry ether (6 mL) at −20°C to form a betaine complex, after 20 min at −20°C, 2-methoxy phenol (0.30 g, 2.41 mmol) taken in dry ether (2 mL) was added. To this resultant mixture was added (*R*-carbamate) (*R*)-**10** (0.45 g, 2.02 mmol) in ether (5 mL) and allowed to reach to room temperature. After completion of the reaction as indicated by the TLC (2 h), the ether solvent was evaporated from the reaction mixture and the residue was purified by column chromatography employing EtOAc–hexane (5:95) as eluent to afford the required product in 60% yield. $[\alpha]_D^{30}=-8.7$ (*c* 1.0, $CHCl_3$); IR (Neat) 3385, 3061, 3031, 2985, 2946, 2838, 1715, 1569, 1485, 1246, 1215, 1115, 1046, 1015 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, 3H, $J=7.30$ Hz), 2.14 (q, 2H, $J=5.86$), 3.22–3.35 (m, 1H), 3.49–3.67 (m, 1H), 3.94 (s, 3H), 4.12 (q, 2H, $J=7.30$ Hz), 5.12 (t, 1H, $J=6.59$ Hz), 6.5 (br s, 1H), 6.55 (d, 1H, $J=10.25$ Hz), 6.60–6.70 (m, 1H), 6.82–6.85 (m, 2H), 7.25–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.67, 38.49, 38.68, 55.41, 60.37, 82.02, 111.18, 115.26, 120.53, 121.44, 125.54, 127.62, 128.57, 141.25, 147.13, 149.46, 156.87; mass (EI) 206, 124, 108, 102, 91, 77; FABMS 352 (M^++Na), 330 (M^++1), 245, 206, 159, 117, 102, 91.

4.13.2. (*R*)-*N*-(Ethoxycarbonyl)-3-(2-(methoxy)-phenoxy)-3-phenyl-1-propanamine, (*R*)-17. Prepared from (*S*)-**10** in 60% yield with inversion at the stereogenic center analogous to (*S*)-**17**. $[\alpha]_D^{30}=+9.0$ (*c* 1.0, $CHCl_3$); NMR, IR, and mass spectral data are identical to (*S*)-**17**.

4.14. Preparation of enantiomers of nisoxetine, (*S*)- and (*R*)-18

4.14.1. (*S*)-*N*-Methyl-3-(2-methoxyphenoxy)-3-phenyl-1-propanamine ((*S*)-nisoxetine) (*S*)-18. To a solution of LAH (0.06 g, 1.52 mmol) in dry THF (9 mL) under N_2 at room temperature was added dropwise a solution of (*S*)-**17** (0.25 g, 0.76 mmol) taken in dry THF (3 mL) and the resultant reaction mixture was heated under reflux for 1 h. After completion of the reaction the mixture was cooled to room temperature and ethyl acetate was slowly added. The resultant mixture was filtered and the residue was thrice treated with ethyl acetate and filtered. The filtrates were combined and evaporated under reduced pressure to leave a residue, which was purified by column chromatography employing NH_4OH–MeOH–EtOAc (1:9:90) as eluent to afford the product in 80% yield. $[\alpha]_D^{30}=-34.6$ (*c* 1.0, $CHCl_3$); IR (Neat) 3385, 3146, 3062, 2962, 2923, 2838, 1492, 1246, 1215, 1108, 1015 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.13–2.40 (m, 2H), 2.62 (s, 3H), 3.07–3.24 (m, 2H), 3.87 (s, 3H), 5.09–5.20 (m, 1H), 6.49 (d, 1H, $J=9.75$ Hz), 6.54–6.68 (m, 1H), 6.77–6.87 (m, 2H), 7.20–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.77, 34.07, 46.81, 55.82, 81.21, 111.69, 116.64, 120.78, 122.36, 125.72, 128.05, 128.68, 140.17, 146.52, 149.59; mass (EI) 141, 124, 109, 91, 44; FABMS 272 (M^++1), 160, 113, 91, 58.

4.14.2. (*R*)-*N*-Methyl-3-(2-methoxyphenoxy)-3-phenyl-1-propanamine ((*R*)-nisoxetine), (*R*)-18. Prepared in 80% yield by subjecting (*R*)-**17** to LAH reduction, using a method analogous to the preparation of (*S*)-nisoxetine. $[\alpha]_D^{30}=+36.1$ (*c* 1.0, $CHCl_3$); NMR, IR, and mass spectral data are identical to (*S*)-**18**.

4.15. (*S*)-3-Hydroxy-3-phenyl propanamide, 19

To a stirred solution of (*S*)-**1** (0.44 g, 3 mmol) in DMSO (3 mL) was added H_2O_2 (1 mL, 100 vol) and K_2CO_3 (0.07 g, 0.50 mmol) while keeping the temperature below 30°C. After stirring the reaction mixture for 15 min, H_2O (5 mL) was added and the mixture was extracted with diethyl ether (3×10 mL). Evaporation of ether and purification of the residue afforded (*S*)-3-hydroxy-3-phenyl propanamide in 70% yield with >99% ee (chiral HPLC). Mp 101–103°C; $[\alpha]_D^{30}=-32.1$ (*c* 1.0, EtOH); IR (KBr) 3377, 3300, 3177, 2961, 2900, 2761, 1623, 1431, 1392, 1331, 1046 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 2.41–2.70 (m, 2H), 4.93–5.11 (m, 1H), 7.20–7.40 (m, 5H); mass (EI) 165, 141, 120, 105, 91, 77, 59.

4.16. (*S*)-3-Hydroxy-3-phenylpropanoic acid, 20

To (*S*)-3-hydroxy-3-phenyl propanamide (0.30 g, 1.82 mmol) was slowly added 6N HCl (3 mL) and the mixture was stirred overnight. The reaction mixture was diluted with water and then extracted with ethyl acetate (2×10 mL). Treatment of the EtOAc layer with 10% Na_2CO_3 and then acidification of the resulting mixture to pH 5–6 gave **20** in 60% yield. Mp 112–114°C; $[\alpha]_D^{30}=-18.1$ (*c* 1, EtOH), lit.[7c] $[\alpha]_D^{22}=-18.9$ (*c* 2.27, EtOH); IR (KBr) 3292, 2969, 2915, 2846, 2631, 2531, 1692, 1262, 1198, 1046, 1008 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.56–2.68 (m, 2H), 5.06 (dd, 1H, $J_1=6.67$ Hz, $J_2=9.78$ Hz), 7.24–7.42 (m, 5H); mass (EI) 166, 149, 107, 79, 77, 51.

4.17. (*S*)-Ethyl 3-hydroxy-3-phenyl propanoate, 21

To a solution of **20** (0.33 g, 1.99 mmol) in dry acetone (15 mL) was added K_2CO_3 (0.82 g, 5.97 mmol) and ethyl iodide (0.62 g, 3.98 mmol) and the mixture was heated under reflux for 24 h while monitoring the progress of the reaction by TLC. On completion of the reaction the mixture was filtered and the solvent in filtrate was evaporated to give crude ester which was purified by column chromatography to yield **21** in 81% yield. $[\alpha]_D^{30}=-49.5$ (*c* 1.0, $CHCl_3$), lit.[7c] $[\alpha]_D^{20}=-50.8$ (*c* 1.07, $CHCl_3$); IR (Neat) 3462, 3062, 3023, 2977, 2931, 2900, 1731, 1446, 1361, 1198, 1146, 1054, 1031 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, 3H, $J=10.00$ Hz), 2.70 (d, 2H, $J=8.50$ Hz), 3.20 (d, 1H, $J=5.00$ Hz), 4.17 (q, 2H, $J=10.00$ Hz), 5.00–5.14 (m, 1H), 7.20–7.40 (m, 5H); mass (EI) 194, 107, 105, 79, 77, 51.

4.18. (*S*)-1-Phenyl-1,3-propanediol, 22

To a stirred solution of LAH (0.06 g, 1.65 mmol) in dry THF (6 mL) under N_2 was added dropwise a solution of **21** (0.32 g, 1.65 mmol) in dry THF (3 mL) at room temperature and stirring was continued for 45 min. After completion of the reaction as indicated by TLC, ethyl acetate was slowly added and the mixture was filtered. The residue was twice treated with ethyl acetate and filtered. Solvents in the combined filtrates were evaporated to leave a residue of crude diol, which was purified by column chromatography to give the required product in 90% yield. $[\alpha]_D^{30}=-67.1$ (*c* 1.0, $CHCl_3$), lit.[7c] $[\alpha]_D^{21.5}=-70.5$ (*c* 1.015, $CHCl_3$); IR (Neat) 3338, 3092, 3062, 3031, 2938, 2885, 1446, 1046, 977, 915 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.84–2.02 (m, 2H), 3.84 (t, 2H, $J=7.56$ Hz), 4.93 (dd, 1H, $J_1=5.34$ Hz, $J_2=9.78$ Hz), 7.26–7.38 (m, 5H); mass (EI) 152, 107, 79, 77, 51.

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