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New chemoenzymatic pathway for β-adrenergic blocking agents

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Abstract—The lipase mediated kinetic resolution of pharmaceutically important β-hydroxy nitriles is described in high enantiomeric excesses and good yields. Some of the chiral β-hydroxy nitriles have been employed in the synthesis of β-adrenergic blocking agents such as propranolol, alprenolol and moprolol. This protocol has also been extended for the enantiopure preparation of 5-(4-tosyloxymethyl)-1,3-oxazolidine-2-one and 3-hydroxy-4-tosyloxybutanenitrile, chiral intermediates of high synthetic value.

1. Introduction

Enantiomerically pure β-amino alcohols[1] are an important class of organic compounds whose structures are present in numerous natural products, such as amino sugars,[1a] antibiotics,[1b–d] β-adrenergic blocking agents,[1e–h] etc. They play an increasingly important role in both the treatment of a wide variety of human disorders and as chiral auxiliaries[1i–l] in organic synthesis. β-Adrenergic blocking agents (β-blockers)[1e–h] mostly comprising of β-amino alcohols are of pharmaceutical significance and have received major attention due to their utility in the management of cardiovascular disorders,[2] including hypertension,[3] anginapectoris, cardiac arrhythmias and also other disorders[4] related to the sympathetic nervous system. After three decades of their evolution, more than 50 different compounds having β-adrenergic blocking activity have been brought to a stage of commercial development with about two dozen of the β-adrenergic blocking agents being approved for medicinal use. The most important ones are propranolol, atenolol, metoprolol and alprenolol.

β-Adrenergic blocking agents are chiral aryloxy propanol amines, which have the general structure as shown in Figure 1. Their therapeutic effect is mostly due to the (*S*)-enantiomer that bears a strong structural resemblance to the adrenergic hormone noradrenaline. The eudismic ratios of the various β-adrenergic blocking agents vary considerably, but in all cases, the (*S*)-enantiomer is the active enantiomer.[5]

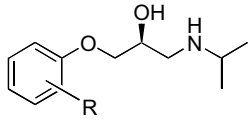

Figure 1.

For example, (*S*)-propranolol is 130 times as active as its (*R*)-enantiomer, which effectively means that the latter is inactive.[6] Moreover, contraceptive activity is believed to be associated with the (*R*)-enantiomer.[5b,7] Most of the β-adrenergic blocking agents are marketed as racemates; this has been probably influenced by the fact that they are difficult to separate by classical methods and that the distomer exhibits no serious side-effects (or no more than the eutomer). However, over a period of time the situation has been changing rapidly, although the distomers generally exhibit no serious side-effects, they are still considered an unnecessary isomeric ballast[8] as they produce the same side-effects as the eutomer without contributing to the desired therapeutic effect. In this connection several methods have been reported for their synthesis in enantiopure form.

Owing to the high biological importance associated with these compounds, many research groups have carried out extensive research over a period of three decades for their preparation. Until the early 1980s only a few methods, all non-enzymatic, have been described for the preparation of optically active β-adrenergic blocking agents. They have been prepared from D-mannitol,[9] (*R*)-glyceraldehyde[10] and from racemic β-adrenergic blocking agents by resolution.[5b,7d,11] Subsequently, enzyme

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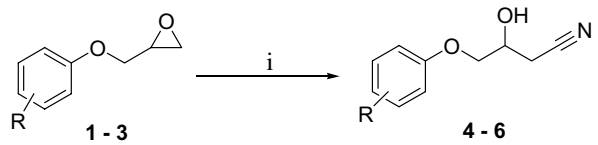
mediated processes[12–14] for chiral intermediates to β-adrenergic blocking agents have been emerging and gaining prominence.

2. Results and discussion

2.1. Preparation of enantiomerically pure β-hydroxy nitriles

In continuation of our earlier efforts towards the preparation of biologically important compounds or their intermediates by employing enantiomerically pure β-hydroxy nitriles,[15] we herein report an efficient chemoenzymatic preparation of some β-adrenergic blocking agents and more importantly a favourable common intermediate[14] for the preparation of a wide range of β-adrenergic blocking agents. Previously we investigated the synthesis of various chiral propanolamines[16] by stereoselective ring opening of epoxides with amines in the presence of rat liver microsomes and various lipases. We have also synthesized (*R*)-propranolol from 3-isopropyl-5-(1-naphthyloxymethyl)-oxazolidine with post mitochondrial supernatant from rat liver in phosphate buffer.[16e]



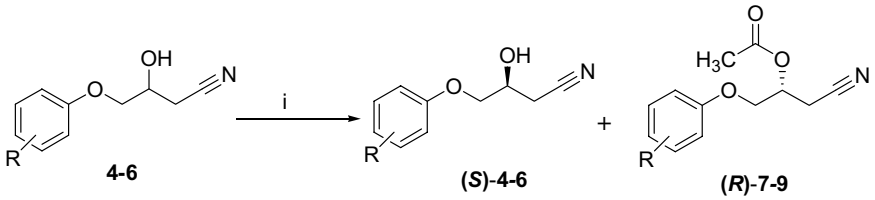
1 - 3 **4 - 6**

R = 2,3-(CH=CH-CH=CH)- **1**; 2-(CH_2-CH=CH_2) **2**; 4-OCH_3 **3**

Reagents and conditions : i. NaCN, EtOH-H_2O, room temp.

(1)

The racemic β-hydroxy nitriles **4**–**6** thus obtained have been independently studied for lipase-catalyzed resolution (Eq. 2). In the first series of experiments, the efficiency of the different commercially available lipases[17] to catalyze the transesterification of cyanohydrins has been investigated. As the solvent variation in many cases of lipase-catalyzed kinetic resolution influences the enantiomeric or enantiotopic selectivity as well as the reaction rate, the effect of the solvents[18] on these substrates has also been studied. The important results of these studies are illustrated in Table 1.



4-6 **(*S*)-4-6** **(*R*)-7-9**

(2)

R = 2,3-(CH=CH-CH=CH)- **4**; 2-(CH_2-CH=CH_2) **5**; 4-OCH_3 **6**

Reagents and conditions: i. lipase from *Pseudomonas cepacia* (*Burkholderia cepacia*), vinyl acetate, diisopropyl ether.

This study represents a facile preparation of 4-aryloxy-3-hydroxybutanenitriles, their successful enzymatic resolution employing lipases and their application towards the synthesis of enantiomerically pure β-adrenergic blocking agents viz., propranolol, alprenolol and moprolol. In our earlier report[15a] we presented a facile preparation of some β-hydroxy nitriles and their enzymatic resolution. Herein the present investigation 3-hydroxy-4-(1-naphthyloxy)butanenitrile **4**, 4-(2-allylphenoxy)-3-hydroxybutanenitrile **5** and 3-hydroxy-4-(4-methoxyphenoxy)butanenitrile **6** have been envisaged as substrates of special interest as these can be converted into (*S*)-propranolol, (*S*)-alprenolol and (*S*)-moprolol by simple reaction sequence in high enantiomeric excess and good yields. The racemic β-hydroxy nitriles have been prepared by the ring opening of their corresponding epoxides **1**–**3** using NaCN in aqueous-alcoholic conditions with high regioselectivity (Eq. 1). The presence of water in the reaction media makes the reaction slightly basic and also facilitates the availability of the cyanide nucleophile, thus helping us to obtain a complete regioselective, opening resulting in good yields.

The enantiomeric excess was calculated from the enantiomeric ratios obtained by employing chiral HPLC. Initially, the absolute configurations of the alcohol and acetate obtained after enzymatic resolution were arbitrarily assigned as the (*S*)-alcohol and (*R*)-acetate from the enantio-preference for the lipase and from our earlier experiences.[15a] This was later confirmed by the comparison of the chiroptical properties. Comparison of the specific rotations of the compounds derived, with those of the compounds known in the literature, established an (*S*)-configuration for the alcohol and (*R*)-configuration for the acetate.

Racemic 3-hydroxy-4-(1-naphthyloxy)butanenitrile **4** was subjected to transesterification by employing various lipases and vinyl acetate in diisopropyl ether. *Pseudomonas cepacia* lipase was the most suited lipase for this reaction. Immobilization provided a revolutionary change in the enantioselectivity (Table 1: entries 1 and 3) and the reaction rate of this transesterification reaction (Table 1: entries 2 and 3). *P. cepacia* lipase (PS-D) catalyzed the reaction at 20–24 °C affording enantiomerically pure (*S*)-alcohol (***S*)-4** and (*R*)-acetate (***R*)-7** in

Table 1. Lipase-catalyzed transesterification of 4-aryloxy-3-hydroxybutanenitriles in diisopropyl ether

Entry	Compound	Lipase[a]	Time (h)	Alcohol		Acetate		E[19]
				Yield[b] (%)	ee%	Yield[b] (%)	ee%	
1[d]	**4**	PS-D	48	44	92.6[c]	43	>98[c]	311
2[e]	**4**	PS-C	9	44	75.5[c]	46	89.2[c]	41
3[f]	**4**	PS	120	63	35.0[c]	29	>98[c]	139
4[g]	**5**	PS-C	9	46	94.3[h]	44	94.3[h]	127
5[g]	**5**	PS-D	37	45	90.3[h]	45	90.7[h]	65
6[g]	**5**	Lipozyme	111	49	87.6[h]	44	>99[h]	581
7[g]	**5**	PS	114	68	36.8[h]	25	93[h]	41
8[i]	**6**	PS-D	12	43	>99[j]	44	>99[k]	1057
9[i]	**6**	PS-C	05	44	87.2[j]	46	83.4[k]	31
10[i]	**6**	PS	31	50	81.6[j]	41	>99[k]	501

[a] *Pseudomonas cepacia* lipase immobilized on diatomite (PS-D) (Amano Pharmaceutical Company), *Pseudomonas cepacia* lipase immobilized on modified ceramic particles (PS-C) (Amano Pharmaceutical Company), *Pseudomonas cepacia* (PS) (Amano Pharmaceutical Company), immobilized lipase from *Mucor meihei* (Lipozyme) (Fluka).
[b] Isolated yields.
[c] Determined by chiral HPLC (chiral OJ-H column; Diacel) employing hexane–isopropanol (82:18) as mobile phase at 0.5 mL/min and monitored by UV (254 nm).
[d] Reaction carried out at 20–24 °C.
[e] Reaction carried out at 30 °C.
[f] Reaction carried out at 40 °C.
[g] Reaction carried out at 35 °C.
[h] Determined by chiral HPLC (chiral OD column; Diacel) employing hexane–isopropanol (88:12) as mobile phase at 0.5 mL/min and monitored by UV (254 nm).
[i] Reaction carried out at 25–28 °C.
[j] Determined by chiral HPLC (chiral OD column; Diacel) employing hexane–isopropanol (85:15) as mobile phase at 0.75 mL/min and monitored by UV (245 nm).
[k] Determined by chiral HPLC (chiral OJ-H column; Diacel) employing hexane–isopropanol (88:12) as mobile phase at 1.0 mL/min and monitored by UV (245 nm).

high enantiomeric excess and good yields as shown in Table 1. Enantiomerically pure alcohol (***S***)-**4**, which was obtained after enzymatic resolution, was effectively employed in the preparation of (*S*)-propranolol.

Among the various lipases screened, lipases from various sources like *P. cepacia*, *Mucor mehie* and *Pseudomonas fluorescens* gave satisfactory results for the resolution of 4-(2-allylphenoxy)-3-hydroxybutanenitrile **5**. Lipase from *P. cepacia* lipase (PS-C) provided excellent yields with high enantiomeric excess in a short period of time. Furthermore, the transesterification process by this immobilized lipase is comparatively much faster than the use of lipase PS (unimmobilized) as seen from the detailed data given in Table 1 (entries 4 and 7). The resolved (***S***)-**5** was been later employed in the preparation of alprenolol.

3-Hydroxy-4-(4-methoxyphenoxy)butanenitrile **6** is another substrate of high interest and was effectively resolved by transesterification catalyzed by lipase PS-D at 25–28 °C. This substrate shows faster conversion rates in better enantiomeric excess than other substituted substrates probably due to the presence of a *para* electron donating substituent.[15a] Lipase PS-D provides excellent results with high enantiomeric excess and in good yields. The thus obtained enantiopure (***S***)-**6** was employed in the preparation of moprolol.

In this process of resolution, the effect of solvents on the rate of conversion and enantioselectivity on each substrate was also examined. It was observed that diisopropyl ether, hexane, diethyl ether and toluene are the solvents of choice offering remarkable enantioselectivities whereas, in hydrophilic solvents such as acetone, tetrahydrofuran and acetonitrile, the reaction proceeded with low conversion rates. The summarized data is illustrated in Table 2.

2.2. Preparation of β-adrenergic blocking agents

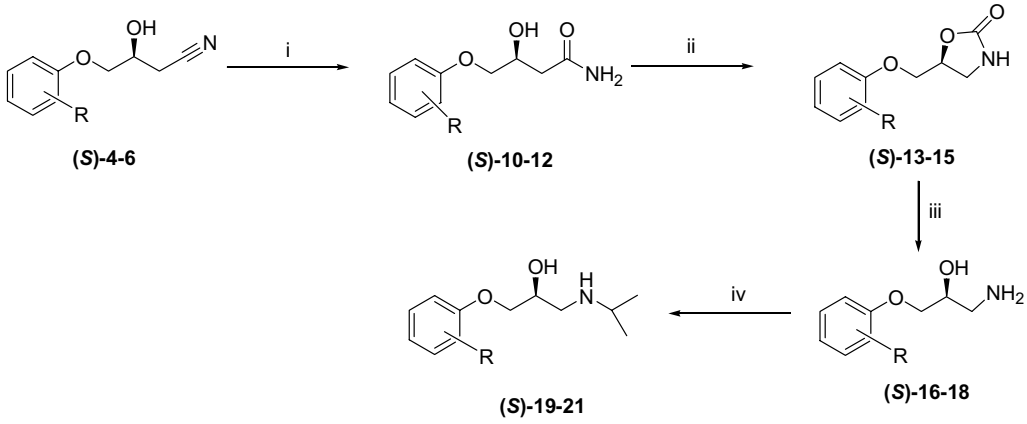
The general schematic representation for the preparation of these β-adrenergic blocking agents is shown in Scheme 1.

The β-hydroxy nitriles obtained after resolution are one homologue higher than the target propanol amines. In order to decrease the aliphatic chain length by one carbon, β-hydroxy nitriles (***S***)-**4**–**6** were treated with H_2O_2 in aqueous ammonia to afford 4-aryloxy-3-hydroxy butanamides (***S***)-**10**–**12**. These hydroxyl amides were then subjected to a Hoffmann type of rearrangement using $Pb(OAc)_4$ in pyridine to provide 5-aryloxymethyl-1,3-oxazolidine-2-one (***S***)-**13**–**15**. Amongst the number of solvents studied for this rearrangement reaction, pyridine has given good results as it also acts as a base, thus increasing the rate of the reaction. In this process, the vicinal hydroxyl group acts as a nucleophile on the isocyanate resulting in cyclization to form an oxazolidinone ring system. Oxazolidinones (***S***)-**13**–**15** were treated with aqueous NaOH in EtOH to afford β-amino alcohols as a clean product. These amino alcohols are the precursors for the preparation of β-adrenergic blocking agents, their treatment with acetone and

Table 2. Effects of solvents on the transesterification of 4-aryloxy-3-hydroxy-butanenitrile by lipases

Sl. no	Compd	Lipase	Solvent	Time (h)	Alcohol		Acetate	
					Yield[a] %	ee%	Yield[a] %	ee%
1	**4**	PS-D	Diisopropyl ether[b]	48	44	92.6[d]	43	>98[b]
2	**4**	PS-D	Toluene[b]	92	52	70.4[d]	35	>98[d]
3	**4**	PS-D	Acetone[c]	120	77	20.0[d]	13	>98[d]
4	**4**	PS-D	Tetrahydrofuran[c]	120	84	13.1[d]	06	>98[d]
5	**5**	PS-C	Diisopropyl ether[e]	9	46	94.3[f]	44	94.3[f]
6	**5**	PS-C	Hexane[e]	8	45	91.1[f]	45	90.9[f]
7	**5**	PS-C	Acetone[e]	108	62	30.7[f]	31	94.4[f]
8	**5**	PS-C	Acetonitrile[e]	108	76	3.9[f]	15	15.7[f]
9	**6**	PS-D	Diisopropyl ether[g]	12	43	>99[h]	44	>99[i]
10	**6**	PS-D	Toluene[g]	13	44	>99[h]	43	>99[i]
11	**6**	PS-D	Tetrahydrofuran[g]	62	63	62.9[h]	20	>99[i]
12	**6**	PS-D	Acetonitrile[g]	62	65	40.9[h]	16	>99[i]

[a] Isolated yields.
[b] Reaction carried out at 20–24 °C.
[c] Reaction carried out at 40 °C.
[d] Determined by chiral HPLC (chiral OJ-H column; Diacel) employing hexane–isopropanol (82:18) as mobile phase at 0.5 mL/min and monitored by UV (254 nm).
[e] Reaction carried out at 35 °C.
[f] Determined by chiral HPLC (chiral OD column; Diacel) employing hexane–isopropanol (88:12) as mobile phase at 0.5 mL/min and monitored by UV (254 nm).
[g] Reaction carried out at 25–28 °C.
[h] Determined by chiral HPLC (chiral OD column; Diacel) employing hexane–isopropanol (85:15) as mobile phase at 0.75 mL/min and monitored by UV (245 nm).
[i] Determined by chiral HPLC (chiral OJ-H column; Diacel) employing hexane–isopropanol (88:12) as mobile phase at 1.0 mL/min and monitored by UV (245 nm).



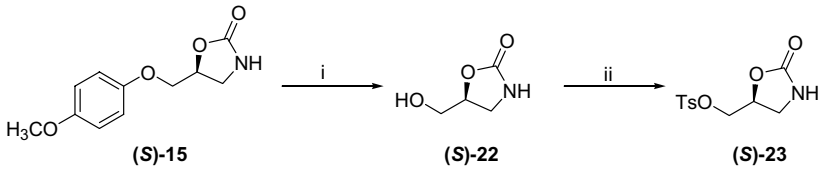
Scheme 1. R = 2,3-(CH=CH–CH=CH) **4**; 2-(CH_2–CH=CH_2) **5**; 4-OCH_3 **6**. Reagents: (i) H_2O_2, aq NH_3; (ii) $Pb(OAc)_4$, pyridine; (iii) NaOH, EtOH–H_2O; (iv) $NaBH_4$, acetone, absolute EtOH.

$NaBH_4$ under anhydrous condition providing the required β-adrenergic blocking agents (***S***)-**19**–**21** in high enantiomeric excess and almost quantitative yield.

2.3. Preparation of chiral intermediates of synthetic importance

Another interesting aspect of this investigation is that one of the substrates, 3-hydroxy-4-(4-methoxyphenoxy)butanenitrile **6**, contains an anisyl group,[20] which has been generally used as a protecting group for primary alcohols and survives through a series of acidic, basic, oxidative and reductive reactions and yet can be readily cleaved under mild conditions. This has been exploited in the preparation of intermediates for the synthesis of GABOB and carnitine and also paved the way for a common intermediate useful in the preparation of various β-blockers (Scheme 2).

5-(4-Methoxyphenoxymethyl)-1,3-oxazolidine-2-one (***S***)-**15** on treatment with a ceric ammonium nitrate (CAN) in acetonitrile–water system, led to the formation of 5-hydroxymethyl-1,3-oxazolidine-2-one (***S***)-**22**, which in turn has been converted to 5-(4-methylphenylsulfonyloxymethyl)-1,3-oxazolidine-2-one (***S***)-**23** when treated with *p*-toluenesulfonyl chloride and Et_3N. As most of the β-blockers have same chemical structure differing only in the aryl group, 5-(4-methylphenylsulfonyloxy-



Scheme 2. Reagents and condition: (i) CAN, CH_3CN–H_2O, 10 min; (ii) *p*-toluenesulfonyl chloride, Et_3N.

methyl)-1,3-oxazolidine-2-one[14] is a favourable common intermediate for the synthesis of various β-adrenergic blocking agents as the tosyl group can be easily displaced with various phenols leading to the formation of various β-adrenergic blocking agents. On the other hand, (*R*)-3-hydroxy-4-(4-methoxyphenoxy)butanenitrile (***R*)-6** prepared from (*R*)-3-acetyloxy-4-(4-methoxyphenoxy)butanenitrile (***R*)-15** was treated with CAN in acetonitrile–water system to afford (*R*)-3,4-dihydroxybutanenitrile, which in turn was transformed to (*R*)-3-hydroxy-4-(4-methylphenylsulfonyloxy)butanenitrile[21] (***R*)-24** an intermediate for synthesis of (*R*)-GABOB and (*R*)-carnitine, compounds of pharmacological importance (Scheme 3).

3. Conclusion

An efficient and practical preparation of β-hydroxy nitriles and their successful enzymatic kinetic resolution using lipases has been demonstrated, which has been further extended for the preparation of biologically important compounds like β-adrenergic blocking agents. Furthermore, some chiral intermediates of high synthetic importance in the preparation of biologically important compounds have also been prepared from these β-hydroxy nitriles.

4. Experimental

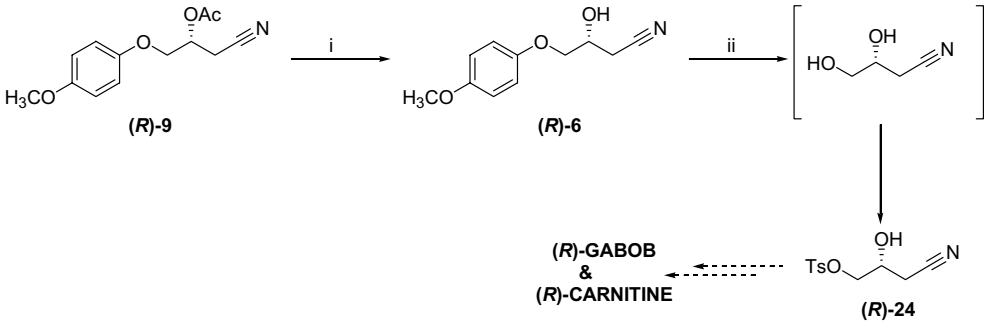
4.1. General

Unless specified all solvents and reagents were reagent grade and used without further purification. Reactions involving moisture-sensitive reagents were performed under an inert atmosphere of nitrogen in glassware, which had been oven dried. Melting points were 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 $CDCl_3$, or DMSO (d_6) and chemical shifts reported in parts per million (ppm, δ) on a Gemini 200 MHz, AV 300 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. 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 60F-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-10AT system controller with a SPD-10A fixed wavelength UV monitor as detector. Optical rotations were measured on SEPA-300 (Horiba) digital polarimeter.

4.2. General procedure for the oxirane ring opening

The epoxide (20 mmol) was dissolved in ethanol (20 mL) and to this was added water (100 mL). After stirring for 5 min, NaCN (28 mmol) was added and stirring continued at room temperature. On completion of the reaction as indicated by TLC, the reaction mixture was concentrated to about half the volume under reduced pressure. The residue was extracted with ethyl acetate, washed with brine and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography employing EtOAc–hexane (3:7) as the eluent afforded pure β-hydroxy nitriles.

4.2.1. 3-Hydroxy-4-(1-naphthyloxy)butanenitrile 4. 3-(1-Naphthyloxy)-1,2-epoxy-propane **1** when treated with NaCN for 18 h as described in the above general



Scheme 3. Reagents and condition: (i) K_2CO_3, methanol; (ii) CAN, CH_3CN–H_2O, 10 min; (iii) *p*-toluenesulfonyl-chloride, Et_3N, dibutyltinoxide, DCM.

procedure for the ring opening of oxiranes resulted in white solid **4** and is previously reported.[15a]

4.2.2. 3-Hydroxy-4-(2-allylphenoxy)butanenitrile 5. 3-(2-Allylphenoxy)-1,2-epoxy-propane **2** when treated with NaCN for 12 h as described in the above general procedure for the ring opening of oxiranes resulted in **5**. Yield 86%; IR (neat): 3443, 3059, 3035, 2988, 2915, 2862, 2235, 1490, 1239, 1106, 1051 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.62–2.84 (m, 2H), 3.15 (br s, 1H), 3.41 (d, 2H, $J = 6.8$ Hz), 4.04–4.15 (m, 2H), 4.24–4.36 (m, 1H), 4.98–5.11 (m, 2H), 5.88–6.06 (m, 1H), 6.83 (d, 1H, $J = 7.9$ Hz), 6.90–6.99 (m, 1H), 7.13–7.29 (m, 2H); Mass (EI) 217 (M^+), 147, 134, 119, 117, 103, 91, 77, 43.

4.2.3. 3-Hydroxy-4-(4-methoxyphenoxy)butanenitrile 6. 3-(4-Methoxyphenoxy)-1,2-epoxy-propane **3** when treated with NaCN for 12 h as described in the above general procedure for the ring opening of oxiranes resulted in white crystalline solid **6**. Yield 85%; mp 66–69 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.61–2.77 (m, 2H), 3.75 (s, 3H), 3.98 (d, 2H, $J = 5.7$ Hz), 4.24–4.29 (m, 1H), 6.75–6.83 (m, 4H); Mass (EI) 207 (M^+), 180, 166, 149, 137, 124, 123, 77.

4.3. General procedure for preparation of 3-acetyloxy-4-aryloxybutanenitrile

To 4-aryloxy-3-hydroxybutanenitrile (5.00 mmol) under N_2 was added acetic anhydride (20.00 mmol) and pyridine (5.50 mmol) and the resultant mixture stirred at room temperature overnight. After completion of the reaction (TLC), the reaction mixture was diluted with ethyl acetate (25 mL) and treated with 1 M 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-4-aryloxybutanenitrile in nearly quantitative yield.

4.3.1. 3-Acetyloxy-4-(1-naphthyloxyphenoxy)butanenitrile 7. 3-Hydroxy-4-(1-napthyloxy)butanenitrile was acetylated using acetic anhydride and pyridine employing the above general procedure to obtain **7** in almost quantitative yield. IR (neat) 3059, 2937, 2255, 1742, 1393, 1218, 1105 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 8.13–8.20 (m, 1H), 7.75–7.83 (m, 1H), 7.25–7.52 (m, 4H), 6.8 (d, $J = 7.14$ Hz, 1H), 5.41–5.52 (m, 1H), 4.26–4.40 (m, 2H), 2.97 (d, $J = 4.76$ Hz, 2H), 2.18 (s, 3H); Mass (EI) 269, 164, 126.

4.3.2. 3-Acetyloxy-4-(2-allylphenoxy)butanenitrile 8. 3-Hydroxy-4-(2-allylphenoxy)butanenitrile was acetylated using acetic anhydride and pyridine employing the above general procedure to obtain **8** in almost quantitative yield. ^1H NMR (200 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.87 (d, 2H, $J = 4.5$ Hz), 3.35 (d, 2H, $J = 6.3$ Hz), 4.06–4.22 (m, 2H), 4.94–5.03 (m, 2H), 5.25–5.36 (m, 1H), 5.83–6.00 (m, 1H), 6.81 (d, 1H, $J = 7.9$ Hz), 6.88–6.95 (m, 1H), 7.10–7.25 (m, 2H); Mass (EI) 259 (M^+), 126, 91, 43.

4.3.3. 3-Acetyloxy-4-(4-methoxyphenoxy)butanenitrile 9. 3-Hydroxy-4-(4-methoxyphenoxy)butanenitrile was acetylated using acetic anhydride and pyridine employing the above general procedure to obtain **9** in almost quantitative yield. ^1H NMR (200 MHz, $CDCl_3$) 2.14 (s, 3H), 2.86 (d, 2H, $J = 5.8$ Hz), 3.76 (s, 3H), 3.99–4.16 (m, 2H), 5.19–5.31 (m, 1H), 6.75–6.81 (m, 4H); Mass (EI) 249 (M^+), 207, 167, 149, 139, 124, 123, 77.

4.4. General procedure for the resolution of β-hydroxy nitriles

β-Hydroxy nitriles (5 mmol) were dissolved in diisopropyl ether (50 mL) and to this, lipase and vinyl acetate (12.5 mmol) were added successively and shaken in an orbital shaker. After about 50% completion of the reaction, as indicated by the HPLC, the reaction mixture was filtered and washed with EtOAc. Solvents were evaporated and purification accomplished by column chromatography employing EtOAc–hexane (25:75) as the eluent to afford the corresponding (*R*)-acetate followed by the unreacted (*S*)-β-hydroxy nitrile.

4.4.1. (*R*)-3-Acetyloxy-4-(1-naphthyloxy)butanenitrile (*R*)-7. Resolution of 3-hydroxy-4-(1-naphthyloxy)-butanenitrile **4** by employing the typical procedure using *P. cepacia* lipase immobilized on diatomite (PS-D) afforded (*R*)-**7** in 43% yield and >98% ee after 48 h. $[\alpha]_D^{25} = +26.84$ (*c* 1.0, $CHCl_3$); IR, NMR and mass spectral data are identical to **7**.

4.4.2. (*S*)-3-Hydroxy-4-(1-naphthyloxy)butanenitrile (*S*)-4. Resolution of 3-hydroxy-4-(1-naphthyloxy)butanenitrile **4** by employing the above general procedure for the resolution of β-hydroxy nitriles by employing *P. cepacia* lipase immobilized on diatomite (PS-D) in diisopropyl ether at 22 °C afforded (*S*)-**4** in 44% yield and 92.6% ee after 48 h. Mp 65–68 °C; $[\alpha]_D^{26} = -15.2$ (*c* 1.05, $CHCl_3$); IR, NMR and mass spectral data are identical to **4**.

4.4.3. (*R*)-3-Acetyloxy-4-(2-allylphenoxy)butanenitrile (*R*)-8. The resolution of 3-hydroxy-4-(2-allylphenoxy)-butanenitrile **5** was carried out by employing the typical procedure at 35 °C using *P. cepacia* lipase immobilized on modified ceramic particles (PS-C) to afford (*R*)-**8** in 44% yield and 94.3% ee after 9 h. $[\alpha]_D^{26} = +28.7$ (*c* 1.25, $CHCl_3$); NMR and mass spectral data are identical to **8**.

4.4.4. (*S*)-3-Hydroxy-4-(2-allylphenoxy)butanenitrile (*S*)-5. The resolution of 3-hydroxy-4-(2-allylphenoxy)-butanenitrile **5** was carried out by employing the typical procedure at 35 °C using *P. cepacia* lipase immobilized on modified ceramic particles (PS-C) to afford ((*S*)-**5**) in 46% yield and 94.3% ee after 9 h. $[\alpha]_D^{26} = -1.9$ (*c* 2.6, $CHCl_3$); IR, NMR and mass spectral data are identical to **5**.

4.4.5. (*R*)-3-Acetyloxy-4-(4-methoxyphenoxy)butanenitrile (*R*)-9. The resolution of 3-hydroxy-4-(4-methoxyphenoxy)butanenitrile **6** was carried out by employing the typical procedure using *P. cepacia* lipase

immobilized on diatomite (PS-D) to afford (***R***)-**9** in 44% yield and >99% ee after 12 h. $[\alpha]_D^{27} = +24.1$ (*c* 1.3, $CHCl_3$); NMR and mass spectral data are identical to **9**.

4.4.6. (*S*)-3-Hydroxy-4-(4-methoxyphenoxy)butanenitrile (*S*)-6. The resolution of 3-hydroxy-4-(4-methoxyphenoxy)butanenitrile **6** was carried out by employing the typical procedure using *P. cepacia* lipase immobilized on diatomite (PS-D) to afford (***S***)-**6** in 43% yield and >99% ee after 12 h. Mp 57–60 °C; $[\alpha]_D^{27} = -5.5$ (*c* 1.2, $CHCl_3$); NMR and mass spectral data are identical to **6**.

4.5. (*R*)-3-Hydroxy-4-(4-methoxyphenoxy)butanenitrile (*R*)-6

To a stirring solution of (*R*)-3-acetyloxy-4-(4-methoxyphenoxy)butanenitrile (5.00 g, 20.08 mmol) in 80 mL of methanol was added K_2CO_3 (11.08 g, 80.32 mmol) at room temperature and the reaction progress monitored by TLC. After completion of the reaction (1 h), methanol was evaporated and the residue was separated between ethyl acetate (60 mL) and water (40 mL). The aqueous layer was then extracted with EtOAc (3×50 mL) and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The organic solvent was evaporated to leave a residue of (*R*)-3-hydroxy-4-(4-methoxyphenoxy)butanenitrile in almost quantitative yield. Mp 56–59 °C; $[\alpha]_D^{27} = +5.1$ (*c* 1.2, $CHCl_3$); NMR and mass spectral data are identical to **6**.

4.6. (*S*)-3-Hydroxy-4-(1-naphthyloxy)butanamide (*S*)-10

3-Hydroxy-4-(1-naphthyl-oxy)butanenitrile (4.54 g, 20.00 mmol) was dispersed in 15 mL of ethanol and aq NH_3 (65 mL) was added to it at room temperature. To the resulting mixture was added H_2O_2 (100 vol) (45 mL, 400 mmol) in portions, while maintaining the temperature of the reaction mixture below 25 °C. After complete addition, the resultant reaction mixture was stirred vigorously at 25–30 °C and the reaction progress monitored by TLC. After completion of the reaction (45 min), the reaction volume was concentrated to about 50% of the original volume under reduced pressure and the resultant mixture was extracted with dichloromethane (3×80 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated to leave a residue, which was purified by column chromatography employing EtOAc–hexane (80:20) as eluent to afford 3-hydroxy-4-(1-naphthyloxy)butanamide in almost quantitative yield. Mp 123–125 °C; $[\alpha]_D^{25} = -7.5$ (*c* 1.0, MeOH); ^{1}H NMR (200 MHz, DMSO (d_6)) δ 2.39–2.58 (m, 2H), 3.97–4.12 (m, 2H), 4.33–4.42 (m, 1H), 5.10 (br s, 1H), 6.42 (br s, 1H), 6.77 (d, 1H, $J = 6.6$ Hz), 7.16 (br s, 1H), 7.23–7.40 (m, 4H), 7.67–7.71 (m, 1H), 8.21–8.26 (m, 1H); Mass (EI) 227 ($M^+ - 18$), 218, 167, 149, 144, 127, 115, 102, 71, 57, 43.

4.7. (*S*)-4-(2-Allylphenoxy)-3-hydroxybutanamide (*S*)-11

The title compound was prepared using a similar procedure to that of the preparation of **10** employing 4-(2-allylphenoxy)-3-hydroxy butanenitrile (4.00 g, 18.43 mmol), aqueous NH_3 (60 mL) and H_2O_2 (100 vol) (42 mL, 368.00 mmol). $[\alpha]_D^{27} = -18.1$ (*c* 1.0, $CHCl_3$); IR (neat): 3388, 3075, 2973, 2925, 2871, 1671, 1490, 1435, 1239, 1114, 1035; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.47–2.54 (m, 2H), 3.36 (d, 2H, $J = 5.9$ Hz), 3.95 (d, 2H, $J = 5.3$ Hz), 4.23–4.40 (m, 1H), 4.94–5.05 (m, 2H), 5.75–6.00 (m, 1H), 6.79 (d, 1H, $J = 8.1$ Hz), 6.85–6.92 (m, 1H), 7.08–7.25 (m, 2H); Mass (EI) 235 (M^+), 218, 208, 133, 131, 102, 91, 77, 44.

4.8. (*S*)-3-Hydroxy-4-(4-methoxyphenoxy)butanamide (*S*)-12

The title compound was prepared using a similar procedure to that of the preparation of **10** employing 3-hydroxy-4-(4-methoxyphenoxy)butanenitrile (2.86 g, 13.82 mmol), 10–15 mL of ethanol, aq NH_3 (48 mL) and H_2O_2 (100 vol) (32 mL, 276.40 mmol) and carrying out the reaction for 2 h. Mp 126–127 °C; $[\alpha]_D^{27} = -7.1$ (*c* 0.95, EtOH); ^{1}H NMR (200 MHz, DMSO(d_6)) δ 2.21–2.40 (m, 2H), 3.66 (s, 3H), 3.68–3.82 (m, 2H), 4.09–4.19 (m, 1H), 4.99 (d, 1H (OH), $J = 4.3$ Hz), 6.52 (br s, 1H), 6.67–6.79 (m, 4H), 7.18 (br s, 1H); Mass (EI) 225 (M^+), 207, 137, 124, 123, 109, 77.

4.9. (*S*)-5-(1-Naphthyloxymethyl)-1,3-oxazolidine-2-one (*S*)-13

To a solution of 3-hydroxy-4-(1-naphthyloxy)butanamide (***S***)-**10** (3.60 g, 14.70 mmol) in pyridine (35 mL) was added $Pb(OAc)_4$ (9.10 g, 20.50 mmol) and the resultant reaction mixture was stirred under N_2 at room temperature for 1 h. After completion of the reaction as indicated by TLC, the reaction mixture was taken up in CH_2Cl_2 (100 mL) and then treated with 10% HCl (125 mL). The resultant reaction mixture was filtered through a celite pad and the residue washed three times with CH_2Cl_2 (50 mL). The organic layer from the combined filtrates and washings were separated and the aqueous layer extracted with CH_2Cl_2 (2×100 mL). The organic layer, free from pyridine, was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to leave a residue of crude oxazolidinone (***S***)-**13**, which was purified by column chromatography employing EtOAc–hexane (40:60) as eluent to afford pure 5-(1-naphthyloxymethyl)-1,3-oxazolidine-2-one (***S***)-**13** in 85% yield. Mp 152–154 °C; $[\alpha]_D^{24} = -20.4$ (*c* 0.75, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.66–3.96 (m, 2H), 4.31 (d, 2H, $J = 5.0$ Hz), 5.02–5.20 (m, 1H), 5.73 (br s, 1H), 6.80 (d, 1H, $J = 6.8$ Hz), 7.29–7.58 (m, 4H), 7.73–7.87 (m, 1H), 8.13–8.26 (m, 1H); Mass (EI) 243 (M^+), 144, 127, 115, 57, 43.

4.10. (*S*)-5-(2-Allylphenoxymethyl)-1,3-oxazolidine-2-one (*S*)-14

The title compound was prepared using a similar procedure to that of the preparation of **13** employing 4-(2-allylphenoxy)-3-hydroxy butanamide (1.80 g, 7.66 mmol), pyridine (18 mL) and $Pb(OAc)_4$ (4.76 g, 10.73 mmol). Yield 88% yield; $[\alpha]_D^{25} = +8.1$ (*c* 1.1, $CHCl_3$); IR (neat) 3286, 3075, 2980, 2915, 1741, 1498, 1239,

1098; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.34 (d, 2H, J = 6.1 Hz), 3.60–3.87 (m, 2H), 4.14 (d, 2H, J = 5.4 Hz), 4.94–5.03 (m, 3H), 5.81–5.99 (m, 1H), 6.25 (br s, 1H), 6.79 (d, 1H, J = 7.5 Hz), 6.83–6.97 (m, 1H), 7.10–7.26 (m, 2H); Mass (EI) 234 (M^++1), 206, 190, 173, 159, 145, 133, 131, 91, 56, 43.

4.11. (*S*)-5-(4-Methoxyphenoxymethyl)-1,3-oxazolidine-2-one (*S*)-15

The title compound was prepared using a similar procedure to that of the preparation of **13** employing 3-hydroxy-4-(4-methoxyphenoxy)butanamide (2.60 g, 11.56 mmol), pyridine (25 mL) and $Pb(OAc)_4$ (7.18 g, 16.20 mmol) and carrying out the reaction for 90 min. Yield 80%; mp 118–120 °C; $[\alpha]_D^{26} = +16.8$ (c 1.05, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.42–3.50 (m, 1H), 3.60–3.66 (m, 1H), 3.72 (s, 3H), 3.98–4.10 (m, 2H), 4.76–4.89 (m, 1H), 6.71–6.82 (m, 4H), 7.26 (br s, 1H); Mass (EI) 223 (M^+), 137, 124, 109, 77.

4.12. (*S*)-1-Amino-3-(1-naphthyloxy)-2-propanol (*S*)-16

To a solution of oxazolidinone (***S*)-13** (1.46 g, 6.00 mmol) in 15 mL of ethanol was added NaOH (1.20 g, 30.00 mmol) dissolved in 8 mL of water at room temperature and the resultant reaction mixture refluxed for 1 h. After completion of the reaction (TLC) ethanol was evaporated and the resultant mixture was diluted with water and then extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to leave a residue, which was purified by column chromatography employing MeOH–$CHCl_3$ (10:90) as eluent to afford pure 1-amino-3-(1-naphthyloxy)-2-propanol in 80% yield. Mp 113–116 °C; $[\alpha]_D^{25} = -10.4$ (c 0.9, EtOH); lit.[12c] $[\alpha]_D^{25} = -7.3$ (c 0.51, $CHCl_3$). ^{1}H NMR (200 MHz, DMSO (d_6)) δ 2.92–3.20 (m, 2H), 4.00–4.22 (m, 3H), 6.80 (d, 1H, J = 6.9 Hz), 7.28–7.55 (m, 4H), 7.70–7.80 (m, 1H), 8.18–8.30 (m, 1H); Mass (EI) 217 (M^+), 169, 155, 144, 115, 74, 43.

4.13. (*S*)-3-(2-Allylphenoxy)-1-amino-2-propanol (*S*)-17

The title compound was prepared using a similar procedure to that of the preparation of **16** employing 5-(2-allylphenoxymethyl)-1,3-oxazolidine-2-one (1.20 g, 5.15 mmol), 15 mL of ethanol and NaOH (1.03 g, 25.75 mmol) in 8 mL of water. Yield 82%; mp 41–42 °C; $[\alpha]_D^{25} = -8.3$ (c 1.8, $CHCl_3$); ^{1}H NMR (200 MHz, DMSO (d_6)) 2.80–3.04 (m, 2H), 3.36 (d, 2H, J = 5.9 Hz), 3.80–3.96 (m, 3H), 4.95–5.04 (m, 2H), 5.80–6.01 (m, 1H), 6.77–6.90 (m, 2H), 7.07–7.17 (m, 2H); Mass (EI) 207 (M^+), 190, 134, 133, 102, 91, 77.

4.14. (*S*)-1-Amino-3-(4-methoxyphenoxy)-2-propanol (*S*)-18

The title compound was prepared using a similar procedure to that of the preparation of **16** employing 5-(4-methoxyphenoxymethyl)-1,3-oxazolidine-2-one (1.20 g, 5.38 mmol), 15 mL of ethanol and NaOH (1.08 g, 27.00 mmol) in 8 mL of water and carrying out the reaction for 80 min. Yield 80%; mp 100–103 °C; $[\alpha]_D^{28} = -5.5$ (c 0.85, EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.70–3.00 (m, 2H), 3.75 (s, 3H), 3.85–4.00 (m, 3H), 6.75–6.90 (m, 4H); Mass (EI) 197 (M^+), 167, 150, 137, 124, 109.

4.15. (*S*)-1-Isopropylamino-3-(1-naphthyloxy)-2-propanol (propranolol) (*S*)-19

To a solution of 1-amino-3-(1-naphthyloxy)-2-propanol (0.44 g, 2.03 mmol) in 10 mL of absolute ethanol was added 0.8 mL of acetone under N_2 at room temperature. To the resultant reaction mixture, $NaBH_4$ (0.20 g, 5.26 mmol) was added slowly over a period of 3 min in three portions. Five minutes later, the entire set of $NaBH_4$ additions were repeated after adding another 0.8 mL of acetone. After complete additions, the reaction mixture was flushed with N_2, stirred at room temperature and the reaction progress was monitored by TLC. After completion of the reaction (45 min) H_2O (20 mL) was added to the reaction mixture and then extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of the residue by column chromatography employing MeOH–$CHCl_3$ (5:95) as eluent afforded propranolol in 85–90% yield. Mp 70–72 °C; $[\alpha]_D^{25} = -9.8$ (c 1.0, EtOH); lit.[12e] $[\alpha]_D^{25} = -10.2$ (c 1.02, EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15 (d, 6H, J = 6.4 Hz), 2.80–3.01 (m, 3H), 3.42 (br s, 1H), 4.06–4.20 (m, 3H), 6.75 (d, 1H, J = 6.9 Hz), 7.25–7.45 (m, 4H), 7.71–7.77 (m, 1H), 8.16–8.22 (m, 1H); Mass (EI) 260 (M^++1), 216, 145, 128, 116, 72, 57, 43.

4.16. (*S*)-3-(2-Allylphenoxy)-1-isopropylamino-2-propanol (alprenolol) (*S*)-20

The title compound was prepared using a similar procedure to that of the preparation of **19** employing 3-(2-allylphenoxy)-1-amino-2-propanol (0.68 g, 3.29 mmol), 10–12 mL of absolute ethanol, 1.2 mL of acetone and $NaBH_4$ (0.31 g, 8.23 mmol). Yield 88%; $[\alpha]_D^{27} = -15.7$ (c 1.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (d, 6H, J = 6.0 Hz), 2.94–3.19 (m, 3H), 3.34 (d, 2H, J = 6.9 Hz), 3.85–4.04 (m, 2H), 4.22–4.25 (m, 1H), 4.93–5.01 (m, 2H), 5.80–6.01 (m, 1H), 6.75 (d, 1H, J = 7.4 Hz), 6.80–6.88 (m, 1H), 7.05–7.14 (m, 2H); Mass (EI) 250 (M^++1), 91, 77.

4.17. (*S*)-1-Isopropylamino-3-(4-methoxyphenoxy)-2-propanol (moprolol) (*S*)-21

The title compound was prepared using a similar procedure to that of the preparation of **19** employing 1-amino-3-(4-methoxyphenoxy)-2-propanol (0.50 g, 2.54 mmol), 10 mL of absolute ethanol, 0.9 mL of acetone and $NaBH_4$ (0.24 g, 6.40 mmol) and carrying out the reaction for 1 h. Yield 88%; mp 50–53 °C; $[\alpha]_D^{28} = -7.5$ (c 0.9, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.11 (d, 6H, J = 6.8 Hz), 2.32 (br s), 2.68–2.94 (m, 3H), 3.76 (s, 3H), 3.94 (d, 2H, J = 4.2 Hz), 3.98–4.07 (m, 1H), 6.84–7.27 (m, 4H); Mass (EI) 239 (M^+), 195, 166, 150, 137, 124, 123, 109, 77.

4.18. (*S*)-5-Hydroxymethyl-1,3-oxazolidine-2-one (*S*)-22

To a stirred solution of 5-(4-methoxyphenoxymethyl)-1,3-oxazolidine-2-one (0.60 g, 2.69 mmol) in 30 mL of CH_3CN-H_2O (4:1) at 0 °C was added ceric ammonium nitrate (2.95 g, 5.38 mmol) and the progress of the reaction monitored by TLC. After completion of the reaction (10 min) the reaction mixture was filtered through a silica pad and the filtrate was concentrated to leave a residue, which was purified by column chromatography employing MeOH–EtOAc (5:95) as eluent to afford 5-hydroxymethyl-1,3-oxazolidine-2-one in 45% yield. Mp 70–73 °C; $[\alpha]_D^{27} = +32.8$ (*c* 0.6, EtOH); ^{1}H NMR (200 MHz, DMSO (d_6)) δ 3.35–3.75 (m, 4H), 4.50–4.64 (m, 1H), 4.85 (br s, 1H).

4.19. (*S*)-5-(4-Methylphenylsulfonyloxymethyl)-1,3-oxazolidine-2-one (*S*)-23

p-Toluene-sulfonyl chloride (0.30 g, 1.60 mmol) and Et_3N (0.16 g, 1.60 mmol) were added to 5-hydroxymethyl-1,3-oxazolidine-2-one (0.12 g, 1.03 mmol) dispersed in 8 mL of CH_2Cl_2 and stirred overnight at room temperature under N_2. After completion of the reaction (TLC), the solvent in the reaction mixture was evaporated and the residue purified by column chro matography employing EtOAc–hexane (75:25) as eluent to afford 5-(4-methylphenylsulfonyloxymethyl)-1,3-oxazolidine-2-one in 80% yield. Mp 96–99 °C; $[\alpha]_D^{27} = +44.4$ (*c* 1.25, $CHCl_3$); IR (KBr) 3247, 2933, 2886, 2824, 1741, 1012, 949 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.24 (dd, 1H, $J_1 = 4.5$ Hz, $J_2 = 10.4$ Hz), 3.36–3.48 (m, 3H), 3.57–3.64 (m, 1H), 4.71–4.77 (m, 1H), 5.27 (br, s, 1H), 7.21–7.44 (m, 9H), 7.46–7.47 (m, 6H); Mass (EI) 274, 258, 243, 183, 165, 105, 77.

4.20. (*R*)-3-Hydroxy-4-(4-methylphenylsulfonyloxy)butanenitrile (*R*)-24

To a stirring solution of (*R*)-3-hydroxy-4-(4-methoxyphenoxy)butanenitrile (2.07 g, 10.00 mmmol) in 100 mL of CH_3CN–H_2O (4:1) at 0 °C was added ceric ammonium nitrate (10.96 g, 20.00 mmol) and the progress of the reaction monitored by TLC. After completion of the reaction (10 min) the reaction mixture was filtered through a silica pad and the filtrate concentrated to leave a residue, which was purified by column chromatography employing acetone–hexane (70:30) as eluent to afford 3,4-dihydroxy butanenitrile (40%). To 3,4-dihydroxy butanenitrile (10.10 g, 100.00 mmol) dispersed in 250 mL of CH_2Cl_2 was added dibutyltinoxide (4.98 g, 20.00 mmol), Et_3N (25.25 g, 250.00 mmol) and *p*-toluenesulfonyl chloride (20.95 g, 110.00 mmol) at room temperature and under N_2. The resultant reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After completion of the reaction (2 h), 150 mL of water was added and organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3×150 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, concentrated and the residue was purified by column chromatography employing EtOAc–hexane (30:70) as eluent to afford pure 3-hydroxy-4-(4-methylphenyl-sulfonyloxy)butanenitrile in 65% yield. $[\alpha]_D^{26} = +13.5$ (*c* 1.45, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (s, 3H), 2.52–2.67 (m, 2H), 4.06 (d, 2H, $J = 5.4$ Hz), 4.15–4.22 (m, 1H), 7.38 (d, 2H, $J = 8.3$ Hz), 7.80 (d, 2H, $J = 8.3$ Hz); Mass (EI) 255 (M^+), 173, 155, 139, 122, 91.

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