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Lipase-mediated resolution of 3-hydroxy-4-trityloxybutanenitrile: synthesis of 2-amino alcohols, oxazolidinones and GABOB

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Abstract—Lipase-mediated kinetic resolution of 3-hydroxy-4-trityloxybutanenitrile gave the (*S*)-alcohol and (*R*)-acetate in good yields and high enantioselectivities. The resolution using *Pseudomonas cepacia* lipase (*Burkholderia cepacia*) immobilized on modified ceramic particles (PS-C) in diisopropyl ether gave the best results. The use of base additives in this transesterification drastically reduces the reaction time without effecting the yields or enantioselectivities. Resolved 3-hydroxy-4-trityloxybutanenitrile has been utilized for the synthesis of enantiomerically pure 5-tosyloxymethyl-1,3-oxazolidine-2-one, which is an important intermediate for the preparation of β-adrenergic blocking agents and oxazolidinone based antimicrobial agents. Enantiomerically pure (*R*)-3-hydroxy-4-trityloxybutanenitrile and (*S*)-5-tosyloxymethyl-1,3-oxazolidine-2-one have been utilized in the enantioconvergent synthesis of (*R*)-GABOB.

1. Introduction

The importance of β-hydroxy nitriles is well known in organic chemistry and they have been extensively studied and employed[1] in the preparation of various intermediates, particularly for the synthesis of naturally occurring as well as synthetic biologically important compounds,[2] while chiral β-hydroxy nitriles have enormous synthetic potential for the preparation of optically active β-hydroxy amides,[3] β-hydroxy acids,[4] β-hydroxy esters,[4c,5] diols[4c,6] and amino alcohols[7] as the cyano group can be readily transformed into different functional groups by simple procedures. 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 derived compounds has been used to control the generation of new stereocentres, thus offering a potential diastereoselective route to 1,3-diols[8] and 1,3-amino alcohols,[9] intermediates in a large number of natural products, antibiotics[10] and chiral auxiliaries.[11]

Enantiomerically pure 5-tosyloxymethyl-1,3-oxazolidine-2-one is an important intermediate for the synthesis of a wide variety of biologically important compounds, such as oxazolidinone based antimicrobials, β-adrenergic blocking agents and γ-amino-β-hydroxybutyric acid (GABOB). In view of the need for the development of practically efficient procedures for the preparation of these compounds in enantiomerically pure forms, we considered enantiomerically pure 5-hydroxymethyl-1,3-oxazolidine-2-one, as an important intermediate for the synthesis of these compounds. This oxazolidinone intermediate can be prepared from enantiomerically pure 3-hydroxy-4-trityloxybutanenitrile (Fig. 1). In conjunction with our previous studies towards the synthesis of biologically important compounds employing lipases,[12] we herein report an enzymatic resolution of 3-hydroxy-4-trityloxybutanenitrile and its application in the synthesis of optically active β-adrenergic blocking agents, oxazolidinone based antimicrobial agents

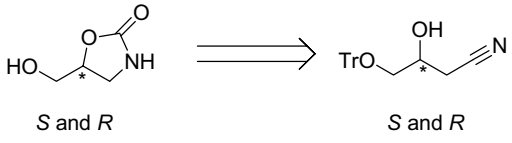

Figure 1.

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and (*R*)-GABOB via optically active 5-tosyloxymethyl-1,3-oxazolidine-2-one.

2. Results and discussion

2.1. Preparation of 3-hydroxy-4-trityloxybutanenitrile (β-hydroxy nitrile)

Herein, (±)-3-hydroxy-4-trityloxybutanenitrile **3** has been prepared. Glycidol was protected with trityl group by employing trityl chloride and pyridine. Trityl protected glycidol **2** was then subjected to nucleophilic ring opening with NaCN in aqueous alcohol to afford (±)-3-hydroxy-4-trityloxybutanenitrile **3** (see Scheme 1).

2.2. Lipase-mediated kinetic resolution of 3-hydroxy-4-trityloxybutanenitrile

The preparation of enantiomerically pure β-hydroxynitriles has been generally carried out by employing enzymatic approaches such as, the reduction of a carbonyl group of a ketonitrile by microbes[13] or by lipase-mediated enantioselective hydrolysis of their corresponding acetates.[14] However, in the present investigation and in continuation of the earlier efforts towards the preparation of enantiomerically pure β-hydroxynitriles,[12] lipase-mediated transesterification process has been applied and studied in detail (Scheme 2).

In the first series of experiments, the efficiency of different commercially available lipases to catalyze the transesterification of (±)-3-hydroxy-4-trityloxybutanenitrile **3** was investigated. As the solvent variation in many cases of lipase-catalyzed kinetic resolution can influence the enantiomeric or enantiotopic selectivity, as well as the reaction rates, the effect of the solvents on this substrate was also studied.

Enantiomeric excesses have been calculated from the enantiomeric ratios obtained by HPLC employing a Chiralcel OD column. Initially, the absolute configuration of the alcohol and acetate obtained after enzymatic resolution was arbitrarily assigned as (*S*)-alcohol and (*R*)-acetate and then later confirmed by comparison of their chiroptical and chromatographic properties with those of the compounds of known configuration. In this process, enantiomerically pure 3-hydroxy-4-trityloxybutanenitrile was converted to enantiomerically pure 3-hydroxy-4-tosyloxybutanenitrile. Comparison of the specific rotation of the derived 3-hydroxy-4-tosyloxybutanenitrile with that of the reported[15] hydroxynitrile established the *S* configuration of the alcohol (*S*)-**3** and the (*R*)-configuration of the acetate (*R*)-**4**.

In the first instance, a number of lipases were examined for the transesterification of (±)-3-hydroxy-4-trityloxybutanenitrile **3** in diisopropylether. This process gave poor conversions at room temperature. Therefore, this process was carried out at higher temperature and optimized between 45 and 47 °C. The results are illustrated in Table 1.

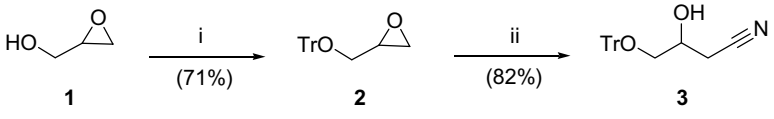
Table 1. Transesterification of 3-hydroxy-4-trityloxybutanenitrile with various lipases[a] in diisopropyl ether between 45 and 47 °C

Entry	Lipases[a]	Time (h)	Alcohol		Acetate		*E*
			Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)	
1	PS-C	60	45	>99	45	>99	1057
2	PS-D	232	49	88	42	>99	581
3	AK	238	71	34	21	>99	280
4	PS	232	74	26	18	>99	257
5	Lipozyme	232	74	27	17	>99	257
6	CRL	240	82	15	10	>99	230
7	CCL	242	86	10	8	>99	219
8	AYS	250	90	6	6	>99	212
9	P	232	90	5	5	>99	210
10	CAL-B	240	90	2	<5	>99	203

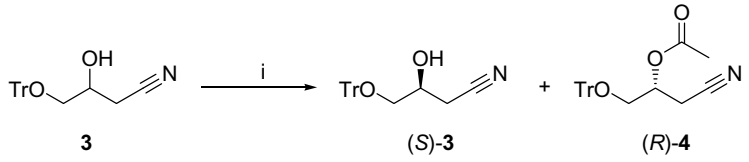
[a] *Pseudomonas cepacia* lipase immobilized on modified ceramic particles (PS-C), *P. cepacia* lipase immobilized on diatomite (PS-D), *Pseudomonas fluorescens* lipase (AK), *P. cepacia* (PS), *Candida rugosa* lipase (AYS) were obtained from Amano Pharmaceutical company, Japan; *Mucor meihei* (Lipozyme), *Candida Pseudomonas fluorescens* lipase immobilized in Sol–Gel-AK on sintered glass (P) from Fluka; *Candida antartica* lipase immobilized in Sol–Gel-AK on sintered glass (CAL B) (Fluka), *Candida rugosa* lipase (CRL) and *cyclindracea* lipase (CCL) from Sigma.

[b] Isolated yields.

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



Scheme 1. Reagents and conditions: (i) TrCl, pyridine, CH_2Cl_2; (ii) NaCN, EtOH–H_2O, rt.



Scheme 2. Reagents and conditions: (i) PS-C, vinyl acetate, diisopropyl ether, 45–47 °C.

Amongst all lipases examined, it was observed that the lipase from *Pseudomonas cepacia* (*Burkholderia cepacia*) provided better conversions. However, the lipase from *P. cepacia* immobilized on ceramic particles (PS-C) gave both the required (*S*)-alcohol and (*R*)-acetate in 45% yields with more than 99% enantiomeric excess (Table 1, entry 1). Moreover, this transesterification takes place in about 60 h in comparison to other lipases, which required longer durations.

Furthermore, the effect of solvents has also been investigated and it was observed that the transesterification in hydrophobic solvents such as diisopropyl ether, toluene and hexane not only provided good yields, but also high enantiomeric excess for both (*S*)-alcohol and (*R*)-acetate. However, the hydrophilic solvents such as THF or dioxane gave low yields, particularly the (*R*)-acetate and as a result the enantiomeric excess of (*S*)-alcohol was also greatly reduced. Therefore, diisopropylether appears to be the solvent of choice for this type of a transesterification with regard to yields and enantiomeric excess (Table 2).

In addition to the screening of lipases and effect of solvents, in this investigation the role of certain additives in the transesterification of 3-hydroxy-4-trityloxybutanenitrile **3** was also studied. It is known that the addition of crown ethers,[16a,b] amino alcohols[16c–e] and certain bases[16f] influence the enzymatic resolution process. In this context, the effect of DMAP, Et_3N, 2,6-lutidine and pyridine as additives in the transesterification of 3-hydroxy-4-trityloxybutanenitrile **3** was examined and it was observed that all these bases enhanced the rate of transesterification process as shown in Table 3. DMAP in particular, enhances the reaction rate considerably (Table 3, entry 1).

It is interesting to note that in all the experiments conducted,[24] there is no instance wherein the (*S*)-enantiomer (less reactive enantiomer) has been acetylated. This clearly suggests that the identity of the protecting group on the primary hydroxyl group is very important and the steric bulk of the trityl group may abrogate the binding of its (*S*)-enantiomer to the enzyme active site leading to very effective kinetic resolution process as seen from the very high enantiomeric excess values.

Table 3. Effect of base additives on the transesterification of 3-hydroxy-4-trityloxybutanenitrile by lipase PS-C between 45 and 47 °C

Entry	Bases	Time (h)	Alcohol		Acetate	
			Yield[a] (%)	ee[b] (%)	Yield[a] (%)	ee[b] (%)
1	DMAP	24	45	>99	45	>99
2	Et_3N	40	46	98	44	>99
3	2,6-Lutidine	40	49	89	42	>99
4	Pyridine	51	53	75	38	>99

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

2.3. Preparation of the intermediate for β-adrenergic blocking agents

β-Adrenergic blocking agents are well-established pharmaceutical products used in the treatment of cardiovascular disorder[17] or angina pectoris.[18] After three decades of their use, more than 50 different compounds possessing β-blocking activity have been brought to a stage of commercial development. A large number of these compounds are in clinical usage and all of them possess a stereogenic centre with a general structure of 3-aryloxypropanol amine (Fig. 2).

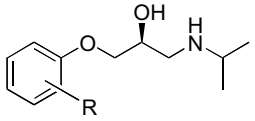


Figure 2.

Therefore, it was of interest to prepare an intermediate that could provide compounds with different aryl substitutions. In view of the above objective, an intermediate (*S*)-5-tosyloxymethyl-1,3-oxazolidine-2-one (*S*)-**8** has been designed and prepared wherein different β-blockers can be synthesized by simple displacement of the tosyloxy group with sodium salt of various phenols. In the present investigation,

Table 2. Effects of solvents on the transesterification of 3-hydroxy-4-trityloxybutanenitrile **3** by lipase PS-C between 45 and 47 °C

Entry	Solvent	Log *P*	Time (h)	Alcohol		Acetate	
				Yield[a] (%)	ee[b] (%)	Yield[a] (%)	ee[b] (%)
1	Diisopropyl ether	1.9	60	45	>99	45	>99
2	Hexane	3.5	64	50	83	42	>99
3	Toluene	2.5	72	54	73	38	>99
4	Acetonitrile	−0.33	232	75	24	17	>99
5	Tetrahydrofuran	0.49	232	80	15	12	>99
6	Acetone	−0.23	232	86	11	08	>99
7	Dioxane	−1.1	232	90	<5	<5	>99
8	Chloroform	2.0	232	93	—	—	—

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

(*S*)-3-hydroxy-4-trityloxybutanenitrile (*S*)-**3** was effectively employed for the preparation of this oxazolidinone intermediate.

In this process, the nitrile functionality of the enantiomerically pure (*S*)-3-hydroxy-4-trityloxybutanenitrile (*S*)-**3** was hydrolyzed to provide the corresponding amide (*S*)-**5** employing H_2O_2 in aqueous ammonia. A Hoffmann-like rearrangement of the amide using $Pb(OAc)_4$ resulted in the formation of (*S*)-5-trityloxymethyl-2-oxazolidinone (*S*)-**6**. The trityloxy group of this oxazolidinone was transformed to its tosyloxy group by using PTSA and TsCl to obtain the required (*S*)-5-tosyloxymethyl-1,3-oxazolidine-2-one (*S*)-**8** as shown in Scheme 3. This common intermediate (*S*)-**8** has been utilized in a straightforward manner and is well documented in the literature[19] in the preparation of β-adrenergic blocking agents.

2.4. Preparation of the intermediate for oxazolidinone based antimicrobials

In another application, some common intermediates for a variety of antimicrobials possessing an oxazolidinone ring structure[20] have been designed and developed starting from (*R*)-**4**, wherein the synthesis of a wide divergent 3-aryl substituted oxazolidinones from a common intermediate is feasible. This process proceeds with high efficiency from commercially available glycidol and is represented in Scheme 4.

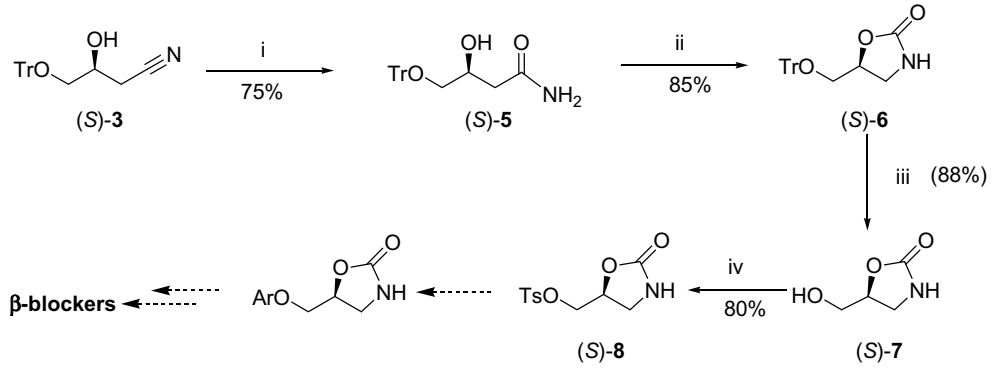
(*R*)-5-Tosyloxymethyl-1,3-oxazolidine-2-one (*R*)-**8** was prepared as shown in Scheme 4, which was then transformed to azidooxazolidinone (*R*)-**9** by displacement of the tosyloxy group with NaN_3. The intermediates (*R*)-**7** and (*R*)-**9** can be utilized for the preparation of various antimicrobial agents containing oxazolidinone ring system by simple arylation of the oxazolidinone ring.[21]

2.5. Enantioconvergent synthesis of (*R*)-GABOB

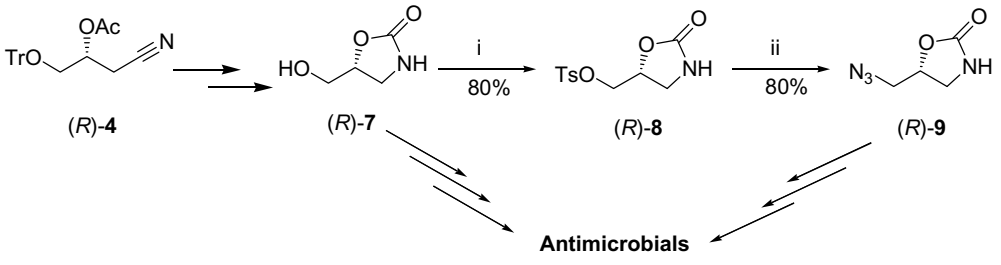
In yet another application, the enantiomerically pure (*S*)-3-hydroxy-4-trityloxybutanenitrile (*S*)-**3** and (*R*)-3-acetyloxy-4-trityloxybutanenitrile (*R*)-**4**, obtained by enzymatic resolution have been employed in an enantioconvergent synthesis of (*R*)-GABOB by functional group switching, as illustrated in Scheme 5.

The activated alcohol group (tosyloxygroup) of (*S*)-5-tosyloxymethyl-1,3-oxazolidine-2-one (*S*)-**8** was displaced by a cyanide group using NaCN in aqueous-methanol system leading to a functional group switching. Hydrolysis of the nitrile group of (*R*)-**10** to carboxylic acid and cleavage of the oxazolidinone ring has been achieved by using concd HCl at 80–90 °C to afford (*R*)-GABOB.[22]

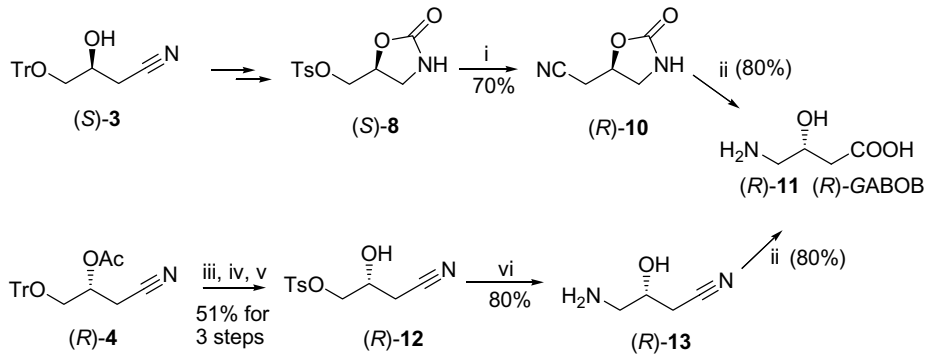
In an alternative approach, (*R*)-3-acetyloxy-4-trityloxybutanenitrile (*R*)-**4** has been treated with K_2CO_3 in methanol and then by PTSA in methanol to afford 3,4-dihydroxybutanenitrile, which without purification has been transformed to (*R*)-3-hydroxy-4-tosyloxybutanenitrile (*R*)-**12**. This upon treating with aqueous ammonia in refluxing ethanol and then treating with concd HCl at 80 °C afforded the desired (*R*)-GABOB (*R*)-**11** in high yield with excellent enantiomeric excess. The above two processes in combination is an illustrative example of an enantioconvergent synthesis of (*R*)-GABOB.



Scheme 3. Reagents and conditions: (i) H_2O_2, aq NH_3, rt; (ii) $Pb(OAc)_4$, pyridine, rt; (iii) PTSA, MeOH, rt; (iv) TsCl, Et_3N, CH_2Cl_2.



Scheme 4. Reagents and conditions: (i) TsCl, Et_3N, CH_2Cl_2; (ii) NaN_3, DMF, 60–70 °C.



Scheme 5. Reagents and conditions: (i) NaCN, MeOH–H_2O, reflux; (ii) concd HCl, 80 °C; (iii) K_2CO_3, MeOH; (iv) PTSA, MeOH, rt; (v) TsCl, Et_3N, Bu_2SnO, CH_2Cl_2; (vi) aq NH_3, EtOH, reflux.

3. Conclusion

An efficient method for the preparation of (±)-3-hydroxy-4-trityloxybutanenitrile and its successful enzymatic resolution have been described. This lipase-mediated transesterification process has been optimized with respect to different lipases, solvents and additives. Furthermore, enantiomerically pure (*S*)-3-hydroxy-4-trityloxybutanenitrile and (*R*)-3-acetyloxy-4-trityloxybutanenitrile have been employed in the preparation of common intermediates for β-adrenergic blocking agents and antimicrobials possessing oxazolidinone ring system. Furthermore, the present investigation also describes an enantioconvergent synthesis of (*R*)-GABOB.

4. Experimental

4.1. General

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 unless specified all solvents and reagents were of reagent grade and used without further purification. 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. Enantiomeric excess has been determined by chiral HPLC (chiral column OD; Diacel).

4.1.1. 3-Trityloxy-1,2-epoxypropane 2. To a stirred solution of glycidol (5.00 g, 67.57 mmol) in 150 mL of dry CH_2Cl_2 under N_2 was added trityl chloride (18.82 g, 67.57 mmol) and pyridine (5.87 g, 74.33 mmol) at room temperature, and the progress of the reaction was monitored by TLC. After completion of the reaction (overnight), 100 mL of 1 M HCl was added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3×125 mL) and the combined organic layers washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give a residue of crude **2**. Purification of the crude epoxide was accomplished by column chromatography employing EtOAc–hexane (10:90) as eluent to afford **2** in 71% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 3.26 (dd, 1H, $J_1 = 3$ Hz, $J_2 = 9.4$ Hz), 3.29 (dd, 1H, $J_1 = 4.9$ Hz, $J_2 = 9.4$ Hz), 3.60 (dd, 1H, $J_1 = 6.0$ Hz, $J_2 = 10.9$ Hz), 3.68 (dd, 1H, $J_1 = 5.4$ Hz, $J_2 = 10.0$ Hz), 3.83–3.92 (m, 1H), 7.18–7.38 (m, 9H), 7.38–7.42 (m, 6H); mass (EI) 259, 243, 165, 77.

4.1.2. (±)-3-Hydroxy-4-triphenylmethoxybutanenitrile 3. To a stirred solution of **2** (15.80 g, 50.00 mmol) in 50 mL of ethanol were added 150 mL of H_2O and NaCN (2.94 g, 60.00 mmol). The resultant reaction mixture was stirred overnight at room temperature and on completion of the reaction (TLC), the reaction mixture was concentrated to about 50% of the total volume under reduced pressure. The residue was extracted with ethyl acetate (3×125 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 3-hydroxy-4-triphenylmethoxybutanenitrile in 82% yield. IR (neat) 3506, 3043, 2996, 2918, 2855, 2275, 1106, 1051 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.45–2.56 (m, 2H), 3.27 (d, 2H, $J = 5.2$ Hz), 3.92–4.02 (m, 1H), 7.23–7.41 (m, 15H); mass (EI) 259, 243, 165, 105, 77.

4.1.3. (±)-3-Acetyloxy-4-triphenylmethoxybutanenitrile 14. To (±)-3-hydroxy-4-triphenylmethoxybutanenitrile **3** (1.03 g, 3.00 mmol) under N_2 were added acetic anhydride (1.53 g,

15.00 mmol) and pyridine (0.26 g, 3.30 mmol), and the resultant mixture stirred overnight at room temperature. 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 purified by column chromatography employing EtOAc–hexane (15:85) as eluent to afford the required 3-acetyloxy-4-triphenylmethoxybutanenitrile in nearly quantitative yield. IR (KBr) 3466, 3066, 3019, 2925, 2863, 2235, 1741, 1223, 1004 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.76 (d, 2H, $J = 5.69$), 3.92–4.02 (m, 1H), 7.23–7.41 (m, 15H); mass (EI) 259, 243, 165, 105, 77.

4.1.4. Procedure for resolution of 3-hydroxy-4-triphenylmethoxybutanenitrile 3. To a solution of 3-hydroxy-4-trityloxybutanenitrile **3** (1.50 g) in diisopropyl ether (160 mL) was successively added lipase (1.50 g) and vinyl acetate (6 equiv). The reaction mixture was shaken at room temperature 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 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 (*R*)-**4** followed by (*S*)-alcohol (*S*)-**3**.

4.1.5. (*S*)-3-Hydroxy-4-triphenylmethoxybutanenitrile (*S*)-3. Mp 144–146 °C; $[\alpha]_D^{29} = -7.6$ (*c* 1.5, $CHCl_3$); IR, NMR and mass spectral data are identical to that of **3**.

4.1.6. (*R*)-3-Acetyloxy-4-triphenylmethoxybutanenitrile (*R*)-4. Mp 155–158 °C; $[\alpha]_D^{29} = +24.4$ (*c* 1.35, $CHCl_3$); IR, NMR and mass spectral data are identical to that of **14**.

4.1.7. (*S*)-3-Hydroxy-4-triphenylmethoxy butanamide (*S*)-5. To a stirred solution of (*S*)-3-hydroxy-4-triphenylmethoxybutanenitrile (5.15 g, 15.01 mmol) in 15 mL of ethanol at room temperature was added aqueous NH_3 (50 mL), after which H_2O_2 (34 mL, 300.00 mmol) was added 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 progress of the reaction monitored by TLC. On completion of the reaction (overnight) as indicated by the TLC, the reaction volume was concentrated to about 50% of the original volume under reduced pressure, and the resultant mixture extracted with CH_2Cl_2 (3×75 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated to give a residue, which was purified by column chromatography employing EtOAc–hexane (80:20) as eluent to afford (*S*)-3-hydroxy-4-triphenylmethoxy butanamide (*S*)-5 in 75% yield. Mp 96–100 °C; $[\alpha]_D^{27} = -18.1$ (*c* 1.0, MeOH); lit.[23] $[\alpha]_D^{25} = -53.5$ (*c* 0.5, MeOH); IR (KBr) 3467, 3349, 3012, 2980, 2918, 2839, 1671, 1098, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (d, 2H, $J = 6.5$ Hz), 3.13–3.16 (m, 2H), 3.28 (S, 1H), 4.11–4.15 (m, 1H), 5.44 (br, s, 1H), 7.18–7.38 (m, 9H), 7.39–7.42 (m, 6H); mass (EI) 361, 259, 243, 165, 77.

4.1.8. (*R*)-3-Hydroxy-4-triphenylmethoxy butanamide (*R*)-5. (*R*)-3-Hydroxy-4-triphenylmethoxy butanamide was prepared from (*R*)-3-acetyloxy-4-triphenylmethoxy butanenitrile (3.85 g, 10.00 mmol), aqueous NH_3 (60 mL) and H_2O_2 (45 mL, 400.00 mmol) employing a similar procedure as that of the preparation of (*S*)-3-hydroxy-4-triphenylmethoxy butanamide. Mp 98–100 °C; $[\alpha]_D^{27} = +18.9$ (*c* 0.9, MeOH); IR, NMR and mass spectral data are identical to that of (*S*)-**5**.

4.1.9. (*S*)-5-Triphenylmethoxymethyl-1,3-oxazolidine-2-one (*S*)-6. To a solution of (*S*)-3-hydroxy-4-triphenylmethoxy butanamide (*S*)-**5** (4.33 g, 12.00 mmol) in pyridine (25 mL) was added $Pb(OAc)_4$ (7.45 g, 16.80 mmol) and the resultant reaction mixture stirred under N_2 at room temperature for 1 h. On completion of the reaction as indicated by the TLC, the reaction mixture was taken up in CH_2Cl_2 (100 mL) and then treated with 1 M 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 was separated while the aqueous layer was 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*)-**6**, which was purified by column chromatography employing EtOAc–hexane (50:50) as eluent to afford pure 5-triphenylmethoxymethyl-1,3-oxazolidine-2-one in 85% yield. $[\alpha]_D^{26} = +25.0$ (*c* 1.0, MeOH); lit.[23] $[\alpha]_D^{25} = +35.5$ (*c* 1.0, MeOH); IR (KBr) 3247, 2933, 2886, 2824, 1741, 1012, 949 cm^{-1}; ^1H NMR (300 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.

4.1.10. (*R*)-5-Triphenylmethoxymethyl-1,3-oxazolidine-2-one (*R*)-6. (*R*)-5-Triphenylmethoxymethyl-1,3-oxazolidine-2-one was prepared from (*R*)-**5** (3.61 g, 10.00 mmol), pyridine (25 mL) and $Pb(OAc)_4$ (6.21 g, 14.00 mmol) employing a similar procedure to that of the preparation of (*S*)-**6**. $[\alpha]_D^{26} = -25.5$ (*c* 1.0, MeOH); IR, NMR and mass spectral data are identical to that of (*S*)-**6**.

4.1.11. (*S*)-5-Hydroxymethyl-1,3-oxazolidine-2-one (*S*)-7. To a stirred solution of (*S*)-5-triphenylmethoxymethyl-1,3-oxazolidine-2-one (7.18 g, 20.00 mmol) in 60 mL of methanol at room temperature was added *p*-toluenesulfonic acid (7.16 g, 40.00 mmol) and stirring was continued overnight. After completion of the reaction (TLC), the solvent in the reaction mixture was evaporated and the residue purified by column chromatography employing MeOH–EtOAc (5:95) as eluent to afford pure 5-hydroxymethyl-1,3-oxazolidine-2-one in 88% yield. Mp 70–73 °C; $[\alpha]_D^{27} = +32.8$ (*c* 0.6, EtOH); ^1H NMR (200 MHz, DMSO-d_6) δ 3.35–3.75 (m, 4H), 4.50–4.64 (m, 1H), 4.85 (br s, 1H).

4.1.12. (*R*)-5-Hydroxymethyl-1,3-oxazolidine-2-one (*R*)-7. (*R*)-5-Hydroxymethyl-1,3-oxazolidine-2-one was prepared in 85% yield analogous to the preparation of (*S*)-**7** employing (*R*)-5-triphenylmethoxymethyl-1,3-oxazolidine-

2-one (2.87 g, 8.00 mmol) and *p*-toluenesulfonic acid (3.04 g, 16.00 mmol). Mp 70–73 °C; $[\alpha]_D^{27} = -33.3$ (*c* 0.45, EtOH); lit.[21c] $[\alpha]_D^{25} = -29.6$ (*c* 2.7, EtOH); NMR spectral data is identical to that of (*S*)-**7**.

4.1.13. (*S*)-5-(4-Methylphenylsulfonyloxymethyl)-1,3-oxazolidine-2-one (*S*)-8. *p*-Toluenesulfonyl chloride (2.74 g, 14.36 mmol) and Et_3N (1.45 g, 14.36 mmol) were added to 5-hydroxymethyl-1,3-oxazolidine-2-one (1.40 g, 11.97 mmol) dispersed in 20 mL of CH_2Cl_2 and stirred overnight at room temperature under N_2. After completion of the reaction (TLC), the reaction mixture was evaporated and the residue obtained, was purified by column chromatography employing EtOAc–hexane (70:30) as eluent to afford 5-(4-methylphenylsulfonyloxymethyl)-1,3-oxazolidine-2-one in 80% yield. Mp 96–99 °C; $[\alpha]_D^{27} = +45.4$ (*c* 1.25, $CHCl_3$); IR (KBr) 3302, 2980, 2925, 2871, 1757, 1694, 1357, 1184, 1090, 996, 965 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.40–3.50 (m, 1H), 3.64–3.74 (m, 1H), 4.14 (d, 2H, $J = 4.4$ Hz), 4.71–4.82 (m, 1H), 7.35 (d, 2H, $J = 8.2$ Hz), 7.78 (d, 2H, $J = 8.2$ Hz); mass (EI) 271, 207, 173, 155, 139, 91.

4.1.14. (*R*)-5-(4-Methylphenylsulfonyloxymethyl)-1,3-oxazolidine-2-one (*R*)-8. (*R*)-5-(4-Methylphenylsulfonyloxymethyl)-1,3-oxazolidine-2-one was prepared from *p*-toluenesulfonyl chloride (1.17 g, 6.14 mmol), Et_3N (0.62 g, 6.14 mmol) and 5-hydroxymethyl-1,3-oxazolidine-2-one (0.60 g, 5.13 mmol), employing a similar approach to the preparation of (*S*)-5-(4-methylphenylsulfonyloxymethyl)-1,3-oxazolidine-2-one. Mp 96–99 °C; $[\alpha]_D^{27} = -44.4$ (*c* 1.25, $CHCl_3$); $[\alpha]_D^{27} = -38.75$ (*c* 1.2, EtOH); IR, NMR and mass spectral data are identical to that of (*S*)-**8**.

4.1.15. (*R*)-5-Azidomethyl-1,3-oxazolidine-2-one (*R*)-9. To a stirred solution of (*R*)-5-(4-methylphenylsulfonyloxymethyl)-1,3-oxazolidine-2-one (2.17 g, 8.00 mmol) in 20 mL of DMF equipped with a calcium chloride guard tube was added NaN_3 (3.12 g, 48.00 mmol) at room temperature and the resultant mixture heated to 60–70 °C. The progress of the reaction was monitored by TLC, and on completion of the reaction (10 h), the reaction mixture was diluted with 40 mL of ice-cold water and then extracted with ethyl acetate (4 × 40 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to leave a residue, which on purification by column chromatography employing EtOAc–hexane (50:50) as eluent afforded 5-azidomethyl-1,3-oxazolidine-2-one in 80% yield. $[\alpha]_D^{29} = -62.2$ (*c* 1.12, $CHCl_3$); IR (neat) 3302, 2941, 2886, 2839, 2102, 1749, 1231, 1074, 957 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.42 (dd, 1H, $J_1 = 6.2$ Hz, $J_2 = 8.8$ Hz), 3.52–3.59 (m, 2H), 3.63–3.88 (m, 1H), 4.66–4.79 (m, 1H); mass (EI) 86, 87.

4.1.16. (*R*)-5-Cyanomethyl-1,3-oxazolidine-2-one (*R*)-10. To a stirred solution of (*S*)-5-(4-methylphenylsulfonyloxymethyl)-1,3-oxazolidine-2-one (0.54 g, 1.99 mmol) in MeOH (15 mL)–water (3 mL) was added NaCN (0.39 g, 8.00 mmol) at room temperature and then heated at reflux for 4 h. After completion of the reaction, the reaction mixture was completely evaporated and the residue purified by column chromatography employing EtOAc–hexane (70:30) as eluent to afford pure 5-cyanomethyl-1,3-oxazolidine-2-one in 70% yield. $[\alpha]_D^{26} = +4.5$ (*c* 1.0, MeOH); IR (neat) 3349, 2918, 2839, 2243, 1710, 1255, 1051 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 2.57 (d, 2H, $J = 6.6$ Hz), 3.20–3.55 (m, 2H), 4.00–4.18 (m, 1H).

4.1.17. (*R*)-3-Hydroxy-4-(4-methylphenylsulfonyloxy)butanenitrile (*R*)-12. To a solution of (*R*)-3-acetyloxy-4-triphenylmethoxybutanenitrile (*R*)-**5** (3.85 g, 10.00 mmol) in methanol (40 mL) was added K_2CO_3 (6.90 g, 50.00 mmol) and stirred at room temperature for 2 h. After completion of the reaction, K_2CO_3 was filtered and the residue washed with 20 mL of methanol. To the combined filtrates was added *p*-toluenesulfonic acid (7.61 g, 40.00 mmol) and the reaction stirred overnight at room temperature. After completion of the reaction, the solvent in the reaction mixture was evaporated and the residue purified by column chromatography to obtain 3,4-dihydroxybutanenitrile. To this, were added dry CH_2Cl_2 (100 mL), dibutyltinoxide (0.50 g, 2.00 mmol) and *p*-toluenesulfonyl chloride (2.29 g, 12.00 mmol) and stirred for about 1 h. The reaction mixture was treated with water (100 mL), then the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (125 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give a residue, which was purified by column chromatography employing EtOAc–hexane (30:70) as eluent to afford (*R*)-**12** in 51% yield. $[\alpha]_D^{26} = +13.5$ (*c* 1.45, EtOH); lit.[15] $[\alpha]_D^{25} = -14.2$ (*c* 1.72, EtOH) for (*S*)-isomer; IR (neat) 3474, 3059, 2933, 2902, 2220, 1584, 1349, 1169, 1098, 996 cm^{-1}; ^1H 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.

4.1.18. (*R*)-4-Amino-3-hydroxybutanoic acid (*R*)-11. A mixture of (*R*)-5-cyanomethyl-1,3-oxazolidine-2-one (0.15 g, 1.2 mmol) and concd HCl (15 mL) was stirred and heated to 80–90 °C for 6 h. After completion of the reaction, as indicated by the TLC the solvent in the reaction mixture was evaporated and the residue purified by an ion exchange column chromatography (Amberlite IR 120 H^+). The column was first eluted with water until the fractions collected were neutral and later with 10% NH_4OH. The solvent in the basic fractions was evaporated and redissolved in minimum amount of H_2O and triturated with EtOH to obtain (*R*)-GABOB as a white solid after evaporation of the solvent. Mp 211–213 °C; $[\alpha]_D^{28} = -20.7$ (*c* 1.0, H_2O); ^1H NMR (200 MHz, D_2O) δ 2.43 (d, 2H, $J = 5.9$ Hz), 2.95 (dd, 1H, $J_1 = 9.66$ Hz, $J_2 = 13.38$ Hz), 3.18 (dd, 1H, $J_1 = 3.72$ Hz, $J_2 = 13.38$ Hz), 4.10–4.30 (m, 1H); ^{13}C NMR (50 MHz, D_2O) δ 42.3, 44.0, 65.5, 178.5; mass (EI) 118 ($M^+ - H$), 74, 60, 43.

4.1.19. (*R*)-4-Amino-3-hydroxybutanoic acid (*R*)-11. To a solution of (*R*)-3-hydroxy-4-tosyloxybutanenitrile (4.07 g, 13.70 mmol) in ethanol (40 mL), was added excess aq NH_3, refluxed overnight and the solvent in the reaction mixture was evaporated. To the resulting residue was added concd HCl and heated to 80 °C for 6 h. After evaporation of the solvent, the residue containing crude

(*R*)-GABOB was purified over an ion exchange column chromatography (Amberlite IR-120 H^+). The column was first eluted with water until the fractions were neutral and later with 10% NH_4OH. Evaporation of the basic fractions gave a thick oil, which was dissolved in minimum amount of water and absolute ethanol was added to provide (*R*)-GABOB as a white solid after evaporation of the solvent (80% yield). Mp 211–213 °C; $[\alpha]_D^{28} = -20.7$ (*c* 1.0, H_2O); ^1H NMR (200 MHz, D_2O) δ 2.43 (d, 2H, $J = 5.9$ Hz), 2.95 (dd, 1H, $J_1 = 9.66$ Hz, $J_2 = 13.38$ Hz), 3.18 (dd, 1H, $J_1 = 3.72$ Hz, $J_2 = 13.38$ Hz), 4.10–4.30 (m, 1H); ^{13}C NMR (50 MHz, D_2O) δ 42.3, 44.0, 65.5, 178.5; mass (EI) 118 (M^+−H), 74, 60, 43.

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