Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 405–410

TETRAHEDRON: *ASYMMETRY*

A facile preparation of (±)-β-hydroxy nitriles and their enzymatic resolution with lipases

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Received 18 December 2000; accepted 5 February 2001

Abstract—A simple and efficient method for the preparation of racemic 4-aryloxy-3-hydroxybutanenitriles is described. Lipase mediated kinetic resolution in organic media was then utilised to effect enantioseparation. Lipases from different sources were screened in the resolution reaction using a number of organic solvents. Enantiomeric excesses of up to 99% were obtained by employing lipase from *Pseudomonas cepacia* in di-*iso*-propyl ether medium.

1. Introduction

β-Hydroxy nitriles have importance both as reagents and as technical products in organic chemistry and have been extensively investigated and employed in synthetic chemistry for the preparation of intermediates of many naturally occurring bioactive compounds.[1,2] Chiral non-racemic β-hydroxy nitriles are useful chiral building blocks in asymmetric synthesis, as the cyano group is a precursor of both amino and carbonyl groups. Furthermore, the stereogenicity at the hydroxyl group can be used to control the generation of new stereocentres, thus offering potential routes to homochiral 1,3-diols[3] and 1,3-amino alcohols.[4] The synthesis of homochiral 1,3-amino alcohols still remains an attractive target because of their versatility as synthetic intermediates for a large number of natural products, antibiotics[5] and chiral auxiliaries.[6]

There are few reports on the preparation of homochiral β-hydroxy nitriles and in continuation of our earlier efforts towards the synthesis of biologically important compounds employing enzymatic methodologies,[7] we herein report a simple practical preparation of β-hydroxy nitriles and their resolution employing lipases.

Earlier enzymatic methods described for the preparation of homochiral β-hydroxy nitriles are mainly based on lipase catalysed hydrolysis reactions.[8] An enhancement in the enantioselectivity of the reaction was seen when the substrate was suitably modified, particularly when sulphur functionalities were incorporated.[8] However, the mechanism of this enhancement is unclear. The incubation of α-cyanoketones in the presence of baker's yeast under typical enzymatic reaction conditions produced mainly the reduced alkylated product;[9] more recently, the yeast mediated reduction[10] of α-cyanoketones at 4°C over 7 days afforded (*S*)-3-hydroxy nitrile in 59% yield.

2. Results and discussion

2.1. Synthesis of β-hydroxy nitriles

The method reported herein describes the stereoselective acylation of 4-aryloxy-3-hydroxybutanenitrile with lipases by a transesterification process. These nitriles have been described in the literature[11] as precursors for compounds having different pharmaceutical properties, namely cardiovascular, anti-arrhythmic and sympatholytic. The (±)-β-hydroxy nitriles required as substrates for the enzymatic resolution were obtained by the facile ring opening of oxiranes, a direct and simple method for β-hydroxy nitriles.

In the literature, ring opening of epoxides with cyanide as a nucleophile has been carried out by employing volatile and toxic HCN,[12] non-volatile alkali cyanides in the presence of perchlorate salts[13] or $Yb(CN)_3$.[13,14] Some methods employ acetone cyanohydrin in the presence of a base[15] or lanthanide alkoxides,[16] alkyl aluminium cyanides[17] and $Ce(OTf)_4$.[18] In most literature

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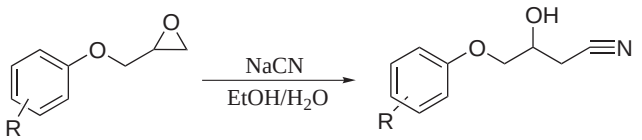
0957-4166/01/$ - see front matter
PII: S0957-4166(01)00058-1



Scheme 1.

methods the reaction conditions are usually severe, some reagents are commercially unavailable and have to be prepared from alkali cyanides, whilst the use of alkyl aluminium cyanides presents a difficulty in large scale reactions. Trimethylsilylcyanide (TMSCN)[14,17b,19] has been used in the preparation of β-hydroxy nitriles, but a problem with this is that the isonitrile can be formed[14,19d] as the main product. To overcome these limitations we developed a new approach of oxirane ring opening with sodium cyanide in aqueous–alcoholic conditions to afford β-hydroxy nitriles (Scheme 1) in good to excellent yields, as shown in Table 1.

Table 1. Ring opening of racemic epoxides with sodium cyanide

Substrate **1**	R	Time (h)	Yield[a] (%)
a	H	12	80
b	2-CH_3	12	86
c	4-CH_3	12	87
d	4-Cl	10	90
e	4-Br	10	82
f	2,3-(CH=CH–CH=CH)–	15	70
g	3,4-(CH=CH–CH=CH)–	18	55

[a] Isolated yields.

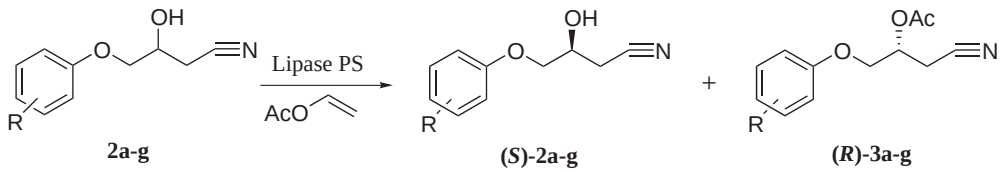
2.2. Enzymatic resolution of β-hydroxy nitriles

The enantioselective resolution of racemic β-hydroxy nitriles has been carried out by employing different lipases such as *Pseudomonas cepacia* (Amano), *Candida rugosa* (Sigma), *Candida cylindracea* (Sigma), Lipozyme (*Mucor meihei*, Novo Nordisk) and porcine pancreas (Sigma) in a number of organic solvents including di-*iso*-propyl ether, tetrahydrofuran, *tert*-butyl methyl ether and toluene. It was observed that lipase from *P. cepacia* produced good conversions in di-*iso*-propyl ether, as shown in Scheme 2.

E.e.s were calculated from the enantiomeric ratios measured using a Chiralcel OD column. The absolute configuration of the enantiomerically pure (*S*)-4-aryloxy-3-hydroxybutanenitriles was assigned by preparing standards from enantiomerically pure 1-chloro-3-aryloxy-2-propanol using lipase from *Pseudomonas* sp. as described in the literature.[20] Comparison of the specific rotation established the (*S*)-configuration of the alcohol and the (*R*)-configuration of the acetate. The configurations were further confirmed by comparison of the chiral HPLC data. In this study, all acetates were obtained in high enantiomeric purities. The substrates with *para*-substitution (**2c**–**2e**), as given in Table 2, show comparatively higher conversion rates with better e.e. In the case of **2b**, **2f** and **2g** as the reaction proceeds slowly, efforts have been made to shorten the reaction time by increasing the temperature to 40°C, which improved the conversion rates.

3. Conclusion

In summary, we have demonstrated an efficient and practical preparation of β-hydroxy nitriles and their



Scheme 2.

Table 2. Kinetic resolution of 4-aryloxy-3-hydroxybutanenitriles

Substrate **2**	R	Time (h)	Alcohol		Acetate	
			E.e.[a] (%)	Yield[b] (%)	E.e.[a] (%)	Yield[b] (%)
a	H	98	82.7	52	>99.0	42
b[c]	2-CH_3	102	71.0	51	91.1	42
c	4-CH_3	50	91.8	46	>99.0	45
d	4-Cl	46	92.2	42	92.1	45
e	4-Br	44	93.8	41	88.7	55
f[c]	2,3-(CH=CH–CH=CH)–	116	35.0	60	>98.0	36
g[c]	3,4-(CH=CH–CH=CH)–	105	44.0	62	>99.0	34

[a] Determined by chiral HPLC (Chiralcel OD column; Daicel) employing hexane–isopropanol (85:15) as mobile phase at 0.5 mL/min and monitored by UV (254 nm).
[b] Isolated yields.
[c] Reaction carried out at 40°C.

enzymatic resolution using lipase from *P. cepacia* (PS). This method affords biologically important 4-aryloxy-3-hydroxybutanenitriles in good yields and high enantiomeric excesses.

4. Experimental

4.1. General

Column chromatography was carried out using 100–200 mesh silica gel (Acme India Ltd.). TLC analyses were performed on Merck 60 PF254 silica gel plates. Melting points were taken on electrothermal melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on Perkin–Elmer model 683 or 1310 spectrometers. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on CEC-21-100B Finnigan Mat 1210 or Micromass 7070 spectrometers. Optical rotations were measured on a Jasco Dip 360 digital polarimeter. HPLC was performed on a Chiralcel OD column (Daicel) and monitored by UV (254 nm).

4.2. General procedure for oxirane ring opening

To a solution of epoxide (20 mmol) in ethanol (20 mL) was added water (100 mL). After stirring for 5 min, NaCN (28 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 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-phenoxybutanenitrile 2a. 3-Phenoxy-1,2-epoxypropane **1a** was stirred with NaCN for 12 h, as described in the above general procedure for the ring opening of oxiranes, to afford **2a** in 80% yield. IR (film): 3437, 3066, 2930, 2256, 1228, 1047 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.14–7.29 (m, 2H), 6.77–7.00 (m, 3H), 4.20–4.31 (m, 1H), 3.96 (d, $J=5.12$ Hz, 2H), 2.73 (dd, $J_1=5.12$ Hz, $J_2=17.95$ Hz, 1H), 2.60 (dd, $J_1=5.12$ Hz, $J_2=11.50$ Hz, 1H); MS: m/z 177, 119, 107, 94, 77.

4.2.2. 3-Hydroxy-4-(2-methylphenoxy)butanenitrile 2b. 3-(2-Methylphenoxy)-1,2-epoxypropane **1b** was stirred with NaCN for 12 h, as described in the above general procedure for the ring opening of oxiranes, to afford **2b** in 86% yield. IR (film): 3477, 3028, 2931, 2255, 1193, 1044 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.06–7.19 (m, 2H), 6.73–6.94 (m, 2H), 4.23–4.40 (m, 1H), 3.93–4.10 (m, 2H), 3.16 (d, $J=4.76$ Hz, 2H), 2.60–2.84 (m, 2H), 2.22 (s, 3H); MS: m/z 191, 139, 108, 91, 77.

4.2.3. 3-Hydroxy-4-(4-methylphenoxy)butanenitrile 2c. 3-(4-Methylphenoxy)-1,2-epoxypropane **1c** when stirred with NaCN for 12 h, as described in the above general procedure for the ring opening of oxiranes, resulted in a white crystalline solid of **2c**. Yield 87%; mp 57–59°C; IR (KBr): 3401, 3023, 2938, 2274, 1240, 1102, 1052 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.08 (d, $J=7.62$ Hz, 2H), 6.79 (d, $J=7.62$ Hz, 2H), 4.21–4.34 (m, 1H), 4.01 (d, $J=3.57$ Hz, 2H), 2.74 (dd, $J_1=3.81$ Hz, $J_2=11.90$ Hz, 1H), 2.64 (dd, $J_1=4.76$ Hz, $J_2=15.47$ Hz, 1H), 2.29 (s, 3H); MS: m/z 191, 121, 108, 91.

4.2.4. 4-(4-Chlorophenoxy)-3-hydroxybutanenitrile 2d. 3-(4-Chlorophenoxy)-1,2-epoxypropane **1d** when stirred with NaCN for 10 h, as described in the above general procedure for the ring opening of oxiranes, resulted in a white crystalline solid of **2d**. Yield 90%; mp 65–68°C; IR (KBr): 3438, 3098, 2879, 2255, 1242, 1092, 1043 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.24 (d, $J=6.90$ Hz, 2H), 6.84 (d, $J=6.90$ Hz, 2H), 4.24–4.34 (m, 1H), 3.99 (d, $J=4.60$ Hz, 2H), 3.19 (br. s, 1H), 2.79 (dd, $J_1=3.45$ Hz, $J_2=11.49$ Hz, 1H), 2.63 (dd, $J_1=4.60$ Hz, $J_2=16.09$ Hz, 1H); MS: m/z 211, 141, 128, 94.

4.2.5. 4-(4-Bromophenoxy)-3-hydroxybutanenitrile 2e. 3-(4-Bromophenoxy)-1,2-epoxypropane **1e** when stirred with NaCN for 10 h, as described in the above general procedure for the ring opening of oxiranes, resulted in a white crystalline solid of **2e**. Yield 82%; mp 79–81°C; IR (KBr): 3496, 3092, 2926, 2252, 1250, 1107 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35 (d, $J=8.43$ Hz, 2H), 6.76 (d, $J=8.43$ Hz, 2H), 4.20–4.33 (m, 1H), 3.99 (d, $J=4.82$ Hz, 2H), 2.74 (dd, $J_1=4.82$ Hz, $J_2=14.46$ Hz, 1H), 2.61 (dd, $J_1=6.02$ Hz, $J_2=9.64$ Hz, 1H); MS: m/z 255, 257, 187, 185, 174, 172.

4.2.6. 3-Hydroxy-4-(1-naphthyloxy)butanenitrile 2f. 3-(1-Naphthyloxy)-1,2-epoxypropane **1f** when stirred with NaCN for 15 h, as described in the above general procedure for the ring opening of oxiranes, resulted in a white crystalline solid of **2f**. Yield 70%; mp 89–92°C; IR (KBr): 3503, 3050, 2929, 2244, 1272, 1095 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.10–8.20 (m, 1H), 7.76–7.81 (m, 1H), 7.25–7.51 (m, 4H), 6.8 (d, $J=5.13$ Hz, 1H), 4.39–4.50 (m, 1H), 4.21 (d, $J=3.85$, 2H), 2.70–2.91 (m, 2H); MS: m/z 227, 144, 127.

4.2.7. 3-Hydroxy-4-(2-naphthyloxy)butanenitrile 2g. 3-(2-Naphthyloxy)-1,2-epoxypropane **1g** when stirred with NaCN for 18 h, as described in the above general procedure for the ring opening of oxiranes, resulted in a white crystalline solid of **2g**. Yield 55%; mp 134–138°C; IR (KBr): 3399, 3045, 2927, 2268, 1217, 1103 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.66–7.78 (m, 3H), 7.26–7.55 (m, 2H), 7.14–7.20 (m, 2H), 3.99–4.33 (m, 3H), 2.84 (dd, $J_1=3.41$ Hz, $J_2=12.50$ Hz, 1H), 2.69 (dd, $J_1=5.68$ Hz, $J_2=14.77$ Hz, 1H); MS: m/z 227, 144, 115.

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

The β-hydroxy nitrile (5 mmol) was dissolved in di-*iso*-propyl ether (50 mL) and to this *P. cepacia* lipase (750 mg) and vinyl acetate (12.5 mmol) were added successively and shaken at 25°C in an orbital shaker. After about 50% completion of the reaction, as indicated by

HPLC analysis, the reaction mixture was filtered and washed with EtOAc. Solvents were evaporated and purification was 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.

4.3.1. 3-Hydroxy-4-phenoxy-(*S*)-butanenitrile (*S*)-2a. Resolution of 3-hydroxy-4-phenoxybutanenitrile **2a** by employing the above general procedure for the resolution of β-hydroxy nitriles afforded **(*S*)-2a** in 52% yield and e.e. = 82.7%; $[\alpha]_D^{25} = -6.4$ (*c* 1.0, $CHCl_3$); IR (film): 3437, 3066, 2930, 2256, 1228, 1047 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.14–7.29 (m, 2H), 6.77–7.00 (m, 3H), 4.20–4.31 (m, 1H), 3.96 (d, $J = 5.12$ Hz, 2H), 2.73 (dd, $J_1 = 5.12$ Hz, $J_2 = 17.95$ Hz, 1H), 2.60 (dd, $J_1 = 5.12$ Hz, $J_2 = 11.50$ Hz, 1H); MS: *m*/*z* 177, 119, 107, 94, 77.

4.3.2. 3-Hydroxy-4-(2-methylphenoxy)-(*S*)-butanenitrile (*S*)-2b. Resolution of 3-hydroxy-4-(2-methylphenoxy)butanenitrile **2b** by employing the above general procedure for the resolution of β-hydroxy nitriles at 40°C afforded **(*S*)-2b** in 51% yield and 71.0% e.e. $[\alpha]_D^{25} = -8.0$ (*c* 1.0, $CHCl_3$); IR (film): 3477, 3028, 2931, 2255, 1193, 1044 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.06–7.19 (m, 2H), 6.73–6.94 (m, 2H), 4.23–4.40 (m, 1H), 3.93–4.10 (m, 2H), 3.16 (d, $J = 4.76$ Hz, 2H), 2.60–2.84 (m, 2H), 2.22 (s, 3H); MS: *m*/*z* 191, 139, 108, 91, 77.

4.3.3. 3-Hydroxy-4-(4-methylphenoxy)-(*S*)-butanenitrile (*S*)-2c. Resolution of 3-hydroxy-4-(4-methylphenoxy)butanenitrile **2c** by employing the above general procedure for the resolution of β-hydroxy nitriles afforded **(*S*)-2c** in 46% yield and 91.8% e.e. Mp 57–59°C; $[\alpha]_D^{25} = -7.2$ (*c* 1.0, $CHCl_3$); IR (KBr): 3401, 3023, 2938, 2274, 1240, 1102, 1052 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.08 (d, $J = 7.62$ Hz, 2H), 6.79 (d, $J = 7.62$ Hz, 2H), 4.21–4.34 (m, 1H), 4.01 (d, $J = 3.57$ Hz, 2H), 2.74 (dd, $J_1 = 3.81$ Hz, $J_2 = 11.90$ Hz, 1H), 2.64 (dd, $J_1 = 4.76$ Hz, $J_2 = 15.47$ Hz, 1H), 2.29 (s, 3H); MS: *m*/*z* 191, 121, 108, 91.

4.3.4. 4-(4-Chlorophenoxy)-3-hydroxy-(*S*)-butanenitrile (*S*)-2d. Resolution of 4-(4-chlorophenoxy)-3-hydroxybutanenitrile **2d** by employing the above general procedure for the resolution of β-hydroxy nitriles afforded **(*S*)-2d** in 42% yield and 92.2% e.e. Mp 65–68°C; $[\alpha]_D^{25} = -7.0$ (*c* 1.0, $CHCl_3$); IR (KBr): 3438, 3098, 2879, 2255, 1242, 1092, 1043 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.24 (d, $J = 6.90$ Hz, 2H), 6.84 (d, $J = 6.90$ Hz, 2H), 4.24–4.34 (m, 1H), 3.99 (d, $J = 4.60$ Hz, 2H), 3.19 (br. s, 1H), 2.79 (dd, $J_1 = 3.45$ Hz, $J_2 = 11.49$, 1H), 2.63 (dd, $J_1 = 4.60$ Hz, $J_2 = 16.09$ Hz, 1H); MS: *m*/*z* 211, 141, 128, 94.

4.3.5. 4-(4-Bromophenoxy)-3-hydroxy-(*S*)-butanenitrile (*S*)-2e. Resolution of 4-(4-bromophenoxy)-3-hydroxybutanenitrile **2e** by employing the above general procedure for the resolution of β-hydroxy nitriles afforded **(*S*)-2e** in 41% yield and 93.8% e.e. Mp 79–81°C; $[\alpha]_D^{25} = -3.2$ (*c* 1.0, $CHCl_3$); IR (KBr): 3496, 3092, 2926, 2252, 1250, 1107 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.35 (d, $J = 8.43$ Hz, 2H), 6.76 (d, $J = 8.43$ Hz, 2H), 4.20–4.33 (m, 1H), 3.99 (d, $J = 4.82$ Hz, 2H), 2.74 (dd, $J_1 = 4.82$ Hz, $J_2 = 14.46$ Hz, 1H), 2.61 (dd, $J_1 = 6.02$ Hz, $J_2 = 9.64$ Hz, 1H); MS: *m*/*z* 255, 257, 187, 185, 174, 172.

4.3.6. 3-Hydroxy-4-(1-naphthyloxy)-(*S*)-butanenitrile (*S*)-2f. Resolution of 3-hydroxy-4-(1-naphthyloxy)-butanenitrile **2f** by employing the above general procedure for the resolution of β-hydroxy nitriles at 40°C afforded **(*S*)-2f** in 60% yield and 35.0% e.e. Mp 89–92°C; $[\alpha]_D^{25} = -2.25$ (*c* 1.0, $CHCl_3$); IR (KBr): 3503, 3050, 2929, 2244, 1272, 1095 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.10–8.20 (m, 1H), 7.76–7.81 (m, 1H), 7.25–7.51 (m, 4H), 6.8 (d, $J = 5.13$ Hz, 1H), 4.39–4.50 (m, 1H), 4.21 (d, $J = 3.85$, 2H), 2.70–2.91 (m, 2H); MS: *m*/*z* 227, 144, 127.

4.3.7. 3-Hydroxy-4-(2-naphthyloxy)-(*S*)-butanenitrile (*S*)-2g. Resolution of 3-hydroxy-4-(2-naphthyloxy)-butanenitrile **2g** by employing the above general procedure for the resolution of β-hydroxy nitriles at 40°C afforded **(*S*)-2g** in 62% yield and 44.0% e.e. Mp 134–138°C; $[\alpha]_D^{25} = -4.7$ (*c* 0.5, $CHCl_3$); IR (KBr): 3399, 3045, 2927, 2268, 1217, 1103 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.66–7.78 (m, 3H), 7.26–7.55 (m, 2H), 7.14–7.20 (m, 2H), 3.99–4.33 (m, 3H), 2.84 (dd, $J_1 = 3.41$ Hz, $J_2 = 12.50$ Hz, 1H), 2.69 (dd, $J_1 = 5.68$ Hz, $J_2 = 14.77$ Hz, 1H); MS: *m*/*z* 227, 144, 115.

4.3.8. 3-Acetyloxy-4-phenoxy-(3*R*)-butanenitrile (*R*)-3a. Resolution of 3-hydroxy-4-phenoxybutanenitrile **2a** by employing the above general procedure for the resolution of β-hydroxy nitriles afforded **(*R*)-3a** in 42% yield and >99.0% e.e. $[\alpha]_D^{25} = +30.5$ (*c* 1.0, $CHCl_3$); IR (film): 3041, 2939, 2255, 1745, 1373, 1222, 1047 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.2–7.34 (m, 2H), 6.81–7.02 (m, 3H), 5.21–5.34 (m, 1H), 4.18 (dd, $J_1 = 4.76$ Hz, $J_2 = 9.52$ Hz, 1H), 4.09 (dd, $J_1 = 5.95$ Hz, $J_2 = 7.14$ Hz, 1H), 2.88 (d, $J = 4.76$ Hz, 2H), 2.13 (s, 3H); MS: *m*/*z* 219, 126, 94, 77.

4.3.9. 3-Acetyloxy-4-(2-methylphenoxy)-(3*R*)-butanenitrile (*R*)-3b. Resolution of 3-hydroxy-4-(2-methylphenoxy)butanenitrile **2b** by employing the above general procedure for the resolution of β-hydroxy nitriles at 40°C afforded **(*R*)-3b** in 42% yield and 91.1% e.e. $[\alpha]_D^{25} = +23.4$ (*c* 1.0, $CHCl_3$); IR (film): 3028, 2918, 2254, 1775, 1312, 1188, 1128, 1023 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.04–7.16 (m, 2H), 6.72–6.90 (m, 2H), 5.25–5.37 (m, 1H), 4.02–4.21 (m, 2H), 2.89 (d, $J = 4.82$ Hz, 2H), 2.20 (s, 3H), 2.13 (s, 3H); MS: *m*/*z* 233, 126, 91, 77.

4.3.10. 3-Acetyloxy-4-(4-methylphenoxy)-(3*R*)-butanenitrile (*R*)-3c. Resolution of 3-hydroxy-4-(4-methylphenoxy)butanenitrile **2c** by employing the above general procedure for the resolution of β-hydroxy nitriles afforded **(*R*)-3c** in 45% yield and >99.0% e.e. $[\alpha]_D^{25} = +27.05$ (*c* 1.0, $CHCl_3$); IR (film): 3033, 2939, 2254, 1755, 1372, 1232, 1052 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.06 (d, $J = 7.14$ Hz, 2H), 6.78 (d, $J = 7.14$ Hz,

2H), 5.20–5.33 (m, 1H), 4.14 (dd, $J_1=3.57$ Hz, $J_2=9.52$ Hz, 1H), 4.05 (dd, $J_1=4.76$ Hz, $J_2=10.71$ Hz, 1H), 2.88 (d, $J=4.76$ Hz, 2H), 2.28 (s, 3H), 2.13 (s, 3H); MS: m/z 233, 126, 108, 91.

4.3.11. 3-Acetyloxy-4-(4-chlorophenoxy)-(3*R*)-butanenitrile (*R*)-3d. Resolution of 4-(4-chlorophenoxy)-3-hydroxybutanenitrile **2d** by employing the above general procedure for the resolution of β-hydroxy nitriles afforded **(*R*)-3d** in 45% yield and 92.1% e.e. $[\alpha]_D^{25}=+26.7$ (c 1.0, $CHCl_3$); IR (film): 3071, 2938, 2255, 1742, 1373, 1212, 1047 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.21 (d, $J=7.69$ Hz, 2H), 6.80 (d, $J=7.69$ Hz, 2H), 5.20–5.31 (m, 1H), 4.00–4.20 (m, 2H), 2.73–2.97 (m, 2H), 2.11 (s, 3H); MS: m/z 253, 148, 125.

4.3.12. 3-Acetyloxy-4-(4-bromophenoxy)-(3*R*)-butanenitrile (*R*)-3e. Resolution of 4-(4-bromophenoxy)-3-hydroxybutanenitrile **2e** by employing the above general procedure for the resolution of β-hydroxy nitriles afforded **(*R*)-3e** in 55% yield and 88.7% e.e. $[\alpha]_D^{25}=+29.45$ (c 0.5, $CHCl_3$); IR (film): 3023, 2937, 2255, 1755, 1373, 1246, 1045 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.38 (d, $J=6.02$ Hz, 2H), 6.76 (d, $J=6.02$ Hz, 2H), 5.20–5.30 (m, 1H), 4.00–4.19 (m, 2H), 2.74–2.95 (m, 2H), 2.11 (s, 3H); MS: m/z 297, 299, 187, 185, 174, 172.

4.3.13. 3-Acetyloxy-4-(1-naphthyloxy)-(3*R*)-butanenitrile (*R*)-3f. Resolution of 3-hydroxy-4-(1-naphthyloxy)-butanenitrile **2f** by employing the general procedure at 40°C afforded **(*R*)-3f** in 36% yield and >98.0% e.e. $[\alpha]_D^{25}=+26.8$ (c 1.0, $CHCl_3$); IR (film): 3059, 2937, 2255, 1742, 1393, 1218, 1105 cm^{-1}; ^1H NMR (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); MS: m/z 269, 164, 126.

4.3.14. 3-Acetyloxy-4-(2-naphthyloxy)-(3*R*)-butanenitrile (*R*)-3g. Resolution of 3-hydroxy-4-(2-naphthyloxy)-butanenitrile **2g** by employing the general procedure for the resolution of β-hydroxy nitriles at 40°C afforded **(*R*)-3g** in 34% yield and >99.0% e.e. Mp 77–80°C; $[\alpha]_D^{25}=+34.13$ (c 0.8, $CHCl_3$); IR (KBr): 3073, 2926, 2250, 1739, 1374, 1249, 1037 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.68–7.75 (m, 3H), 7.24–7.46 (m, 2H), 7.08–7.13 (m, 2H), 5.28–4.00 (m, 1H), 4.16–4.31 (m, 2H), 2.91 (d, $J=3.61$ Hz, 2H), 2.16 (s, 3H); MS: m/z 267, 144, 115.

Acknowledgements

The authors are grateful to Amano Pharmaceutical Co. and Novo Nordisk for providing the gift samples of Amano PS lipase and Lipozyme, respectively. One of the authors (G.B.R.K.) thanks CSIR, New Delhi for the award of a research fellowship.

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