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An expedient chemo-enzymatic method for the synthesis of optically active masked 1,2-amino alcohols

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ABSTRACT

The expedient synthesis of enantiopure masked 1,2-amino alcohols (ee >99%) including their alkyl substituted analogues has been achieved by the regioselective ring opening of epoxides using phthalimide, followed by highly efficient kinetic resolution under mild and environmentally friendly conditions. The addition of co-solvents during kinetic resolution significantly improved the enantioselectivity with reduction in time.

1. Introduction

The importance of vicinal amino alcohols continues to stimulate the development of new efficient methods for their synthesis in enantiomerically pure form.[1] 1,2-Amino alcohols are not only the key pharmacophores in many drug molecules,[1a,2] but also constitute as substructures in various important natural products.[1a,3] Non-aromatic *vic* amino alcohols are used as inhibitors of phenylethanolamine *N*-methyltransferase (PNMT),[4] as perfumes,[5] and exhibit potent inhibitory activity against human platelet phospholipase (PLA_2).[6]

In addition to their biological importance, enantiomerically pure amino alcohols, especially 1,2-amino alcohols, have also been successfully employed as chiral auxiliaries and resolving agents for acids, and as chiral ligands for applications in catalytic asymmetric synthesis.[7] Chiral 1,2-amino alcohols are generally prepared from naturally occurring amino acids,[8] whose products are restricted to chiral secondary amines with primary hydroxy groups. Those containing secondary hydroxyl groups can be obtained from the stereo-, regio-, and enantioselective ring opening of epoxides[9] catalyzed by chiral metal complexes, and by chemocatalytic[10] or microbial[11] reduction of masked amino ketones. The importance of biocatalytic methods for the preparation of optically active compounds is now well recognized.[12] Moreover, the resolution of alkyl substituted 1,2-amino alcohol analogues are difficult to achieve by chemical methods due to the possibility of a non-crystalline nature of their diastereomeric salts. Therefore, in continuation of our research programme, which is aimed at synthesizing natural and non-natural compounds of biomedical importance utilizing enzymes as biological catalysts,[13] we report herein an efficient and facile methodology for the synthesis of optically active masked 1,2-amino alcohols **1**–**6** (Fig. 1). The generation of optically active amino alcohols from their masked precursors can easily be achieved by the known methods.[14]

The successful strategy involved the tagging of a phthalimide as a masking group, since free amino functions generally cause inhibition of lipases. The other advantages of incorporating a phthalimide subunit are the facilitation of their separation and UV detection by HPLC, also easy handling; additionally, phthalimide analogues are also reported to have anti-inflammatory,[15] analgesic,[16] anticonvulsant,[17] herbicidal,[18] and insecticidal[19] activities.

Recently, we have reported the chemoenzymatic synthesis of masked *vic* amino alcohols through reduction of protected amino ketones; however, this protocol had some limitations as it was generally difficult to introduce bromine and thereafter amines at a less substituted position in unsymmetrical ketones.[20] The alternative strategy herein involved an efficient method of preparation of masked amino alcohols through regioselective ring opening of the epoxides using phthalimide.[21]

2. Results and discussion

Our attempts began with the synthesis of racemic 2-phthalimide alcohols **1**–**4** via regioselective ring opening of epoxides with phthalimide. The optimized conditions involved refluxing the epoxy compound with phthalimide in isopropyl alcohol using pyridine as catalyst; the final isolated yield varied from 75% to 85% (Scheme 1).

For the kinetic resolution and preparation of target molecules, enantioselective hydrolysis of racemic 2-phthalimide acetates **8** and **9** was carried out with a panel of micro organisms bearing

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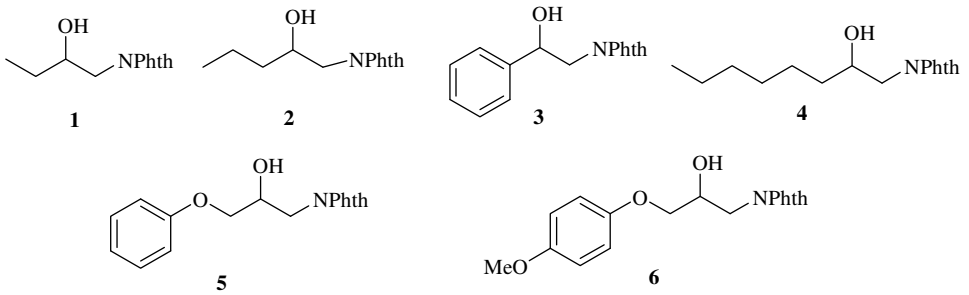
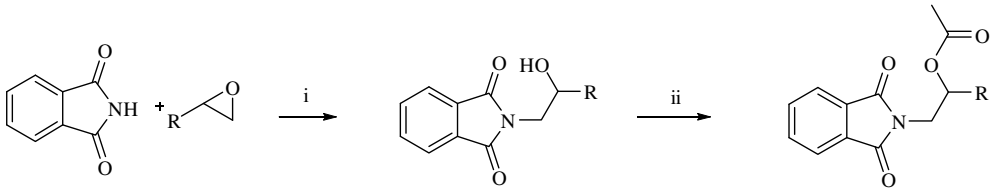
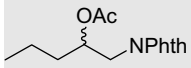
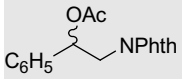


Figure 1.



Scheme 1. Reagent and conditions: (i) IPA, Py, reflux; (ii) Ac_2O, DMAP/DCM.

Table 1
Enzymatic hydrolysis of 2-phthalimide acetates, that is, (±)-**8** and (±)-**9** in aqueous phosphate buffer

Substrate	Lipase	Conversion (%)	Time (h)	ee_p (%)	ee_s (%)
 **8**	Amano AS	ND	24	—	—
	PSL	2.6	24	38.5	1.0
	MM	ND	24	—	—
	PSC-II	8.5	120	5.8	0.5
	ABL	29.3	6	13.3	5.5
	CRL	ND	24	—	—
 **9**	PSL	ND	120	—	—
	MM	ND	120	—	—
	ABL	46.5	16	8.6	9.2
	CCL	24.3	46	13.5	0.9
	AA	17.8	46	38.2	9.2
	MM	ND	120	—	—
	PSC-II	ND	46	—	—

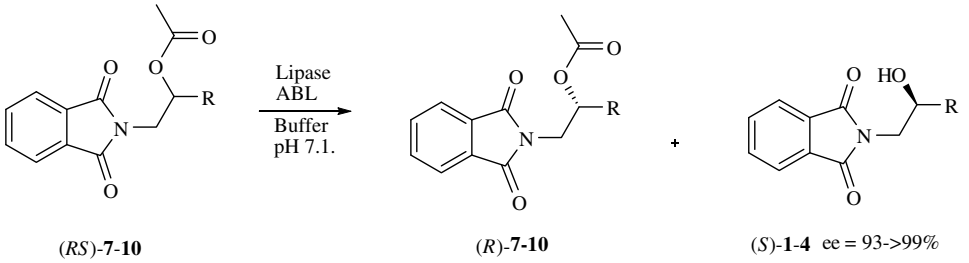
CCL: *Candida cylindrica lipase*; MM: *Mucor miehei*; CRL: *Candida rugosa* lipase; CAL: *Candida antarctica* lipase; PSL: *Pseudomonas cepacia* lipase; PSC-II: *Pseudomonas cepacia* lipase on ceramics; ABL: *Arthrobacter* sp. lipase; AA: *Amano acylase*; AS: Lipase from *Aspergillus niger*; ND = not detected.

lipases belonging to the institute's repository as well as being obtained from commercial sources (Table 1, Scheme 2). The kinetic resolution reactions of (±)-**8** and (±)-**9** were carried out in an aqueous phosphate buffer (0.1 M, pH 7.0); however, the rate of hydrolysis was found to be slow while the enantioselectivity was also poor (Table 1). Therefore, in order to improve the rate of hydrolysis, as well as the enantioselectivity, the use of co-solvents was envisaged as a convenient option, and the kinetic resolution reactions of (±)-**7**–**10** were carried out in biphasic systems.

A biphasic system using an organic solvent proved to be highly advantageous. Both non-polar and polar solvents in the ratio 10% (v/v) in buffer were used. Finally, the use of ether solvents for the hydrolysis of (±)-**7** and (±)-**8** and toluene for the hydrolysis of (±)-**9** and (±)-**10** was considered to be the best (Table 2). Here, a native strain *Arthrobacter* sp. lipase[22] designated as ABL (MTCC no. 5125) has been identified for its excellent performance in the kinetic resolutions of (±)-**7**, (±)-**8**, (±)-**9**, and (±)-**10** (*E* values 397, 1059, 1059, and 54, respectively).

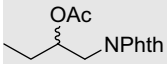
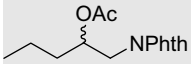
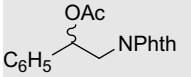
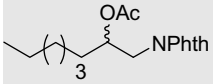
While commercial lipase PSC-II was most suited for the resolution of racemic 2-hydroxy butyl amine precursor **7** (*E* = 397), the higher alkyl analogues **8** and **10** were easily resolved using ABL, so also the phenyl analogue **9**.

In the experiments for the resolution of the substrate **7** with ABL, it was observed that the enantiomeric excess was strongly dependent on the extent of hydrolysis and so it was important to carry the reaction beyond 50% hydrolysis (~58%) in order to obtain the enantiopure acetate **7** in good yields. It was thus necessary to



Scheme 2.

Table 2
Enzymatic hydrolysis of racemic 2-phthalimide acetates **7**, **8**, **9**, and **10** at 20 g/L concentration in biphasic systems

Substrate	Lipase	Co-solvent	Conversion (%)	Time (h)	ee_p (%)	ee_s (%)	*E*
	PPL	Toluene	1.7	90	88.2	1.5	15.9
	CCL	Tetrahydrofuran	46.7	90	22.1	21.2	1.8
	MM	Toluene	4.6	90	60.8	5.2	4.3
	CRL	Toluene	23.7	44	33.3	9.3	2.2
	PSC-II	Toluene	30.6	90	98.4	43.3	154
	PSL	Toluene	14.4	90	93.1	15.8	32.9
	AS	Toluene	22.5	90	3.1	3.2	1.1
	ABL	Toluene	39.8	6	71.8	47.5	9.7
	Lipase M	Toluene	2.1	90	38.1	0.5	2.3
	ABL	Nil	33.1	6	54.6	27.1	4.4
	**ABL**	**Diisopropylether**	**58**	**5**	**67**	**>99**	**16.1**
	ABL	Diisopropylether	46.5	3	85.8	72.5	29.3
	ABL	Tetrahydrofuran	ND	6	–	–	
7	ABL	Toluene	39.8	6	71.8	47.5	9.7
	ABL	Dimethoxyethane	30.3	6	82.2	35.7	14.5
	ABL	Diethylether	38.7	6	86.6	54.6	24.1
	ABL	DMF	2.8	6	>99	2.8	57
	ABL	DMSO	32.9	6	73.2	35.9	9.4
	PSC-II	Toluene	30.6	90	98.4	43.3	194.5
	PSC-II	**Tetrahydrofuran**	**40**	**120**	**>99**	**66.6**	**397.4**
	PSC-II	Diisopropylether	25.7	120	>99	34.6	278.4
	PSC-II	Dimethoxyethane	49.1	120	97	91.3	230.4
	PSC-II	Diethylether	18.9	120	94.2	21.9	41.9
	PSC-II	Hexane	30.7	120	94.1	40.3	49.5
	ABL	Tetrahydrofuran	ND	6	–	–	–
	ABL	**Diethylether**	**50**	**6**	**>99**	**>99**	**1059**
	ABL	Toluene	4.8	6	87.5	5.5	15.6
	ABL	**Diisopropylether**	**50**	**6**	**>99**	**>99**	**1059**
	ABL	Dimethoxyethane	47	6	>99	88.7	580
	PSC-II	Toluene	18.3	120	70.5	15.8	6.8
	PSC-II	Diisopropylether	24.8	120	87.1	26.1	19.1
8	PSC-II	Tetrahydrofuran	17.6	120	76.1	16.3	8.6
	PSC-II	DMF	11.2	120	65.1	9.5	5.2
	PSC-II	Hexane	9.4	120	19.1	2.2	1.5
	ABL	Tetrahydrofuran	5.0	26	>99	5.2	105
	**ABL**	**Toluene**	**50**	**30**	**>99**	**>99**	**1059**
	ABL	DMF	50	32	>99	>99	1059
	ABL	Diisopropylether	51	40	95	80	203
9	ABL	Nil	26.6	20	24.8	8.9	1.8
	ABL	**Toluene**	**35.6**	**16**	**93.8**	**51.8**	**54.3**
	ABL	Diisopropylether	21	12	85.7	22.8	16.4
	ABL	Diisopropylether	46.4	20	75.4	65.3	13.8
	ABL	DMF	27.8	20	90	35.5	26.7
	ABL	Tetrahydrofuran	1.6	20	99	1.6	32.3
10	PSL	Diisopropylether	20.4	20	82.3	21.2	12.9

Experimental conditions: all the reactions were performed at 25 °C in a shaker at 320 rpm, ee (%) and conversions (%) were measured by a chiral HPLC.

determine the enantiomeric excess of the product as a function of conversion. Figure 2 shows the results of these investigations.

Encouraged by the efficacy of *Arthrobacter* sp. lipase on the kinetic resolution of 2-phthalimide acetates of an aryl and alkyl ethanolamine series, we also examined its versatility in the kinetic resolution of 1-aryloxy-3-phthalimide-2-propanol derivatives,

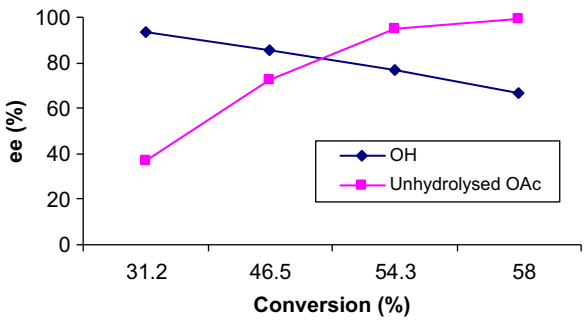


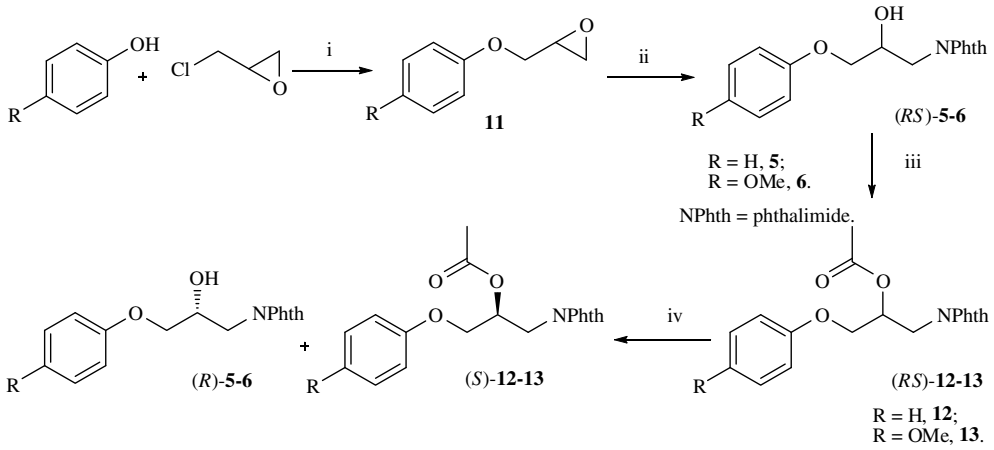
Figure 2. Enantioselective hydrolysis of *N*-(2-acetoxy)-butylphthalimide **7** using *Arthrobacter* sp. lipase.

which are the precursors of aryloxy propanolamines. This class of compounds of which propranolol[23] is a prominent example has found widespread applications in medicine.[24] Their synthetic strategy involves the coupling of epichlorohydrin with the substituted phenols in butanone, followed by the ring opening of epoxides with phthalimide (Scheme 3).

In the kinetic resolution under the optimized conditions, the addition of 10% organic co-solvent with buffer was again found to be the best option, in terms of both hydrolysis and enantioselectivity (*E* values >250) (Table 3).

The absolute configurations of the final products **1** and **3** were assigned by comparing the signs of the observed specific rotations with those reported in the literature, whereas for unknown compounds such as **2**, **4**, **5**, and **6**, an analogy was made with Kazlauskas's rule[25] for assignments.

It is evident from our earlier report[20] that *Arthrobacter* sp. lipase exhibited preference for the opposite configuration in a chiral molecule as predicted by Kazlauskas's rule, whereas PSC-II follows Kazlauskas's rule (Fig. 3). On applying the Cahn–Ingold–Prelog priority rules to **1,** the highest priority is assigned to sterically larger group (*N*-Phth) and a lower priority to sterically medium group



Scheme 3. Reagents and conditions: (i) K_2CO_3, butanone, reflux, yield 95%; (ii) phthalimide, Py/IPA, reflux, yield 85%; (iii) Ac_2O/DMAP, DCM, yield 98%; (iv) lipase, buffer.

Table 3
Enzymatic hydrolysis of acetyl derivatives of racemic 1-aryloxy-3-phthalimide-2-propanols (**12** and **13**) at 20 g/L concentration in biphasic systems

Substrate	Lipase	Co-solvent	Conversion (%)	Time (h)	ee_p (%)	ee_s (%)	*E*
12	ABL	Benzene	30	52	48.2	20.7	3.5
12	ABL	DIE	30.5	52	37.9	16.7	2.6
12	ABL	DME	28.9	50	84.2	34.5	15.9
12	ABL	DMSO	22	12	77.4	21.9	9.8
12	ABL	Toluene	50.5	22	87.5	85.7	45.0
12	**ABL**	**Toluene**	**38.3**	**15**	**>99**	**63**	**375**
13	RRLY-15	Toluene	16.4	36	13.4	2.7	1.3
13	PPL	Toluene	9.2	36	99	11	224
13	PLAP	Toluene	46.5	36	12.6	11	1.4
13	PSL	DIE	4.5	40	99	4.7	93.7
13	Amano AS	DIE	45.9	40	10.4	9.6	1.3
13	Amano AS	Toluene	13.8	40	82	13.1	11.5
13	ABL	Dioxane	23.2	36	99	30	266.9
13	ABL	DIE	40	40	37	24.7	2.7
13	ABL	DMSO	56.9	40	17.4	22.9	1.7
13	**ABL**	**Toluene**	**24**	**14**	**>99**	**34.3**	**270**

RRLY-15 = *Trichosporon* sp.; PLAP, pig liver acetone powder; PPL, porcine pancreatic lipase.

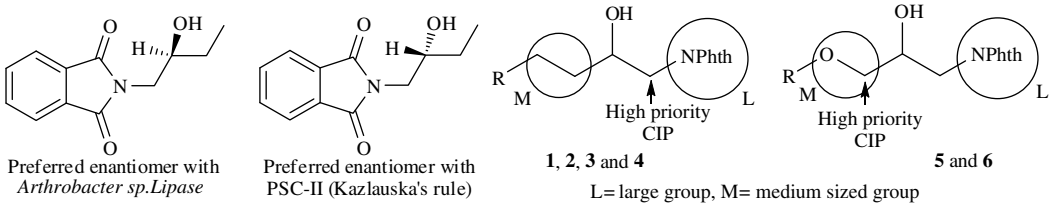


Figure 3. Preferred enantiomer of **1** using *Arthrobacter simplex* and PSC-II.

(CH_2CH_3), which results in our assigning an (*R*)-configuration [(*S*) with ABL] to its hydrolyzed enantiomer (Fig. 3**)**. This observation is also supported by the absolute configuration determined, on the basis of the comparison of the signs of the specific rotations, with those reported in the literature for **1**[11a] and **3**.[10a] Similar arguments can be applied for assigning the absolute configurations of **2** and **4**. On the other hand, a lower priority can be assigned to sterically larger group (*N*-Phth) in compounds **5** and **6**, and a higher priority to a sterically medium group ($ArOCH_2$), which results in our assigning an (*S*)-configuration [(*R*) with ABL] to its hydrolyzed enantiomers (Fig. 3).

3. Conclusion

In conclusion, an efficient chemoenzymatic approach for the preparation and resolution to high enantiomeric purity from racemic alkyl, aryl, and aryloxypropyl masked β-amino alcohols through an efficient lipase catalyzed hydrolysis in presence of co-solvents has been demonstrated.

4. Experimental

4.1. General

^1H NMR spectra in $CDCl_3$ were recorded on Bruker 200 MHz spectrometers with TMS as the internal standard. Chemical shifts were expressed in parts per million (δ ppm). Reagents and solvents used were mostly LR grade. Silica gel coated aluminum plates coated on alumina from M/s Merck were used for TLC. MS were recorded on Jeol MSD-300 and Bruker Esquire 3000 GC–Mass spectrometer. IR was recorded on a FT-IR Bruker (270–30) spectrophotometer. Elemental analyses were performed on Elementar

Vario EL-III. Optical rotations were measured on Perkin-Elmer 241 polarimeter at 25 °C using sodium D light. Enantiomeric excess (ee) was determined on a chiral stationary phase HPLC column.

4.2. General procedure for the hydrolysis of acetyl derivatives of protected amino alcohols

Racemic acetate (50 mg), aqueous phosphate buffer (2.5 mL, 0.1 M, pH. 7.0), toluene (250 μL), and whole cells of *Arthrobacter* sp. lipase (150 mg) were shaken (320 rpm) continuously at 25 ± 1 °C. After a certain degree of conversion (~50%) as indicated by thin layer chromatography (TLC) and chiral high performance liquid chromatography (HPLC), the reaction was terminated by adding ethyl acetate and centrifuging the mixture at 10,000–15,000*g* to remove the enzyme and the suspended particles. The clear solution was decanted, and the centrifuged mass was extracted separately with ethyl acetate (3 × 25 mL). The organic layer was combined and washed with water. The combined organic layer was then dried and evaporated under reduced pressure to furnish a mixture comprising of hydrolyzed alcohol and unhydrolyzed ester, which were separated by column chromatography (100–200 mesh) using a gradient of ethyl acetate and hexane as eluent.

4.3. General procedure for the synthesis of β-phthalimide alcohols

A catalytic amount of pyridine was added to a solution of epoxy compound (1 mmol) and phthalimide (1.2 mmol) in isopropyl alcohol (20 mL) and the mixture was refluxed for two hours. After the reaction was completed as indicated by TLC, solvent was removed by distillation at reduced pressure bringing the total volume to one-fourth. The contents were then poured into cold water and extracted with ethylacetate (4 × 20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product. The mixture was separated by column chromatography on silica gel to obtain the pure product (yield 75–85%).

4.3.1. *N*-(2-Hydroxy)-butylphthalimide 1

($C_{12}H_{13}NO_3$): HPLC purity >99%; HPLC ee >99%; $[\alpha]_D^{25}$ = +18.4 (*c* 0.5, $CHCl_3$); {lit.[11a] $[\alpha]_D^{25}$ = +5.6 (*c* 1.08, $CHCl_3$); ee = 15%}; mp = 70–72 °C; Abs. config (*S*); HPLC condition {OJH chiral column, eluent 2-propanol-hexane-acetic acid (2:98:0.1), flow rate: 1 mL/min, t_1 = 29.7 and t_2 = 38.3 min}. ^{1}H NMR: δ 1.65 (t, *J* = 7.4 Hz, 3H), 1.54–1.67 (m, 2H), 3.75–3.88 (m, 3H), 7.74–7.81 (m, 2H), 7.85–7.93 (m, 2H); ^{13}C NMR: δ 8.7, 27.0, 43.1, 70.8, 122.4, 130.9, 133.1, 167.9; ESI-MS (*m*/*z*): 219; Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.70; H, 6.03; N, 6.38.

4.3.2. *N*-(2-Hydroxy)-pentylphthalimide 2

($C_{13}H_{15}NO_3$): HPLC purity >99%; HPLC ee >99%; $[\alpha]_D^{25}$ = +10.7 (*c* 1, $CHCl_3$); mp = 73–75 °C; Abs. config (*S*); HPLC condition {OJH chiral column, eluent 2-propanol-hexane-acetic acid (1:99:0.1), flow rate: 1.5 mL/min, t_1 = 19.6 and t_2 = 22.3 min}. ^{1}H NMR: δ 0.84 (t, *J* = 6.7 Hz, 3H), 1.41–1.45 (m, 4H), 3.67–3.71 (m, 2H), 3.80–3.85 (m, 1H), 7.64–7.70 (m, 2H), 7.75–7.81 (m, 1H). ^{13}C NMR: δ 14.0, 18.7, 37.2, 44.5, 70.3, 123.4, 132.0, 134.1, 169.1. ESI-MS (*m*/*z*): 233. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.90; H, 6.55; N, 6.07.

4.3.3. *N*-(2-Hydroxy-2-phenyl)ethylphthalimide 3

HPLC purity >99%; HPLC ee >99%; $[\alpha]_D^{25}$ = +23.2 (*c* 1, $CHCl_3$); {lit.[10a] for (*R*)-enantiomer $[\alpha]_D^{25}$ = –25.6 (*c* 1, $CHCl_3$)}; mp = 161–163 °C; Abs. config (*S*); HPLC condition {(*R*,*R*)-Whelk-01 chiral column, eluent 2-propanol-hexane (5:95), flow rate: 0.8 mL/min, t_1 = 19.0 min and t_2 = 21.9 min}. ^{1}H NMR: δ 3.88–4.02 (m, 2H), 5.01 (dd, *J* = 4.2 Hz, 3.3 Hz, 1H), 7.1–7.3 (m, 5H), 7.73–7.77 (m, 2H), 7.84–7.86 (m, 2H). ^{13}C NMR: δ 45.8, 72.6, 123.4, 123.5, 125.9, 127.8, 128.5, 128.9, 131.9, 134.0, 134.1, 141.1, 168.8. ESI-MS (*m*/*z*): 267.

4.3.4. *N*-(2-Hydroxy)-octylphthalimide 4

($C_{16}H_{21}NO_3$): HPLC purity >99%; HPLC ee = 93.8%; $[\alpha]_D^{25}$ = +7.5 (*c* 1, $CHCl_3$); mp = 76–78 °C; Abs. config (*S*); HPLC condition {OJH chiral column, eluent 2-propanol-hexane-acetic acid (2:98:0.1), flow rate: 0.8 mL/min, t_1 = 13.7 min and t_2 = 16.7 min}. ^{1}H NMR: δ 0.84 (t, *J* = 6.6 Hz, 3H), 1.28–1.50 (m, 10H), 3.71–3.79 (m, 2H), 3.84–3.90 (m, 1H), 7.71–7.77 (m, 2H), 7.82–788 (m, 2H). ^{13}C NMR: δ 14.4, 23.0, 25.8, 29.6, 32.2, 35.5, 44.9, 71.1, 123.8, 132.4, 134.7, 169.4. ESI-MS (*m*/*z*): 275. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.80; H, 7.75; N, 5.07.

4.3.5. *N*-(2-Hydroxy-3-phenoxy)propylphthalimide 5

($C_{17}H_{15}NO_4$): HPLC purity >99%; HPLC ee >99%; $[\alpha]_D^{25}$ = +23.2 (*c* 0.5, $CHCl_3$), mp = 83–85 °C; Abs. config (*R*); HPLC condition {ODH chiral column, eluent 2-propanol-hexane-acetic acid (7:93:0.1), flow rate: 0.5 mL/min, t_1 = t_2 = 81.5 min}. ^{1}H NMR: δ 3.72 (m, 2H), 3.92 (d, *J* = 5.3 Hz, 2H), 4.13–4.19 (m, 1H), 6.85–6.96 (m, 3H), 7.23–7.31 (m, 2H), 7.81–7.89 (m, 4H). ^{13}C NMR: δ 41.3, 68.4, 69.8, 114.5, 121.2, 123.4, 129.2, 131.6, 132.8, 158.4, 168.8. ESI-MS (*m*/*z*): 297. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.65; H, 5.12; N, 4.77.

4.3.6. *N*-[2-Hydroxy-3-(*p*-methoxy-phenoxy)]-propylphthalimide 6

($C_{18}H_{17}NO_5$): HPLC purity >99%; HPLC ee >99%; $[\alpha]_D^{25}$ = +25.5 (*c* 0.5, $CHCl_3$); mp = 115–117 °C; Abs. config (*R*); HPLC condition {OJH chiral column, eluent 2-propanol–hexane–acetic acid (15:85:0.1), flow rate: 0.8 mL/min, t_1 = t_2 = 28.8 min}. ^{1}H NMR: δ 3.76 (s, 3H), 3.88–4.01 (m, 4H), 4.08–4.27 (m, 1H), 6.78–6.88 (m, 4H), 7.71–7.77 (m, 2H), 7.83–7.89 (m, 2H). ^{13}C NMR: δ 40.7, 55.2, 68.3, 70.0, 114.1, 115.2, 122.9, 131.4, 133.5, 151.9, 153.7, 167.2. ESI-MS (*m*/*z*): 327. Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 66.08; H, 5.22; N, 4.27.

4.4. Acylation of protected amino alcohols 1, 2, 3, 4, 5 and 6

Acetic anhydride (1.2 mmol) and a catalytic amount of DMAP were added to a solution of racemic protected amino alcohols (1 mmol) in dry dichloromethane after which the reaction mixture was kept overnight at room temperature. The contents of the reaction mixture were poured into ice-cold water and extracted with dichloromethane. The organic layer was washed, dried, and evaporated to give the protected amino acetoxy derivatives.

4.4.1. *N*-(2-Acetoxy)-butylphthalimide 7

($C_{14}H_{15}NO_4$): HPLC purity >99%; HPLC ee >99%; $[\alpha]_D^{25}$ = +35.9 (*c* 1, $CHCl_3$); mp = 67–69 °C; Abs. config (*R*); HPLC condition {OJH chiral column, eluent 2-propanol-hexane-acetic acid (2:98:0.1), flow rate: 1 mL/min, t_1 = 17.2 and 18.3 min}. ^{1}H NMR: δ 1.03 (t, *J* = 7.4 Hz, 3H), 1.61–1.74 (m, 2H), 2.05(s, 3H), 3.89 (d, *J* = 5.0 Hz, 2H), 5.07–5.14 (m, 1H), 7.75–7.81 (m, 2H), 7.86–7.92 (m, 2H), ^{13}C NMR: δ 8.6, 19.5, 24.6, 40.3, 73.3, 122.8, 131.8, 134.1, 168.3, 171.4. ESI-MS (*m*/*z*): 261. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.32; H, 5.72; N, 5.37.

4.4.2. *N*-(2-Acetoxy)-pentylphthalimide 8

($C_{15}H_{17}NO_4$): HPLC purity >99%; HPLC ee >99%; $[\alpha]_D^{25}$ = +23.5 (*c* 1, $CHCl_3$); mp = 55–57 °C; Abs. config (*R*); HPLC condition {OJH chiral column, eluent 2-propanol-hexane-acetic acid (1:99:0.1), flow rate: 1.5 mL/min, t_1 = t_2 = 8.7 min}. ^{1}H NMR: δ 0.92 (t, *J* = 7.1 Hz, 3H), 1.39–1.43 (m, 2H), 1.59–1.62 (m, 2H), 1.90 (s, 3H), 3.82 (d,

J = 5.2 Hz, 2H), 5.10–5.16 (m, 1H), 7.74–7.80 (m, 2H), 7.85–7.92 (m, 2H). ^{13}C NMR: δ 13.1, 18.6, 19.9, 33.9, 41.0, 72.1, 123.2, 131.2, 134.5, 165.0, 169.9. ESI-MS (m/z): 275. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.40; H, 6.18; N, 5.00.

4.4.3. *N*-(2-Acetoxy-2-phenyl)ethylphthalimide 9

($C_{18}H_{15}NO_4$): HPLC purity >99%; HPLC ee >99%; $[\alpha]_D^{25}$ = –21.7 (c 1, $CHCl_3$); mp = 111–113 °C; Abs. config (R); HPLC condition {(R,R)-Whelk-01 chiral column, eluent 2-propanol-hexane (5:95), flow rate: 0.8 mL/min, t_1 = 13.9 and t_2 = 16.9 min}. ^{1}H NMR: δ 2.03 (s, 3H, CH_3CO), 3.93 (dd, J = 10.5 Hz, 3.8 Hz, 1H), 4.17 (dd, J = 8.9 Hz, 5.3 Hz, 1H), 6.13 (dd, J = 3.7 Hz, 5.2 Hz), 7.35–7.45 (m, 5H), 7.70–7.75 (m, 2H), 7.84–7.86 (m, 2H). ^{13}C NMR: δ 21.0, 43.0, 73.3, 123.4, 126.6, 128.6, 128.7, 134.1, 137.2, 167.9, 170.3. ESI-MS (m/z): 309. Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.73; H, 5.03; N, 4.37.

4.4.4. *N*-(2-Acetoxy)-octylphthalimide 10

($C_{18}H_{23}NO_4$): HPLC purity >99%; HPLC ee 65.3%; $[\alpha]_D^{25}$ = +11.1 (c 1, $CHCl_3$); mp = 50–52 °C; Abs. config (R); HPLC condition {OJH chiral column, eluent 2-propanol-hexane-acetic acid (2:98:0.1), flow rate: 0.8 mL/min, t_1 = 7.0 and t_2 = 8.1 min}. ^{1}H NMR: δ 0.84 (t, J = 6.8 Hz, 3H), 1.27–1.52 (m, 8H), 1.56–1.67 (m, 2H), 3. 88 (d, J = 5.2 Hz, 2H), 5.09–5.16 (m, 1H), 7.70–7.76 (m, 2H), 7.81–788 (m, 2H). ^{13}C NMR: δ 13.55, 20.53, 20.05, 24.73, 28.49, 31.15, 31.37, 40.55, 71.59, 122.85, 131.44, 133.53, 167.89, 170.52. ESI-MS (m/z): 317. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.08; H, 7.35; N, 4.40.

4.4.5. *N*-(2-Acetoxy-3-phenoxy)propylphthalimide 12

($C_{19}H_{17}NO_5$): HPLC purity >99%; HPLC ee 51%; $[\alpha]_D^{25}$ = −10.5 (c 1, $CHCl_3$); mp = 89–91 °C; Abs. config (S); HPLC condition {ODH chiral column, eluent 2-propanol-hexane-acetic acid (7:93:0.1), flow rate: 0.5 mL/min, t_1 = 39.3 and t_2 = 44.4 min}. ^{1}H NMR: δ 4.03–4.17 (m, 4H), 5.44–5.48 (m, 1H), 6.86–6.93 (m, 3H), 7.21–7.26 (m, 2H), 7.80–787 (m, 4H). ^{13}C NMR: δ 20.7, 40.0, 68.8, 71.5, 116.1, 122.7, 124.9, 130.9, 133.4, 135.6, 159.7, 167.3, 171.2. ESI-MS (m/z): 339. Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.31; H, 5.03; N, 4.17.

4.4.6. *N*-(2-Acetoxy-3-(*p*-methoxy-phenoxy)propylphthalimide 13

($C_{20}H_{19}NO_6$): HPLC purity >99%; HPLC ee >99%; $[\alpha]_D^{25}$ = −14.4 (c 0.5, $CHCl_3$); mp = 90–92 °C; Abs. config (S); HPLC condition {OJH chiral column, eluent 2-propanol-hexane-acetic acid (15:85:0.1), flow rate: 0.8 mL/min, t_1 = 36.6 and t_2 = 40.4 min}. ^{1}H NMR: δ 2.03 (s, 1H), 3.76 (s, 3H), 4.00–4.11 (m, 4H), 5.39–5.47 (m, 1H), 6.83–6.86 (m, 4H), 7.71–7.77 (m, 2H), 7.83–7.89 (m, 2H). ^{13}C NMR: δ 20.2, 37.4, 54.5, 67.2, 69.0, 113.5, 114.7, 122.3, 130.5, 132.9, 149.8, 152.6, 167.2, 169.1. ESI-MS (m/z): 369. Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 65.10; H, 5.15; N, 3.77.

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References

1. (a) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561; (b) Kolb, H. C.; Sharpless, K. B. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; p 243.
2. (a) Howarth, J.; Lloyd, D. G. *J. Antimicrob. Chem.* **2000**, *46*, 625; (b) Caballero, E.; Puebla, P.; Medarde, M.; Sanchez, M.; Salvado, M. A.; Granda, S. G.; Feliciano, A. S. *J. Org. Chem.* **1996**, *61*, 1890; (c) Schnur, R. C.; Corman, M. L.; Gallaschun, R. J.; Cooper, B. A.; Dee, M. F.; Doty, J. L.; Muzzi, M. L.; Moyer, J. D.; Diorio, C. I.; Barbacci, E. G.; Miller, P. E.; O'Brien, A. T.; Morin, M. J.; Foster, B. A.; Pollack, V. A.; Sloan, D. E.; Pustilnik, L. R.; Moyer, M. P. *J. Med. Chem.* **1995**, *38*, 3806.
3. Guillou, Y.; Robin, Y. *J. Biol. Chem.* **1973**, *248*, 5668.
4. Vincek, W. C.; Aldrich, C. S.; Borchardt, R. T.; Grunewald, G. L. *J. Med. Chem.* **1981**, *24*, 7.
5. Yang, Y.; Wahler, D.; Reymond, J.-L. *Helv. Chim. Acta* **2003**, *86*, 2928.
6. Kokotos, G.; Padron, J. M.; Noula, C.; Gibbons, W. A.; Martin, V. S. *Tetrahedron: Asymmetry* **1996**, *7*, 857.
7. (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835; (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley, 1994; (c) Tomioka, K. *Synthesis* **1990**, 541; (d) Noyari, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49.
8. (a) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517; (b) Periasamy, M.; Kanth, J. V. B. *Tetrahedron* **1993**, *49*, 5127; (c) Drauz, K.; Schwarm, M.; Mckennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568.
9. (a) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420; (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421; (c) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**, *6*, 3973.
10. (a) Lei, A.; Wu, S.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 1626; (b) Hu, A.; Lin, W. *Org. Lett.* **2005**, *7*, 455.
11. (a) Fujisawa, T.; Hayashi, H.; Kishioka, Y. *Chem. Lett.* **1987**, *19*, 129; (b) Sorrilha, Anna E. P. M.; Marques, M.; Joekes, I.; Moran, P. J. S.; Rodriques, A. R. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 191.
12. Faber, K. *Biotransformations in Organic Chemistry*, 4th ed.; Institute of Organic Chemistry: University of Graz, 2000.
13. (a) Kapoor, M.; Anand, N.; Ahmad, K.; Koul, S.; Chimni, S. S.; Taneja, S. C.; Qazi, G. N. *Tetrahedron: Asymmetry* **2005**, *16*, 717; (b) Anand, N.; Kapoor, M.; Ahmad, K.; Koul, S.; Parshad, R.; Manhas, K. S.; Sharma, R. L.; Qazi, G. N.; Taneja, S. C. *Tetrahedron: Asymmetry* **2007**, *18*, 1059.
14. (a) Ing, H. R.; Manske, R. H. F. *J. Chem. Soc.* **1926**, 2349; (b) Arffin, A.; Khan, M. N.; Lan, L. C.; May, F. Y.; Yun, C. S. *Synth. Commun.* **2004**, *34*, 4439.
15. (a) Machado, A. L.; Lima, L. M.; Araujo-Jr, J. X.; Fraga, C. A. M.; Koatzc, V. L. G.; Barreiro, E. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1169; (b) Collin, X.; Robert, J.; Wielgosz, G.; Le Baut, G.; Bobin-Dubigeon, C.; Grimaud, N.; Petit, J. *Eur. J. Med. Chem.* **2001**, *36*, 639.
16. Antunes, R.; Batista, H.; Srivastava, R. M.; Thomas, G.; Araujo, C. C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3071.
17. Abdel-Hafez, A. A. *Arch. Pharm. Res.* **2004**, *27*, 495.
18. Kawagushi, S.; Ikeda, O. *Jpn. Pat. Appl. JP2001328911*, **2001**.
19. Ebihara, K.; Oora, T.; Nakaya, M.; Shiraishi S.; Yasui, N. *Jpn. Pat. Appl. JP08245585*, **1996**.
20. Gupta, P.; Shah, B. A.; Parshad, R.; Qazi, G. N.; Taneja, S. C. *Green Chem.* **2007**, *9*, 1120.
21. Henryk, M.; Leonard, G.; Barbara, F. *Acta Polym. Pharm. EN* **1996**, *53*, 47.
22. (a) *Arthrobacter sp.* cell biomass was prepared in shake flasks and in a 10 L fermentor containing medium (1% peptone, 0.5% NaCl and 0.5% beef extract, pH 7.0). The medium was inoculated with an overnight preculture prepared in the same broth. The culture was grown at 30 °C for 16–18 h at 200 rpm. The cell pellet was separated from the broth by centrifugation at 10,000×g for 15 min at 4 °C and was preserved at −20 °C until further use. *Arthrobacter sp.* microbial culture (ABL, MTCC no. 5125), isolated at institute has been deposited in the MTCC culture collection under the Budapest Treaty (2004); (b) Johri, S.; Verma, V.; Parshad, R.; Koul, S.; Taneja, S. C.; Qazi, G. N. *Bioorg. Med. Chem.* **2001**, *9*, 269; (c) Koul, S.; Taneja, S. C.; Parshad, R.; Qazi, G. N. *Tetrahedron: Asymmetry* **1998**, *9*, 3395; (d) Chaubey, A.; Parshad, R.; Koul, S.; Taneja, S. C.; Qazi, G. N. *J. Mol. Catal. B: Enzym.* **2006**, *42*, 39.
23. Crowther, A. F.; Smith, L. H. *J. Med. Chem.* **1968**, *11*, 1009.
24. (a) Wright, J. L.; Gregory, T. J.; Heffner, T. G.; MacKenzie, R. G.; Pugsley, T. A.; Meulen, S. V.; Wise, L. D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1377; (b) Lis, R.; Morgan, T. K., Jr.; Marisca, A. J.; Gomez, R. P.; Lind, J. M.; Davey, D. D.; Phillips, G. B.; Sullivan, M. E. *J. Med. Chem.* **1990**, *33*, 2883; (c) Walsh, D. A.; Chen, Y.-H.; Green, J. B.; Nolan, J. C.; Yanni, J. M. *J. Med. Chem.* **1990**, *33*, 1823; (d) Baker, N. R.; Byrne, N. G.; Economides, A. P.; Javed, T. *Chem. Pharm. Bull.* **1995**, *43*, 1045.
25. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656.