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Application of a one-pot lipase resolution strategy for the synthesis of chiral γ- and δ-lactones

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Abstract—A successful one-pot reduction of γ-ketoesters, δ-ketoesters and lactones to the corresponding 1,4- and 1,5-diols followed by a lipase catalyzed kinetic resolution coupled with hydrolysis to afford optically active diols is described. The synthetic utility of this one-pot method was illustrated by the oxidation of these chiral diols to respective chiral γ-butyrolactone and δ-lactones. Lipase from *Pseudomonas cepacia*, immobilized on ceramic afforded the product with high enantiomeric excess in good yields under mild reaction conditions. This approach has been used to develop a convenient enantioselective route for several γ- and δ-lactones using achiral and corresponding racemic starting material.

1. Introduction

A cyclic ester moiety constitutes a frequently encountered structural motif within a large variety of natural products and biologically active compounds. Moreover, the lactone functionality exists in common flavour components[1] and hence is employed in the perfumery and food industry. Derivatives of various lactones play an important role as sex attraction pheromones of different insects[2] and plant-growth regulators.[3] Chiral lactones (five- and six-membered) are important building blocks for the synthesis of natural products such as alkaloids and terpenoids,[4] and biologically active compounds (e.g. antitumour, antidepressant and antiviral agents).[5]

A variety of synthetic methods have been reported in the literature for the preparation of racemic and enantiomerically pure γ- and δ-lactones.[6] Among these methods, asymmetric induction from a chiral auxilliary[7] in the intramolecular asymmetric reduction of ketoacids with chiral hydroborating agents is prominent.[5c,8] Microbial or enzymatic reductions[9] of ketoesters followed by chemical lactonization methods are common but require coenzyme regeneration and isolation which is an inherent problem of processes based on enzymatic reductions. In recent years lipase-mediated kinetic resolutions[2c,10] and dynamic kinetic resolutions[11] of hydroxy acids, hydroxy esters and racemic lactones have been extensively studied. Furthermore, Hwang et al. suggested the possibility of enantiomeric separation of γ- and δ-lactones by *Pseudomonas cepacia* lipase using molecular modelling studies.[12] Some of these methods have limitations such as multistep low yielding processes, poor enantioselectivities and use of expensive chiral metal catalysts. These lactones have been prepared in the literature in an enantioselective manner mainly by two enzyme-based methodologies. In some procedures[2c,13a,b] two different lipases were employed for transesterification followed by hydrolysis or cyclization. There are some reports[13c] in the literature for the preparation of γ- and δ-lactones that employ microbial reduction followed by lipase-mediated acetylation before cyclization. Therefore, development of efficient synthetic methods producing enantiomerically pure lactones remains promising. In continuation to our previous work on one-pot lipase catalyzed synthesis of secondary alcohols from carbonyl compounds[14] and its utility for the synthesis of biologically important intermediates,[15] we are now reporting a new lipase catalyzed facile synthesis of chiral five- and six-membered lactones.

2. Results and discussion

The aim of this investigation has been to develop a practical synthetic route for optically active lactones

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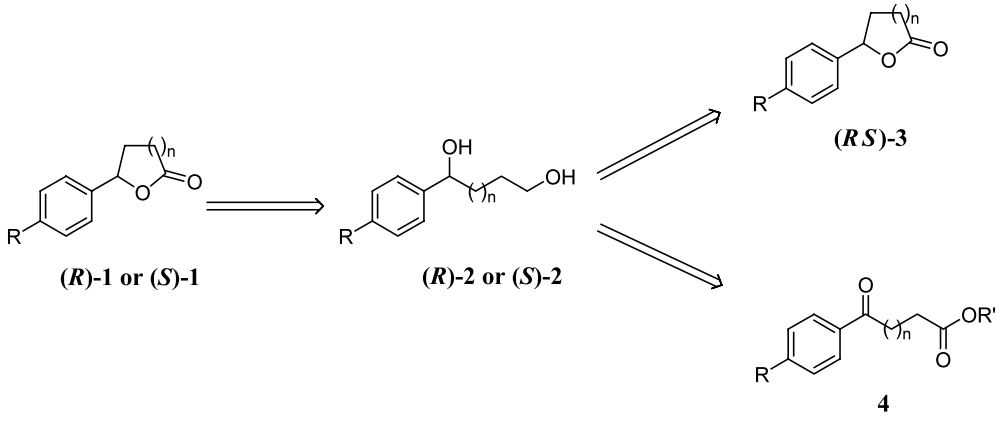
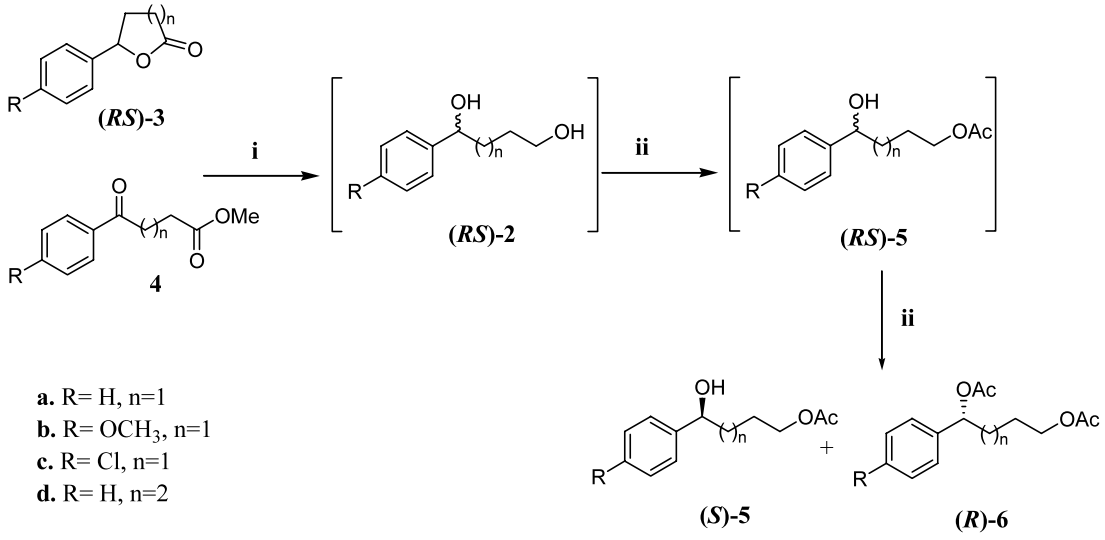
using commercially available starting materials. This has been accomplished by employing homochiral 1,4- and 1,5-diols as intermediates. In the literature there are several methods known for the preparation of 1,4- and 1,5-diols and their selective oxidation to the corresponding lactones.[16] Furthermore, 1,4- and 1,5-diols are versatile building blocks in organic synthesis and have been readily derived from commercially available synthones such as ketoesters and lactones. A retrosynthetic analysis for the formation of lactones (*R*)-**1** and (*S*)-**1** is given in Scheme 1. This strategy involves disconnection of **1** to the key intermediate diol **2**, which could be prepared from the corresponding ketoester **4** or racemic lactone **3**. Based on this and in conjunction with the one-pot lipase catalyzed synthesis of chiral secondary alcohols[14] developed by us, we have carried out the one pot reduction followed by the resolution of the corresponding lactones and ketoesters to obtain the desired chiral diols. Both the lactones **3** (γ and δ) and the ketoesters **4** have been reduced to their corresponding diols **2** by alumina assisted sodium borohydride in hexane under mild conditions (Scheme 2). Racemic diol has been subjected to lipase (*P. cepacia* immobilized on ceramic) mediated acetylation in the same pot to produce the racemic monoacetate **5** and subsequent acetylation affords non-racemic mono- and diacetates (*S*)-**5**, (*R*)-**6** in high enantioselectivity. The formation of 1,3-diols has been earlier observed by Izquierdo et al. during the lipase-mediated kinetic resolution by Chirazyme.[17] In this process it has been noticed that the regioselective monoacetylation of primary alcohol is faster than the enantioselective acetylation of the secondary alcohol at the 1-position of **5**. These products (*S*)-**5** and (*R*)-**6** can be easily separated by column chromatography and have been identified by their spectroscopic data. The effect of alumina for this enzymatic resolution process has been examined by carrying out the lipase mediated resolution directly for the diol **2a**. It is noticed that the one-pot reductive resolution process is faster in comparison to the resolution of diol **2a** in the absence of alumina (2–3 days). This difference may be due to the presence of activated alumina that could bind to the substrate and assist in the formation of enzyme–substrate complex for enhancing the rate of this reaction.[18] Different substituted ketoesters and racemic lactones have been investigated for this one-pot



Scheme 1.



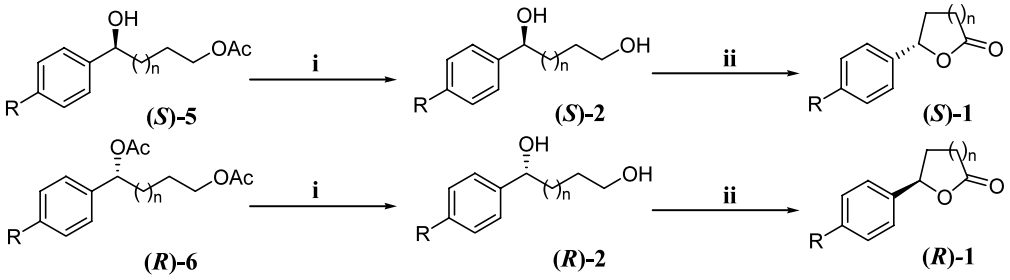
Scheme 2. *Reagents and conditions*: (i) $NaBH_4$, activated alumina, hexane; (ii) Lipase PS-C 'Amano' II, isopropenyl acetate.

reduction followed by lipase-mediated transacetylation process and the results are illustrated in Table 1. These mono **5** and diacetate **6** diols are important non-racemic precursors for the preparation of optically active γ- and δ-lactones. Accordingly, these have been hydrolyzed to the corresponding chiral diols (*S*)-**2** and (*R*)-**2** by using potassium carbonate in methanol. These upon selective oxidation of the primary hydroxy group[16a] produced the corresponding optically active γ- and δ-lactones in good enantioselectivity (Scheme 3, Table 2).

Table 1. One-pot reduction of lactones **3** and ketoesters **4** to the corresponding diols **2** and their lipase-mediated transacetylation by lipase (PS-C 'Amano' II)

Entry	Substrate **3** or **4**	Time[a] (h)	Conv.[b] (%)	**5**			**6**			E[b]
				Yield[c] (%)	E.e.[d] (%)	Config.[e]	Yield[c] (%)	E.e.[f] (%)	Config.[e]	
1	**3a**, **4a**	20	58	38	97	*S*	40	70	*R*	22
2	**3b**, **4b**	24	50	42	>99	*S*	45	>99	*R*	>500
3	**3c**, **4c**	16	54	36	92	*S*	41	77	*R*	24
4	**3d**, **4d**	16	41	46	67	*S*	39	94	*R*	64

[a] Time taken for diacetylation.
[b] Conversion calculated from ee_s and ee_6; $E = \{\ln[1-c[1+ee(6)]\}/\{\ln[1-c[1+ee(5)]\}$
[c] Isolated yields after column chromatography.
[d] Determined by chiral HPLC analysis of the corresponding diol.[21,22]
[e] The configuration were assigned based on the sign of rotation of the corresponding cyclised lactone.
[f] Determined from chiral HPLC analysis on chiracel OD-H column.[22]



a. R= H, n=1
b. R= OCH_3, n=1
c. R= Cl, n=1
d. R= H, n=2

Scheme 3. *Reagents and conditions*: (i) K_2CO_3, MeOH, 4 h; (ii) TEMPO, NCS, TBAI, CH_2Cl_2, 12 h.

Table 2. Synthesis of γ- and δ-lactones **1** by oxidation of enantiomerically pure diol **2** obtained from the hydrolysis of monoacetate **5** and diacetate **6**

Entry	Substrate **5**, **6**	**2**			**1**		
		E.e.[a] (%)	$[\alpha]_D$ (conc)[b]	Config.[c]	E.e.[a] (%)	$[\alpha]_D$ (Conc)[b]	Config.[c]
1	**5a**	97	−28.0 (1.27)	*S*	97[d]	−17.6 (1.17)	*S*
2	**5b**	>99	−25.9 (1.20)	*S*	>99	−5.2 (1.30)	*S*
3	**5c**	–[e]	−42.4 (0.82)	*S*	92	−17.2 (1.78)	*S*
4	**5d**	65	−25.4 (1.28)	*S*	65	−25.9 (0.52)	*S*
5	**6a**	70	+24.0 (1.64)	*R*	70[d]	+10.5 (0.91)	*R*
6	**6b**	>99	+19.1 (1.21)	*R*	>99	+5.5 (1.06)	*R*
7	**6c**	–[e]	+41.1 (1.24)	*R*	76	+14.8 (0.46)	*R*
8	**6d**	90	+23.4 (1.05)	*R*	90	+41.4 (1.01)	*R*

[a] Determined by HPLC with chiral column (chiracel OD or OJ).[21,22]
[b] Optical rotation recorded at 25°C in $CHCl_3$, CH_2Cl_2 and benzene (see experimental).
[c] The absolute configuration assigned by the sign of rotation of lactone **1**.
[d] Determined from chiral HPLC analysis of the corresponding diol.[22a]
[e] Not determined.

In one of the procedures[19] δ-lactone (*R*)-**1d** has been prepared by esterase (*horse liver*) hydrolysis of racemic δ-lactone **1** in 53% ee in about 2 days, whereas in the present lipase catalyzed methodology the same lactone has been prepared in 90% ee and the resolution of corresponding diol takes place in 16 h. Furthermore, the lactone **1b** has been obtained in excellent enantiomeric excess (>99% ee) by employing this one-pot protocol.

3. Conclusion

A new efficient enzymatic pathway has been developed for the synthesis of both (*R*) and (*S*) enantiopure γ- and δ-lactones from the corresponding racemic lactones and ketoesters. We have described for the first time, the lipase catalyzed in situ transesterification of 1,4- and 1,5-diols after the reduction of the corresponding lactones and ketoesters with alumina-assisted sodium borohydride in one-pot. The enhanced reaction rates in presence of alumina with high regio- and enantioselectivity in organic media like hexane provides a practical in situ biocatalytic resolution process of diols from their carbonyl precursors under mild conditions.

4. Experimental

4.1. General

Unless specified otherwise all solvents and reagents were reagent grade and used without purification. Moist neutral alumina was prepared according to the procedure of Yakabe et al.[20] Enzymatic reactions were carried out on 'Lab-line environ-shaker' at 150 rpm. Melting points have been recorded on an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on KBr pellet (unless otherwise mentioned) and are reported in wave numbers (cm^{-1}). ^1H NMR was recorded as solutions in $CDCl_3$ and chemical shifts are reported in parts per million (PPM, δ) on a 200 MHz instrument. Coupling constants are reported in hertz (Hz). Low resolution mass spectra were recorded on VG 7070H Micromass mass spectrometer at 200°C, 70 eV with a trap current of 200 μA and 4 KV acceleration voltage. Analytical TLC of all reactions was performed on Merck prepared plates (silica gel 60 F-254 on glass). Column chromatography was performed using Acme silica gel (60–120 mesh, unless otherwise mentioned). HPLC analysis was performed on an instrument that consisted of a Shimadzu LC-10AT system controller, SPD-10A fixed wavelength UV monitor as detector using chiracel OJ-H and OD column (Daicel) employing hexane and isopropanol. Specific rotation were recorded on SEPA-300 Horiba high sensitive polarimeter, fixed with sodium lamp of wavelength 589 nm.

4.2. Synthesis of the substrates

Racemic lactone **3a** and **3d** were purchased from Lancaster. Lactone **3b** and **3c** were prepared from their respective methyl 4-oxoproionate, **4a** and **4c** by $NaBH_4$ reduction in methanol. γ-Ketoesters **4a**–**4d** were prepared from commercially available respective 4-oxopropionic acid.

4.3. General procedure for one-pot synthesis of enantiopure hydroxy acetates 5a–d and diacetates 6a–d

To a solution of the lactone **3** or ketoester **4** (1 mmol) in hexane (10 mL) was added activated alumina[20] (1.0 g) and $NaBH_4$ (2 mmol). The suspension was shaken at 150 rpm at 40°C in a conical flask for 4–5 h and monitored by TLC for the complete reduction to diol. Then lipase 'Amano' PS-C II (1 equiv. w/w) and isopropenyl acetate (1.1 mL) were added to the reaction mixture. The shaking was continued further, the intermediate diol was completely consumed within 2 h to give regioselective monoacylated product **5** and little of diacetate **6**. Enantioselective acetylation of **5** to **6** was monitored by HPLC[22] analysis and stopped after 16–24 h (as indicated in Table 1). The reaction was filtered through Celite and thoroughly washed with ethyl acetate. The combined filtrate was washed with water, followed by brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue obtained was purified by silica gel column chromatography to afford enantiopure product **5** and **6**, which were analyzed by chiral HPLC[22] and compared with corresponding racemic products.

4.3.1. (*S*)-4-Hydroxy-4-phenylbutyl acetate 5a. Yield: 38%; mp 64–65°C; 97% ee (from the chiral HPLC of **2a**)[22a] t_R 29.94 min; $[\alpha]_D^{25}$ −27.3 (*c* 1.36, benzene); IR (KBr): 3450, 1740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.8 (4H, m), 2.0 (3H, s), 4.0 (2H, t, $J=5.94$ Hz), 4.6 (1H, m), 7.3 (5H, m); EIMS (*m*/*z*): 208 (M^+), 107 (M^+-101); anal. calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.0; H, 7.52%.

4.3.2. 4-Methylcarbonyloxy-1-phenyl-(1*R*)-phenylbutyl acetate 6a. Yield: 40%; 70% ee;[22d] t_R 30.18 min; $[\alpha]_D^{25}$ +48.5 (*c* 1.52, benzene); IR (KBr): 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.5–1.9 (4H, m), 2.0 (3H, s), 2.1 (3H, s), 4.0 (2H, t, $J=6.32$ Hz), 5.7 (1H, t, $J=5.94$ Hz), 7.3 (5H, m); EIMS (*m*/*z*): 207 (M^+-43); anal. calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.10; H, 7.12%.

4.3.3. (*S*)-4-Hydroxy-4-(4-methoxyphenyl) butyl acetate 5b. Yield: 42%; >99% ee;[22a] t_R 22.63 min; $[\alpha]_D^{25}$ −11.8 (*c* 1.14, benzene); IR (neat): 3450, 1730, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.7 (4H, m), 2.0 (3H, s), 3.8 (3H, s), 4.1 (2H, t, $J=5.68$ Hz), 4.6 (1H, dd, $J=7.40$, 4.91 Hz), 6.8 (2H, d, $J=8.74$ Hz), 7.3 (2H, d, $J=8.74$ Hz); EIMS (*m*/*z*): 238 (M^+), 137 (M^+-101); anal. calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.28; H, 7.53%.

4.3.4. 1-(4-Methoxyphenyl)-4-methylcarbonyloxy-(1*R*)-butyl acetate 6b. Yield: 45%; >99% ee;[22a] t_R 15.13 min; $[\alpha]_D^{25}$ +80.3 (*c* 1.01, benzene); IR (neat): 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.5–1.9 (4H, m), 2.0 (6H,

s), 3.8 (3H, s), 4.0 (2H, t, $J=6.54$), 5.7 (1H, dd, $J=6.57$, 7.38), 6.8 (2H, d, $J=8.72$), 7.2 (2H, d, $J=8.72$); EIMS (m/z): 280 (M^+-36), 237 (M^+-43); anal. calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.12; H, 7.02%.

4.3.5. (*S*)-4-(4-Chlorophenyl)-4-hydroxybutyl acetate 5c. Yield: 36%; 92% ee;[22a] t_R 18.86 min; $[\alpha]_D^{25}$ −17.0 (*c* 0.47, benzene); IR (KBr): 3454, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.5–1.8 (4H, m), 2.0 (3H, s), 4.0 (2H, t, $J=5.94$), 4.6 (1H, dd, $J=7.06$, 4.83), 7.3 (4H, m); EIMS (m/z): 242 (M^+), 141 (M^+-101); anal. calcd for $C_{12}H_{15}ClO_3$: C, 59.39; H, 6.23; Cl, 14.61. Found: C, 59.35; H, 6.20; Cl, 14.53%.

4.3.6. 1-(4-Chlorophenyl)-4-methylcarbonyloxy-(1*R*)-butyl acetate 6c. Yield: 41%; 77% ee[22c] t_R 15.93 min; $[\alpha]_D^{25}$ +60.4 (*c* 0.48, benzene); IR (KBr): 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.5–1.8 (4H, m), 2.02 (3H, s), 2.05 (3H, s), 4.0 (2H, t, $J=6.32$), 5.6 (1H, dd, $J=5.94$, 7.43), 7.3 (4H, m); EIMS (m/z): 183 (M^+-103); anal. calcd for $C_{14}H_{17}ClO_4$: C, 59.06; H, 6.02; Cl, 12.45. Found: C, 59.94; H, 6.00; Cl, 12.33%.

4.3.7. (*S*)-5-Hydroxy-5-phenylpentyl acetate 5d. Yield: 46%; 67% ee (from the chiral HPLC of **2d**)[22a] t_R 21.51 min; $[\alpha]_D^{25}$ −28.8 (*c* 0.97, benzene); IR (KBr): 3450, 1735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.3–1.9 (6H, m), 2.0 (3H, s), 4.0 (2H, t, $J=6.69$ Hz), 4.6 (1H, t, $J=6.69$ Hz), 7.2–7.4 (5H, m); EIMS (m/z): 222 (M^+); anal. calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 70.05; H, 8.0%.

4.3.8. 5-Methylcarbonyloxy-1-phenyl-(1*R*)-pentyl acetate 6d. Yield: 39%; 94% ee;[22a] t_R 11.76 min; $[\alpha]_D^{25}$ +43.2 (*c* 0.98, benzene); IR (KBr): 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.3–1.9 (6H, m), 2.0 (3H, s), 2.1 (3H, s), 4.0 (2H, t, $J=6.68$ Hz), 5.7 (1H, dd, $J=7.42$, 5.94 Hz), 7.2–7.4 (5H, m); EIMS (m/z): 264 (M^+); anal. calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.98; H, 7.35%.

4.4. General procedure for ester hydrolysis reaction

To the solution of ester **5** and **6** (1 mmol) in 10 mL methanol was added K_2CO_3 (1.5 mmol) and (2.5 mmol), respectively. The mixture was stirred for 4 h, acidified with 1N HCl and extracted with ether, after evaporation of the methanol.

4.4.1. 1-Phenyl-(1*S*)-butane-1,4 diol 2a. Yield: 98%; mp 82–83°C; >97% ee;[22a] $[\alpha]_D^{25}$ −28.0 (*c* 1.27, methanol); IR (KBr): 3350 cm^{-1} (broad); ^1H NMR (200 MHz, $CDCl_3$): δ 1.6 (2H, m), 1.8 (2H, m), 3.7 (2H, t, $J=5.73$ Hz), 4.7 (1H, t, $J=6.24$ Hz), 7.4 (5H, m); EIMS (m/z): 166 (M^+), 107 (M^+-59); anal. calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.15; H, 8.30%.

4.4.2. 1-(4-Methoxyphenyl)-(1*S*)-butane-1,4 diol 2b. Yield: 97%; mp 60°C; >99% ee;[22a] $[\alpha]_D^{25}$ −25.9 (*c* 1.20, benzene); IR (neat): 3354 cm^{-1} (broad); ^1H NMR (200 MHz, $CDCl_3$): δ 1.5 (2H, m), 1.8 (2H, m), 3.6 (2H, m), 3.8 (3H, s), 4.6 (1H, t, $J=6.74$ Hz), 6.8 (2H, d, $J=8.90$ Hz), 7.2 (2H, d, $J=8.90$ Hz); EIMS (m/z): 196 (M^+), 137 (M^+-59); anal. calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22, Found: C, 67.28; H, 8.10%.

4.4.3. 1-(4-Chlorophenyl)-(1*S*)-butane-1,4 diol 2c. Yield: 96%; mp 83–84°C; $[\alpha]_D^{25}$ −42.4 (*c* 0.82, $CHCl_3$); IR (neat): 3380 cm^{-1} (broad); ^1H NMR (200 MHz, $CDCl_3$): δ 1.6–1.9 (4H, m), 3.7 (2H, m), 4.8 (1H, t, $J=6.20$ Hz), 7.3 (4H, m); EIMS (m/z): 166 (M^+), 107 (M^+-59); anal. calcd for $C_{10}H_{13}ClO_2$: C, 59.86; H, 6.53; Cl, 17.67. Found: C, 59.64; H, 6.48; Cl, 17.50%.

4.4.4. 1-Phenyl-(1*S*)-pentane-1,5 diol 2d. Yield: 99%; 65% ee;[22a] $[\alpha]_D^{25}$ −25.4 (*c* 1.28, benzene); IR (neat): 3353 cm^{-1} (broad); ^1H NMR (200 MHz, $CDCl_3$): δ 1.2–1.8 (6H, m), 3.5 (2H, t, $J=5.73$ Hz), 4.5 (1H, t, $J=6.24$ Hz), 7.2–7.4 (5H, m); EIMS (m/z): 180 (M^+); anal. calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.18; H, 8.82%.

4.5. Oxidation of diol 2 to (*S*) and (*R*) lactone 1[15]

A solution of diol **2** (1 mmol), TEMPO (0.1 mmol, 15.6 mg), TBAI (0.1 mmol, 37.0 mg), in 10 mL of dichloromethane and 10 mL of an aqueous solution of $NaHCO_3$ (0.5 M) and K_2CO_3 (0.05 M) were vigorously stirred at room temperature. *N*-Chlorosuccinamide (3 mmol, 400 mg) was then added and the reaction was monitored for the completion. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The dichloromethane extract were washed with brine, dried, and evaporated. The residue was purified by silica gel column chromatography.

4.5.1. 5-Phenyl-5(*R*)-tetrahydro-2-furanone 1a[10b]. Yield: 78%; 70% ee (from the chiral HPLC of **2a**);[22a] $[\alpha]_D^{25}$ +10.5 (*c* 0.91, CH_2Cl_2); lit.[10b] $[\alpha]_D^{25}$ +31.0 (*c* 0.67, CH_2Cl_2); IR (KBr): 1769 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.2 (1H, m), 2.5–2.7 (3H, m), 5.5 (1H, t, $J=7.2$ Hz), 7.3 (5H, m); EIMS (m/z): 162 (M^+), 107 (M^+-55); anal. calcd for $C_{10}H_{10}O_2$: C, 74.60; H, 6.21. Found: C, 74.0; H, 6.30%.

4.5.2. 5-(4-Methoxyphenyl)-(5*R*)-tetrahydro-2-furanone 1b[10b]. Yield: 83%; >99% ee;[21] $[\alpha]_D^{25}$ +5.5 (*c* 1.06, CH_2Cl_2); lit.[10b] $[\alpha]_D^{25}$ +4.9 (*c* 1.30, CH_2Cl_2); IR (KBr): 1770 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.1–2.3 (2H, m), 2.4–2.7 (2H, m), 3.8 (3H, s), 5.4 (1H, t, $J=6.0$ Hz), 6.9 (2H, d, $J=8.54$ Hz), 7.2 (2H, d, $J=8.54$ Hz); EIMS (m/z): 192 (M^+); anal. calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 78.67; H, 6.24%.

4.5.3. 5-(4-Chlorophenyl)-(5*R*)-tetrahydro-2-furanone 1c. Yield: 68%; 76% ee; $[\alpha]_D^{25}$ +14.8 (*c* 0.46, CH_2Cl_2); IR (neat): 1770 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.0–2.2 (2H, m), 2.6 (2H, m), 5.4 (1H, t, $J=6.69$ Hz), 7.3 (4H, m); EIMS (m/z): 198 (M^++2), 196 (M^+); anal. calcd for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61; Cl, 18.03. Found: C, 61.00; H, 4.56; Cl, 17.93%.

4.5.4. 6-Phenyl-(6*R*)-tetrahydro-2*H*-2-pyranone 1d[7a]. Yield: 72%; 90% ee;[22b] $[\alpha]_D^{25}$ +41.4 (*c* 1.01, $CHCl_3$); lit.[7a] $[\alpha]_D^{25}$ +38.5 (*c* 1.0, $CHCl_3$); IR (KBr): 1740 cm^{-1}; ^1H

NMR (200 MHz, $CDCl_3$): δ 1.7–2.0 (4H, m), 2.4–2.8 (2H, m), 5.2–5.4 (1H, m), 7.2–7.4 (5H, m); EIMS (m/z): 176 (M^+); anal. calcd for $C_{11}H_{12}O_2$: C, 74.98; Hγ, 6.86. Found: C, 74.88; H, 6.82%.

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21. Determined by chiral HPLC (Chiracel, OJ-H column, Daicel) employing hexane/isopropanol = 90/10 (v/v) as mobile phase, 0.5 mL/min flow and monitored at 254 nm wavelength.
22. Determined by chiral HPLC (Chiracel OD column, Daicel) employing (a) hexane/isopropanol = 90/10 (v/v), (b) hexane/isopropanol = 85/15 (v/v), (c) hexane/isopropanol = 80/20 (v/v), (d) hexane/isopropanol = 98/02 as mobile phase, 0.5 mL/min flow and monitored at 254 nm wavelength.