Lipase PS (*Pseudomonas cepacia*) Mediated Resolution of γ-Substituted γ-((Acetyloxy)methyl)-γ-butyrolactones: Complete Stereochemical Reversion by Substituents

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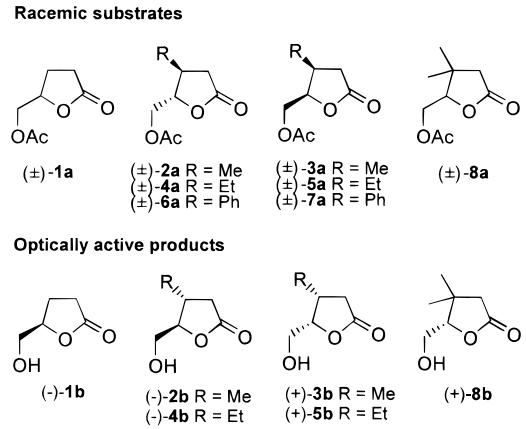
Introduction

During the past decade many organic chemists have used enzyme as biocatalysts to prepare enantiomerically pure compounds.[1] Lipases (triacylgycerol hydrolases, EC 3.1.1.3) are the most widely employed enzymes not only because they are cheap and readily available from many different sources but because they possess high enantioselectivity for a broad range of substrates and high stability in organic solvents. The utility of lipases has been demonstrated by successful kinetic resolution of diverse substrates including some γ-lactones.[2] One of the most popular lipases used in organic synthesis is lipase PS (*Pseudomonas cepacia*) from Amano Pharmaceutical Co., Ltd.[3] In the absence of an X-ray structure of the active site of this enzyme, it is difficult to predict suitable substrates and enantioselectivity. To overcome this limitation predictive active site models were proposed on the basis of the structure of known substrates and their stereoselectivities.[4,5] A three-dimensional active site model incorporating hydrophobicity and steric effects has allowed prediction of the stereoselectivity in certain cases. However all of these models work only for secondary alcohols and none is generally applicable to predict the reactivity and stereoselectivity of primary alcohols.

Chart 1



In this paper we report the successful resolution of the synthetically valuable β-substituted γ-((acetyloxy)methyl)-γ-butyrolactones in optically active form by use of lipase PS (LPS). The stereochemical results have allowed us to postulate an active site model with a more detailed description nearby the serine residue of enzyme.

Results and Discussion

The β-substituted γ-((acetyloxy)methyl)-γ-butyrolactone substrates (**1a**−**7a**) (Chart 1) were prepared by the acetylation with AgOAc of the corresponding β-substituted-γ-(iodomethyl)-γ-butyrolactones derived from stereoselective iodolactonization from ayclic carboxylates.[6,7] β,β-Dimethyl substrates (**8a**) were prepared from commercially available 4,4-dimethyl-5-(hydroxymethyl)tetrahydrofuran-2-one with AcCl and pyridine.

With γ-((acetyloxy)methyl)-γ-butyrolactone (**1a**) the hydrolytic reaction in phosphate buffer was quite fast and the enantioselectivity was moderate (entry 1 of Table 1). Use of a two-phase solvent system of aqueous buffer and hexane (1:3, v/v) accelerated the reaction, but a poorer resolution was obtained (entry 2). Addition of 3% acetone in buffer, however, produced optically active (−)-(*R*)-γ-(hydroxymethyl)-γ-butyrolactone (**1b**) at 33% conversion with 91% ee (entries 3 and 4). Thereafter a mixed solvent of buffer and acetone (97:3, v/v) was used as the reaction medium. Under this condition the successful resolution of *trans*- (**2a**) and *cis*-β-methyl-γ-((acetyloxy)methyl)-γ-butyrolactones (**3a**) were also achieved (entries 5 and 6). LPS hydrolyzed (±)-**2a** to (−)-trans-β-methyl-γ-(hydroxymethyl)-γ-butyrolactone (**2b**) with 89% ee along the unre-

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(3) Lipase PS is the industrial grade enzyme isolated from the microbe *Pseudomonas cepacia* that was previously classified as *Pseudomonas fluorescens*.

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(5) Three-dimensional active site model were proposed on the basis of substrate mapping and molecular modeling for substrates: (a) Lemke, K.; Lemke, M.; Theil, F. *J. Org. Chem.* **1997**, *62*, 6268. (b) Grabuleda, X.; Jaime, C.; Guerrero, A. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3675.

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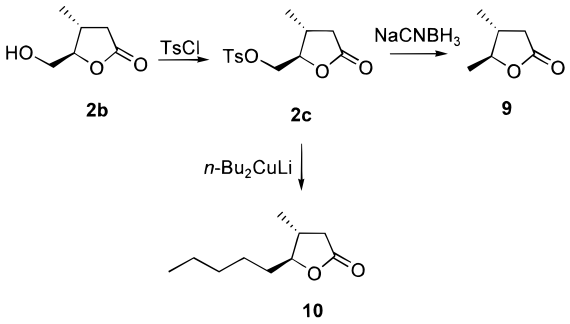
Table 1. LSP-Mediated Hydrolysis of γ-((Acetyloxy)methyl)-γ-butyrolactones (±)-[1a−8a]

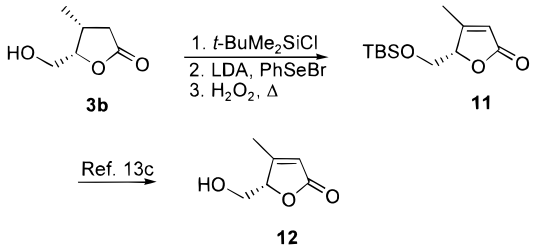
entry	substrate	solvent (v/v)	time (h)[a]	convn (%)[b]	$[\alpha]_D$	ee_s, %/config[c]	$[\alpha]_D$	ee_p, %/config[c]	E[d]
1	(±)-**1a**	buffer	0.4	29	+18.8	43/*S*	−25.4	82/*R*	9
2	(±)-**1a**	buffer/hexane (1:3)	>0.1	70	+25.6	57/*S*	−7.6	24/*R*	3
3	(±)-**1a**	buffer/acetone (97:3)	0.8	50	+38.9	84/*S*	−26.1	79/*R*	30
4	(±)-**1a**	buffer/acetone (97:3)	0.2	33	+20.1	42/*S*	−29.4	91/*R*	18
5	(±)-**2a**	buffer/acetone (97:3)	5.3	53	+49.4	94/*S*	−41.3	89/*R*	38
6	(±)-**3a**	buffer/acetone (97:3)	0.3	50	−67.8	95/*R*	+69.2	96/*S*	145
7	(±)-**4a**	buffer/acetone (97:3)	4.9	50	+53.4	76/*S*	−54.8	77/*R*	16
8	(±)-**5a**	buffer/acetone (97:3)	0.3	50	−24.8	51/*R*	+34.6	48/*S*	5
9	(±)-**6a**	buffer/acetone (97:3)	7.7	44	−0.5	2	+0.8	3	
10	(±)-**7a**	buffer/acetone (97:3)	58.1	39	−15.5	4	+27.4	7	
11	(±)-**8a**	buffer/acetone (97:3)	6.8	52	−25.3	28/*R*[e]	+17.6	26/*S*[e]	2

[a] All reactions were carried out at 35 °C. [b] Conversion rate was deduced by the NaOH consumption. This results as the same value obtained from the ee_s and ee_p within 2% errors. [c] Absolute configurations were determined by the comparison of the known compounds or the authentic samples prepared from the known starting configuration except **8**. ee values were determined by either 200 or 400 MHz ^{1}H NMR using tris[3-((trifluoromethyl)hydroxymethylene)-D-camphorato]europium(III) [Eu(hfc)$_3$] or HPLC with CHIRALPAK-AS and the eluent of ethanol. [d] E value = $\ln[(1 - \text{convn})(1 - ee_s)/\ln[(1 - \text{convn})(1 + ee_s)]$. [e] Absolute configurations were tentatively assigned on the basis of the shift behavior with Eu(hfc)$_3$ and the sign of $[\alpha]_D$ values.[8]

Scheme 1



Scheme 2



acted ester with 94% ee. The hydrolyzed product of (−)-**2b** was tosylated to give **2c** with the $[\alpha]^{20}_D$ value as −61.3 (*c* 2.7, $CHCl_3$) indicating that the absolute configurations of both asymmetric centers are *R*.[9] Reduction of **2c** by $NaCNBH_3$ in HMPA gave a natural product, (4*R*,5*S*)-4,5-dimethyltetrahydrofuran-2-one (**9**).[10] The tosylate of **2c** was treated with di-*n*-butylcuprate to yield the natural product (3*R*, 4*S*)-cognac lactone (**10**) in 84% yield[11] (Scheme 1).

In the same manner (±)-*cis*-*β*-methyl-*γ*-((acetyloxy)-methyl)-*γ*-butyrolactone (**3a**) was hydrolyzed giving (+)-*cis*-*β*-methyl-*γ*-hydroxymethyl-*γ*-butyrolactone (**3b**) with 96% ee. The reaction rates for *trans* and *cis* substrates were quite different requiring 5.3 and 0.3 h to achieve 53 and 50% conversions, respectively. The *cis* product (+)-**3b** after hydrolysis by LPS was protected by *tert*-butyldimethylsilylation and was then converted by phenylselenation and oxidation[12] to 4-methyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,5-dihydrofuran-2-one (**11**) having $[\alpha]^{20}_D$ −52.1 (*c* 1.3, $CHCl_3$).[13c] Simple deprotection led an efficient synthetic route to the natural product Umberlactone,[13] which had been isolated from *Memycelon umbelatum* Burm (Scheme 2). The absolute configurations of the hydrolyzed product **3b** were deduced as 4*R* and 5*S* by comparison with the known values of compound **11** and **12**.

Once we established the absolute stereochemistry for the favorable substrates of *trans*- (**2a**) and *cis*-*β*-methyl-*γ*-((acetyloxy)methyl)-*γ*-butyrolactones (**3a**), we realized that the configurations of the *γ*-positions were opposed.[14]

Under the established hydrolytic reaction condition *trans*- ((±)-**4a**) and *cis*-*β*-ethyl-*γ*-((acetyloxy)methyl)-*γ*-butyrolactones ((±)-**5a**) were also hydrolyzed to give *trans*- ((−)-**4b**) and *cis*-*β*-ethyl-*γ*-((acetyloxy)methyl)-*γ*-butyrolactones ((+)-**5b**) with 77 and 48% ee, respectively (entries 7 and 8). The reaction rates were quite similar to the corresponding methyl substituted substrates. To determine the absolute configurations of the hydrolyzed *trans*- and *cis*-*β*-ethyl compounds of (−)-**4b** and (+)-**5b** the authentic (4*S*,5*S*)-4-ethyl-5-(((*tert*-butyldimethylsilyl)-oxy)methyl)tetrahydrofuran-2-one (**4c**) and (5*S*)-4-ethyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,5-dihydrofuran-2-one (**14**) were prepared from available (5*S*)-5-(hydroxy-methyl)-2,5-dihydrofuran-2-one (**13**).

(8) When R = H, Me, and Et, the hydrolyzed alcohols of *R* configuration at the *γ*-position have negative $[\alpha]_D$ values, while the *S* configuration showed positive values. The methyl peak of unreacted acetyl compounds with *S* configuration at the *γ*-position was shifted further downfield compared to the corresponding peak of *R* configuration in 400 MHz ^{1}H NMR in the presence of Eu(hfc)$_3$ for the substrates of **1a**, **2a**, and **4a**.

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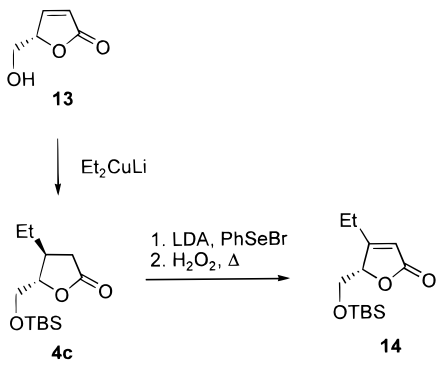
(14) Substrates **1a** and **2a**,**b** were hydrolyzed with relatively poor enantiodifferentiation by porcine pancreas lipase in phosphate buffer. We could obtain (+)-**1b**, (+)-**2b**, and (+)-**3b** with 54, 23, and 29% ee's of products at 47, 44, and 55% conversion. The absolute configurations of the *γ*-position for all three favorable substrate lactones are *S* regardless of substituents at the *β*-position.

Scheme 3



TBS protection and ethylation gave **4c** which was converted to **14 (**Scheme 3). The same compound of **4c** was prepared from the hydrolyzed alcohol of *trans*-*β*-ethyl-*γ*-(hydroxymethyl)-*γ*-butyrolactones ((−)-**4b**). The hydrolyzed product of *cis*-*β*-ethyl-*γ*-(hydroxymethyl)-*γ*-butyrolactones ((+)-**5b**) was likewise converted to **14** by the same reaction sequence shown in Scheme 3. Comparison of the optical rotation values with the authentic compounds allowed establishing the absolute configurations of (−)-**4b** and (+)-**5b** as *R* and *S* at the *γ*-position. Again, we have observed the stereochemical reversion of the hydrolytic reaction by LSP in the favorable substrates between *cis* and *trans* from the viewpoint of *γ*-(acetyloxy)-methyl) configuration. It is quite surprising that the configuration of the favorable substrates at the *γ*-position as a hydrolytic site toward LPS is completely opposite by the remote substituents at the *β*-position. The hydrolytic carbonyl site of the substrates is distanced from the *β*-position by four bonds including three carbon−carbon and one carbon−oxygen bond. Though a few cases of bioactivity difference toward the hydrolytic enzyme by remote stereocenters were reported,[15] *this is a unique observation that the favorable substrate configurations at the carbon bearing the ester functionality to be hydrolyzed by lipase is completely reversed by the other stereocenter*.

Unlike methyl and ethyl substituents, almost no stereochemical discrimination was observed for **6a** and **7a** bearing a phenyl substituent (entries 9 and 10). This means that the pocket accommodating methyl and ethyl is not compatible with the phenyl substituent. In the case of a disubstituted substrate represented by *β*,*β*-dimethyl-*γ*-acetoxymethyl-*γ*-butyrolactone (**8a**) the reaction showed poor enantioselectivity (entry 11).

All of these observations imply that there are binding pockets near the active site of the enzyme to accommodate the substituents at the *β*-position of *γ*-((acetyloxy)methyl)-*γ*-butyrolactone with the proper orientation of the backbone ring. Once the rigid part of the substrate sits on the active site properly, the relatively free acetyloxymethyl at the *γ*-position is properly aligned toward the serine residue of the enzyme to be hydrolyzed.[16] On the basis of this idea is proposed a new model with the spatial position of a hydrophobic pocket and polar surface or pocket along the flat wall relative to the reaction site as in Figure 1. The enantioselectivity of

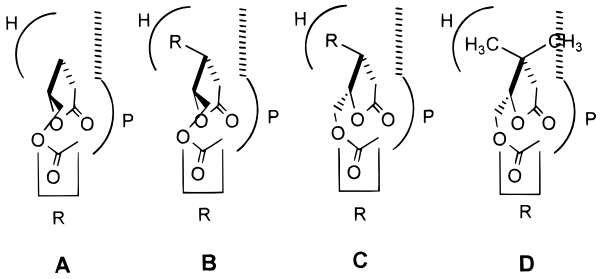


Figure 1. Active site model of LPS (H, hydrophobic; P, polar; R, reactive site).

hydrolytic reaction depends on the proper orientation of the favorable substrate toward all pockets at the reaction site by LPS. Additional hydrophobic interactions as in **B** and **C** improved the stereospecificity of the reaction with better ee for **2a** and **3a** compared to **1a** as **A** without any substituent at the *β*-position. The site that accommodates methyl is too small for an ethyl substituent, resulting in comparably poor enantioselectivity for **4a** and **5a**. Substrates with larger substituents such as phenyl were even worse, with almost no stereodifferentiation between the two enantiomers of both **6a** and **7a**. The site opposite to the hydrophobic pocket is an almost flat wall not roomy enough to afford even methyl substituent (**D**).[5] This model of binding resulted very poor stereodifferentiation of the racemic substrates bearing dimethyl substituents at the *β*-position of **8a**.

The flexibility of the bond attached to the stereocenter makes stereochemical predictions for primary alcohols difficult. Thus there have been no good models to explain the configuration of the reactive primary alcohol, while reliable and simple models have been proposed for secondary alcohols. Extension of a model for the secondary alcohols to include primary alcohols is successful with most cases lacking an oxygen atom near the reactive site of the substrate.[4e] However compounds with polar atoms or groups including oxygen are exceptions to this empirical rule. Our findings suggest that the arm of the primary alcohol is aligned properly toward the serine residue of the enzyme after the groups nearby fit the pockets. Therefore the configuration of the favorable substrate for the primary alcohol depends on the nearby groups based on size and polarity.

In conclusion enantioselectivity was achieved by the LPS-catalyzed reaction of *β*-substituted *γ*-((acetyloxy)-methyl)-*γ*-butyrolactones. Observation of the reversal of stereochemical preference by the *β*-substitutent suggests the possible stereodifferentiation by the remote stereocenters from the reactive site of the substrate.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 200 or 400 (200 and MHz for ^{1}H and 50.3 and 100.6 MHz for ^{13}C). Chemical shifts were given in ppm using TMS as internal standard. The silica gel used for column chromatography was Merck 200−230 mesh. Thin-layer chromatography was carried out with Merck 60F-254 plates with 0.25 mm thickness. Lipase PS was obtained from Amano Pharmaceutical Co., Ltd.

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(16) The minimum energy conformer generated by PM3 calculation with the program of Chem3D showed rigidity and conformational similarity of the *γ*-lactone ring between *trans*- and *cis*-*β*-methyl-*γ*-((acetyloxy)methyl)-*γ*-butyrolactones with opposite dihedral angles of *γ*-acetoxymethyl groups. However the dihedral angle of one substrate could be changed with an energy less than 1.7 kcal/mol.

Preparation of Substrates. All substrates of β-substituted γ-((acetyloxy)methyl)-γ-butyrolactones (**1a**−**7a**) were prepared from acetylation by AgOAc of the corresponding β-substituted γ-(iodomethyl)-γ-butyrolactones except **8a** which came from commercially available 4,4-dimethyl-5-(hydroxymethyl)tetrahydrofuran-2-one with AcCl and pyridine. β-Substituted γ-(iodomethyl)-γ-butyrolactones were easily prepared from acyclic olefin through reported method of stereoselective iodolactonization.[6,7]

(4*R,5*R**)-4-Ethyl-5-(iodomethyl)tetrahydrofuran-2-one**: ^{1}H NMR δ 0.94 (t, 3H, *J* = 7.2 Hz), 1.33−1.70 (m, 2H), 2.14−2.33 (m, 2H), 2.79 (dd, 1H, *J* = 19.8, 11.2 Hz), 3.31 (dd, 1H, *J* = 10.8, 4.8 Hz), 3.41 (dd, 1H, *J* = 10.8, 5.4 Hz), 4.10 (dd, 1H, *J* = 10.2, 5.0 HZ); ^{13}C NMR δ 7.08, 11.3, 26.2, 34.3, 42.1, 82.9, 175.5. Anal. Calcd for $C_7H_{11}O_2I$: C, 33.1; H, 4.36. Found: C, 33.2; H, 4.57.

(4*R,5*S**)-4-Ethyl-5-(iodomethyl)tetrahydrofuran-2-one**: ^{1}H NMR δ 0.92 (t, 3H, *J* = 7.2 Hz), 1.21−1.33 (m, 1H), 1.51−1.64 (m, 1H), 2.34−2.65 (m, 3H), 3.15−3.32 (m, 2H), 4.64 (dd, 1H, *J* = 12.8, 6.8 Hz); ^{13}C NMR δ 1.0, 11.5, 19.7, 33.8, 39.6, 81.6, 175.6. Anal. Calcd for $C_7H_{11}O_2I$: C, 33.1; H, 4.36. Found: C, 33.4; H, 4.18.

(4*R,5*R**)-4-Methyl-5-((acetyloxy)methyl)tetrahydrofuran-2-one (2a).** ^{1}H NMR δ 1.19 (d, 3H, *J* = 6.6 Hz), 2.09 (s, 3H), 2.21 (dd, 1H, *J* = 16.8, 8.6 Hz), 2.32−2.43 (m, 1H), 2.74 (dd, 1H, *J* = 16.8, 8.0 Hz), 4.09−4.37 (m, 3H); ^{13}C NMR δ 17.2, 20.2, 31.8, 36.1, 63.6, 83.5, 170.4, 175.7.

(4*R,5*S**)-4-Methyl-5-((acetyloxy)methyl)tetrahydrofuran-2-one (3a)**: ^{1}H NMR δ 1.08 (d, 3H, *J* = 7.0 Hz), 2.07 (s, 3H), 2.26 (dd, 1H, *J* = 16.4, 6.4 Hz), 2.59−2.81 (m, 2H), 4.16 (dd, 1H, *J* = 12.2, 6.0 Hz), 4.32 (dd, 1H, *J* = 12.2, 3.6 Hz), 4.60−4.68 (m, 1H); ^{13}C NMR δ 13.5, 20.4, 31.6, 36.2, 62.7, 79.4, 170.3, 176.1.

(4*R,5*R**)-4-Ethyl-5-((acetyloxy)methyl)tetrahydrofuran-2-one (4a)**: ^{1}H NMR δ 0.77 (t, 3H, *J* = 7.2 Hz), 1.24−1.83 (m, 2H), 1.89 (s, 3H), 1.97−2.21 (m, 2H), 2.46−2.62 (m, 1H), 3.94 (dd, 1H, *J* = 12.6, 6.0 Hz), 3.89−4.16 (m, 2H); ^{13}C NMR δ 11.0, 20.0, 25.4, 33.7, 38.0, 46.0, 81.8, 170.1, 175.7. Anal. Calcd for $C_9H_{14}O_4$: C, 58.1; H, 7.58. Found: C, 58.2; H,7.64.

(4*R,5*S**)-4-Ethyl-5-((acetyloxy)methyl)tetrahydrofuran-2-one (5a)**: ^{1}H NMR δ 0.97 (t, 3H, *J* = 0.97 Hz), 1.28−1.64 (m, 2H), 2.08 (s, 3H), 2.21−2.66 (m, 3H), 4.14 (dd, 1H, *J* = 12.4, 5.2 Hz), 4.36 (dd, 1H, *J* = 12.6, 1.8 Hz), 4.69 (dd, 1H, *J* = 10.2, 5.4 Hz); ^{13}C NMR δ 12.4, 20.7, 21.7, 33.8, 39.4, 63.0, 79.2, 170.5, 176.3. Anal. Calcd for $C_9H_{14}O_4$: C, 58.1; H, 7.58. Found: C, 57.9; H, 7.78.

(4*R,5*R**)-4-Phenyl-5-((acetyloxy)methyl)tetrahydrofuran-2-one (6a)**: ^{1}H NMR δ 2.03 (s, 3H), 2.74 (dd, 1H, *J* = 17.8, 9.8 Hz), 3.00 (dd, 1H, *J* = 17.8, 9.0 Hz), 3.49 (dd, 1H, *J* = 17.8, 9.0 Hz), 4.15 (dd, 1H, *J* = 12.4, 5.4 Hz), 4.32 (dd, 1H, *J* = 12.4, 2.8), 4.64 (ddd, 1H, *J* = 7.4, 5.4, 2.8 Hz), 7.21−7.40 (m, 5H); ^{13}C NMR δ 20.4, 36.7, 43.1, 63.4, 83.2, 127.0, 127.9, 129.2, 138.4, 170.4, 172.0. Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.7; H, 6.02. Found: C, 66.6, 5.93.

(4*R,5*S**)-4-Phenyl-5-((acetyloxy)methyl)tetrahydrofuran-2-one (7a)**: ^{1}H NMR δ 1.94 (s, 3H), 2.88 (d, 2H, *J* = 9.0 Hz), 3.66 (dd, 1H, *J* = 12.6, 6.6 Hz), 3.83−4.00 (m, 2H), 4.87 (td, 1H, *J* = 6.3, 3.4 Hz), 7.11−7.35 (m, 5H); ^{13}C NMR δ 20.4, 34.2, 42.5, 63.4, 80.0, 127.3, 128.0, 129.0, 136.2, 170.1, 176.0. Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.7; H, 6.02. Found: C, 66.8, 6.11.

4,4-Dimethyl-5-((acetyloxy)methyl)tetrahydrofuran-2-one (8a). Acetyl chloride (0.22 g, 2.8 mmol) and Et_3N (0.28 g, 2.8 mmol) were added to the solution of 4,4,-dimethyl-5-(hydroxymethyl)tetrahydrofuran-2-one (0.20 g, 1.4 mmol) in 5 mL of CH_2Cl_2 under N_2 atmosphere at room temperature. The resultant solution was stirred until all starting material was consumed checking by TLC in 1 h. Water was added, and the reaction product was extracted with CH_2Cl_2 three times. The organic layer was combined, washed in water and brine, dried over anhydrous $MgSO_4$, and filtered. The filterate was concentrated under reduced pressure and purified by distillation to yield 0.24 g of 4,4,-dimethyl-5-((acetyloxy)methyl)tetrahydrofuran-2-one in 92% yield: ^{1}H NMR δ 1.06 (s, 3H), 1.20 (s, 3H), 2.05 (s, 3H), 2.34 (d, 2H, *J* = 4.8 Hz), 4.09 (dd, 1H, *J* = 13.0, 8.2 Hz), 4.21−4.31 (m, 2H); ^{13}C NMR δ 20.6, 21.3, 26.1, 38.2, 43.9, 62.5, 84.8, 170.6, 175.5.

Enzymatic Resolution of Racemic γ-Lactones: Enzyme LPS (3.0 mass equiv) was added to a stirred solution of β-substituted methyl-γ-butyrolactone (0.72 mmol) in the specified solvent (15 mL). The resulting solution was stirred well at 35 °C while pH of the solution was maintained to 7.2 by adding NaOH solution (0.1 M). After the conversion of the reaction reached at certain percentage according to NaOH consumption, the reaction was quenched by adding Celite and ice. The cake was filtered through Celite with water and EtOAc. The combined organic layer was washed with water twice, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Hydrolyzed product and starting substrate were isolated and purified by flash chromatography on silica gel in more than 95% of combined yield. ee values were measured by either 200 or 400 MHz ^{1}H NMR of γ-((acetyloxy)methyl)-γ-butyrolactone in the presence of 12−15 mol % of tris[3-((trifluoromethyl)hydroxymethylene)-D-camphorato]europium(III) [Eu(hfc)$_3$]. HPLC also was used with CHIRALPAK-AS (0.46 cm i.d. × 25 cm) and the eluent of ethanol.

(4*R*,5*R*)-4-Methyl-5-(hydroxymethyl)tetrahydrofuran-2-one (2b): ^{1}H NMR δ 1.09 (d, 3H, *J* = 6.8 Hz), 2.14 (dd, 1H, *J* = 17.0, 8.4 Hz), 2.37−2.62 (m, 1H), 2.42 (bs, 1H), 2.68 (dd, 1H, *J* = 17.0, 8.4 Hz), 3.54−3.85 (m, 2H), 4.08 (dd, 1H, *J* = 6.8, 4.4 Hz); ^{13}C NMR δ 17.5, 30.8, 36.8, 62.1, 87.4, 177.4.

(4*R*,5*R*)-4-Methyl-5-((tosyloxy)methyl)tetrahydrofuran-2-one (2c). This was prepared by the reported method starting from the hydrolyzed product **2b**: $[\alpha]^{20}_D$ −61.3 (*c* 2.7, $CHCl_3$); lit.[9a] $[\alpha]^{21}_D$ −60.9 (*c* 1.25, dioxane).

(4*R*,5*S*)-4,5-Dimethyltetrahydrofuran-2-one (9). The tosylated product of **2c** (446 mg, 1.57 mmol) and $NaBH_3CN$ (394 mg, 6.28 mmol) were dissolved in 10 mL of HMPA. The resultant solution was stirred at 100 °C for 27 h for the reaction to be completed. The reaction chamber was cooled to the room temperature before adding the water. The product was extracted by 20 mL of ether twice. The organic layer was separated, washed twice with each of a $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product. This was purified by chromatography to give 84 mg of product in 47% yield: $[\alpha]^{20}_D$ −56.8 (*c* 0.18, $CHCl_3$); lit.[10b] $[\alpha]^{24}_D$ −59.7 (*c* 2.06, $CHCl_3$).

(3*R*,4*S*)-Cognac Lactone (10). This was prepared by the reported method[9] with di-*n*-butylcuprate to yield the natural product of (3*R*,4*S*)-cognac lactone in 84% yield: {$[\alpha]^{20}_D$ −73.4 (*c* 1.45, CH_2Cl_2); lit.[11c] $[\alpha]^{24}_D$ +83.2 (for the enantiomer, *c* 0.69, MeOH)}.

(4*R*,5*S*)-4-Methyl-5-(hydroxymethyl)tetrahydrofuran-2-one (3b): ^{1}H NMR δ 1.07 (d, 3H, *J* = 6.8 Hz), 2.79 (dd, 1H, *J* = 16.8, 8.0 Hz), 2.55 (dd, 1H, *J* = 17.0, 8.4 Hz), 2.91 (q, 1H, *J* = 7.4 Hz), 3.44 (bs, 1H), 3.75 (d, 2H, *J* = 4.6 Hz), 4.43−4.51 (m, 1H); ^{13}C NMR δ 13.6, 32.0, 36.6, 61.5, 83.2, 177.8.

(5S)-4-Methyl-5-((*tert*-butyldimethylsilyl)oxy)methyl)-2,5-dihydrofuran-2-one (11). *tert*-Butyldimethylsilyl chloride (1.29 g, 8.6 mmol) in CH_2Cl_2 (7 mL) was added to a solution of **3b** (91 mg, 7.9 mmol) and imidazole (0.79 mg, 11.7 mmol) in CH_2Cl_2 (7 mL). The resultant suspension was stirred at room temperature for 4 h and diluted with CH_2Cl_2, washed with 2 M HCl solution, water, and $NaHCO_3$ solution, dried, and concentrated to give an oily product. This crude product dissolved in 8 mL of THF was added at −78 °C to the reaction flask containing HMDS (0.32 g, 1.51 mmol) and *n*-BuLi (0.60 mL of 2.5 M solution, 1.51 mmol) that was premixed at 0 °C for 30 min. The resultant solution was stirred for 45 min. Into this reaction flask was added phenylseleniun bromide (0.15 g, 0.81 mol), and the mixture was stirred for 2 h before 35 mL of NH_4Cl solution was added. The reaction product was extracted with EtOAc three times. The organic layer was washed successively with $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give oily product. This crude phenyl selenide was dissolved in 16 mL of EtOAc. Into the solution was added H_2O_2 (30%, 2.5 mL), and the resultant reaction mixture was stirred in 45 min. After the reaction was completed the organic layer was separated, washed twice with each of a $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude product. This was purified by column chromatography to give 0.15 g of product in 91% yield: ^{1}H NMR δ 0.10 (s, 6H), 0.69 (s, 9H), 1.95 (s, 3H), 3.79 (dd, 1H,

J = 11.4, 3.4 Hz), 3.81 (dd, 1H, J = 11.2, 3.4 Hz), 4.69−4.72 (m, 1H), 5.66 (d, 1H, J = 1.4 Hz); ^{13}C NMR δ 6.1, 13.5, 17.6, 25.2, 61.4, 84.4, 117.3, 166.7, 173.0; $[\alpha]_D = -52.1$ (c 1.3, $CHCl_3$), lit.[13c] $[\alpha]^{23}_D$ +54.9 (for the enantiomer, c 0.85, $CHCl_3$). Anal. Calcd for $C_{12}H_{22}O_3Si$: C, 59.5; H, 9.15. Found: C, 59.7, 9.33.

(4*R*,5*R*)-4-Ethyl-5-(hydroxymethyl)tetrahydrofuran-2-one (4b): ^{1}H NMR δ 0.89 (t, 3H, J = 7.0 Hz), 1.29−1.61 (m, 2H), 2.10−2.34 (m, 2H), 2.69 (dd, 1H, J = 16.4, 7.8 Hz), 3.58 (dd, 2H, J = 12.6, 4.4 Hz), 3.82 (d, 1H, J = 12.6 Hz), 4.17 (bs, 1H); ^{13}C NMR δ 11.4, 26.0, 34.6, 37.4, 62.8, 90.0, 177.6. Anal. Calcd for $C_7H_{12}O_3$: C, 58.3; H, 8.39. Found: C, 58.5, 8.58.

(4*R*,5*S*)-4-Ethyl-5-(hydroxymethyl)tetrahydrofuran-2-one (5b): ^{1}H NMR δ 0.90 (t, 3H, J = 7.4 Hz), 1.35−1.61 (m, 2H), 2.34−2.51 (m, 3H), 3.36 (bs, 1H), 3.71 (dd, 1H, J = 12.8, 2.4 Hz), 3.82 (dd, 1H, J = 12.6, 3.2 Hz), 4.45−4.53 (m, 1H); ^{13}C NMR δ 12.4, 24.6, 34.2, 39.5, 61.2, 82.8, 178.1. Anal. Calcd for $C_7H_{12}O_3$: C, 58.3; H, 8.39. Found: C, 58.1, 8.42.

(4*R,5*R**)-4-Phenyl-5-(hydroxymethyl)tetrahydrofuran-2-one (6b)**: ^{1}H NMR δ 2.76 (dd, 1H, J = 17.8, 9.6 Hz), 2.96−3.10 (m, 2H), 3.62−3.77 (m, 2H), 3.94 (dd, 1H, J = 12.8, 2.4 Hz), 4.55 (ddd, 1H, J = 7.6, 5.2, 2.4 Hz), 7.23−7.41 (m, 5H); ^{13}C NMR δ 37.1, 41.9, 51.8, 87.1, 127.2, 127.4, 129.2, 139.3, 176.5. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.7; H, 6.29. Found: C, 68.6, 6.08.

(4*R,5*S**)-4-Phenyl-5-(hydroxymethyl)tetrahydrofuran-2-one (7b)**: ^{1}H NMR δ 2.42 (bs, 1H), 2.85 (dd, 1H, J = 17.4, 8.8 Hz), 3.03 (dd, 1H, J = 17.4, 8.4 Hz), 3.38 (dd, 1H, J = 12.4, 5.4 Hz), 3.51 (dd, 1H, J = 12.4, 3.4 Hz), 3.90 (dd, 1H, J = 16.6, 8.2 Hz), 7.48 (ddd, 1H, J = 7.6, 5.6, 3.4 Hz), 7.19−7.40 (m, 5H); ^{13}C NMR δ 34.5, 42.9, 62.0, 83.4, 127.7, 127.8, 128.9, 136.5, 177.1. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.7; H, 6.29. Found: C, 68.5, 6.12.

(4*S*,5*S*)-4-Ethyl-5-((*tert*-butyldimethylsilyl)oxy)methyl)-tetrahydrofuran-2-one (4c). The authentic compound was prepared with EtMgBr/CuCN starting from (5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,5-dihydrofuran-2-one:[17] ^{1}H NMR δ 0.40 (s, 6H), 0.89 (s, 9H), 0.91 (t, 3H, J = 7.0 Hz), 1.31−1.62 (m, 2H), 2.12 (dd, 1H, J = 17.2, 5.8 Hz), 2.26−2.36 (m, 1H), 2.71 (dd, 1H, J = 17.4, 8.8 Hz), 3.65 (dd, 1H, J = 11.4, 3.2 Hz), 3.81 (dd, 1H, J = 11.2, 3.0 Hz), 4.12−4.18 (m, 1H); ^{13}C NMR δ 5.7, 3.8, 11.3, 25.6, 26.7, 34.7, 37.9, 64.2, 85.2, 117.2; $[\alpha]_D = +24.6$ (c 1.15, $CHCl_3$). Anal. Calcd for $C_{13}H_{26}O_3Si$: C, 60.4; H, 10.1. Found: C, 60.6, 9.95. The same compound was prepared from the hydrolyzed product of **4b**: $[\alpha]_D = -18.2$ (c 0.23, $CHCl_3$).

(5*S*)-4-Ethyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,5-dihydrofuran-2-one (14). This was prepared from the hydrolyzed product of **4b** in the same manner to make (5*S*)-4-methyl-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,5-dihydrofuran-2-one (**11**): ^{1}H NMR δ 0.03 (s, 6H), 0.83 (s, 9H), 1.21 (t, 3H, J = 7.2 Hz), 2.28−2.46 (m, 2H), 3.85 (dd, 1H, J = 11.4, 3.4 Hz), 3.93 (dd, 1H, J = 11.2, 3.6 Hz), 4.82−4.87 (m, 1H), 5.80 (d, 1H, J = 1.6 Hz); ^{13}C NMR δ 5.84, 11.1, 17.9, 21.5, 25.5, 61.7, 84.1, 115.8, 172.8, 173.4; $[\alpha]_D = -68.4$ (c 0.27, $CHCl_3$). Anal. Calcd for $C_{13}H_{24}O_3Si$: C, 60.9; H, 9.43. Found: C, 60.9, 9.23. The authentic titled compound originated from (5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,5-dihydrofuran-2-one was also prepared: $[\alpha]_D = -82.1$ (c 0.85, $CHCl_3$).

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