Synthesis of α-Ketobutyrolactones and γ-Hydroxy-α-Keto Acids

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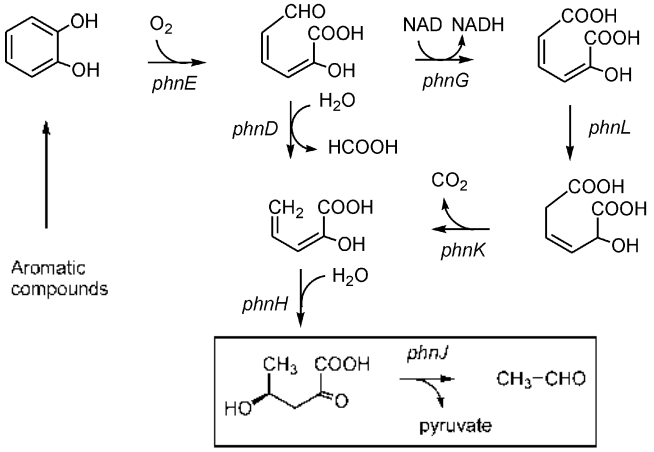
In connection with the studies for developing new enzymes that could be useful in organic synthesis, practical preparation of racemic and enantiopure forms of γ-hydroxy-α-keto acids has been successfully achieved. For racemic form of γ-hydroxy-α-keto acids, indium-mediated allylation of aldehydes with 2-(bromomethyl)acrylic acid has been employed as a key step. Oxidative cleavage of the thus formed 2-methylenebutyrolactones provided the desired α-ketobutyrolactones. Enzymatic resolution of the γ-hydroxy-α-methylene esters provided the desired γ-hydroxy-α-methylene acids which were successfully converted to γ-hydroxy-α-ketobutyrolactones in optically pure forms.

Key Words : α-Ketobutyrolactones, γ-Hydroxy-α-keto acids, Indium, Enzymes, Enantiomeric resolution

Introduction

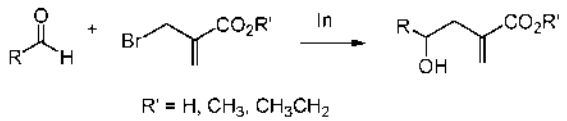
Developing new enzymes for asymmetric organic synthesis has been an attractive subject due to the possibility of practical industrial applications as well as academic interests. In connection with our research interests in exploring new enzymes, which have the potentials for useful application in organic synthesis, we have focused our investigations on the enzymes involved in the degradation pathway of arenes from *Sphingomonas sp. DJ77*.[1] One of the enzymes we have been interested in the degradation pathway is 4-hydroxy-2-oxovalerate aldolase which is responsible for converting 4-hydroxy-2-oxovalerate to acetaldehyde (Scheme 1). We have been interested in securing new useful enzymes by genetic techniques. In order to evaluate the usefulness of target enzymes, we expect to test the substrate specificity spectrum for the newly secured enzymes. Thus it is required to prepare a variety of substrates for the target enzyme, that is, 4-hydroxy-2-oxovalerate aldolase to study the substrate specificity of the enzymes expected to be obtained by the on-going genetic investigation.



Scheme 1. Degradation pathway of aromatic compounds from *Sphingomonas sp. DJ77*.

The substrates, γ-hydroxy-α-keto acids, have been known to be a part of a number of natural products. *N*-Acetylneuramic acid, 3-deoxy-D-manno-octurosonic acid (KDO), and 3-deoxy-D-arabino-hepturosonic acid-7-phosphate (DAHP) are some examples. There are several methods known for the synthesis of γ-hydroxy-α-keto acids. Key methods used are: (1) direct aldol condensation of pyruvic acid esters with aldehydes,[2] (2) reaction of anions derived from pyruvic acid dimethyl hydrazone,[3] (3) Lewis acid-promoted reaction of enol trimethylsilyl ethers of pyruvate esters with acetals,[4] (4) use of 3-bromopropyne for the introduction of the pyruvate moiety,[5] (5) use of thiazoles as a synthetic equivalent of a formyl group,[6] and (6) allylation of aldehydes using 2-(bromomethyl)acrylic acid.[7,8] We needed to secure a variety of γ-hydroxy-α-keto acids for evaluating specificity for new aldolase enzymes. Among all the methods available in the literature, we decided to adopt indium-mediated allylation of aldehydes using 2-(bromomethyl)acrylic acid as a key step due to the operational simplicity of the reaction (Scheme 2).

The indium-mediated allylation of aldehydes with 2-(bromomethyl)acrylic acid (R' = H) or 2-(bromomethyl)-acrylates (R' = Me or Et) has already been reported. Indium-mediated allylation has been widely used due to its compatibility with a variety of functional groups. Indium-mediated reaction is also unique since it could be carried out in various solvents including aqueous media.[9,10] Although utilization of this method has been reported for the synthesis



R' = H, CH_3, CH_3CH_2

Scheme 2. Indium-mediated allylation of aldehydes with 2-(bromomethyl)acrylic acids.

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of 4-substituted-4-hydroxy-2-methylenealkanoic acids, preparation of the corresponding γ-hydroxy-α-keto acids has not been yet reported.

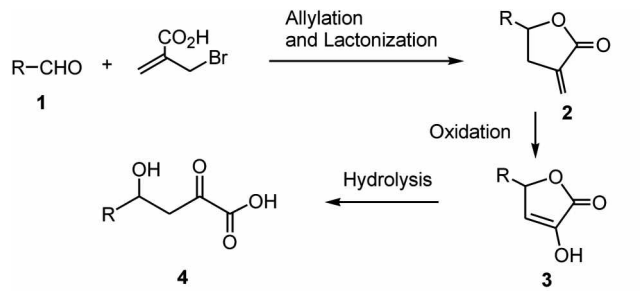
An asymmetric synthesis of γ-hydroxy-α-keto acids has also been reported. Enders and co-workers studied the asymmetric synthesis of γ-hydroxy-α-keto acids utilizing the selective aldol reaction of the corresponding keto acids derivatives.[11] Albeit being successful, this method employed a hydrazine derivative commercially unavailable and involved relatively long steps, which makes this method impractical to our purpose. A more accessible method could come from the resolution by enzymes. Therefore, the indium-mediated allylation procedure can be employed to prepare both racemic and enantiomerically pure form of γ-hydroxy-α-keto acids. Here, we report our systematic studies on the preparation of γ-hydroxy-α-keto acids in both racemic and enantiomerically pure forms in connection with our search for new enzymes that are useful in organic synthesis.

Results and Discussion

Desired γ-hydroxy-α-keto acids **4** could be prepared by indium-mediated allylation followed by lactonization (Scheme 3). Carbon-carbon double bonds in thus formed products can be cleaved oxidatively to provide α-ketobutyrolactones. The free acid form of these lactones could be obtained by hydrolysis, although cyclization back to the starting lactones is expected to be facile.

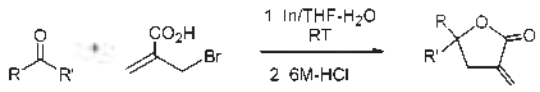
Preparation of 2-methylenebutyrolactones **2** by allylation with metals has been known.[12] However, it suffers from some difficulties such as low yield and inconvenience of handling. Indium-mediated allylation has been known for the ease of the reactions and high yields. In fact, preparation of the desired 2-methylenebutyrolactones, by indium-mediated allylation, has been reported recently.[8] We have followed the same conditions as reported. After the reaction of carbonyl compounds and 2-(bromomethyl)acrylic acid with indium in THF-H_2O (1 : 3) (for 30 min-5 h) at room temperature followed by the acid treatment led to the desired lactones in good yields. Table 1 summarized the results for the allylation using indium followed by cyclization. Aldehydes reacted faster than ketones (Table 1, entry 4 *vs.* entry 8). For unsaturated aldehydes only 1,2-addition was observed (entries 3 and 6).

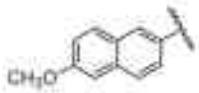
Two methods were applied for synthesizing α-keto-butyrolactones. The Johnson-Lemieux oxidation [cat. OsO_4



Scheme 3. Synthetic route for γ-hydroxy-α-keto acids.

Table 1. Preparation of 2-methylenebutyrolactones



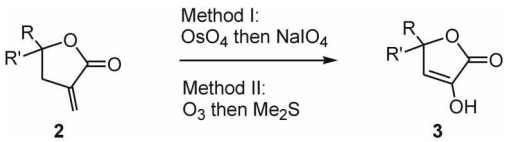
Entry	R	R'	Product (yield)
1	CH_3	H	**2a** (91)
2	$CH_3CH_2CH_2$	H	**2b** (78)
3	*trans*-CH_3CH=CH	H	**2c** (86)
4	Ph	H	**2d** (97)
5	$PhCH_2CH_2$	H	**2e** (87)
6	*trans*-PhCH=CH	H	**2f** (46)
7	$(CH_3)_3C$	H	**2g** (87)
8	Ph	CH_3	**2h** (33)
9		H	**2i** (59)

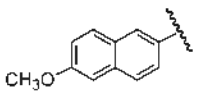
in the presence of 4-methylmorpholine *N*-oxide (NMO) to form the corresponding diols followed by oxidation with $NaIO_4$] has been successfully applied (Method I). Ozonolysis can be used also (Method II). The results are shown in Table 2. In the case of 2-methylenebutyrolactones (**2**, R = Ph and $PhCH_2CH_2$), oxidation by both methods gave similar yields. Naphthyl derivative (entry 6) is of special importance since the corresponding 2-oxobutyrolactone would generate the starting 6-methoxy-2-naphthaldehyde with interaction of aldolase and could be useful for the high-throughput screening system of aldolases.[13]

The free acid form of the α-ketobutyrolactone **3** could be obtained by hydrolysis. The free acids should be in equilibrium with the lactones. But it turned out to be difficult to obtain the acids in pure forms due to the polar nature of the acids. It has been reported that the acids could be obtained by hydrolysis by 3 N NaOH. We treated the α-ketobutyrolactones **3a** (R = CH_3) under the basic hydrolysis conditions. Formation of the new compound by TLC (hexane : ethyl acetate = 1 : 1, R_f = 0.1) was observed. The desired acid was also confirmed by the new absorption on the UV spectrum at 271 nm. These results were identical to those previously reported in the literature.[14]

After having successfully established an efficient preparation method for γ-hydroxy-β-keto acids using the indium-mediated allylation of 2-bromomethylacrylic acid, we realized that the asymmetric synthesis of the series of compounds obtained above might be needed for the future study for developing new and efficient enzymes for organic transformations. Since it has already been known that preparation of the enantiopure γ-hydroxy-α-keto acids is not easy by chemical synthesis,[11] we decided to develop an enzymatic method to prepare γ-hydroxy-α-keto acid derivatives in enantiomerically pure forms. Advantage of employing enzymatic kinetic resolution is that the same synthetic pathways as those employed for preparation of the racemic γ-hydroxy-α-keto acids could be used in principle. For searching the proper enzymes for resolution of γ-hydroxy-α-methylene esters, we

Table 2. Preparation of α-ketobutyrolactones

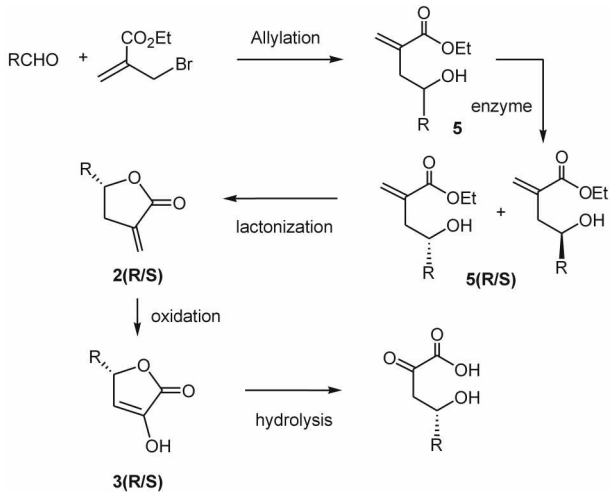


Entry	Starting lactone			Product (yield)
	2	R	R'	
1	**2a**	CH_3	H	**3a** (53)[a]
2	**2d**	Ph	H	**3d** (51)[a] **3d** (83)[b]
3	**2e**	$PhCH_2CH_2$	H	**3e** (57)[a] **3e** (56)[b]
4	**2g**	$(CH_3)_3C$	H	**3g** (74)[b]
5	**2h**	Ph	CH_3	**3h** (51)[b]
6	**2i**		H	**3i** (33)[a]

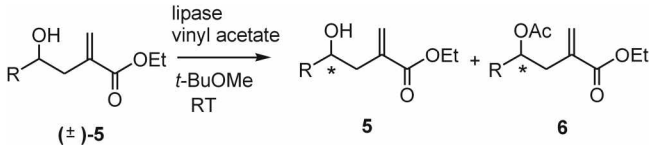
[a]Method I. [b]Method II

have screened the enzymes using the commercially available enzyme kit (ChiroScreen™-TE by Altus) having various transesterification enzymes. We tested the reactivity of the enzymes with 4-hydroxy-2-methylene-4-phenylbutyrolactone (**5**, R = Ph) as a substrate. After screening, only one enzyme (ChiroCLEC-PC) was found to be practical, since all the other enzymes showed very slow reactions with the substrate. During the course of this study we also realized that a relevant paper appeared on the preparation of 4-hydroxy-2-methylenebutanoic acid derivatives in enantiomerically pure forms by enzymatic resolution (Scheme 4).[15,16] In this paper, CHIRAZYME L-6, a lipase from Roche, was claimed to be effective for the resolution of the 4-hydroxy-2-methylenebutanoate **5**.

After screening the enzymes, we decided to use two lipases [ChriroCLEC-PC and CHIRAZYME L-6] in order to resolve the 4-hydroxy-2-methylene esters **5** and prepare



Scheme 4. Synthetic route for optically active γ-hydroxy-α-keto acids.



Scheme 5. Enzymatic resolution of 4-hydroxy-2-methylenebutanoate **5**.

the desired 2-oxobutyrolactones **3** in enantiomerically pure forms.

The substrates for resolution, that is, hydroxyesters **5** were efficiently prepared by indium-mediated allylation in THF-H_2O (1 : 3) as a solvent. The reaction mixture was quenched with HCl (1 M). Under this condition, the lactonization of the γ-hydroxy-α-methylene esters **5** was minimized.

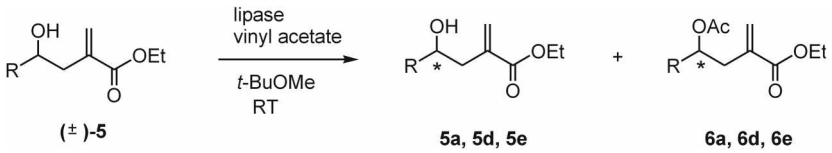
Enzymatic resolution of **5** was carried out using ChiroCLEC-PC or CHIRAZYME L-6 in *tert*-butyl methyl ether (*t*-BuOMe) as a solvent in the presence of vinyl acetate (5-10 equivalents) at room temperature (Scheme 5).

R groups tested in **5** were phenyl, phenylethyl, methyl, and *tert*-butyl. The enzyme reactions were stopped after 8-40 h. The results of the enzymatic resolution are shown in Table 3. Enantiomeric excesses were determined by HPLC with chiral columns.

In the case that R = Ph, satisfactory ee values were obtained for both hydroxy esters and acetoxy esters with both enzymes. When ChiroCLEC-PC was used, the hydroxy ester and the acetoxy ester were obtained in 94% ee and 82% ee, respectively. In contrast, when CHIRAZYME L-6 was employed, the % ee values of both esters were higher than 99%. The absolute stereochemistry of the hydroxy ester and the acetoxy ester were identified according to the literature.[15] and they are identical with both enzymes. In the case that R = phenylethyl, resolution of the ester by ChiroCLEC-PC was not as efficient as that by CHIRAZYME L-6. The former enzyme needed 40 h for the resolution, the latter, however, gave good resolution after 8 h. And the enantiomeric purity of the resulting esters also indicated the efficiency of CHIRAZYME L-6. In the case that CHIRAZYME L-6 both the % ee values and chemical yields were excellent [98% ee (93% yield) for the hydroxy ester and >99% ee (85% yield) for the acetoxy ester]. Assignment of the absolute stereochemistry was achieved by converting the hydroxy ester to the corresponding ester with Mosher's reagent.[18] Both (*R*)- and (*S*)-MTPA chloride [2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid chloride] were employed. The ^1H NMR spectra of the resulting esters were analyzed. The configuration of the carbon bearing hydroxy group in the hydroxyester is (*R*) and that of the carbon with acetoxy group in the acetoxyester is assigned as (*S*).

When R = Me, the ester could be resolved in 1-1.5 h with ChiroCLEC-PC. The isolated yields [45% (hydroxy ester) and 76% (acetoxy ester)] were relatively lower than those obtained for the previous esters. In this case, the esters obtained from the resolution by CHIRAZYME L-6 were different in terms of the sign of the optical rotation. According to the literature,[15] the hydroxy ester and the acetoxy ester from ChrioCLEC-PC were (*S*)-(+) and (*R*)-(−),

Table 3. Enzymatic Resolution of γ-hydroxy-α-methylene esters **5**



Enzyme	R	conver-sion%[b]	Compd [% ee[c] (yield[d])]		Configuration		E[e]
			5a-d	**6a-d**	**5a-d**	**6a-d**	
ChiroCLEC-PC	Ph	53	**5d** [94(97)]	**6d** [82(93)]	**5d** *S* (−)	**6d** *R* (+)	33
	$PhCH_2CH_2$	50	**5e** [68(−[a])]	**6e** [69(−[a])]	−[a]	−[a]	11
	Me	58	**5a** [90(45)]	**6a** [67(76)]	**5a** *S* (+)	**5a** *R* (−)	16
	t-butyl	NR[f]	–		–	–	–
CHIRAZYME L-6	Ph	50	**5d** [>99(85)]	**6d** [>99(92)]	**5d** *S* (−)	**6d** *R* (+)	>200
	$PhCH_2CH_2$	50	**5e** [98(93)]	**6e** [>99(85)]	**5e** *R* (+)	**6e** *S* (+)	>200
	Me	80	**5a** [88(61)]	**6a** [22(62)]	**5a** *R* (−)	**6a** *S* (+)	4
	t-butyl	NR[f]	–		–	–	–

[a]Not isolated due to the low %ee values. [b]The % conversion was calculated from the enantiomeric excess of the starting material (ee_s) and the product (ee_p) according to % conversion = $ee_s/(ee_s + ee_p)$[17]. [c]The enantiomeric excess (ee) was determined by HPLC analysis [CHIRALCEL OD and OB-H columns]. [d]Normalized to 100% conversion. [e]The enantionselectivity (ee_s) and conversion (*c*) according to $E = \ln[(1-c)(1-ee_s)]/\ln[(1-c)(1+ee_s)]$[17]. [f]No reaction.

respectively. In contrast. CHIRAZYME L-6 provided (*R*)-(−)-hydroxy ester and (*S*)-(+)-acetoxy ester. In this case. however. the E values were relatively low with both enzymes. Not surprisingly, when R group is bulky such as *tert*-butyl. resolution by both enzymes was not successful.

Esters **5**. obtained by the above-mentioned enzymatic resolution procedure. were treated with an acid. Lactonization was successfully achieved to give the corresponding lactones **2**. Ozonolysis was performed to prepare the 4-substituted-2-oxobutyrolactones **3**. The summary of this two-step transformation is shown in Table 4.

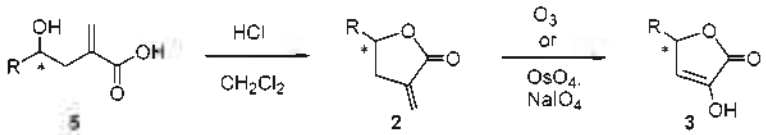
The enantiomeric purity was checked by HPLC and similar optical purity was maintained during the lactonization and ozonolysis sequence. The yields for the oxidation step were somewhat lower. Oxidation by the Lemieux-Johnson procedure could provide better results. However. we did not optimize the yields for the oxidation steps since our main concern was to test the feasibility of obtaining 2-oxobutyrolactones **3** in optically pure forms.

In conclusion. we have successfully developed a synthetic sequence for synthesizing α-ketobutyrolactones in racemic and enantiopure forms. Since the lactones could be hydrolyzed to 4-substituted-4-hydroxy-2-oxobutanoic acids, these methods also completed the synthesis of 4-hydroxy-2-oxobutanoic acids. These methods can be used for preparing the compounds that are needed for assaying enzymatic activities for aldolases.

Experimental Section

General Procedures. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM300. The chemical shifts are reported in ppm on δ scale downfield from TMS. and signal patterns are indicated as follows: s. singlet; d, doublet; t, triplet; m. multiplet. br. broad peak. Optical rotations were measured by JASCO DIP-1000 digital polarometer in solution in a 1-dm cell. Mass spectra (and HRMS) were obtained on VG AUTOSPEC Ultma GC/MS system using direct insertion probe (DIP) and electron impact (EI) (70 eV) method. HPLC analyses were performed on Gilson HPLC Model 321 322 (UV/Vis-151). The stationary phases were chiral columns (Daicel® CHIRACEL OD and CHIRALCEL OB-H). The commercially available lipases were obtained from Altus Biologics Inc. (ChriroCLEC-PC). and Roche

Table 4. Asymmetric synthesis of 2-oxobutyrolactones



R	product [%ee (yield)]					
	starting ester 5 (%ee)		**2** [%ee (yield)]		**3** [%ee (yield)]	
Ph	**5d** (>99)	*S* (−)	**2d** [92 (90)]	*S* (+)	**3d** [91 (30)]	*S* (+)
$PhCH_2CH_2$	**5e** (98)	*R* (+)	**2e** [94 (98)]	*R* (+)	**3e** [94 (45)]	*R* (+)
Me	**5a** (90)	*S* (+)	**2a** [88 (59)]	*S* (−)	**3a** [85 (29)]	*S* (+)

Diagnostics (CHIRAZYME L-6).

Synthesis of 2-methylenebutyrolactones 2. 4-Methyl-2-methylenebutyrolactone (2a): Typical Procedure. Acetaldehyde (2.20 mL, 40.0 mmol) was dissolved in THF-H_2O (1 : 3, 40 mL). Indium (4.59 g, 40.0 mmol) and 2-(bromomethyl)acrylic acid (6.59 g, 40.0 mmol) were added to the solution. The mixture was stirred for 1 h at room temperature. After the reaction was completed, HCl solution (6 M, 30 mL) was added to the reaction mixture and stirred for additional 12 h at room temperature. The solution was extracted with ethyl acetate and the organic layer was separated and dried ($MgSO_4$). After the extract was concentrated, flash chromatography (hexane : ethyl acetate = 1 : 1) provided the product **2a** as a transparent oil (4.10 g, 91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, J = 6.3 Hz, 3H, -CH_3), 2.55 (ddt, J = 16.9, 5.7, 3.0 Hz, 1H, -CH-C*H*H-C=CH_2), 3.11 (ddt, J = 16.9, 5.2, 2.3 Hz, 1H, -CH-C*H*H-C=CH_2), 4.62-4.73 (m, 1H, -OC*H*-), 5.64 (t, J = 2.1 Hz, 1H, -C=CH*H*), 6.45 (t, J = 2.1 Hz, 1H, -C=CH*H*). MS (EI): m/z (%) = 112 (M^+), 105, 100, 97, 77, 71, 70, 68 (100), 67, 65, 57, 56, 55, 53, 52.

HRMS: m/z Calcd for $C_6H_8O_2$: 112.0524. Found: 112.0523.

2-Methylene-4-propylbutyrolactone (2b): Typical Procedure. Starting from butyraldehyde (120 μL, 1.20 mmol) was dissolved in THF-H_2O (1 : 3, 3 mL). Indium (138 mg, 1.20 mmol) and 2-(bromomethyl)acrylic acid (198 mg, 1.20 mmol) were added to the solution. The mixture was stirred for 1 h at room temperature. After the reaction was completed, HCl solution (6 M, 5 mL) was added to the reaction mixture and stirred for additional 1 h at room temperature. The solution was extracted with ethyl acetate and the organic layer was separated and dried ($MgSO_4$). After the extract was concentrated, and flash chromatography (hexane : ethyl acetate = 2:1) provided the product **2b** as a transparent oil (140 mg, 78%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 7.2 Hz, 3H, -CH_3), 1.34-1.79 (m, 4H, $CH_3(CH_2)_2$-), 2.58 (ddt, J = 15.0, 5.9, 3.0 Hz, 1H, -CHCH*H*-), 3.07 (ddt, J = 15.0, 5.6, 1.98 Hz, 1H, -CHCH*H*-) 4.09-4.58 (m, 1H, -OC*H*-), 5.63 (t, J = 2.3 Hz, 1H, -C=CH*H*), 6.22 (t, J = 2.2 Hz, 1H, -C=CH*H*). MS (EI): m/z (%) = 140 (M^+), 111, 98, 97 (100), 91, 73, 71, 69, 68, 67, 57, 55, 53.

HRMS: m/z Calcd for $C_8H_{12}O_2$: 140.0837. Found: 140.0834.

2-Methylene-4-[(*E*)-1-propenyl]butyrolactone (2c). Yield 86%, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (dd, J = 6.5, 1.0 Hz, 3H, -CH_3), 2.68 (ddt, J = 17.0, 6.3, 3.1 Hz, 1H, -CHCH*H*-), 3.11 (ddt, J = 17.0, 7.8, 2.5 Hz, 1H, -CHCH*H*-), 4.90 (dd, J = 14.3, 7.2 Hz, 1H, -OC*H*-), 5.51 (ddq, J = 15.3, 7.7, 1.6 Hz, 1H, CH_3CH=CH-), 5.63 (t, J = 2.4 Hz, 1H, -C=CH*H*), 5.75-5.90 (m, 1H, CH_3C*H*=CH-), 6.23 (t, J = 2.4 Hz, 1H, -C=CH*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.6 (-CH_3), 34.2 (-CH_2-), 77.8 (-CHO-), 121.9 (-C=CH_2), 128.9 (CH_3CH=CH-), 130.8 (CH_3CH=CH-), 134.5 (-C=CH2), 170.1 (-C=O). MS (EI): m/z (%) = 138 (M^+, 100), 123, 110, 97, 95, 91, 82, 79, 77, 69, 68, 55, 53. HRMS: m/z Calcd for $C_8H_{10}O_2$: 138.0681. Found: 138.0676.

2-Methylene-4-phenylbutyrolactone (2d). Yield 97%, mp 52-54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84 (ddt, J = 17.1, 6.4, 3.2 Hz, 1H, -CHCH*H*-), 3.34 (ddt, J = 17.1, 8.1, 2.5 Hz, 1H, -CHCH*H*-), 5.46 (t, J = 7.0 Hz, 1H, -OC*H*-), 5.62 (t, J = 2.5 Hz, 1H, -C=CH*H*), 6.25 (t, J = 2.5 Hz, 1H, -C=CH*H*), 7.24-7.36 (m, 5H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 37.2 (-CH_2-), 79.0 (-CHO-), 123.5 (-C=CH_2), 126.4, 129.5, 129.9 (ArC), 135.2 (-C=CH_2), 140.8 (ArC), 171.2 (-C=O). MS (EI): m/z (%) = 174 (M^+), 129, 115, 105, 77, 68(100), 51. HRMS: m/z Calcd for $C_9H_{10}O_2$: 174.0681. Found: 174.0681.

2-Methylene-4-phenethylbutyrolactone (2e). Yield 87%, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91-2.11 (m, 2H, $PhCH_2CH_2$-), 2.61 (ddt, J = 17.0, 5.9, 3.1 Hz, 1H, -CHCH*H*-), 2.74-2.89 (m, 2H, $PhCH_2CH_2$-), 3.07 (ddt, J = 17.0, 7.7, 2.5 Hz, 1H, -CHCH*H*-), 4.48-4.57 (m, 1H, -OC*H*-), 5.65 (t, J = 2.5 Hz, 1H, -C=CH*H*), 6.27 (t, J = 2.8 Hz, 1H, -C=CH*H*), 7.21-7.35 (m, 5H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 32.0 ($PhCH_2CH_2$-), 34.2 (-CH_2-), 38.8 ($PhCH_2CH_2$-), 78.1 (-CHO-), 122.9 (-C=CH_2), 126.9, 129.1, 129.2, 135.2 (ArC), 141.3 (-C=CH_2), 170.9 (-C=O). MS (EI): m/z (%) = 202 (M^+), 118, 117(100), 115, 111, 105, 104, 103, 97, 92, 91, 79, 77, 69, 68, 65, 63, 51. HRMS: m/z Calcd for $C_{13}H_{14}O_2$: 202.0994. Found: 202.0999.

2-Methylene-4-[2-(*E*)-phenylethen-1-yl]butyrolactone (2f). Yield 46%, mp 40-44 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 (ddt, J = 17.0, 6.1, 3.0 Hz, 1H, -CHCH*H*-), 3.22 (ddt, J = 17.0, 7.9, 2.5 Hz, 1H, -CHCH*H*-), 5.13 (dd, J = 14.0, 7.0 Hz, 1H,-OC*H*-), 5.68 (t, J = 2.5 Hz, 1H, -C=CH*H*), 6.19 (dd, J = 15.8, 7.0 Hz, 1H, PhCH=C*H*-), 6.28 (t, J = 2.5 Hz, 1H, -C=CH*H*), 6.69 (d, J = 15.8 Hz, 1H, Ph*CH*=CH-), 7.26-7.41 (m, 5H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 34.9 (-CH_2-), 78.2 (-CHO-), 123.1 (-C=CH_2), 127.3, 127.4 (Ph-CH=CH- and Ph-CH=CH-), 129.1, 129.3, 133.8, 134.7 (ArC), 136.2, (-C=CH2), 170.7 (-C=O). MS (EI): m/z (%) = 200 (M^+), 172, 144, 141, 131, 129, 128, 115, 104, 103, 91, 78, 77, 69, 68 (100), 51. HRMS: m/z Calcd for $C_{13}H_{12}O_2$: 200.0837. Found: 200.0837.

4-(*t*-Butyl)-2-methylenebutyrolactone (2g). Yield 87%, **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.95 (s, 9H, -$C(CH_3)_3$), 2.73 (ddt, J = 17.5, 6.2, 3.1 Hz, 1H, -CHCH*H*-), 2.88 (ddt, J = 17.4, 7.0, 2.4 Hz, 1H, -CHCH*H*-), 4.23 (t, J = 6.9 Hz, 1H, -OC*H*-), 5.63 (t, J = 2.9 Hz, 1H, -C=CH*H*), 6.21 (t, J = 2.9 Hz, 1H, -C=CH*H*). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.3 (-$C(CH_3)_3$), 29.5 (-CH_2-), 34.9 (-$C(CH_3)_3$), 85.3 (-CHO-), 122.3 (-C=CH_2), 135.9 (-C=CH2), 171.3 (-C=O). MS (EI): m/z (%) = 154 (M^+), 139, 111, 100, 99, 98, 97, 96, 93, 69, 68, 57(100), 56, 55, 53. HRMS: m/z Calcd for $C_9H_{14}O_2$: 154.0994. Found: 154.0988.

4-Methyl-2-methylene-4-phenylbutyrolactone (2h). Yield 33%, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (s, 3H, -CH_3), 3.05 (s, 2H, -$CHCH_2$-), 5.53 (t, J = 1.0 Hz, 1H, -C=CH*H*), 6.16 (t, J = 1.0 Hz, 1H, -C=CH*H*), 7.15-7.28 (m, 5H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 30.6 (-CH_3), 43.2 (-CCH_2-), 84.6 (-CHO-), 123.3 (-C=CH_2), 124.7, 128.3, 129.2, (ArC), 135.6 (-C=CH_2), 145.1 (ArC), 170.3 (-C=O). MS (EI): m/z (%) = 188 (M^+), 173(100), 145, 130, 128, 117, 115, 105, 91, 77, 68, 51. HRMS: m/z Calcd for $C_{12}H_{12}O_2$: 188.0837. Found:

188.0843

4-(6'-Methoxynaphthalen-2'-yl)-2-methylenebutyrolactone (2i). Yield 59%. mp 112-120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90 (ddt, J = 17.1, 6.3, 3.1 Hz, 1H, -CHCH*H*-), 3.36 (ddt, J = 17.1, 8.0, 2.2 Hz, 1H, -CHCH*H*-), 3.84 (s, 3H, -OC*H*$_3$), 5.56 (t, J = 7.1 Hz, 1H, -OC*H*-), 5.62 (t, J = 2.5 Hz, 1H, -C=CH*H*), 6.25 (t, J = 2.5 Hz, 1H, -C=CH*H*), 7.05-7.11 (m, 2H, ArH), 7.25-7.28 (m, 1H, ArH), 7.63-7.70 (m, 3H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 36.2 (-*C*H$_2$-), 55.3 (-O*C*H$_3$), 78.2 (-*C*HO-), 105.6, 119.4, 122.4 (ArC), 123.4 (-*C*=CH$_2$), 124.5, 127.7, 128.4, 129.5, 134.3, 134.4 (ArC), 134.6 (-*C*=CH$_2$), 158.1 (ArC), 170.2 (-*C*=O). MS (EI): *m/z* (%) = 255 (M^++1), 254 (M^+), 209, 186, 185, 179, 165, 115, 114, 68 (100). HRMS: *m/z* Calcd for $C_{16}H_{14}O_3$: 254.0943. Found: 254.0943.

Synthesis of α-ketobutyrolactones 3. γ-Methyl-α-ketobutyrolactone (3a): Typical Procedure-Ozonolysis (Method II). A solution of 4-methylenebutyrolactone (**2a**) (4.10 g, 35.0 mmol) in CH_2Cl_2 (30 mL) was cooled down to -78 °C. Ozone was passed into the solution until the color of the solution turned to pale blue. After dimethyl sulfide (7.50 mL, 100 mmol) was added, the resulting solution was stirred for 2 h. The solution was extracted with dichloromethane and the organic layer was separated and dried ($MgSO_4$). After the extract was concentrated, and flash chromatography (hexane : ethyl acetate = 1 : 2) provided the product **3a** as a white solid (2.10 g, 53%). mp 55-60 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (d, J = 6.6 Hz, 3H, -C*H*$_3$), 5.08 (qd, J = 5.0, 1.4 Hz, 1H, -OC*H*-), 6.25 (d, J = 1.4 Hz, 1H, -C*H*=C-), 7.08 (br, 1H, -CH=C-O*H*). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.7 (-*C*H$_3$), 73.1 (-*C*HO), 120.8 (-*C*H=C-), 138.6 (-CH=*C*-), 170.8 (-*C*=O). MS (EI): *m/z* (%) = 114 (M^+), 110, 95, 93, 91, 86, 84, 79, 77, 71, 69(100), 68, 57, 55. HRMS: *m/z* Calcd for $C_5H_6O_3$: 114.0317. Found: 114.0318.

2-Oxo-4-phenylbutyrolactone (3d): Typical Procedure (Method I) OsO_4-$NaIO_4$ method. A solution of 2-methylene-4-phenylbutyrolactone (**2d**) (35 mg, 0.20 mmol), 4-methylmorpholine *N*-oxide (94 mg, 0.40 mmol), and osmium tetroxide (catalytic amount) in a solvent (acetone : H_2O : *t*-BuOH = 8 : 3 : 1) (3 mL) was stirred for 1h at room temperature. Hydrogen sulfide gas was passed into the solution for terminating the reaction. After filtration with the aid of Celite, the solution was extracted by ethyl acetate. The organic layer was separated and dried ($MgSO_4$). After the extract was concentrated, it was dissolved with dichloromethane (3 mL). $NaIO_4$ (86 mg, 0.40 mmol) and water (3 drops) was added to the solution. The resulting solution was stirred for 3 h at room temperature. After the reaction was completed, the mixture was extracted with dichloromethane (5 mL × 3) After the extracted was dried ($MgSO_4$) and concentrated, flash chromatography (hexane : ethyl acetate = 1 : 1) provided the desired product (**3d**) as a yellow solid (18 mg, 51%).

(Method II) Ozonolysis: A solution of 2-Methylene-4-phenylbutyrolactone (**2d**) (348 mg, 2.00 mmol) in CH_2Cl_2 (5 mL) was cooled down to −78 °C. Ozone was passed into the solution until the color of the solution turned to pale blue. After dimethyl sulfide (588 μL, 8.00 mmol) was added, the resulting solution was stirred for 2 h. The solution was extracted with dichloromethane and the organic layer was separated and dried ($MgSO_4$). After the extract was concentrated, flash chromatography (hexane : ethyl acetate = 1 : 1) provided the product **3d** as a yellow solid (289 mg, 83%). mp 72-80 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (d, J = 1.4 Hz, 1H, -OC*H*-), 6.29 (d, J = 1.6 Hz, 1H, -C*H*=C-), 6.47 (br, 1H, -CH=C-O*H*), 7.19-7.60 (m, 5H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 80.7 (-*C*HO-), 118.8 (-*C*H=CH-OH), 127.2, 129.1, 129.3, 137.6 (ArC), 142.2 (-CH=*C*H-OH), 170.1 (-*C*=O). MS (EI): *m/z* (%) = 176 (M^+), 147, 131(100), 120, 103, 91, 77, 63, 51. HRMS: *m/z* Calcd for $C_{10}H_8O_3$: 176.0473. Found: 176.0474.

2-Oxo-4-phenetylbutyrolactone (3e). Yields 57% (Method I), 56% (Method II). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.67-2.76 (m, 4H, PhC*H*$_2$C*H*$_2$- and PhCH$_2$C*H*$_2$-), 4.85-4.88 (m, 1H, -C*H*O-), 6.12 (d, 1H, -C*H*=C-OH), 7.11-7.26 (m, 5H, ArH). MS (EI): *m/z* (%) = 204 (M^+), 159, 131, 113, 105, 92, 91(100), 77, 65, 51. HRMS: *m/z* Calcd for $C_{13}H_{13}O_2$: 204.0786. Found: 204.0773.

4-(*t*-Butyl)-2-oxobutyrolactone (3g). Yield 74% (Method II). mp 110-114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 9H, -C(C*H*$_3$)$_3$), 4.57 (s, 1H, -OC*H*-), 6.17 (s, 1H, -C*H*=C-), 6.85 (br, 1H, -CH=C-O*H*). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.5 (-C(*C*H$_3$)$_3$), 34.9 (-*C*(CH$_3$)$_3$), 87.2 (-*C*HO-), 117.0 (-*C*H=C-), 142.8 (-CH=*C*-), 170.6 (-*C*=O). MS (EI): *m/z* (%) = 156 (M^+), 141, 111, 100, 99, 95, 71, 69, 67, 58, 57 (100), 55, 53, 51. HRMS: *m/z* Calcd for $C_8H_{12}O_3$: 156.0786. Found: 156.0789.

4-Methyl-2-oxo-4-phenylbutyrolactone (3h). Yield 51% (Method II), mp 58-62 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82 (s, 3H, -C*H*$_3$), 6.47 (s, 1H, -C*H*=C-), 7.18-7.35 (m, 5H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.3 (-*C*H$_3$), 86.6 (Ph(CH$_3$)*C*-), 125.0 (-*C*H=C-), 125.5, 129.0, 129.3, 140.8 (ArC), 141.6 (-CH=*C*-), 170.7 (-*C*=O). MS (EI): *m/z* (%) = 190 (M^+), 175, 145, 134 (100), 119, 115, 105, 91, 77, 51. HRMS: *m/z* Calcd for $C_{11}H_{10}O_3$: 190.0630. Found: 190.0632.

4-(6'-Methoxynaphthalen-2-yl)-2-oxobutyrolactone (3i). Yield 33% (Method I), mp 156-162 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3H, -OC*H*), 5.66 (br, 1H, -C*H*=C-OH), 6.05 (d, J = 1.8 Hz, 1H, -OCH), 6.51 (d, J = 1.9 Hz, 1H, -CH=C-), 7.10-7.90 (m, 7H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.3 (-OCH$_3$), 80.9 (-OCH-), 118.3 (-*C*H=CH-OH) 105.7, 119.5, 124.4, 126.7, 127.7, 128.5, 129.5, 129.9, 135.0, 142.1 (ArC), 158.4 (-CH=*C*H-OH), 170.2 (-*C*=O). MS (EI): *m/z* (%) = 256 (M^+), 211(100), 183, 168, 152, 140, 139, 114, 99, 69, 56. HRMS: *m/z* Calcd for $C_{15}H_{12}O_4$: 256.0736. Found: 256.0735.

Asymmetric Synthesis of γ-hydroxy-α-keto acid derivatives. Enzymatic resolution of γ-hydroxy-α-methylene esters 5. (*S*)-(−)-Ethyl 4-hydroxy-2-methylene-4-phenylbutanoate [(*S*)-(−)-5d] and (*R*)-(+)-4-Ethyl acetoxy-2-methylene-4-phenylbutanoate [(*R*)-(+)-6d]: Method I (using ChiroCLEC-PC), Typical Procedure. Hydroxyester (±)-**5d** (44 mg, 0.20 mmol) was dissolved into *t*-butyl methyl ether (1 mL) and to this solution was added vinyl

acetate (37 μL, 0.40 mmol) and ChiroCLEC-PC (12 mg). Progress of the reaction was monitored by TLC and the reaction was terminated when the amount of ester and acetoxy ester appeared to be equal. After stirring for 8 h at room temperature, the enzyme was removed by filtering with the aid of Celite. The filtrate was concentrated under reduced pressure. Flash chromatography (hexane : ethyl acetate = 4 : 1) provided hydroxy ester ((*S*)-(−)-**5d**, 21 mg, 97%) and acetoxy ester ((*R*)-(+)-**6d**, 26 mg, 93%). The ee's of the compounds were measured by HPLC.

(*S*)-(−)-5d: HPLC t_R [CHIRALCEL OD (*n*-hexane/*iso*-propanol 90 : 10), flow 0.5 mL/min, 254 nm] = 13.63, 14.12. $[\alpha]_D^{24.8}$ = -20.4° (*c* 1.04, $CHCl_3$), % ee = 94.

(*R*)-(+)-6d: HPLC t_R [CHIRALCEL OD (*n*-hexane/*iso*-propanol 90 : 10), flow 0.5 mL/min, 254 nm] = 8.47, 9.03. $[\alpha]_D^{24.1}$ = +40.7 (*c* 1.48, $CHCl_3$), % ee = 82.

(*S*)-(−)-Ethyl 4-hydroxy-2-methylene-4-phenylbutanoate [(S)-(−)-5d] and (*R*)-(+)-Ethyl 4-acetoxy-2-methylene-4-phenylbutanoate [(*R*)-(+)-6d]: Method II (using CHIRAZYME L-6), Typical procedure. Hydroxy ester (±)-**5d** (0.11 g, 0.50 mmol) was dissolved into *t*-butyl methyl ether (1 mL) and to this solution was added vinyl acetate (0.43 mL, 5.0 mmol) and L-6 (10 mg). Progress of the reaction was monitored by TLC and the reaction was terminated when the amount of ester and acetoxy ester appeared to be equal. After stirring for 8 h at room temperature, the enzyme was removed by filtering with the aid of Celite. The filtrate was concentrated under reduced pressure. Flash chromatography (hexane : ethyl acetate = 5 : 1) provided hydroxy ester ((*S*)-(−)-**5d**, 47 mg, 85%) and acetoxy ester ((*R*)-(+)-**6d**, 61 mg, 92%). The ee's of the compounds were measured by HPLC.

(*S*)-(−)-5d: HPLC t_R [CHIRALCEL OD (*n*-hexane/*iso*-propanol 90 : 10), flow 0.5 mL/min, 254 nm] = 13.77. $[\alpha]_D^{25.9}$ = -26.7° (c 1.11, $CHCl_3$), % ee = > 99.

(*R*)-(+)-6d: HPLC t_R [CHIRALCEL OD (*n*-hexane/*iso*-propanol 90 : 10), flow 0.5 mL/min, 254 nm] = 8.70. $[\alpha]_D^{25.7}$ = +64.6° (*c* 1.08, $CHCl_3$), % ee = > 99.

(*R*)-(+)-Ethyl 4-hydroxy-2-methylene-6-phenylhexanoate [(*R*)-(+)-5e] and (*S*)-(−)-Ethyl 4-acetoxy-2-methylene-6-phenylhexanoate [(*S*)-(−)-6e]: Method I (using Chiro-CLEC-PC).

(*R*)-(+)-5e: HPLC t_R [CHIRALCEL OD (*n*-hexane/*iso*-propanol 90 : 10), flow 0.5 mL/min, 254 nm] = 13.49, 16.26; % ee = 68. **(*S*)-(−)-6e:** HPLC t_R [CHIRALCEL OD (*n*-hexane/*iso*-propanol 90 : 10), flow 0.5 mL/min, 254 nm] = 7.97, 9.57; % ee = 69.

Ethyl (*R*)-(+)-4-hydroxy-2-methylene-6-phenylhexanoate [(*R*)-(+)-5e] and Ethyl (*S*)-(−)-4-acetoxy-2-methylene-6-phenylhexanoate[(*S*)-(−)-6e]; Method II (using CHIRAZYME L-6).

(*R*)-(+)-5e (Yield 93%): HPLC t_R [CHIRALCEL OD (*n*-hexane/*iso*-propanol 90 : 10), flow 0.5 mL/min, 254 nm] = 14.20, 15.71. $[\alpha]_D^{28.7}$ = +20.3 (*c* 1.04, $CHCl_3$), % ee = 98.

(*S*)-(+)-6e (Yield 85%): HPLC t_R [CHIRALCEL OD (*n*-hexane/*iso*-propanol 90 : 10), flow 0.5 mL/min, 254 nm] = 9.47. $[\alpha]_D^{28.2}$ = +11.8 (*c* 1.22, $CHCl_3$), % ee = > 99.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, *J* = 7.1 Hz, 3H, -OCH_2CH_3). 1.93-2.04 (m, 2H, $PhCH_2CH_2$-), 2.07 (s, 3H, -$(CO)CH_3$). 2.55 (dd, *J* = 13.9, 8.3 Hz, 1H, -CHCH*H*-). 2.70-2.81 (m, 3H, $PhCH_2CH_2$- and -CHCH*H*-). 4.29 (q, *J* = 7.1 Hz, 2H, -OCH_2CH_3), 5.12 (m, 1H, -C*H*(OH)CH_2-). 5.64 (d, *J* = 1.0 Hz, 1H, -C=CH*H*). 6.28 (d, *J* = 1.0 Hz, 1H, -C=CH*H*), 7.24-7.41 (m, 5H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (-OCH_2CH_3), 21.0 (-CH_3), 31.7 ($PhCH_2CH_2$-), 35.8 ($PhCH_2CH_2$-), 37.0 (-$CHCH_2$-), 60.8 (-OCH_2CH_3), 72.1 (-CH(OAc)-), 125.9 (-C=CH_2), 126.3, 127.2, 128.3, 128.4, 136.7 (ArC), 141.4 (-C=CH_2), 166.6 (-C=O), 170.5 (-OC=O).

Ethyl (*S*)-(+)-4-hydroxy-2-methylenepentanoate [(*S*)-(+)-5a] and Ethyl (*R*)-(−)-4-acetoxy-2-methylenepentanoate [(*R*)-(−)-6a]: Method I (using ChiroCLEC-PC).

(*S*)-(+)-5a (Yield 45%); HPLC t_R [CHIRALCEL OB-H (*n*-hexane/*iso*-propanol 98 : 2), flow 0.6 mL/min, 220 nm] = 18.19, 21.32. $[\alpha]_D^{27.7}$ = +13.0° (*c* 1.12, $CHCl_3$), % ee = 90.

(*R*)-(−)-6a (Yield 76%): HPLC t_R [CHIRALCEL OB-H (*n*-hexane/*iso*-propanol 98 : 2), flow 0.6 mL/min, 220 nm] = 11.69, 13.02. $[\alpha]_D^{26.4}$ = -0.98° (*c* 1.14, $CHCl_3$), % ee = 67.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.8 Hz, 3H, -CH_3), 1.27 (t, *J* = 7.1 Hz, 3H, -OCH_2CH_3), 1.96 (s, 3H, -$(CO)CH_3$). 2.47 (dd, *J* = 14.0, 7.8 Hz, 1H, -CHCH*H*-). 2.56 (d, *J* = 14.1, 5.0 Hz, 1H, -CHCH*H*-), 4.18 (q, *J* = 7.1 Hz, 2H, -OCH_2CH_3). 5.02-5.12 (m, 1H, CH_3CH(OH)-). 5.55 (d, *J* = 1.1 Hz, 1H, -C=CH*H*). 6.18 (d, *J* = 1.1 Hz, 1H, -C=CH*H*). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.8 (-OCH_2CH_3), 21.1 (-$(CO)CH_3$), 21.8 (-$CHCH_3$), 39.0 (-(COH)CH_2-), 61.5 (-OCH_2CH_3), 69.9 (-C(OAc)CH_2-), 127.8 (-C=CH_2), 137.5 (-C=CH_2), 167.4 (-C=O), 171.1 (-OC=O).

Ethyl (*R*)-(−)-4-hydroxy-2-methylenepentanoate [(*R*)-(−)-5a] and Ethyl (*S*)-(+)-4-acetoxy-2-methylenepentanoate [(*S*)-(+)-6a]; Method II (using CHIRAZYME L-6).

(*R*)-(−)-5a (Yield 61%): HPLC t_R [CHIRALCEL OB-H (*n*-hexane/*iso*-propanol 98 : 2), flow 0.6 mL/min, 220 nm] = 19.10, 21.19, % ee = 88.

(*S*)-(+)-6a (Yield 62%); HPLC t_R [CHIRALCEL OB-H (*n*-hexane/*iso*-propanol 98 : 2), flow 0.6 mL/min, 220 nm] = 11.69, 13.65, % ee = 22.

Lactonization. (*S*)-(+)-2-Methylene-4-phenylbutyrolactone [(*S*)-(+)-2d]: Typical Procedure. (*S*)-(−)-Hydroxy ester **5d** (38 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (1 mL) and HCl (6 M, 1 mL) was added. The solution was stirred for 12 h at room temperature. After the reaction was completed, the solution was extracted with ethyl acetate and the organic layer was separated and dried ($MgSO_4$). Flash chromatography (hexane : ethyl acetate = 5 : 1) provided lactone **(*S*)-(+)-2d** as a transparent oil (27 mg, 90%).

HPLC t_R [CHIRALCEL OD (*n*-hexane/*iso*-propanol 90 : 10), flow 0.5 mL/min, 220 nm] = 18.68, 21.11. $[\alpha]_D^{25.8}$ = +17.6 (*c* 1.44, $CHCl_3$), % ee = 92.

(*R*)-(+)-2-Methylene-4-phenetylbutyrolactone [(*R*)-(+)-2e]: Typical Procedure. (*R*)-(+)-Hydroxy ester **5e** (0.12 g, 0.60 mmol) was dissolved in CH_2Cl_2 (1 mL) and HCl (6 M, 1 mL) was added. The solution was stirred for 12 h at room temperature. After the reaction was completed, the solution

was extracted with CH_2Cl_2 and the organic layer was separated and dried ($MgSO_4$). Flash chromatography (hexane : ethyl acetate = 5 : 1) provided lactone **(*R*)-(+)-2e** as a transparent oil (0.12 g, 98%).

HPLC t_R [CHIRALCEL OD (*n*-hexane/*iso*-propanol 90 : 10), flow 0.5 mL/min, 220 nm] = 23.00, 24.53. $[\alpha]_D^{27.8}$ = +76.5° (*c* 1.04, $CHCl_3$), % ee = 94.

(*S*)-(−)-4-Methyl-2-methylenebutyrolactone [(*S*)-(−)-2a]. Yield 59%, HPLC t_R [CHIRALCEL OB-H (*n*-hexane/*iso*-propanol 98 : 2), flow 0.8 mL/min, 220 nm] = 3.51, 6.25. $[\alpha]_D^{23.6}$ = -30.3° (*c* 1.01, $CHCl_3$), % ee = 88.

(*S*)-(+)-2-Oxo-4-phenylbutyrolactone ((*S*)-(+)-3d): Typical procedure. A solution of (*S*)-(+)-α-methylene lactone **2d** (31 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was cooled down to 78 °C. Ozone was passed into the solution until the color of the solution turned to pale blue. After dimethyl sulfide (66 μL, 0.90 mmol) was added, the resulting solution was stirred for 2 h. The solution was extracted with dichloromethane and the organic layer was separated and dried ($MgSO_4$). After the extract was concentrated, and flash chromatography (hexane : ethyl acetate = 2 : 1) provided the product **(*S*)-(+)-3d** as a white solid (9.0 mg, 30%).

HPLC: t_R [CHIRALCEL OD (*n*-hexane/*iso*-propanol 90 : 10), flow 0.6 mL/min, 220 nm] = 18.32, 21.07. $[\alpha]_D^{25.7}$ = +46.6° (*c* 0.71, $CHCl_3$), % ee = 91.

(*R*)-(+)-2-Oxo-4-phenetylbutyrolactone ((*R*)-(+)-3e). Yield 45%. HPLC t_R [CHIRALCEL OD (*n*-hexane/*iso*-propanol 90 : 10), flow 0.6 mL/min, 220 nm] = 23.94, 30.45. $[\alpha]_D^{23.9}$ = +51.2 (*c* 0.62, $CHCl_3$), % ee = 94.

(*S*)-(+)-2-Oxo-4-methylbutyrolactone ((*S*)-(+)-3a). Yield 29%, HPLC t_R [CHIRALCEL OB-H (*n*-hexane/*iso*-propanol 98 : 2), flow 0.8 mL/min, 220 nm] = 4.68, 7.51. $[\alpha]_D^{25.5}$ = +164.0° (*c* 0.53, $CHCl_3$), % ee = 85.

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