Yasutaka Shimotori*, Masayuki Hoshi, Keita Inoue, Takeshi Osanai, Hayato Okabe and Tetsuo Miyakoshi

Preparation of optically active 4-substituted γ-lactones by lipase-catalyzed optical resolution

Abstract: Optically active 4-substituted γ-lactones (**3** and **4**) were synthesized effectively using lipase-catalyzed optical resolution. *N*-methyl-4-hydroxyalkanamides (*rac*-**1a–i**) as substrates were prepared from *N*-methylsuccinimide. The alkylation of *N*-methylsuccinimide using Grignard reagents generated from various alkyl halides followed by reduction resulted in *N*-methyl-4-hydroxyalkanamides. The optical resolution of *rac*-**1a–g** was performed using Novozym 435-catalyzed stereoselective acetylation. The stereoselective preparation of 4-substituted γ-lactones (**3** and **4**) possessing various side chains such as isopentyl, phenyl, and phenethyl groups was achieved with more than 90% enantiopurity.

Keywords: enantioselective acetylation; enzymatic resolution; Grignard reaction; γ-lactone; organolithium reagent.

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Introduction

γ-Lactones are well-known natural flavor and fragrance compounds [1–3], pheromone components [4–7], and useful building blocks [8–11] for pharmaceutical synthesis. These lactones are present in a wide variety of natural products, such as mango [12, 13], peach [14, 15], strawberry [16, 17], Gouda cheese [18, 19], and other dairy products [20, 21]. The preparation of optically active compounds has become very important for the development of new biologically active substances containing one or several chiral centers, considering that many chiral drugs [22, 23] and agrochemicals [24, 25] display quite different activity and toxicity profiles with respect to their absolute configuration. Chiral lactones are important components in the synthesis of natural products and biologically active compounds, such as antitumor, antidepressant, and antiviral agents. Ghosh et al. [26] synthesized (+)-cryptophycin 52, a potent antimitotic antitumor agent, by using chiral 4-phenyl-γ-butyrolactone as a building block. This γ-lactone was also used for the preparation of other biologically active compounds [27, 28]. In addition, Kotkar et al. [29] reported the synthesis of (+)-harzialactone starting with chiral 5-phenyl-γ-pentalactone. This lactone exhibits strong antitumor and cytotoxic activities against cultured P388 cells. Here we report the preparation of various chiral γ-lactones by optical resolution using lipase-catalyzed enantioselective acetylation.

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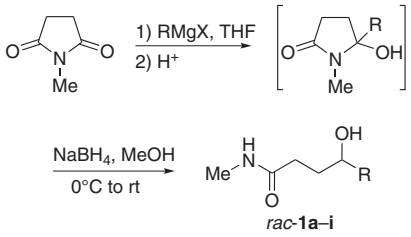
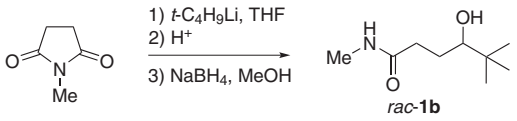
Results and discussion

Preparation of *N*-methyl-4-hydroxyalkanamides

We have previously reported the preparation of various *N*-methyl-4-hydroxyalkanamides from *N*-methylsuccinimide by the Grignard reaction and subsequent reductive reaction [30]. In this paper, the introduction of various functional groups was investigated (Scheme 1, Table 1). Alkylations with primary alkyl halides yielded the corresponding *N*-methyl-4-hydroxyalkanamides (*rac*-**1a**,**e**,**f**) in the yields ranging from 61% to 79% (entries 1, 5, and 6). With aryl bromides, *N*-methyl-4-hydroxyalkanamides (*rac*-**1c**,**d**,**g**) were synthesized with yields in the range of 87–94% (entries 3, 4, and 7). By contrast, the purification of *N*-methyl-4-hydroxyalkanamides (*rac*-**1b**,**h**,**i**) obtained from secondary and tertiary alkyl bromides was not satisfactory, and the crude yields were very low (entries 2, 8,



Scheme 1: Synthesis of *N*-methyl-4-hydroxyalkanamides with Grignard reagent.



Scheme 2: Synthesis of *N*-methyl-4-hydroxy-5,5-dimethylhexanamide *rac*-**1b**.

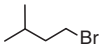
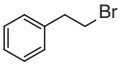
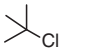
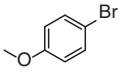
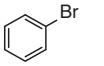
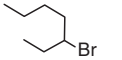
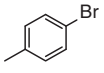
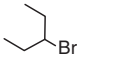
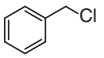
and 9). These decreases in yield result from the side reactions such as the Wurtz reaction and olefin formation, and the low reactivity is caused by steric hindrance [31, 32]. Accordingly, the reactions with organolithium reagents were attempted (Scheme 2). The reactivity of organolithium reagents is higher than that of Grignard reagents and organozinc reagents [33]. Organolithium reagents can generally be used as nucleophiles. Many reports have been published about effective alkylation using organolithium reagents [34–39]. *N*-methyl-4-hydroxy-5,5-dimethylhexanamide (*rac*-**1b**) substituted with a *tert*-butyl group was synthesized with 44% yield using *tert*-butyllithium.

Lipase-catalyzed enantioselective acetylation of *N*-methyl-4-hydroxyalkanamides

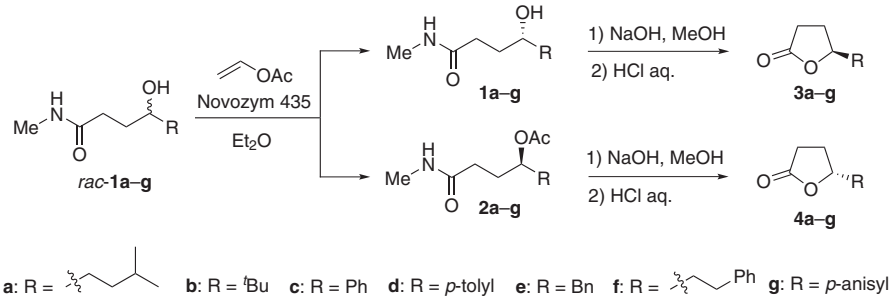
We have previously reported detailed studies of lipase-catalyzed enantioselective acetylation [30, 40]. The lipase-catalyzed acetylation was performed in diethyl ether using *N*-alkyl-4-hydroxyalkanamides as substrates, vinyl acetate as acyl donor, and Novozym 435 as lipase. These conditions result in high enantioselectivity, and both enantiomers of various γ-lactones have successfully been obtained with more than 99% enantiopurity. In that previous work, lipase screening has been examined using Novozym 435 (immobilized from *Candida antarctica*), porcine pancreas lipase (PPL) (from porcine pancreas), lipase from *pseudomonas fluorescens*, immobilized (LPI) (immobilized from *Pseudomonas fluorescens*), and Lipozym IM (immobilized from *Mucor miehei*) in the acetylation of racemic *N*-methyl-4-hydroxyundecanamide that is similar in structure to *rac*-**1**. With a notable exception of Novozym 435, these lipases exhibit no reactivity toward racemic *N*-methyl-4-hydroxyundecanamide.

To determine the optimal amount of Novozym 435, the reaction was conducted in diethyl ether at room temperature with different ratios of Novozym 435–1.0 mmol of the substrate. It was concluded that 0.4 g is the optimal amount of Novozym 435–1.0 mmol of the substrate. The acetylation with Novozym 435 proceeds well for all substrates except *rac*-**1b**, although the time required to reach approximately 50% conversion varies for different starting materials (Scheme 3, Table 2). We have previously studied Novozym 435-catalyzed acetylation of racemic *N*-methyl-4-hydroxynonanamide [40]. The 50% conversion was reached in 2 h, and (*R*)- and (*S*)-γ-nonalactone were obtained with 98% and more than 99% enantiopurities, respectively. In this work, Novozym 435-catalyzed acetylation of *rac*-**1a** required 4 h despite the structural small difference between *n*-pentyl and isopentyl groups.

Table 1: Preparation of compounds *rac*-**1a–i** (see Schemes 1 and 2).

Entry	R-X	Product	Yield (%)	Entry	R-X	Product	Yield (%)
1		*rac*-**1a**	68	6		*rac*-**1f**	61
2		*rac*-**1b**	10[a]	7		*rac*-**1g**	87
3		*rac*-**1c**	94	8		*rac*-**1h**	6[a]
4		*rac*-**1d**	94	9		*rac*-**1i**	10[a]
5		*rac*-**1e**	79				

[a]Crude product.



Scheme 3: Novozym 435-catalyzed stereoselective acetylation of *rac*-**1a–g**.

Table 2: Lipase-catalyzed acetylation of *rac*-**1**[a] and lactonization.

Entry	Substrate	Time (h)	Yield (%)		Yield (%)/enantiomeric excess (% e.e.)[b]/ absolute configuration	
			1	**2**	**3**	**4**
1	*rac*-**1a**	4	47	47	>99/96/*R*	>99/>99/*S*
2[c]	*rac*-**1b**	24	No reaction		–	–
3	*rac*-**1c**	12	44	51	>99/91/*S*	>99/94/*R*
4	*rac*-**1d**	20	38	43	>99/95/*S*	>99/93/*R*
5	*rac*-**1e**	14	48	36	>99/>99/*S*	>99/95/*R*
6	*rac*-**1f**	7	34	46	>99/>99/*R*	>99/99/*S*
7	*rac*-**1g**	11	47	50	>99/racemic/–	>99/racemic/–

[a]Conditions: *rac*-**1**, 1.0 mmol; vinyl acetate, 2.0 mmol; Novozym 435, 0.4 g; Et_2O, 20 mL; room temperature.

[b]Determined by GC using a Chirasil-Dex CB column.

[c]Acetylation conducted at 40°C.

In addition, (*R*)- and (*S*)-7-methyl-γ-octalactones (**3a** and **4a**) derived from optically active **1** and **2** were obtained with 96% and more than 99% enantiomeric excesses. The enantiopurity of (*R*)-7-methyl-γ-octalactone was slightly low compared with that of (*R*)-γ-nonalactone. These results show that Novozym 435 exhibits not only low substrate affinity but also low substrate selectivity toward *rac*-**1a**, which has a sterically bulky R group. Therefore, a long reaction time can be predicted because the substrate possesses a sterically bulky side chain. An attempted acetylation failed for *rac*-**1b** substituted with a bulky *tert*-butyl group (entry 2). It appears that the substrate affinity of Novozym 435 is low for a substrate with a large steric hindrance around the asymmetric carbon atom. The reaction times for *N*-methyl-4-hydroxy-4-phenylbutanamide (*rac*-**1c**, entry 3) and *N*-methyl-4-hydroxy-4-*p*-tolylbutanamide (*rac*-**1d**, entry 4) are longer than those for *rac*-**1a** (entry 1) and *N*-methyl-4-hydroxy-6-phenylhexanamide (*rac*-**1f**, entry 6). By contrast, *rac*-**1c** with a phenyl group and *rac*-**1d** with a tolyl group are acetylated by Novozym 435. Phenyl and tolyl groups are more bulky than the isopentyl group; thus, a long reaction time is required to reach 50% conversion. In the case of *rac*-**1c** and *rac*-**1d**, both enantiomers of 4-phenyl-γ-butyrolactone (**3c** and **4c**) and 4-(*p*-tolyl)-γ-butyrolactone (**3d** and **4d**) were obtained with more than 90% enantiopurities. These optical purities are approximately 5–10% lower than that of *rac*-**1a**. These results suggest that the substrate selectivity and the affinity of Novozym 435 toward the high steric hindrance substrate around an asymmetric carbon are low. Naoshima et al. [41] explained the enantioselectivity of lipase by using computer modeling. They measured the C-O distance between the carbonyl carbon atom of the acetyl group in the substrate and the oxygen atom at the active center of lipase. The large difference of the C-O distance among each enantiomer correlated with high enantioselectivity. It appears that for the large steric hindrance around asymmetric carbon atom, the hydroxy group in the substrate and the active center in Novozym 435 are difficult to be approached. It can be suggested that the enantioselectivity of Novozym 435 toward the substrate with large steric hindrance decreases. Although approximately 50% conversion was reached at 11 h for *N*-methyl-4-hydroxy-4-(*p*-anisyl)butanamide (*rac*-**1g**) with a *p*-anisyl group, both 4-(*p*-anisyl)-γ-butyrolactones (**3g** and **4g**) exhibit racemic similarities (entry 7). Phenyl, tolyl, and *p*-anisyl

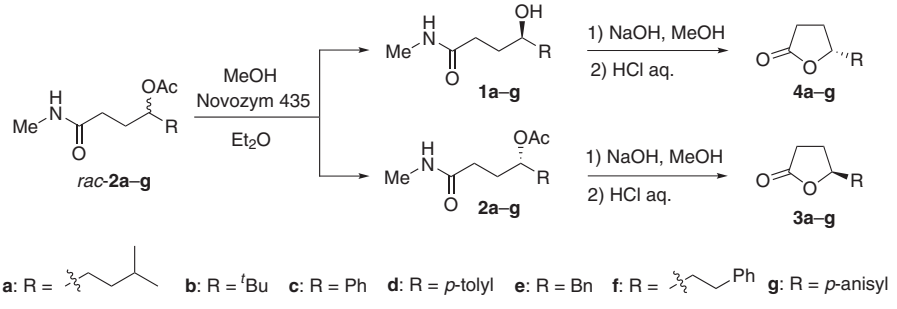
groups are structurally similar. However, only the reaction of *rac*-**1g** gave racemic γ-lactones (**3g** and **4g**), and this result can be attributed to the presence of the methoxy group. The reaction times required for *rac*-**1c** and *rac*-**1d** to reach 50% conversion by Novozym 435-catalyzed acetylation were 12 and 20 h, respectively, and that for *rac*-**1g** took 11 h. These substrates require comparably long reaction time to reach 50% conversion compared with *rac*-**1a** and *rac*-**1f**. As mentioned earlier, it was assumed that Novozym 435 shows higher substrate affinity toward the small R group in substrates such as *rac*-**1a** and **1f**. The reaction time of *rac*-**1g** was similar to *rac*-**1c**. These results also show that Novozym 435 exhibits low affinity toward the bulky substrates around the asymmetric carbon atom. By contrast, it can be suggested that the high substrate affinity of Novozym 435 is due to hydrogen bonding between the oxygen at the methoxy group and the amino acid residues that constitute the lipase. Both enantiomers of *rac*-**1g** can be incorporated into the active site by this hydrogen bonding, which causes the observed lack of enantioselectivity. Novozym 435-catalyzed acetylation of all *rac*-**1** except *rac*-**1g** progressed with more than 90% enantioselectivity. The stereoselectivity of Novozym 435 varies with structural differences of the R group. The absolute configurations of γ-lactones prepared from hydroxyamide **1** are (*R*)-form for *rac*-**1a** with an isopentyl group and *rac*-**1f** with a phenethyl group. By contrast, the corresponding γ-lactones derived from **1** have (*S*)-configuration in the case of *rac*-**1c** with a phenyl group, *rac*-**1d** with a tolyl group, and *rac*-**1e** with a benzyl group. As shown in Scheme 3, the hydroxyl group is acetylated by Novozym 435 in all substrates. Previously, we have reported a synthetic methodology of the chiral γ-lactones, which combines Novozym 435-catalyzed reaction and Mitsunobu reaction [42, 43]. In this work, Novozym 435-catalyzed stereoselective hydrolysis of *N*-benzyl-4-acetoxyalkanamides was conducted. The hydrolysis was conducted at 60°C in diisopropyl ether; the reaction progressed with more than 90% enantioselectivity. However, the 50% conversion was reached after a relatively long period of 24–30 h. In summary, Novozym 435 shows high enantioselectivity for both acetylation and hydrolysis.

Lipase-catalyzed enantioselective hydrolysis of *N*-methyl-4-acetoxyalkanamides

In the acetylation using Novozym 435, *rac*-**1b** was inert (Table 2, entry 2). Enantioselectivity was not observed for *rac*-**1g**, although approximately 50% conversion was reached in 11 h (Table 2, entry 7). Novozym 435-catalyzed hydrolysis of *rac*-**2** was investigated to prepare optically active lactones **3b**, **g** and **4b**, **g** (Scheme 4, Table 3). In all cases, the time required for the hydrolysis to reach approximately 50% conversion is much longer than that for acetylation. Novozym 435 is inert toward the hydrolysis of *rac*-**2b** as well as the acetylation of *rac*-**1b** (entry 2). It appears that the bulky *tert*-butyl group is not compatible with the substrate specificity of Novozym 435. Although *rac*-**2g** is hydrolyzed, the obtained lactone **3g**/**4g** is racemic (entry 7). Because *rac*-**2c** and *rac*-**2d** are hydrolyzed enantioselectively, it can be suggested that the anisyl group of r*ac*-**2g** is a factor that does not promote enantioselectivity. The reaction mechanism of lipase was reported [44, 45].

Conclusions

N-methyl-4-hydroxyalkanamides with various side chains were prepared in a high yield by the addition reaction of organometallic reagents with *N*-methylsuccinimide. Novozym 435-catalyzed acetylation of all *rac*-**1** except *rac*-**1b** and *rac*-**1g** the respective products **2** with more than 90% enantioselectivity. Both enantiomers of γ-lactones with various side chains were successfully synthesized with enantiopurities more than 90%.



Scheme 4: Novozym 435-catalyzed stereoselective hydrolysis of *rac*-**2a–g**.

Table 3: Lipase-catalyzed hydrolysis of *rac*-**2**[a] and lactonization.

Entry	Substrate	Time (h)	Yield (%)		Yield (%)/enantiomeric excess (% e.)[b]/ absolute configuration	
			1	**2**	**4**	**3**
1	*rac*-**2a**	33	41	44	>99/98/*S*	>99/79/*R*
2	*rac*-**2b**	48	No reaction		–	–
3	*rac*-**2c**	48	37	56	>99/91/*R*	>99/72/*S*
4	*rac*-**2d**	48	43	50	>99/92/*R*	>99/75/*S*
5	*rac*-**2e**	48	42	53	>99/95/*R*	>99/70/*S*
6	*rac*-**2f**	48	44	46	>99/91/*S*	>99/96/*R*
7	*rac*-**2g**	48	49	43	>99/racemic/–	>99/racemic/–

[a]Conditions: *rac*-**2**, 1.0 mmol; MeOH, 3.0 mmol; Novozym 435, 0.4 g; Et_2O, 20 mL; 40°C.
[b]Determined by GC using a CycloSil B column.

Experimental

Column chromatography was conducted with silica gel FL60D (Fuji Silysia Chemical Ltd., Aichi, Japan). Thin-layer chromatography was performed with silica gel F-254 on aluminum plates (Merck Ltd., Darmstadt, Germany). ^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra were recorded in $CDCl_3$ on a JNM-ECA-500 spectrometer (JEOL, Tokyo, Japan), using an internal standard of tetramethylsilane and the central peak of $CDCl_3$ (77 ppm). Near-infrared spectra were recorded in KBr pellets on an FT-IR 460plus spectrophotometer (JASCO Corp., Tokyo, Japan). Enantiomeric excesses of γ-lactones were determined using a Perkin Elmer Auto System XL gas chromatograph equipped with a chiral capillary column CycloSil B (30 m×0.25 mm i.d.×0.25 μm film thickness; Agilent Technologies, Santa Clara, CA, USA). The carrier gas was helium. Optical rotations were measured on a Jasco P-1010 spectropolarimeter (JASCO Corp.), and the reported data refer to the Na-line value using a 25 mL cuvette. High-resolution mass spectral (HRMS) analyses were performed on an AccuTOF GCv 4G instrument (JEOL, Tokyo, Japan). Novozym 435 immobilized lipase from *C. antarctica* was obtained as a gift from Novozymes A/S (Paraná, Brazil).

Preparation of racemic *N*-methyl-4-hydroxyalkanamides *rac*-1a,c–g

Organomagnesium reagents were freshly prepared by the slow addition of the corresponding bromides or chlorides (16.5 mmol) in Tetrahydrofuran (THF) (50 mL) onto magnesium turnings (0.37 g, 15.0 mmol) previously activated with a crystal of iodine. Under vigorous stirring and cooling with an ice bath, *N*-methylsuccinimide (1.13 g, 10.0 mmol) dissolved in THF (30 mL) was then added to the suspension, and the mixture was stirred for 8 h at room temperature. The residual Grignard reagent was hydrolyzed by gradual addition of ice (10 g) and saturated aqueous NH_4Cl (100 mL). The organic phase was separated, and the aqueous phase was extracted with $CHCl_3$ (4×50 mL). The combined extracts were washed with water and dried with $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was not purified. $NaBH_4$ (0.76 g, 20 mmol) in methanol (20 mL) was added to the crude product with stirring, and the mixture was stirred for 1 h at room temperature. The solvent was evaporated under reduced pressure, and water (50 mL) was added. The aqueous phase was extracted with $CHCl_3$ (4×50 mL). The combined extracts were washed with water and dried with $MgSO_4$. The solvent was evaporated, and the residue was purified by flash chromatography on silica eluting with EtOAc to give the corresponding *N*-methyl-4-hydroxyalkanamide **1**.

***N*-methyl-4-hydroxy-7-methyloctanamide (1a)** Yield 68%; colorless solid; mp 62–63°C (dec); R_f=0.33 (eluent: $CHCl_3$-MeOH, 10:1, *v*/*v*); IR: 3293 (N-H, O-H), 2954 (-CH_3), 2934 (-CH_2-), 2871 (-CH_3), 2846 (-CH_2-), 1645 cm^{-1} (-NHC=O); ^{1}H NMR: δ 0.88 (d, 6H, *J* = 6.9 Hz, -CH(CH_3)$_2$), 1.19 (m, 1H, -CH_2CH(CH$_3$)$_2$), 1.32 (m, 1H, -CH_2CH(CH$_3$)$_2$), 1.46 (m, 2H, -CH_2CH$_2$CH(CH$_3$)$_2$), 1.53 (quint, 1H, *J* = 6.8, 6.4 Hz, -CH$_2$CH(CH$_3$)$_2$), 1.66 (m, 1H, -NHC(=O)CH$_2$CH_2-), 1.87 (m, 1H, -NHC(=O)CH$_2$CH_2-), 2.36 (m, 2H, -NHC(=O)CH_2-), 2.81 (d, 3H, *J* = 4.6 Hz, -NHCH_3), 2.99 (br, 1H, -OH), 3.60 (m, 1H, -CH(OH)-), 5.79 (br, 1H, -NH-); ^{13}C NMR: δ 22.6, 22.6 (-CH(CH_3)$_2$), 26.4 (-NHCH_3), 28.1 (-CH(CH$_3$)$_2$), 32.5 (-CH_2-), 33.2 (-C(=O)CH_2-), 34.8 (-CH_2CH-), 35.6 (-CH_2-), 71.8 (-CHOH), 174.4 (-NHC(=O)-). HRMS (FI). Calcd for $C_{10}H_{22}NO_2$ (M+H)$^+$: *m/z* 188.1651. Found: *m/z* 188.1645.

***N*-methyl-4-hydroxy-4-phenylbutanamide (1c)** Yield 94%; colorless oil; R_f=0.35 (eluent: $CHCl_3$-MeOH, 10:1, *v*/*v*); IR: 3328 (O-H, N-H), 3109 (Ar, C-H), 2937 (-CH_3), 2877 (-CH_2), 1649 (-NC=O), 1495, 1450 (Ar, C=C), 760, 702 cm^{-1} (Ar, C-H); ^{1}H NMR: δ 2.02 (m, 2H, -NHC(=O)CH_2CH_2-), 2.30 (t, 2H, *J* = 6.9 Hz, -NHC(=O)CH_2-), 2.75 (d, 3H, *J* = 4.6 Hz, -NHCH_3), 4.28 (br, 1H, -OH), 4.73 (m, 1H, -CH(OH)-), 6.02 (br, 1H, -NH-), 7.22–7.36 (m, 5H, -Ph); ^{13}C NMR: δ 26.4 (-NHCH_3), 32.7 (-C(=O)CH_2-), 34.3 (-CH_2-), 73.5 (-CHOH), 125.7, 127.3, 128.3, 144.4 (-Ph), 174.3 (-NHC(=O)-). HRMS (FD). Calcd for $C_{11}H_{16}NO_2$ (M)$^+$: *m/z* 193.1103. Found: *m/z* 193.1096.

***N*-methyl-4-hydroxy-4-(*p*-tolyl)butanamide (1d)** Yield 94%; colorless oil; R_f=0.24 (eluent: $CHCl_3$-MeOH, 10:1, *v*/*v*); IR: 3321 (O-H, N-H), 3039 (Ar, C-H), 2937 (-CH_3), 2905 (-CH_2), 1645 (-NC=O), 1568, 1515 (Ar, C=C), 816 cm^{-1} (Ar, C-H); ^{1}H NMR: δ 1.96 (m, 2H, -NHC(=O)CH$_2$CH_2-), 2.27 (t, 2H, *J* = 6.9 Hz, -NHC(=O)CH_2-), 2.31 (s, 3H, -PhCH_3), 2.70 (d, 3H, *J* = 4.6 Hz, -NHCH_3), 4.55 (br, 1H, -OH), 4.64 (q, 1H, *J* = 3.7, 4.1 Hz, -CH(OH)-), 6.43 (br, 1H, -NH-), 7.10 (d, 2H, *J* = 7.8 Hz, -Ph-), 7.19 (d, 2H, *J* = 8.2 Hz, -Ph-); ^{13}C NMR: δ 21.0 (-PhCH_3), 26.2 (-NHCH_3), 32.7 (-CH_2-), 34.5 (-CH_2-), 73.2 (-CHOH), 125.6, 128.9, 136.7, 141.4 (-Ph-), 174.4 (-NHC(=O)-). HRMS (FD). Calcd for $C_{12}H_{18}NO_2$ (M)$^+$: *m/z* 207.1259. Found: *m/z* 207.1257.

***N*-methyl-4-hydroxy-5-phenylpentanamide (1e)** Yield 79%; colorless solid; mp 100–101°C (dec); R_f=0.30 (eluent: $CHCl_3$-MeOH, 10:1, *v*/*v*); IR: 3412, 3370 (N-H), 3285 (O-H), 3094, 3058, 3033 (Ar, C-H), 2944 (-CH_3), 2926 (-CH_2-), 1651 (-NHC=O), 1495, 1454 cm^{-1} (Ar, C=C); ^{1}H NMR: δ 1.69 (m, 1H, -NHC(=O)CH_2CH_2-), 1.89 (m, 1H, -NHC(=O)CH_2CH_2-), 2.34 (t, 2H, *J* = 6.9 Hz, -NHC(=O)CH_2-), 2.73–2.85 (m, 5H, -CH_2Ph, -NHCH_3), 3.21 (br, 1H, -OH), 3.84 (m, 1H, -CH(OH)-), 5.92 (br, 1H, -NH-), 7.17–7.35 (m, 5H, -Ph); ^{13}C NMR: δ 26.3 (-NHCH_3), 31.8 (-CH_2-), 33.1 (-C(=O)CH_2-), 44.2 (-CH_2Ph), 72.3 (-CHOH), 126.4, 128.5, 129.4, 138.4 (-Ph), 174.2 (-NHC(=O)-). HRMS (FD). Calcd for $C_{12}H_{18}NO_2$ $(M+H)^+$: *m/z* 208.1338. Found: *m/z* 208.1305.

***N*-methyl-4-hydroxy-6-phenylhexanamide (1f)** Yield 61%; colorless solid; mp 40–41°C (dec); R_f=0.29 (eluent: $CHCl_3$-MeOH, 10:1, *v*/*v*); IR: 3315 (N-H, O-H), 3085, 3064, 3029 (Ar, C-H), 2950 (-CH_3), 2929 (-CH_2-), 2878 (-CH_3), 2861 (-CH_2-), 1645 (-NHC=O), 1497, 1456 cm^{-1} (Ar, C=C); ^{1}H NMR: δ 1.74 (m, 2H, -CH_2CH_2Ph), 1.86 (m, 2H, -NHC(=O)CH_2CH_2-), 2.36 (m, 2H, -NHC(=O)CH_2-), 2.68–2.88 (m, 2H, -CH_2Ph), 2.80 (d, 3H, *J* = 4.6 Hz, -NHCH_3), 3.23 (br, 1H, -OH), 3.66 (m, 1H, -CH(OH)-), 5.70 (br, 1H, -NH-), 7.13–7.36 (m, 5H, -Ph); ^{13}C NMR: δ 26.4 (-NHCH_3), 32.1 (-CH_2Ph), 32.5 (-CH_2-), 33.1 (-C(=O)CH_2-), 39.4 (-CH_2-), 70.8 (-CHOH), 125.8, 128.3, 128.4, 128.6, 129.0, 142.1 (-Ph), 174.3 (-NHC(=O)-). HRMS (FD). Calcd for $C_{13}H_{20}NO_2$ $(M)^+$: *m/z* 221.1416. Found: *m/z* 221.1405.

***N*-methyl-4-hydroxy-4-(*p*-anisyl)butanamide (1g)** Yield 87%; colorless oil; R_f=0.24 (eluent: $CHCl_3$-MeOH, 10:1, *v*/*v*); IR: 3313 (O-H, N-H), 3106 (Ar, C-H), 2938 (CH_3), 2836 (CH_2), 1645 (-NC=O), 1563, 1513 (Ar, C=C), 834 cm^{-1} (Ar, C-H); ^{1}H NMR: δ 2.05 (m, 2H, -NHC(=O)CH_2CH_2-), 2.32 (t, 2H, *J* = 6.9 Hz, -NHC(=O)CH_2-), 2.81 (d, 3H, *J* = 4.6 Hz, -NHCH_3), 3.61 (br, 1H, -OH), 3.80 (s, 3H, -PhOCH_3), 4.72 (t, 1H, *J* = 6.0 Hz, -CH(OH)-), 5.67 (br, 1H, -NH-), 6.87 (d, 2H, *J* = 8.2 Hz, -Ph-), 7.28 (d, 2H, *J* = 9.6 Hz, -Ph-); ^{13}C NMR: δ 26.4 (-NHCH_3), 32.9 (-C(=O)CH_2-), 34.3 (-CH_2-), 55.3 (-PhOCH_3), 73.2 (-CHOH), 113.7, 126.9, 136.6, 158.9 (-Ph), 174.1 (-NHC(=O)-). HRMS (FD). Calcd for $C_{12}H_{18}NO_3$ $(M)^+$: *m/z* 223.1208. Found: *m/z* 223.1207.

Preparation of *N*-methyl-4-hydroxy-5,5-dimethylhexanamide (1b)

A solution of *tert*-butyllithium in pentane (6.29 mL, 10.0 mmol) was added dropwise to a solution of *N*-methylsuccinimide (1.13 g, 10.0 mmol) in THF (20 mL) at -78°C under argon atmosphere, and the mixture was stirred at the same temperature for 2 h. The reaction mixture was poured onto saturated NH_4Cl at 0°C and extracted with EtOAc (5×50 mL). The combined organic layers were washed with water, dried with $MgSO_4$, and concentrated *in vacuo*. The crude product was not purified. $NaBH_4$ (0.76 g, 20.0 mmol) was added to a solution of the crude product in MeOH (20 mL) at 0°C, and the mixture was stirred for 1 h. The solvent was evaporated, and water (50 mL) was added to the residue. The aqueous phase was extracted with EtOAc (5×50 mL), and the combined organic layers were washed with water, dried with $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by crystallization from *n*-hexane to give *N*-methyl-4-hydroxy-5,5-dimethylhexanamide (**1b**, 0.76 g, 44%) as a colorless solid; mp 117–118°C (dec); R_f=0.30 (eluent: $CHCl_3$-MeOH, 10:1, *v*/*v*); IR: 3292 (N-H, O-H), 2954 (-CH_3), 2932 (-CH_2-), 2868 (-CH_3), 2846 (-CH_2-), 1645 cm^{-1} (-NHC=O); ^{1}H NMR: δ 0.91 (s, 9H, -C(CH_3)$_3$), 1.60 (m, 1H, -NHC(=O)CH_2CH_2-), 1.89 (m, 1H, -NHC(=O)CH_2CH_2-), 2.37 (m, 2H, -NHC(=O)CH_2-), 2.63 (br, 1H, -OH), 2.82 (d, 3H, *J* = 4.6 Hz, -NHCH_3), 3.20 (m, 1H, -CH(OH)-), 5.66 (br, 1H, -NH-); ^{13}C NMR: δ 25.6 (-C(CH_3)$_3$), 26.4 (-NHCH_3), 27.0 (-CH_2-), 34.1 (-C(=O)CH_2-), 35.0 (-C(CH_3)$_3$), 79.7 (-CHOH), 174.6 (-NHC(=O)-). HRMS (ESI). Calcd for $C_9H_{20}NO_2$ $(M+H)^+$: *m/z* 174.1494. Found: *m/z* 174.1513.

General procedure for Novozym 435-catalyzed acetylation and lactonization

Novozym 435 (0.4 g) was added to a racemic mixture of *N*-methyl-4-hydroxyalkanamides (**1**, 1.0 mmol) and vinyl acetate (2.0 mmol) in diethyl ether (20 mL). After stirring at room temperature for a period specified in Table 2, the reaction mixture was filtered. Concentration under a reduced pressure followed by flash chromatography of the residue on silica gel (eluent: EtOAc) afforded the corresponding optically active *N*-methyl-4-hydroxyalkanamide **1a**–**g** and *N*-methyl-4-acetoxyalkanamide **2a**–**g**. Then NaOH (2.0 g) was added to a solution of **1a**–**g** or **2a–g** in methanol (20 mL), and the mixture was heated under reflux for 3 h. After cooling, methanol was removed under reduced pressure and water (50 mL) was added. The aqueous phase was acidified with 10% HCl to pH 3.0, and the mixture was stirred for 8 h then extracted with EtOAc (4×20 mL). The combined organic layers were washed with water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with *n*-hexane-EtOAc, 4:1, to give the corresponding γ-lactone (**3** or **4**) as a colorless oil. The enantiomeric excess was measured by using the chiral GC analysis. The absolute configurations of **3** and **4** were determined by optical activity compared with the literature data.

***N*-methyl-4-acetoxy-7-methyloctanamide (2a)** Colorless oil; R_f=0.33 (eluent: $CHCl_3$-MeOH, 10:1, *v*/*v*); IR: 3298 (N-H), 2957 (-CH_3), 2933 (-CH_2-), 2871 (-CH_3), 1738 (-OC=O), 1649 (-NHC=O), 1242 cm^{-1} (-OC=O);^{1}H NMR: δ 0.87 (d, 6H, *J* = 6.3 Hz, -CH(CH_3)$_2$), 1.18 (m, 2H, -CH_2CH_2CH(CH_3)$_2$), 1.53 (m, 3H, -CH_2CH_2CH(CH_3)$_2$), 1.85 (m, 1H, -NHC(=O)CH_2CH_2-), 1.94 (m, 1H, -NHC(=O)CH_2CH_2-), 2.06 (s, 3H, -OC(=O)CH_3), 2.18 (m, 2H, -NHC(=O)CH_2-), 2.80 (d, 3H, *J* = 4.6 Hz, -NHCH_3), 4.84 (quint, 1H, *J* = 3.4, 9.2 Hz, -CHOC(=O)CH_3), 5.87 (s, 1H, -NH-); ^{13}C NMR: δ 21.2 (-C(=O)CH_3), 22.4, 22.5 (-CH(CH_3)$_2$), 26.3 (-NHCH_3), 27.8 (-CH_2CH(CH_3)$_2$), 30.2 (-CH_2-), 32.1 (-C(=O)CH_2-), 32.5 (-CH_2-), 34.3 (-CH_2CH(CH_3)$_2$), 74.1 (-CHOC(=O)CH_3), 171.3 (-OC(=O)CH_3), 172.9 (-NHC(=O)-). HRMS (FI). Calcd for $C_{12}H_{24}NO_3$ $(M)^+$: *m/z* 229.1678. Found: *m/z* 229.1662.

***N*-methyl-4-acetoxy-4-phenylbutanamide (2c)** Colorless oil; R_f=0.33 (eluent: $CHCl_3$-MeOH, 10:1, *v*/*v*); IR: 3302 (N-H), 3035 (Ar, C-H), 2941 (CH_3, CH_2), 1736 (-OC=O), 1651 (-NHC=O), 1556, 1493 (Ar, C=C), 1240 (C-O-C), 760, 700 cm^{-1} (Ar, C-H); ^{1}H NMR: δ 2.05 (s, 3H, -OC(=O)CH_3), 2.16 (m, 2H, -NHC(=O)CH_2CH_2-), 2.24 (m, 2H, -NHC(=O)CH_2-), 2.76 (d, 3H, *J* = 4.6 Hz, -NHCH_3), 5.75 (m, 1H, -CHOC(=O)CH_3), 7.20–7.41 (m, 5H, -Ph); ^{13}C NMR: δ 21.2 (-C(=O)CH_3), 26.3 (-NHCH_3), 32.0 (-CH_2-), 32.3 (-C(=O)CH_2-), 75.3 (-CHOC(=O)CH_3), 126.3, 128.0, 128.5, 139.8 (-Ph), 170.5 (-OC(=O)CH_3), 172.6 (-NHC(=O)-). HRMS (FD). Calcd for $C_{13}H_{18}NO_3$ $(M)^+$: *m/z* 235.1208. Found: *m/z* 235.1194.

***N*-methyl-4-acetoxy-4-(*p*-tolyl)butanamide (2d)** Colorless oil; R_f=0.33 (eluent: $CHCl_3$-MeOH, 10:1, *v*/*v*); IR: 3300 (N-H), 3029 (Ar, C-H) 2943 (CH_3, CH_2), 1738 (-OC=O), 1651 (-NHC=O), 1556, 1520 (Ar, C=C),

1240 (C-O-C), 818 cm^{-1} (Ar, C-H); ^1H NMR: δ 2.02 (s, 3H, -OC(=O)C$\underline{H}_3$), 2.13 (m, 2H, -NHC(=O)CH$_2$C$\underline{H}_2$-), 2.24 (m, 2H, -NHC(=O)C$\underline{H}_2$-), 2.31 (s, 3H, -PhC$\underline{H}_3$), 2.72 (d, 3H, *J* = 4.6 Hz, -NHC$\underline{H}_3$), 5.69 (m, 1H, -C$\underline{H}$OC(=O)CH$_3$), 6.18 (br, 1H, -N$\underline{H}$-), 7.12 (d, 2H, *J* = 7.8 Hz, -Ph-), 7.19 (d, 2H, *J* = 7.8 Hz, -Ph-); ^{13}C NMR: δ 20.9 (-OC(=O)C$\underline{H}_3$), 21.0 (-PhC$\underline{H}_3$), 26.1 (-NHC$\underline{H}_3$), 31.7 (-C(=O)C$\underline{H}_2$-), 32.1 (-C$\underline{H}_2$-), 75.1 (-C$\underline{H}$OC(=O)CH$_3$), 126.2, 129.0, 136.7, 137.6 (-Ph-), 170.3 (-OC$\underline{(=O)}$CH$_3$), 172.7 (-NHC$\underline{(=O)}$-). HRMS (FD). Calcd for $C_{14}H_{20}NO_3$ $(M)^+$: *m/z* 249.1365. Found: *m/z* 249.1368.

***N*-methyl-4-acetoxy-5-phenylpentanamide (2e)** Colorless oil; R_f=0.33 (eluent: $CHCl_3$-MeOH, 10:1, *v*/*v*). IR: 3308 (N-H), 3086, 3062, 3029 (Ar, C-H), 2938 (-CH_3), 1735 (-OC$\underline{=O}$), 1646 (-NHC$\underline{=O}$), 1496, 1455 (Ar, C=C), 1242 cm^{-1} (-OC$\underline{=O}$); ^1H NMR: δ 1.88 (m, 1H, -NHC(=O)CH$_2$C$\underline{H}_2$-), 2.13 (m, 1H, -NHC(=O)CH$_2$C$\underline{H}_2$-), 1.98 (s, 3H, -OC(=O)C$\underline{H}_3$), 2.21 (m, 2H, -NHC(=O)C$\underline{H}_2$-), 2.77 (d, 3H, *J* = 4.6 Hz, -NHC$\underline{H}_3$), 2.87 (m, 2H, -C$\underline{H}_2$Ph), 5.07 (m, 1H, -C$\underline{H}$OC(=O)CH$_3$), 5.79 (s, 1H, -N$\underline{H}$-), 7.15–7.39 (m, 5H, -Ph); ^{13}C NMR: δ 21.0 (-OC(=O)C$\underline{H}_3$), 26.2 (-NHC$\underline{H}_3$), 29.7 (-C$\underline{H}_2$-), 32.6 (-C(=O)C$\underline{H}_2$-), 40.7 (-C$\underline{H}_2$Ph), 74.4 (-C$\underline{H}$OC(=O)CH$_3$), 126.5, 128.3, 129.3, 137.0 (-Ph), 170.9 (-OC$\underline{(=O)}$CH$_3$), 172.7 (-NHC$\underline{(=O)}$-). HRMS (FD). Calcd for $C_{14}H_{20}NO_3$ $(M+H)^+$: *m/z* 250.1443. Found: *m/z* 250.1444.

***N*-methyl-4-acetoxy-6-phenylhexanamide (2f)** Colorless oil; R_f=0.33 (eluent: $CHCl_3$-MeOH, 10:1, *v*/*v*); IR: 3297 (N-H), 3087, 3062, 3026 (Ar, C-H), 2943, 2864 (-CH_3), 1736 (-OC$\underline{=O}$), 1644 (-NHC$\underline{=O}$), 1496, 1454 (Ar, C=C), 1242 cm^{-1} (-OC$\underline{=O}$); ^1H NMR: δ 1.79–2.01 (m, 4H, -C$\underline{H}_2$CH(OC(=O)CH$_3$)C$\underline{H}_2$-), 2.04 (s, 3H, -OC(=O)C$\underline{H}_3$), 2.19 (m, 2H, -NHC(=O)C$\underline{H}_2$-), 2.63 (m, 2H, -C$\underline{H}_2$Ph), 2.78 (d, 3H, *J* = 4.6 Hz, -NHC$\underline{H}_3$), 4.92 (m, 1H, -C$\underline{H}$OC(=O)CH$_3$), 5.94 (s, 1H, -N$\underline{H}$-), 7.11–7.35 (m, 5H, -Ph); ^{13}C NMR: δ 21.1 (-OC(=O)C$\underline{H}_3$), 26.3 (-NHC$\underline{H}_3$), 30.2 (-C$\underline{H}_2$Ph), 31.6 (-C$\underline{H}_2$-), 32.4 (-C(=O)C$\underline{H}_2$-), 35.9 (-C$\underline{H}_2$CH$_2$Ph), 73.5 (-C$\underline{H}$OC(=O)CH$_3$), 125.9, 128.2, 128.4, 141.8 (-Ph), 171.3 (-OC$\underline{(=O)}$CH$_3$), 173.0 (-NHC$\underline{(=O)}$-). HRMS (FD). Calcd for $C_{15}H_{22}NO_3$ $(M)^+$: *m/z* 263.1521. Found: *m/z* 263.1517.

***N*-methyl-4-acetoxy-4-(*p*-anisyl)butanamide (2g)** Colorless oil; R_f=0.33 (eluent: $CHCl_3$-MeOH, 10:1, *v*/*v*); IR: 3306 (N-H), 3094 (Ar, C-H), 2938 (CH_3), 2838 (CH_2), 1736 (-OC$\underline{=O}$), 1648 (-NHC$\underline{=O}$), 1613, 1516 (Ar, C=O), 1241 (C-O-C), 832 cm^{-1} (Ar, C-H); ^1H NMR: δ 2.05 (s, 3H, -OC(=O)C$\underline{H}_3$), 2.14 (m, 2H, -NHC(=O)CH$_2$C$\underline{H}_2$-), 2.24 (m, 2H, -NHC(=O)C$\underline{H}_2$-), 2.79 (d, 3H, *J* = 4.6 Hz, -NHC$\underline{H}_3$), 3.80 (s, 3H, -PhOC$\underline{H}_3$), 5.54 (s, 1H, -N$\underline{H}$-), 5.71 (t, 1H, *J* = 5.0 Hz, -C$\underline{H}$OC(=O)CH$_3$), 6.87 (d, 2H, *J* = 8.7 Hz, -Ph-), 7.26 (d, 2H, *J* = 6.9 Hz, -Ph-); ^{13}C NMR: δ 21.3 (-OC(=O)C$\underline{H}_3$), 26.3 (-NHC$\underline{H}_3$), 31.8 (-C(=O)C$\underline{H}_2$-), 32.6 (-C$\underline{H}_2$-), 55.3 (-PhOC$\underline{H}_3$), 75.1 (-C$\underline{H}$OC(=O)CH$_3$), 113.9, 127.9, 131.9, 159.4 (-Ph-), 170.5 (-OC$\underline{(=O)}$CH$_3$), 172.4 (-NHC$\underline{(=O)}$-). HRMS (FD). Calcd for $C_{14}H_{20}NO_4$ $(M)^+$: *m/z* 265.1314. Found: *m/z* 265.1313.

7-Methyl-γ-octalactone (3a, 4a) Colorless oil; R_f=0.25 (eluent: *n*-Hexane-EtOAc, 4:1, *v*/*v*); IR: 2951 (CH_3), 2868 (CH_2), 1776 (-OC$\underline{=O}$), 1184 cm^{-1} (C-O-C); ^1H NMR: δ 0.90 (d, 6H, *J* = 6.3 Hz, -CH(C$\underline{H}_3$)$_2$), 1.24 (m, 1H, -C$\underline{H}_2$CH(CH$_3$)$_2$), 1.36 (m, 1H, -C$\underline{H}_2$CH(CH$_3$)$_2$), 1.52–1.66 (m, 2H, -C$\underline{H}_2$CH$_2$C$\underline{H}$(CH$_3$)$_2$), 1.74 (m, 1H, -C$\underline{H}_2$CH$_2$CH(CH$_3$)$_2$), 1.86 (m, 1H, -OC(=O)CH$_2$C$\underline{H}_2$-), 2.33 (m, 1H, -OC(=O)CH$_2$C$\underline{H}_2$-), 2.54 (t, 2H, *J* = 8.0 Hz, -OC(=O)C$\underline{H}_2$CH$_2$-), 4.47 (quint, 1H, *J* = 6.3, 7.4 Hz, -OC$\underline{H}$(CH$_2$-)CH$_2$-); ^{13}C NMR: δ 22.4 (-CH(C$\underline{H}_3$)$_2$), 27.8 (-C$\underline{H}$(CH$_3$)$_2$), 28.0 (-C(=O)CH$_2$C$\underline{H}_2$-), 28.8 (-C(=O)C$\underline{H}_2$CH$_2$-), 33.4 (-CHC$\underline{H}_2$CH$_2$-), 34.1 (-C$\underline{H}_2$CH(CH$_3$)$_2$-), 81.3 (-OC$\underline{H}$CH$_2$-), 177.26 (-C$\underline{(=O)}$O-). HRMS (FI). Calcd for $C_9H_{17}O_2$ $(M+H)^+$: *m/z* 157.1229. Found: *m/z* 157.1202.

4-Phenyl-γ-butyrolactone (3c, 4c) Colorless oil; R_f=0.15 (eluent: *n*-hexane-EtOAc, 4:1, *v*/*v*); IR: 3033 (Ar, C-H), 2950 (CH_2), 1776 (-OC$\underline{=O}$), 1606, 1496 (Ar, C=C), 1176 (C-O-C), 760, 700 cm^{-1} (Ar, C-H); ^1H NMR: δ 2.10 (m, 1H, -OC(=O)CH$_2$C$\underline{H}_2$-), 2.63–2.72 (m, 3H, -OC(=O)C$\underline{H}_2$C$\underline{H}_2$-), 5.52 (t, 1H, *J* = 6.9 Hz, -OC$\underline{H}$(CH$_2$-)Ph), 7.31–7.46 (m, 5H, -Ph); ^{13}C NMR: δ 28.9 (-C(=O)CH$_2$C$\underline{H}_2$-), 31.0 (-C(=O)C$\underline{H}_2$CH$_2$-), 81.2 (-OC$\underline{H}$Ph), 125.2, 128.4, 128.7, 139.3 (-Ph), 176.9 (-C$\underline{(=O)}$O-). HRMS (ESI). Calcd for $C_{10}H_{11}O_2$ $(M)^+$: *m/z* 162.0681. Found: $(M)^+$, 162.0653.

4-(*p*-Tolyl)-γ-butyrolactone (3d, 4d) Colorless oil; R_f=0.18 (eluent: *n*-hexane-EtOAc, 4:1, *v*/*v*); IR: 3025 (Ar, C-H), 2985 (CH_3), 2949 (CH_2), 1774 (-OC$\underline{=O}$), 1616, 1518 (Ar, C=C), 1176 (C-O-C), 806 cm^{-1} (Ar, C-H); ^1H NMR: δ 2.18 (m, 1H, -OC(=O)CH$_2$C$\underline{H}_2$-, 2.35 (s, 3H, -PhC$\underline{H}_3$), 2.56–2.69 (m, 3H, -OC(=O)C$\underline{H}_2$C$\underline{H}_2$-), 5.47 (t, 1H, *J* = 7.3 Hz, -OC$\underline{H}$(CH$_2$-)Ph-), 7.11–7.25 (m, 4H, -Ph-); ^{13}C NMR: δ 21.1 (-PhC$\underline{H}_3$), 29.0 (-C(=O)CH$_2$C$\underline{H}_2$-), 30.9 (-C(=O)C$\underline{H}_2$CH$_2$-), 81.3 (-OC$\underline{H}$Ph-), 125.3, 129.3, 132.2, 138.3 (-Ph-), 177.0 (-C$\underline{(=O)}$O-). HRMS (FI). Calcd for $C_{11}H_{13}O_2$ $(M)^+$: *m/z* 176.0837. Found: *m/z* 176.0834.

5-Phenyl-γ-pentalactone (3e, 4e) Colorless oil; R_f=0.15 (eluent: *n*-hexane-EtOAc, 4:1, *v*/*v*). IR: 3030 (Ar, C-H), 2943 (CH_2), 1774 (-OC$\underline{=O}$), 1603, 1496 (Ar, C=C), 1178 (C-O-C), 750, 702 cm^{-1} (Ar, C-H); ^1H NMR: δ 1.96 (m, 1H, -OC(=O)CH$_2$C$\underline{H}_2$-), 2.25 (m, 1H, -OC(=O)CH$_2$C$\underline{H}_2$-), 2.42 (m, 2H, -OC(=O)C$\underline{H}_2$CH$_2$-), 2.93 (q, 1H, *J* = 6.0, 6.4 Hz, -CHC$\underline{H}_2$Ph), 3.08 (q, 1H, *J* = 6.0, 6.4 Hz, -CHC$\underline{H}_2$Ph), 4.74 (quint, 1H, *J* = 6.9, 6.4 Hz, -OC$\underline{H}$(CH$_2$-)CH$_2$Ph), 7.18–7.38 (m, 5H, -Ph); ^{13}C NMR: δ 27.1 (-C(=O)CH$_2$C$\underline{H}_2$-), 28.6 (-C(=O)C$\underline{H}_2$CH$_2$-), 41.3 (-CHC$\underline{H}_2$Ph), 80.8 (-OC$\underline{H}$CH$_2$Ph), 127.0, 128.6, 129.4, 135.8 (-Ph), 177.0 (-C$\underline{(=O)}$O-). HRMS (FI). Calcd for $C_{11}H_{13}O_2$ $(M)^+$: *m/z* 176.0837. Found: *m/z* 176.0812.

6-Phenyl-γ-hexalactone (3f, 4f) Colorless oil; R_f=0.18 (eluent: *n*-hexane-EtOAc, 4:1, *v*/*v*); IR: 3028 (Ar, C-H), 2943 (CH_2), 1770 (-OC$\underline{=O}$), 1603, 1495 (Ar, C=C), 1180 (C-O-C), 750, 702 cm^{-1} (Ar, C-H); ^1H NMR: δ 1.82–1.96 (m, 2H, -C(=O)CH$_2$C$\underline{H}_2$CH(O-)C$\underline{H}_2$-), 2.05 (m, 1H, -CHC$\underline{H}_2$CH$_2$Ph), 2.31 (m, 1H, -OC(=O)CH$_2$C$\underline{H}_2$-), 2.53 (m, 2H, -OC(=O)C$\underline{H}_2$CH$_2$-), 2.73 (m, 1H, -C$\underline{H}_2$Ph), 2.83 (m, 1H, -C$\underline{H}_2$Ph), 4.47 (quint, 1H, *J* = 6.9, 6.9 Hz, -C(=O)CH$_2$CH$_2$C$\underline{H}$(O-)CH$_2$-), 7.16–7.36 (m, 5H, -Ph); ^{13}C NMR: δ 27.9 (-C(=O)CH$_2$C$\underline{H}_2$-), 28.8 (-C(=O)C$\underline{H}_2$CH$_2$-), 31.6 (-C$\underline{H}$Ph), 37.3 (-OCHC$\underline{H}_2$-), 79.8 (-OC$\underline{H}$CH$_2$-), 126.1, 128.4, 128.5, 140.7 (-Ph), 177.1 (-C$\underline{(=O)}$O-). HRMS (FI). Calcd for $C_{12}H_{15}O_2$ $(M)^+$: *m/z* 190.0994. Found: *m/z* 190.0977.

4-(*p*-Anisyl)-γ-butyrolactone (3g, 4g) Colorless oil; R_f=0.10 (eluent: *n*-hexane-EtOAc, 4:1, *v*/*v*); IR: 3037 (Ar, C-H), 2956 (CH_3), 2937 (CH_2), 1773 (-OC$\underline{=O}$), 1613, 1517 (Ar, C=C), 1176 (C-O-C), 837 cm^{-1} (Ar, C-H); ^1H NMR: δ 2.20 (m, 1H, -OC(=O)CH$_2$C$\underline{H}_2$-), 2.57–2.71 (m, 3H, -OC(=O)C$\underline{H}_2$C$\underline{H}_2$-), 3.28 (s, 3H, -PhOC$\underline{H}_3$), 5.47 (t, 1H, *J* = 7.4 Hz, -C(=O)CH$_2$CH$_2$C$\underline{H}$(O-)Ph-), 6.92 (d, 2H, *J* = 8.6 Hz, -Ph-), 7.27 (d, 2H, *J* = 7.4 Hz, -Ph-); ^{13}C NMR: δ 29.2 (-C(=O)CH$_2$C$\underline{H}_2$-), 30.9 (-C(=O)C$\underline{H}_2$CH$_2$-), 55.3 (-PhOC$\underline{H}_3$), 81.3 (-OC$\underline{H}$Ph-), 114.1, 126.9, 131.3, 165.3 (-Ph-), 177.1 (-C$\underline{(=O)}$O-). HRMS (FI). Calcd for $C_{11}H_{13}O_3$ $(M)^+$: *m/z* 192.0786. Found: *m/z* 192.0758.

General procedure for Novozym 435-catalyzed hydrolysis

Racemic *N*-methyl-4-acetoxyalkanamides *rac*-**2a**–**g** were prepared almost quantitatively from *N*-methyl-4-hydroxyalkanamides *rac*-**1a**–**g** by acetylation using acetic anhydride [30]. Briefly, a mixture of racemic *N*-methy-5-acetoxyalkanamide (*rac*-**2a**–**g**, 1.0 mmol), methanol (3.0 mmol, 0.10 g), Novozym 435 (0.4 g), and diethyl ether (20 mL) was stirred at 40°C for a period specified in Table 3, then filtered to remove Novozym 435, and concentrated. The purification of

the crude product by silica gel column chromatography eluenting with EtOAc gave optically active *N*-methyl-4-hydroxyalkanamide **1a**–**g** and *N*-methyl-4-acetoxyalkanamide **2a**–**g**. Lactonization is described earlier.

Determination of enantiomeric excess

Enantiomeric excesses of optically active γ-lactone **3** and **4** were measured by chiral GC. General GC conditions: chiral column, CycloSil B; injector temperature, 250°C; detector temperature, 250°C; He gas, 2.0 mL/min.

7-Methyl-γ-octalactone **3a** and **4a**: Oven temperature, 140°C (isothermal); retention time, 8.5 min for (*R*)-**3a**, 8.8 min for (*S*)-**4a**.

4-Phenyl-γ-butyrolactone **3c** and **4c**: Oven temperature, 150°C (isothermal); retention time, 17.2 min for (*S*)-**3c**, 19.0 min for (*R*)-**4c**.

4-*p*-Tolyl-γ-butyrolactone **3d** and **4d**: Oven temperature, 150°C (isothermal); retention time, 27.0 min for (*S*)-**3d**, 30.4 min for (*R*)-**4d**.

5-Phenyl-γ-pentalactone **3e** and **4e**: Oven temperature, 140°C (isothermal); retention time, 27.3 min for (*S*)-**3e**, 28.2 min for (*R*)-**4e**.

6-Phenyl-γ-hexalactone **3f** and **4f**: Oven temperature, 140°C (isothermal); retention time, 76.0 min for (*R*)-**3f**, 77.8 min for (*S*)-**4f**.

4-*p*-Anisyl-γ-butyrolactone **3g** and **4g**: Oven temperature, 160°C (isothermal); retention time, 39.0 min for **3f**, 42.6 min for **4f**.

Specific rotation of optically active amides 1 and 2

The absolute configuration and the enantiomeric excesses were determined by using the values of the corresponding lactones **3** and **4**.

(*R*)-*N*-methyl-4-hydroxy-7-methyloctanamide [(*R*)-**1a**]: $[\alpha]^{25}_{D}$=-4.8 (*c* 1.0, MeOH, 96% e.e.).

(*S*)-*N*-methyl-4-hydroxy-4-phenylbutanamide [(*S*)-**1c**]: $[\alpha]^{25}_{D}$=-40.7 (*c* 1.0, $CHCl_3$, 91% e.e.).

(*S*)-*N*-methyl-4-hydroxy-4-(*p*-tolyl)butanamide [(*S*)-**1d**]: $[\alpha]^{25}_{D}$= -48.6 (*c* 1.0, $CHCl_3$, 95% e.e.).

(*S*)-*N*-methyl-4-hydroxy-5-phenylpentanamide [(*S*)-**1e**]: $[\alpha]^{25}_{D}$= +4.7 (*c* 1.0, $CHCl_3$, >99% e.e.).

(*R*)-*N*-methyl-4-hydroxy-6-phenylhexanamide [(*R*)-**1f**]: $[\alpha]^{25}_{D}$=+8.4 (*c* 1.0, MeOH, >99% e.e.).

(*S*)-*N*-methyl-4-acetoxy-7-methyloctanamide [(*S*)-**2a**]: $[\alpha]^{25}_{D}$=+8.0 (*c* 1.0, MeOH, >99% e.e.).

(*R*)-*N*-methyl-4-acetoxy-4-phenylbutanamide [(*R*)-**2c**]: $[\alpha]^{25}_{D}$= +58.8 (*c* 1.0, $CHCl_3$, 94% e.e.).

(*R*)-*N*-methyl-4-acetoxy-4-(*p*-tolyl)butanamide [(*R*)-**2d**]: $[\alpha]^{25}_{D}$= +65.7 (*c* 1.0, $CHCl_3$, 93% e.e.).

(*R*)-*N*-methyl-4-acetoxy-5-phenylpentanamide [(*R*)-**2e**]: $[\alpha]^{25}_{D}$= +13.1 (*c* 1.0, $CHCl_3$, 95% e.e.).

(*S*)-*N*-methyl-4-acetoxy-6-phenylhexanamide [(*S*)-**2f**]: $[\alpha]^{25}_{D}$=+8.1 (*c* 1.0, MeOH, 99% e.e.).

Assignment of absolute configuration for lactones 3 and 4

The absolute configuration of γ-lactones **3** and **4** was determined by comparison of the sign of the measured specific rotation with that in the literature.

(*S*)-7-Methyl-γ-octalactone **4a**: $[\alpha]^{25}_{D}$=-46.7 (*c* 1.0, MeOH, >99% e.e); Lit. $[\alpha]^{20}_{D}$=-38.6° (*c* 0.26, MeOH) [46].

(*R*)-4-Phenyl-γ-butyrolactone **4c**: $[\alpha]^{25}_{D}$=+32.8 (*c* 1.0, $CHCl_3$, 94% e.e.); Lit. $[\alpha]^{25}_{D}$=+20.3° (62% e.e.) [47].

(*R*)-4-*p*-Tolyl-γ-butyrolactone **4d**: $[\alpha]^{25}_{D}$=+25.7 (*c* 1.0, $CHCl_3$, 93% e.e.); Lit. $[\alpha]^{25}_{D}$=+10.8° (91% e.e.) [48].

(*S*)-5-Phenyl-γ-pentalactone **3e**: $[\alpha]^{25}_{D}$=+19.0 (*c* 1.0, $CHCl_3$, >99% e.e.); Lit. $[\alpha]^{25}_{D}$=+24.7° (*c* 1, $CHCl_3$, 97% e.e.) [29].

(*R*)-6-Phenyl-γ-hexalactone **3f**: $[\alpha]^{25}_{D}$=+65.8 (*c* 1.0, MeOH, >99% e.e.); Lit. $[\alpha]^{25}_{D}$=+39.2° (*c* 0.2–1.0, MeOH, >99% e.e.) [46].

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