HETEROCYCLES, Vol. 85, No. 5, 2012, pp. 1061 - 1075. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 12th January, 2012, Accepted, 19th March, 2012, Published online, 30th March, 2012
DOI: 10.3987/COM-12-12426

# ENANTIOSELECTIVE SYNTHESIS OF ε-LACTONES BY LIPASE-CATALYZED RESOLUTION

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**Abstract** – Synthesis of optically active *ε*-dodecalactone (**1**) by lipase-catalyzed enantioselective acylation with racemic *N*-alkyl-6-hydroxydodecanamide (*rac*-**2**) as a substrate was attempted. Lipase PS-catalyzed acetylation using *rac*-**2** progressed efficiently, and both enantiomers of **1** were obtained with over 90% optical purities.

## INTRODUCTION

A cyclic ester moiety constitutes a frequently encountered structural motif in a large variety of natural products and biologically active compounds. Lactone functionality exists in common flavor components and is employed in the perfumery and food industries.[1,2] However, the existence of *ε*-lactones in natural products has not been reported. *ε*-Decalactone has a nut-like note and *ε*-dodecalactone has a peach-like note, and they have been used as food flavorings. It is also well-known that both enantiomers of *γ*- and *δ*-lactones have different odors and tastes.[3,4] It is conceivable that *ε*-lactones also show these differences, but they have not been reported. However, several methods of synthesizing optically active *ε*-lactones have been reported.[5-8] Pchelka *et al.* synthesized (*S*)-*ε*-decalactone [(*S*)-**1'**] and (*S*)-*ε*-dodecalactone [(*S*)-**1**] by lipase-catalyzed enantioselective perhydrolysis resulted from Baeyer-Villiger oxidation of racemic 1-alkylcyclohexanone,[9]

but (*S*)-**1'** and (*S*)-**1** were synthesized with only 72% and 57% optical purities, respectively. Fellous *et al.* synthesized (*R*)-**1'** and (*R*)-**1** by esterase-catalyzed enantioselective hydrolysis of racemic **1'** and **1** with optical purities of 88% and 33%, respectively.[10] (*R*)-**1'** had high optical purity, but it can hardly be said that (*R*)-**1** did. In this study, we attempted to synthesize optically active ε-lactones (**1'** and **1**) by optical resolution using lipase-catalyzed enantioselective acylation.

## RESULTS AND DISCUSSION

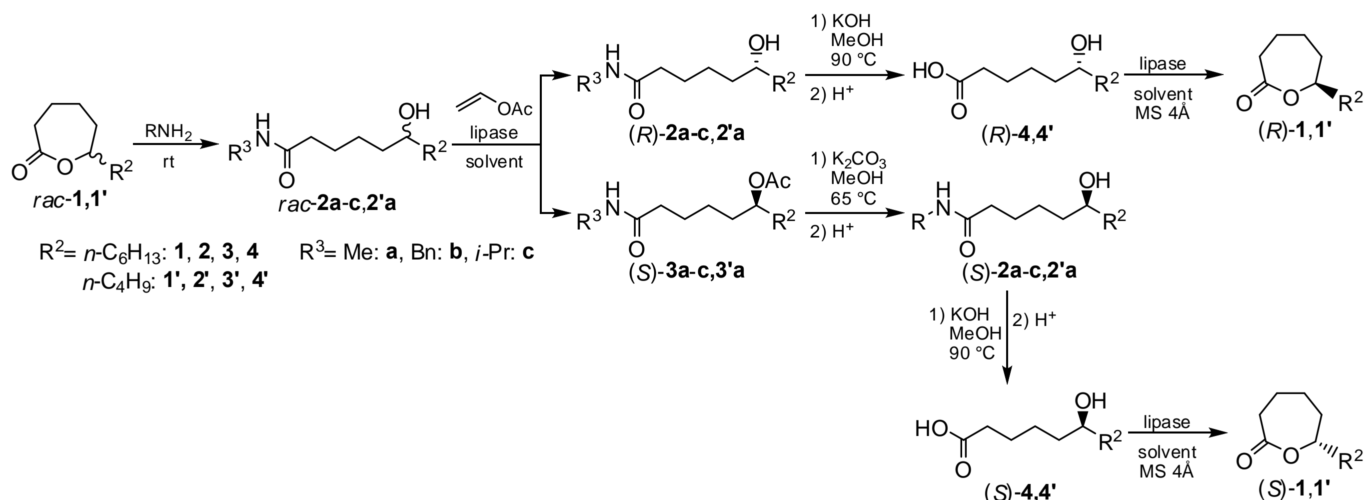
### Lipase-catalyzed acetylation of *rac*-2

We previously reported that synthesis of optically active γ-lactones by lipase-catalyzed kinetic resolution.[11,12] Novozym 435-catalyzed acetylation of racemic *N*-alkyl-4-hydroxyalkylamides gave both enantiomers with over 99% optical purities. In this paper, *N*-alkyl-6-hydroxydodecanamides (**2**) that have similar structure to above-mentioned substrates were acetylated using Novozym 435. *N*-alkyl-6-hydroxydodecanamide (*rac*-**2a**-**c**) was synthesized by aminolysis of *rac*-**1** with various amines (**Scheme 1**). The reaction conversion and enantioselectivity by lipase-catalyzed acetylation were investigated using racemic *N*-methyl-6-hydroxydodecanamide (*rac*-**2a**) as a substrate and various lipases (**Table 1**). Vinyl acetate was used as an acyl donor and two solvents, *n*-hexane and *i*-$Pr_2O$, were used. Five lipases, Lipase PS (entries 1-4), Novozym 435 (entries 5 and 6), Lipase AYS (entries 7 and 8), PPL (entries 9 and 10), and Lipozyme RM IM (entries 11 and 12), were used. The reaction hardly progressed at all in either solvent over three days reaction time with Lipase AYS, PPL, and Lipozyme RM IM (entries 7-12). The reaction time required to reach 50% conversion was 30 hours when using Lipase PS as a lipase (entries 1 and 2) and 24 hours using Novozym 435 (entries 5 and 6). This result showed that the substrate affinity of Novozym 435 to *rac*-**2a** was higher than that of Lipase PS. When Novozym 435 was used as a lipase, the acetylation in *i*-$Pr_2O$ was faster than that in *n*-hexane. However, the enantiomeric excesses of (*R*)-*N*-methyl-6-hydroxydodecanamide [(*R*)-**2a**] and (*S*)-*N*-methyl-6-acetoxydodecanamide [(*S*)-**3a**] using Novozym 435 were lower than those using Lipase PS. The enantioselectivity of Lipase PS for *rac*-**2a** was higher than that of Novozym 435. The reaction time to reach 50% conversion required 30 hours in both solvents using Lipase PS (entries 1 and 2). The enantiomeric excesses of (*R*)-**2a** and (*S*)-**3a** in *n*-hexane were higher than those in *i*-$Pr_2O$. Consequently, the effect of the $R^3$ group on reaction conversion and enantiomeric excess was confirmed using *rac*-**2a**-**c**, Lipase PS and *n*-hexane (entries 1, 3 and 4). Benzyl and isopropyl groups were attempted as $R^3$ as well as a methyl group. The reaction time required to reach 50% conversion was 30 hours with *rac*-**2a** or *rac*-**2c** as a substrate (entries 1 and 3) and 40 hours with *rac*-**2b** (entry 4). Therefore, the enantiomeric excess of (*R*)-**2** and (*S*)-**3** using *rac*-**2a** and *rac*-**2c** afforded over 90% conversion, and that using *rac*-**2b** afforded about 80% conversion. The substrate affinity of Lipase PS for *rac*-**2b** was higher than that for

*rac*-**2a** and *rac*-**2c**. In contrast, the enantioselectivity for *rac*-**2a** and *rac*-**2c** was higher than for *rac*-**2b**. *E* value was calculated by using Chen's equation, and it shows substrate selectivity of enzyme.[13] Lipase PS-catalyzed acetylation of *rac*-**2a** and *rac*-**2c** in *n*-hexane gave both enantiomers with over 90% optical purities, respectively. *E* value that obtained by enantioselective acetylation of *rac*-**2c** was higher than that of *rac*-**2a** (entries 1 and 4). In case of using *rac*-**2a**, the highest optical purity was expressed in all (*R*)-**2**. In fact, *E* value is used as a measurement of enantioselectivity of lipase. Even if *E* value showed somewhat low, it was possible to synthesize both enantiomers with over 90% optical purities (entry 1). Therefore, it was thought that *rac*-**2a** with methyl $R^3$ group was suitable for lipase PS-catalyzed acetylation compared with *rac*-**2c** with *iso*-propyl group.

Novozym 435-catalyzed acetylation of **2a** was about 60% enantioselectivity. Lipase PS-catalyzed acetylation, however, showed over 90% enantioselectivity. It was assumed that the difference of enantioselectivity was caused by the structure of active site on each lipase. X-Ray crystallography, which provides important information on the active site of enzymes, has allowed the determination of the crystal structures of lipases, i.e. human pancreatic lipase, *Geotrichum candidum*, *Candida rugosa* and *Pseudomonas glumae*.[14-17] The active site of *Candida antarctica* lipase B (Novozym 435) and *Pseudomonas cepacia* lipase (Lipase PS), which were used in this investigation, was also reported.[18,19] Active site of lipase, catalytic triad, is generally formed by three amino acids. These are serine, which is active center, histidine, and aspartate. Since the base sequence of amino acid changes with kinds of lipase, the shape of activity site also changes with lipase. The active site of *Candida antarctica* lipase B is composed by Ser105, His187, and Asp224 and *Pseudomonas cepacia* lipase is Ser87, His286, and Asp264.[18,19] This base sequence has a huge effect on enantioselectivity of lipase. Kazlauskas *et al.* suggested the relationship between the structure of active site and substrate to enantioselectivity.[20] An empirical rule, which is based only on the presence of steric factors in substrate molecules, was proposed to predict the enantioselectivity toward secondary alcohols and their esters displayed by lipase. Recently, the relationship between structure of active site and substrate and enantioselectivity of lipase is reported.[21-24] Lemke *et al.* investigated particularly about the enantioselectivity of *Paseudomonas cepacia* lipase using 69 kinds of substrates.[25] The kinetic resolution of 3-(aryloxy)propan-2-ol derivatives by transesterification with vinyl acetate in organic solvents in the presence of *Pseudomonas cepacia* lipase was subjected. This lipase showed high *E* value (>100) to the substrates which have acyloxy group such as *n*-pentanoate, *n*-nonanoate, and *n*-pentadecanoate. In contrast, it expressed low *E* value, about 30, to the similar substrate possessed *n*-hexanoate, *n*-octanoate, and *n*-heptadecanoate. The slight difference of chain length has a great effect on the enantioselectivity. Furthermore, Lemke *et al.* concluded that the enantioselectivity of lipase was determined not by volume of active site but by shape. Reaction mechanism of lipase-catalyzed acetylation of **2a** was shown in Figure 1.[26] The reaction of

esterification starts with the formation of tetrahedral intermediate with alcohol, where vinyl acetate is covalently linked to side-chain oxygen of catalytic serine. The crucial hydrogen bonds from H of catalytic histidine to serine O and the oxygen of the alcohol moiety are formed. Transfer of H to the oxygen of the alcohol moiety splits away the alcohol and an acyl enzyme complex is formed, which is hydrolyzed by the substrate, *N*-methyl-6-hydroxydodecanamide (**2a**), to the tetrahedral intermediate with **2a**. *N*-Methyl-6-acetoxydodecanamide (**3a**) is split from enzyme and free enzyme is formed. Naoshima *et al.* explained the enantioselectivity of lipase by computer modeling.[27] The hydrolysis of 1-phenylethyl acetate in the presence of *Pseudomonas cepacia* lipase was investigated, and the (*R*)-enantiomer was preferentially hydrolyzed with high enantioselectivity.[28] Carbonyl carbon of the substrate bound the oxygen of Ser87 in *Pseudomonas cepacia* lipase-catalyzed hydrolysis. It was proven that the C-O distance of (*R*)-enantiomer was shorter than that of (*S*)-enantiomer by computer modeling. Furthermore, the large difference of C-O distance among each enantiomer gave high enantioselectivity. The oxygen of hydroxy group in the substrate bound the carbonyl carbon of acetyl group linked Ser87 in acetylation of **2a**. It was assumed that the C-O distance of (*S*)-enantiomer was shorter than that of (*R*)-enantiomer for the shape of active site, and the large difference of C-O distance gave over 90% enantioselectivity.




**Scheme 1**

## Lipase-catalyzed lactonization of *rac*-4

Generally, *γ*- and *δ*-lactones could be synthesized from corresponding hydroxycarboxylic acid under acidic conditions because they were stable as cyclic esters. However, when the synthesizing medium and large ring size lactones had more than seven members, the corresponding hydroxycarboxylic acid reacted under acidic conditions, and inter-molecular esterification had priority over intra-molecular

**Table 1.** Lipase screening in enantioselective acetylation of *rac*-**2**[1)]

| Entry | Substrate | $R^3$ | Lipase | Solvent | Temp. [°C] | Time [h] | Yield [%] / Enantiomeric Excess [% e.e.][2)] (*R*)-**2** | Yield [%] / Enantiomeric Excess [% e.e.][2)] (*S*)-**3** | *E*[4)] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | *rac*-**2a** | Me | Lipase PS | *n*-hexane | 50 | 30 | 44 / 98 | 52 / 90 | 87 |
| 2 | | | | *i*-$Pr_2O$ | | 30 | 45 / 83 | 49 / 86 | 34 |
| 3 | *rac*-**2b** | Bn | | *n*-hexane | | 40 | 51 / 79 | 49 / 85 | 30 |
| 4 | *rac*-**2c** | *i*-Pr | | | | 30 | 50 / 90 | 50 / 94 | 100 |
| 5 | *rac*-**2a** | Me | Novozym 435 | *n*-hexane | 60 | 24 | 42 / 65 | 56 / 57 | 7 |
| 6 | | | | *i*-$Pr_2O$ | | | 33 / 64 | 67 / 39 | 4 |
| 7 | | | Lipase AYS | *n*-hexane | 45 | 72 | 91 / n.d.[3)] | 2 / n.d.[3)] | - |
| 8 | | | | *i*-$Pr_2O$ | | | 94 / n.d.[3)] | 1 / n.d.[3)] | - |
| 9 | | | PPL | *n*-hexane | 30 | 72 | 96 / n.d.[3)] | 3 / n.d.[3)] | - |
| 10 | | | | *i*-$Pr_2O$ | | | 99 / n.d.[3)] | trace / n.d.[3)] | - |
| 11 | | | Lipozyme RM IM | *n*-hexane | 55 | 72 | 91 / n.d.[3)] | 3 / n.d.[3)] | - |
| 12 | | | | *i*-$Pr_2O$ | | | 89 / n.d.[3)] | 7 / n.d.[3)] | - |

1) *rac*-**2**: 1.0 mmol, vinyl acetate: 2.0 mmol, Lipase PS, Lipase AYS and PPL: 0.5w/w, Novozym 435 and Lipozyme RM IM: 0.4 g, solvent: 20 mL
2) Determined by GC using InertCap CHIRAMIX column.
3) Not determined
4) $E = \ln[1-c(1+ee_p)]/\ln[1-c(1-ee_p)]$, $c = ee_s/(ee_s+ee_p)$, ee(s)= (*R*)-**2**, ee(p): (*S*)-**3**

esterification. For this reason, these lactones were generally synthesized by Yamaguchi macrolactonization, Mukaiyama-Corey macrolactonization, or Shiina macrolactonization.[29-31] These methods required high dilution and complicated processes. We focused on the high molecular recognition of lipase and hypothesized that lipase produced only ε-dodecalactone from 6-hydroxydodecanoic acid (**4**). Lipase-catalyzed lactonization of racemic 6-hydroxydodecanoic acid (*rac*-**4**) prepared from ε-dodecalactone (*rac*-**1**) by alkaline hydrolysis was investigated using various were used in this investigation. **1** was not or hardly produced in all solvents despite three days reaction time using Lipase AYS, and Lipozyme RM IM. In contrast, **1** was produced in all solvents using Novozym 435 (entries 1-3) and the (*S*)-enantiomer was lactonized preferentially. **1** was obtained with over 50% yield in three hours reaction time in *n*-hexane and *i*-$Pr_2O$. On the other hand, the yield of **1** was 20%

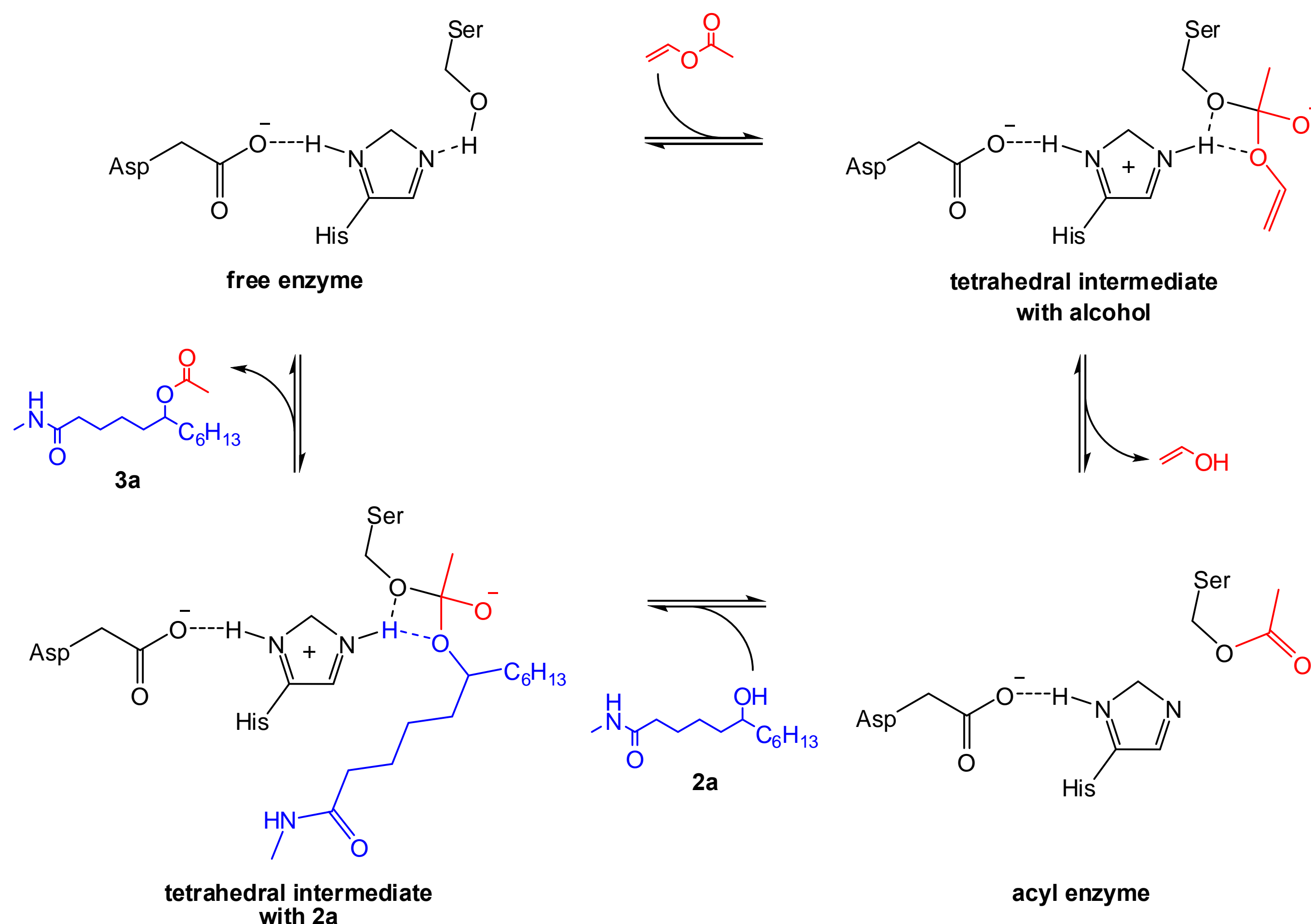



**Figure 1**

despite three days reaction time in THF. This investigation was designed to synthesize both enantiomers of **1** using the same conditions. In other words, it was designed so that lipase-catalyzed lactonization progressed with no enantioselectivity and to afford racemic **1** with high yield. Three solvents were used in this investigation. **1** was synthesized with 30% yield at 40 °C and 3 hours reaction time in $Et_2O$ (entry 4). Lactonization was performed at 80 °C to afford **1** with 79% yield in cyclohexane and CPME (entries 5 and 6). Additionally, the enantiomeric excess of **1** in CPME was more racemic than that in cyclohexane. Therefore, entry 9 was determined as the optimum conditions.

### Total synthesis of optically active *ε*-lactones

The results of Lipase PS-catalyzed enantioselective acetylation, alkaline hydrolysis, and Novozym 435-catalyzed lactonization are shown in Table 3. Lipase PS-catalyzed enantioselective acetylation of *rac*-**2a** reached about 50% conversion in 30 hours (entry 1). The conversion was 40% at 30 h using *rac*-**2'a** as a substrate (entry 2). A reaction time of 48 h was required to reach about 50% Conversion (entry 3). The substrate affinity of Lipase PS to *rac*-**2a** was higher than that to *rac*-**2'a**.

**Table 2.** Lipase screening in intra-esterification of *rac*-**4**[1)]

| Entry | Lipase | Solvent | Temp. [°C] | Time [h] | Yield [%] / Enantiomeric Excess [% e.e.][2)] / Config. |
|---|---|---|---|---|---|
| 1 | Novozym 435 | *n*-hexane | 60 | 3 | 51 / 60 / (*S*) |
| 2 | | *i*-$Pr_2O$ | | | 62 / 29 / (*S*) |
| 3 | | THF | | 72 | 20 / 27 / (*S*) |
| 4 | | $Et_2O$ | | 3 | 30 / 65 / (*S*) |
| 5 | | Cyclohexane | | | 79 / 6 / (*S*) |
| 6 | | CPME | | | 79 / 3 / (*S*) |
| 7 | Lipase AYS | *n*-hexane | 45 | 72 | 3 / - / - |
| 8 | | *i*-$Pr_2O$ | | | not produced / - / - |
| 9 | | THF | | | not produced / - / - |
| 10 | PPL | *n*-hexane | 30 | 72 | not produced / - / - |
| 11 | | *i*-$Pr_2O$ | | | 1 / - / - |
| 12 | | THF | | | trace / - / - |
| 13 | Lipozyme RM IM | *n*-hexane | 55 | 72 | trace / - / - |
| 14 | | *i*-$Pr_2O$ | | | trace / - / - |
| 15 | | THF | | | Not produced / - / - |

1) *rac*-**4**: 1.0 mmol, Lipase AYS and PPL: 0.5*w*/*w*, Novozym 435 and Lipozyme RM IM: 0.4 g, solvent: 20 mL, MS 4Å: 1.0 g

2) Determined by GC using InertCap CHIRAMIX column.

Alkaline hydrolysis of **2** and **2’** afforded **4** and **4’** with a midium yield of 70-83%. Both enantiomers of ε-dodecalactone were successfully synthesized with excellent enantiomeric excesses: (*R*)-**1** and (*S*)-**1** were 98% and 90%, respectively. In the case of lipase-catalyzed acetylation of *rac*-**2’a** at 30 hours, (*S*)-**1’** was synthesized with the excellent enantiomeric excess of 92%. (*R*)-**1’** was synthesized at 63% enantiomeric excess. The acetylation progressed for 48 hours and reached about 50% conversion, and (S)-**1’** and (*R*)-**1’** were produced with 87% and 77% enantiomeric excesses, respectively. The enantiomeric excess of (*R*)-**1’** increased 14%, while that of (*S*)-**1’** decreased 5%. These results showed that the (*S*)-**2a’** in the reaction mixture decreased, and it seems that the molecular recognition of Lipase PS decreased.

**Table 3.** Synthesis of optically active **1** and **1'**

| Entry | Substrate | $R^2$ | Time [h] | Yield [%] | | Yield [%] | Yield [%] | | Yield [%] / Enantiomeric Excess [% e.e.][1)] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | (*R*)-**2** | (*S*)-**3** | (*S*)-**2** | (*R*)-**4** | (*S*)-**4** | (*R*)-**1** | (*S*)-**1** |
| 1 | *rac*-**2a** | *n*-$C_6H_{13}$ | 30 | 44 | 52 | 93 | 83 | 71 | 74 / 98 | 70 / 90 |
| 2 | *rac*-**2'a** | *n*-$C_4H_9$ | 30 | 60 | 40 | 73 | 75 | 74 | 72 / 63 | 71 / 92 |
| 3 | | | 48 | 51 | 48 | 71 | 70 | 77 | 73 / 77 | 70 / 87 |

1) Determined by GC using InertCap CHIRAMIX column.

## EXPERIMENTAL

Thin-layer chromatography (TLC) was performed on prepared plates (silica gel F-254 on aluminum; Merck Ltd., Damstadt, Germany). Crude products were purified by column chromatography on silica gel FL60D purchased from Fuji Silysia Chemical Ltd. (Aichi, Japan). Melting points (mp) were recorded on a MP-500D micro-melting-point apparatus from Yanaco Technical Science Co., Ltd. (Kyoto, Japan) and are uncorrected. Infrared (IR) spectra were recorded on a Fourier transform (FT) IR-460-plus spectrometer from JASCO Corporation (Tokyo, Japan) and are reported as wave numbers ($cm^{-1}$). $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ solution on 500 MHz FT-NMR spectrometer (JEOL JNM-ECA 500 system). Chemical shifts are reported as parts per million with respect to the internal tetramethylsilane (TMS). Coupling constants (*J*) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were analyzed on a Mariner Biospectrometry Workstation (PerSeptive Biosystems, Framingham, MA, USA). The enantiomeric excesses were determined using a PerkinElmer Autosystem XL gas chromatograph equipped with the chiral capillary column InertCap CHIRAMIX (30 m × 0.25 mm I.D. 0.25 µm film thickness, GC Science Co., Ltd. Tokyo, Japan). The carrier gas was helium and the flow rate was 2.5 mL/min for *ε*-Decalactone and *ε*-dodecalactone or 2.0 mL/min for *N*-methyl-6-acetoxydecanamide and *N*-methyl-6-acetoxydodecanamide. *ε*-Decalactone and *ε*-dodecalactone were gifts from Soda Aromatic Co., Ltd. (Tokyo, Japan). Novozym 435 (immobilized lipase from *Candida antarctica*) and Lipozyme RM IM (immobilized lipase from *Rhizomucor miehei*) were gifts from Novozymes A/S (Paraná, Brazil). Lipase PS (from *Burkholderia cepacia*) and Lipase AYS (from *Candida rugosa*) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Porcine pancreatic lipase (PPL) was purchased from Nacalai Tesque Inc. (Kyoto, Japan). All other materials were commercially obtained. Diethyl ether ($Et_2O$), diisopropyl ether (*i*-$Pr_2O$), cyclopentyl methyl ether (CPME), and tetrahydrofuran (THF) were dried before used.

**Preparation of racemic *N*-methyl-6-hydroxyalkylamide (*rac*-2a and *rac*-2'a)**

Racemic *N*-methyl-6-hydroxyalkylamides (*rac*-**2a** and *rac*-**2'a**) were prepared by adding methylamine hydrochloride (1.0 g, 15.0 mmol) and potassium acetate (1.5 g, 15.0 mmol) to a solution of racemic $\varepsilon$-lactones (10.0 mmol) in THF (30 mL). The mixture was stirred at room temperature. After evaporation of the corresponding alcohol, $H_2O$ was added, and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (eluent: AcOEt) to afford the corresponding *N*-methyl-6-hydroxyalkylamides (*rac*-**2a** and *rac*-**2a'**) as a colorless solid.

**Data for racemic *N*-methyl-6-hydroxydodecanamide (*rac*-2a)**

Colorless solid; mp 74-75 °C; $R_f$ = 0.14 (eluent: AcOEt); IR (KBr, $\nu_{max}/cm^{-1}$): 3305 (-O-H), 3106 (-N-H), 2953 ($-CH_3$), 2925 ($-CH_2-$), 2870 ($-CH_3$), 2856 ($-CH_2-$), 1644 (-C(=O)-N-H); $^1$H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.88 (t, $J$ = 6.9 Hz, $-C\underline{H}_3$, 3H), 1.27-1.53 (m, $-C\underline{H}_2- \times 7$, 14H), 1.59-1.75 (m, $-C\underline{H}_2-$, 2H), 2.13-2.24 (m, $-C(=O)-C\underline{H}_2-$, 2H), 2.81 (d, $J$ = 4.6 Hz, $-NH-C\underline{H}_3$, 3H), 3.57-3.65 (m, $-C\underline{H}-OH$, 1H), 5.51 (br s, $-N\underline{H}-$, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ (ppm): 14.1 ($-\underline{C}H_3$), 22.6 ($-\underline{C}H_2CH_3$), 25.3 ($-\underline{C}H_2-$), 25.6 ($-\underline{C}H_2-$), 26.3 ($-NH-\underline{C}H_3$), 29.3 ($-\underline{C}H_2-$), 31.8 ($-\underline{C}H_2-$), 36.5 ($-C(=O)-\underline{C}H_2-$), 37.0 ($-\underline{C}H_2-$), 37.6 ($-\underline{C}H_2-$), 71.7 ($-\underline{C}H-OH$), 173.6 ($-NH-\underline{C}(=O)-$); HRMS (ESI) calcd. for $C_{13}H_{28}NO_2$ $(M+H)^+$, 230.2120; found $(M+H)^+$, 230.2125.

**Data for racemic *N*-methyl-6-hydroxydecanamide (*rac*-2'a)**

Colorless solid; mp 62-63 °C; $R_f$ = 0.14 (eluent: AcOEt); IR (KBr, $\nu_{max}/cm^{-1}$): 3306 (-O-H, -N-H), 2953 ($-CH_3$), 2934 ($-CH_2-$), 2869 ($-CH_3$), 2860 ($-CH_2-$), 1644 (-C(=O)-N-H); $^1$H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.90 (t, $J$ = 6.9 Hz, $-C\underline{H}_3$, 3H), 1.25-1.52 (m, $-C\underline{H}_2- \times 5$, 10H), 1.57-1.75 (m, $-C\underline{H}_2-$, 2H), 2.19 (t, $J$ = 7.3 Hz, $-C(=O)-C\underline{H}_2-$, 2H), 2.80 (d, $J$ = 5.0 Hz, $-NH-C\underline{H}_3$, 3H), 3.60 (m, $-C\underline{H}-OH$, 1H), 5.59 (br s, $-N\underline{H}-$, 1H); $^{13}$C NMR (126 Hz, $CDCl_3$) δ (ppm): 14.1 ($-\underline{C}H_3$), 22.7 ($-\underline{C}H_2CH_3$), 25.3 ($-\underline{C}H_2-$), 25.6 ($-\underline{C}H_2-$), 26.3 ($-NH-\underline{C}H_3$), 27.8 ($-\underline{C}H_2-$), 36.5 ($-C(=O)-\underline{C}H_2-$), 37.2 ($-\underline{C}H_2-$), 71.6 ($-\underline{C}H-OH$), 173.6 ($-NH-\underline{C}(=O)-$); HRMS (ESI) calcd. for $C_{11}H_{24}NO_2$ $(M+H)^+$, 202.1807; found $(M+H)^+$, 202.1815.

**Preparation of racemic *N*-alkyl-6-hydroxydodecanamide (*rac*-2b and *rac*-2c)**

Racemic $\varepsilon$-dodecalactone (*rac*-**1**) (1.9 g, 10.0 mmol) was added to the corresponding amine (20.0 mmol) and stirred at room temperature. $H_2O$ was added and neutralized with 1 M HCl aq. The aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with aqueous $NaHCO_3$ and brine and dried over $Na_2SO_4$. After evaporation of $CHCl_3$, the residue was purified by flash chromatography on silica (eluent: AcOEt) to afford the corresponding *N*-alkyl-6-hydroxydodecanamide (*rac*-**2b** and *rac*-**2c**) as a colorless solid.

**Data for racemic *N*-benzyl-6-hydroxydodecanamide (*rac*-2b)**

Colorless solid; mp 72-73 °C; $R_f$ = 0.25 (eluent: *n*-hexane-AcOEt, 1:1, *v*/*v*); IR (KBr, $\nu_{max}/cm^{-1}$): 3292

(-O-H, -N-H), 3087, 3064 (Ar, -C-H), 2956 (-$CH_3$), 2925 (-$CH_2$-), 2873 (-$CH_3$), 2855 (-$CH_2$-), 1634 (-C(=O)-N-H), 1496, 1456 (Ar, -C=C-); $^1$H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.88 (t, $J$ = 6.9 Hz, -$C\underline{H}_3$, 3H), 1.28-1.49 (m, -$C\underline{H}_2$- × 7, 14H), 1.58-1.78 (m, -$C\underline{H}_2$-, 2H), 2.22 (t, $J$ = 7.3 Hz, -C(=O)-$C\underline{H}_2$-, 2H), 3.57 (m, -C$\underline{H}$-OH, 1H), 4.42 (m, -NH-$C\underline{H}_2$-Ar, 2H), 5.97 (br s, -N$\underline{H}$-, 1H), 7.26-7.35 (m, Ar, 5H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ (ppm): (-$\underline{C}H_3$), 19.2 (-$\underline{C}H_2CH_3$), 22.6 (-$\underline{C}H_2$-), 25.2 (-$\underline{C}H_2$-), 25.5 (-$\underline{C}H_2$-), 25.6 (-$\underline{C}H_2$-), 29.3 (-$\underline{C}H_2$-), 31.8 (-C(=O)-$\underline{C}H_2$-), 36.5 (-$\underline{C}H_2$-), 36.9 (-$\underline{C}H_2$-), 43.5 (-NH-$\underline{C}H_2$-Ar), 71.6 (-$\underline{C}$H-OH), 126.4, 127.4, 127.8, 128.6, 138.4 (Ar), 172.9 (-NH-$\underline{C}$(=O)-); HRMS (ESI) calcd. for $C_{19}H_{32}NO_2$ $(M+H)^+$, 306.2433; found $(M+H)^+$, 306.2442.

**Data for racemic *N*-isopropyl-6-hydroxydodecanamide (*rac*-2c)**

Colorless solid; mp 87-88 °C; $R_f$ = 0.15 (eluent: *n*-hexane-AcOEt, 1:1, *v/v*); IR (KBr, $\nu_{max}/cm^{-1}$): 3305 (-O-H, -N-H), 2955 (-$CH_3$), 2926 (-$CH_2$-), 2871 (-$CH_3$), 2854 (-$CH_2$-), 1640 (-C(=O)-N-H); $^1$H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.88 (t, $J$ = 6.9 Hz, -$C\underline{H}_3$, 3H), 1.14 (d, $J$ = 6.4 Hz, -NH-CH($C\underline{H}_3$)$_2$, 6H), 1.28-1.51 (m, -$C\underline{H}_2$- × 7, 14H), 2.09-2.20 (m, -C(=O)-$C\underline{H}_2$-, 2H), 3.57-3.64 (m, -C$\underline{H}$-OH, 1H), 4.08 (m, -NH-C$\underline{H}$($CH_3$)$_2$, 1H), 5.27 (br s, -N$\underline{H}$-, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ (ppm): 14.1 (-$\underline{C}H_3$), 22.6 (-$\underline{C}H_2CH_3$), 22.8 (-NH-CH($\underline{C}H_3$)$_2$), 25.2 (-$\underline{C}H_2$-), 25.6 (-$\underline{C}H_2$-), 29.3 (-$\underline{C}H_2$-), 31.8 (-$\underline{C}H_2$-), 36.8 (-C(=O)-$\underline{C}H_2$-), 37.0 (-$\underline{C}H_2$-), 37.6 (-$\underline{C}H_2$-), 41.2 (-NH-CH($\underline{C}H_3$)$_2$), 71.6 (-$\underline{C}$H-OH), 172.0 (-NH-$\underline{C}$(=O)-); HRMS (ESI) calcd. for $C_{15}H_{32}NO_2$ $(M+H)^+$, 258.2433; found $(M+H)^+$, 258.2440.

**General procedure for lipase-catalyzed acetylation**

Lipase (Lipase PS, Lipase AYS and PPL: 0.5 *w/w*, Novozym 435 and Lipozyme RM IM: 0.4 g) was added to a solution of *rac*-**2a**-**c** (1.0 mmol) and vinyl acetate (0.2 g, 2.0 mmol) in the solvent (20 mL), the mixture was stirred. After stirring, the mixture was filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica (eluent: AcOEt) to afford the corresponding (*R*)-**2a**-**c** as a colorless solid and (*S*)-*N*-alkyl-6-acetoxydodecanamide [(*S*)-**3a**-**c**] as a colorless oil.

**Data for (*R*)-*N*-methyl-6-hydroxydodecanamide [(*R*)-2a]**

Colorless solid; $[\alpha]_D^{20}$ -5.0 (98% e.e., *c* 0.20, MeOH)

**Data for (*R*)-*N*-benzyl-6-hydroxydodecanamide [(*R*)-2b]**

Colorless solid; $[\alpha]_D^{20}$ -9.3 (79% e.e., *c* 0.20, MeOH)

**Data for (*R*)-*N*-isopropyl-6-hydroxydodecanamide [(*R*)-2c]**

Colorless solid; $[\alpha]_D^{20}$ -5.6 (90% e.e., *c* 0.20, MeOH)

**Data for (*R*)-*N*-methyl-6-hydroxydecanamide [(*R*)-2’a]**

Colorless solid; $[\alpha]_D^{20}$ +3.2 (77% e.e., *c* 0.20, MeOH)

**Data for (*S*)-*N*-methyl-6-acetoxydodecanamide [(*S*)-3a]**

Colorless oil; $[\alpha]_D^{20}$ -22.5 (90% e.e., *c* 0.20, MeOH); $R_f$ = 0.54 (eluent: AcOEt); IR (NaCl, $\nu_{max}/cm^{-1}$):

3301 (-N-H), 2933, 2860 (-$CH_2$-), 1737 (-O-C(=O)-), 1650 (-C(=O)-N-H), 1244 (-C-C(=O)-O); $^1$H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.88 (t, $J$ = 6.9 Hz, -$\underline{C}H_3$, 3H), 1.26-1.40 (m, -C$\underline{H}_2$- × 5, 10H), 1.47-1.57 (m, -C$\underline{H}_2$- × 2, 4H), 1.59-1.72 (m, -C$\underline{H}_2$-, 2H), 2.04 (s, -O-C(=O)-C$\underline{H}_3$, 3H), 2.17 (t, $J$ = 7.8 Hz, -C(=O)-C$\underline{H}_2$-, 2H), 2.80 (d, $J$ = 5.0 Hz, -NH-C$\underline{H}_3$, 3H), 4.85 (quin, $J$ = 6.9 Hz, -C$\underline{H}$-O-C(=O)-, 1H), 5.55 (br s, -N$\underline{H}$-, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ (ppm): 14.0 (-$\underline{C}H_3$), 21.3 (-O-C(=O)-$\underline{C}H_3$), 22.5 (-$\underline{C}H_2CH_3$), 25.0 (-$\underline{C}H_2$-), 25.3 (-$\underline{C}H_2$-), 25.5 (-$\underline{C}H_2$-), 26.2 (-NH-$\underline{C}H_3$), 29.1 (-$\underline{C}H_2$-), 31.7 (-$\underline{C}H_2$-), 33.8 (-$\underline{C}H_2$-), 34.1 (-$\underline{C}H_2$-), 36.5 (-C(=O)-$\underline{C}H_2$-), 74.1 (-$\underline{C}$H-O-C(=O)-), 171.0 (-O-$\underline{C}$(=O)-$CH_3$), 173.4 (-NH-$\underline{C}$(=O)-); HRMS (ESI) calcd. for $C_{15}H_{30}NO_3$ $(M+H)^+$, 272.2226; found (M+H$)^+$, 272.2222.

**Data for (*S*)-*N*-benzyl-6-acetoxydodecanamide [(*S*)-3b]**

Colorless oil; $[\alpha]_D^{20}$ -8.9 (85% e.e., *c* 0.20, MeOH); $R_f$ = 0.65 (eluent: *n*-hexane-AcOEt, 1:1, *v*/*v*); IR (NaCl, $\nu_{max}/cm^{-1}$): 3292 (-N-H), 3087, 3064 (Ar, -C-H), 2952 (-$CH_3$), 2930, 2859 (-$CH_2$-), 1735 (-O-C(=O)-), 1647 (-C(=O)-N-H), 1496, 1455 (Ar, -C=C-), 1243 (-C-C(=O)-O); $^1$H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.88 (t, $J$ = 6.9 Hz, -C$\underline{H}_3$, 3H), 1.24-1.41 (m, -$CH_2$- × 5, 10H), 1.47-1.57 (m, -C$\underline{H}_2$- × 2, 4H), 1.58-1.74 (m, -C$\underline{H}_2$-, 2H), 2.02 (s, -O-C(=O)-C$\underline{H}_3$, 3H), 2.20 (t, $J$ = 7.8 Hz, -C(=O)-C$\underline{H}_2$-, 2H), 4.43 (d, $J$ = 5.6 Hz, -NH-C$\underline{H}_2$-Ar, 2H), 4.84 (quin, $J$ = 6.8 Hz, -C$\underline{H}$-O-C(=O)-, 1H), 5.85 (br s, -N$\underline{H}$-, 1H), 7.26-7.35 (m, Ar, 5H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ (ppm): 14.0 (-$\underline{C}H_3$), 19.2 (-O-C(=O)-$\underline{C}H_3$), 21.2 (-$\underline{C}H_2CH_3$), 25.0 (-$\underline{C}H_2$-), 25.2 (-$\underline{C}H_2$-), 25.5 (-$\underline{C}H_2$-), 29.1 (-$\underline{C}H_2$-), 31.7 (-$\underline{C}H_2$-), 33.8 (-$\underline{C}H_2$-), 34.1 (-$\underline{C}H_2$-), 36.5 (-C(=O)-$\underline{C}H_2$-), 43.5 (-NH-$\underline{C}H_2$-Ar), 74.1 (-$\underline{C}$H-O-C(=O)-), 127.4, 127.8, 128.7, 138.4 (Ar), 170.9 (-O-$\underline{C}$(=O)-$CH_3$), 172.6 (-NH-$\underline{C}$(=O)-); HRMS (ESI) calcd. for $C_{21}H_{34}NO_3$ $(M+H)^+$, 348.2539; found $(M+H)^+$, 348.2543.

**Data for (*S*)-*N*-isopropyl-6-acetoxydodecanamide [(*S*)-3c]**

Colorless oil; $[\alpha]_D^{20}$ -0.7 (94% e.e., *c* 0.20, MeOH); $R_f$ = 0.50 (eluent: *n*-hexane-AcOEt, 1:1, *v*/*v*); IR (NaCl, $\nu_{max}/cm^{-1}$): 3292 (-N-H), 2956 (-$CH_3$), 2932, 2860 (-$CH_2$-), 1738 (-O-C(=O)-O), 1642 (-C(=O)-N-H), 1243 (-C-C(=O)-O); $^1$H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.88 (t, $J$ = 6.9 Hz, -C$\underline{H}_3$, 3H), 1.14 (d, $J$ = 6.4 Hz, -NH-CH(C$\underline{H}_3$)$_2$, 6H), 1.26-1.40 (m, -C$\underline{H}_2$- × 5, 10H), 1.47-1.57 (m, -C$\underline{H}_2$- × 2, 4H), 1.58-1.71 (m, -C$\underline{H}_2$-, 2H), 2.03 (s, -O-C(=O)-C$\underline{H}_3$, 3H), 2.12 (t, $J$ = 7.3 Hz, -C(=O)-C$\underline{H}_2$-, 2H), 4.02-4.15 (m, -NH-C$\underline{H}$($CH_3$)$_2$, 1H), 4.85 (quin, $J$ = 6.9 Hz, -C$\underline{H}$-O-C(=O)-, 1H), 5.37 (br s, -N$\underline{H}$-, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ (ppm): 14.0 (-$\underline{C}H_3$), 21.2 (-O-C(=O)-$\underline{C}H_3$), 22.5 (-$\underline{C}H_2CH_3$), 22.8 (-NH-CH($\underline{C}H_3$)$_2$), 24.9 (-$\underline{C}H_2$-), 25.2 (-$\underline{C}H_2$-), 25.6 (-$\underline{C}H_2$-), 29.1 (-$\underline{C}H_2$-), 31.7 (-$\underline{C}H_2$-), 33.8 (-$\underline{C}H_2$-), 34.1 (-$\underline{C}H_2$-), 36.7 (-C(=O)-$\underline{C}H_2$-), 41.2 (-NH-$\underline{C}$H($CH_3$)$_2$), 74.1 (-$\underline{C}$H-O-C(=O)-), 170.9 (-O-$\underline{C}$(=O)-$CH_3$), 171.8 (-NH-$\underline{C}$(=O)-); HRMS (ESI) calcd. for $C_{17}H_{34}NO_3$ $(M+H)^+$, 300.2539; found $(M+H)^+$, 300.2549.

**Data for (*S*)-*N*-methyl-6-acetoxydecanamide [(*S*)-3’a]**

Colorless oil; $[\alpha]_D^{20}$ -20.5 (87% e.e., *c* 0.20, MeOH); $R_f$ = 0.43 (eluent: AcOEt); IR (NaCl, $\nu_{max}/cm^{-1}$): 3300 (-N-H), 2953 (-$CH_3$), 2936, 2863 (-$CH_2$-), 1738 (-O-C(=O)-O), 1652 (-C(=O)-N-H), 1243

(-C-C(=O)-O); $^{1}$H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.89 (t, *J* = 6.9 Hz, -C<u>H</u>$_3$, 3H), 1.17-1.40 (m, -C<u>H</u>$_2$- × 3, 6H), 1.47-1.57 (m, -C<u>H</u>$_2$- × 2, 4H), 1.59-1.72 (m, -C<u>H</u>$_2$-, 2H), 2.04 (s, -O-C(=O)-C<u>H</u>$_3$, 3H), 2.17 (t, *J* = 7.3 Hz, -C(=O)-C<u>H</u>$_2$-, 2H), 2.80 (d, *J* = 5.0 Hz, -NH-C<u>H</u>$_3$, 3H), 4.85 (quin, *J* = 6.0 Hz, -C<u>H</u>-O-C(=O)-, 1H), 5.55 (br s, -N<u>H</u>-, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ (ppm): 14.0 (-<u>C</u>H$_3$), 21.3 (-O-C(=O)-<u>C</u>H$_3$), 22.5 (-<u>C</u>H$_2$CH$_3$), 25.0 (-<u>C</u>H$_2$-), 25.5 (-<u>C</u>H$_2$-), 26.2 (-<u>C</u>H$_2$-), 27.5 (-NH-<u>C</u>H$_3$), 33.7 (-<u>C</u>H$_2$-), 33.8 (-CH$_2$-), 36.5 (-C(=O)-<u>C</u>H$_2$-), 74.1 (-<u>C</u>H-O-C(=O)-), 171.0 (-O-<u>C</u>(=O)-CH$_3$), 173.4 (-NH-<u>C</u>(=O)-); HRMS (ESI) calcd. for $C_{13}H_{26}NO_3$ $(M+H)^+$, 244.1913; found $(M+H)^+$, 244.1915.

**Preparation of racemic 6-hydroxydodecanaoic acid (*rac*-4)**

Racemic 6-hydroxydodecanoic acid (*rac*-**4**) was prepared by adding NaOH (3 g) to a solution of *ε*-dodecalactone (*rac*-**1**) (1.9 g, 10.0 mmol) in MeOH (50 mL). The mixture was stirred at 65 °C for 3 h. After evaporation of MeOH, $H_2O$ was added and neutralized with $H_3PO_4$ at 0 °C. The aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (eluent: *n*-hexane-AcOEt, 1:1, *v*/*v*) to afford racemic 6-hydroxydodecanoic acid (*rac*-**6**) as a colorless solid (1.6 g, 76%). mp 54-55 °C; IR (KBr, $\nu_{max}$/cm$^{-1}$): 3242 (-O-H), 2949 (-CH$_3$), 2926 (-CH$_2$-), 2870 (-CH$_3$), 2851 (-CH$_2$-), 1701 (-C=O); $^{1}$H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.89 (t, *J* = 6.9 Hz, -C<u>H</u>$_3$, 3H), 1.29-1.54 (m, -C<u>H</u>$_2$- × 7, 14H), 1.58-1.74 (m, -C<u>H</u>$_2$-, 2H), 2.37 (t, *J* = 7.3 Hz, -C(=O)-<u>C</u>H$_2$-, 2H), 3.58-3.64 (m, -C<u>H</u>-OH, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ (ppm): 14.1 (-<u>C</u>H$_3$), 22.6 (-<u>C</u>H$_2$CH$_3$), 24.6 (-<u>C</u>H$_2$-), 25.1 (-<u>C</u>H$_2$-), 25.6 (-<u>C</u>H$_2$-), 29.3 (-<u>C</u>H$_2$-), 31.8 (-<u>C</u>H$_2$-), 33.9 (-C(=O)-<u>C</u>H$_2$-), 36.9 (-<u>C</u>H$_2$-), 37.5 (-CH$_2$-), 71.8 (-<u>C</u>H-OH), 179.1 (-<u>C</u>(=O)-OH).

**General procedure for lipase-catalyzed lactonization**

Lipase (Lipase PS, Lipase AYS and PPL: 0.5 *w*/*w*, Novozym 435 and Lipozyme RM IM: 0.2 g) and 0.5 g 4Å molecular sieves were added to a solution of *rac*-**4** (0.5 mmol) in solvent (10 mL), and the mixture was stirred. After stirring, the mixture was filtered, and the solvent was evaporated under reduced pressure. The crude mixture was purified by flash chromatography on silica (eluent: *n*-hexane-AcOEt, 4:1, *v*/*v*) to afford the corresponding *ε*-lactones [(*R*)- and (*S*)-**1** and (*R*)- and (*S*)-**1'**].

**Data for (*R*)-*ε*-dodecalactone [(*R*)-1]**

Colorless oil; $[\alpha]_D^{20}$ +34.8 (98% e.e., *c* 0.10, $CHCl_3$); $R_f$ = 0.40 (eluent: *n*-hexane-AcOEt, 4:1, *v*/*v*); IR (NaCl, $\nu_{max}$/cm$^{-1}$): 2931, 2860 (-CH$_2$-), 1730 (-C=O), 1254 (-C-C(=O)-O); $^{1}$H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.88 (t, *J* = 6.4 Hz, -C<u>H</u>$_3$, 3H), 1.28-1.37 (m, -C<u>H</u>$_2$- × 4, 7H), 1.43-1.76 (m, -C<u>H</u>$_2$- × 3, 6H), 1.89-1.96 (m, -C<u>H</u>$_2$- ×2, 3H), 2.57-2.69 (m, -C(=O)-C<u>H</u>$_2$-, 2H), 4.21-4.26 (m, -O-C<u>H</u>CH$_2$-, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ (ppm): 14.0 (-<u>C</u>H$_3$), 22.5 (-<u>C</u>H$_2$CH$_3$), 23.0 (-C<u>H</u>$_2$-), 25.3 (-C<u>H</u>$_2$-), 28.2 (-<u>C</u>H$_2$-), 29.0 (-<u>C</u>H$_2$-), 31.6 (-<u>C</u>H$_2$-), 34.5 (-<u>C</u>H$_2$-), 34.9 (-C(=O)-<u>C</u>H$_2$-), 36.3 (-<u>C</u>H$_2$-), 80.5 (-O-<u>C</u>HCH$_2$-), 175.8 (-O-<u>C</u>(=O)-); HRMS (ESI) calcd. for $C_{12}H_{23}O_2$ $(M+H)^+$, 199.1698; found $(M+H)^+$, 199.1692.

**Data for (*S*)-*ε*-dodecalactone [(*S*)-1]**

Colorless oil; $[\alpha]_D^{20}$ -31.7 (90% e.e., *c* 0.10, $CHCl_3$), lit., $[\alpha]_D$ -35.1 (98% e.e., *c* 1.10, $CHCl_3$)[32]

**Data for (*R*)-*ε*-decalactone [(*R*)-1']**

Colorless oil; $[\alpha]_D^{20}$ +14.4 (77% e.e., *c* 0.10, $CHCl_3$); $R_f$ = 0.41 (eluent: *n*-hexane-AcOEt, 4:1, *v*/*v*); IR (NaCl, $\nu_{max}/cm^{-1}$): 2935, 2862 (-$CH_2$-), 1730 (-C=O), 1257 (-C-C(=O)-O); $^1H$ NMR (500 MHz, $CDCl_3$) δ (ppm): 0.91 (t, *J* = 6.9 Hz, -C<u>H</u>$_3$, 3H), 1.32-1.40 (m, -C<u>H</u>$_2$- × 2, 3H), 1.42-1.76 (m, -C<u>H</u>$_2$- × 3, 6H), 1.90-1.96 (m, -C<u>H</u>$_2$- ×2, 3H), 2.59-2.68 (m, -C(=O)-C<u>H</u>$_2$-, 2H), 4.23-4.28 (m, -O-C<u>H</u>CH$_2$-, 1H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ (ppm): 13.7 (-<u>C</u>H$_3$), 22.2 (-<u>C</u>H$_2$CH$_3$), 22.8 (-<u>C</u>H$_2$-), 27.3 (-<u>C</u>H$_2$-), 28.0 (-<u>C</u>H$_2$-), 34.3 (-<u>C</u>H$_2$-), 34.7 (-C(=O)-<u>C</u>H$_2$-), 35.9 (-<u>C</u>H$_2$-), 80.3 (-O-<u>C</u>HCH$_2$-), 175.6 (-O-<u>C</u>(=O)-); HRMS (ESI) calcd. for $C_{10}H_{19}O_2$ $(M+H)^+$, 171.1385; found $(M+H)^+$, 171.1381.

**Data for (*S*)-*ε*-decalactone [(*S*)-1']**

Colorless oil; $[\alpha]_D^{20}$ -17.1 (92% e.e., *c* 0.10, $CHCl_3$), lit., $[\alpha]_D$ -18.6 (≥98% e.e., *c* 1.11, $CHCl_3$)[33]

**Preparation of (*S*)-*N*-alkyl-6-hydroxyalkylamide [(*S*)-2a-c and (*S*)-2'a]**

(*S*)-*N*-alkyl-6-hydroxyalkylamides [(*S*)-**2a**-**c** and (*S*)-**2'a**] were prepared by adding $Na_2CO_3$ (1 g) to a solution of (*S*)-*N*-alkyl-6-acetoxyalkylamides in MeOH (20 mL). The mixture was stirred at 65 °C for 3 h. After evaporation of MeOH, $H_2O$ was added and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (eluent: AcOEt) to afford (*S*)-**2a**-**c** and (*S*)-**2'a** as a colorless solid with over 90% yield.

**Preparation of (*R*)- and (*S*)-6-hydroxyalkanoic acid [(*R*)- and (*S*)-4, (*R*)- and (*S*)-4']**

NaOH (3.0 g) was added to a solution of (*R*)- and (*S*)-*N*-alkyl-6-hydroxyalkylamides [(*R*)- and (*S*)-**2a**-**c**, **2'a**], and the mixture was stirred at 90 °C. After evaporation of MeOH, $H_2O$ was added and neutralized with $H_3PO_4$ at 0 °C. The aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (eluent: *n*-hexane-AcOEt, 1:1, *v*/*v*) to afford the corresponding 6-hydroxyalkanoic acid [(*R*)- and (*S*)-**4**, (*R*)- and (*S*)-**4'**] as a colorless solid.

**Data for (*R*)- and (*S*)-6-hydroxydodecanoic acid [(*R*)- and (*S*)-4]**

Colorless solid; $[\alpha]_D^{20}$ -34.4 [(*R*)-enantiomer, 98% e.e., *c* 0.20, MeOH]; $[\alpha]_D^{20}$ +20.7 [(*S*)-enantiomer, 90% e.e., *c* 0.20, MeOH].

**Data for (*R*)- and (*S*)-6-hydroxydecanoic acid [(*R*)- and (*S*)-4']**

Colorless solid; mp 29-30 °C; $[\alpha]_D^{25}$ -27.8 [(*R*)-enantiomer, 77% e.e., *c* 0.20, MeOH]; $[\alpha]_D^{25}$ +47.1 [(*S*)-enantiomer, 87% e.e., *c* 0.20, MeOH]; IR (KBr, $\nu_{max}/cm^{-1}$): 3227 (-O-H), 2952 (-$CH_3$), 2926 (-$CH_2$-), 2871 (-$CH_3$), 2858 (-$CH_2$-), 1709 (-C=O); $^1H$ NMR (500 MHz, $CDCl_3$) δ (ppm): 0.91 (t, *J* = 6.9 Hz, -C<u>H</u>$_3$, 3H), 1.25-1.54 (m, -C<u>H</u>$_2$- × 5, 10H), 1.59-1.72 (m, -C<u>H</u>$_2$-, 2H), 2.36 (t, *J* = 7.4 Hz, -C(=O)-C<u>H</u>$_2$-, 2H),

3.59-3.65 (m, -C<u>H</u>-OH, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ (ppm): 14.0 (-<u>C</u>$H_3$), 22.7 (-<u>C</u>$H_2CH_3$), 24.6 (-<u>C</u>$H_2$-), 25.0 (-<u>C</u>$H_2$-), 27.8 (-<u>C</u>$H_2$-), 33.9 (-C(=O)-<u>C</u>$H_2$-), 36.8 (-<u>C</u>$H_2$-), 37.1 (-<u>C</u>$H_2$-), 71.8 (-<u>C</u>H-OH), 179.2 (-<u>C</u>(=O)-OH).

**Chiral GC analyses**

**Conditions for *N*-methyl-6-acetoxydodecanamide (3a)**

GC Column: InertCap CHIRAMIX (30 m × 0.25 mm × 0.25 μm film thickness). Oven temp.: 160 °C. $t_R$-(*S*) enantiomer = 287.2 min, $t_R$-(*R*) enantiomer = 289.6 min.

**Conditions for *N*-methyl-6-acetoxydecanamide (3a')**

GC Column: InertCap CHIRAMIX (30 m × 0.25 mm × 0.25 μm film thickness). Oven temp.: 160 °C. $t_R$-(*S*) enantiomer = 121.1 min, $t_R$-(*R*) enantiomer = 122.9 min.

**Conditions for *ε*-Dodecalactone (1)**

GC Column: InertCap CHIRAMIX (30 m × 0.25 mm × 0.25 μm film thickness). Program: 130-170 °C at 1.0 °C/min. $t_R$-(*R*) enantiomer = 34.6 min, $t_R$-(*S*) enantiomer = 32.0 min.

**Conditions for *ε*-Decalactone (1')**

GC Column: InertCap CHIRAMIX (30 m × 0.25 mm × 0.25 μm film thickness). Program: 120-160 °C at 1.0 °C/min. $t_R$-(*R*) enantiome r= 28.1 min, $t_R$-(*S*) enantiomer = 24.9 min.

## ACKNOWLEDGEMENTS

We are grateful to Novozymes A/S for the generous gift of Novozym 435 and Lipozyme RM IM. A generous gift of *ε*-decalactone and *ε*-dodecalactone from Soda Aromatic Co., Ltd. is also acknowledged.

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