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Preparation of Optically Active δ-Tri- and δ-Tetradecalactones by a Combination of Novozym 435-catalyzed Enantioselective Methanolysis and Amidation

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Abstract: A combination of Novozym 435-catalyzed methanolysis and amidation using racemic *N*-methyl-5-acetoxytridecan- and tetradecanamides as a substrate proceeded in good enantioselectivity to afford the corresponding (*R*)-*N*-methyl-5-acetoxyalkanamides, (*S*)-*N*-methyl-5-hydroxyalkanamides, and (*S*)-*N*-cyclohexyl-5-hydroxyalkanamides. Both enantiomers of δ-tri- and δ-tetradecalactones were synthesized in over 90% enantiomeric excesses from the corresponding (*R*)- or (*S*)-alkanamides. Addition of cyclohexylamine to Novozym 435-catalyzed methanolysis shortened 24-hour reaction time to reach about 50% conversion. Enantiomers of optically active δ-tri- and δ-tetradecalactones had different odors and thresholds.

Key words: δ-tridecalactone, δ-tetradecalactone, lipase-catalyzed kinetic resolution, methanolysis, amidation

1 INTRODUCTION

Lactones are well-known flavor component in many natural products[1-5], sex pheromone components[6-9] and useful building blocks for various drugs[10-12]. These lactones play important roles in the food and fragrance industries because they add sweet, milky, and fruity notes to many products[13-15]. However, the odor quality and threshold depend to a large extent on the chiral configuration and enantiomeric composition[13, 16-18]. Lactones are found naturally enantiomeric excess in various compositions[19-21]. Therefore, use of similar enantiomeric excesses of optically active lactones is prerequisite to artificially simulate a natural flavor. δ-Tri- and δ-tetradecalactones are found in milk and dairy products such as cheddar, Gouda and blue cheese[22-27]. The enantiomeric excess composition of δ-tetradecalactone contained in these dairy products is generally (*R*)-enantiomer dominant[28]. Additionally, δ-tetradecalactone is widely found in cooked beef, sheep and chicken fats[29-31]. Sensory evaluation of racemic δ-tetradecalactone was performed by Schlutt *et al.*[32], differences in odor properties and thresholds among enantiomers of δ-tri- and δ-tetradecalactones have not been reported. We synthesized these optically active lactones and evaluated their sensory properties. Tanaka *et al.* reported that racemic δ-tri- and δ-tetradecalactones have anti-tumor and anti-invasive activities[33]. Different biological activities, such as anti-bronchoconstrictor, enzyme inhibitory, and anti-inflammatory activity, are generally exhibited by each enantiomer in many cases[34-39]. Therefore, the anti-tumor and anti-invasive effects of optically active enantiomers could be expected to be different than those of racemates. We previously reported a method for the synthesis of optically active δ-hexadecalactone by a combination of lipase-catalyzed enantiomeric methanolysis and amidation[40]. It was clear that the addition of two equivalent amounts of cyclohexylamine to the substrate increased enantiolselectivity over 10% relative to the absence of the amine. In this study, we attempted to synthesize optically active δ-tri- and δ-tetradecalactones using this method.

2 EXPERIMENTAL

2.1 General

All reagents and solvents were obtained from commercial sources. ^{1}H NMR spectra were recorded in $CDCl_3$ using a JNM-ECA-400 spectrometer (400 MHz; JEOL, Tokyo, Japan). Chemical shifts are expressed in parts/million (ppm), with tetramethylsilane as the internal standard. ^{13}C NMR spectra were recorded in $CDCl_3$ using a JNM-ECA-

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400 spectrometer (100 MHz, JEOL). Chemical shifts are expressed in parts/million (ppm), with tetramethylsilane as the internal standard. Structural determination of all compounds was performed by the use of COSY, HMQC, and HMBC NMR techniques. Optical rotations were measured with a P-1010 (JASCO Corp., Tokyo, Japan). IR spectra were measured with an IR-4100 (JASCO Corp.). Melting points were recorded on a MP-500D (Yanaco Technical Science Co., Ltd., Kyoto, Japan) and are uncorrected. Enantiomeric excesses were determined by capillary GC using an InertCap CHIRAMIX (30 m × 0.25 mm I.D. 0.25 μm film thickness, GL Science Co., Ltd., Tokyo, Japan) column (Inj. 250℃, Det. 250℃). High-resolution mass spectra were analyzed on an AccuTof GCv 4G (JEOL).

2.2 Preparation of racemic *N*-alkyl-5-acetoxyalkanamides (*rac*-1 and *rac*-2)[40]

Racemic δ-tridecalactone (10.0 mmol, 2.12 g) or δ-tetradecalactone (10.0 mmol, 2.26 g) was added to a solution of methylamine hydrochloride (15.0 mmol, 1.0 g) and potassium acetate (15.0 mmol, 1.47 g) in THF (50 mL) and stirred at room temperature. Alternatively, a crude mixture containing lactone (10.0 mmol) and the corresponding amine (20.0 mmol) was stirred at room temperature. The mixture was evaporated, the residue was dissolved in $CHCl_3$ and water was then added. The aqueous layer was separated, and the organic layer was washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification of the crude product by recrystallization from *n*-hexane gave the corresponding *N*-alkyl-5-hydroxyalkanamides (*rac*-**1** and **2**). Acetic anhydride (16.0 mmol, 1.63 g) and 4-dimethylaminopyridine (1.60 mmol, 0.20 g) were added to a stirred solution of *rac*-**1** or **2** in anhydrous CH_2Cl_2 (20 mL) at room temperature. After 24 hours, CH_2Cl_2 was removed under reduced pressure. Water (50 mL) was then added, and the solution was neutralized with $NaCO_3$. CH_3Cl was added to the mixture and the organic layer was separated, washed with water, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane/EtOAc, 1:1, v/v) gave the desired compounds *rac*-**1a-e** and **2a-e**.

2.2.1 *N*-Methyl-5-acetoxytridecanamide (*rac*-**1a**)

Yield: 2.62 g, 92% (from *rac*-**5**); colorless solid; mp = 35-36℃; $[\alpha]^{25}_D = -6.34$ [*c* = 0.5, MeOH, 77% e.e. for (*R*)-**1a**]. IR (NaCl): cm^{-1} 3300 (N-H), 2952 (-CH_3), 2925 (-CH_2-), 2872 (-CH_3), 2857 (-CH_2-), 1738 (O<u>C</u>=O), 1652 (NH<u>C</u>=O), 1242 (C-O). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88 (t, *J* = 7.2 Hz, 3H, -CH_2CH_3), 1.25 (m, 12H, -CH_2- × 6), 1.52 (m, 4H, -CH_2CH(OAc)CH_2-), 1.65 (m, 2H, -NHC(=O)CH_2CH_2-), 2.04 (s, 3H, -OC(=O)CH_3), 2.16 (m, 2H, -NHC(=O)CH_2-), 2.80 (d, *J* = 4.4 Hz, 3H, CH_3NHC(=O)-), 4.86 (m, 1H, -CH_2CH(OAc)CH_2-), 5.59 (br s, 1H, NH). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 13.9 (-CH_2CH_3), 21.1 (-OC(=O)CH_3), 21.3 (-NHC(=O)CH_2CH_2-), 22.5 (-CH_2CH(OAc)CH_2CH_2-), 25.2, 26.1, 29.0, 29.2, 29.3 (-CH_2- × 5), 31.7 (CH_3NHC(=O)-), 33.4, 33.9 (-CH_2CH(OAc)CH_2-), 35.8 (-NHC(=O)CH_2-), 73.7 (-CH_2CH(OAc)CH_2-), 171.0 (-OC(=O)CH_3), 173.5 (-NHC(=O)-). HRMS (FD) calcd. for $C_{16}H_{32}NO_3$ $(M+H)^+$, 286.2382; found $(M+H)^+$, 286.23314.

2.2.2 *N*-*n*-Propyl-5-acetoxytridecanamide (*rac*-**1b**)

Yield: 2.73 g, 87% (from *rac*-**5**); colorless solid; mp = 35-36℃; $[\alpha]^{25}_D = +0.89$ [*c* = 0.5, MeOH, 34% e.e. for (*R*)-**1b**]. IR (KBr): cm^{-1} 3306 (N-H), 2919 (-CH_3), 2850 (-CH_2-), 1731 (O<u>C</u>=O), 1638 (NH<u>C</u>=O), 1241 (C-O). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H, -CH_2CH_3), 0.92 (t, *J* = 7.5 Hz, 3H, $CH_3CH_2CH_2$NH(C=O)-), 1.25 (m, 11H, -CH_2- × 6), 1.52 (m, 4H, -CH_2CH(OAc)CH_2-), 1.57 (m, 2H, $CH_3CH_2CH_2$NHC(=O)-), 1.62 (m, 1H, -NHC(=O)CH_2CH_2-), 1.68 (m, 1H, -NHC(=O)CH_2CH_2-), 2.04 (s, 3H, -OC(=O)CH_3), 2.17 (m, 2H, -NHC(=O)CH_2-), 3.20 (dt, *J* = 6.3, 6.9 Hz, 2H, $CH_3CH_2CH_2$NHC(=O)-), 4.87 (tt, *J* = 5.7, 5.7 Hz, 1H, -CH_2CH(OAc)CH_2-), 5.78 (br s, 1H, NH). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 11.3 ($CH_3CH_2CH_2$NHC(=O)-), 14.0 (-CH_2CH_3), 21.2 (-NHC(=O)CH_2CH_2-), 21.5 (-CH_2-), 22.5 ($CH_3CH_2CH_2$NHC(=O)-), 22.8, 25.2, 29.1, 29.4, 31.7 (-CH_2- × 5), 33.5, 34.0 (-CH_2CH(OAc)CH_2-), 36.1 (-NHC(=O)CH_2-), 41.1 ($CH_3CH_2CH_2$NHC(=O)-), 73.6 (-CH_2CH(OAc)CH_2-), 171.0 (-OC(=O)CH_3), 172.5 (-NHC(=O)-). HRMS (FD) calcd. for $C_{18}H_{36}NO_3$ $(M+H)^+$, 314.2695; found $(M+H)^+$, 314.27011.

2.2.3 *N*-*iso*-Propyl-5-acetoxytridecanamide (*rac*-**1c**)

Yield: 2.69 g, 86% (from *rac*-**5**); colorless solid; mp = 35-36℃; $[\alpha]^{25}_D = -5.74$ [*c* = 0.5, MeOH, 70% e.e. for (*R*)-**1c**]. IR (KBr): cm^{-1} 3306 (N-H), 2920 (-CH_3), 2850 (-CH_2-), 1731 (O<u>C</u>=O), 1640 (NH<u>C</u>=O), 1242 (C-O). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H, -CH_2CH_3), 1.13 (d, *J* = 2.9 Hz, 3H, $(CH_3)_2$CHNHC(=O)-), 1.15 (d, *J* = 2.3 Hz, 3H, $(CH_3)_2$CHNHC(=O)-), 1.26 (m, 12H, -CH_2- × 6), 1.56 (m, 4H, -CH_2CH(OAc)CH_2-), 1.60 (m, 1H, -NHC(=O)CH_2CH_2-), 1.68 (m, 1H, -NHC(=O)CH_2CH_2-), 2.04 (s, 3H, -OC(=O)CH_3), 2.13 (m, 2H, -NHC(=O)CH_2-), 4.07 (dq, *J* = 6.3, 6.9 Hz, 1H, $(CH_3)_2CH$NHC(=O)-), 4.86 (tt, *J* = 6.3, 5.7 Hz, 1H, -CH_2CH(OAc)CH_2-), 5.45 (br s, 1H, NH). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 14.2 (-CH_2CH_3), 21.3 (-NHC(=O)CH_2CH_2-), 21.6 (-CH_2-), 22.7, 22.8 ($(CH_3)_2$CHNHC(=O)-), 25.4, 29.3, 29.5, 31.9 (-CH_2- × 4), 33.5, 34.1 (-CH_2CH(OAc)CH_2-), 36.4 (-NHC(=O)CH_2-), 41.3 ($(CH_3)_2CH$NHC(=O)-), 73.8 (-CH_2CH(OAc)CH_2-), 171.1 (-OC(=O)CH_3), 171.8 (-NHC(=O)-). HRMS (FD) calcd. for $C_{18}H_{36}NO_3$ $(M+H)^+$, 314.2695; found $(M+H)^+$, 314.26682.

2.2.4 *N*-Cyclohexyl-5-acetoxytridecanamide (*rac*-**1d**)

Yield: 3.32 g, 94% (from *rac*-**5**); colorless solid; mp = 40-41℃; $[\alpha]^{25}_D = +1.64$ [*c* = 0.5, MeOH, 32% e.e. for (*R*)-**1d**]. IR (KBr): cm^{-1} 3303 (N-H), 2920 (-CH_3), 2852 (-CH_2-), 1729 (O<u>C</u>=O), 1635 (NH<u>C</u>=O), 1246 (C-O). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H, -CH_2CH_3), 1.13 (m, 3H, -CH_2CH(CH_2-)NHC(=O)-), 1.26 (m, 12H, -CH_2- × 6), 1.37 (m, 2H, -CH_2- at cHx), 1.56 (m, 6H, -CH_2CH(Ac)

$C\underline{H_2}$-, -$C\underline{H_2}C\underline{H_2}CH(CH_2\text{-})NHC(=O)$-), 1.69 (m, 3H, -NHC(=O)$CH_2C\underline{H_2}$-, -$C\underline{H_2}CH_2CH(CH_2\text{-})NHC(=O)$-), 1.90 (m, 2H, -$C\underline{H_2}CH_2CH(CH_2\text{-})NHC(=O)$-), 2.04 (s, 3H, -OC(=O)$C\underline{H_3}$), 2.14 (m, 2H, -NHC(=O)$C\underline{H_2}$-), 3.76 (m, 1H, -$CH_2C\underline{H}(CH_2\text{-})NHC(=O)$-), 4.87 (tt, J = 6.3, 5.7 Hz, 1H, -$CH_2C\underline{H}(OAc)CH_2$-), 5.43 (br s, 1H, NH). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 14.2 (-$CH_2\underline{C}H_3$), 21.3 (-OC(=O)$\underline{C}H_3$), 21.7 (-NHC(=O)$CH_2\underline{C}H_2$-), 22.7 (-$\underline{C}H_2$-), 24.9 (-$\underline{C}H_2CH_2CH(CH_2\text{-})NHC(=O)$-), 25.4 (-$\underline{C}H_2$- at cHx), 25.6, 29.3, 29.6, 31.9 (-$\underline{C}H_2$- × 4), 33.3 (-$\underline{C}H_2CH(CH_2\text{-})NHC(=O)$-), 33.5, 34.1 (-$\underline{C}H_2CH(OAc)\underline{C}H_2$-), 36.5 (-NHC(=O)$\underline{C}H_2$-), 48.2 (-$CH_2\underline{C}H(CH_2\text{-})NHC(=O)$-), 73.8 (-$CH_2\underline{C}H(OAc)CH_2$-), 171.2 (-O$\underline{C}$(=O)$CH_3$), 171.8 (-NH$\underline{C}$(=O)-). HRMS (FD) calcd. for $C_{21}H_{40}NO_3$ $(M+H)^+$, 354.3008; found $(M+H)^+$, 354.29927.

2.2.5 *N*-Benzyl-5-acetoxytridecanamide (*rac*-**1e**)

Yield: 3.47 g, 96% (from *rac*-**5**); colorless solid; mp = 40-41℃; $[\alpha]^{25}_D = -2.62$ [c = 0.5, MeOH, 47% e.e. for (*R*)-**1e**]. IR (KBr): cm^{-1} 3301 (N-H), 3030 (Ar, C-H), 2919 (-CH_3), 2852 (-CH_2-), 1723 (O$\underline{C}$=O), 1625 (NH$\underline{C}$=O), 1544, 1455 (Ar, C=C), 1242 (C-O), 746, 699 (Ar, C-H). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3H, -$CH_2C\underline{H_3}$), 1.25 (m, 12H, -$C\underline{H_2}$- × 6), 1.51 (m, 2H, -$C\underline{H_2}CH(OAc)CH_2$-), 1.57 (m, 2H, -$CH_2CH(OAc)C\underline{H_2}$-), 1.63 (m, 1H, -NHC(=O)$CH_2C\underline{H_2}$-), 1.71 (m, 1H, -NHC(=O)$CH_2C\underline{H_2}$-), 2.01 (s, 3H, -OC(=O)$C\underline{H_3}$), 2.21 (m, 2H, -NHC(=O)$C\underline{H_2}$-), 4.42 (d, J = 6.0 Hz, 2H, Ph$C\underline{H_2}$NHC(=O)-), 4.86 (tt, J = 6.9, 5.7 Hz, 1H, -$CH_2C\underline{H}(OAc)CH_2$-), 5.92 (br s, 1H, NH), 7.27 (m, 3H, Ph), 7.32 (m, 2H, Ph). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 14.0 (-$CH_2\underline{C}H_3$), 21.2 (-OC(=O)$\underline{C}H_3$), 21.4 (-NHC(=O)$CH_2\underline{C}H_2$-), 22.6, 25.3, 29.2, 29.4, 31.8 (-$\underline{C}H_2$- × 5), 33.5, 34.0 (-$\underline{C}H_2CH(OAc)\underline{C}H_2$-), 36.1 (-NHC(=O)$\underline{C}H_2$-), 43.5 (Ph$\underline{C}H_2$NHC(=O)-), 73.6 (-$CH_2\underline{C}H(OAc)CH_2$-), 127.4, 127.8, 128.6, 138.3 (Ph × 4), 171.0 (-O$\underline{C}$(=O)CH_3), 172.4 (-NH$\underline{C}$(=O)-). HRMS (FD) calcd. for $C_{22}H_{35}NO_3(M)^+$, 361.2617; found $(M)^+$, 361.25891.

2.2.6 *N*-Methyl-5-acetoxytetradecanamide (*rac*-**2a**)

Yield: 2.81 g, 94% (from *rac*-**6**); colorless solid; mp = 47-48℃; $[\alpha]^{25}_D = -0.18$ [c = 0.5, MeOH, 84% e.e. for (*R*)-**2a**]. IR (KBr): cm^{-1} 3271, 3091 (N-H), 2952 (-CH_3), 2925 (-CH_2-), 2872 (-CH_3), 2857 (-CH_2-), 1738 (O$\underline{C}$=O), 1652 (NH$\underline{C}$=O), 1242 (C-O). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88 (t, J = 7.2 Hz, 3H, -$CH_2C\underline{H_3}$), 1.22 (m, 14H, -$C\underline{H_2}$- × 7), 1.52 (m, 4H, -$C\underline{H_2}CH(OAc)C\underline{H_2}$-), 1.65 (m, 2H, -NHC(=O)$CH_2C\underline{H_2}$-), 2.04 (s, 3H, -OC(=O)$C\underline{H_3}$), 2.17 (m, 2H, -NHC(=O)$C\underline{H_2}$-), 2.80 (d, J = 4.8 Hz, 3H, $C\underline{H_3}$NHC(=O)-), 4.86 (m, 1H, -$CH_2C\underline{H}(OAc)CH_2$-), 5.54 (br s, 1H, NH). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 14.1 (-$CH_2\underline{C}H_3$), 21.2 (-OC(=O)$\underline{C}H_3$), 21.5 (-NHC(=O)$CH_2\underline{C}H_2$-), 22.6 (-$CH_2CH(OAc)CH_2\underline{C}H_2$-), 25.3, 26.2, 29.3, 29.4, 29.5, 29.6 (-$\underline{C}H_2$- × 6), 31.8 ($\underline{C}H_3$NHC(=O)-), 33.6, 34.0 (-$\underline{C}H_2CH(OAc)\underline{C}H_2$-), 36.1 (-NHC(=O)$\underline{C}H_2$-), 73.7 (-$CH_2\underline{C}H(OAc)CH_2$-), 171.0 (-O$\underline{C}$(=O)$CH_3$), 173.2 (-NH$\underline{C}$(=O)-). HRMS (FD) calcd. for $C_{17}H_{34}NO_3(M+H)^+$, 300.2539; found $(M+H)^+$, 300.25039.

2.2.7 *N*-*n*-Propyl-5-acetoxytetradecanamide (*rac*-**2b**)

Yield: 2.95 g, 90% (from *rac*-**6**); colorless solid; mp = 35-36℃; $[\alpha]^{25}_D = +0.24$ [c = 0.5, MeOH, 78% e.e. for (*R*)-**2b**]. IR (KBr): cm^{-1} 3304 (N-H), 2917 (-CH_3), 2850 (-CH_2-), 1730 (O$\underline{C}$=O), 1639 (NH$\underline{C}$=O), 1242 (C-O). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3H, -$CH_2C\underline{H_3}$), 0.92 (t, J = 7.5 Hz, 3H, $C\underline{H_3}CH_2CH_2NHC(=O)$-), 1.25 (m, 14H, -$C\underline{H_2}$- × 7), 1.55 (m, 7H, $CH_3C\underline{H_2}CH_2NHC(=O)$-, -$C\underline{H_2}C\underline{H_2}CH(OAc)C\underline{H_2}$-), 1.69 (m, 1H, -NHC(=O)$CH_2C\underline{H_2}$-), 2.04 (s, 3H, -OC(=O)$C\underline{H_3}$), 2.17 (m, 2H, -NHC(=O)$C\underline{H_2}$-), 3.20 (dt, J = 5.7, 5.7 Hz, 2H, $CH_3CH_2C\underline{H_2}NHC(=O)$-), 4.87 (tt, J = 5.7, 5.7 Hz, 1H, -$CH_2C\underline{H}(OAc)CH_2$-), 5.66 (br s, 1H, NH). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 11.4 ($C\underline{H_3}CH_2CH_2NHC(=O)$-), 14.2 (-$CH_2\underline{C}H_3$), 21.4 (-NHC(=O)$CH_2\underline{C}H_2$-), 21.6, (-$\underline{C}H_2$-), 22.7 ($CH_3\underline{C}H_2CH_2NHC(=O)$-), 23.0, 25.4, 29.4, 29.6, 29.6, 32.0 (-$\underline{C}H_2$- × 6), 33.6, 34.1 (-$\underline{C}H_2CH(OAc)\underline{C}H_2$-), 36.3 (-NHC(=O)$\underline{C}H_2$-), 41.2 ($CH_3\underline{C}H_2CH_2NHC(=O)$-), 73.8 (-$CH_2\underline{C}H(OAc)CH_2$-), 171.2 (-OC(=O)$CH_3$), 172.7 (-NH$\underline{C}$(=O)-). HRMS (FD) calcd. for $C_{19}H_{38}NO_3(M+H)^+$, 328.2852; found $(M+H)^+$, 328.28214.

2.2.8 *N*-*iso*-Propyl-5-acetoxytetradecanamide (*rac*-**2c**)

Yield: 2.88 g, 88% (from *rac*-**6**); colorless solid; mp = 38-39℃; $[\alpha]^{25}_D = +4.18$ [c = 0.5, MeOH, 50% e.e. for (*R*)-**2c**]. IR (KBr): cm^{-1} 3305 (N-H), 2918 (-CH_3), 2848 (-CH_2-), 1730 (O$\underline{C}$=O), 1639 (NH$\underline{C}$=O), 1242 (C-O). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3H, -$CH_2C\underline{H_3}$), 1.13 (d, J = 2.3 Hz, 3H, $(C\underline{H_3})_2CHNHC(=O)$-), 1.15 (d, J = 2.9 Hz, 3H, $(C\underline{H_3})_2CHNHC(=O)$-), 1.25 (m, 14H, -$C\underline{H_2}$- × 7), 1.55 (m, 4H, -$C\underline{H_2}CH(OAc)C\underline{H_2}$-), 1.60 (m, 1H, -NHC(=O)$CH_2C\underline{H_2}$-), 1.68 (m, 1H, -NHC(=O)$CH_2C\underline{H_2}$-), 2.04 (s, 3H, -OC(=O)$C\underline{H_3}$), 2.13 (m, 2H, -NHC(=O)$C\underline{H_2}$-), 4.07 (dq, J = 6.3, 6.9 Hz, 1H, $(CH_3)_2C\underline{H}NHC(=O)$-), 4.86 (tt, J = 5.7, 5.7 Hz, 1H, -$CH_2CH(OAc)CH_2$-), 5.37 (br s, 1H, NH). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 14.2 (-$CH_2\underline{C}H_3$), 21.4 (-NHC(=O)$CH_2\underline{C}H_2$-), 21.6 (-$\underline{C}H_2$-), 22.7, 22.8 ($(\underline{C}H_3)_2CHNHC(=O)$-), 22.9, 25.4, 29.4, 29.6, 29.6, 32.0 (-$\underline{C}H_2$- × 6), 33.6, 34.1 (-$\underline{C}H_2CH(OAc)\underline{C}H_2$-), 36.4 (-NHC(=O)$\underline{C}H_2$-), 41.3 ($(CH_3)_2\underline{C}HNHC(=O)$-), 73.8 (-$CH_2\underline{C}H(OAc)CH_2$-), 171.1 (-O$\underline{C}$(=O)$CH_3$), 171.8 (-NH$\underline{C}$(=O)-). HRMS (FD) calcd. for $C_{19}H_{38}NO_3(M+H)^+$, 328.2852; found $(M+H)^+$, 328.28933.

2.2.9 *N*-Cyclohexyl-5-acetoxytetradecanamide (*rac*-**2d**)

Yield: 3.38 g, 92% (from *rac*-**6**); colorless solid; mp = 40-41℃; $[\alpha]^{25}_D = +1.42$ [c = 0.5, MeOH, 74% e.e. for (*R*)-**2d**]. IR (KBr): cm^{-1} 3301 (N-H), 2920 (-CH_3), 2851 (-CH_2-), 1728 (O$\underline{C}$=O), 1637 (NH$\underline{C}$=O), 1245 (C-O). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3H, -$CH_2C\underline{H_3}$), 1.12 (m, 3H, -$C\underline{H_2}CH(C\underline{H_2}\text{-})NHC(=O)$-), 1.25 (m, 14H, -$C\underline{H_2}$- × 7), 1.36 (m, 2H, -$C\underline{H_2}$- at cHx), 1.56 (m, 6H, -$C\underline{H_2}CH(OAc)C\underline{H_2}$-, -$C\underline{H_2}C\underline{H_2}CH(CH_2\text{-})NHC(=O)$-), 1.70 (m, 3H, -NHC(=O)$CH_2C\underline{H_2}$-, -$C\underline{H_2}CH_2CH(CH_2\text{-})NHC(=O)$-), 1.90 (m, 2H, -$C\underline{H_2}CH_2CH(CH_2\text{-})NHC(=O)$-), 2.04 (s, 3H, -OC(=O)$C\underline{H_3}$), 2.13 (m, 2H, -NHC(=O)$C\underline{H_2}$-), 3.76 (m, 1H, -$CH_2C\underline{H}(CH_2\text{-})NHC(=O)$-), 4.87 (tt, J = 6.3, 5.7 Hz, 1H, -$CH_2C\underline{H}$

(OAc)CH_2-), 5.43 (br s, 1H, NH). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 14.2 (-$CH_2$$\underline{C}H_3$), 21.4 (-OC(=O)$\underline{C}H_3$), 21.6 (-NHC(=O)$CH_2$$\underline{C}H_2$-), 22.7 (-$\underline{C}H_2$-), 24.9 (-$\underline{C}H_2CH_2CH(CH_2$-)NHC(=O)-), 25.4 (-$\underline{C}H_2$- at cHx), 25.6, 29.4, 29.6, 29.6, 32.0 (-$\underline{C}H_2$-×5), 33.3 (-$\underline{C}H_2CH(CH_2$-)NHC(=O)-), 33.6, 34.1 (-$\underline{C}H_2CH$(OAc)$\underline{C}H_2$-), 36.5 (-NHC(=O)$\underline{C}H_2$-), 48.1 (-$CH_2\underline{C}H(CH_2$-)NHC(=O)-), 73.8 (-$CH_2\underline{C}H$(OAc)CH_2-), 171.1 (-O$\underline{C}$(=O)CH_3), 171.6 (-NH$\underline{C}$(=O)-). HRMS (FD) calcd. for $C_{22}H_{42}NO_3$ (M+H)$^+$, 368.3165; found (M+H)$^+$, 368.31073.

2.2.10 *N*-Benzyl-5-acetoxytetradecanamide (*rac*-**2e**)

Yield: 3.57 g, 95% (from *rac*-**6**); colorless solid; mp = 32-33℃; $[\alpha]^{25}_D$ = +1.78 [*c* = 0.5, MeOH, 70% e.e. for (*R*)-**2e**]. IR (KBr): cm^{-1} 3303 (N-H), 3031 (Ar, C-H), 2917 (-CH_3), 2853 (-CH_2-), 1720 (O$\underline{C}$=O), 1626 (NH$\underline{C}$=O), 1543, 1455 (Ar, C=C), 1242 (C-O), 747, 697 (Ar, C-H). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H, -$CH_2C\underline{H}_3$), 1.25 (m, 14H, -$C\underline{H}_2$-×7), 1.53 (m, 4H, -$C\underline{H}_2CH$(OAc)$C\underline{H}_2$-), 1.62, 1.70 (m, 2H, -NHC(=O)$CH_2C\underline{H}_2$-), 2.00 (s, 3H, -OC(=O)$C\underline{H}_3$), 2.20 (m, 2H, -NHC(=O)$C\underline{H}_2$-), 4.40 (d, *J* = 5.7 Hz, 2H, PhC$\underline{H}_2$NHC(=O)-), 4.85 (quin, *J* = 6.9, 5.7 Hz, 1H, -$CH_2C\underline{H}$(OAc)CH_2-), 6.12 (br s, 1H, NH), 7.26 (m, 3H, Ph), 7.31 (m, 2H, Ph). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 14.0 (-$CH_2$$\underline{C}H_3$), 21.1 (-OC(=O)$\underline{C}H_3$), 21.4 (-NHC(=O)$CH_2$$\underline{C}H_2$-), 22.6, 25.2, 29.2, 29.4, 29.5, 31.8 (-CH_2-×6), 33.4, 34.0 (-$\underline{C}H_2CH$(OAc)$\underline{C}H_2$-), 36.0 (-NHC(=O)$\underline{C}H_2$-), 43.4 (Ph$\underline{C}H_2$NHC(=O)-), 73.6 (-$CH_2\underline{C}H$(OAc)CH_2-), 127.3, 127.7, 128.5, 138.3 (Ph×4), 170.9 (-OC(=O)CH_3), 172.4 (-NH$\underline{C}$(=O)-). HRMS (FD) calcd. for $C_{23}H_{37}NO_3$ (M)$^+$, 375.2773; found (M)$^+$, 375.27488.

2.3 General procedure for Novozym 435-catalyzed methanolysis

In a typical experiment (**Table 1**, Entry 3), racemic *N*-methy-5-acetoxytridecanamide (*rac*-**1a**) (1.0 mmol, 0.29 g), methanol (3.0 mmol, 0.10 g), and Novozym 435 (0.4 g) in cyclohexane (20 mL) was stirred at 80℃ for 96 h, then filtered to remove Novozym 435, and concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane/EtOAc, 1:1, v/v) gave (*R*)-*N*-methyl-5-acetoxytridcanamide [(*R*)-**1a**] (0.13 g, 46%), (*S*)-*N*-methyl-5-hydroxytridecanamide [(*S*)-**3a**] (0.05 g, 21%), and (*S*)-δ-tridecalactone [(*S*)-**5**] (0.06 g, 27%). The lactonization of (*R*)-**1a** and (*S*)-**3a** is described in reference 41[41]. (*R*)-**1a** and (*S*)-**3a** were hydrolyzed 10% NaOH in methanol (20 mL) at 90℃ for 3 h, and then cooled. A 10% H_2SO_4 methanol solution was added dropwise to the mixture at 0℃ to pH 3. After evaporation, water (50 mL) and EtOAc (20 mL) were added, and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layer was washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane/EtOAc, 4/1, v/v) gave (*R*)-**5** (0.07 g, 78%) and (*S*)-**5** (0.04 g, 75%), respectively. Enantiomeric excesses of (*R*)-**1a** and (*S*)-**3a** were determined by GC from the corresponding **5**. Absolute configuration of all compounds was determined from the corresponding **5** compared with the literature data.

2.3.1 (*S*)-*N*-Methyl-5-hydroxytridecanamide [(*S*)-**3a**]

Colorless solid; mp = 74-75℃; $[\alpha]^{25}_D$ = −2.62 [*c* = 0.5, MeOH, 74% e.e. for (*S*)-**3a**]. IR (KBr): cm^{-1} 3289 (O-H, N-H), 3099 (N-H), 2955 (-CH_3), 2923 (-CH_2-), 2873 (-CH_3), 2848 (-CH_2-), 1639 (NH$\underline{C}$=O). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88 (t, *J* = 7.5 Hz, 3H, -$CH_2C\underline{H}_3$), 1.23 (m, 12H, -$C\underline{H}_2$-×6), 1.47 (m, 4H, -$C\underline{H}_2CH$(OH)$C\underline{H}_2$-), 1.75 (m, 2H, -NHC(=O)$CH_2C\underline{H}_2$-), 1.86 (br s, 1H, OH), 2.23 (m, 2H, -NHC(=O)$C\underline{H}_2$-), 2.81 (d, *J* = 5.0 Hz, 3H, $C\underline{H}_3$NHC(=O)-), 3.58 (m, 1H, -$CH_2C\underline{H}$(OH)CH_2-), 5.55 (br s, 1H, NH). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 14.1 (-$CH_2$$\underline{C}H_3$), 21.6 (-NHC(=O)$CH_2$$\underline{C}H_2$-), 22.7 (-$\underline{C}H_2$-), 25.7 (-$CH_2CH(OH)CH_2$$\underline{C}H_2$-), 26.3 ($\underline{C}H_3$NHC(=O)-), 29.3, 29.6, 29.7, 31.9 (-$\underline{C}H_2$-×4), 36.2 (-NHC(=O)$\underline{C}H_2$-), 36.7, 37.6 (-$\underline{C}H_2CH$(OH)$\underline{C}H_2$-), 71.4 (-$CH_2\underline{C}H$(OH)CH_2-), 173.7 (-NH$\underline{C}$(=O)-). HRMS (FD) calcd. for $C_{14}H_{30}NO_2$ (M+H)$^+$, 244.2277; found (M+H)$^+$, 244.22375.

2.3.2 (*S*)-*N*-*n*-Propyl-5-hydroxytridecanamide [(*S*)-**3b**]

Colorless solid; mp = 76-77℃; $[\alpha]^{25}_D$ = −2.20 [*c* = 0.5, MeOH, 85% e.e. for (S)-3b]. IR (KBr): cm^{-1} 3286 (O-H, N-H), 2919 (-CH_3), 2848 (-CH_2-), 1635 (NH$\underline{C}$=O). ^{1}H NMR

Table 1 Effect of amount of Novozym 435 using *rac*-**1a**[a].

Entry	Novozym 435 [g]	Yield [%] / Enantiomeric excess [% e.e.][b]		
		(*R*)-**1a**	(*S*)-**3a**	(*S*)-**5**
1	0.2	81 / 29	10 / 86	9 / 87
2	0.3	50 / 66	19 / 82	19 / 84
3	0.4	46 / 77	21 / 74	27 / 79
4	0.5	46 / 70	22 / 76	23 / 80
5	0.6	35 / 89	23 / 62	34 / 67

a) *rac*-**1a**: 1.0 mmol, MeOH: 3.0 mmol, Cy-hexane: 20 mL, 80℃, 96 h
b) Determined by GC using InertCap CHIRAMIX column.

(400 MHz, TMS/$CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3H, -CH_2CH_3), 0.92 (t, J = 7.4 Hz, 3H, -CH_2CH_3), 1.27 (m, 12H, -CH_2-×6), 1.43 (m, 4H, -CH_2-×2), 1.51 (sext, J = 7.4 Hz, 3H, $CH_3CH_2CH_2$-), 1.75 (m, 2H, -NHC(=O)CH_2CH_2-), 2.22 (t, J = 7.4 Hz, 2H, -NHC(=O)CH_2-), 2.53 (br s, 1H, OH), 3.20 (q, J = 7.4, 5.7 Hz, 2H, -CH_2CH_2NHC(=O)-), 3.58 (m, 1H, -CH_2CH(OH)CH_2-), 5.93 (br s, 1H, NH). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 11.3 ($CH_3CH_2CH_2$-), 14.0 (-CH_2CH_3), 21.6 (-NHC(=O)CH_2CH_2-), 22.6 (-CH_2-), 22.8 ($CH_3CH_2CH_2$-), 25.7, 29.2, 29.5, 29.7, 31.8 (-CH_2-×5), 36.3 (-NHC(=O)CH_2-), 36.6 (-CH_2CH(OH)CH_2-), 37.5 (-CH_2CH(OH)CH_2-), 41.2 ($CH_3CH_2CH_2$NHC(=O)-), 71.1 (-CH_2CH(OH)CH_2-), 173.2 (-NHC(=O)-). HRMS (FD) calcd. for $C_{16}H_{34}NO_2$ $(M+H)^+$, 272.2590; found $(M+H)^+$, 272.26113.

2.3.3 (*S*)-*N*-*iso*-Propyl-5-hydroxytridecanamide [(*S*)-**3c**]

Colorless solid; mp = 58-59℃; $[\alpha]^{25}_D$ = +0.08 [c = 0.5, MeOH, 49% e.e. for (*S*)-**3c**]. IR (KBr): cm^{-1} 3285 (O-H, N-H), 2918 (-CH_3), 2850 (-CH_2-), 1635 (NHC=O). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3H, -CH_2CH_3), 1.14 (d, J = 6.3 Hz, 6H, (CH_3)$_2$CH-), 1.27 (m, 11H, -CH_2-×6), 1.43 (m, 4H, -CH_2CH(OH)CH_2-), 1.48 (m, 1H, -CH_2CH(OH)CH_2CH_2-), 1.74 (quin, J = 7.5 Hz, 2H, -NHC(=O)CH_2CH_2-), 2.18 (t, J = 7.4 Hz, 2H, -NHC(=O)CH_2-), 2.59 (br s, 1H, OH), 3.75 (m, 1H, -CH_2CH(OH)CH_2-), 4.07 (quin, J = 6.3, 6.3, 6.9 Hz, 1H, (CH_3)$_2$CH-), 5.73 (br s, 1H, NH). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 14.0 (-CH_2CH_3), 21.6 (-NHC(=O)CH_2CH_2-), 22.6 (-CH_2-), 22.7 ((CH_3)$_2$CH-), 25.7 (-CH_2CH(OH)CH_2CH_2-), 29.2, 29.5, 29.6, 31.8 (-CH_2-×4), 36.4 (-NHC(=O)CH_2-), 36.6 (-CH_2CH(OH)CH_2-), 37.5 (-CH_2CH(OH)CH_2-), 41.2 ((CH_3)$_2$CH-), 71.2 (-CH_2CH(OH)CH_2-), 172.3 (-NHC(=O)-). HRMS (FD) calcd. for $C_{16}H_{34}NO_2$ $(M+H)^+$, 272.2590; found $(M+H)^+$, 272.25768.

2.3.4 (*S*)-*N*-Cyclohexyl-5-hydroxytridecanamide [(*S*)-**3d**]

Colorless solid; mp = 86-87℃; $[\alpha]^{25}_D$ = +3.00 [c = 0.5, MeOH, 91% e.e. for (*S*)-**3d**]. IR (KBr): cm^{-1} 3300 (O-H, N-H), 2919 (-CH_3), 2850 (-CH_2-), 1637 (NHC=O). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3H, -CH_2CH_3), 1.14 (m, 3H, -CH_2CH(CH_2-)NHC(=O)-), 1.27 (m, 11H, -CH_2-×6), 1.34, 1.37 (m, 1H, -CH_2- at cHx), 1.43 (m, 4H, -CH_2CH(OH)CH_2-), 1.50 (m, 1H, -CH_2CH(OH)CH_2CH_2-), 1.62 (m, 1H, -CH_2CH(CH_2-)NHC(=O)-), 1.70 (m, 2H, -CH_2CH_2CH(CH_2-)NHC(=O)-), 1.75 (m, 2H, -NHC(=O)CH_2CH_2-), 1.90 (d, J = 12.0 Hz, 2H, -CH_2CH_2CH(CH_2-)NHC(=O)-), 2.19 (m, 2H, -NHC(=O)CH_2-), 2.34 (br s, 1H, OH), 3.58 (m, 1H, -CH_2CH(OH)CH_2-), 3.76 (m, 1H, -CH_2CH(CH_2-)NHC(=O)-), 5.61 (br s, 1H, NH). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 14.0 (-CH_2CH_3), 21.6 (-NHC(=O)CH_2CH_2-), 22.6 (-CH_2-), 24.8 (-CH_2CH_2CH(CH_2-)NHC(=O)-), 25.5 (-CH_2- at cHx), 25.7, 29.2, 29.5, 29.7, 31.8 (-CH_2-×5), 33.1 (-CH_2CH(CH_2-)NHC(=O)-), 36.5 (-NHC(=O)CH_2-), 36.6, 37.5 (-CH_2CH(OH)CH_2-), 48.1 (-CH_2CH(CH_2-)NHC(=O)-), 71.1 (-CH_2CH(OH)CH_2-), 172.2 (-NHC(=O)-). HRMS (FD) calcd. for $C_{19}H_{38}NO_2$ $(M+H)^+$, 312.2903; found $(M+H)^+$, 312.29382.

2.3.5 (*S*)-*N*-Benzyl-5-hydroxytridecanamide [(*S*)-**3e**]

Colorless solid; mp = 71-72℃; $[\alpha]^{25}_D$ = +0.53 [c = 0.5, MeOH, 89% e.e. for (*S*)-**3e**]. IR (KBr): cm^{-1} 3297 (O-H, N-H), 3031 (Ar, C-H), 2919 (-CH_3), 2848 (-CH_2-), 1639 (NHC=O), 1556, 1456 (Ar, C=C), 730, 696 (Ar, C-H). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3H, -CH_2CH_3), 1.26 (m, 11H, -CH_2-×6), 1.40 (m, 4H, -CH_2CH(OH)CH_2-), 1.47 (m, 1H, -CH_2CH(OH)CH_2CH_2-), 1.75 (m, 2H, -NHC(=O)CH_2CH_2-), 2.24 (t, J = 7.4 Hz, 2H, -NHC(=O)CH_2-), 2.30 (br s, 1H, OH), 3.55 (m, 1H, -CH_2CH(OH)CH_2-), 4.40 (d, J = 5.7 Hz, 2H, PhCH_2NHC(=O)-), 6.17 (br s, 1H, NH), 7.26 (m, 3H, Ph), 7.31 (m, 2H, Ph). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 14.1 (-CH_2CH_3), 21.6 (-NHC(=O)CH_2CH_2-), 22.6 (-CH_2-), 25.7 (-CH_2CH(OH)CH_2CH_2-), 29.2, 29.6, 29.7, 31.8 (-CH_2-×4), 36.2 (-NHC(=O)CH_2-), 36.6 (-CH_2CH(OH)CH_2-), 37.5 (-CH_2CH(OH)CH_2-), 43.5 (PhCH_2NHC(=O)-), 71.2 (-CH_2CH(OH)CH_2-), 127.4, 127.7, 128.6, 138.3 (Ph×4), 173.1 (-NHC(=O)-). HRMS (FD) calcd. for $C_{20}H_{33}NO_2$ $(M)^+$, 319.2511; found $(M)^+$, 319.24899.

2.3.6 (*S*)-*N*-Methyl-5-hydroxytetradecanamide [(*S*)-**4a**]

Colorless solid; mp = 79-80℃; $[\alpha]^{25}_D$ = +2.62 [c = 0.5, MeOH, 71% e.e. for (*S*)-**4a**]. IR (KBr): cm^{-1} 3294 (O-H, N-H), 3101 (N-H), 2954 (-CH_3), 2922 (-CH_2-), 2872 (-CH_3), 2848 (-CH_2-), 1639 (NHC=O). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88 (t, J = 7.0 Hz, 3H, -CH_2CH_3), 1.22 (m, 14H, -CH_2-×7), 1.47 (m, 4H, -CH_2CH(OH)CH_2-), 1.76 (m, 2H, -NHC(=O)CH_2CH_2-), 1.86 (br s, 1H, OH), 2.23 (m, 2H, -NHC(=O)CH_2-), 2.81 (d, J = 4.5 Hz, 3H, CH_3NHC(=O)-), 3.59 (m, 1H, -CH_2CH(OH)CH_2-), 5.54 (br s, 1H, NH). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 14.1 (-CH_2CH_3), 21.6 (-NHC(=O)CH_2CH_2-), 22.7 (-CH_2-), 25.7 (-CH_2CH(OH)CH_2CH_2-), 26.3 (CH_3NHC(=O)-), 29.3, 29.5, 29.6, 29.7, 31.9 (-CH_2-×5), 36.2 (-NHC(=O)CH_2-), 36.7, 37.6 (-CH_2CH(OH)CH_2-), 71.4 (-CH_2CH(OH)CH_2-), 173.7 (-NHC(=O)-). HRMS (FD) calcd. for $C_{15}H_{32}NO_2$ $(M+H)^+$, 258.2433; found $(M+H)^+$, 258.24683.

2.3.7 (*S*)-*N*-*n*-Propyl-5-hydroxytetradecanamide [(*S*)-**4b**]

Colorless solid; mp = 80-81℃; $[\alpha]^{25}_D$ = +1.12 [c = 0.5, MeOH, 72% e.e. for (*S*)-**4b**]. IR (KBr): cm^{-1} 3284 (O-H, N-H), 2920 (-CH_3), 2848 (-CH_2-), 1636 (NHC=O). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3H, -CH_2CH_3), 0.92 (t, J = 7.5 Hz, 3H, CH_3CH_2-), 1.26 (m, 14H, -CH_2-×7), 1.43 (m, 4H, -CH_2CH(OH)CH_2-), 1.51 (m, 2H, $CH_3CH_2CH_2$-), 1.75 (m, 2H, -NHC(=O)CH_2CH_2-), 2.22 (t, J = 7.5 Hz, 2H, -NH(C=O)CH_2-), 2.42 (br s, 1H, OH), 3.20 (q, J = 6.9 Hz, 1H, $CH_3CH_2CH_2$NHC(=O)-), 3.58 (m, 1H, -CH_2CH(OH)CH_2-), 5.86 (br s, 1H, NH). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 11.5 ($CH_3CH_2CH_2$-), 14.2 (-CH_2CH_3), 21.7 (-NHC(=O)CH_2CH_2-), 22.7 (-CH_2-), 22.9 ($CH_3CH_2CH_2$-), 25.8, 29.4, 29.6, 29.7, 29.8, 32.0 (-CH_2-×6), 36.4 (-NHC(=O)CH_2-), 36.8, 37.7 (-CH_2CH(OH)CH_2-), 41.3 ($CH_3CH_2CH_2$-), 71.3 (-CH_2CH(OH)CH_2-), 173.3 (-NHC(=O)-). HRMS (FD) calcd. for $C_{17}H_{36}NO_2$ $(M+H)^+$, 286.2746; found $(M+H)^+$,

258.27735.

2.3.8 (*S*)-*N*-iso-Propyl-5-hydroxytetradecanamide[(*S*)-**4c**]

Colorless solid; mp = 65-66℃; $[\alpha]^{25}_{D}$ = +0.95[*c* = 0.5, MeOH, 70% e.e. for(S)-**4c**]. IR(KBr): cm^{-1} 3284(O-H, N-H), 2919(-CH_3), 2850(-CH_2-), 1634(NHC=O). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88(t, *J* = 6.9 Hz, 3H, -CH_2CH_3), 1.14(d, *J* = 6.3 Hz, 6H, $(CH_3)_2$CHNHC(=O)-), 1.26(m, 13H, -CH_2-×7), 1.43(m, 4H, -$CH_2CH(OH)CH_2$-), 1.49(m, 1H, -$CH_2CH(OH)CH_2CH_2$-), 1.74(quin, *J* = 7.5 Hz, 2H, -NHC(=O)CH_2CH_2-), 2.18(m, 2H, -NHC(=O)CH_2-), 3.58 (m, 1H, -$CH_2CH(OH)CH_2$-), 4.08(m, 1H, $(CH_3)_2CH$NHC (=O)-), 5.47(br s, 1H, NH). ^{13}C NMR(100 MHz, TMS/ $CDCl_3$): δ 14.2(-CH_2CH_3), 21.6(-NHC(=O)CH_2CH_2-), 22.7 (-CH_2-), 22.9($(CH_3)_2$CHNHC(=O)-), 25.8(-$CH_2CH(OH)$ CH_2CH_2-), 29.4, 29.7, 29.8, 32.0(-CH_2-×4), 36.6(-NHC(= O)CH_2-), 36.8, 37.6(-$CH_2CH(OH)CH_2$-), 41.3($(CH_3)_2$ CHNHC(=O)-), 71.3(-$CH_2CH(OH)CH_2$-), 172.3(-NHC(= O)-). HRMS(FD) calcd. for $C_{17}H_{36}NO_2(M+H)^+$, 286.2746; found$(M+H)^+$, 286.27138.

2.3.9 (*S*)-*N*-Cyclohexyl-5-hydroxytetradecanamide[(*S*)-**4d**]

Colorless solid; mp = 78-79℃; $[\alpha]^{25}_{D}$ = +2.44[*c* = 0.5, MeOH, 71% e.e. for(*S*)-**4d**]. IR(KBr): cm^{-1} 3301(O-H, N-H), 2918(-CH_3), 2849(-CH_2-), 1636(NHC=O). ^{1}H NMR (400 MHz, TMS/$CDCl_3$): δ 0.88(t, *J* = 6.9 Hz, 3H, -CH_2CH_3), 1.13(m, 3H, -$CH_2CH(CH_2$-)NHC(=O)-), 1.26(m, 13H, -CH_2-×7), 1.35, 1.37(m, 1H, -CH_2- at cHx), 1.43(m, 4H, -$CH_2CH(OH)CH_2$-), 1.49(m, 1H, -$CH_2CH(OH)CH_2CH_2$-), 1.62(m, 1H, -$CH_2CH(CH_2$-)NHC(=O)-), 1.69(m, 1H, -$CH_2CH_2CH(CH_2$-)NHC(=O)-), 1.72(m, 1H, -CH_2CH_2CH $(CH_2$-)NHC(=O)-), 1.75(quin, *J* = 8.0, 7.5 Hz, 2H, -NHC (=O)CH_2CH_2-), 1.91(d, *J* = 12.0 Hz, 2H, -CH_2CH_2CH $(CH_2$-)NHC(=O)-), 2.19(m, 2H, -NHC(=O)CH_2-), 3.58 (m, 1H, -$CH_2CH(OH)CH_2$-), 3.76(m, 1H, -$CH_2CH(CH_2$-) NHC(=O)-), 5.52(br s, 1H, NH). ^{13}C NMR(100 MHz, TMS/ $CDCl_3$): δ 14.1(-CH_2CH_3), 21.6(-NHC(=O)CH_2CH_2-), 22.6 (-CH_2-), 24.8(-$CH_2CH_2CH(CH_2$-)NHC(=O)-), 25.5 (-$CH_2CH_2CH_2CH(CH_2$-)NHC(=O)-), 25.7(-CH_2- at cHx), 29.3, 29.5, 29.6, 29.7, 31.9(-CH_2-×5), 33.2(-$CH_2CH(CH_2$-) NHC(=O)-), 36.5(-NHC(=O)CH_2-), 36.6, 37.5(-CH_2CH $(OH)CH_2$-), 48.1(-$CH_2CH(CH_2$-)NHC(=O)-), 71.2 (-$CH_2CH(OH)CH_2$-), 172.1(-NHC(=O)-). HRMS(FD) calcd. for $C_{20}H_{40}NO_2(M+H)^+$, 326.3059; found$(M+H)^+$, 326.30233.

2.3.10 (*S*)-*N*-Benzyl-5-hydroxytetradecanamide[(*S*)-**4e**]

Colorless solid; mp = 74-75℃; $[\alpha]^{25}_{D}$ = +1.64[*c* = 0.5, MeOH, 79% e.e. for(*S*)-**4e**]. IR(KBr): cm^{-1} 3296(O-H, N-H), 3030(Ar, C-H), 2919(-CH_3), 2848(-CH_2-), 1639 (NHC=O), 1555, 1457(Ar, C=C), 729, 695(Ar, C-H). ^{1}H NMR(400 MHz, TMS/$CDCl_3$): δ 0.88(t, *J* = 6.9 Hz, 3H, -CH_2CH_3), 1.26(m, 13H, -CH_2-×7), 1.41(m, 4H, -CH_2CH $(OH)CH_2$-), 1.49(m, 1H, -$CH_2CH(OH)CH_2CH_2$-), 1.77(m, 2H, -NHC(=O)CH_2CH_2-), 2.09(br s, 1H, OH), 2.25(t, *J* = 7.4 Hz, 2H, -NHC(=O)CH_2-), 3.57(m, 1H, -$CH_2CH(OH)$ CH_2-), 4.42(d, *J* = 5.7 Hz, 2H, PhCH_2NHC(=O)-), 6.02(br s, 1H, NH), 7.27(m, 3H, Ph), 7.32(m, 2H, Ph). ^{13}C NMR (100 MHz, TMS/$CDCl_3$): δ 14.1(-CH_2CH_3), 21.6(-NHC(= O)CH_2CH_2-), 22.7, 25.7, 29.3, 29.5, 29.6, 29.7, 31.9(-CH_2-× 7), 36.3(-NHC(=O)CH_2-), 36.6, 37.5(-$CH_2CH(OH)CH_2$-), 43.5(PhCH_2NHC(=O)-), 71.2(-$CH_2CH(OH)CH_2$-), 127.5, 127.8, 128.7, 138.3(Ph×4), 173.0(-NHC(=O)-). HRMS (FD) calcd. for $C_{21}H_{35}NO_2(M)^+$, 333.2668; found$(M)^+$, 333.26295.

2.3.11 δ-Tridecalactone(**5**)

Yield: 0.08 g, 79%[(*S*)-**5**], 0.04 g, 76%[(*R*)-**5**]; colorless oil. Enantiomeric excess determined by GC on an InertCap CHIRAMIX(30 m×0.25 mm i.d. 0.25 μm film thickness)column, temperature: 150℃(isothermal), flow rate: 2.0 mL/min, t_S = 128.518 min, t_R = 132.940 min; $[\alpha]^{20}_{D}$ = −35.4[*c* = 0.2, MeOH, (*S*)-**5** with 99% e.e., lit$[\alpha]^{20}_{D}$ = −35.0 (*c* = 1.38, $CHCl_3$, >98% e.e.)][42], $[\alpha]^{20}_{D}$ = +38.0[*c* = 0.2, MeOH, (*R*)-**5** with 99% e.e., lit$[\alpha]_D$ = +45.2(*c* = 1.58, THF, >98% e.e.)][43]. IR(NaCl): cm^{-1} 2953(-CH_3), 2926(-CH_2-), 2872(-CH_3), 2855(-CH_2-), 1734(OC(=O)), 1241(C-O). ^{1}H NMR(400 MHz, TMS/$CDCl_3$): δ 0.88(t, *J* = 7.0 Hz, 3H, -CH_2CH_3), 1.28(m, 10H, -CH_2-×5), 1.52(m, 4H, -CH_2-×2), 1.68(m, 1H, -$CH_2CH(CH_2$-)OC(=O)-), 1.87(m, 3H, -$CH_2CH_2CH(CH_2$-)OC(=O)-), 2.51(m, 2H, -$CH_2C(=O)$ O-), 4.28(m, 1H, -$CH_2CH(CH_2$-)OC(=O)-). ^{13}C NMR(100 MHz, TMS/$CDCl_3$): δ 14.1(-CH_2CH_3), 18.5(-CH_2CH_2CH $(CH_2$-)OC(=O)-), 22.6, 24.9, 27.8(-CH_2-×3), 29.2 (-$CH_2CH_2CH_3$), 29.3(-CH_2CH_3), 29.4(-CH_2-), 29.5(-CH_2CH $(CH_2$-)OC(=O)-), 31.8(-$CH_2CH(CH_2$-)OC(=O)-), 35.8 (-$CH_2C(=O)$O-), 80.6(-$CH_2CH(CH_2$-)OC(=O)-), 172.0 (-C(=O)O-). HRMS(FI) calcd. for $C_{13}H_{24}O_2(M)^+$, 212.1776; found$(M)^+$, 212.17757.

2.3.12 δ-Tetradecalactone(**6**)

Yield: 0.06 g, 81%[(*S*)-**6**], 0.03 g, 78%[(*R*)-**6**]; colorless oil. Enantiomeric excess determined by GC on an InertCap CHIRAMIX(30 m×0.25 mm i.d. 0.25 μm film thickness)column, temperature: 160℃(isothermal), flow rate: 2.0 mL/min, t_S = 117.444 min, t_R = 122.523 min; $[\alpha]^{20}_{D}$ = −40.8[*c* = 1.0, MeOH, (*S*)-**6** with 99% e.e.], $[\alpha]^{20}_{D}$ = +40.2[*c* = 1.0, MeOH, (*R*)-**6** with 99% e.e.]. IR(NaCl): cm^{-1} 2954(-CH_3), 2925(-CH_2-), 2870(-CH_3), 2855(-CH_2-), 1734 (OC(=O)), 1248(C-O). ^{1}H NMR(400 MHz, TMS/$CDCl_3$): δ 0.88(t, *J* = 6.8 Hz, 3H, -CH_2CH_3), 1.28(m, 12H, -CH_2-×6), 1.54(m, 4H, -CH_2-×2), 1.70(m, 1H, -$CH_2CH(CH_2$-)OC(= O)-), 1.87(m, 3H, -$CH_2CH_2CH(CH_2$-)OC(=O)-), 2.50(m, 2H, -$CH_2C(=O)$O-), 4.28(1H, m, -$CH_2CH(CH_2$-)OC(=O)-). ^{13}C NMR(100 MHz, TMS/$CDCl_3$): δ 14.1(-CH_2CH_3), 18.5 (-$CH_2CH_2CH(CH_2$-)OC(=O)-), 22.7, 24.9, 27.8, 29.3(-CH_2-×4), 29.4(-$CH_2CH_2CH_3$), 29.5(-CH_2CH_3), 29.5(-CH_2-), 31.9(-$CH_2CH(CH_2$-)OC(=O)-), 35.9(-$CH_2CH(CH_2$-)OC (=O)-), 80.6(-$CH_2CH(CH_2$-)OC(=O)-), 172.0(-C(=O) OCH_3). HRMS(FI) calcd. for $C_{14}H_{26}O_2(M)^+$, 226.1933; found $(M)^+$, 226.19376.

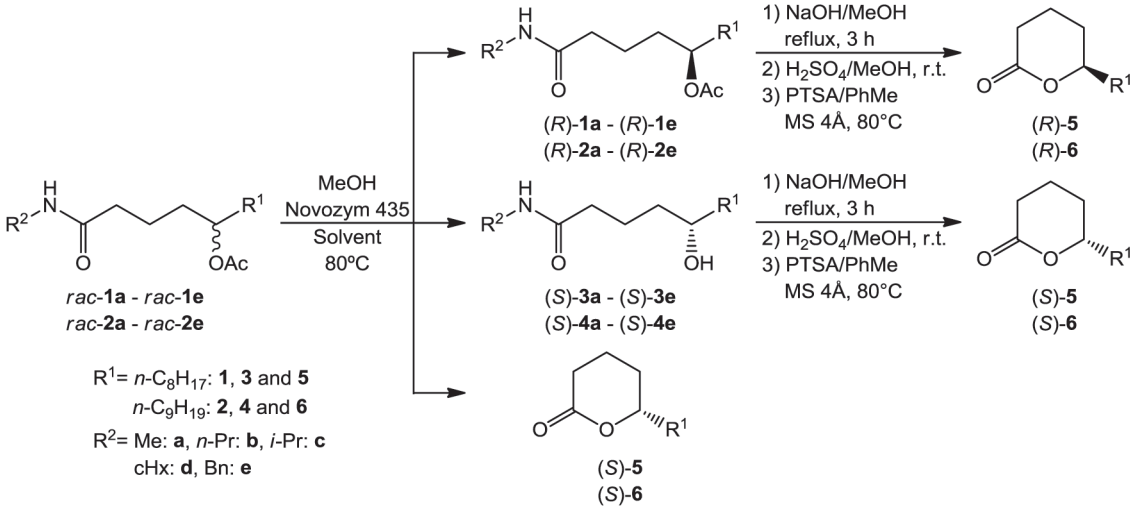
2.4 Cyclohexylamine additive Novozym 435-catalyzed methanolysis of *rac*-1a and *rac*-2a[40]

In a typical experiment (Table 5, Entry 9), a mixture of racemic *N*-methyl-5-acetoxytridecanamide (1.0 mmol, 0.29 g), methanol (3.0 mmol, 0.10 g), cyclohexylamine (2.0 mmol, 0.20 g), Novozym 435 (0.4 g) in the mixed solvent (20 mL, cyclohexane/CPME, 4/1, v/v) were stirred at 80℃ for 96 h. Novozym 435 was removed by filtration, and the remaining solution was concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane/EtOAc, 1/1, v/v) gave the mixture of (*R*)-1a, (*S*)-3d, and (*S*)-3a (0.06 g, 23%). The crude mixture of (*R*)-1a and (*S*)-3d was hydrolyzed with Na_2CO_3 (2.0 g) in methanol (20 mL) at 80℃ for 5 h, cooled, and then concentrated. Water (50 mL) and $CHCl_3$ (20 mL) were added, and the organic layer was separated. The aqueous phase was extracted with $CHCl_3$, and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane/EtOAc, 1/1, v/v) gave (*R*)-3a (0.11 g, 47%) and (*S*)-3d (0.07 g, 22%). The lactonization method and determination of enantiomeric excess and absolute configuration were described above.

3 Results and discussion

3.1 Effect of amount of Novozym 435 on reactivity and enantioselectivity

We previously reported synthesis of optical activity δ-hexadecalactone by lipase-catalyzed resolution[40]. Rodrigues *et al*. reported that Novozym 435 showed high enzyme activity for methanolysis, and we used methanol as proton donor[44]. Methanolysis was performed using 0.4 g Novozym 435 to 1.0 mmol substrate. Although about 80% enantioselectivity was shown, seven days were required to reach about 50% conversion. In this paper, we aimed at synthesis of optical activity δ-tri- and δ-tetradecalactones. The amount of Novozym 435 added was investigated for the purpose of shortening the reaction time and the effect on enantioselectivity (Scheme 1, Table 1). Racemic *N*-methyl-5-acetoxytridecanamide (*rac*-1a) was used as a substrate, and methanolysis was performed in cyclohexane adding 0.2-0.6 g of Novozym 435 for four days. When 0.3, 0.4, or 0.5 g was added, a great difference in the conversion rate was not observed (Table 1, Entries 2, 3, and 4). On the other hand, in the case of 0.2 g, the conversion was low, and it was high with 0.6 g (Table 1, Entries 1 and 5). With 0.2 g of Novozym 435, although there were only small amounts of (*S*)-3a and (*S*)-5, the reaction progressed with about 90% enantioselectivity (Table 1, Entry 1). (*R*)-1a showed 89% enantiomeric excess using 0.6 g Novozym 435 (Table 1, Entry 5). When 0.3-0.5 g of Novozym 435 was used, methanolysis progressed with about 80% enantioselectivity. It was seemed that (*S*)-3a and (*S*)-5 shows about 80% enantiomeric excess, respectively, in 50% conversion with addition of 0.2 g and 0.6 g. Based on these results, although the amount of Novozym 435 added affects the conversion rate, it does not affect enantioselectivity greatly. The yields of (*S*)-3a and (*S*)-5 increased with the amount of Novozym 435, and the comparably long reaction time was required. It was seemed that substrate affinity of Novozym 435 to *rac*-1a was low. As the amount of Novozym 435 was increased, the amount of substrate incorporated into the active site in the enzyme increased, and the yields of (*S*)-3a and (*S*)-5 were increased. However, in (*R*)-1a, (*S*)-3a, and (*S*)-5, an average high enantiomeric excess was shown in the case of 0.4 g. Therefore, it was determined that the addition of 0.4 g Novozym 435 to 1.0 mmol substrate was optimal.



Scheme 1 Novozym 435-catalyzed kinetic resolution of *rac*-**1** and *rac*-**2**.

3.2 Effect of solvent and structure on enantioselectivity

The effect of a solvent on enantioselectivity and conversion was observed using *rac*-**1a** as a substrate (Table 2). Methanolysis was performed for four days using various solvents. Methanolysis progressed in almost all solvents except THF, acetone, and phosphate buffer (Table 2, Entries 6-8). Permittivity is high for these three solvents compared with the solvent in which a reaction progressed. Enzyme is required free water to exhibit activity[45]. The relationship between water activity and enzyme activity was reported by Degn *et al.*[46] It was assumed that because these three solvent with high permittivity took free water from enzyme, Novozym 435 was deactivated, and methanolysis was not progressed. In the case of *n*-hexane and cyclohexane, the conversion was high compared with ether and toluene. The enantioselectivity was high, but the reaction was slowest in the case using toluene. These indicated that Novozym 435-catalyzed methanolysis of *rac*-**1a** was slow in high polar solvent compared with in low polar solvent. When *n*-hexane and cyclohexane were compared, the conversion was high using cyclohexane, although *n*-hexane showed a slightly higher enantioselectivity than cyclohexane (Table 2, Entries 1 and 2). *i*-Pr_2O and CPME also indicated the same tendency (Table 2, Entries 3 and 4). There are no great differences in the permittivity among these solvents, such as *n*-hexane and cyclohexane or *i*-Pr_2O and CPME. These results showed that the methanolysis at 80℃ was faster than that at 60℃. In other words, it is expected to shorten the reaction time at 80℃. The enantiomeric excesses of (*S*)-**3a** and (*S*)-**5** produced with cyclohexane or CPME were slightly low relative to these with *n*-hexane or *i*-Pr_2O, but unreacted (*R*)-**1a** had high enentiomeric excess. The enantiomeric excess of (*R*)-**1a** was high although the conversion using cyclohexane was higher than that using CPME. Conversely, CPME showed low conversion compared with cyclohexane, but the enantiomeric excesses of (*S*)-**3a** and (*S*)-**5** were high. From these results, it seemed that the mixed solvent of cyclohexane and CMPE produced high conversion and enantioselectivity for Novozym 435-catalyzed methanolysis of *rac*-**1** and *rac*-**2** at 80℃.

The effect of an R^2 group on the reactivity and enantioselectivity was confirmed (Table 3). *Rac*-**1** and *rac*-**2** were hydrolyzed with Novozym 435 in cyclohexane for 4 and 5 days, respectively. 4 and 5 days were required to reach about 50% conversions for Novozym 435-catalyzed methanolysis of *rac*-**1a** and *rac*-**2a**, respectively. The substrate possessed long chain at R^1 group took long reaction time for Novozym 435-catalyzed methanolysis[40]. The reaction time of *rac*-**1a-e** was 4 days, and *rac*-**2a-e** was 5 days to confirm the effect of R^2 group. In the case of *N*-alkyl-5-acetoxytridecanamides (*rac*-**1**) showed high conversion compared with those with cHx and Bn groups. It seemed that a substrate with a small R^2 group has high reactivity for Novozym 435-catalyzed methanolysis. The low conversion substrates (*rac*-**1b**, **d** and **e**) gave (*S*)-**3** and (*S*)-**5** with higher enantiomeric excesses than the high conversion substrates (*rac*-**1a** and **c**). Conversely, *rac*-**1** with Me and *i*-Pr groups afforded higher enantiomeric excesses of (*R*)-**1**. When the Me group was compared with the *i*-Pr group, there were no great differences in the enantiomeric excesses of (*R*)-**1**. However, the Me group showed higher enantiomeric excesses for both (*S*)-**3** and (*S*)-**5**. From these results, it was assumed that the Me group was optimal as an R^2 group, considering the conversion and respective enantiomeric excesses (Table 3, Entry 1). On the other hand, when using *N*-alkyl-5-acetoxytetradecanamides (*rac*-**2**) with *n*-C_9H_{19} as a substrate, great differences in the conversion for all substrates (*rac*-**2a**, **b**, **d** and **e**) except *rac*-**2c** were not observed, and *rac*-**2c** with *i*-Pr as R^2 group showed low conversion. In *rac*-**1**, *rac*-**1b**, which has a comparatively small *n*-Pr group showed low conversion as with

Table 2 Effect of solvent using *rac*-**1a**[a].

Entry	Solvent	Temp. [℃]	Yield [%] / Enantiomeric excess [% e.e.][b]			Permittivity
			(*R*)-**1a**	(*S*)-**3a**	(*S*)-**5**	
1	*n*-Hexane	60	54 / 61	25 / 89	16 / 90	1.89[c]
2	Cy-Hexane	80	46 / 77	21 / 74	27 / 79	2.02[c]
3	*i*-Pr_2O	60	77 / 33	15 / 95	6 / 91	4.04[d]
4	CPME	80	67 / 45	21 / 84	11 / 88	4.76[e]
5	PhMe	80	87 / 30	9 / 90	4 / 85	2.4 [f]
6	THF	60		No reaction		7.58[d]
7	Acetone	50		No reaction		21 [g]
8	Phosphate buffer (pH=7)	60		No reaction		–

a) *rac*-**1a**: 1.0 mmol, MeOH: 3.0 mmol, Novozym 435: 0.4 g, Solvent: 20 mL, 96 h

b) Determined by GC using InertCap CHIRAMIX column.

c) Ref. 47 d) Ref. 48 e) Ref. 49 f) Ref. 50 g) Ref. 51

Table 3 Effect of R^2 group[a].

Entry	Substrate	R^1	R^2	Time [h]	Yield [%] / Enantimeric excess [% e.e.][b]		
					(*R*)-**1** and **2**	(*S*)-**3** and **4**	(*S*)-**5** and **6**
1	*rac*-**1a**	*n*-C_8H_{17}	Me	96	46 / 77	21 / 74	27 / 79
2	*rac*-**2a**	*n*-C_9H_{19}		120	44 / 84	23 / 71	27 / 82
3	*rac*-**1b**	*n*-C_8H_{17}	*n*-Pr	96	67 / 34	20 / 85	13 / 84
4	*rac*-**2b**	*n*-C_9H_{19}		120	44 / 78	30 / 72	26 / 76
5	*rac*-**1c**	*n*-C_8H_{17}	*i*-Pr	96	41 / 70	29 / 49	30 / 61
6	*rac*-**2c**	*n*-C_9H_{19}		120	54 / 50	19 / 70	17 / 67
7	*rac*-**1d**	*n*-C_8H_{17}	cHx	96	68 / 32	20 / 91	2 / 90
8	*rac*-**2d**	*n*-C_9H_{19}		120	42 / 74	44 / 71	13 / 80
9	*rac*-**1e**	*n*-C_8H_{17}	Bn	96	59 / 47	27 / 89	8 / 88
10	*rac*-**2e**	*n*-C_9H_{19}		120	52 / 70	26 / 79	22 / 88

a) *rac*-**1** and **2**: 1.0 mmol, MeOH: 3.0 mmol, Novozym 435: 0.4 g, Cy-hexane: 20 mL, 80℃
b) Determined by GC using InertCap CHIRAMIX column.

rac-1d and *rac*-1e (Table 3, Entry 3). These results show only that the bulkiness of R^2 group does not affect conversion. Lemke *et al*. reported that enzyme recognizes the shape of a substrate molecule, not the size[52]. R^2 groups in the substrates used in this paper had various shapes. It was assumed that Novozym 435 had high substrate specificity for all substrates except *rac*-2c because there was no great difference in the conversions and enantiomeric excesses among all substrates except *rac*-2c with a *i*-Pr group. In other words, Novozym 435 exhibited low substrate affinity and selectivity for *rac*-2c. *Rac*-2a with a Me group gave (*R*)-2 and (*S*)-6 with high enantiomeric excesses, although no great difference in the results among all *rac*-2 except *rac*-2c was observed, and *rac*-2a was the optimal substrate in *rac*-2. When *rac*-1a is compared to *rac*-2a, the substrate affinity of Novozym 435 for *rac*-1a was higher because the reaction time of *rac*-1a required until the conversion reached about 50% was shorter than that of *rac*-2a. In contrast, the substrate selectivity of Novozym 435 for *rac*-2a was slightly high compared with that of *rac*-1a.

When *rac*-1a was hydrolyzed using Novozym 435, cyclohexane gave a high conversion with a short reaction time and CPME showed high enantioselectivity (Table 2). It seemed that the optimal conditions, a short reaction time with high enantioselectivity was obtained by using mixture of these two solvents (Table 4). The solvent in which CPME was mixed at 5-25% with cyclohexane showed almost the same conversion as using only cyclohexane or any more when *rac*-1a was hydrolyzed as a substrate (Table 4, Entries 1, 3, 5, 7, 9, and 11). When a solvent including 5, 10, or 15% CPME was used, the enantiomeric excess of (*S*)-3a decreased compared with only cyclohexane (Table 4, Entries 3, 5, and 7). The mixed CPME including cyclohexane reduced the reaction time until 50% conversion was reached compared with the case when only CPME was used. When CPME was used as the solvent, Novozym 435-catalyzed methanolysis of *rac*-1a progressed with the highest enantioselectivity, although the mixed solvent of cyclohexane/CPME = 25:75 gave the highest enantiomeric excess of (*S*)-3a (Table 4, Entry 17). From these results, it was assumed that the mixed solvent of cyclohexane/CPME = 80:20 or 75:25 was suitable because these solvents gave shorter reaction times with only a slight decrease of enantioselectivity (Table 4, Entries 9 and 11). Similarly, CPME was suitable because although it required longer reaction time, but it showed high enantioselectivity (Table 4, Entry 17). In the case of *rac*-2a, the mixed solvent which included 5-25% CPME did not affect the conversion compared with cyclohexane alone, and it had the same tendency as *rac*-1a (Table 4, Entries 2, 4, 6, 8, 10 and 12). The solvent with which CPME was mixed up to 25% didn't have a great effect on enantioselectivity. When optically active δ-hexadecalactone was synthesized by the same method, the ratio of cyclohexane to CPME widely affected the conversion and enantioselectivity[40]. However, it cannot be said that the mixing ratio greatly affected the conversion and enantioselectivity of *rac*-1a and *rac*-2a.

3.3 Amine added Novozym 435-catalyzed methanolysis

We previously synthesized optically active δ-hexadecalactone using Novozym 435-catalyzed enantioselective methanolysis of *N*-methyl-5-acetoxyhexadecanamide[40]. The addition of two equivalent amounts of cyclohexylamine to *N*-methyl-5-acetoxyhexadecanamide increased enantioselectivity about 10% relative to the absence of it. In this investigation, we considered that Novozym 435 catalyzed methanolysis of *N*-methyl-5-acetoxyhexadecanamide enantioselectively to afford optically active *N*-methyl-5-hydroxyhexadecanamide and subsequently intra-esterized it enantioselectively, and catalysis

Table 4 Effect of Mixed solvent[a].

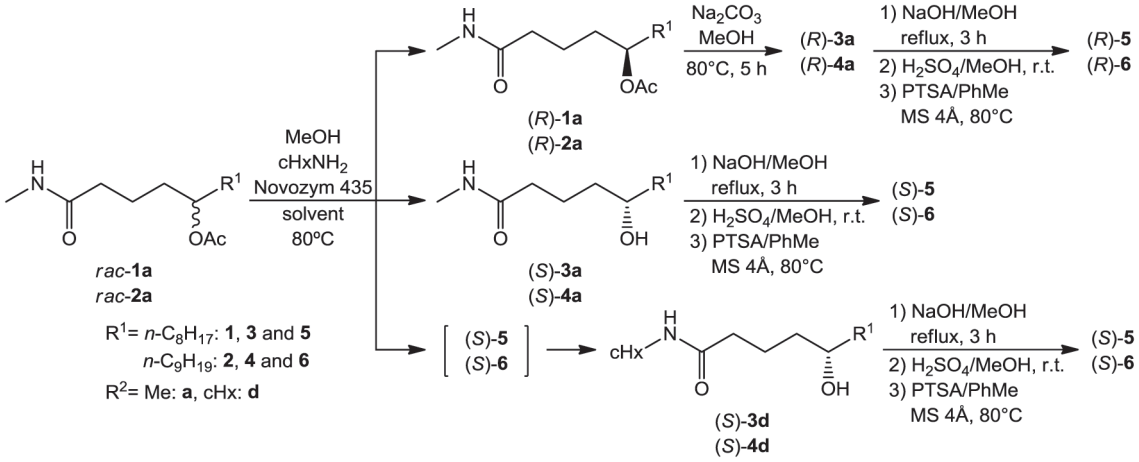
Entry	Substrate	Cy-hexane / CPME	Time [h]	Yield [%] / Enantimeric excess [% e.e.][b]		
				(*R*)-**1** and **2**	(*S*)-**3** and **4**	(*S*)-**5** and **6**
1	*rac*-**1a**	100 / 0	96	46 / 77	21 / 74	27 / 79
2	*rac*-**2a**		120	44 / 84	23 / 71	27 / 82
3	*rac*-**1a**	95 / 5	96	41 / 88	28 / 58	26 / 75
4	*rac*-**2a**		120	40 / 86	25 / 70	22 / 80
5	*rac*-**1a**	90 / 10	96	41 / 86	31 / 62	28 / 78
6	*rac*-**2a**		120	42 / 87	25 / 72	28 / 79
7	*rac*-**1a**	85 / 15	96	41 / 87	37 / 63	21 / 73
8	*rac*-**2a**		120	38 / 89	21 / 71	33 / 79
9	*rac*-**1a**	80 / 20	96	45 / 85	24 / 73	29 / 79
10	*rac*-**2a**		120	49 / 81	29 / 75	21 / 80
11	*rac*-**1a**	75 / 25	96	50 / 72	23 / 79	23 / 82
12	*rac*-**2a**		120	43 / 86	21 / 74	28 / 78
13	*rac*-**1a**	50 / 50	120	49 / 74	22 / 69	28 / 84
14	*rac*-**2a**		144	46 / 67	20 / 80	18 / 82
15	*rac*-**1a**	25 / 75	168	55 / 67	20 / 81	25 / 87
16	*rac*-**2a**		168	50 / 72	20 / 79	23 / 86
17	*rac*-**1a**	0 / 100	192	49 / 73	19 / 76	24 / 86
18	*rac*-**2a**		168	58 / 60	24 / 85	15 / 88

a) *rac*-**1a** and **2a**: 1.0 mmol, MeOH: 3.0 mmol, Novozym 435: 0.4 g, Solvent: 20 mL, 80℃
b) Determined by GC using InertCap CHIRAMIX column.

of these two reactions at the same time caused a decrease of enantioselectivity for the methanolysis of *N*-methyl-5-acetoxyhexadecanamide. Novozym 435 also catalyzed the methanolysis and intra-esterification enantioselectively for *rac*-1a and *rac*-2a at the same time because optically active lactones[(*S*)-5 and 6] were produced at the methanolysis and the enantiomeric excesses of lactones were higher than those of hydroxyamides[(*S*)-3 and 4](Table 4). Therefore, it seemed that addition of cyclohexylamine increased the enantioselectivity for the Novozym 435-catalyzed methanolysis of *rac*-1a and *rac*-2a(Scheme 2, Table 5). The enantioselectivity of Novozym 435 was increased by the addition of cyclohexylamine in almost all conditions. The enantiomeric excess improved more than 20% from 10%(Table 5, Entries 3, 11, 13, 14, and 18). Additionally, it was possible to shorten reaction time until reaching approximately 50% conversion by 24 hours in many cases. Whereas all mixed solvents showed about 80% enantioselectivity without addition of cyclohexylamine, methanolysis of mixtures to which cyclohexylamine was added progressed with about 90% enantioselectivity. When only cyclohexane or the mixed solvent of cyclohexane/CPME = 90:10 or 80:20 was used, both enantiomers[(*R*)-3a and (*S*)-3d] were obtained with over 90% enantiomeric excesses while (*S*)-3a showed a somewhat low enantiomeric excess for *rac*-1a as a substrate(Table 5, Entries 5 and 9). On the other hand, only cyclohexane and the mixed solvent of cyclohexane/CPME = 90:10, 85:15, 75:25, or 50:50 gave both enantiomers[(*R*)-3a and (*S*)-4d]with over 90% enantiomeric excesses for Novozym 435-catalyzed methanolysis of *rac*-2a(Table 5, Entries 6, 8, 12 and 14). These results confirmed that addition of cyclohexylamine increased the enantioselectivity for Novozym 435-catalyzed methanolysis of *rac*-1a and *rac*-2a, like the case of *N*-methyl-5-acetoxyhexadecanamide. The enantiomeric excesses of both enantiomers for δ-tri- and δ-tetradecalactones(5 and 6)were over 90% without racemization.

3.4 Sensory properties of optically active δ-tri- and δ-tetradecalactone

The enantiomers of δ-tri- and δ-tetradecalactone(5 and 6)showed different odor characteristics(Table 6). The odor intensity of the(*R*)-enantiomer[(*R*)-5] was about two times stronger than that of(*S*)-enantiomer[(*S*)-5]. Some differences in odor quality were also detected. The (*R*)-enantiomer of 5 exhibited a hay-like note. The(*S*)-enantiomer showed some resemblance to a walnut note. In contrast, both 6 exhibited a hay-like note, and there was no great difference of odor quality among each enantiomer of 6. Additionally, no difference of odor intensity was felt



Scheme 2 Amine added methanolysis in Novozym 435-catalyzed kinetic resolution.

Table 5 Effect of solvent on $cHxNH_2$ added Novozym 435-catalyzed methanolysis[a].

Entry	Substrate	Cy-hexane / CPME	Time [h]	Yield [%] / Enantiomeric excess [% e.][b]		
				(*R*)-**3a** and **4a**	(*S*)-**3a** and **4a**	(*S*)-**3d** and **4d**
1	*rac*-**1a**	100 / 0	96	50 / 94	23 / 76	27 / 91
2	*rac*-**2a**		96	33 / 98	17 / 57	30 / 91
3	*rac*-**1a**	95 / 5	96	48 / 83	24 / 80	28 / 88
4	*rac*-**2a**		96	46 / 94	18 / 74	31 / 87
5	*rac*-**1a**	90 / 10	72	38 / 90	20 / 77	29 / 90
6	*rac*-**2a**		96	45 / 97	21 / 76	34 / 91
7	*rac*-**1a**	85 / 15	72	39 / 88	26 / 82	21 / 88
8	*rac*-**2a**		96	36 / 98	25 / 75	24 / 91
9	*rac*-**1a**	80 / 20	96	47 / 96	23 / 76	22 / 90
10	*rac*-**2a**		96	40 / 97	23 / 81	30 / 89
11	*rac*-**1a**	75 / 25	96	40 / 97	23 / 72	27 / 88
12	*rac*-**2a**		96	37 / 97	21 / 80	26 / 90
13	*rac*-**1a**	50 / 50	96	46 / 71	22 / 90	17 / 89
14	*rac*-**2a**		96	40 / 95	25 / 89	15 / 94
15	*rac*-**1a**	25 / 75	144	42 / 77	26 / 89	16 / 92
16	*rac*-**2a**		120	44 / 80	27 / 88	15 / 93
17	*rac*-**1a**	0 / 100	168	50 / 76	33 / 90	11 / 91
18	*rac*-**2a**		168	43 / 84	24 / 88	15 / 83

a) *rac*-**1** and **2**: 1.0 mmol, MeOH: 3.0 mmol, $cHxNH_2$: 2.0 mmol, Novozym 435: 0.4 g, Cy-hexane: 20 mL, 80℃
b) Determined by GC using InertCap CHIRAMIX column.

for 6.

4 CONCLUSIONS

Enantiomers of both δ-tri- and δ-tetradecalactones were synthesized with over 90% enantiomeric excesses using Novozym 435-catalyzed methanolysis as a key step. The addition of 0.4 g Novozym 435 was suitable for a 1.0 mmol substrate. When cyclohexane was used as the solvent, high conversion was shown in a short time. Methanolysis progressed with high enantioselectivity using CPME. It differed from the preparation of δ-hexadecalactone, and a remarkable increase of enantioselectivity for Novozym 435 was not observed for the mixed solvent of cyclohexane and CPME. Addition of cyclohexylamine for Novozym 435-cata-

Table 6 Odor properties of optically active δ-tri- and δ-tetradecalactone[a].

Entry	δ-Lactone	% e.e.[b] / $[\alpha]^{20}_{D}$ (MeOH)	Odor properties[c]	Threshold [ppm][d]
1	(*R*)-**5**	99 / +38.0 (*c*= 0.2)	weak, hay-like note	2800
2	(*S*)-**5**	99 / −35.4 (*c*= 0.2)	weak, some reminiscence to walnut	5600
3	(*R*)-**6**	99 / +40.2 (*c*= 0.2)	weak, hay-like note	10000
4	(*S*)-**6**	99 / −40.8 (*c*= 0.2)	weak, hay-like note	10000

a) All samples tested were prepared by previous method[53].
b) Determined by GC using InertCap CHIMIX column.
c) Odor was evaluated on blotters. Neat samples were taken on blotters.
d) Odor threshold concentrations in 30% ethanol aqueous solution were determined.

lyzed methanolysis of *rac*-1a and *rac*-2a increased enantioselectivity about 10-20% compared with the absence of it, and the reaction time was shortened. Optically active δ-tri- and δ-tetradecalactones could also be prepared in high enantiomeric excess by the use of mixed solvent compared with the case when cyclohexane or CPME was used individually. Different odor characteristics were confirmed for δ-tridecalactone. The(*R*)-enantiomer showed a hay-like note, and the(*S*)-enantiomer exhibited some resemblance to walnuts. However, there was no great difference in odor intensity for δ-tri- and δ-tetradecalactones among each enantiomer.

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