Synthesis of Optically Active γ -Lactones with Lipase Catalyst

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Abstract: Lipase-catalyzed transesterification of racemic *N*-benzyl-4-hydroxyalkanamides with vinyl acetate proceeded enantioselectively to afford the reacted (*S*)-*N*-benzyl-4-acetoxyalkanamides and the unreacted (*R*)-*N*-benzyl-4-hydroxyalkanamides, which were separated easily by recrystallization in *n*-hexane. Both enantiomers were converted easily to optically active 4-substituted γ -lactones.

Key words: γ -lactones, lipase, *N*-benzyl-4-hydroxyalkanamide, enantiomeric excess

1 Introduction

γ -Lactones are widespread in nature; some are flavor compounds existing in plants and others are significant in insect behavior (1-5). Many naturally occurring γ -lactones are optically active compounds. Chiral discrimination is an important principle in odor perception and insect sex pheromones. Therefore, the development of a convenient method for synthesis for chiral γ -lactones has attracted the attention of synthetic chemists.

Recently, several chemists have reported the synthesis of chiral γ -lactones with sufficient optical purity by the lipase-catalyzed resolution of the 4-substituted 4-hydroxybutyric acid esters (6-9). In these cases, however, a mixture of the reaction product and unreacted substrate was separated by chromatography, which is difficult to apply to industrial-scale preparations. Previously, the drawback was improved by the use of succinic anhydride as an acyl donor, which led the formation of the succinic acid monoester that was easily separated from the unreacted alcohol by treatment with an alkaline solution (10). Now, we would like to report a novel method for a lipase-catalyzed kinetic resolution, which is applicable to alkaline-sensitive substrates and does not need any troublesome chromatographic methods.

2 Experimental

2.1 General

Melting points were determined with Yanaco MP-500D and were uncorrected. NMR spectra were obtained with a 500 MHz FT-NMR spectrometer (JEOL JNM-ECA500 system) with an internal standard. IR spectra were recorded on a JASCO FT/IR-460plus spectrometer. Optical rotations were measured on a JASCO P-1010. γ -Lactones were commercially obtained from the Tokyo Chemical Industry Co.. Benzylamine was obtained from Nacalai Tesque. Novozym 435 (lipase B from *C. antarctica*, EC 3.1.1.3, a non-specific lipase immobilized on macroporous acrylic resin, 1-2 % water content, 10,000 (propyl laurate units (PLU)/g) was obtained from Novo Nordisk A/S. Other materials were obtained commercially.

2.2 Preparation of *N*-benzyl-4-hydroxyalkanamide *rac*-2a-e

rac- γ -Lactones (10.0 mmol) were added to benzylamine (20.0 mmol) and stirred at room temperature. When the reaction was complete (TLC), *n*-hexane was added, and the reaction product was purified by recrystallization. The physical and spectral data of the obtained *N*-benzyl-4-hydroxyalkanamides *rac*-2a-e are

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as follows:

rac-N-Benzyl-4-hydroxyoctaneamide rac-2a:

Yield: 75.5 %; mp: 54°C; Rf=0.20 (Eluent; chloroform : methanol=10 : 1); ¹H NMR (δ, ppm): 0.89 (3H, t, *J*=6.9Hz, H-8), 1.29 (3H, m, H-6, H-7), 1.41 (3H, m, H-5, H-6), 1.64 (1H, m, H-2), 1.83 (1H, m, H-2), 2.36 (2H, td, *J*=2.9, 6.9Hz, H-3), 3.20 (1H, br, OH), 3.58 (1H, m, H-4), 4.38 (2H, d, *J*=5.7Hz, H-1'), 6.40 (1H, br, NH), 7.28 (5H, m, H-3', H-4', H-5'); ¹³C NMR (δ, ppm): 14.02 (C-8), 22.65 (C-7), 27.82 (C-6), 32.56 (C-2), 33.06 (C-3), 37.30 (C-5), 43.55 (C-1'), 71.23 (C-4), 127.40 (C-5'), 127.68 (C-3'), 128.60 (C-4'), 138.15 (C-2'), 173.68 (C-1); IR (KBr, cm⁻¹): 1550 (R-Ph), 1636 (C=O), 2852 (-CH₃), 2925 (-CH₂-), 3306 (O-H), 3429 (N-H)

rac-N-Benzyl-4-hydroxynonanamide rac-2b:

Yield: 97.0 %; mp: 62°C; Rf=0.23 (Eluent; chloroform : methanol=10 : 1); ¹H NMR (δ, ppm): 0.88 (3H, t, *J*=6.9Hz, H-9), 1.29 (5H, m, H-2, H-6, H-8), 1.42 (3H, m, H-5, H-6), 1.66 (1H, m, H-7), 1.84 (1H, m, H-7), 2.37 (2H, td, *J*=2.9, 6.9Hz, H-3), 3.09 (1H, br, OH), 3.59 (1H, m, H-4), 4.39 (2H, d, *J*=5.7Hz, H-1'), 6.31 (1H, br, NH), 7.28 (5H, m, H-3', H-4', H-5'); ¹³C NMR (δ, ppm): 14.01 (C-9), 22.59 (C-8), 25.34 (C-6), 31.82 (C-2), 32.55 (C-7), 33.10 (C-3), 37.63 (C-5), 43.55 (C-1'), 71.23 (C-4), 127.40 (C-5'), 127.68 (C-3'), 128.60 (C-4'), 138.15 (C-2'), 173.68 (C-1); IR (KBr, cm⁻¹): 1553 (R-Ph), 1635 (C=O), 2856 (-CH₃), 2926 (-CH₂-), 3296 (O-H)

rac-N-Benzyl-4-hydroxydecanamide rac-2c:

Yield: 97.5 %; mp: 69°C; Rf=0.22 (Eluent; chloroform : methanol=10 : 1); ¹H NMR (δ, ppm): 0.88 (3H, t, *J*=6.9Hz, H-10), 1.28 (7H, m, H-2, H-6, H-7, H-9), 1.43 (3H, m, H-5, H-6), 1.68 (1H, m, H-8), 1.87 (1H, m, H-8), 2.38 (2H, td, *J*=2.9, 6.9Hz, H-3), 2.62 (1H, br, OH), 3.62 (1H, m, H-4), 4.42 (2H, d, *J*=5.7Hz, H-1'), 6.07 (1H, br, NH), 7.30 (5H, m, H-3', H-4', H-5'); ¹³C NMR (δ, ppm): 14.07 (C-10), 22.58 (C-9), 25.63 (C-6), 29.30 (C-7), 31.79 (C-2), 32.49 (C-8), 33.17 (C-3), 37.73 (C-5), 43.68 (C-1'), 71.41 (C-4), 127.52 (C-5'), 127.78 (C-3'), 128.69 (C-4'), 138.14 (C-2'), 173.50 (C-1); IR (KBr, cm⁻¹): 1560 (R-Ph), 1610 (C=O), 2850 (-CH₃), 2921 (-CH₂-), 3268 (O-H), 3468 (N-H)

rac-N-Benzyl-4-hydroxyundecanamide rac-2d:

Yield: 99.0 %; mp: 66°C; Rf=0.23 (Eluent; chloroform : methanol=10 : 1); ¹H NMR (δ, ppm): 0.88 (3H, t, *J*=6.9Hz, H-11), 1.27 (9H, m, H-2, H-6, H-7, H-8, H-10), 1.43 (3H, m, H-5, H-6), 1.67 (1H, m, H-9), 1.85

(1H, m, H-9), 2.38 (2H, td, *J*=2.9, 6.9Hz, H-3), 2.84 (1H, br, OH), 3.60 (1H, m, H-4), 4.41 (2H, d, *J*=5.7Hz, H-1'), 6.13 (1H, br, NH), 7.29 (5H, m, H-3', H-4', H-5'); ¹³C NMR (δ, ppm): 14.08 (C-11), 22.63 (C-10), 25.67 (C-6), 29.25 (C-8), 29.59 (C-7), 31.79 (C-2), 32.52 (C-9), 33.16 (C-3), 37.71 (C-5), 43.66 (C-1'), 71.39 (C-4), 127.50 (C-5'), 127.77 (C-3'), 128.68 (C-4'), 138.15 (C-2'), 173.54 (C-1); IR (KBr, cm⁻¹): 1550 (R-Ph), 1636 (C=O), 2852 (-CH₃), 2925 (-CH₂-), 3306 (O-H), 3429 (N-H)

rac-N-Benzyl-4-hydroxydodecanamide rac-2e:

Yield: 96.4 %; mp: 69°C; Rf=0.30 (Eluent; chloroform : methanol=10 : 1); ¹H NMR (δ, ppm): 0.88 (3H, t, *J*=6.9Hz, H-12), 1.27 (11H, m, H-2, H-6, H-7, H-8, H-9, H-11), 1.42 (3H, m, H-5, H-6), 1.67 (1H, m, H-10), 1.86 (1H, m, H-10), 2.37 (2H, td, *J*=2.9, 6.9Hz, H-3), 2.81 (1H, br, OH), 3.60 (1H, m, H-4), 4.42 (2H, d, *J*=5.7Hz, H-1'), 6.10 (1H, br, NH), 7.29 (5H, m, H-3', H-4', H-5'); ¹³C NMR (δ, ppm): 14.09 (C-12), 22.64 (C-11), 25.67 (C-6), 29.24 (C-9), 29.55 (C-8), 29.64 (C-7), 31.85 (C-2), 32.51 (C-10), 33.16 (C-3), 37.73 (C-5), 43.67 (C-1'), 71.40 (C-4), 127.50 (C-5'), 127.77 (C-3'), 128.68 (C-4'), 138.15 (C-2'), 173.52 (C-1); IR (KBr, cm⁻¹): 1551 (R-Ph), 1633 (C=O), 3305 (O-H), 2850 (-CH₃), 2923 (-CH₂-), 3429 (N-H)

2.3 Enzymatic Acetylation

Novozym 435 (0.4 g) was added to a solution of the appropriate *rac-N*-benzyl-4-hydroxyalkanamides ***rac-2a-e*** (1.0 mmol) in vinyl acetate (2.0 mmol), and diethyl ether (20 mL), while stirring at room temperature. After stirring, the mixture was filtered. After evaporation of the solvent, the crude reaction mixture was added to *n*-hexane and cooled. After the mixture was filtered, the (*R*)-*N*-benzyl-4-hydroxyalkanamides (***R*-2a-e**) and (*S*)-*N*-benzyl-4-acetoxyalkanamides (***S*-3a-e**) were purified.

(R)-N-Benzyl-4-hydroxyalkanamides (R)-2a-e:

The NMR, the IR-spectroscopic data and Rf value data are omitted because they were the same as those for the racemic modification ***rac-2a-e***.

(S)-N-Benzyl-4-acetoxyoctanamide (S)-3a:

Rf=0.53 (Eluent; chloroform : methanol=10 : 1); ¹H NMR (δ, ppm): 0.88 (3H, t, *J*=6.9Hz, H-8), 1.28 (4H, m, H-6, H-7), 1.53 (2H, m, H-5), 1.86 (1H, m, H-2), 1.96 (1H, m, H-2), 2.03 (3H, s, H-2'), 2.22 (2H, m, H-3), 4.43 (2H, d, *J*=5.7Hz, H-1'), 4.88 (1H, m, H-4), 6.04 (1H, br, NH), 7.30 (5H, m, H-3', H-4', H-5');

^{13}C NMR (δ , ppm): 13.92 (C-8), 21.17 (C-2'), 22.45 (C-7), 27.41 (C-6), 30.18 (C-2), 32.63 (C-3), 33.96 (C-5), 43.63 (C-1''), 73.75 (C-4), 127.45 (C-5''), 127.81 (C-3''), 128.66 (C-4''), 138.66 (C-2''), 171.21 (C-1'), 172.05 (C-1); IR (NaCl, cm^{-1}): 1243 (C-O-C), 1545 (R-Ph), 1648 (C=O, Amide), 1735 (C=O, Ester), 2865 ($-\text{CH}_3$), 2932 ($-\text{CH}_2-$), 3296 (O-H)

(S)-N-Benzyl-4-acetoxynonanamide (S)-3b:

Rf=0.55 (Eluent; chloroform : methanol=10 : 1); ^1H NMR (δ , ppm): 0.87 (3H, t, $J=6.9\text{Hz}$, H-9), 1.27 (6H, m, H-3, H-6, H-8), 1.52 (2H, m, H-5), 1.86 (1H, m, H-2), 1.97 (1H, m, H-2), 2.03 (3H, s, H-2'), 2.22 (2H, m, H-7), 4.43 (2H, d, $J=5.7\text{Hz}$, H-1''), 4.88 (1H, m, H-4), 6.02 (1H, br, NH), 7.30 (5H, m, H-3'', H-4'', H-5''); ^{13}C NMR (δ , ppm): 13.94 (C-9), 21.17 (C-2'), 22.47 (C-8), 24.92 (C-6), 30.17 (C-2), 31.54 (C-3), 32.64 (C-7), 34.23 (C-5), 43.63 (C-1''), 73.78 (C-4), 127.46 (C-5''), 127.81 (C-3''), 128.66 (C-4''), 138.27 (C-2''), 171.21 (C-1'), 172.03 (C-1); IR (NaCl, cm^{-1}): 1243 (C-O-C), 1546 (R-Ph), 1648 (C=O, Amide), 1735 (C=O, Ester), 2861 ($-\text{CH}_3$), 2931 ($-\text{CH}_2-$), 3296 (O-H)

(S)-N-Benzyl-4-acetoxyldecanamide (S)-3c:

Rf=0.47 (Eluent; chloroform : methanol=10 : 1); ^1H NMR (δ , ppm): 0.87 (3H, t, $J=6.9\text{Hz}$, H-10), 1.26 (8H, m, H-3, H-6, H-7, H-9), 1.53 (2H, m, H-5), 1.86 (1H, m, H-2), 1.96 (1H, m, H-2), 2.03 (3H, s, H-2'), 2.21 (2H, m, H-8), 4.43 (2H, d, $J=5.7\text{Hz}$, H-1''), 4.88 (1H, m, H-4), 6.00 (1H, br, NH), 7.30 (5H, m, H-3'', H-4'', H-5''); ^{13}C NMR (δ , ppm): 14.03 (C-10), 21.18 (C-2'), 22.52 (C-9), 25.23 (C-6), 29.05 (C-7), 30.19 (C-2), 31.65 (C-3), 32.66 (C-8), 34.29 (C-5), 43.65 (C-1''), 73.79 (C-4), 127.48 (C-5''), 127.82 (C-3''), 128.68 (C-4''), 138.27 (C-2''), 171.23 (C-1'), 172.04 (C-1); IR (NaCl, cm^{-1}): 1243 (C-O-C), 1548 (R-Ph), 1647 (C=O, Amide), 1736 (C=O, Ester), 2858 ($-\text{CH}_3$), 2929 ($-\text{CH}_2-$), 3293 (O-H)

(S)-N-Benzyl-4-acetoxylundecanamide (S)-3d:

Rf=0.53 (Eluent; chloroform : methanol=10 : 1); ^1H NMR (δ , ppm): 0.88 (3H, t, $J=6.9\text{Hz}$, H-11), 1.25 (10H, m, H-3, H-6, H-7, H-8, H-10), 1.53 (2H, m, H-5), 1.86 (1H, m, H-2), 1.97 (1H, m, H-2), 2.03 (3H, s, H-2'), 2.22 (2H, m, H-9), 4.44 (2H, d, $J=5.7\text{Hz}$, H-1''), 4.88 (1H, m, H-4), 5.99 (1H, br, NH), 7.30 (5H, m, H-3'', H-4'', H-5''); ^{13}C NMR (δ , ppm): 14.06 (C-11), 21.19 (C-2'), 22.60 (C-10), 25.27 (C-6), 29.13 (C-8), 29.35 (C-7), 30.19 (C-2), 31.72 (C-3), 32.66 (C-9), 34.29 (C-5), 43.65 (C-1''), 73.80 (C-4), 127.48 (C-5''), 127.83 (C-3''), 128.68 (C-4''), 138.27 (C-2''), 171.23 (C-1'),

172.03 (C-1); IR (NaCl, cm^{-1}): 1242 (C-O-C), 1548 (R-Ph), 1647 (C=O, Amide), 1736 (C=O, Ester), 2857 ($-\text{CH}_3$), 2927 ($-\text{CH}_2-$), 3293 (O-H)

(S)-N-Benzyl-4-acetoxyltridecanamide (S)-3e:

Rf=0.52 (Eluent; chloroform : methanol=10 : 1); ^1H NMR (δ , ppm): 0.88 (3H, t, $J=6.9\text{Hz}$, H-12), 1.25 (14H, m, H-3, H-6, H-7, H-8, H-9, H-11), 1.53 (2H, m, H-5), 1.86 (1H, m, H-2), 1.97 (1H, m, H-2), 2.03 (3H, s, H-2'), 2.21 (2H, m, H-10), 4.44 (2H, d, $J=5.7\text{Hz}$, H-1''), 4.88 (1H, m, H-4), 5.97 (1H, br, NH), 7.30 (5H, m, H-3'', H-4'', H-5''); ^{13}C NMR (δ , ppm): 14.08 (C-12), 21.19 (C-2'), 22.62 (C-11), 25.27 (C-6), 29.17 (C-9), 29.39 (C-8), 29.42 (C-7), 30.19 (C-2), 31.82 (C-3), 32.67 (C-10), 34.30 (C-5), 43.65 (C-1''), 73.80 (C-4), 127.48 (C-5''), 127.83 (C-3''), 128.68 (C-4''), 138.26 (C-2''), 171.23 (C-1'), 172.03 (C-1); IR (NaCl, cm^{-1}): 1242 (C-O-C), 1548 (R-Ph), 1647 (C=O, Amide), 1736 (C=O, Ester), 2856 ($-\text{CH}_3$), 2926 ($-\text{CH}_2-$), 3293 (O-H)

2.4 General Procedure for Lactonization of Each Alkanamides

Each (R)-N-benzyl-4-hydroxyalkanamides (**R**)-2a-e or (S)-N-benzyl-4-acetoxylalkanamides (**S**)-3a-e were refluxed with sodium hydroxide (2.0 g) and methanol (20.0 mL) for 2 h. The mixture was evaporated under reduced pressure and 2 N hydrochloric acid was added until pH=3. After stirring for 1 h, *n*-hexane was added, and the mixture was partitioned between water and *n*-hexane. The aqueous phase was extracted with *n*-hexane, and the extracts were dried (Na_2SO_4) and evaporated under reduced pressure to provide each γ -lactones (**R**)-1a-e, and (**S**)-1a-e as a colorless oil. The specific rotation was measured in methanol.

(R)- γ -octalactone (R)-1a:

Yield: quant.; Rf=0.82 (Eluent; chloroform : methanol=10:1), Capillary GC, Chirasil-DEX CB column; 130°C ; isothermal; $t_R=7.40$ min; $[\alpha]_D^{20}=+54.0$ (CH_3OH , lit. $[\alpha]_D^{20}=+56.2$ (1)); ^1H NMR (δ , ppm): 0.92 (3H, t, $J=6.3\text{Hz}$, H-8), 1.36-1.44 (4H, m, H-6, H-7), 1.61 (1H, m, H-5), 1.73 (1H, m, H-5), 1.86 (1H, q, $J=8.0$, 4.6Hz, H-3), 2.34 (1H, m, H-3), 2.52 (1H, d, $J=9.7\text{Hz}$, H-2), 4.49 (1H, quin, $J=6.3\text{Hz}$, H-4); ^{13}C NMR (δ , ppm): 13.64 (C-8), 22.15 (C-7), 27.08 (C-6), 27.73 (C-3), 28.58 (C-2), 34.97 (C-5), 80.80 (C-4), 177.07 (C-1); IR (NaCl, cm^{-1}): 1184 (C-O-C), 1774 (C=O), 2868 ($-\text{CH}_3$), 2935 ($-\text{CH}_2-$)

(S)- γ -octalactone (S)-1a:

Yield: quant.; Capillary GC, Chirasil-DEX CB col-

umn; 130°C; isothermal; t_R =7.63 min; $[\alpha]_D^{20}$ =-55.9 (CH₃OH, lit. $[\alpha]_D^{20}$ =-56.6 (1)); NMR and IR spectra and Rf value data were the same as those for **(R)-1a**.

(R)- γ -nonalactone (R)-1b:

Yield: quant.; Rf=0.78 (Eluent; chloroform : methanol=10 : 1); Capillary GC, Chirasil-DEX CB column; 130°C; isothermal; t_R =11.77 min; $[\alpha]_D^{20}$ =+51.7 (CH₃OH, lit. $[\alpha]_D^{20}$ =+51.8 (1)); ¹H NMR (δ , ppm): 0.90 (3H, t, J =6.9Hz, H-9), 1.32-1.46 (6H, m, H-6, H-7, H-8), 1.60 (1H, m, H-5), 1.73 (1H, m, H-5), 1.86 (1H, m, H-3), 2.34 (1H, m, H-3), 2.52 (2H, d, J =9.7Hz, H-2), 4.49 (1H, quin, 6.9, 6.9Hz, H-4); ¹³C NMR (δ , ppm): 13.71 (C-9), 22.25 (C-8), 24.67 (C-6), 27.77 (C-3), 28.62 (C-2), 31.26 (C-7), 35.30 (C-5), 80.85 (C-4), 177.10 (C-1); IR (NaCl, cm⁻¹)=1182 (C-O-C), 1775 (C=O), 2862 (-CH₃), 2933 (-CH₂-)

(S)- γ -nonalactone (S)-1b:

Yield: quant.; Capillary GC, Chirasil-DEX CB column; 130°C; isothermal; t_R =12.15 min; $[\alpha]_D^{20}$ =-50.7 (CH₃OH, lit. $[\alpha]_D^{20}$ =-51.6 (1)); NMR and IR spectra and Rf value data were the same as those for **(R)-1b**.

(R)- γ -decalactone (R)-1c:

Yield: 93.8%; Rf=0.74 (Eluent; chloroform : methanol=10 : 1); Capillary GC, Chirasil-DEX CB column; 135°C; isothermal; t_R =15.45 min; $[\alpha]_D^{20}$ =+48.3 (CH₃OH, lit. $[\alpha]_D^{20}$ =+48.5 (1)); ¹H NMR (δ , ppm): 0.89 (3H, t, J =6.9Hz, H-10), 1.30-1.45 (8H, m, H-6, H-7, H-8, H-9), 1.60 (1H, m, H-5), 1.73 (1H, m, H-5), 1.86 (1H, m, H-3), 2.33 (1H, m, H-3), 2.52 (2H, d, J =9.7Hz, H-2), 4.49 (1H, quin, J =6.9, 6.9Hz, H-4); ¹³C NMR (δ , ppm): 13.86 (C-10), 22.35 (C-9), 25.01 (C-6), 27.83 (C-3), 28.69 (C-7), 28.81 (C-2), 31.47 (C-8), 35.40 (C-5), 80.90 (C-4), 177.15 (C-1); IR (NaCl, cm⁻¹)=1181 (C-O-C), 1776 (C=O), 2858 (-CH₃), 2930 (-CH₂-)

(S)- γ -decalactone (S)-1c:

Yield: 93.1%; Capillary GC, Chirasil-DEX CB column; 135°C; isothermal; t_R =15.80 min; $[\alpha]_D^{20}$ =-47.5 (CH₃OH, lit. $[\alpha]_D^{20}$ =-48.1 (1)); NMR and IR spectra and Rf value data were the same as those for **(R)-1c**.

(R)- γ -undecalactone (R)-1d:

Yield: quant.; Rf=0.74 (Eluent; chloroform : methanol=10 : 1); Capillary GC, Chirasil-DEX CB column; 135°C; isothermal; t_R =25.92 min; $[\alpha]_D^{20}$ =+44.8 (CH₃OH, lit. $[\alpha]_D^{20}$ =+45.3 (1)); ¹H NMR (δ , ppm): 0.88 (3H, t, J =6.9Hz, H-11), 1.29-1.45 (10H, m, H-6, H-7, H-8, H-9, H-10), 1.60 (1H, m, H-5), 1.73 (1H, m, H-5), 1.86 (1H, m, H-3), 2.34 (1H, m, H-3), 2.52 (2H, d, J =9.2Hz, H-2), 4.49 (1H, quin, J =6.9, 6.9Hz, H-4); ¹³C

NMR (δ , ppm): 13.75 (C-11), 22.30 (C-10), 24.93 (C-6), 27.70 (C-3), 28.54 (C-8), 28.82 (C-7), 28.98 (C-2), 31.42 (C-9), 35.26 (C-5), 80.75 (C-4), 176.99 (C-1); IR (NaCl, cm⁻¹)=1178 (C-O-C), 1774 (C=O), 2857 (-CH₃), 2927 (-CH₂-)

(S)- γ -undecalactone (S)-1d:

Yield: quant.; Capillary GC, Chirasil-DEX CB column; 135°C; isothermal; t_R =26.37 min; $[\alpha]_D^{20}$ =-45.6 (CH₃OH, lit. $[\alpha]_D^{20}$ =-45.8 (1)); NMR and IR spectra and Rf value data were the same as those for **(R)-1d**.

(R)- γ -dodecalactone 1e:

Yield: quant.; Rf=0.74 (Eluent; chloroform : methanol=10 : 1); Capillary GC, Chirasil-DEX CB column; 140°C; isothermal; t_R =34.19 min; $[\alpha]_D^{20}$ =+42.1 (CH₃OH, lit. $[\alpha]_D^{20}$ =+42.2 (1)); ¹H NMR (δ , ppm): 0.88 (3H, t, J =6.9Hz, H-12), 1.27-1.45 (12H, m, H-6, H-7, H-8, H-9, H-10, H-11), 1.59 (1H, m, H-5), 1.73 (1H, m, H-5), 1.85 (1H, m, H-3), 2.32 (1H, m, H-3), 2.52 (2H, d, J =9.7Hz, H-2), 4.49 (1H, quin, J =7.4, 6.3Hz, H-4); ¹³C NMR (δ , ppm): 14.02 (C-12), 22.57 (C-11), 25.16 (C-6), 27.94 (C-3), 28.80 (C-9), 29.11 (C-8), 29.27 (C-7), 29.34 (C-2), 31.76 (C-9), 35.52 (C-5), 81.01 (C-4), 177.25 (C-1); IR (NaCl, cm⁻¹)=1179 (C-O-C), 1776 (C=O), 2856 (-CH₃), 2927 (-CH₂-)

(S)- γ -dodecalactone (S)-1e:

Yield: 97.4 %; Capillary GC, Chirasil-DEX CB column; 140°C; isothermal; t_R =33.00 min; $[\alpha]_D^{20}$ =-42.2 (CH₃OH, lit. $[\alpha]_D^{20}$ =-42.6 (1)); NMR and IR spectra and Rf value data were the same as those for **(R)-1e**.

3 Results and Discussion

3.1 Synthesis of *rac-N*-benzyl-4-hydroxyalkanamides

The *rac-N*-benzyl-4-hydroxyalkanamides **rac-2a-e** were synthesized from five kinds of commercial *rac*- γ -lactones and benzylamine. These five γ -lactones were selected because these lactones were frequently found in perfume. For example, the γ -nonalactone was known as coconut aldehyde, and the γ -undecalactone was called as peach aldehyde. Although the similar synthesis for hydroxyalkanamides have been reported, the previous methods needs amine hydrochloride under harsh conditions (11-12). Our synthesis method includes only a stirring procedure at room temperature and is the mildest and most concise method. As shown in **Scheme 1** and **Table 1**, racemic lactones **1a-e** and benzylamine were mixed and were reacted at room temperature for

2-5 days, affording *N*-benzyl-4-hydroxyalkanamides in excellent yields regardless of the chain lengths of the substrates. Although our method requires long reaction times, purification of the product is very simple. Adding *n*-hexane to the reaction mixture since *N*-benzyl-4-hydroxyalkanamides was scarcely soluble in *n*-hexane and was crystallized from the mixture easily separated the product. Recrystallization of the crude product afforded pure *N*-benzyl-4-hydroxyalkanamides in excellent yields as shown in **Table 1**.

3.2 Asymmetric Acetylation of *rac*-*N*-benzyl-4-hydroxyalkanamides

Asymmetric acetylation was performed with *rac*-*N*-benzyl-4-hydroxyalkanamides *rac*-**2a-e** as the substrate, Novozym 435 as the lipase, vinyl acetate as the acyl donor, and diethyl ether as the solvent. The mixture was stirred at room temperature and the progress of esterification was monitored by gas chromatography and the reaction was stopped at 50 % conversion. Four kinds of lipases that were PPL, LPI, Lipozym IM and Novozym 435 were screened. However, when PPL, LPI and

Scheme 1 Synthesis of *N*-benzyl-4-hydroxyalkanamides.

Scheme 2 Asymmetric Acetylation of *rac*-*N*-benzyl-4-hydroxyalkanamides.

Scheme 3 Lactonization of (*R*)-*N*-benzyl-4-hydroxyalkanamides and (*S*)-*N*-benzyl-4-acetoxyalkanamides.

Table 1 Yield of *rac*-2a-e.

Entry	R	Yield [%]
1	$n\text{-C}_4\text{H}_9$	75.5
2	$n\text{-C}_5\text{H}_{11}$	97.0
3	$n\text{-C}_6\text{H}_{13}$	97.5
4	$n\text{-C}_7\text{H}_{15}$	quant.
5	$n\text{-C}_8\text{H}_{17}$	96.7

Table 2 Asymmetric acetylation of *rac*-2a-e.

Entry	R	Reaction time [h]	Yield [%]	
			(<i>R</i>)-2a-e	(<i>S</i>)-3a-e
1	$n\text{-C}_4\text{H}_9$	6	45.1	46.5
2	$n\text{-C}_5\text{H}_{11}$	8	47.7	50.4
3	$n\text{-C}_6\text{H}_{13}$	8	48.7	48.4
4	$n\text{-C}_7\text{H}_{15}$	18	47.6	47.7
5	$n\text{-C}_8\text{H}_{17}$	18	45.9	48.1

Table 3 Lactonization of (*R*)-2a-e and (*S*)-3a-e.

Entry	R	Yield [%]		e.e. [% e.e.]*)	
		(<i>R</i>)-1a-e	(<i>S</i>)-1a-e	(<i>R</i>)-1a-e	(<i>S</i>)-1a-e
1	$n\text{-C}_4\text{H}_9$	quant.	quant.	>99	>99
2	$n\text{-C}_5\text{H}_{11}$	quant.	quant.	>99	>99
3	$n\text{-C}_6\text{H}_{13}$	93.8	93.1	>99	>99
4	$n\text{-C}_7\text{H}_{15}$	quant.	quant.	>99	>99
5	$n\text{-C}_8\text{H}_{17}$	quant.	97.4	>99	>99

*) Determined by GC using CP-Chirasil-Dex CB column.

Lipozym IM were used in asymmetric acetylation, reacted acetoxyalkanamides were not produced. Novozym 435 was shown to have the best lipase. Vinyl acetate was shown to be the best acyl donor. In case of using acetic anhydride as acyl donor, enantioselectivity was decreased. Since the product (**S**)-**3a-e** could be dissolved in *n*-hexane while the starting material was insoluble, both could be separated by recrystallization with *n*-hexane. The result was summarized in **Table 2**. In the enzymatic reaction, substrates with short alkyl chains reacted faster than those of long alkyl chains. The absolute configurations of the produced acetates (*S*) and the unreacted alcohols (*R*) were determined by converting them to the corresponding lactones.

3.3 Lactonization of (*R*)-*N*-benzyl-4-hydroxyalkanamides and (*S*)-*N*-benzyl-4-acetoxyalkanamides

Lactonization was performed by alkaline hydrolysis using a 10 wt% sodium hydroxide methanol solution for (*R*)-*N*-benzyl-4-hydroxyalkanamides (**R**)-**2a-e** and (*S*)-*N*-benzyl-4-acetoxyalkanamides (**S**)-**3a-e**, and then hydrochloric acid. As shown in **Table 3**, γ -lactones could be synthesized in high yield regardless of the difference in the chain length from the (*R*)-*N*-benzyl-4-hydroxyalkanamides (**R**)-**2a-e** and the (*S*)-*N*-benzyl-4-acetoxyalkanamides (**S**)-**3a-e**. These compounds could be synthesized in high yield with >99 %e.e.. The absolute configuration was determined by comparing the specific rotation measured in this work with the value reported in the literature (1).

4 Conclusion

rac-*N*-benzyl-4-hydroxyalkanamides that were substrates for lipase-catalyzed acetylation could be synthesized at room temperature in high yield from commercial *rac*- γ -lactones and benzylamine. It was possible to acetylate with high selectivity using *rac*-*N*-benzyl-4-hydroxyalkanamides as the substrate, Novozym 435 as the lipase, vinyl acetate as the acyl donor, and diethyl ether as the solvent. Each alkanamide could be isolated by recrystallization in *n*-hexane, without the necessity of silica gel column chromatography. Moreover, five kinds of γ -lactones could be synthesized with a high selectivity and an optical purity that exceeded 99 %ee by lactonizing for each alkanamides.

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