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COMBINATION OF NOVOZYM 435–CATALYZED HYDROLYSIS AND MITSUNOBU REACTION FOR PRODUCTION OF (*R*)-γ-LACTONES

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Chiral γ-lactones of both enantiomers were synthesized with more than 90% optical purities. The key step was Novozym 435–catalyzed hydrolysis of racemic N-benzyl-4-acetoxyalkylamides. Additionally, because (R)-γ-lactones are predominant in apricot, mango, peach, passion fruit, and strawberry, synthesis was attempted using only one enantiomer selectively. The (R)-enantimer was synthesized with more than 80% total yield and more than 90% optical purity by a combination of Novozym 435–catalyzed hydrolysis and the Mitsunobu reaction.

Keywords: Enzymatic resolution; Mitsunobu reaction; optical purity; (*R*)-γ-lactone

INTRODUCTION

Optically active γ-lactones are important heterocyclic aliphatic compounds.[1] They are versatile building blocks for the synthesis of bioactive molecules and are also widespread in nature, especially as pheromones and aromatic components of many fruits and other natural products.[2,3] Therefore, we attempted to synthesize optically active γ- and δ-lactones using a lipase catalyst.[4–6] Recently, we reported synthesis of (*S*)-γ-lactones with a combination of lipase-catalyzed resolution and the Mitsunobu reaction.[7] This system efficiently produces only one enantiomer of γ-lactones. However, Mosandl and Guenther reported that the (*R*)-enantiomer of γ-lactones has a stronger odor in most cases.[8] Additionally, the (*R*)-enantiomer is often more plentiful than the (*S*)-enantiomer in natural products.[9] Previously, we reported synthesis of optically active γ-lactones with Novozym 435–catalyzed hydrolysis of *rac*-*N*-methyl-4-acetoxyalkylamides.[5] It has been shown that Novozym 435 selectively hydrolyzes the (*S*)-enantiomer. Therefore, we attempted to synthesize the (*R*)-enantiomer by a combination of Novozym 435–catalyzed hydrolysis and the Mitsunobu reaction.

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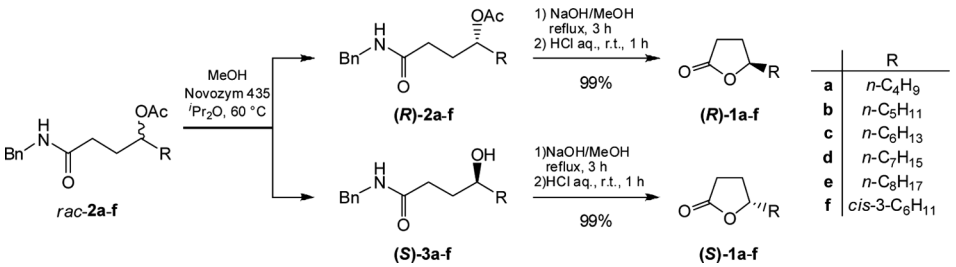
RESULTS AND DISCUSSION

Novozym 435–Catalyzed Hydrolysis

We recently reported a synthesis of (*S*)-γ-lactones [(*S*)-**1**] with a combination of Novozym 435–catalyzed resolution and the Mitsunobu reaction.[7] When the acetylation of racemic *N*-benzyl-4-hydroxyalkylamides (*rac*-**3**) were performed using Novozym 435, predominantly (*S*)-enantiomers [(*S*)-**3**] were acetylated to afford (*R*)-*N*-benzyl-4-acetoxyalkylamides [(*R*)-**2**].[4] (*R*)-*N*-Benzyl-4-hydroxyalkylamides [(*R*)-**3**], which are secondary alcohols, were inverted to (*S*)-enantiomers [(*S*)-**4**] by the Mitsunobu reaction, and the subsequent lactonization of the reaction mixture afforded (*S*)-**1**. Therefore, we attempted to obtain a reaction mixture of (*R*)-**2** and (*S*)-**3** to synthesize (*R*)-**1** with a combination of a lipase-catalyzed resolution and the Mitsunobu reaction. We previously performed Novozym 435–catalyzed hydrolysis of racemic *N*-methyl-4-acetoxyalkylamides in diethyl ether at 40 °C.[5] (*S*)-Enantiomers were predominantly hydrolyzed to afford (*S*)-*N*-methyl-4-hydroxyalkylamides. After separation of the reaction mixture of (*R*)-*N*-methyl-4-acetoxyalkylamides and (*S*)-*N*-methyl-4-hydroxyalkylamides, lactonization afforded (*R*)-**1** in the range of 76–88% ee and (*S*)-**1** with more than 97% ee. Therefore, Novozym 435–catalyzed hydrolysis of *rac*-**2e** was performed under the same conditions (Scheme 1). As the result, predominantly (*S*)-**2e** was hydrolyzed, and the lactonization of both enantiomers after separation afforded (*S*)-**1e** with 90% ee and (*R*)-**1e** with >99% ee (Table 1, entry 5). This indicates that the substrate specificity of Novozym 435 to *rac*-**2e** was greater than that to racemic *N*-methyl-4-acetoxydodecanamide. It is assumed that maximum Novozym 435 activity occurs at 60 °C, and the hydrolysis of *rac*-**2e** was performed at 60 °C by changing diethyl ether to diisopropyl ether to increase the optical purity. After separation of (*R*)-**2e** and (*S*)-**3e** and lactonization, (*R*)-**1e** and (*S*)-**1e** were obtained with 95% ee and >99% ee, respectively (Table 1, entry 6). The optical purity of (*S*)-**1e** was the same as before, but that of (*R*)-**1e** was increased from 90% ee to 95% ee. Additionally, the reaction time required to reach 50% conversion was shortened from 36 h (Table 1, entry 5) to 24 h (Table 1, entry 6). The optimum conditions of Novozym 435–catalyzed hydrolysis of *rac*-**2** were determined to be these conditions, which used diisopropyl ether as the solvent at 60 °C, and the conditions were applied to various substrates. In this article, six kinds of γ-lactones (γ-octa-, nona-, deca-, undeca-, dodeca-, and jasmolactone) are described. Novozym 435–catalzed hydrolysis and lactonization were performed on



Scheme 1. Optical resolution of *rac*-**2** by Novozym 435–catalyzed hydrolysis.

Table 1. Novozym 435–catalyzed resolution of *rac*-**2**[a]

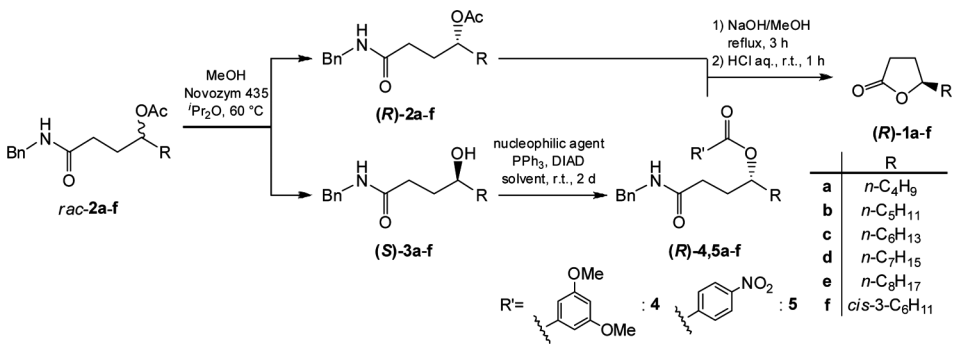
Entry	Substrate	R	Solvent	Time (h)	Yield (%)		Enantiomeric excess (% ee.)[b]		E[c]
					(*R*)-**2**	(*S*)-**3**	(*R*)-**1**	(*S*)-**1**	
1	*rac*-**2a**	*n*-C_4H_9	$^iPr_2O$	30	51	45	93	96	108
2	*rac*-**2b**	*n*-C_5H_{11}	$^iPr_2O$	30	52	47	93	99	145
3	*rac*-**2c**	*n*-C_6H_{13}	$^iPr_2O$	27	51	45	92	95	89
4	*rac*-**2d**	*n*-C_7H_{15}	$^iPr_2O$	24	51	47	94	>99	243
5	*rac*-**2e**	*n*-C_8H_{17}	Et_2O	36	44	51	90	>99	141
6		*n*-C_8H_{17}	$^iPr_2O$	24	51	47	95	>99	294
7	*rac*-**2f**	*cis*-3-C_6H_{11}	$^iPr_2O$	24	47	50	>99	>99	>500

[a]Substrate: 1.0 mmol, MeOH: 3.0 mmol, Novozym 435: 0.4 g, Pr_2O: 20 ml, 60 °C.
[b]Determined by GC using Chirasil-Dex CB column.
[c]$E = \ln[1 - c\ (1 + ee_p)]/\ln[1 - c\ (1 - ee_p)]$, where $c = ee_s/(ee_s + ee_p)$, ee_s = enantiomeric excess of (*R*)-**1**, ee_p = enantiomeric excess of (*S*)-**1**.

all substrates (*rac*-**2**), and the results are shown in Table 1. (*S*)-**1** and (*R*)-**1** were synthesized with >95% ee and >92% ee, respectively. The E-value exceeded 100 in all substrates except *rac*-**2c**, but (*R*)-**1c** and (*S*)-**1c** had good optical purity, showing that Novozym 435 had excellent substrate selectivity. The short side-chain substrates required longer reaction time to reach 50% conversion than the long side-chain substrates. Moreover, the enantiomeric excess of long side-chain γ-lactones was greater than that of short side-chain γ-lactones. Therefore, the substrate specificity of Novozym 435 to long side-chain substrate was greater than that to short side-chain substrates. The subsequent Mitsunobu reaction was performed with a reaction mixture that was obtained under these conditions.

Combination of Novozym 435–Catalyzed Hydrolysis and Mitsunobu Reaction

The Mitsunobu reaction was performed with the mixture of (*R*)-*N*-benzyl-4-acetoxyalkylamides [(*R*)-**2**] and (*S*)-*N*-benzyl-4-hydroxyalkylamides [(*S*)-**3**], which was prepared from *rac*-*N*-benzyl-4-acetoxyalkylamides (*rac*-**2**) by Novozym 435–catalyzed hydrolysis. The optimum Mitsunobu conditions for the mixture of **2** and



Scheme 2. Synthesis of (*R*)-**1** with Novozym 435–catalyzed hydrolysis and Mitsunobu reaction.

Table 2. Synthesis of (*R*)-**1** by Novozym 435–catalyzed hydrolysis[a] and Mitsunobu reaction[b]

Entry	Substrate	R	Nucleophilic agent	Solvent	Time (h)	Yield (%)[c] of (*R*)-**1**	Enantiomeric excess (% e.e.)[c] of (*R*)-**1**
1	*rac*-**2a**	*n*-C_4H_9	4-Nitrobenzoic acid	Benzene	24	77	89
2			3,5-dimethoxybenzoic acid	THF	24	82	92
3	*rac*-**2b**	*n*-C_5H_{11}	4-Nitrobenzoic acid	Benzene	24	91	89
4			3,5-Dimethoxybenzoic acid	THF	24	92	92
5	*rac*-**2c**	*n*-C_6H_{13}				92	92
6	*rac*-**2d**	*n*-C_7H_{15}	4-Nitrobenzoic acid	Benzene	48	98	92
7	*rac*-**2e**	*n*-C_8H_{17}				92	96
8	*rac*-**2f**	*cis*-3-C_6H_{11}				90	>99

[a]Substrate: 1.0 mmol, MeOH: 3.0 mmol, Novozym 435: 0.4 g, $^iPr_2O$: 20 ml, 60 °C.
[b]Nucleophile: 1.0 mmol, PPh_3: 1.0 mmol, DIAD: 1.0 mmol, solvent: 5 ml, rt.
[c]Total yield based on *rac*-**2**.
[d]Determined by GC using Chirasil-Dex CB column.

3 were evaluated previously, and the conditions were the use of 4-nitrobenzoic acid as the nucleophilic agent and benzene as the solvent.[7] The conditions were also applied to the synthesis of (*R*)-γ-lactones [(*R*)-**1**] (Scheme 2). The results are shown in Table 2. The yield of (*R*)-**1** was calculated from *rac*-**2**. (*R*)-**1a** was synthesized with a somewhat lesser yield of 77% (Table 2, entry 1), but all other (*R*)-**1b**–**f** were synthesized with more than 90% yield (Table 2, entries 3 and 5–8). The optical purities of (*R*)-**1a** and (*R*)-**1b** were 89% ee (Table 2, entries 1 and 3), but all other (*R*)-**1c**–**f** optical purities were more than 99% ee (Table 2, entries 5–8). The optical purities of all (*R*)-**1** except (*R*)-**1f** produced via the Mitsunobu reaction were about 2% less than that of the average of both enantiomers of (*S*)-**1** and (*R*)-**1** in Table 1. According to the results of thin-layer chromatography (TLC), (*S*)-**3** was completely reactive. It was thought that the optical purity was decreased because the estefirication of (*S*)-**3** and 4-nitrobenzoic acid, which acted as the carboxylic acid reagent and acid catalyst, respectively, did not accompany the progression of steric inversion. (*R*)-**1a** and (*R*)-**1b** may have low optical purities because this degree was somewhat more than the other (*R*)-**1**. The Mitsunobu reaction was performed to improve the optical purities of (*R*)-**1a** and (*R*)-**1b** under the Mitsunobu conditions that provided the best optical purity using 3,5-dimethoxybenzoic acid as the nucleophilic agent and tetrahydrofuran (THF) as the solvent, under conditions that were reported previously.[7] As a result, the optical purity was increased to 92% ee, which was 3% more than the use of 4-nitrobenzoic acid and benzene, although there was no big difference in yield (Table 2, entries 2 and 4). In conclusion, (*R*)-**1** was synthesized with more than 80% yield and 90% ee with a combination of Novozym 435–catalyzed hydrolysis and the Mitsunobu reaction.

CONCLUSION

Chiral γ-lactones of both enantiomers were synthesized with Novozym 435–catalyzed hydrolysis. (*S*)- and (*R*)-enantiomers were synthesized with more than 95% and 90% optically purities, respectively. Novozym 435–catalyzed hydrolysis

of racemic *N*-benzyl-4-acetoxyalkylamides was performed efficiently with diidopropyl ether as the solvent at 60 °C within 36 h. Additionally, (*R*)-γ-lactones were synthesized successfully in the range of 82 to 98% total yield and 92 to >99% optical purities by a combination of Novozym 435–catalyzed hydrolysis and the Mitsunobu reaction. The Mitsunobu reaction for synthesis of (*R*)-nona- and -decalactone was performed efficiently by the use of 3,5-dimethoxybenzoic acid as the nucleophilic agent and tetrahydrofuran (THF) as the solvent, and the Mitsunobu reaction for the synthesis of (*R*)-undeca-, (*R*)-dodeca-, and (*R*)-jasmolactone was performed efficiently with the use of 4-nitrobenzoic acid and benzene.

EXPERIMENTAL

General

TLC was performed using silica gel F-254 on aluminum purchased from Merck Ltd. (Darmstadt, Germany). Crude products were purified by column chromatography on silica gel FL60D purchased from Fuji Silysia Chemical Ltd. (Aichi, Japan). Melting points (mp) were determined using a MP-500D micro-melting-point apparatus from Yanaco Technical Science Co., Ltd. (Kyoto, Japan) and were uncorrected. Infrared (IR) spectra were recorded on a Fourier transform (FT)–IR-460-plus spectrometer from Jasco Corporation (Tokyo, Japan). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a 500-MHz FT-NMR spectrometer (Jeol JNM-ECA 500 system). Chemical sifts are reported in parts per million with respect to the internal tetramethylsilane (TMS). Coupling constants (*J*) are quoted in hertz. High-resolution mass spectral (HRMS) analyses were measured on a Mariner Biospectrometry Workstation (PerSeptive Biosystems, Framingham, MA, USA). The enantiomeric excesses were determined using a Shimadzu GC-18A gas chromatograph equipped with the chiral capillary column Chirasil-Dex CB (25 m × 0.25 mm I.D. × 0.25 μm film thickness, Varian, Walnut Creek, CA, USA). The carrier gas was helium. γ-Octalactone, γ-nonalactone, γ-decalactone, γ-undecalactone, γ-dodecalactone, 4-nitrobenzoic acid, and 3,5-dimethoxybenzoic acid were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). *Cis*-3-hexanol was purchased from Soda Aromatic Co., Ltd. (Tokyo, Japan). Succinic anhydride and triphenylphosphine (TPP) were purchased from Nacalai Tesque Inc. (Kyoto, Japan). Diisopropyl azodicarboxylate (95%, d 1.0127) (DIAD) was purchased from Sigma-Aldrich Corp. (St. Louis, MO, USA). Novozym 435 (immobilized lipase from *Candida antarctica*) was a gift from Novozymes A/S (Paraná, Brazil). All other materials were commercially obtained. Diethyl ether, THF, and benzene were dried before used.

Preparation of *rac-N*-Benzyl-4-acetoxyalkylamides (*rac*-2a–f)

Rac-*N*-Benzyl-4-acetoxyalkylamides (*rac*-**2a**–**f**) were prepared by adding acetic anhydride (0.82 g, 8.0 mmol) and 4-dimethylaminopyridine (0.10 g, 0.8 mmol) to a stirred solution of *rac*-*N*-benzyl-4-hydroxyalkylamides (4.0 mmol) in CH_2Cl_2 (25 ml) and stirring the mixture for 24 h. CH_2Cl_2 was evaporated, and the mixture was extracted with AcOEt. The combined extracts were washed with brine and dried

over Na_2SO_4. After filtration, AcOEt was evaporated to afford *rac*-*N*-benzyl-4-acetoxyalkylamides (*rac*-**2a**–**f**). The yields of *rac*-*N*-benzyl-4-acetoxyalkylamides except *rac*-**2f** were more than 99%, and the *rac*-**2f** yield was 95%. The spectra data were reported previously.[4,7] The preparation of *rac*-*N*-benzyl-4-hydroxyalkylamides was previously reported.[4]

General Procedure for Novozym 435–Catalyzed Hydrolysis

Novozym 435 (0.4 g) was added to a solution of the appropriate *rac*-**2a**–**f** (1.0 mmol) and MeOH (0.10 g, 3.0 mmol) in diisopropyl ether (20 ml), while stirring at 60 °C in a water bath. After stirring, the mixture was filtered, and the solvent was evaporated. The crude product was purified by flash chromatography on silica and AcOEt to afford the corresponding (*R*)-*N*-benzyl-4-acetoxyalkylamides [(*R*)-**2a**–**f**] and (*S*)-*N*-benzyl-4-hydroxyalkylamides [(*S*)-**3a**–**f**]. Lactonization of both amides [(*R*)-**2a**–**f** and (*S*)-**3a**–**f**] was performed by hydrolysis under alkaline conditions and subsequent intraesterification under acidic conditions. The spectra data of **3a**–**d** and **1a**–**f** were reported previously.[4,5]

General Procedure for Synthesis of (*R*)-γ-Lactones with a Combination of Novozym 435–Catalyzed Hydrolysis and Mitsunobu Reaction

Triphenylphosphine (TPP) (0.26 g, 1.0 mmol), a nucleophilic agent (1.0 mmol), and DIAD (0.21 ml, 1.0 ml) were added to a solution of a crude mixture of (*R*)-**2a**–**f** and (*S*)-**3a**–**f**, which had been obtained by Novozym 435–catalyzed hydrolysis in THF or benzene (5 ml) and stirred at room temperature. The benzene was removed under reduced pressure, H_2O was added, and the mixture was neutralized with Na_2CO_3. The aqueous phases were extracted with EtOAc (3×30 ml). The combined organic phases were washed with brine and dried over Na_2SO_4, then concentrated under reduced pressure. The crude products were subjected to lactonization without purification. The spectral data of **5a**–**f** and (*R*)-**1a**–**f** were reported previously.[4,5]

Data for *N*-Benzyl-4-(3,5-dimethoxybenzoyl)oxyoctanamide [(*R*)-4a]

Colorless oil; R_f 0.34 (eluent: *n*-hexane–AcOEt, 3:2, *v*/*v*). IR (NaCl): cm^{-1} 3297 (−N−H), 3087, 3066, 3003 (Ar, −C−H), 2956 ($-CH_3$), 2934 ($-CH_2-$), 2871 ($-CH_3$), 2862 ($-CH_2-$), 1714 (−C=O), 1648 (−C(=O)−N−H), 1598, 1496, 1456 (Ar, −C=C−), 1235, 1050 (−C−O−C−). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.9$ Hz, 3H, CH_3), 1.34 (m, 4H, $CH_2 \times 2$), 1.63 (m · m, 2H, CH_2), 2.06 (m, 2H, CH_2), 2.27 (m, 2H, CH_2), 3.83 (s, 6H, $OCH_3 \times 2$), 4.38 (qd, $J = 14.9$, 5.7 Hz, 2H, CH_2), 5.15 (m, 1H, CH), 5.95 (br, 1H, NH), 6.65 (t, $J = 2.3$ Hz, 1H, CH), 7.18 (d, $J = 2.3$ Hz, 2H, $CH \times 2$), 7.25 (m, 3H, $CH \times 3$), 7.32 (m, 2H, $CH \times 2$). ^{13}C NMR (126 MHz, $CDCl_3$): δ 13.9 (CH_3), 22.5 (CH_2), 27.4 (CH_2), 30.3 (CH_2), 32.8 (CH_2), 34.2 (CH_2), 43.6 (Ar-CH_2), 55.6 ($OCH_3 \times 2$), 74.7 (CH), 105.4 (Ar), 107.3 (Ar), 127.4 (Ar), 127.8 (Ar), 128.6 (Ar), 132.2 (Ar), 138.2 (Ar), 160.6 (Ar), 166.4 (C=O), 172.0 (C=O). HRMS (ESI) calcd. for $C_{24}H_{32}NO_5$ $(M + H)^+$, 414.2280; found $(M + H)^+$, 414.2287.

Data for *N*-Benzyl-4-(3,5-dimethoxybenzoyl)oxynonanamide [(*R*)-4b]

Colorless oil; R_f 0.39 (eluent: *n*-hexane–AcOEt, 3:2, *v*/*v*). IR (NaCl): cm^{-1} 3297 (N-H), 3087, 3065, 3003 (Ar, –C–H), 2955 (–CH_3), 2932, 2859 (–CH_2–), 1715 (–C=O), 1648 (–C(=O)–N–H), 1597, 1496, 1456 (Ar, –C=C–), 1236, 1051 (–C–O–C–). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (t, $J = 6.9$ Hz, 3H, CH_3), 1.34 (m, 6H, $CH_2 \times 3$), 1.63 (m · m, 2H, CH_2), 2.06 (m, 2H, CH_2), 2.27 (m, 2H, CH_2), 3.83 (s, 6H, $OCH_3 \times 2$), 4.38 (qd, $J = 14.9$, 5.7 Hz, 2H, CH_2), 5.15 (m, 1H, CH), 5.98 (br, 1H, NH), 6.64 (t, $J = 2.3$ Hz, 1H, CH), 7.17 (d, $J = 2.3$ Hz, 2H, $CH \times 2$), 7.25 (m, 3H, $CH \times 2$), 7.31 (m, 2H, $CH \times 2$). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.5 (CH_2), 24.9 (CH_2), 30.3 (CH_2), 31.6 (CH_2), 32.7 (CH_2), 34.5 (CH_2), 43.6 (Ar-CH_2), 55.6 ($OCH_3 \times 2$), 74.7 (CH), 105.4 (Ar), 107.2 (Ar), 127.4 (Ar), 127.8 (Ar), 128.6 (Ar), 132.2 (Ar), 138.2 (Ar), 160.6 (Ar), 166.3 (C=O), 172.0 (C=O). HRMS (ESI) calcd. for $C_{25}H_{34}NO_5$ $(M + H)^+$, 428.2437; found $(M + H)^+$, 428.2447.

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