

HETEROCYCLES, Vol. 95, No. 1, 2017, pp. 370-379. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 9th August, 2016, Accepted, 30th September, 2016, Published online, 31st October, 2016
DOI: 10.3987/COM-16-S(S)28

PREPARATION OF (*R*)-3-HYDROXY-*N*-METHYLPYPERIDINE, A SYNTHETIC KEY INTERMEDIATE OF (*R*)-MEPENZOLATE, BASED ON THE LIPASE-CATALYZED RESOLUTION OF THE RACEMIC FORM

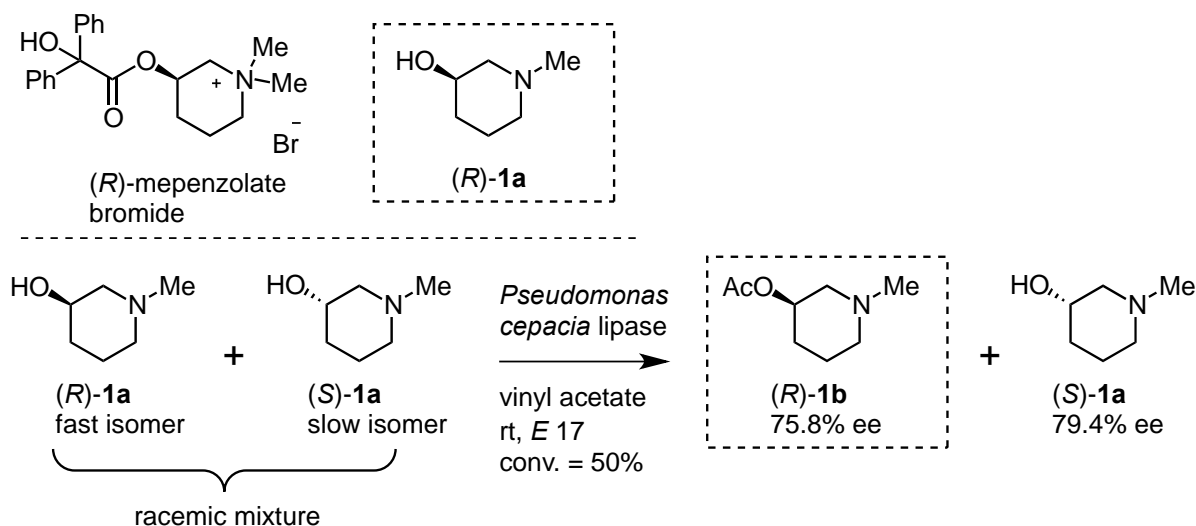
Yasunobu Yamashita, Kengo Hanaya, Mitsuru Shoji, and Takeshi Sugai*

Department of Pharmaceutical Sciences, Keio University, 1-5-30 Shibakoen, Minato-ku, Tokyo 105-8512, Japan; E-mail: sugai-tk@pha.keio.ac.jp

Abstract – In this study, a two-step method for the gram-scale synthesis of (*R*)-3-hydroxy-*N*-methylpiperidine in 97.8% enantiomeric excess (ee) is reported. The key chiral synthetic intermediate of (*R*)-mepenzolate was formed in 22% yield over two steps using a commercially available and inexpensive racemic alcohol as the starting material. In the first step, *Candida antarctica* lipase B-catalyzed kinetic resolution of the racemic alcohol under acetylation conditions was performed to obtain the acetate form of the (*R*)-enantiomer in 82.1% ee (*E* 18). The second step involved enantio-enrichment using the same lipase to catalyze deacetylation. The ee of the product (*R*)-alcohol was further enriched to 97.8%.

INTRODUCTION

Mepenzolate bromide, which is currently used to treat irritable bowel syndrome, has been shown to possess both anticholinergic and anti-inflammatory properties, and potential therapeutic use in the treatment for chronic obstructive pulmonary disease (COPD) is expected.¹ Recently, it has been found that (*R*)-mepenzolate bromide has a higher affinity for the muscarinic M3 receptor compared to the (*S*)-enantiomer and that the bronchodilatory activity of the (*R*)-enantiomer *in vivo* is superior to that of the (*S*)-enantiomer.² The key chiral intermediate is (*R*)-3-hydroxy-*N*-methylpiperidine (**1a**, Scheme 1). However, the enantiomerically enriched form of **1a** is very expensive [PharmaBlock Sciences (Nanjing), Inc.: 1 g = \$252 in 2016]. Our goal was to achieve gram-scale production using the lipase-catalyzed resolution of the racemic form of **1a** (Tokyo Chemical Industry Co., Ltd.: 1 g = *ca.* \$3.2 in 2016).

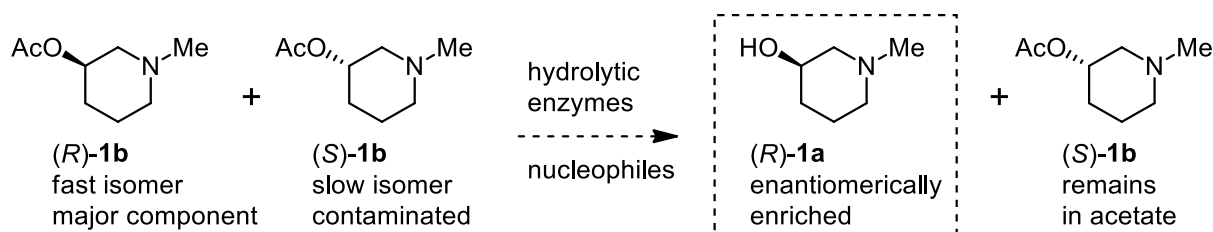


Scheme 1. Mepenzolate bromide and the lipase-catalyzed kinetic resolution of the precursor **1a**

RESULTS AND DISCUSSION

Pseudomonas cepacia lipase-catalyzed kinetic resolution of (\pm)-**1a** under acylation conditions have been previously reported.³ The (*R*)-enantiomer reacted faster than (*S*)-isomer to predominantly give (*R*)-acetate **1b**. The enantiomeric ratio⁴ was moderate (*E* 17), and (*R*)-**1b** was obtained in 75.8% ee at 50% conversion (Scheme 1). First, we re-examined this reaction by applying four different types of lipases. In our experiment, *Candida rugosa* lipase (Meito OF, *E* 2) and *Pseudomonas stutzeri* lipase (Meito TL, *E* 7) had low enantioselectivities; moreover, *Candida antarctica* lipase B (Novozym 435, *E* 15) and *Burkholderia cepacia* lipase (Amano PS-IM, *E* 15) were comparable biocatalysts.

To obtain highly enantiomerically pure (*R*)-isomer as alcohol, a lipase that possesses (*R*)-selectivity in deacetylation is desirable (Scheme 2). According to simulation studies, beginning from (*R*)-**1b** in 75.8% ee (Scheme 1), deacetylation with an *E* of 17 and 50% conversion will give an (*R*)-**1a** in *ca.* 97.7% ee and 50% conversion.⁴

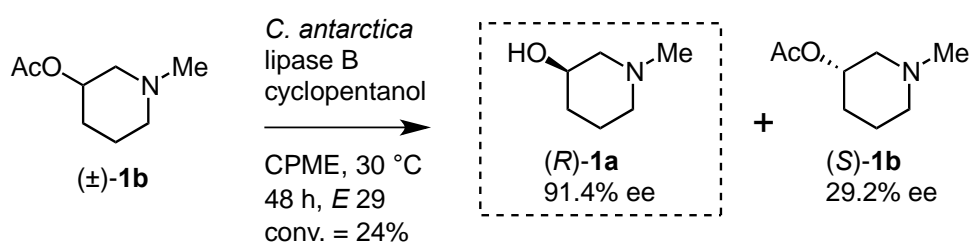


Scheme 2. Enrichment of (*R*)-enantiomer in **1a** by enzyme-catalyzed deacetylation with (*R*)-preference

However, experimental results reported using lipase-catalyzed acylation have been discouraging.³ The enzyme-catalyzed hydrolysis of acetate (\pm)-**1b** in buffer solution was not observed even after the

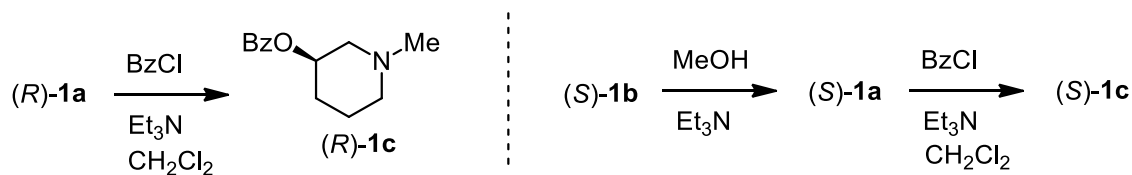
screening of several hydrolytic enzymes.³ We re-examined this transformation, applying abovementioned four kinds of lipases (Amano PS-IM, Novozym 435, Meito OF, and Meito TL). After 24 h of incubation at 30 °C, in every case, the conversion was less than 1%, judged by each ¹H NMR spectrum. We hypothesized that the low conversion was likely related to the buffer conditions employed in the lipase-catalyzed hydrolysis of **1b**, probably owing to protonation of the tertiary amine of its substrate. In contrast, in a non-buffered aqueous environment, the tertiary amine moiety of this substrate may act as a base in the hydrolysis reaction. The hydrolysis proceeded substantially, when phosphate buffer ingredient was removed from the reaction mixture (conv. = 17%), even in the absence of lipase.

In this study, we explore the transesterification reaction under non-aqueous deacetylation conditions using the abovementioned for kinds of lipases, with 2-propanol as the nucleophile and tetrahydrofuran (THF) as the solvent.⁵ High reactivity is required, which overcomes non-enzymatic deacetylation caused by the implicit basicity suggested in aqueous media. According to the ¹H NMR spectra, a conversion of less than 1% using Amano PS-IM, Meito OF, and Meito TL and a reasonable conversion of 7% using Novozym 435 was observed. In order to improve the reactivity, nucleophile was changed from 2-propanol to cyclopentanol which has enhanced reactivity.⁶ Moreover, the solvent was changed from THF to cyclopentyl methyl ether (CPME).⁷ Recently, we have reported that the resin in Novozyme 435, upon which the lipase is immobilized, would swell when immersed in CPME, effectively increasing the concentration of the enzyme.^{8,9} The combined use of cyclopentanol and CPME enhanced the conversion to 24%, as was expected (Scheme 3).



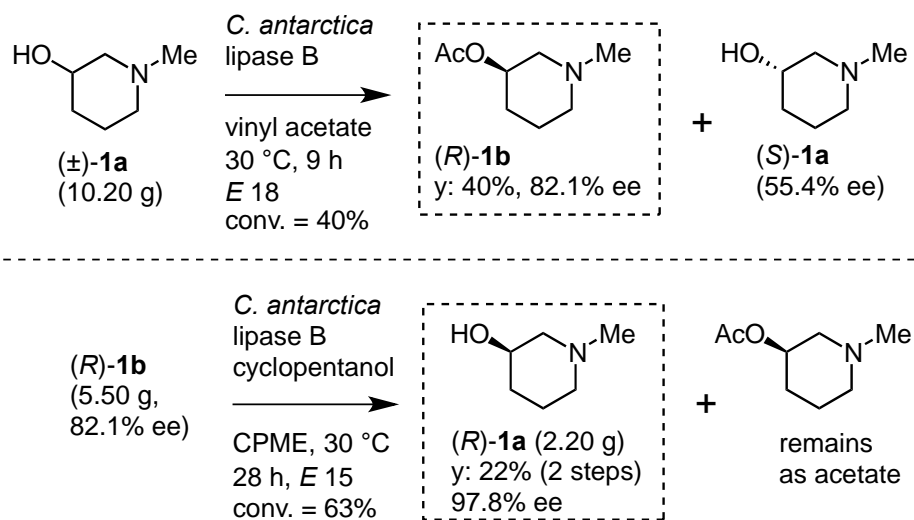
Scheme 3. Lipase-catalyzed deacetylation of (±)-**1b** under transesterification conditions

Enantiomeric excesses of (*R*)-**1a** and (*S*)-**1b** were analyzed by HPLC with chiral stationary phase, after derivatization to the corresponding benzoate **1c** (Scheme 4). Ee values of the product (*R*)-**1a** and that of unreacted recovery (*S*)-**1b** were 91.4% and 29.2%, respectively, indicating an *E* of 29. Fortunately, the abovementioned non-enzymatic side-reaction was not observed under the conditions used in this study.



Scheme 4. Derivatization of the products **1a** and **1b** to **1c**, for the analysis of their enantiomeric excess by HPLC

Based on the above results, we attempted the tandem use of Novozym 435 in the acetylation of (\pm)-**1a** and the deacetylation of partially enriched (*R*)-**1b**. This sequence could be performed on the gram-scale (Scheme 5). Alcohol (\pm)-**1a** (10.20 g) was treated with *C. antarctica* lipase B (1.00 g) in freshly distilled vinyl acetate (100 mL) to give 82.1% ee of (*R*)-**1b** in 40% yield (*E* 18). In this case, acetaldehyde, an unwanted byproduct of the lipase-catalyzed reaction, derived from vinyl acetate, was continuously removed under a slow purge of nitrogen gas.¹⁰ As a result, the extent of *E* under these conditions was higher than that in the small scale reaction with a closed vessel. The next step was deacetylation catalyzed by the same lipase. Beginning from 5.50 g of (*R*)-**1b**, further enantiomerically enriched (*R*)-**1a** (2.20 g, 97.8% ee) was obtained at 63% conversion. The extent of *E* was inversely related to the conversion [29 at 24% conv. (Scheme 3); 15 at 63% conv. (Scheme 5)]. This apparent decrease in *E* suggests that the high nucleophilicity of **1a** toward the acyl-enzyme complex slows down the enzyme-catalyzed transesterification from **1b** to **1a**.¹¹



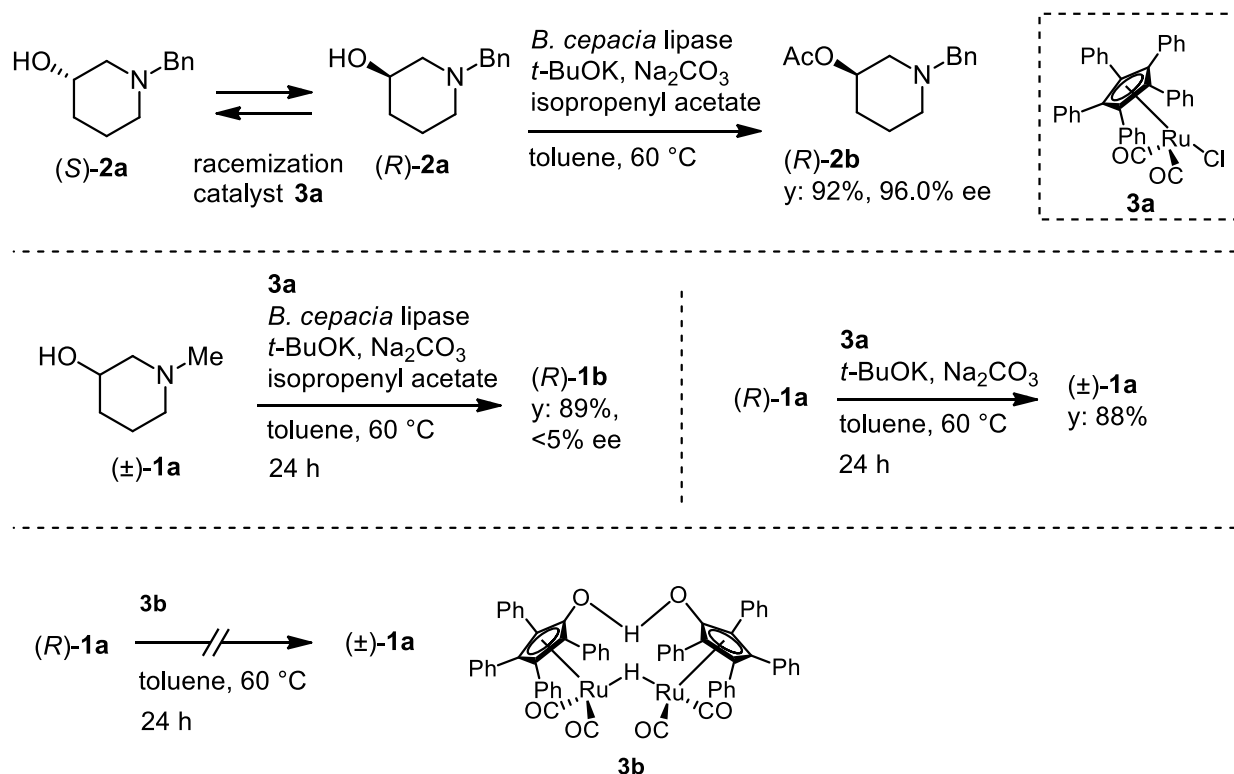
Scheme 5. Preparation of (*R*)-**1a** by the tandem use of lipase-catalyzed enantioselective acetylation and deacetylation

In the abovementioned transformations, the undesired enantiomer, (*S*)-**1a**, in the starting material was wasted. In order to overcome this disadvantage, deracemization¹² and *ex situ* enantioconvergent approaches¹³ were applied. Dynamic kinetic resolution (DKR), a combination of a kinetic resolution

and a racemization of the substrate within a single reaction vessel, is a very important tool for the enantioconvergence of the undesired enantiomer in a racemic mixture to the desired enantiomer.¹²

Bäckvall and co-workers reported the enantioconvergence of *N*-benzylated substrate **2a**, whose structure is similar to **1a**, using a ruthenium-based racemization catalyst **3a** (Scheme 6).¹⁴ They successfully used DKR with **3a** to obtain a 91% yield of (*R*)-**2b** in 96% ee. Another ruthenium-centered racemization catalyst **3b** was also examined.

DKR of the *N*-methylated (\pm)-**1a** with **3a** was attempted; however, the ee of acetylated form **1b** was about 0%. An independent experiment was conducted without lipase and an acylating agent. The racemization of enantiomerically enriched **1a** with the same catalyst was found to recover racemic **1a** in 88% yield. From these results, we suspected that non-enzymatic acylation occurred under the strong basic conditions of the DKR. Therefore, we examined another ruthenium-based racemization catalyst, **3b**, under neutral conditions. To our disappointment, racemization of **1a** was not observed. It seems that the *N*-methyl derivative **1a** is not compatible with Bäckvall's DKR.



Scheme 6. Lipase-catalyzed deracemization of (\pm)-**2a** under transesterification conditions, the attempts for dynamic kinetic resolution of (\pm)-**1a**, and the racemization of (*R*)-**1a**

Alternatively, we attempted *ex situ* recycling of the undesired isomer by way of oxidation of the recovered (*S*)-**1a** and the subsequent reduction of the resultant ketone. As the ketone was highly hydrophilic and difficult to extract into an organic phase, oxidation conditions where the workup was

only filtration were chosen. Even with the application of such conditions (PCC, AZADO, AZADO/copper¹⁵ oxidation), the maximum yield was as low as 9%.

The starting material (\pm)-**1a** is commercially available and inexpensive, but the cost of **3a** is very high even under catalytic conditions (2.5 mol%). From this perspective, we did not persist in further exploration of different reactions and conditions for the reuse of (*S*)-**1a** involved in an inexpensive racemic form.

In conclusion, **1a**, the key chiral synthetic intermediate of (*R*)-mepenzolate bromide, was conveniently prepared from an inexpensive racemic form. Tandem use of *C. antarctica* lipase B-catalyzed enantioselective acetylation and deacetylation resulted in gram-scale yields in 97.8% ee of (*R*)-**1a** and a 22% yield over two steps. The results presented in this study indicate that secondary alcohol transesterification conditions are only effective in the lipase-catalyzed deacetylation of substrates containing an amine moiety. The removal of acetyl group in this particular substrate had been impossible under hydrolytic conditions.

EXPERIMENTAL

¹H NMR spectra were measured at 500 MHz and ¹³C NMR spectra were measured at 125 MHz on an Agilent INOVA-500 spectrometer. IR spectra were measured as ATR on a Jeol FT-IR SPX60 spectrometer. High resolution mass spectra were recorded on Jeol JMS-T100LP AccuTOF. Optical rotation value was recorded on a Jasco P-1010 polarimeter. Silica Gel 60 (spherical and neutral; 100-210 μ m, 37560-79) from Kanto Chemical Co. was used for column chromatography. *C. rugosa* lipase (Meito OF) and *P. stutzeri* lipase (Meito TL) are gift from Meito Sangyo Co. Ltd. CHCl₃/MeOH solvent system was used to avoid irreversible adsorption for chromatographic isolation, because compounds have high affinity to silica gel.

(\pm)-3-Acetoxy-*N*-methylpiperidine (**1b**)

To a solution of alcohol (\pm)-**1a** (2.00 g, 17 mmol) in acetic anhydride (5 mL) and pyridine (10 mL) was added 4-dimethylaminopyridine (207 mg), and the mixture was stirred for 24 h at room temperature. The reaction mixture was quenched with NaHCO₃ aq. solution and extracted with AcOEt three times. The combined organic phase was washed with brine and dried over anhydrous Na₂SO₄, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (50 g). Elution with CHCl₃/MeOH (10:1) afforded (\pm)-**1b** as colorless oil (2.00 g, 76%).

IR cm⁻¹: 3344, 2944, 2832, 1448, 1253, 1112, 1024; ¹H-NMR (500 MHz, CDCl₃) δ : 1.45-1.52 (1H, m), 1.55-1.61 (1H, m), 1.70-1.82 (2H, m), 2.04 (3H, s), 2.26 (3H, s), 2.30-2.40 (3H, m), 2.55-2.61 (1H, m), 4.84-4.90 (1H, m); ¹³C-NMR (125 MHz, CDCl₃) δ : 21.4, 22.2, 28.4, 46.3, 55.3, 58.9, 69.1, 170.6;

HR-MS (ESI+) Calcd for C₈H₁₆NO₂ [M+H]⁺ 158.1181, Found 158.1175.

(±)-3-Benzoyloxy-N-methylpiperidine (**1c**)

To a solution of alcohol (±)-**1a** (193 mg, 1.68 mmol) in CH₂Cl₂ (20 mL) were added triethylamine (1.2 mL, 8.4 mmol) and benzoyl chloride (750 μL, 6.50 mmol) and the mixture was stirred for 3 h at room temperature. The reaction mixture was quenched with NaHCO₃ aq. solution and extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na₂SO₄, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (5 g). Elution with CHCl₃/MeOH (15:1) afforded (±)-**1c** as colorless oil (352 mg, 96%).

IR cm⁻¹: 2944, 2782, 1716, 1448, 1261, 1105; ¹H-NMR (500 MHz, CDCl₃) δ: 1.58-1.64 (1H, m), 1.70-1.79 (1H, m), 1.90-2.01 (2H, m), 2.37-2.42 (1H, m), 2.43 (3H, s), 2.43-2.59 (1H, m), 2.60-2.69 (1H, m), 2.90-2.98 (1H, m), 5.17-5.21 (1H, m), 7.42 (2H, dd, *J* = 7.6, 7.5), 7.53 (1H, t, *J* = 7.5), 8.08 (2H, d, *J* = 7.6); ¹³C-NMR (125 MHz, CDCl₃) δ: 22.6, 28.9, 46.2, 55.2, 59.1, 69.9, 128.2, 129.5, 130.4, 132.7, 165.8; HR-MS (ESI+) Calcd for C₁₃H₁₈NO₂ [M+H]⁺ 220.1338, Found 220.1345.

C. antarctica lipase B-catalyzed transesterification of (±)-**1b**

To a solution of acetate (±)-**1b** (10 mg, 67 μmol) in a mixture of cyclopentanol (0.20 mL) and CPME (0.40 mL), was added *C. antarctica* lipase B (Novozym 435, 10 mg), and the mixture was stirred for 48 h at 30 °C. After removal of insoluble materials by filtration with a Celite pad, the filtrate and washings were concentrated *in vacuo*. The conversion (24%) was calculated by ¹H NMR analysis, by the comparison of the area of signals δ 3.73 for **1a** and 4.80 for **1b**. The residue was purified by silica gel column chromatography (1 g). Gradient elution with CHCl₃/MeOH (3:1 – 1:3) afforded (*R*)-**1a** (2 mg, 24%) and (*S*)-**1b** (8 mg, 73%), respectively.

In a similar manner as described for the benzylation of (±)-**1a**, (*R*)-**1a** was benzyloxy to give (*R*)-**1c**. HPLC [Daicel Chiralcel ID-3, 0.46 cm × 25 cm; hexane/*i*-PrOH/diethylamine (90:10:0.1), 0.5 mL/min; detected at 280 nm], tR (min) = 12.3 [(*R*)-**1c**, 95.7%], 14.4 [(*S*)-**1c**, 4.3%].

To a solution of acetate (*S*)-**1b** (8 mg, 48 μmol) in MeOH (0.40 mL) was added triethylamine (26 μL, 0.19 mmol), and the mixture was stirred for 48 h under reflux. The reaction mixture was concentrated *in vacuo* to give (*S*)-**1a** (6 mg). This was employed for the next step without further purification. In a similar manner as described for the benzylation of (±)-**1a**, (*S*)-**1a** was benzyloxy to give (*S*)-**1c**. HPLC analysis was performed with Daicel Chiralcel ID-3 under the same conditions as above, tR (min) = 12.3 [(*R*)-**1c**, 35.4%], 14.4 [(*S*)-**1c**, 64.6%]. *E* value was calculated by ee(*S*) for (*S*)-**1c** derived from (*S*)-**1b** and ee(*P*) for (*R*)-**1c** derived from (*R*)-**1a**.

***B. cepacia* lipase-catalyzed acetylation of (±)-1a**

To a solution of alcohol (±)-**1a** (100 mg, 0.87 mmol) in vinyl acetate (10 mL) was added *B. cepacia* lipase (Amano PS-IM, 100 mg), and the mixture was stirred for 24 h at 30 °C. After similar workup as described for *C. antarctica* lipase-catalyzed transesterification, the conversion (47%) was calculated by ¹H NMR analysis of the crude product as above. The residue was purified by silica gel column chromatography (2 g). Gradient elution with CHCl₃/MeOH (3:1 – 1:3) afforded (*S*)-**1a** (35 mg, 35%) and (*R*)-**1b** (50 mg, 37%), respectively.

In a similar manner as described for the benzylation of (±)-**1a**, (*S*)-**1a** was benzyolated to give (*S*)-**1c**. HPLC analysis: tR (min) = 12.3 (6.8%), 14.4 (93.2%).

In a similar manner as described for the deacetylation of (*S*)-**1b** and following benzyolation in *C. antarctica* lipase B-catalyzed transesterification of (±)-**1b**, (*R*)-**1b** was transformed to (*R*)-**1c**. HPLC analysis: tR (min) = 12.3 (84.5%), 14.4 (15.5%).

***C. antarctica* lipase B-catalyzed acetylation of (±)-1a**

In a similar manner to above-mentioned lipase-catalyzed acetylation, alcohol **1a** (100 mg, 0.87 mmol) was treated with *C. antarctica* lipase B (100 mg) for 24 h, and the conversion reached 53%. (*S*)-**1a** (40 mg, 40%) and (*R*)-**1b** (58 mg, 43%) were obtained. (*S*)-**1a** was transformed to (*S*)-**1c**. HPLC analysis: tR (min) = 12.3 (5.4%), 14.4 (94.6%). (*R*)-**1b** was transformed to (*R*)-**1c**. HPLC analysis: tR (min) = 12.3 (83.5%), 14.4 (16.5%).

***C. rugosa* lipase-catalyzed acetylation of (±)-1a**

In a similar manner to above-mentioned lipase-catalyzed acetylation, alcohol **1a** (100 mg, 0.87 mmol) was treated with *C. rugosa* lipase (100 mg) for 24 h, and the conversion reached 47%. (*S*)-**1a** (38 mg, 38%) and (*R*)-**1b** (42 mg, 31%) were obtained. HPLC analysis of (*S*)-**1c**: tR (min) = 12.3 (46.6%), 14.4 (53.4%). HPLC analysis of (*R*)-**1c**: tR (min) = 12.3 (58.6%), 14.4 (41.4%).

***P. stutzeri* lipase-catalyzed acetylation of (±)-1a**

In a similar manner to above-mentioned lipase-catalyzed acetylation, alcohol **1a** (100 mg, 0.87 mmol) was treated with *P. stutzeri* lipase (100 mg) for 1 h, and the conversion reached 66%. (*S*)-**1a** (28 mg, 28%) and (*R*)-**1b** (48 mg, 36%) were obtained. HPLC analysis of (*S*)-**1c**: tR (min) = 12.3 (6.6%), 14.4 (93.4%). HPLC analysis (*R*)-**1c**: tR (min) = 12.3 (72.2%), 14.4 (27.8%).

Tandem use of *C. antarctica* lipase B-catalyzed enantioselective acetylation and deacetylation under scaled-up conditions

In a similar manner to above-mentioned lipase-catalyzed acetylation under a slow purge with nitrogen gas, alcohol **1a** (10.20 g, 88.6 mmol) was treated with *C. antarctica* lipase B (1.00 g) in vinyl acetate (100 mL) for 9 h, and the conversion reached 40%. (*S*)-**1a** (3.70 g, 37%) and (*R*)-**1b** (5.50 g, 40%) were obtained. HPLC analysis of (*S*)-**1c**: tR (min) = 12.3 (22.3%), 14.4 (77.7%). HPLC analysis of (*R*)-**1c**: tR (min) = 12.3 (91.0%), 14.4 (9.0%).

In a similar manner to above-mentioned lipase-catalyzed deacetylation, acetate **1b** (5.50 g, 35 mmol) was treated with *C. antarctica* lipase B (5.50 g) in a mixture of cyclopentanol (20 mL) and CPME (40 mL) for 28 h. The conversion reached 63% and (*R*)-**1a** (2.20 g, 55%) was obtained; $[\alpha]_{\text{D}}^{22} +5.5$ (*c* 2.0, EtOH), [lit.¹⁶ $[\alpha]_{\text{D}}^{20} +5.4$ (*c* 2.1, EtOH)]; HPLC analysis of (*R*)-**1c**: tR (min) = 12.3 (98.9%), 14.4 (1.1%). IR cm^{-1} : 3315, 2935, 1444, 1136, 1067, 1018, 972. Its ¹H-NMR spectrum was identical with that of authentic specimen of (\pm)-**1a**, the starting material of this study.

ACKNOWLEDGEMENTS

We thank Mr. Masahiro Miyamoto, Daicel Corp, for his information on the HPLC analysis of stereoisomers. This work was supported both by a Grant-in-Aid for Scientific Research (No. 26450143 and 15J00535) and Platform for Drug Discovery, Informatics, and Structural Life Science from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and is gratefully acknowledged with thanks. Y. Y. thanks all members of the former “Division of Drug Discovery and Development” of this faculty, for their encouragement.

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