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Enzymatic resolution of methyl (2*E*, 4*R**,5*S**)-4-(*N*-benzyl-*N*-methyl)amino-5-hydroxyhex-2-enoate

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ABSTRACT

For the purpose of preparation of optically active aminoalcohol congeners possessing both hydroxyl- and dialkylamino-substituted vicinal chiral carbons, lipase-assisted acylation of methyl (2*E*,4*R**,5*S**)-4-(*N*-benzyl-*N*-methyl)amino-5-hydroxyhex-2-enoate (**4**) using CAL-B with vinyl hexanoate as an acyl donor was carried out to give (4*S*,5*R*)-hexenoate (**7**) (44%, 99.2% ee) as the reaction product and (4*R*,5*S*)-alcohol (**4**) (46%, 98.2% ee) as the unreacted starting material. The *E*-value of the present lipase-assisted resolution was estimated to be more than 1000. Thus obtained acylated product was successfully converted into methyl β-D-vicenisaminide (**12**).

1. Introduction

Racemic acylamino- or dialkylaminoalcohols have been the substrates for enzymatic resolution and the resulting optically pure products are important building blocks for the synthesis of biologically and pharmacologically active compounds[1]. Meanwhile aminosugars are isolated from many antibiotics or natural products as constituents of those compounds, and the role of the whole structure has a close connections with their biological activities [2]. For the synthesis of deoxy-aminosugars such as D-vicenisamine (**1**) [3] and L-forosamine (**2**) possessing methylamino and dimethylamino group, respectively, effective methods for the construction of chiral form of moiety **A** as shown in Scheme 1 are desirable. D-Vicenisamine (**1**) is the constituted aminosugar of vicenistatin which is isolated from *Streptomyces* sp. HC34 as a novel antitumour antibiotics[4]. The chiral structural unit **A** possessing hydroxyl and *N*,*N*-disubstituted amino groups with vicinal relationship could be derived from a chiral moiety **B** possessing azido alcohol functionality. On the other hand, we reported that the reaction of (±) *trans*-4,5-epoxy-2(*E*)-hexenoate (**3**) with *N*-methylbenzylamine or dimethylamine gave (±)-**4** or (±)-**5** respectively, in highly regioselective manner[5]. D-Vicenisamine (**1**) and L-forosamine (**2**) could be synthesized from optically active (4*S*,5*R*)-**4** and (4*S*,5*R*)-**5**, respectively. Although lipase-catalysed resolution of (±)-*N*,*N*-dimethylaminopropan-2-ol was reported,[6] none of the methods describe examples whose both of hydroxyl- and dialkylamino-substituted vicinal carbons are chiral. Herein, we report enzymatic resolution of (±)-**4** and show an application toward the synthesis of D-vicenisamine (**1**).

2. Methods and materials

2.1. General

All melting points were measured on a Mettler FP-62 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on JEOL AL 400 spectrometer or Bruker AV400M digital spectrometer in $CDCl_3$, MeOH-d_4, and DMSO-d_6 with or without Me_4Si as an internal reference. High-resolution mass spectra (HRMS) and the fast atom bombardment mass spectra (FAB MS) were obtained with a JEOL JMS-600H (matrix; glycerol, *m*-nitrobenzyl alcohol) spectrometer. High-resolution FAB MS were obtained with a JEOL JMS-SX-102A or JMS-T100LP.

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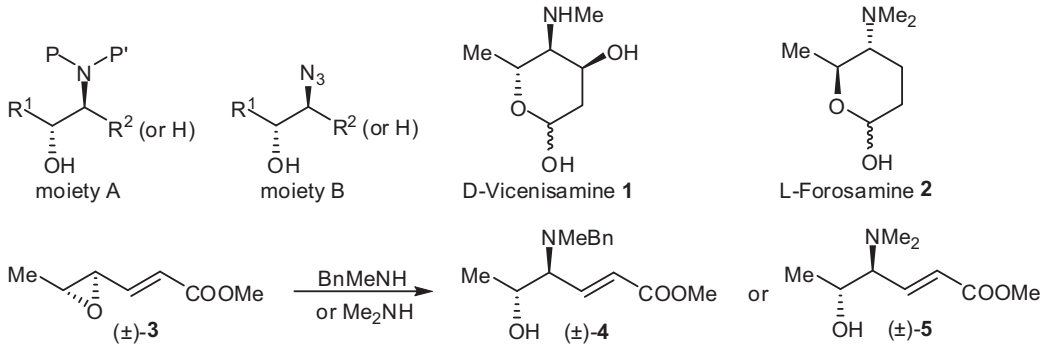


Scheme 1.

IR spectra were recorded on a JASCO FT/IR-300 spectrometer. Optical rotations were measured with a JASCO DIP-370 or P-1020 digital polarimeter. HPLC analysis was performed on SSC-3210 pump equipped with chiral column, SSC-5200 UV detector and SIR Chromatocorder 21. Chemicals were purchased from Tokyo Kasei Industry Co. Ltd., and Wako Chemicals or Aldrich Inc. otherwise indicated. Lipase PS and CAL-B were purchased from Amano Enzymes Co. and Sigma–Aldrich Inc., respectively. For column chromatography, silica gel (Kieselgel 60, Merck) or Chromatorex® NH (Fuji Silysia Chermical Ltd.) were employed.

2.2. Enzymatic resolution of methyl (2E,4R*,5S*)-4-(N-benzyl-N-methyl)amino-5-acetoxyhex-2-enoate (**6**)

A suspension of the reported (±)-**6** [4] (230 mg, 0.75 mmol) and lipase "Amano PS" (0.1 g) in phosphate buffer (0.1 M, pH 7.25, 20 mL) was stirred at 35 °C for 6d. The reaction mixture was diluted with Et_2O (50 mL) and solid materials were removed by filtration through celite pad. The reaction mixture was extracted with Et_2O and organic extracts were dried over $MgSO_4$ and filtered. Evaporation of the organic solvent gave a crude product, which was purified by silica gel column chromatography (20 g) to afford (4*R*,5*S*)-**6** (108 mg, 47%, 36% ee by HPLC analysis) from *n*-hexane/EtOAc = 10/1 elution and (4*S*,5*R*)-**4** (53 mg, 27%, 53% ee by HPLC analysis) from *n*-hexane/EtOAc = 5/1 elution. HPLC equipped Chiralcel AD-H (4.6 mm × 250 mm), eluents: *n*-hexane/*i*-PrOH = 20/1, Flow rate; 0.4 mL/min, Detection; 254 nm. (±)-**4**; t_R = 42.1 and 45.2 min. The ee of (4*R*,5*S*)-**6** was calculated based on HPLC analysis after conversion of (4*R*,5*S*)-**6** into (4*R*,5*S*)-**4** with K_2CO_3 in MeOH.

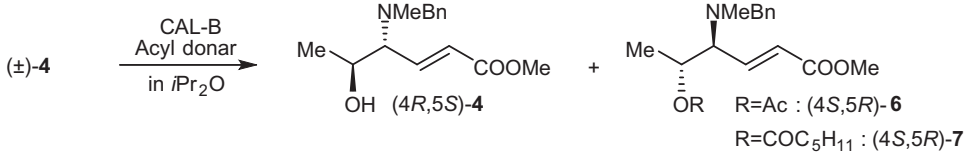
2.3. General procedure for enzymatic resolution of methyl (2E,4R*,5S*)-4-(N-benzyl-N-methyl)amino-5-hydroxyhex-2-enoate (**4**)

To a solution of (±)-**4** (50 mg, 0.19 mmol) and acyl donor (500 mg) in various amount of *i*-Pr_2O (0, 1, 3, 10 mL) was added CAL-B (50 mg), then the mixture was stirred at room temperature. The reaction mixture was filtrated through Celite 545 and the filtrate was evaporated under reduced pressure. The ee and absolute configuration of recovered **4** was determined by HPLC analysis. The ee of acylated compound (**6** or **7**) was estimated based on the conversion yield by NMR analyses of reaction mixture and the ee of recovered **4**. The results are shown in Table 1.

2.4. Methyl (2E,4S,5R)-4-(N-benzyl-N-methyl)amino-5-hexanoyloxyhex-2-enoate ((4S,5R)-**7**) and methyl (2E,4R,5S)-4-(N-benzyl-N-methyl)amino-5-hydoxyhex-2-enoate ((4R,5S)-**4**)

To a solution of (±)-**4** (623 mg, 2.40 mmol) and vinyl hexanoate (1.15 g, 8.04 mmol) in *i*-Pr_2O (50 mL) was added CAL-B (200 mg), then the mixture was stirred at room temperature for 3 days. The reaction mixture was filtrated through Celite 545 and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography [silica gel: Chromatorex® NH (10 g)] to afford (4*S*,5*R*)-**7** (376 mg, 44%) from hexane/AcOEt (5/1) fractions and (4*R*,5*S*)-**4** (287 mg, 46%, 98.2% ee by HPLC) from hexane/AcOEt (1/2) fractions. (4*R*,5*S*)-**4**: $[\alpha]_D^{19}$ −55.6 (*c* 0.76, $CHCl_3$). NMR data of (4*R*,5*S*)-**4** were identical with those of the reported (±)-**4** [5]. (4*S*,5*R*)-**7**: $[\alpha]_D^{19}$ +48.4 (*c* 1.16, $CHCl_3$),

Table 1
Enzymatic resolution of (±)-**4** using CAL-B in the presence of acyl donor.



Entry	Acyl donor	*i*Pr_2O (mL)	Time (h)	Conv. (%)[a]	Ee of **4** (%)[b]	Ee of **6** or **7** (%)[c]	*E* value
1	Vinyl acetate	0	–	–[d]	–	–	–
2	Vinyl acetate	1	5	27.7	35.6	92.2	39
3	Vinyl acetate	3	6	26.1	34.7	98.2	160
4	Vinyl acetate	10	26	48.5	94.1	99.9	>1000
5	Vinyl hexanoate	10	26	49.5	98.1	>99.9	>1000

[a] Estimated by ^{1}H NMR.
[b] Measured by HPLC analysis.
[c] Calculated value from conv. and ee of **4**.
[d] Polymerized with vinyl acetate.

^{1}H NMR(400 MHz, $CDCl_3$): δ 0.87 (3H, t, J = 7.0 Hz), 1.20–1.33 (4H, m), 1.32 (3H, d, J = 6.0 Hz), 1.51–1.59 (2H, m), 2.20 (2H, t, J = 7.6 Hz), 2.24 (3H, s), 3.07 (1H, dd, J = 6.0, 8.8 Hz), 3.47 (1H, d, J = 13.2 Hz), 3.66 (1H, d, J = 13.2 Hz), 3.77 (1H, s), 4.82 (1H, s), 5.18–5.25 (1H, m), 5.90 (1H, d, J = 12.0 Hz), 6.94 (1H, dd, J = 9.0, 12.0 Hz), 7.21–7.34 (5H, m); ^{13}C NMR ($CDCl_3$): 13.8, 18.1, 22.2, 24.6, 31.2, 34.6, 37.8, 51.6, 58.9, 67.6, 69.7, 125.3, 127.1, 128.3 (2C), 128.6 (2C), 138.8, 143.6, 166.0, 173.1. IR:(neat) 1727, 1654, 1495, 1172 cm^{-1}. HR-EI-MS calcd. for $C_{21}H_{31}NO_4$: 361.2255, found: 361.2253.

2.5. Methyl (2E,4S,5R)-4-(N-benzyl-N-methyl)amino-5-hydoxyhex-2-enoate ((4S,5R)-**4**)

To a solution of (4*S*,5*R*)-**7** (350 mg, 0.970 mmol) in MeOH (10 mL) and *i*-Pr_2O (30 mL) was added CAL-B (200 mg), then the mixture was stirred at room temperature for 3 days. After the spot of (4*S*,5*R*)-**7** was disappeared on TLC analysis of the reaction mixture, the reaction mixture was filtrated through Celite 545 and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography [silica gel: Chromatorex® NH (10 g), hexane/AcOEt (1/2)] to afford (4*S*,5*R*)-**4** (230 mg, 90%, 99.2% ee by HPLC). $[\alpha]_D^{17}$ + 54.0 (*c* 1.16, $CHCl_3$).

2.6. Methyl [(4S,5R,6R)-5-(N-benzyl-N-methyl)amino-6-methyl-2-phenyl-[1,3]dioxan-4-yl]-acetate (**8**)

To a solution of (4*S*,5*R*)-**4** (530 mg, 2.0 mmol) in THF (4 mL) at 0 °C was added benzaldehyde (430 mg, 4.0 mmol), followed by KO^{t}Bu (340 mg, 3.0 mmol), then the orange solution was stirred at same temperature for 15 min. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was purified by silica gel column chromatography (20 g, hexane/EtOAc = 15/1) to afford (4*S*,5*R*,6*R*)-**8** (349 mg, 47%) as a homogeneous oil. (4*S*,5*R*,6*R*)-**8**: $[\alpha]_D^{22}$ −27.3 (*c* 0.54, $CHCl_3$). IR (neat): 1739 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.47 (3H, d, J = 6 Hz), 2.32 (3H, s), 2.42 (1H, t, J = 10 Hz), 2.57 (1H, dd, J = 8, 16 Hz), 3.09 (1H, dd, J = 4, 16 Hz), 3.69 (3H, s), 3.79, 3.85 (each 1H, d, J = 14 Hz), 4.10 (1H, dq, J = 6, 10 Hz), 4.37 (1H, ddd, J = 4, 8, 10 Hz), 5.54 (1H, s), 7.23–7.48 (10H, m). *Anal.* Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.56; H, 7.77; N, 3.69.

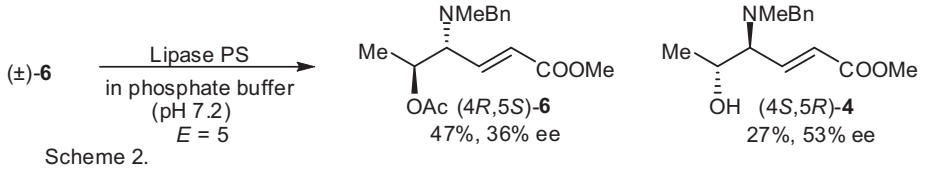
2.7. (2R,3R,4S)-3-(N-Benzyl-N-methyl)amino-4-hydroxy-2-methyl-6-oxotetrahydropyran (**9**)

To a solution of (4*S*,5*R*,6*R*)-**8** (640 mg, 1.7 mmol) in THF (5 mL) was added conc. HCl (3 mL) and the mixture was stirred at 70 °C for 2 h. The reaction mixture was evaporated to give a residue which was diluted with 2 M HCl (5 mL). The HCl layer was extracted with ether and HCl layer was evaporated to afford a residue. To this residue was added sat. Na_2CO_3 (3 mL) and the whole was evaporated to give a residue which was extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to give a residue which was subjected to silica gel column chromatography (20 g, *n*-hexane/AcOEt = 5/1) to afford (2*R*,3*R*,4*S*)-**9** (230 mg, 53%) as an oil. (2*R*,3*R*,4*S*)-**9**: $[\alpha]_D^{22}$ + 68.1 (*c* 0.63, $CHCl_3$). IR (KBr): 3398, 1697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (3H, d, J = 6.0 Hz), 2.41 (3H, s), 2.69 (2H, d, J = 4.4 Hz), 2.72 (1H, dd, J = 4.0, 9.6 Hz), 3.74 (1H, d, J = 13.0 Hz), 3.87 (1H, d, J = 13.0 Hz), 4.38 (1H, q, J = 4.0 Hz), 4.94 (1H, dd, J = 8.4, 9.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5, 39.1, 39.8, 59.7, 62.5, 64.0, 73.6, 127.1, 128.2 (2C), 128.3 (2C), 138.6, 169.6. *Anal.* Calcd for $C_{14}H_{19}NO_3$:C, 67.45; H, 7.78; N, 5.62. Found: C, 67.10; H, 7.85; N, 5.33.

2.8. Methyl β-D-vicenisaminide (**12**) and methyl α-D-vicenisaminide (**13**)

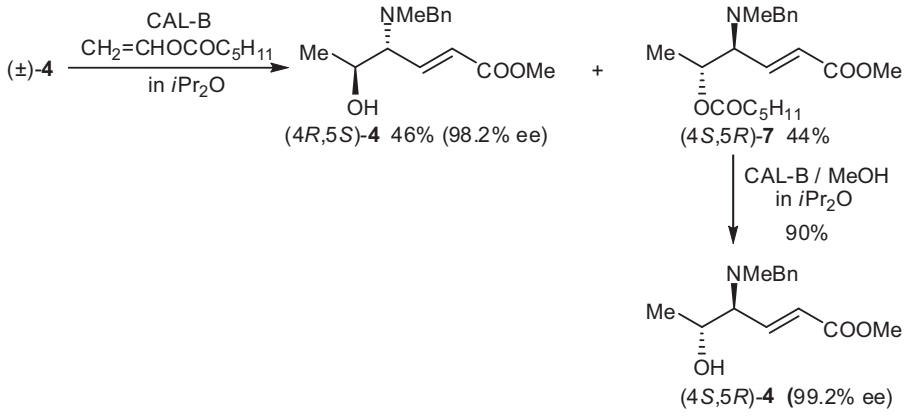
(i) To a solution of (2*R*,3*R*,4*S*)-**9** (610 mg, 2.4 mmol) in toluene (10 mL) at −40 °C was added 1 M solution of diisobutylaluminum hydride (Dibal-H) in toluene (4.9 mL, 4.9 mmol), then the mixture was stirred at 40 °C for 1 h. To the reaction mixture was added Et_2O (30 mL) and 1 M NaOH solution (20 mL) at 0 °C and the organic layer was separated. The organic layer was dried over $MgSO_4$ and evaporated to give a residue which was used for the next reaction without further purification. To a solution of acetyl chloride (AcCl; 10 mL) in MeOH (5 mL) was added a solution of the above residue in MeOH (2 mL) and the whole was stood for 3 d. The reaction mixture was evaporated and diluted with sat. Na_2CO_3 (10 mL), extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a residue which was subjected to silica gel column chromatography (20 g, *n*-hexane/AcOEt = 5/1) to afford **11** (86 mg, 13%) and **10** (140 mg, 22%) in elution order. **10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (3H, d, J = 8.0 Hz), 1.70 (1H, d, J = 4.0 Hz), 1.99 (1H, dd, J = 2.0, 4.0 Hz), 2.01 (1H, dd, J = 2.0, 4.0 Hz), 2.39 (3H, s), 2.46 (1H, d, J = 3.4 Hz), 3.48 (3H, s), 3.78 (1H, s), 3.81 (1H, s), 4.11 (1H, s), 4.36 (1H, q, J = 4.2 Hz), 4.67 (1H, d, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2, 39.0, 39.4, 56.2, 59.2, 66.5, 66.8, 67.9, 98.6, 126.7, 128.0 (4C), 138.6. **11**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (3H, d, J = 6.0 Hz), 1.83 (1H, dd, J = 3.8, 6.2 Hz), 1.87 (1H, dd, J = 3.8, 6.2 Hz), 2.37 (1H, d, J = 3.6 Hz), 2.40 (3H, s), 3.40 (3H, s), 3.58 (1H, br. s), 3.81 (1H, s), 3.87 (1H, s), 4.32 (1H, q, J = 5.6 Hz), 4.37 (1H, s), 4.77 (1H, d, J = 4.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0, 37.0, 38.5, 54.9, 58.0, 62.3, 65.9, 66.5, 98.8 126.4, 127.9 (4C), 140.1. (ii) A solution of **10** (150 mg, 0.6 mmol) in AcOEt (10 mL) was hydrogenated over 10% $Pd(OH)_2$/C (100 mg) at room temperature under atmospheric pressure of hydrogen for 12 h. After removal of the catalyst by filtration through Celite pad, evaporation of the organic solvent gave a crude product, which was purified by NH-silica gel column chromatography (3 g, gradient, CH_2Cl_2 to CH_2Cl_2/MeOH = 19/1) to afford methyl β-D-vicenisaminide **12** (64 mg, 64%) as pale yellow oil. **12**: $[\alpha]_D^{22}$ −3.7 (*c* 0.40, MeOH). HRMS (FAB+) Calcd for $C_8H_{18}NO_3$: 176.1287. Found: 176.1286. The free form was dissolved in Et_2O (1 mL) and 4 M HCl in dioxane was added to the solution. The resulted white needle was collected by filtration to afford **12** hydrochloride (48 mg, 62%) as a colorless needles. **12** hydrochloride: mp 182 °C, ^{1}H NMR (hydrochloride, MeOH-d_4): δ 1.35 (3H, d, J = 6.3 Hz), 1.67 (1H, ddd, J = 2.8, 9.1, 14 Hz), 2.03 (1H, ddd, J = 2.3, 4.3, 14 Hz), 2.74 (3H, s), 2.92 (1H, dd, J = 3.2, 9.3 Hz), 3.44 (3H, s), 4.01 (1H, dq, J = 6.3, 9.3 Hz), 4.35 (1H), 4.75 (1H, dd, J = 2.3, 9.1 Hz). ^{13}C NMR (hydrochloride, MeOH-d_4): δ 18.6, 31.2, 38.8, 56.7, 62.4, 63.3, 67.9, 100.4.

(iii) A solution of **11** (92 mg, 0.35 mmol) in AcOEt (10 mL) was hydrogenated over 10% $Pd(OH)_2$/C (100 mg) at room temperature under atmospheric pressure of hydrogen for 12 hr. After removal of the catalyst by filtration through Celite pad, evaporation of the organic solvent gave a crude product, which was purified by NH-silica gel column chromatography (3 g, gradient, CH_2Cl_2 to CH_2Cl_2/MeOH = 19/1) to afford methyl α-D-vicenisaminide **13** (44 mg, 72%) as pale yellow oil. **13**: $[\alpha]_D^{22}$ +198.0 (*c* 0.6, $CHCl_3$), HRMS (FAB+) Calcd for $C_8H_{18}NO_3$: 176.1287. Found: 176.1300. ^{1}H NMR ($CDCl_3$): δ 1.32 (3H, d, J = 6.3 Hz), 1.85 (1H, dt, J = 3.5, 14.4 Hz), 2.08 (1H, dd, J = 3.0, 9.9 Hz), 2.15 (1H, ddd, J = 1.3, 3.5, 14.4 Hz), 2.44 (3H, s), 3.37 (3H, s), 3.69 (1H, dq, J = 6.3, 9.9 Hz), 4.07 (1H, dq, J = 6.3, 9.3 Hz), 4.77 (1H, d, J = 3.5 Hz). ^{13}C NMR ($CDCl_3$): δ 18.7, 33.9, 35.3, 55.1, 62.9, 63.9, 64.1, 98.5.

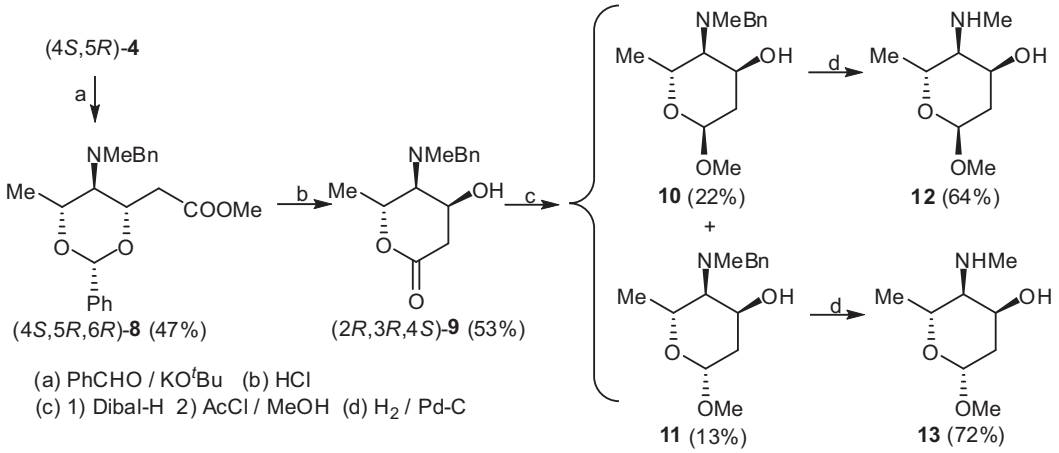


Scheme 2.

Scheme 2.



Scheme 3.



Scheme 4.

3. Results and discussion

3.1. The lipase-catalysed resolution of methyl (2E,4R*,5S*)-4-(N-benzyl-N-methyl)amino-5-acetoxyhex-2-enoate (6)

Firstly, the enantioselective hydrolysis of (±)-**6** using the lipase "Amano PS" from *Burkholderia cepacia* (EC 3.1.1.34) in phosphate buffer solution at pH 7.25 gave (4*S*,5*R*)-**4** (27%, 53% ee) and (4*R*,5*S*)-**6** (47%, 36% ee). The enantiomeric excess (ee) of the hydrolyzed product **4** was calculated by the reported equation [7]. The absolute structure and enantiomeric excess (ee) of the hydrolyzed product **4** (t_R = 45.2 min: t_R = 42.1 min = 76.5: 23.5) were determined by a comparison of retention times of authentic (4*S*,5*R*)-**4** ($[\alpha]_D^{25}$ + 52.2 (*c* 1.01, $CHCl_3$), >99% ee, t_R = 45.2 min),[5] thence absolute structure of the present **4** was confirmed to possess 4*S*, 5*R* configurations. Methanolysis of acetate **6** with K_2CO_3 provided the hydrolyzed product **4** (t_R = 45.2 min: t_R = 42.1 min = 32: 68), thence absolute structure of the present **6** was confirmed to possess 4*R*, 5*S* configurations. The *E* value of the present enzymatic hydrolysis of (±)-**6** was found to be 5 (*E* = 5) by the reported equation [7] and should be much improved. In the next section, lipase-catalysed acylation of methyl (2*E*,4*R**,5*S**)-4-(*N*-benzyl-*N*-methyl)amino-5-hydroxyhex-2-enoate (**4**) in the presence of acyl donor was carried out (Scheme 2).

3.2. Screening experiment

Previously we reported enantioselective lipase-catalysed acylation of methyl (2*E*,4*R**,5*R**)-4-aryl-5-hydroxyhex-2-enoate possessing the similar structure of (±)-**4** by CAL-B from *Candida antarctica* (lipase B, supported by polyacrylic ester)[8]. We considered CAL-B could catalyze the enantioselective acylation of (±)-**4**. By a screening experiment in the presence of vinyl acetate as an acyl donor, CAL-B was found to be suitable lipase. Firstly, in the reaction of (±)-**4** using CAL-B with vinyl acetate, the products were not obtained because the polymerization of vinyl acetate occurred. (Table 1, entry 1). This polymerization was considered to be caused by basicty of substrate (±)-**4**. Meanwhile, the reaction of (±)-**4** using CAL-B with vinyl acetate and diisopropyl ether as a reaction solvent to avoid the polymerization gave (4*R*,5*S*)-**4** (35.6% ee) and an

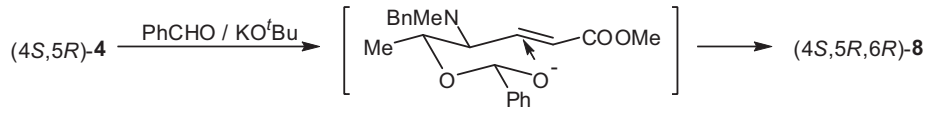
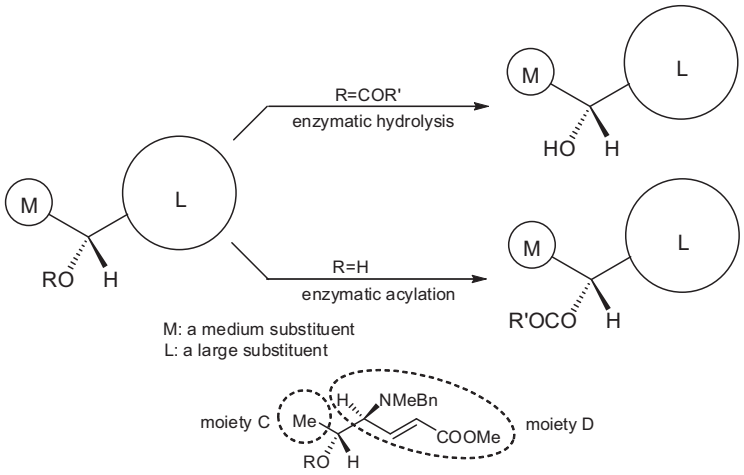


Fig. 1. Plausible mechanism for the formation of (4S,5R,6R)-8 from (4S,5R)-4.



Scheme 5.

acetate (4*S*,5*R*)-**6** (92.9% ee) at 5 h (Table 1, entry 2). However the prolonged reaction time in order to reach 50% conversion caused the polymerization reaction. Dilution of vinyl acetate concentration with diisopropyl ether (10 mL) allowed prolonged reaction time to reach 48.5% conversion and gave the ee of (4*R*,5*S*)-**4** (94.1% ee) and acetate (4*S*,5*R*)-**6** (99.9% ee). *E*-value (*E* > 1000) was also improved dramatically by the dilution (Table 1, entry 4). This improvement of *E* value was depended on the ratio of vinyl acetate and diisopropyl ether, since the use of large volume (5 mL) of vinyl acetate in diisopropyl ether (ca. 33%, v/v corresponding to entry 2) gave about the same *E* value as entry 2 and caused polymerization by long reaction time. Above results indicated diisopropyl ether was considered as good solvent for the stereoselective enzymatic reaction. The influence of acyl donor on ee in lipase-catalysed acylation of alcoholic substrate was reported[9–11]. For the purpose of both enrichment of the ee of reaction products and being speeded up reaction rate, the reaction of (±)-**4** with vinyl hexanoate as an acyl donor under the same reaction condition as entry 4 was carried out to afford of (4*R*,5*S*)-**4** (98.1% ee) and hexanoate **7** (more than 99.9% ee), and *E*-value was estimated to be more than 1000 (Table 1, entry 5). To confirm the absolute structure of hexanoate **7**, preparative scale experiment of entry 5 was carried out in the next section.

3.3. Preparative scale experiment (preparation of (4R,5S)- and (4S,5R)-4)

Lipase-catalysed optical resolution of 623 mg of (±)-**4** using 1.15 g of vinyl hexanoate and 200 mg of CAL-B in 50 mL of diisopropyl ether was carried out to give (4*R*,5*S*)-**4** (46%, $[\alpha]_D$ −55.6 (*c* 0.76, $CHCl_3$), 98.2% ee) and (+)-hexanoate **7** (44%, $[\alpha]_D$ +48.4 (*c* 1.16, $CHCl_3$) (Scheme 3). To confirm the absolute structure of (+)-**7**, methanolysis of (+)-**7** using CAL-B in MeOH and diisopropyl ether was performed to afford (4*S*,5*R*)-**4** (90%, $[\alpha]_D$ +54.0 (*c* 1.16, $CHCl_3$), 99.2% ee)). Thence the absolute structure of (+)-**7** was determined to possess 4*S*, 5*R* configurations.

3.4. Synthesis of methyl β-D-vicenisaminide12 from (4S,5R)-4

Conversion of (4*S*,5*R*)-**4** into methyl β-D-vicenisaminide (**12**) was performed as shown in Scheme 4. To introduce the oxygen functionality at the 3-position of (4*S*,5*R*)-**4**, treatment of (4*S*,5*R*)-**4** with benzaldehyde in the presence of KO^{t}Bu afforded acetal (4*S*,5*R*,6*R*)-**8** ($[\alpha]_D$ −27.3 (*c* 0.54, $CHCl_3$)) in 47% yield with high diastereoselectivity from the ^{1}H NMR measurement. This high diastereoselectivity could be explained via a chair-like intermediate as shown in Fig. 1. Acid treatment of (4*S*,5*R*,6*R*)-**8** gave *δ*-lactone (2*R*,3*R*,4*S*)-**9**: ($[\alpha]_D$+68.1 (*c* 0.63, $CHCl_3$)) in 53% yield, which was subjected to consecutive treatment of Dibal-H and anhydrous hydrogen chloride in MeOH to afford β-methyl glycoside (**10**) (22%) and α-methyl glycoside (**11**) (13%). Catalytic debenzylation of both β-anomer **10** and α-anomer **11** gave β-D-vicenisaminide (**12**) (64%, $[\alpha]_D$ −3.7 (*c* 0.40, MeOH)) and α-D-vicenisaminide (**13**) (72%, $[\alpha]_D$ +198.0 (*c* 0.6, $CHCl_3$)), respectively. Treatment of **12** in Et_2O with 4 M HCl in dioxane gave the corresponding hydrochloride salt, whose spectroscopic data were identical with those previously reported[12].

4. Discussion

In case of lipase-catalysed hydrolysis of (±)-**6**, poor results (*E* = 5) were obtained and could be explained as follows. Previously, we reported optical resolution of the neutral methyl (2*E*,4*R**,5*R**)-4-aryl-5-acetoxyhex-2-enoate possessing similar structure of (±)-**6** by Amano PS to give low reactivity and unsatisfied stereoselectivity. While the transesterification of the above neutral compounds by CAL-B afforded good results [8]. The low *E* value for the hydrolysis of (±)-**6** by Amano PS was not concerned with basicity of (±)-**6** and (±)-**6** could be not good substrate for Amano PS. The results of the enantioselective hydrolysis of (±)-**6** with the lipase PS from *Burkholderia cepacia* (EC 3.1.1.34) and enantioselective acylation of (±)-**4** with CAL-B from *Candida antarctica* were coincided well with the theoretical transition state model [13,14] to indicate which enantiomer possessing secondary hydroxyl or acyloxyl groups reacts faster in lipase-catalysed reactions by comparing the relative sizes of substituents at the stereocenter. The moiety C

seems to be a relatively small-sized substituent (M) and the moiety D appears to be a relatively large-sized substituent (L) (Scheme 5).

5. Conclusion

For the purpose of preparation of optically active aminoalcohol congener possessing hydroxyl and *N*,*N*-disubstituted amino groups with vicinal relationship, enzymatic hydrolysis of methyl (2*E*,4*R**, 5*S**)-4-(*N*-benzyl-*N*-methyl)amino-5-acetoxyhex-2-enoate (**6**) and lipase-assisted acylation of methyl (2*E*,4*R**,5*S**)-4-(*N*-benzyl-*N*-methyl)amino-5-hydroxyhex-2-enoate (**4**) in the presence of vinyl hexanoate were carried out. In case of hydrolysis of (±)-**6** using lipase PS, poor results were obtained from the standpoint of isolation yield and enantiomeric excess (ee). Meanwhile, enantioselective acylation of (±)-**4** using CAL-B with vinyl hexanoate as an acyl donor afforded (4*S*,5*R*)-4-(*N*-benzyl-*N*-methylamino)-5-hexanoyloxy-2(*E*)-hexenoate (**7**) (44%, 99.2% ee) and (4*R*,5*S*)-alcohol **4** (46%, 98.2% ee) corresponding to starting material. The *E*-value of the present lipase-assisted resolution was estimated to be more than 1000. Thus obtained (4*S*,5*R*)-**7** was successfully converted into methyl β-D-vicenisaminide (12).

References

[1] J. Irurre, M. Riera, M. Guixa, Chirality 14 (2002) 490–494, and references cited therein.
[2] K.C. Nicolaou, H.J. Mitchell, Angew. Chem. Int. Ed. Engl. 40 (2001) 1576–1624.
[3] Formal synthesis Y. Matsushima, J. Kino, Tetrahedron Lett. 46 (2005) 8609–8612.
[4] K. Shido, M. Kamishohara, M. Odagawa, A. Matsuoka, H. Kawai, J. Antibiot. 46 (1993) 1076–1081.
[5] C. Saotome, M. Ono, H. Akita, Chem. Pharm. Bull. 49 (2001) 849–853.
[6] J.D. Hull, F. Scheinmann, N.J. Turner, Tetrahedron:Asymmetry 14 (2003) 567–576.
[7] C.-S. Chen, C.J. Sih, Angew. Chem. Int. Ed. Engl. 28 (1989) 695–707.
[8] M. Fujii, S. Yasuhara, H. Akita, Tetrahedron:Asymmetry 20 (2009) 1286–1294.
[9] T. Ema, S. Maeno, Y. Takaya, T. Sakai, M. Utaka, J. Org. Chem. 61 (1996) 8610–8616.
[10] K. Nakamura, K. Takenaka, A. Ohno, Tetrahedron:Asymmetry 11 (2000) 4429–4439.
[11] M. Kawasaki, M. Goto, S. Kawabata, T. Kometani, Tetrahedron:Asymmetry 12 (2001) 585–596.
[12] Y. Ichikawa, M. Osada, I. Ohtani, M. Isobe, J. Chem. Soc., Perkin Trans. 1 (1997) 1449–1455.
[13] M. Cygler, P. Grochulski, R.J. Kazlauska, J.D. Schrag, F. Bouthillier, B. Rubin, A.N. Serreqi, A.K. Gupta, J. Am. Chem. Soc. 116 (1994) 3180–3186.
[14] T. Ema, Curr. Org. Chem. 8 (2004) 1009–1025.