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Lipase-catalyzed enantio- and regioselective transformation of 3-*epi*-shikimic acid derivatives as the key step for the entry of polyoxygenated carbacycles

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ABSTRACT

Candida antarctica lipase B (Novozym 435)-catalyzed transesterification on methyl (±)-3,4-di-*O*-acetyl-5-*O*-(*tert*-butyldimethyl)silyl-3-*epi*-shikimate worked highly regio- and enantioselective manner. Only (3*R*,4*S*,5*S*)-isomer reacted with an *E* value over 500, exclusively on C-3 acetate. The regio- and enantioselectivity were greatly affected by the substitution pattern on the hydroxy groups. Towards polyoxygenated carbacycles, the above-mentioned highly selective transformation enabled the subsequent stereoselective inversion and dihydroxylation, to give methyl (3*S*,4*R*,5*S*)-3,4,5-triacetoxy-1-cyclohexenecarboxylate [antipode of naturally occurring methyl (−)-3,4,5-tri-*O*-acetylshikimate], and methyl (1*R*,2*S*,3*S*,4*R*,5*R*)-3,4-diacetoxy-5-(*tert*-butyldimethyl)silyloxy-1,2-dihydroxy-cyclohexanecarboxylate.

1. Introduction

Regioselective protection and deprotection of polyoxygenated carbacycles are of much importance towards the synthetic transformation to bioactive cyclohexanoids. Gotor and co-workers [1] attempted *Candida antarctica* lipase B-catalyzed regioselective acetylation on methyl ester of natural origin of **1a** (Scheme 1). The enzyme mainly worked on C-3 and C-5 hydroxy groups, monoacetates **1b** and **1d** were obtained in 45 and 37% yield, respectively. In contrast, sterically hindered hydroxy group on C-4 was less reactive and such acetylated product was obtained as low as 18% yield. We turned our attention to similar, but the epimeric substrate, methyl 3-*epi*-shikimate **2a** [2]. Moreover, if a racemic mixture of **2a** is applied to what, the difference of the reaction rates between enantiomers (enantioselectivity) and the regioselectivity in each enantiomer are very interesting.

2. Experimental

IR spectra were measured as thin films for oils or ATR for solid on a Jeol FT-IR SPX60 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 400 MHz and 100 MHz respectively, on a VARIAN 400-MR spectrometer. HPLC data were recorded on Jasco MD-2010 and SHIMADZU SPD-M20A multi-channel detectors by detection at 216 nm unless otherwise stated. Optical rotation values were recorded on a Jasco P-1010 polarimeter. Silica gel 60 N (spherical, neutral, 63–210 μm, 37565-79) of Kanto Chemical Co. was used for column chromatography. Preparative TLC was performed with Merck Silica Gel 60 F_{254} plates (0.5 mm thickness, No. 1.05744).

2.1. *C. antarctica* lipase B-catalyzed acetylation of methyl (3R*,4R*,5S*)-3,4,5-trihydroxy-1-cyclohexenecarboxylate (**2a**)

To a solution of (±)-**2a** (50.3 mg, 0.27 mmol) in vinyl acetate (1.25 mL) was added *C. antarctica* lipase B (Novozym 435, 75 mg). The mixture was stirred for 24 h at 30 °C. The reaction was monitored by silica gel TLC (hexane/AcOEt = 1:2). After removal of insoluble materials by filtration with a pad of Celite, the filtrate was concentrated *in vacuo* to give a mixture of (3*R*,4*R*,5*S*)-**2b** and (3*S*,4*S*,5*R*)-**2c** (total 65.0 mg). The conversion was determined to be 100% by ^{1}H NMR analysis of crude mixture. The residue was purified by silica gel column chromatography (2 g). Elution with hexane/AcOEt = 1:2 afforded (3*R*,4*R*,5*S*)-**2b** (12.0 mg, 19%) and (3*S*,4*S*,5*R*)-**2c** (18.0 mg, 29%) as colorless oil.

(3*R*,4*R*,5*S*)-**2b**: $[\alpha]_D^{23}$ −12 (*c* 0.60, $CHCl_3$) [lit. [3] $[\alpha]_D$ +38 (*c* 1.07, $CHCl_3$), for (3*S*,4*S*,5*R*)-**2b**]; ^{1}H NMR: δ 2.15 (s, 3H, Ac), 2.39 (ddd, $J_{2,6a}$ = 2.2 Hz, $J_{5,6a}$ = 6.8 Hz, $J_{6a,6b}$ = 14.4 Hz, 1H, H6a), 2.83 (dd, $J_{5,6b}$ = 4.4 Hz, 1H, H6b), 3.67 (dd, $J_{3,4}$ = 7.2 Hz, $J_{4,5}$ = 10.0 Hz, 1H, H4), 3.75 (s, 3H, Me ester), 3.83 (ddd, 1H, H5), 5.40 (ddd, $J_{2,3}$ = 3.2 Hz, 1H, H3), 6.78 (dd, 1H, H2); ^{13}C NMR: δ 21.1, 31.7, 52.2, 67.3, 69.5, 69.9, 75.0, 128.3, 137.2, 166.4, 172.2; IR: 3490,

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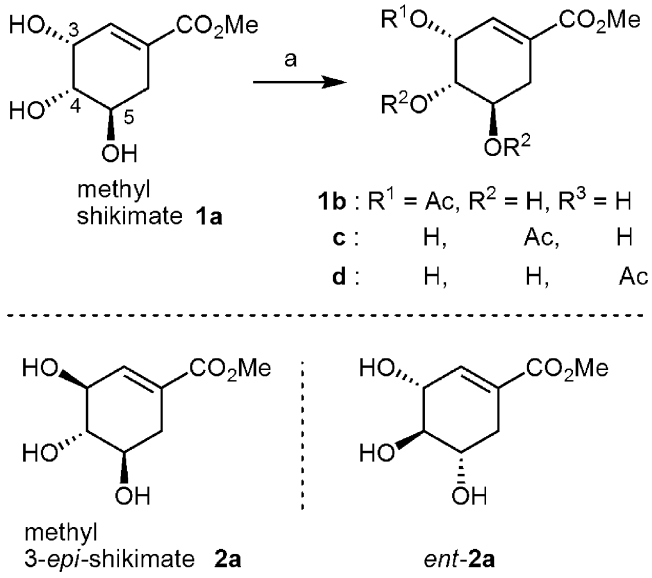


Scheme 1. Reagents and conditions: (a) *C. antarctica* lipase B (Novozym 435), vinyl acetate [45% for **1b**, 18% for **1c** and 37% for **1d**].

3405, 3232, 2859, 1699, 1650, 1427, 1372, 1238, 1184, 1144, 1059, 999 cm^{-1}. Its NMR spectra were identical with those reported previously [3].

(3*S*,4*S*,5*R*)-**2c**: $[\alpha]_D^{23}$ +11 (*c* 0.90, $CHCl_3$); ^1H NMR: δ 2.13 (s, 3H, Ac), 2.28 (ddd, $J_{2,6a}$ = 3.2 Hz, $J_{5,6a}$ = 10.0 Hz, $J_{6a,6b}$ = 17.6 Hz, 1H, H6a), 2.59 (br s, 1H, OH), 2.83 (dd, $J_{5,6b}$ = 6.0 Hz, 1H, H6b), 3.74 (s, 3H, Me ester), 3.99 (ddd, $J_{4,5}$ = 10.0 Hz, 1H, H5), 4.33 (ddd, $J_{2,3}$ = 2.4 Hz, $J_{3,4}$ = 7.2 Hz, 1H, H3), 4.86 (dd, 1H, H4), 6.59 (dd, 1H, H2); ^{13}C NMR: δ 21.1, 31.6, 52.2, 69.5, 74.8, 75.0, 130.5, 134.4, 166.0, 171.5; IR: 3406, 2354, 1714, 1655, 1431, 1371, 1228, 1061, 1026, 960 cm^{-1}.

2.2. Methyl (3R*,4R*,5R*)-5-(tert-butyldimethyl)silyloxy-7-oxabicyclo[4.1.0]hept-1-en-1-carboxylate (3b)

To a solution of **3a** (2.95 g, 17.3 mmol) in CH_2Cl_2 (20 mL) were added *tert*-butyldimethylsilyl chloride (TBSCl, 3.13 g, 20.8 mmol, 1.2 equiv.) and imidazole (1.42 g, 20.8 mmol, 1.2 equiv.) with stirring at 10 °C under argon atmosphere. The reaction was monitored by silica gel TLC (hexane/AcOEt = 6:1). The mixture was stirred for 24 h, with gradually raising the reaction temperature to 25 °C, then the reaction was quenched by adding saturated NH_4Cl aqueous solution. The organic materials were extracted with AcOEt several times, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (100 g). Elution with hexane/AcOEt = 7:1 afforded (±)-**3b** (4.73 g, 96%) as colorless oil. ^1H NMR: δ 0.06 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.84 (s, 9H, *tert*-butyl), 2.22 (ddd, $J_{2,6a}$ = 3.2 Hz, $J_{5,6a}$ = 4.8 Hz, $J_{6a,6b}$ = 17.2 Hz, 1H, H6a), 2.67 (ddd, $J_{4,6b}$ = 2.0 Hz, $J_{5,6b}$ = 2.4 Hz, 1H, H6b), 3.40 (ddd, $J_{3,4}$ = 4.0 Hz, $J_{4,5}$ = 4.4 Hz, 1H, H4), 3.43 (dd, $J_{2,3}$ = 4.0 Hz, 1H, H3), 3.74 (s, 3H, Me ester), 4.50 (ddd, 1H, H5), 7.07 (dd, 1H, H2); ^{13}C NMR: δ −4.8, 18.1, 25.7, 29.4, 46.7, 51.9, 56.4, 64.0, 131.0, 133.0, 166.6; IR: 2963, 2924, 2893, 2868, 1720, 1473, 1259, 1203, 1095 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O_4Si$: C 59.12, H 8.51; found: C 59.17, H 8.55.

2.3. Methyl (3R*,4S*,5S*)-5-(tert-butyldimethyl)silyloxy-4-hydroxy-3-(p-methoxy)benzyloxy-1-cyclohexenecarboxylate (2d)

To a solution of **3b** (1.77 g, 6.22 mmol) in anhydrous CH_2Cl_2 (18 mL), $Yb(OTf)_3$ (0.39 g, 0.62 mmol, 0.1 equiv.) and *p*-methoxybenzyl alcohol (2.33 mL, 18.7 mmol, 3.0 equiv.) were added with stirring. The reaction was monitored by silica gel TLC (hexane/AcOEt = 5:1). The mixture was stirred for 24 h at room temperature, then the reaction was quenched by adding water. The organic materials were extracted with AcOEt, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (100 g). Elution with hexane/AcOEt = 6:1 afforded (±)-**2d** (2.13 g, 81%) as colorless oil. ^1H NMR: δ 0.11 [s, 6H, $Si(CH_3)_2$], 0.90 (s, 9H, *tert*-butyl), 2.20 (ddd, $J_{2,6a}$ = 2.8 Hz, $J_{5,6a}$ = 4.8 Hz, $J_{6a,6b}$ = 14.8 Hz, 1H, H6a), 2.67 (ddd, $J_{5,6b}$ = 2.0 Hz, $J_{3,6b}$ = 4.0 Hz, 1H, H6b), 3.67 (m, 2H, H3, H4), 3.72 (s, 3H, Me ester), 3.78 (s, 3H, OCH_3), 4.10 (ddd, $J_{4,5}$ = 6.4 Hz, 1H, H5), 4.67 (d, *J* = 11.2 Hz, 1H, Bn-C*H*), 4.74 (d, 1H, Bn-C*H*), 6.73 (dd, $J_{2,3}$ = 2.4 Hz, 1H, H2), 6.86 (dd, *J* = 2.4, 6.8 Hz, 2H, Ar-*H*), 7.30 (d, 2H, Ar-*H*); ^{13}C NMR: δ −4.76, −4.23, 18.0, 25.8, 33.0, 52.0, 55.3, 71.1, 72.1, 78.2, 113.8, 128.6, 129.5, 130.3, 137.0, 159.3, 166.5; IR: 3473, 3417, 2954, 2908, 2862, 1686, 1446, 1365, 1254, 1086, 1030 cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_6Si$: C 62.53, H 8.11; found: C 62.71, H 8.01.

2.4. Methyl (3R*,4S*,5S*)-5-(tert-butyldimethyl)silyloxy-3,4-dihydroxy-1-cyclohexenecarboxylate (2e)

To a mixture of **2d** (2.05 g, 4.85 mmol), CH_2Cl_2 (40 mL), and water (16 mL) was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ, 1.32 g, 5.82 mmol, 1.2 equiv.). The reaction was monitored by silica gel TLC (hexane/AcOEt = 2:1). The mixture was stirred for 12 h at 20 °C, then the reaction was quenched by adding water. The aqueous layer was extracted with $CHCl_3$, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (40 g). Elution with hexane/AcOEt = 3:1 afforded (±)-**2e** (1.36 g, 93%) as colorless needles. mp 99.5–100 °C; ^1H NMR: δ 0.10 [s, 6H, $Si(CH_3)_2$], 0.89 (s, 9H, *tert*-butyl), 2.23 (ddd, $J_{2,6a}$ = 2.8 Hz, $J_{5,6a}$ = 6.4 Hz, $J_{6a,6b}$ = 17.6 Hz, 1H, H6a), 2.69 (br s, 2H, OH), 2.70 (ddd, $J_{5,6b}$ = 5.6 Hz, 1H, H6b), 3.55 (dd, $J_{3,4}$ = 7.6 Hz, $J_{4,5}$ = 9.2 Hz, 1H, H4), 3.73 (s, 3H, Me ester), 3.74 (ddd, 1H, H5), 4.27 (ddd, $J_{2,3}$ = 2.4 Hz, 1H, H3), 6.73 (dd, 1H, H2); ^{13}C NMR: δ −4.80, −4.32, 18.0, 25.8, 32.9, 52.0, 70.4, 71.2, 128.2, 138.0, 166.6; IR: 3423, 2947, 2929, 2852, 1714, 1662, 1432, 1257, 1074, 1025, 985 cm^{-1}. Anal. Calcd for $C_{14}H_{26}O_5Si$: C 55.60, H 8.67; found: C 55.68, H 8.65.

2.5. C. antarctica lipase B-catalyzed acetylation of (±)-2e

In a similar manner as described for the acylation of (±)-**2a**, a solution of (±)-**2e** (90.1 mg, 0.31 mmol) was treated with Novozym 435 (90 mg) in vinyl acetate (900 μL) to give (3*R*,4*S*,5*S*)-**2f** (51.0 mg, 48%, 75.4% ee) and (3*S*,4*R*,5*R*)-**2e** (30.2 mg, 34%, 77.6% ee) as colorless oil.

(3*R*,4*S*,5*S*)-**2f**: $[\alpha]_D^{23}$ −15.3 (*c* 1.45, $CHCl_3$); ^1H NMR: δ 0.10 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, *tert*-butyl), 2.10 (s, 3H, Ac), 2.23 (ddd, $J_{2,6a}$ = 2.8 Hz, $J_{5,6a}$ = 10.4 Hz, $J_{6a,6b}$ = 17.6 Hz, 1H, H6a), 2.63 (br s, 1H, OH), 2.75 (ddd, $J_{3,6b}$ = 1.2 Hz, $J_{5,6b}$ = 5.2 Hz, 1H, H6b), 3.55 (dd, $J_{3,4}$ = 8.0 Hz, $J_{4,5}$ = 10.0 Hz, 1H, H4), 3.72 (s, 3H, Me ester), 3.74 (ddd, 1H, H5), 4.27 (ddd, $J_{2,3}$ = 2.4 Hz, 1H, H3), 6.73 (dd, 1H, H2); ^{13}C NMR: δ −4.83, −4.31, 18.0, 21.0, 25.7, 32.9, 52.1, 70.8, 73.4, 74.5, 129.9, 134.9, 166.1, 170.6; IR: 2950, 2917, 2863, 1728, 1444, 1363, 1227, 1097, 968 cm^{-1}. HPLC [column, Daicel CHIRALCEL® AD-H, 0.46 cm × 25 cm; hexane/isopropyl alcohol = 70:1; flow rate 0.5 mL/min]: t_R (min) = 27.9 (87.7%), 33.4 (12.3%). The authentic specimen of (±)-**2f** was prepared by the acetylation of (±)-**2e**.

(3*S*,4*R*,5*R*)-**2e**: $[\alpha]_D^{23}$ –40.0 (*c* 1.50, $CHCl_3$). HPLC [CHIRALCEL® AD-H, 0.46 cm × 25 cm; hexane/isopropyl alcohol = 15:1; flow rate 0.5 mL/min]: t_R (min) = 22.3 (88.8%), 23.9 (11.2%).

2.6. Methyl (3R*,4S*,5S*)-5-(tert-butyldimethyl)silyloxy-3-(p-methoxy)benzyloxy-4-methoxy-1-cyclohexenecarboxylate (2g)

To a solution of **2d** (75.0 mg, 0.18 mmol) in anhydrous CH_2Cl_2 (3 mL), Proton Sponge® (91.3 mg, 0.43 mmol, 2.4 equiv.) and Me_3OBF_4 (32.0 mg, 0.22 mmol, 1.2 equiv.) were added with stirring. The reaction was monitored by silica gel TLC (hexane/AcOEt = 5:1). The mixture was stirred for 14 h at 0 °C under argon atmosphere, then the reaction was quenched by adding water. The organic materials were extracted with AcOEt, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (4 g). Elution with hexane/AcOEt = 5:1 afforded (±)-**2g** (54.2 mg, 69%) as colorless oil. ^{1}H NMR: δ 0.07 (s, 3H, SiCH_3), 0.09 (s, 3H, SiCH_3), 0.89 (s, 9H, *tert*-butyl), 2.23 (ddd, $J_{2,6a}$ = 3.2 Hz, $J_{5,6a}$ = 9.6 Hz, $J_{6a,6b}$ = 18.0 Hz, 1H, H6a), 2.65 (dd, $J_{5,6b}$ = 6.0 Hz,1H, H6b), 3.22 (dd, $J_{3,4}$ = 7.6 Hz, $J_{4,5}$ = 9.6 Hz, 1H, H4), 3.60 (s, 3H, OCH_3), 3.72 (s, 3H, Me ester), 3.73 (ddd, 1H, H5), 3.79 (s, 3H, ArOCH_3), 4.06 (ddd, $J_{2,3}$ = 2.4 Hz, 1H, H3), 4.64 (s, 2H, Bn-CH_2), 6.72 (dd, 1H, H2), 6.87 (dd, *J* = 2.0, 6.8 Hz, 2H, Ar-*H*), 7.28 (d, 2H, Ar-*H*); ^{13}C NMR: δ −4.84, −4.63, 18.1, 25.8, 34.0, 51.9, 55.2, 61.1, 70.7, 71.4, 72.2, 79.4, 86.0, 113.7, 113.8, 129.4, 130.3, 132.0, 136.9, 159.1, 159.2, 166.6; IR: 2941, 2858, 1714, 1605, 1522, 1444, 1246, 1068, 1034, 827 cm^{-1}. This was employed for the next step without further purification.

2.7. Methyl (3R*,4S*,5S*)-5-(tert-butyldimethyl)silyloxy-3-hydroxy-4-methoxy-1-cyclohexenecarboxylate (2h)

In a similar manner as described for the deprotection of (±)-**2d**, treatment of (±)-**2g** (35.2 mg, 0.08 mmol) with DDQ (20.4 mg, 0.09 mmol, 1.2 equiv.) in CH_2Cl_2 (700 μL) and water (280 μL) gave (±)-**2h** (25.5 mg, quant.) as a colorless oil. ^{1}H NMR: δ 0.08 (s, 3H, SiCH_3), 0.11 (s, 3H, SiCH_3), 0.87 (s, 9H, *tert*-butyl), 2.23 (dddd, $J_{3,6a}$ = 1.6 Hz, $J_{2,6a}$ = 2.0 Hz, $J_{5,6a}$ = 6.4 Hz, $J_{6a,6b}$ = 18.0 Hz, 1H, H6a), 2.54 (ddd, $J_{3,6b}$ = 2.0 Hz, $J_{5,6b}$ = 4.4 Hz, 1H, H6b), 2.82 (br s, 1H, OH), 3.36 (dd, $J_{3,4}$ = 4.8 Hz, $J_{4,5}$ = 6.4 Hz, 1H, H4), 3.49 (s, 3H, OCH_3), 3.74 (s, 3H, Me ester), 4.12 (m, 2H, H3, H5), 6.86 (dd, 1H, H2); ^{13}C NMR: δ −5.04, −4.88, 18.0, 25.8, 30,7, 51.9, 59.2, 67.6, 68.4, 81.9, 127.6, 136.8, 167.2. Its NMR spectra were identical with those reported previously [4].

2.8. C. antarctica lipase B-catalyzed acetylation of (±)-2h

In a similar manner as described for the acetylation of (±)-**2a**, treatment of (±)-**2h** (12.3 mg, 0.04 mmol) with Novozym 435 (20 mg) and vinyl acetate (200 μL) gave (3*R*,4*S*,5*S*)-**2i** (2.8 mg, 20%, 44.6% ee) and (3*S*,4*R*,5*R*)-**2h** (4.0 mg, 32%, 16.4% ee) as colorless oil.

(3*R*,4*S*,5*S*)-**2i**: ^{1}H NMR: δ 0.07 (s, 3H, SiCH_3), 0.08 (s, 3H, SiCH_3), 0.89 (s, 9H, *tert*-butyl), 2.10 (s, 3H, Ac), 2.29 (ddd, $J_{2,6a}$ = 2.8 Hz, $J_{5,6a}$ = 8.4 Hz, $J_{6a,6b}$ = 18.0 Hz, 1H, H6a), 2.68 (ddd, $J_{3,6b}$ = 1.2 Hz, $J_{5,6b}$ = 6.0 Hz, 1H, H6b), 3.27 (dd, $J_{3,4}$ = 7.2 Hz, $J_{4,5}$ = 8.8 Hz, 1H, H4), 3.50 (s, 3H, OCH_3), 3.73 (s, 3H, Me ester), 3.84 (ddd, 1H, H5), 5.39 (ddd, $J_{2,3}$ = 2.0 Hz,1H, H3), 6.86 (dd, 1H, H2). Its ee was determined by the HPLC analysis at the stage of **2h**, after the hydrolysis of acetate. HPLC [CHIRALCEL® AD-H, 0.46 cm × 25 cm; hexane/isopropyl alcohol = 50:1; flow rate 0.5 mL/min; detected at 220 nm]: t_R (min) = 26.0 (27.7%), 36.7 (72.3%).

(3*S*,4*R*,5*R*)-**2h**: HPLC: t_R (min) = 26.0 (58.2%), 36.7 (41.8%).

2.9. Methyl (3R*,4S*,5S*)-3,4-diacetoxy-5-(tert-butyldimethyl)silyloxy-1-cyclohexenecarboxylate (2j)

To a solution of **2e** (203 mg, 0.67 mmol) in pyridine (2 mL) were added Ac_2O (204 mg, 2.00 mmol, 3.0 equiv.) and 4-*N*,*N*-dimethylaminopyridine (DMAP, 41.5 mg, 0.34 mmol, 0.5 equiv.) under argon atmosphere. The reaction was monitored by silica gel TLC (hexane/AcOEt = 5:1). The mixture was stirred for 2 h at room temperature, then the reaction was quenched with adding water. The organic materials were extracted with AcOEt, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (12 g). Elution with hexane/AcOEt = 5:1 afforded (±)-**2j** (241 mg, 93%) as colorless oil. ^{1}H NMR: δ 0.04 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3), 0.84 (s, 9H, *tert*-butyl), 2.03 (s, 3H, Ac), 2.04 (s, 3H, Ac), 2.34 (ddd, $J_{2,6a}$ = 3.2 Hz, $J_{5,6a}$ = 9.2 Hz, $J_{6a,6b}$ = 18.0 Hz,1H, H6a), 2.68 (ddd, $J_{3,6b}$ = 1.2 Hz, $J_{5,6b}$ = 5.6 Hz, 1H, H6b), 3.74 (s, 3H, Me ester), 3.91 (ddd, $J_{4,5}$ = 9.6 Hz, 1H, H5), 5.11 (dd, $J_{3,4}$ = 7.6 Hz, 1H, H4), 5.53 (ddd, $J_{2,3}$ = 2.0 Hz, 1H, H3), 6.58 (dd, 1H, H2); ^{13}C NMR: δ −5.00, −4.69, 17.7, 20.8, 21.0, 25.5, 33.2, 52.1, 67.9, 71.5, 74.4, 130.2, 134.1, 165.9, 169.9, 170.3; IR: 2958, 2933, 2863, 2362, 1745, 1724, 1437, 1232, 1124, 1052, 1014 cm^{-1}. Its ^{1}H NMR spectra was identical with that reported previously [5]. Anal. Calcd for $C_{18}H_{30}O_7Si$: C 55.93, H 7.82; found: C 55.62, H 7.77.

2.10. C. antarctica lipase B-catalyzed transesterification of (±)-2j

A solution of **2j** (186 mg, 0.48 mmol) in cyclopentanol (3.7 mL) was added Novozym 435 (370 mg), and the mixture was stirred for 24 h at 65 °C. After removal of insoluble materials by filtration with the pad of Celite, the filtrate was concentrated *in vacuo* to give a mixture of (3*R*,4*S*,5*S*)-**2k** and (3*S*,4*R*,5*R*)-**2j** (total 195 mg). The conversion was determined by ^{1}H NMR analysis of crude reaction mixture. The residue was purified by silica gel column chromatography (2 g). Elution with hexane/AcOEt = 4:3 afforded (3*R*,4*S*,5*S*)-**2k** (60.3 mg, 38%, >99.9% ee) and (3*S*,4*R*,5*R*)-**2j** (89.0 mg, 48%, 90.4% ee) as a colorless oil.

(3*R*,4*S*,5*S*)-**2k**: $[\alpha]_D^{23}$ +19.4 (*c* 0.75, $CHCl_3$); ^{1}H NMR: δ 0.08 (s, 3H, SiCH_3), 0.09 (s, 3H, SiCH_3), 0.86 (s, 9H, *tert*-butyl), 2.07 (s, 3H, Ac), 2.41(ddd, $J_{2,6a}$ = 2.4 Hz, $J_{5,6a}$ = 6.0 Hz, $J_{6a,6b}$ = 18.0 Hz, 1H, H6a), 2.58 (ddd, $J_{3,6b}$ = 1.6 Hz, $J_{5,6b}$ = 4.8 Hz, 1H, H6b), 3.76 (s, 3H, Me ester), 4.08 (ddd, $J_{4,5}$ = 7.2 Hz, 1H, H5), 4.19 (ddd, $J_{4,5}$ = 4.8 Hz, 1H, H3), 4.92 (dd, 1H, H4), 6.84 (dd, 1H, H2); ^{13}C NMR: δ −5.02, −4.83, 17.9, 21.1, 25.6, 31.3, 52.1, 67.0, 68.8, 75.4, 127.8, 136.8, 166.8, 171.0; IR: 2933, 2854, 2366, 2326, 1714, 1518, 1252, 1115, 1047, 1007 cm^{-1}. Anal. Calcd for $C_{16}H_{28}O_6Si$: C 55.79, H 8.19; found: C 55.68, H 8.42. HPLC [CHIRALCEL® OD-H, 0.46 cm × 25 cm; hexane/isopropyl alcohol = 30:1; flow rate 0.5 mL/min]: t_R (min) = 30.0 (single peak). The retention time of the antipode was confirmed to be 24.0 min, by the analysis of an authentic specimen of (±)-**2k**. This was prepared as follows: a solution of (±)-**2d** (55.8 mg, 0.13 mmol) was treated with DMAP (7.2 mg, 0.07 mmol, 0.5 equiv.) and Ac_2O (17.0 mg, 0.17 mmol, 1.2 equiv.) in pyridine (200 μL) to give the acetate. Removal of (*p*-methoxy)benzyl group provided (±)-**2k** (18.8 mg, 68% over two steps) as colorless oil.

(3*S*,4*R*,5*R*)-**2j**: $[\alpha]_D^{23}$ +19.1 (*c* 1.55, $CHCl_3$). HPLC [CHIRALCEL® OD-H, 0.46 cm × 25 cm; hexane/isopropyl alcohol = 150:1; flow rate 0.5 mL/min]: t_R (min) = 18.8 (4.8%), 22.7 (95.2%).

2.11. Methyl (3R*,4R*,5S*)-3,4,5-triacetoxy-1-cyclohexenecarboxylate (2l)

To a solution of **3a** (320 mg, 1.88 mmol) in THF (2 mL) were added water (1 mL) and trifluoroacetic acid (300 μL). After stirring for 40 h at room temperature, the mixture was concentrated *in*

vacuo, and the residue was dissolved in pyridine (2 mL). To the mixture were added Ac_2O (1.15 g, 11.3 mmol, 6.0 equiv.) and DMAP (24.4 mg, 0.20 mmol, 0.1 equiv.). The reaction was monitored by silica gel TLC (hexane/AcOEt = 4:1). The mixture was stirred for 4 h at room temperature, then the reaction was quenched with water. The organic materials were extracted with AcOEt, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (30 g). Elution with hexane/AcOEt = 4:1 afforded (±)-**2l** (334 mg, 56%) as colorless oil. ^{1}H NMR: δ 2.00 (s, 3H, Ac), 2.01 (s, 3H, Ac), 2.02 (s, 3H, Ac), 2.37 (ddd, $J_{2,6a}$ = 2.8 Hz, $J_{5,6a}$ = 9.2 Hz, $J_{6a,6b}$ = 18.0 Hz, 1H, H6a), 2.94 (dd, $J_{5,6b}$ = 6.0 Hz, 1H, H6b), 3.71 (s, 3H, Me ester), 5.11 (ddd, $J_{4,5}$ = 9.2 Hz, 1H, H5), 5.25 (dd, $J_{3,4}$ = 7.6 Hz, 1H, H4), 5.55 (ddd, $J_{2,3}$ = 2.4 Hz, 1H, H3), 6.62 (dd, 1H, H2); ^{13}C NMR: δ 20.7, 20.8, 29.3, 52.3, 68.3, 70.9, 71.3, 129.7, 133.9, 165.5, 169.9, 170.0, 170.1; IR: 2962, 2362, 1734, 1708, 1437, 1363, 1227, 1039, 968 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_8$: C 53.50, H 5.77; found: C 53.73, H 5.79.

2.12. *C. antarctica lipase B-catalyzed transesterification of (±)-**2l***

In a similar manner as described for the transesterification of (±)-**2j**, a solution of (±)-**2l** (150 mg, 0.48 mmol) was treated with Novozym 435 (300 mg) in cyclopentanol (3 mL) to give (3*R*,4*R*,5*S*)-**2m** and (3*S*,4*S*,5*R*)-**2n** (70.8 mg) and (3*S*,4*S*,5*R*)-**2l** (50.8 mg, 34%, 56.8% ee) as colorless oil.

Through ^{1}H NMR measurement of the mixture of **2m** and **2n**, the following signals were assigned for each component, respectively. (3*R*,4*S*,5*S*)-**2m**: δ 2.03 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.39 (ddd, $J_{2,6a}$ = 2.8 Hz, $J_{5,6a}$ = 8.8 Hz, $J_{6a,6b}$ = 17.6 Hz, 1H, H6a), 2.89 (ddd, $J_{3,6b}$ = 1.2 Hz, $J_{5,6b}$ = 5.6 Hz, 1H, H6b), 3.74 (s, 3H, Me ester), 4.40 (ddd, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 6.8 Hz, 1H, H3), 5.02 (dd, $J_{4,5}$ = 10.0 Hz, 1H, H4), 5.12 (ddd, 1H, H5), 6.78 (dd, 1H, H2); (3*S*,4*S*,5*R*)-**2n**: δ 2.05 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.36 (ddd, $J_{2,6a}$ = 3.2 Hz, $J_{5,6a}$ = 9.6 Hz, $J_{6a,6b}$ = 18.0 Hz, 1H, H6a), 2.94 (ddd, $J_{3,6b}$ = 1.2 Hz, $J_{5,6b}$ = 5.2 Hz, 1H, H6b), 3.74 (s, 3H, Me ester), 3.93 (ddd, $J_{4,5}$ = 9.6 Hz, 1H, H5), 5.06 (dd, $J_{3,4}$ = 7.6 Hz, 1H, H4), 5.56 (ddd, $J_{2,3}$ = 2.8 Hz, 1H, H3), 6.78 (dd, 1H, H2).

(3*S*,4*S*,5*R*)-**2l**: $[\alpha]_D^{23}$ +28.3 (*c* 2.50, $CHCl_3$). HPLC [CHIRALCEL® AD-H, 0.46 cm × 25 cm; hexane/isopropyl alcohol = 30:1; flow rate 0.5 mL/min]: t_R (min) = 20.6 (21.6%), 21.9 (78.4%).

2.13. *Methyl (3S,4S,5S)-3,4-diacetoxy-5-(tert-butyldimethylsilyloxy)-1-cyclohexenecarboxylate (**1e**)*

To a solution of **2k** (50.0 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (420 μL) were added Et_3N (44.6 mg, 0.44 mmol, 3.1 equiv.) and MsCl (65.6 mg, 0.44 mmol, 3.1 equiv.) under argon atmosphere, and stirred for 10 min at 0 °C. The reaction was quenched with water, and the organic materials were extracted with AcOEt. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in toluene (500 μL) and to that were added 18-crown-6 (73.9 mg, 0.18 mmol, 1.3 equiv.) and CsOAc (84.5 mg, 0.44 mmol, 3.1 equiv.) at 10 °C under argon atmosphere. The mixture was stirred for 48 h at 25 °C, then the reaction was quenched with water. The organic materials were extracted with AcOEt, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (2 g). Elution with hexane/AcOEt = 5:1 afforded **1e** (35.2 mg, 65% over two steps) as colorless oil. ^{1}H NMR: δ 0.07 (s, 3H, SiC*H*$_3$), 0.08 (s, 3H, SiC*H*$_3$), 0.86 (s, 9H, *tert*-butyl), 2.02 (s, 3H, Ac), 2.05 (s, 3H, Ac), 2.32 (ddd, $J_{2,6a}$ = 1.6 Hz, $J_{5,6a}$ = 4.8 Hz, $J_{6a,6b}$ = 18.4 Hz, 1H, H6a), 2.65 (ddd, $J_{3,6b}$ = 2.0 Hz, $J_{5,6b}$ = 4.4 Hz, 1H, H6b), 3.75 (s, 3H, Me ester), 4.14 (ddd, $J_{4,5}$ = 6.8 Hz, 1H, H5), 5.08 (dd, $J_{3,4}$ = 4.0 Hz, 1H, H4), 5.75 (ddd, $J_{2,3}$ = 3.6 Hz, 1H, H3), 6.69 (dd, 1H, H2); ^{13}C NMR: δ −4.96, −4.87, 17.9, 20.9, 25.6, 31.3, 52.1, 65.9, 66.9, 70.2, 131.0, 133.2, 166.5, 170.0, 170.1; IR: 3419, 2952, 2345, 1718, 1446, 1375, 1238, 1041, 927, 843 cm^{-1}. Its ^{1}H NMR spectrum was identical with that reported previously [5].

2.14. *Methyl (3S,4R,5S)-3,4,5-triacetoxy-1-cyclohexenecarboxylate (**1f**)*

To a solution of **1e** (35.2 mg, 0.09 mmol) in THF (1 mL) were added acetic acid (13.2 mg, 0.22 mmol 2.4 equiv.) and tetra-*n*-butylammonium fluoride (TBAF, 1 M solution in THF, 11 μL, 0.11 mmol, 1.2 equiv.). The mixture was stirred for 40 h at 20 °C, then the reaction was quenched with water. The organic materials were extracted with AcOEt, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (2 g). Elution with hexane/AcOEt = 3:1 afforded diacetate (11.2 mg) as colorless oil. This residue was employed for next step without further purification.

This was dissolved in pyridine (300 μL) were added Ac_2O (4.6 mg, 0.45 mmol, 1.2 equiv.) and DMAP (2.3 mg, 0.20 mmol, 0.5 equiv.). The reaction was monitored by silica gel TLC (hexane/AcOEt = 2:1). The mixture was stirred for 2 h at room temperature, and the reaction was quenched with water. The organic materials were extracted with AcOEt, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC with hexane/AcOEt = 2:1 to afford **1f** (10.2 mg, 36% over two steps) as colorless oil. $[\alpha]_D^{23}$ +180 (*c* 0.52, $CHCl_3$) [lit. [6] $[\alpha]_D$−174 (*c* 1.07, $CHCl_3$), for (3*R*,4*S*,5*R*)-**1f**]; ^{1}H NMR: δ 2.03 (s, 3H, Ac), 2.05 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.41 (ddd, $J_{2,6a}$ = 2.0 Hz, $J_{5,6a}$ = 5.2 Hz, $J_{6a,6b}$ = 18.0 Hz, 1H, H6a), 2.58 (ddd, $J_{3,6b}$ = 1.6 Hz, $J_{5,6b}$ = 4.8 Hz, 1H, H6b), 3.75 (s, 3H, Me ester), 5.25 (dd, $J_{3,4}$ = 4.8 Hz, $J_{4,5}$ = 8.0 Hz, 1H, H4), 5.27 (ddd, 1H, H5), 5.71 (ddd, $J_{2,3}$ = 3.6 Hz, 1H, H3), 6.74 (dd, 1H, H2); ^{13}C NMR: δ 20.7, 20.8, 21.0, 52.2, 66.0, 66.8, 67.7, 131.2, 132.7, 165.9, 169.9, 170.0; IR: 1745, 1714, 1439, 1371, 1216, 1036 cm^{-1}. Its NMR spectra were identical with those reported previously [6].

2.15. *Methyl (1R,2S,3S,4R,5R)-3,4-diacetoxy-5-(tert-butyldimethyl)silyloxy-1,2-dihydroxy-cyclohexanecarboxylate (**5a**)*

Diacetate **2j** (259.4 mg, 0.67 mmol) was dissolved in *tert*-BuOH (1.3 mL) and H_2O (1.3 mL). To this, $K_2OsO_2(OH)_4$ (12.5 mg, 0.034 mmol, 0.05 equiv.) and *N*-methylmorpholine *N*-oxide (NMO, 102.2 mg, 0.87 mmol 1.3 equiv.) were added with stirring. The reaction was monitored by silica gel TLC (hexane/AcOEt = 2:1). The mixture was stirred for 2 h at 40 °C, then the reaction was quenched with water. The organic materials were extracted with AcOEt, and the combined extracts were washed with saturated aqueous $Na_2S_2O_3$, brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (10 g). Elution with hexane/AcOEt = 2:1 afforded **5a** (249.4 mg, 89%) as white solid. mp 59.5–60.5 °C; ^{1}H NMR: δ 0.02 (s, 3H, SiC*H*$_3$), 0.03 (s, 3H, SiC*H*$_3$), 0.82 (s, 9H, *tert*-butyl), 1.88 (dd, $J_{5,6a}$ = 10.8 Hz, $J_{6a,6b}$ = 13.6 Hz, 1H, H6a), 1.96 (dd, $J_{5,6b}$ = 5.2 Hz, 1H, H6b), 2.02 (s, 3H, Ac), 2.05 (s, 3H, Ac), 3.59 (br s, 1H, OH), 3.83 (s, 3H, Me ester), 3.92 (d, $J_{2,3}$ = 9.6 Hz, 1H, H2), 4.02 (ddd, $J_{4,5}$ = 9.2 Hz, 1H, H5), 5.02 (dd, $J_{3,4}$ = 9.8 Hz, 1H, H4), 5.10 (dd, 1H, H3); ^{13}C NMR: δ −4.95, −4.68, 17.8, 20.8, 21.0, 25.5, 39.2, 53.6, 67.7, 73.6, 74.0, 75.1, 169.8, 171.5, 173.9; IR: 2954, 2860, 2368, 2324, 1736, 1517, 1240, 1039 cm^{-1}. Anal. Calcd for $C_{18}H_{32}O_9Si$: C 51.41, H 7.67; found: C 51.64, H 7.56.

2.16. Methyl (1R,2S,3S,4R,5R)-2,3,4,5-tetraacetoxy-1-hydroxycyclohexanecarboxylate (**5b**)

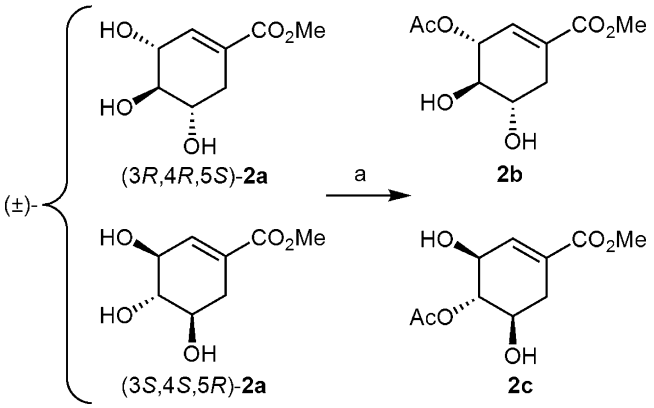
To a solution of **5a** (68.6 mg, 0.15 mmol) in THF (700 μL) were added acetic acid (18 mg, 0.30 mmol, 2 equiv.) and TBAF (1 M in THF, 300 μL, 0.30 mmol, 2 equiv.). The mixture was stirred for 2 d at room temperature, then the reaction was quenched with water. The organic materials were extracted with AcOEt, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was treated with pyridine (100 μL) and Ac_2O (35 μL, 0.33 mmol, 2.2 equiv.) for 12 h at room temperature to afford **5b** (32.0 mg, 55%) as white solid. mp 141–142 °C; ^{1}H NMR: δ 1.96 (s, 3H, Ac), 1.98 (s, 3H, Ac), 1.99 (s, 3H, Ac), 2.00 (s, 3H, Ac), 2.06 (ddd, $J_{2,6a}$ = 2.4 Hz, $J_{5,6a}$ = 4.8 Hz, $J_{6a,6b}$ = 13.6 Hz, 1H, H6a), 2.27 (dd, $J_{5,6b}$ = 4.8 Hz, 1H, H6b), 3.54 (br s, 1H, OH), 3.73 (s, 3H, Me ester), 5.25 (m, 3H), 5.43 (dd, J = 9.6 Hz, J = 10.0 Hz, 1H); ^{13}C NMR: δ 20.4, 20.5, 20.6, 20.8, 34.6, 53.6, 68.6, 70.6, 72.8, 73.6, 169.4, 169.6, 169.7, 169.9, 172.2; IR: 3469, 1741, 1380, 1230, 1034, 956 cm^{-1}. This was employed for the next step without further purification.

2.17. Methyl (3R,4S,5S,6R)-3,4,5,6-tetraacetoxy-1-cyclohexenecarboxylate (**6**)

To a solution of **5b** (29.2 mg, 0.075 mmol) in anhydrous CH_2Cl_2 (600 μL) was added Martin's sulfurane (75.7 mg, 0.11 mmol, 1.5 equiv.). The mixture was stirred for 4 h at room temperature, then the reaction was quenched with water. The organic materials were extracted with AcOEt, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (2 g). Elution with hexane/AcOEt = 3:1 afforded **6** (25.0 mg, 90%) as colorless needles. mp 121–122 °C [lit. [7] mp 122–124 °C]; $[\alpha]_D^{23}$ −39.5 (*c* 1.25, $CHCl_3$) [lit. [7] $[\alpha]_D$ +23 (*c* 0.68, $CHCl_3$), for (2*S*,3*R*,4*R*,5*S*)-**6**]; ^{1}H NMR: δ 1.99 (s, 3H, Ac), 2.01 (s, 3H, Ac), 2.02 (s, 3H, Ac), 2.06 (s, 3H, Ac), 3.74 (s, 3H, Me ester), 5.29 (dd, $J_{2,3}$ = 7.6 Hz, $J_{3,4}$ = 10.4 Hz, 1H, H4), 5.30 (dd, $J_{4,5}$ = 10.4 Hz, 1H, H4), 5.66 (dd, $J_{2,6}$ = 2.0 Hz, 1H, H6), 5.99 (dd, $J_{5,6}$ = 2.8 Hz, 1H, H3), 6.74 (dd, 1H, H2); ^{13}C NMR: δ 20.5, 20.6, 20.6, 20.7, 52.4, 68.9, 69.9, 70.2, 71.7, 130.1, 137.8, 163.9, 169.5, 169.6, 169.8, 169.9; IR: 1734, 1367, 1273, 1223, 1026, 970 cm^{-1}. Its ^{13}C NMR spectra was identical with that reported previously [7].

2.18. (3R,4S,5S,6R)-3,4,5,6-Tetraacetoxy-1-cyclohexenylmethyl acetate (**7b**)

To a solution of **6** (14.3 mg, 0.04 mmol) in anhydrous THF (140 μL) was added DIBAL (300 μL, 0.30 mmol, 7.8 equiv.) at 0 °C. The mixture was stirred for 10 h at room temperature, then the reaction was quenched with water (600 μL) and NaOH aqueous solution (10%, 300 μL). After removal of insoluble materials by filtration with a pad of Celite, the filtrate was concentrated *in vacuo*. The residue was treated with pyridine (100 μL) and Ac_2O (10 μL, 0.33 mmol, 8.3 equiv.) for 12 h at room temperature. Conventional workup and purification afforded **7b** (5.4 mg, 34%) as colorless oil. $[\alpha]_D^{26}$ −61.3 (*c* 0.24, $CHCl_3$); ^{1}H NMR: δ 1.95 (s, 3H, Ac), 1.96 (s, 3H, Ac), 1.98 (s, 3H, Ac), 1.99 (s, 3H, Ac), 2.00 (s, 3H, Ac), 4.32 (d, J = 10.8 Hz, 1H), 4.61 (dd, J = 1.2 Hz, J = 10.4 Hz, 1H), 5.25 (d, J = 14.8 Hz, 1H), 5.30 (d, J = 14.8 Hz, 1H), 5.52 (dd, J = 1.2 Hz, J = 5.6 Hz, 1H), 5.69 (br s, 1H), 5.72 (d, J = 5.6 Hz, 1H); ^{13}C NMR: δ 20.5, 20.6. 20.7, 20.8, 62.4, 70.2, 70.7, 71.9, 72.0, 126.2, 133.6, 169.8, 170.0, 170.2, 170.3; IR: 1745, 1433, 1371, 1209, 1024, 958, 920 cm^{-1}. Its ^{13}C NMR spectra was identical with that reported previously [8].



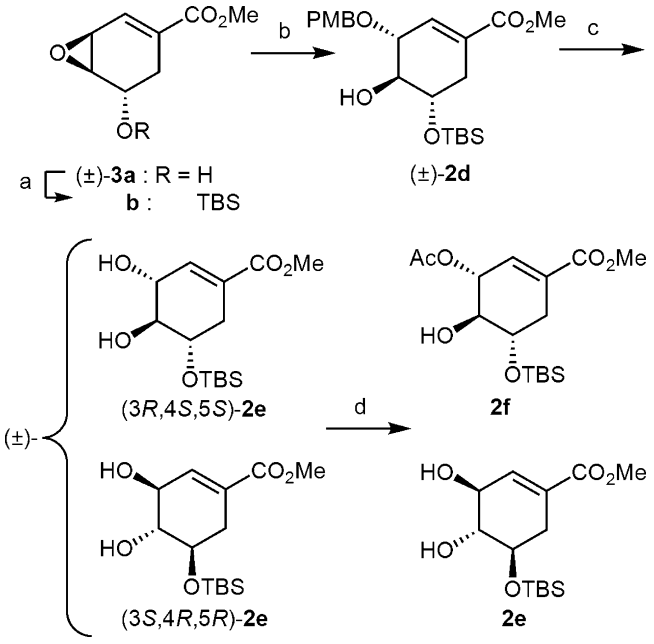
Scheme 2. Reagents and conditions: (a) Novozym 435, vinyl acetate [19% for (3*R*,4*R*,5*S*)-**2b** and 29% for (3*S*,4*S*,5*R*)-**2c**].

3. Results and discussion

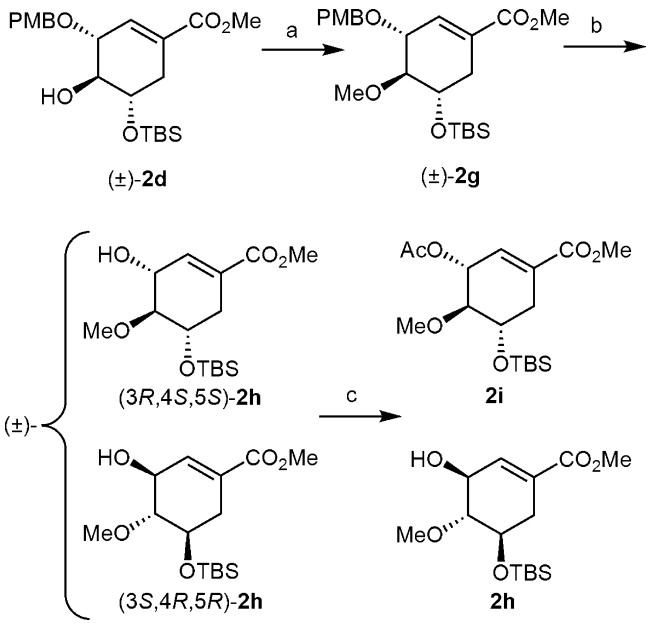
Our first attempt was the acetylation of methyl (±)-3-*epi*-shikimate **2a** (Scheme 2). In contrast to methyl shikimate **1a**, an equimolar formation of C-3 acetate **2b** and C-4 acetate **2c** was observed. The acetylation on C-3 hydroxy group proceeded to give **2b** in an enantioselective manner. By comparison of the sign of optical rotation with a known data [3], the reaction occurred predominantly for the formation of (3*R*,4*R*,5*S*)-isomer.

From the synthetic points of view, the differentiation of two hydroxy group in diols **2b** and **2c** are desirable. Since the hydroxy groups on C-5 in both enantiomers were inert, the introduction of TBS group on that position was considered prior to the lipase-catalyzed reaction.

The preparation of the substrate was shown in Scheme 3. The hydroxy group in literally known racemic epoxide **3** [9] was protected as TBS ether in a conventional manner. For the hydrolysis of epoxy ring, the strong acid such as TFA was not available due to the acid-labile property of TBS ether in this particular case. The formation of PMB ether on an exclusive allylic position was successful by



Scheme 3. Reagents and conditions: (a) TBSCl, imidazole, CH_2Cl_2 (96%); (b) *p*-methoxybenzyl alcohol, $Yb(OTf)_3$ (81%); (c) DDQ, CH_2Cl_2/H_2O (93%); (d) Novozym 435, vinyl acetate [48% for **2f** (73.4% ee) and 34% for **2e** (77.6% ee)].



Scheme 4. Reagents and conditions: (a) Proton Sponge®, Me_3OBF_4, CH_2Cl_2 (69%); (b) DDQ, CH_2Cl_2/H_2O (quant.); (c) Novozym 435, vinyl acetate [20% for **2i** (44.6% ee) and 32% for **2h** (16.4% ee)].

the assistance with $Yb(OTf)_3$ [10], and the subsequent treatment with DDQ provided *trans*-diols (±)-**2e**.

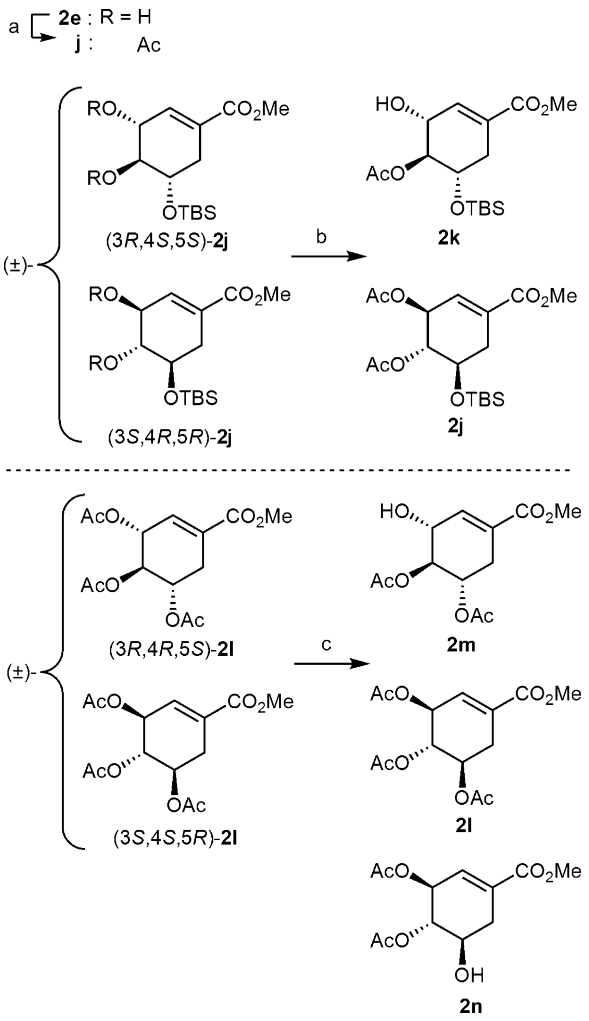
The result of lipase-catalyzed acetylation is shown in Scheme 3. By virtue of bulky TBS ether in an adjacent position, the hydroxy group at C-4 did not react at all. The reaction proceeded on C-3 exclusively and its enantioselective ratio (*E* value) was 15.7. We assumed the reason why the reaction proceeded in an enantioselective manner, to be the difference of steric hindrance of connected to the secondary alcohol at C-3. Then we increased one of hydroxy to methoxy group at C-4 as shown is Scheme 4. From the regioselectively protected synthetic intermediate **2d**, C-4 methoxy derivative (±)-**2h** was prepared by the action of Me_3OBF_4 and Proton Sponge® [11].

To our disappointment, the enantioselectivity (*E* value) was as low as 3.3 for (±)-**2h**, compared with 15.7 for **2e**. Due to an enhanced steric hindrance caused by neighboring methoxy group, it was supposed that the reaction rate of the "fast" (3*R*,4*S*,5*S*)-isomer lowered.

In contrast, we were really surprised that very high enantioselectivity (*E* > 500) was observed when 3,4-diacetate (±)-**2j** was treated with the same enzyme under transesterification conditions (Scheme 5). Even at as high conversion as 47%, the ee of the reaction product [(3*R*,4*S*,5*S*)-**2k**] was >99.9%. We suppose that the higher enantioselectivity is due to an introduction of electron-withdrawing group acetate at C-4, which enhanced the electrophilicity of the acetate at C-3 in (3*R*,4*S*,5*S*)-**2j**, the "fast enantiomer". The repetition of the lipase-catalyzed reaction on the unreacted recovery provided enantiomerically pure (3*S*,4*R*,5*R*)-**2j**.

The blocking of C-5 hydroxy group with bulky TBS group had crucial role on the above successful transformation. When TBS group was replaced with acetate in (±)-**2**, a side reaction, the transesterificaiton on C-5 acetate took place in the "slow" (3*S*,4*S*,5*R*)-isomer to give **2n**. The enantioselectivity (*E* = 3.4) was also lower compared to that in (±)-**2j**.

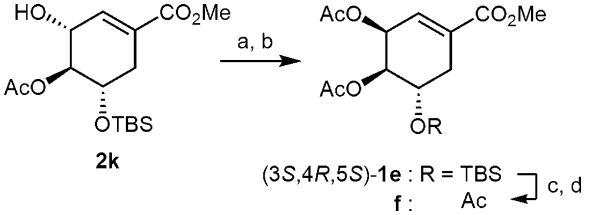
The absolute configuration of the lipase-catalyzed transesterification product, (+)-**2k**, was determined as shown in Scheme 6. First, the stereochemistry of allylic position was invented by the introduction of mesyl group and the subsequent treatment with CsOAc in the presence of 18-crown-6, to give **1e** (65%, over two



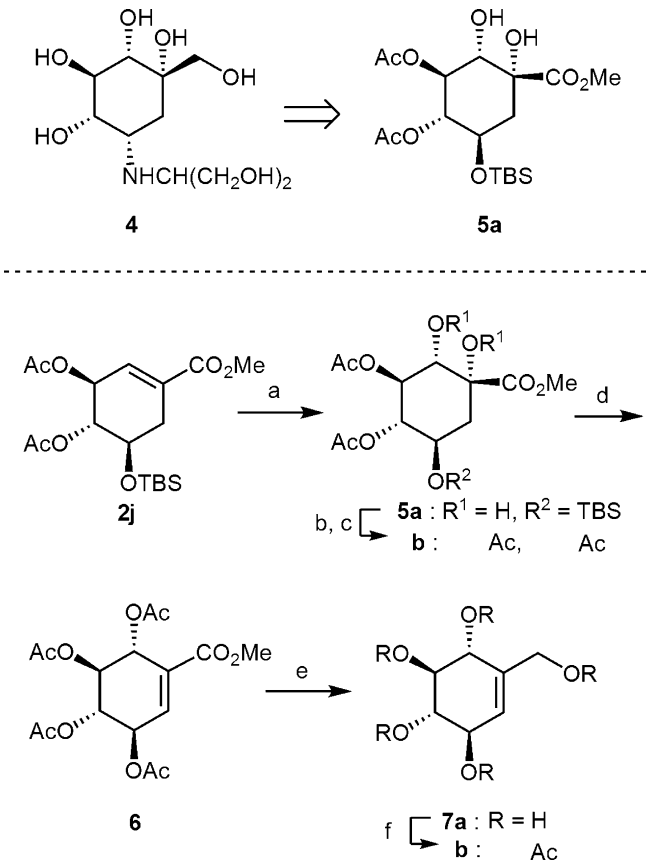
Scheme 5. Reagents and conditions: (a) Ac_2O, DMAP, Py (93%); (b) Novozym 435, cyclopentanol [38% for **2k** (>99.9% ee) and 48% for **2j** (90.4% ee)]; (c) Novozym 435, cyclopentanol [45% for **2m**, 37% for **2b** (56.8% ee) and 18% for **2n**].

steps). During the removal of TBS group in **1e** by treatment with TBAF under weakly acidic conditions, a migration of acetyl group for C-4 hydroxy to C-5 hydroxy group was detected. The liberated C-4 hydroxy group was acetylated to give triacetate (3*S*,4*R*,5*S*)-**1f**. This was an antipodal form of naturally occurring shikimic acid, by comparison of its sign of optical rotation with a literary known data [6].

In this way, the enantiomerically pure 3-*epi*-shikimic acid derivatives **2j** and **2k** became in hand. Towards the bioactive substances with the identical carbon skeleton, such as voglibose **4**, a very potent α-glucosidase inhibitor [12], the stereoselective introduction of additional two hydroxy groups is the indispensable task. *Epi*-shikimate **2j** was found to be a very good precursor



Scheme 6. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2; (b) CsOAc, 18-crown-6, toluene (65% over two steps); (c) TBAF, AcOH, THF; (d) Ac_2O, DMAP, Py (36% over two steps).



Scheme 7. Reagents and conditions: (a) cat. $K_2OsO_2(OH)_4$, NMO, *tert*-BuOH/H_2O (89%); (b) TBAF, AcOH, THF; (c) Ac_2O, Py (55% for two steps); (d) Martin's sulfurane, CH_2Cl_2 (92%); (e) DIBAL, THF; (f) Ac_2O, Py (34% over two steps).

taking advantage of its stereochemistry and protective groups. Dihydroxylation with *in situ*-formed OsO_4 [13] proceeded in an exclusively diastereofacially selective manner to give **5a** in 89% yield (Scheme 7). The orientation of the newly introduced hydroxy groups were unambiguously confirmed to be α, as shown below. After removal of TBS group followed by acetylation of secondary alcohol (66%, over two steps), the resulted tertiary alcohol **5b** was dehydrated by the action of Martin's sulfurane to give (2*R*,3*S*,4*S*,5*R*)-**6** with minus sign of optical rotation. For the antipodal (2*S*,3*R*,4*R*,5*S*)-isomer, plus sign had so far been reported [7]. DIBAL reduction of α,β-unsaturated ester also worked well, 1-*epi*-valienol was obtained as its pentaacetylated form **7b** [8].

4. Conclusion

The effect of substituents on regio- and enantioselectivity for the transformation of polyoxygenated carbacycles under the catalysis by *C. antarctica* lipase B was examined. This achievement is promising to provide new routes to highly oxygenated bioactive cyclohexanoids.

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