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Enzymatic Resolution of the Sterically Hindered *myo*-Inositol Derivative

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A modification of the enzymatic resolution has been developed for the resolution of the sterically hindered *myo*-inositol derivative. In this method, a side chain, which contains a terminal hydroxyl group on it, was introduced to a chiral hydroxyl group, and the terminal hydroxyl group on side chain was used for resolution. Enzymes could recognize the asymmetric center through the distal terminal hydroxyl group. Racemic 3,4,5,6-*O*-tetrabenzyl-*myo*-inositol was resolved by this method.

Lipase-catalyzed kinetic resolution has been developed as a common and efficient method for preparing optically active materials in organic synthesis.[1] However, for some sterically hindered materials, this method does not work. This has been a problem so far.[2] Recently, some reports have appeared concerning the resolution of hindered molecules. N. J. Turner and co-workers had prepared some mixed oxalates of tertiary alcohol (**1**), and wished to resolve the alcohol by hydrolysis of the carboxyl group distal from the chiral center. PPL (*porcine pancreatic* lipase) did hydrolyze the less-hindered carboxyl group. However, good results were obtained when the carboxyl group nearer to the chiral center was hydrolyzed.[3] In preparing optically active 4-aryl-1,4-dihydro-2,6-dimethylpyridine derivatives from 4-aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate (**2**), K. Achiwa and co-workers found that the alkyl ester **2** was inert to enzymatic hydrolysis because of the effect of a sterical hindrance. They have successfully solved this problem by introducing of an acyloxymethyl group to the molecule (**3**) and hydrolysis of the distal carboxyl group (Chart 1).[4]

In our application of enzymes to prepare optically active *myo*-inositol derivatives, we found that some *myo*-inositol derivatives are very sterically hindered and resistant to an enzymatic attack. To release the effect of sterical hindrance, we have considered introducing a side chain containing a terminal hydroxyl group to the sterically hindered hydroxyl group and using the terminal hydroxyl group for resolution. Herein we would like to report on our results.

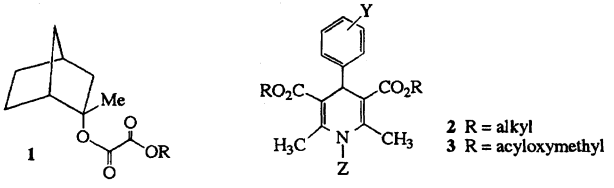
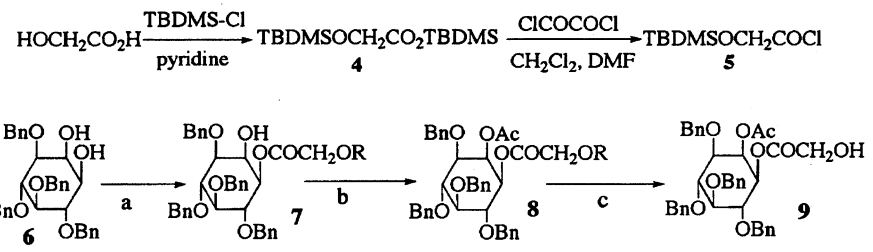


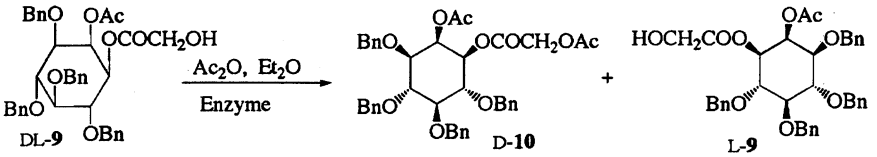
Chart 1.

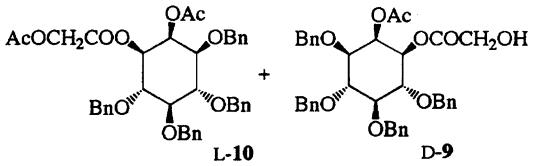
Results and Discussion

3,4,5,6-*O*-Tetrabenzyl-*myo*-inositol, steadily available from *myo*-inositol in high yield,[5] is an important precursor for preparing naturally occuring inositol derivatives.[6] The optical resolution of this material is usually performed by forming its diastereomers and then separating them.[6,7] In our research concerning the preparation of an optically active inositol intermediate and the synthesis of the biologically active inositol phosphate,[8] we have attempted to resolve this material by enzymatic esterification of the hydroxyl groups and enzymatic hydrolysis of the corresponding acetate. We failed, probably due to the effect of hindrance. This prompted us to develop a modification for the enzymatic resolution of such a hindered hydroxyl-group-containing compound. Thus, a side chain having a terminal hydroxyl group was introduced to 3,4,5,6-*O*-tetrabenzyl-*myo*-inositol by an ester bond, because it can be easily cleaved at the same time when the acyl group is removed after resolution. A side chain having two carbons, glycolic acid, was chosen. The preparation of the material is shown in Scheme 1. Both the carboxyl and hydroxyl groups of glycolic acid were protected by silylation to give **4**. Then an acid chloride with a protective group on the hydroxyl group, 2-(*O*-*t*-butyldimethylsilyl) acetyl chloride (**5**), was yielded under a neutral condition from **4**.[9] This acid chloride was used for the acylation of 3,4,5,6-*O*-tetrabenzyl-*myo*-inositol (**6**) without purification. The hydroxyl group at C-1 position of **6** was selectively acylated with 2-(*O*-*t*-butyldimethylsilyl) acetyl chloride to give **7** in the yield of 83%. To prevent the migration of the acyl group, the hydroxyl group at the C-2 position was protected by acetylation. After the silly group had been cleaved,[10]



Scheme 1.



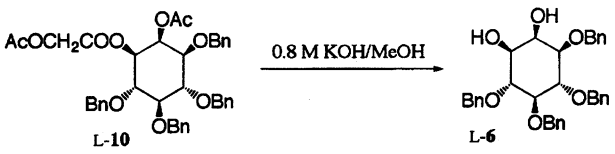
Enzyme	Reaction time	Conversion[a)]	Yield(e.e.)	E[a)]
KWI-56	45 min	49%	39% (66% ee) 49% (64% ee)	10
Lipase PS	12 h	30%	25% (32% ee) 68% (14% ee)	2
Lipase CES	6 h	38%	37% (30% ee) 51% (18% ee)	2
Lipase P	36 h	25%	16% (36% ee) 62% (12% ee)	2
				
SP 435	1 h	67%	64% (46% ee) 25% (94% ee)	9
Lipace AY	3 h	38%	39% (78% ee) 49% (48% ee)	13

a) Calculated by referring to Ref. 2

Scheme 2.

material **9** was obtained in a yield of 95%.

Compound **9** was then subjected to enzymatic esterification. The results are outlined in Scheme 2. The optical purities were analyzed by an HPLC analysis using a chiral column (Chiralcel OD, 2-propanol/hexane=1/5) after the products (D or L-**9** and **10**) were hydrolyzed to tetrabenzyl inositol (**6**). (Scheme 3) The absolute configuration was determined by comparing the specific rotation of the hydrolyzed product (**6**) with the known data.[6e)] Among the enzymes screened, Lipase P, PS, CES (Amano, lipases from *Pseudomunas sp.*), and KWI-56 (Kurita, lipase from *Pseudomonas sp.*) recognized the D-enantiomer through the distal hydroxyl group. Low selectivities were observed with Lipase P, PS, and CES. KWI-56 showed a better selectivity (E=10). Lipase AY (Amano, lipase from *Candida rugosa*) and immobilized enzyme SP-435 (Novo, lipase from *Candida antarctica*) acetylated the hydroxyl group of L-enantiomer [1L-1-*O*-(2-hydroxyacetyl)-2-*O*-acetyl-3,4,5,6-*O*-tetrabenzyl-*myo*-inositol]. A modest selectivity was observed. The E value was 9 and 13, respectively. The D-enantiomer could be obtained in high optical purity (94% e.e.) at the expense of the chemical yield.

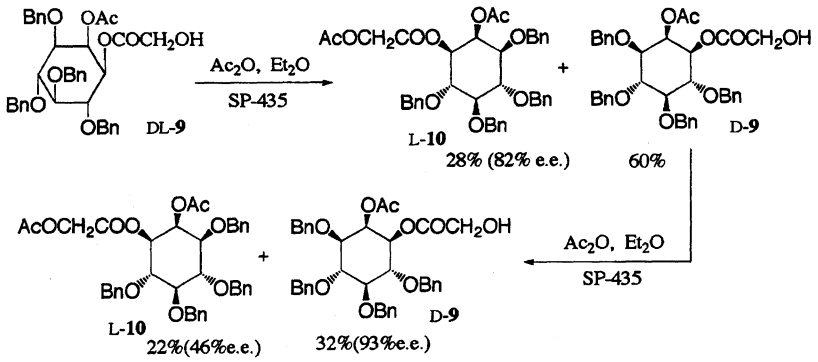


Scheme 3.

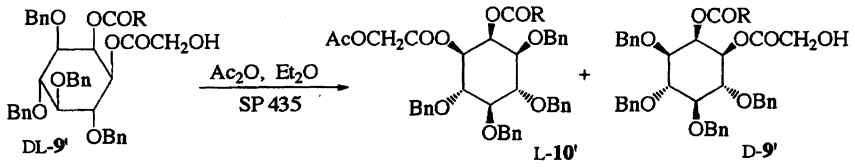
When the esterification was stopped at low conversion, and the recovered material was subjected to the same reaction once more, both enantiomers were obtained at relatively high purity (28%, 82%ee for L-**10** and 32%, 93%ee for D-**9**). (Scheme 4)

The effect of the substituents at the C-2 position and the chain length of the acyl donor has been investigated. The results are shown in Schemes 5 and 6. The selectivity (E value) was strongly affected by the substituents and acyl donor. The E value decreased along with the increasing chain length of the acyl donor and the size of the substituents.

An observation as to whether a sterical hindrance really disturbs the enzymatic reaction was made. Thus, racemic acetate **10** was prepared and subjected to enzymatic hydrolysis, because there are three ester bonds

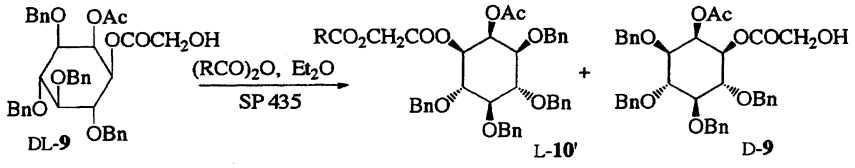


Scheme 4.



R	Reaction time	Conversion	Yield(e.e.)	*E*
Me	45 min	58%	56% (64% ee) 38% (88% ee)	13
Et	30 min	56%	47% (56% ee) 39% (72% ee)	7.5
$(CH_2)_4Me$	1 h	59%	51% (52% ee) 37% (74% ee)	6.6
Ph	1 h	51%	52% (42% ee) 44% (44% ee)	3.7

Scheme 5.

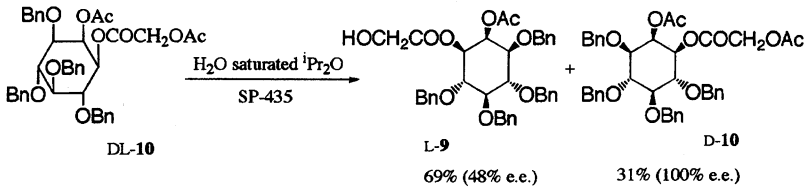


R	Reaction time	Conversion	Yield(e.e.)	*E*
Me	45 min	58%	56% (64% ee) 38% (88% ee)	13
Me_3C	2.5 h	43%	41% (32% ee) 49% (24% ee)	2.4
$(CH_2)_4Me$	45 min	50%	53% (2% ee) 45% (2% ee)	1.1

Scheme 6.

which are all possibly hydrolyzed by an enzyme. If the hindrance really disturbs the attack of the enzyme, then the hydrolysis of **10** should occur at the less-hindered acetate. Considering that the different conformation the enzyme may take in an organic solvent and an aqueous medium and the solubility of the material, the hydrolysis was carried out in an organic solvent, water-saturated diisopropyl ether. (Scheme 7) It was found that the hydrolysis was easier to control than esterification. As has been expected, SP435 hydrolyzed the less-hindered acetate exclusively to give **9**. The reaction was followed by an HPLC analysis (Chiralcel OD column, *i*-PrOH/Hexane=1/20, flow rate, 0.9 ml min^{-1}). The conversion of DL-**10** and the optical purity of both products were analyzed at the same time. The results are shown in Figs. 1 and 2. The change in the optical purity of both products during hydrolysis was clearly observed. The optical purity of L-**9** decreased during hydrolysis, while the optical purity of D-**10** increased. It is thus easy to determine when the reaction should be stopped based on the results shown in Fig. 2. After the reaction had been carried out for 5 d at room temperature, ca. 69% of the material was hydrolyzed to give L-**9** with an enantiomeric excess of 48% and the remaining material (D-**10**, ca. 31%) in optically pure form. After isolation and removal of the acyl groups at D-**10**, optically pure D-**6** was obtained. The calculated *E* value decreased during hydrolysis, indicating the reversible property of the reaction.

3,4,5,6-*O*-Tetrabenzyl-*myo*-inositol (**6**), which is resistant to enzymatic esterification, was resolved by a modified enzymatic resolution in an organic solvent. The phenomenon in which enzyme selectively attacks the less-hindered acetate has been clearly observed in



Scheme 7.

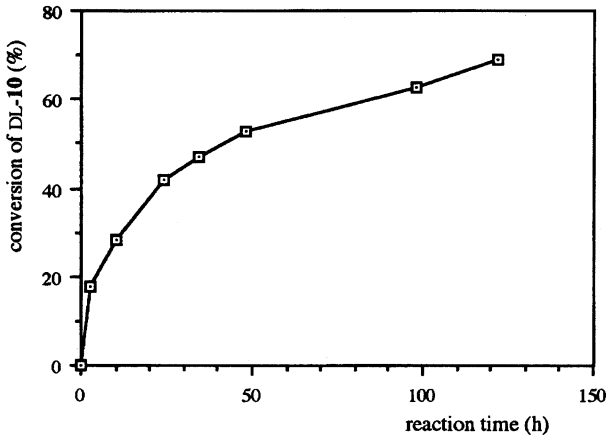


Fig. 1. Enzymatic hydrolysis of DL-**10**.

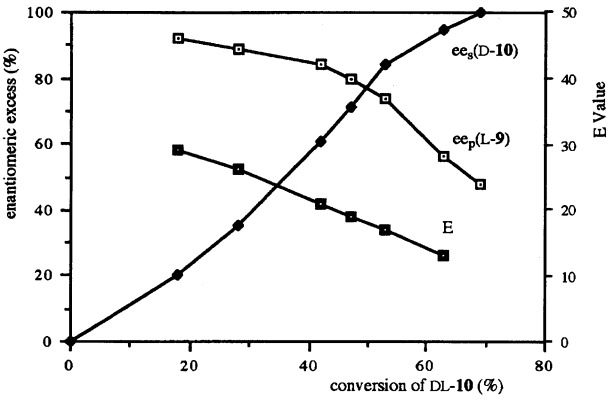


Fig. 2. Enzymatic hydrolysis of DL-**10**.

this method. Application of this method for the resolution of various sterically hindered alcohols and the effect of the length of the side chain on recognizing the asymmetric center by an enzyme are under investigation.

Experimental

All of the solvents and reagents used were of reagent grade; in cases where further purification was required, standard procedures were followed.[11] Thin-layer silica-gel chromatography (silica TLC) was performed on precoated silica gel 60-F254 plates (E. Merck, Darmstadt). Silica gel (300—200 mesh, Wakogel C-300) was used for silica-gel chromatography; the ratio of silica gel to the compound was in the 30 : 1—100 : 1 range. Organic solvents were removed on a rotary evaporator under the vacuum of a water aspirator with a bath temperature of 40 °C or lower. Elemental analyses were performed by the Advanced Center for the Chemical Analysis of Ehime University. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 270 MHz (JEOL GSX-270) with tetramethylsilane ($\delta=0$ in $CDCl_3$) as an internal standard. IR spectra were recorded on a Horiba FT-210 spectrometer. Specific rotations were measured on a Union PM-101 digital polarimeter in a 1 cm cell. The melting points were recorded on a Yanaco melting-point apparatus, and are uncorrected. High-performance liquid chromatography (HPLC) was performed on a Shimazu chromatography system with the purchased column of Chiralcel OD.

Butyldimethylsilyl (Butyldimethylsilyloxy)acetate (4). To a solution of glycolic acid (2.10 g, 27.6 mmol) in anhydrous pyridine (20 ml) was added butyldimethylchlorosilane (9.01 g, 59.7 mmol). The mixture was stirred at room temperature for 2 h. The product was extracted with ether. The ether layer was washed with water, saturated $KHSO_4$, $NaHCO_3$ solution, and brine successively, and dried over Na_2SO_4. After the solvent was removed, the residue was dried under vacuum to give product **4** as a white solid (8.47 g, quantitatively). ^{1}H NMR ($CDCl_3$, 90 MHz) $\delta=0.08$ (s, 6H, $Si(CH_3)_2$), 0.22 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 18H, $C(CH_3)_3$), 4.12 (s, 2H, OCH_2). Calcd for $C_{14}H_{32}O_2Si_2$: C, 55.19; H, 10.61%. Found: C, 54.29; H, 10.75%.

1- *O*- [(Butyldimethylsilyloxy)acetyl]- 3, 4, 5, 6- *O*-tetrabenzyl-*myo*-inositol (7). To a solution of **4** (760.2 mg, 2.5 mmol) in 3 ml CH_2Cl_2 were added successively DMF (40 µl, 0.52 mmol) and oxalyl dichloride (285 µl, 3.27 mmol) at 0 °C. After stirring for 1 h at 0 °C and another 1 h at room temperature, the solvent was removed under reduced pressure by a water aspirator to give crude **5**. Crude **5** was then added to a solution of **6** (344.3 mg, 0.64 mmol) in CH_2Cl_2 (6 ml). To this mixture were added pyridine (2 ml, 39.0 mmol) and a catalytic amount of 4-dimethylaminopyridine at 0 °C. After stirring at 0 °C for 1 h and then room temperature for 1 h, the reaction was quenched by adding water. The product was extracted with ether. The ether layer was washed with a saturated $KHSO_4$ solution, a saturated $NaCO_3$ solution, and brine. The solvent was removed and the residue was subjected to silica chromatography (AcOEt/Hexane=1/6) to afford **7** as crystal (376.1 mg, 83%). R_f 0.24 (AcOEt/Hexane=1/6); mp 79—81 °C; IR (KBr) 3502, 3031, 2931, 1715, 1451, 1360, 1253, and 1139 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) $\delta=0.07$ (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.91 (s, 9H, $C(CH_3)_3$), 1.58 (s, 1H, OH), 3.53 (dd, 1H, $J_{54}=J_{56}=9.5$ Hz, H-5), 3.55 (dd, 1H, $J_{34}=9.5$ Hz, $J_{32}=2.8$ Hz, H-3), 3.94 (dd, 1H, $J_{45}=J_{43}=9.5$ Hz, H-4), 4.06 (dd, 1H, $J_{65}=9.5$ Hz, $J_{61}=10.1$ Hz, H-6), 4.12 (d, 1H, $J=16.9$ Hz, H_A), 4.30 (d, 1H, $J=16.9$ Hz, H_B), 4.30 (dd, 1H, $J_{21}=J_{23}=2.8$ Hz, H-2), 4.63—4.86 (m, 8H, $phCH_2$), 4.89 (dd, 1H, $J_{12}=2.8$ Hz, $J_{16}=10.1$ Hz, H-1), 7.26 (m, 20H, aromatic). Calcd for $C_{42}H_{52}O_8Si$: C, 70.74; H, 7.37%. Found: C, 70.55; H, 7.40%.

1-*O*-[(Butyldimethylsilyloxy)acetyl]-2-*O*-acetyl-3,4,5,6-*O*-tetrabenzyl-*myo*-inositol (8). To a solution of **7** (343.2 mg, 0.48 mmol) in pyridine (6 ml) were added acetic anhydride (2 ml) and a catalytic amount of 4-dimethylaminopyridine. The mixture was stirred at room temperature for 1 h. The reaction was quenched by adding water. The product was extracted with ethyl acetate. The organic layer was washed with a saturated $KHSO_4$ solution, a saturated $NaHCO_3$ solution, and brine. The solvent was removed, and the residue was chromatographed (silica gel, AcOEt/Hexane=1/7) to give **8** as an oil (361.0 mg, 99%). R_f 0.36 (AcOEt/Hexane=1/7); IR (KBr) 3066, 2954, 1774, 1747, 1454, 1367, 1234, and 1128 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=0.07 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $C(CH_3)_3$), 2.12 (s, 3H, Ac), 3.56 (dd, 1H, $J_{54}=J_{56}=9.5$ Hz, H-5), 3.60 (dd, 1H, $J_{34}=9.5$ Hz, $J_{32}=3.1$ Hz, H-3), 3.89 (dd, 1H, $J_{45}=J_{43}=9.5$ Hz, H-4), 3.94 (dd, 1H, $J_{65}=9.5$ Hz, $J_{61}=10.4$ Hz, H-6), 4.13 (dd, 2H, $J=16.8$ Hz, OCH_2), 4.47—4.92 (m, 8H, $phCH_2$), 4.96 (dd, 1H, $J_{12}=2.8$ Hz, $J_{16}=10.4$ Hz, H-1), 5.73 (dd, 1H, $J_{21}=2.8$ Hz, $J_{23}=3.1$ Hz, H-2), 7.25—7.30 (m, 20H, aromatic). Calcd for $C_{44}H_{54}O_9Si$: C, 69.99; H, 7.22%. Found: C, 69.56; H, 7.20%.

1-*O*-(2-Hydroxyacetyl)-2-*O*-acetyl-3,4,5,6-*O*-tetrabenzyl-*myo*-inositol (9). To a solution of **8** (338.8 mg, 0.45 mmol) in THF were added acetic acid (77 µl, 1.35 mmol) and tetrabutylammonium fluoride (1 M in THF, 900 µl, M=mol dm^{-3}). After stirring at room temperature for 3 h, the mixture was diluted with ethyl acetate and washed with water, a saturated $NaHCO_3$ solution, and brine. The solvent was removed, and the residue was chromatographed (silica gel, $CHCl_3/Et_2O$=3/1) to give **9** (270.3 mg, 95%). R_f 0.36 ($CHCl_3/Et_2O$=3/1); mp 122—124 °C, IR (KBr) 3465, 3064, 2875, 1758, 1454, 1363, and 1263 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=2.13 (s, 3H, Ac), 2.23 (s, 1H, OH), 3.58 (dd, 1H, $J_{54}=J_{56}=9.5$ Hz, H-5), 3.61 (dd, 1H, $J_{34}=9.8$ Hz, $J_{32}=2.8$ Hz, H-3), 3.86—4.05 (m, 4H, H-4, H-6, OCH_2), 4.49—4.94 (m, 9H, H-1, $phCH_2$), 5.71 (dd, 1H, $J_{21}=J_{23}=2.8$ Hz, H-2), 7.24 (m, 20H, aromatic). Calcd for $C_{38}H_{40}O_9$: C, 71.22; H, 6.30%. Found: C, 70.86; H, 6.21%.

General Procedure for Enzymatic Esterification of DL-9. To a solution of **9** (33.4 mg, 0.05 mmol) in ether were added enzyme Lipase AY (160.4 mg) and acetic anhydride (15 µl, 0.16 mmol). The suspension was stirred at room temperature. The reaction was monitored by TLC. The enzyme was filtered off after the conversion reached about 50%. The filtrate was evaporated to remove the solvent, and the residue was chromatographed (silica gel, AcOEt/Hexane=1/2) to give ester **10** (13.4 mg, 39%) and unreacted material **9** (16.3 mg, 49%).

10: R_f 0.38 (AcOEt/Hexane=1/2); $[\alpha]_D^{23}$ −5.3° (*c* 1.13, AcOEt, 82% ee from HPLC analysis); IR (neat) 3031, 2941, 1770, 1739, 1454, 1373, 1240, and 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=2.14 (s, 6H, Ac), 3.56 (dd, 1H, $J_{54}=J_{56}=9.5$ Hz, H-5), 3.59 (dd, 1H, $J_{34}=9.8$ Hz, $J_{32}=2.8$ Hz, H-3), 3.89 (dd, 1H, $J_{45}=9.5$ Hz, $J_{43}=9.8$ Hz, H-4), 3.93 (dd, 1H, $J_{65}=9.5$ Hz, $J_{61}=13.1$ Hz, H-6), 4.42 (d, 1H, $J=15.9$ Hz, H_A), 4.50 (d, 1H, $J=15.9$ Hz, H_B), 4.47—4.93 (m, 8H, $phCH_2$), 4.94 (dd, 1H, $J_{12}=2.8$ Hz, $J_{16}=13.1$ Hz, H-1), 5.72 (dd, 1H, $J_{21}=J_{23}=2.8$ Hz, H-2) 7.32 (m, 20H, aromatic). Calcd for $C_{40}H_{42}O_{10}$: C, 70.36; H, 6.21%. Found: C, 70.08; H, 6.21%.

9: R_f 0.16 (AcOEt/Hexane=1/2); $[\alpha]_D^{23}$ +8.0° (*c* 1.13, AcOEt, 93% ee from HPLC analysis).

General Procedure for Enzymatic Hydrolysis of DL-10. To a solution of DL-**10** (30.0 mg, 0.04 mmol) in water-saturated diisopropyl ether was added SP435 (120.0 mg). The suspension was stirred at room temperature. The hydrolysis was followed by an HPLC analysis (Chiralcel OD column, *i*-PrOH/hexane=1/20). After the reaction had been carried out for 5 d, the enzyme was filtered off. The filtrate was subjected to silica-gel chromatography to give L-**9** (19.0 mg, 67%) and D-**10** (9.5 mg, 32%).

Hydrolysis of Acyl Group of 9 and 10. Compound L-**10** (7.4 mg, 0.01 mmol) was dissolved in 0.80 M KOH/MeOH (1 ml). The mixture was stirred at room temperature for 1h. The product was extracted with ethyl acetate. The ethyl acetate layer was washed with water. After the solvent was removed, the residue was chromatographed to give 3,4,5,6-*O*-tetrabenzylinositol (5.9 mg, quantitatively). This sample was used to determine the optical purity by HPLC analysis. $[\alpha]_D^{22}$ +18.4° (*c* 0.76, $CHCl_3$, 82% ee from HPLC analysis); mp 142—143 °C (lit,[6e] $[\alpha]_D^{20}$ +25.0° *c* 0.18, $CHCl_3$; mp 140.2—142.1 °C).

3,4,5,6-*O*-Tetrabenzyl-*myo*-inositol from D-10. $[\alpha]_D^{29}$ −23.0° (*c* 0.17, $CHCl_3$, 100% ee from HPLC analysis); mp 144—145 °C (lit,[6e] $[\alpha]_D^{20}$ −24.3° *c* 1.3, $CHCl_3$; mp 141.0—143.0 °C).

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