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Synthesis of Chiral Building Blocks Using *Pseudomonas Fluorescens* Lipase Catalyzed Asymmetric Hydrolysis of *Meso* Diacetates

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Key Words: asymmetric hydrolysis; *Pseudomonas fluorescens* lipase; *meso*-diacetate; chiral building block; (-)-muscone

Abstract: *Two chiral building blocks were prepared using a lipase-catalyzed asymmetric hydrolysis of the corresponding meso-diacetates. The chirality in the hydrolyzed products was conveniently incorporated into that of (R)-muscone and hunger modulator.*

Introduction

Catalytic asymmetric synthesis (CAS)[1] is still a challenging synthetic endeavour although much progress has been made over the last twenty years. Basically, CAS can be divided into two categories. First is a chemical system. Catalytic asymmetric epoxidation based on titanium-tartrate[2] represents a milestone in the history of CAS. Second is the utilization of a biological system. Among many types of enzymatic reactions, enzyme catalyzed asymmetric hydrolysis[3] is one of the most applicable reactions for the preparation of chiral molecules, which is difficult to emulate chemically. Both the chemical and biological systems have their advantages and disadvantages, and they complement each other.

We have successfully developed several chemical systems[4] for asymmetric operations on prochiral compounds. Also, we have recognized the importance and efficiency of adapting enzymes for asymmetric synthesis.[5] Specifically, our interest involves the use of lipase-catalyzed asymmetric hydrolysis of *meso*-diacetates. The use of a *meso*-substrate as a starting material has the following advantages. Firstly, 100% of the starting material can be consumed theoretically. Secondly, the reaction process in the hydrolysis of a *meso*-diacetate contains the enantioselective hydrolysis of the diacetate and an inherent kinetically resolution, which enhances the enantioselectivity of monoacetate. Finally, the resulting monoacetate has a bifunctional group, which can be elaborated synthetically at both ends. Lipases such as *Pseudomonas fluorescens* lipase (PFL) have been studied extensively in our laboratory.[6] We have successfully used PFL for resolving a series of racemic cyclic acetates and for the asymmetric synthesis of biologically active compounds. In this report, we will emphasize the

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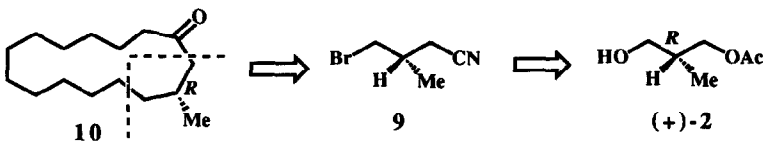
usefulness of PFL in the asymmetric hydrolysis of *meso*-diacetates and the application of this reaction to the conventional synthesis of chiral molecules. The stereospecifity for PFL has also been rationalized according to the stereo model proposed by us.[6] Specifically, this study has the following objectives: To see 1) whether PFL can accept an acyclic acetate and to obtain further understanding of this enzyme's specificity towards the substrate; 2) whether both substrates (**1** and **16**) would be useful chiral precursors, which can be incorporated into more sophisticated molecules.

Results and Discussion

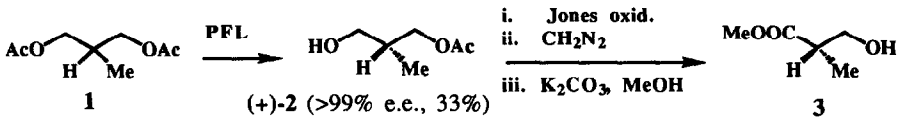
1) Construction of bifunctional chiral C4 and C5 building blocks.

During our synthetic efforts to utilize novel ring expansions for the synthesis of large-sized rings,[7] we became interested in preparing (-)-muscone **10**. It was envisaged that a chiral C5 building block like **9** could be incorporated into **10** by means of a facile three-carbon ring expansion. We therefore turned our attention to preparation of compound **9** *via* compound **2** (Scheme 1).



Scheme 1

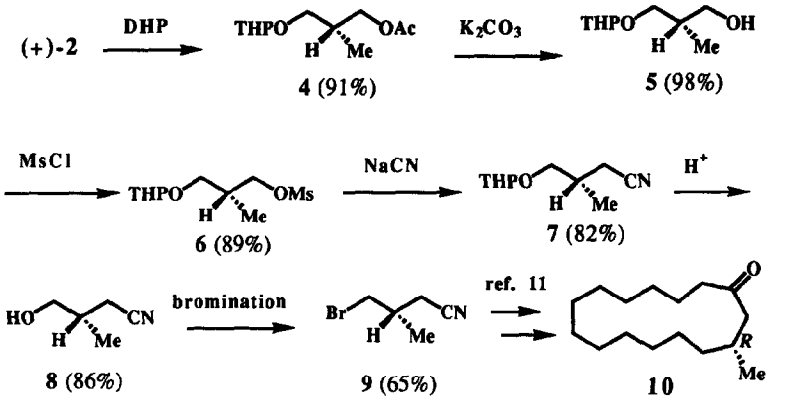
In order to develop a chemo-enzymatic method for the preparation of **9**, 1,3-diacetoxy-2-methylpropane **1** was chosen as a substrate. Substrate **1** (0.03 M solution in 0.1 M phosphate buffer, pH 7) was subjected to hydrolysis with PFL (87 mg/mmol substrate). After being stirred for 1.5 h at 25°C, the monoacetate (+)-**2** (>99% e.e., 33% yield) was obtained in addition to the recovered substrate **1** (62%). The enantiomeric excess of (+)-**2** was determined by Mosher's method[8] after conversion into the corresponding (+)-MTPA ester. In the ^{1}H NMR spectrum of (+)-MTPA ester derived from (*dl*)-**2**, acetoxy signals attributable to the corresponding diastereomers appeared at distinctly different fields (2.06 and 2.04 ppm), while that of (+)-MTPA ester derived from (+)-**2** showed only one peak at 2.04 ppm. The absolute configuration of (+)-**2** was confirmed by conversion into (+)-methyl 3-hydroxyl-2-methylpropionate **3**[9] by a sequence of three-step reactions (i. Jones oxidation; ii. esterification with CH_2N_2; iii. methanolysis with K_2CO_3)(Scheme 2).



Scheme 2

This chiral C4 building block (+)-**2** was readily converted to a bifunctional chiral C5 isoprenoid **9** by standard procedures. Protection of (+)-**2** with DHP in the presence of *p*-TsOH gave **4**. Hydrolysis of **4** provided alcohol **5**. One carbon elongation of **5** was undertaken by conversion into the corresponding mesylate **6** followed by introduction of the nitrile function. Deprotection of **7** generated a free hydroxyl group on the other side, which was converted into the corresponding bromide **9**. A common unit of isoprenoid such as **9** was found in natural products of both synthetic and biological interest; *e.g.* tocopherol, phylloquinones phytol, and insect

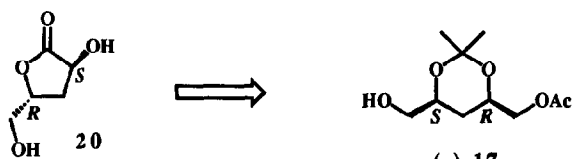
pheromones.[10] A straightforward application of the chiral C5 building block **9** was undertaken by incorporating it into (-)-muscone **10** using a key ring expansion reaction developed by us[11] (Scheme 3). It is noted that chiral alcohols such as (+)-**2** are valuable in the synthesis of polyether antibiotics.[12]



Scheme 3

2 Preparation of a novel chiral building block containing 1,3-*syn*-diol unit

A 1,3-*syn*-diol moiety is often found in polyoxy-generated natural products such as polyene macrolide antibiotics.[13] We designed the novel route to chiral 1,3-*syn*-diol unit based on asymmetric hydrolysis of *meso*-diacetate and its application to the synthesis of hunger modulator **20**[14] (Scheme 4).



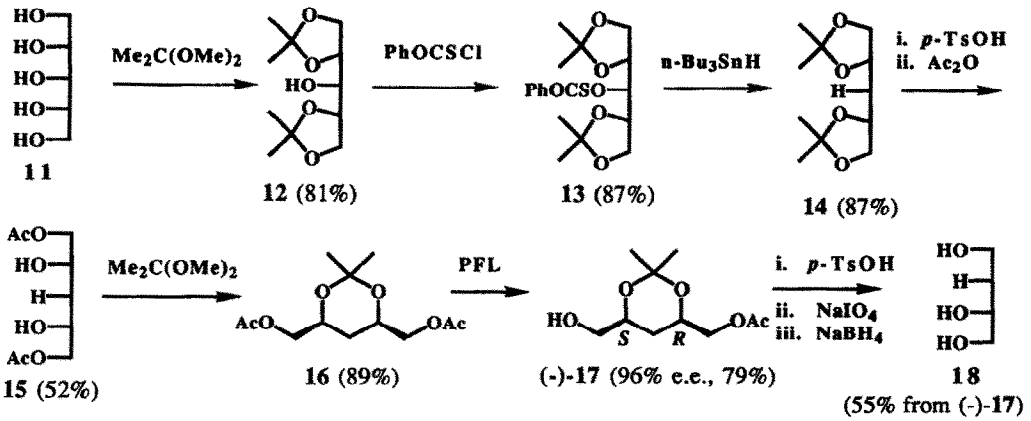
Scheme 4

In a preliminary experiment, we found that hydrolysis of 4,5-*cis*-bis(acetoxymethyl)-2,2-dimethyl-1,3-dioxolane with PFL resulted in the formation of optically inactive monoacetate. One reason may be due to an inherent feature of a five-membered ring system, as observed in the case of porcine liver esterase (PLE)-catalyzed hydrolysis of 1,2-*cis*-cyclopentanedicarboxylate.[15] Another reason may be possible acyl-migration attributable either to the enzyme or to the work-up. To overcome these potential obstacles, we envisaged that the conformationally rigid compound **16** would be a preferable substrate, in which the two acetoxymethyl groups should be located in a 1,3-diequatorial orientation.

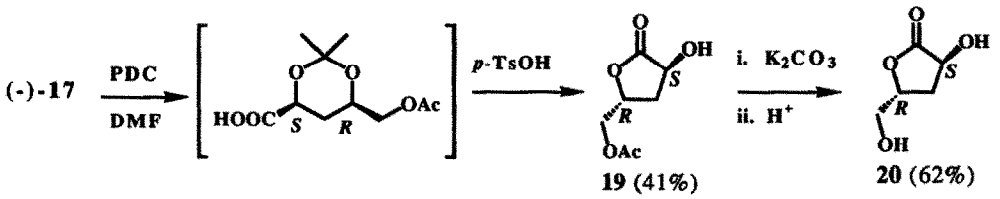
Commercially available adonitol **11** was selected as a starting material to prepare **16**, which needs only removal of C3-hydroxy function. This was realized by conversion of **11** into the phenoxythiocarbonyl ester **13** by means of acetalization with 2,2-dimethoxypropane and subsequent treatment with PhOCSCl/4-(dimethylamino)-pyridine. Deoxygenation of **13** with Bu_3SnH gave diacetonide **14**. Deacetalization of **14** with *p*-TsOH in methanol followed by regioselective acetylation with acetic anhydride/pyridine under ice cooling gave diacetate **15**. Subsequent acetalization of **15** afforded *meso*-diacetate **16**. In accordance with our expectation,

hydrolysis of **16** (0.017 mM solution in 0.1 M phosphate buffer pH 7) with PFL (91 mg/mmol substrate) afforded monoacetate (-)-**17** (96% e.e., 79% yield). The absolute configuration was determined by transforming (-)-**17** into (*R*)-1,2,4-butanetriol **18**[9] by means of deacetalization with *p*-TsOH followed by treatment with $NaIO_4$ and then reduction with $NaBH_4$ (Scheme 5).

The above procedure provided a practical and efficient synthesis of the chiral 1,3-*syn*-diol unit. Next, (-)-**17** was used to synthesize **20** which has hunger modulating activities. Oxidation of (-)-**17** with pyridinium dichromate (PDC) in DMF followed by treatment with *p*-toluenesulfonic acid in CH_2Cl_2 afforded lactone **19**. Hydrolysis of **19** with 4% K_2CO_3 in methanol and subsequent lactonization with 5% aqueous HCl provided the target **20**.



Scheme 5



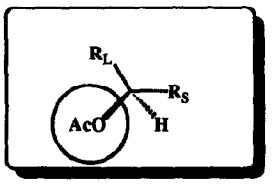
Scheme 6

3) Stereochemical observations relating to the PFL catalyzed hydrolysis of acetates of primary alcohols

Our previous investigations have demonstrated that cyclic acetates of secondary alcohols are in general hydrolyzed by PFL with higher enantioselectivity. A simple model can be deduced as depicted in Figure 1, in which the acetate of a secondary alcohol with *R*-configuration is always preferentially hydrolyzed. RL in this model represents a larger substitutent than RS. In general, RL accepts more polar residues, while a less polar substitutent prefers to fit into the RS region.

In this study, we succeeded in the enantioselective hydrolysis of two kinds of *meso*-diacetates of primary alcohols using PFL. We did not restrict our attention to only their synthetic application, but we were also

interested in proposing a similar model for PFL-catalyzed hydrolysis of acetates of primary alcohol in acyclic or cyclic structure.



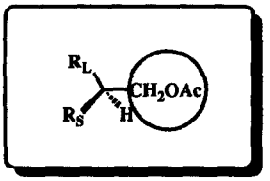
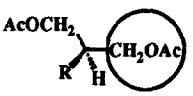


Figure 1



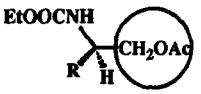


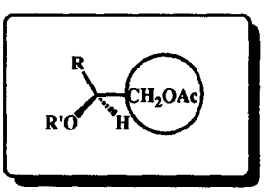
Figure 2

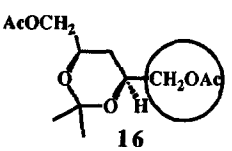
Substrates to be analyzed are divided into two types.

1) Type 1 substrate, in which two side chains contain no oxygen atoms adjacent to the stereogenic carbon, simply follows the rule as shown in Figure 2. The acetate to be hydrolyzed is marked with a circle. The definition of RL and RS is the same as that described in Figure 1. When RS is a methyl group and RL is an acetoxymethyl group, the substrate is 1,3-diacetoxy-2-methylpropane **1**, which is enantioselectivly hydrolyzed to provide *R*-alcohol. This enantioselectivity is also acceptable to the substrate, in which R is an alkyl substitutent as reported by Bianchi *et al.*[16] The substrate, in which RL is represented by a alkoxycarbonylamide and RS is an alkyl substituent, was also hydrolyzed in the same fashion.[17]

2) Type 2 substrate, in which an oxygen atom is directly attached to the stereogenic center, complies in the general fashion shown in Figure 3. Substrates such as bis(acetoxymethyl)-1,3-dioxane **16** in this study, 1,3-dioxolane acetate **21**[18] as well as 2-*O*-benzyl glycerol diacetate **22**[19] belong to this type.

Figure 3





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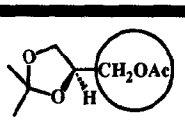

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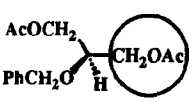

22

We still feel that more literature data are necessary in order to prepare a refined stereomodel. It should be mentioned that such a model is very useful in predicting the stereochemical outcome for a simple substrate. If a substrate contains one or more hetero-atoms near the stereogenic center, extreme care is required in using such a model. We believe that such a substrate model will be certainly helpful in providing necessary information about the active site of enzymes.

Experimental

Infrared (IR) spectra were measured on a JASCO A-202 spectrometer. ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectra were measured with a JEOL JNM-PX-100 or a JNM-GX 270 spectrophotometer. Mass spectra

were taken on a JEOL JMS-D 300 spectrometer. For column chromatography, silica gel (Merck, Kieselgel 60, 70-230 mesh) was used.

(*R*)-3-Acetoxy-2-methyl-1-propanol ((+)-2) A suspension of diacetate **1** (1g, 5.75 mmol) and PFL (500 mg) in 0.1 M phosphate buffer (pH 7) was stirred for 1.5 h at 25°C. The reaction mixture was extracted with ether. Extract was washed with brine and then dried. Removal of organic solvent gave a residue which was purified by silica-gel chromatography eluted with AcoEt/Hexane (1:1) to afford **1** (620 mg, 62%) and (+)-2 (252 mg, 33%) as a colorless oil. $[\alpha]_D^{25}$ +7.11 (*c*=0.9, $CHCl_3$); IR (neat) 3440, 2960, 1740, 1470, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) 4.10 (d, *J*=8.2Hz, 2H), 3.56 (d, *J*=1.3Hz, 2H), 2.06 (s, 3H), 1.98 (s, 1H), 1.89 (m, 1H), 0.97 (d, *J*=10.1Hz, 3H); MS, *m/z* 114 (M^+-H_2O), 72, 61, 43. HRMS for $C_6H_{10}O_2$ (M^+-18): Calcd *m/z* 132.0786; Found 132.0792.

(2*R*)-1-Acetoxy-3-(tetrahydropyran-2-yl)oxy-2-methylpropane (4) A mixed solution of (+)-2 (660 mg, 5 mmol), dihydropyran (460 mg, 5.5 mmol) and *p*-TsOH (20 mg) in CH_2Cl_2 (10 ml) was stirred for 2 h at 25°C. After usual work-up, the crude product was purified by silica-gel column chromatography. Elution with AcOEt/hexane (1:5) gave **4** (980 mg, 91%) as a colorless oil. IR 2950, 1740, 1460, 1370 cm^{-1}; MS, *m/z* 214 (M^+).

(2*S*)-3-(Tetrahydropyran-2-yl)oxy-2-methyl-1-propanol (5) Solvolysis of **4** (2.5 g, 11.7 mmol) with K_2CO_3 (0.5 g) in MeOH (15 ml) at room temperature in usual manner afforded **5** (2.0 g, 98%) as a colorless oil. IR 3450, 2950, 1450, 1380, 1200 cm^{-1}; ^1H NMR 4.95 (m, 1H), 3.90-3.25 (m, 6H), 2.63 (s, 1H), 2.12 (m, 1H), 1.90-1.45 (m, 6H), 0.92 (d, *J*=6.8Hz, 1.5H), 0.90 (d, *J*=6.8 Hz, 1.5H); MS, *m/z* 174 (M^+), 156, 144, 101, 85.

(2*R*)-3-(Tetrahydropyran-2-yl)oxy-1-methanesulfonyloxy-2-methylpropane (6) Methanesulfonyl chloride (1.16 ml, 15 mmol) was added dropwise to a solution of **5** (2 g, 11.5 mmol) in pyridine (10 ml) at 0°C. After being stirred for 2 h at room temperature, the reaction mixture was poured into cold 5% HCl, which was extracted with AcOEt and washed with 5% aqueous $NaHCO_3$, and brine. Chromatography eluted with AcOEt/hexane (1:2) afforded **6** (258 mg, 89%) as a colorless oil. IR 2950, 1470, 1360, 1200 cm^{-1}; ^1H NMR 4.52 (m, 1H), 4.20 (m, 2H), 3.90-3.20 (m, 4H), 3.02 (s, 3H), 2.18 (m, 1H), 1.90-1.40 (m, 6H), 1.04 (d, *J*=6.8Hz, 3H); MS, *m/z* 252 (M^+), 237, 156.

(3*S*)-4-(Tetrahydropyran-2-yl)oxy-3-methylbutanenitrile (7) A mixed solution of **6** (2.25 g, 8.9 mmol) and NaCN (540 mg, 11 mmol) in DMSO (10 ml) was heated at 90°C for 5 h.the reaction mixture was diluted with brine, and extracted with AcOEt. Usual work up gave a crude product, which was subjected to column chromatography on silica gel. Elution with AcOEt/hexane (2:5) afforded **7** (1.33 g, 82%) as a colorless oil. IR 2950, 2250, 1460, 1380 cm^{-1}; ^1H NMR 4.59 (m, 1H), 3.90-3.45 (m, 3H), 3.38 (dd, *J*=9.9, 4.8 Hz, 0.5H), 3.21 (dd, *J*=9.9, 1.9 Hz, 0.5H), 2.59-2.32 (m, 2H), 2.17 (m, 1H), 1.90-1.50 (m, 6H), 1.10 (d, *J*=6.8 Hz, 1.5H), 1.09 (d, *J*=6.8 Hz, 1.5H); MS, *m/z* 183 (M^+), 153, 143.

(*S*)-4-Hydroxy-3-methylbutanenitrile (8) A solution of **7** (1.2 g, 6.6 mmol) in acetic acid (4 ml), tetrahydrofuran (4 ml) and water (4 ml) was stirred for 20 h at 45°C. The mixture was poured into 5% aqueous $NaHCO_3$ solution and extracted with AcOEt. The extract was washed with 5% aqueous $NaHCO_3$ and brine, then dried. Purification by silica-gel column chromatography afforded **8** (559 mg, 86%) as a colorless oil. $[\alpha]_D^{25}$ -32.2 (*c*=1,1, $CHCl_3$); IR 3450, 2950, 2250, 1460, 1260 cm^{-1}; ^1H NMR 3.59 (dd, *J*=18.3, 10.1 Hz, 1H), 3.53 (dd, *J*=18.3, 10.1 Hz, 1H), 2.54 (dd, *J*=16.6, 6.1 Hz, 1H), 2.34 (dd, *J*=16.6, 6.1 Hz, 1H), 2.08 (s, 1H), 2.06 (m, 1H), 1.10 (d, *J*=6.6 Hz, 3H); MS, *m/z* 99 (M^+), 81, 68.

(*S*)-4-Bromo-3-methylbutanenitrile (9) To a solution of **8** (500 mg, 5 mmol) and *N*,*N*'-carbonyldiimidazole (810 mg, 5 mmol) in acetonitrile (15 ml), allyl bromide (2.15 ml, 25 mmol) was added dropwise at 0°C. The whole was stirred for 30 min at room temperature, and then refluxed for 2 h. After being cooled, the mixture was diluted with brine. The whole was extracted with AcOEt. The extract was successively washed with 10% HCl, 5% $NaHCO_3$ and brine. Removal of the solvent gave an oily residue, which was purified by chromatography on silica gel to afford **9** (505 mg, 65%) as a colorless oil. $[\alpha]_D^{21}$ -20.1 (*c*=1.6, $CHCl_3$); IR 2250, 1460, 1380 cm^{-1}; ^1H NMR 3.45 (dd, *J*=15, 10.6 Hz, 1H), 3.40 (dd, *J*=10.4, 10.4 Hz, 1H), 2.60 (dd, J=16.7, 6.6 Hz, 1H), 2.42 (dd, *J*=16.7, 5.1 Hz, 1H), 2.22 (m, 1H), 1.21 (d, *J*=6.6 Hz, 3H); MS,

m/z 163 (M^++2), 161 (M^+), 148, 146, 123, 121. HRMS for C_5H_8NBr (M^+): Calcd *m/z* 160.9841; Found 160.9849.

(1,2),(4,5)-Bis-*O*-(isopropylidene)adonitol (12) A mixture of adonitol **11** (5 g, 33 mmol), 2,2-dimethoxypropane (6 ml, 49 mmol), acetone (2.5 ml, 34 mmol) and *p*-TsOH H_2O (20 mg, 0.11 mmol) in dry *N,N*-dimethylformamide (20 ml) was stirred for 5 h at room temperature. The mixture was diluted with benzene (150 ml), washed with 5% $NaHCO_3$ and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to silica gel column chromatography. Eluent from AcOEt/hexane (1:4) afforded **12** (6.2 g, 81%) as a colorless oil. IR 3450, 2975, 1455 cm^{-1}; ^1H NMR 4.30-3.70 (m, 7H), 2.43 (s, 1H), 1.43 (s, 6H), 1.36 (s, 6H); ^{13}C NMR 109.2 (s), 75.9 (d), 71.2 (d), 65.5 (t), 26.6 (s), 25.2 (s); MS, *m/z* 232 (M^+), 217, 214, 101.

(1,2),(4,5)-Bis-*O*-(isopropylidene)-3-*O*-phenoxythiocarbonyladonitol (13) Phenylchlorothionocarbonate (3.04 ml, 22 mmol) was added dropwise to a stirred solution of **12** (4.46 g, 20 mmol) and 4-(*N,N*-dimethylamino)pyridine (80 mg, 0.65 mmol) in pyridine (20 ml) and acetonitrile (40 ml) at 0°C. After being stirred for 12 h at room temperature, the mixture was poured into cold 5% HCl. The whole was extracted with AcOEt. The extract was washed with 5% $NaHCO_3$, brine and dried. Purification by silica-gel column chromatography afforded **13** (6.4 g, 87%) as a colorless oil. IR 1590, 1480, 1455 cm^{-1}; ^1H NMR 7.53-7.21 (m, 3H), 7.15-7.04 (m, 2H), 5.77 (t, *J*=4.2 Hz, 1H), 4.43 (td, *J*=6.1, 4.3 Hz, 2H), 4.16 (dd, *J*=8.6, 6.7Hz, 2H), 4.05 (dd, *J*=8.6, 6.5 Hz, 2H), 1.47 (s, 6H), 1.38 (s, 6H); MS, *m/z* 353 (M^+-15), 295, 214, 156.

(1,2),(4,5)-Bis-*O*-(isopropylidene)-3-deoxyadonitol (14) Tributyltin hydride (2.4 ml, 8.82 mmol) was added dropwise to a refluxed solution of **13** (2.2 g, 5.88 mmol) and AIBN (100 mg, 0.59 mmol) in benzene (120 ml). After being refluxed for 8 h, the reaction mixture was cooled to room temperature. Potassium fluoride (512 mg, 8.82 mmol) was added to the mixture. The whole was stirred for 30 min at room temperature. The mixture was filtered. The filtrate was washed with brine. Removal of the solvent gave a crude product, which was subjected to column chromatography on silica gel to afford **14** (1.1 g, 87%) as a colorless oil. IR 2980, 1450, 1380 cm^{-1}; ^1H NMR 4.25-4.15 (m, 2H), 4.08 (dd, *J*=1.9, 5.9 Hz, 2H), 3.61 (dd, *J*=1.5, 1.4 Hz, 2H), 2.01 (dt, *J*=14.0, 6.1 Hz, 1H), 1.78 (dt, *J*=14.0, 6.1 Hz, 1H), 1.41 (s, 6H), 1.35 (s, 6H); ^{13}C NMR 108.8 (s), 72.8 (d), 69.3 (t), 36.7 (t), 26.9 (q), 25.7 (q); MS, *m/z* 216 (M^+), 201, 143, 101.

1,5-Di-*O*-acetyl-3-deoxyadonitol (15) A mixed solution of **14** (1.0 g, 4.6 mmol) and *p*-TsOH H_2O (30 mg) in MeOH (10 ml) was stirred for 5 h at room temperature. After removal of the solvent *in vacuo*, an oily residue was dissolved in pyridine (10 ml). Acetic anhydride (1.1 ml, 11.6 mmol) was added dropwise at 0°C. The whole was stirred for 8 h at 0-20°C. The reaction mixture was poured into brine, and extracted with AcOEt. The combined extracts were dried. Removal of the solvent and purification by silica-gel column chromatography afforded **15** (529 mg, 52% from **14**) as a colorless oil. IR 3450, 2955, 1735, 1440 cm^{-1}; ^1H NMR 4.20-3.85 (m, 6H), 3.55 (br, 2H), 2.11 (s, 6H), 1.66 (t, *J*=6.1 Hz, 2H); MS, *m/z* 221(M^++1), 203.

(4*RS*,6*SR*)-4,6-Diacetoxymethyl-2,2-dimethyl-1,3-dioxane (16) Acetonization of **15** (0.5 g, 2.3 mmol) in a similar manner to that of **12** gave **16** (526 mg, 89%) as a colorless oil. IR 2995, 1738, 1450 cm^{-1}; ^1H NMR 4.20-4.02 (m, 6H), 2.09 (s, 6H), 1.47 (s, 3H), 1.43 (s, 3H), 1.53-1.29 (m, 2H); ^{13}C NMR 170.9 (s), 99.1 (s), 67.0 (t), 66.9 (d), 29.9 (q), 29.3 (t), 20.9 (q), 19.6 (s), 67.0 (t), 66.9 (d), 29.9 (q), 29.3 (t), 21.0 (q), 19.6 (q); MS, *m/z* 245 (M^+-15), 203, 187

(4*R*,6*S*)-4-Acetoxymethyl-6-hydroxymethyl-2,2-dimethyl-1,3-dioxane ((-)-17) PFL (140 mg) was added to a suspension of **16** (400 mg, 1.54 mmol) in phosphate buffer (pH 7.0, 0.1 M) (90 ml) at 30°C. After being stirred for 50 min, the mixture was extracted with AcOEt. Concentration of solvent *in vacuo* gave an oily residue, which was subjected to column chromatography on silica gel. Elution with AcOEt/hexane (1:2) afforded **16** (75 mg, 19%) and (-)-**17** (270 mg, 79%) as a colorless oil. $[\alpha]_D^{25}$ -4.6 (*c*=1.0, $CHCl_3$); IR 3450, 2950, 1738, 1450 cm^{-1}; ^1H NMR 4.19-3.98 (m, 4H), 3.64 (dd, *J*=11.6, 3.3 Hz, 1H), 3.52 (dd, *J*=11.6, 6.0 Hz, 1H), 2.09 (s, 3H), 1.48 (s, 3H), 1.43 (s, 3H), 1.45-1.26 (m, 2H); MS, *m/z* 218 (M^+), 200, 186. HRMS for $C_{10}H_{18}O_5$ (M^+): Calcd *m/z* 218.1154; Found 218.1148.

(3*S*,5*R*)-5-Acetoxymethyl-3-hydroxy-1-oxacyclopentan-2-one (19) A mixture of (-)-**17** (250 mg, 1.15 mmol) and pyridinium dichromate (2.163 g, 5.75 mmol) in DMF (10 ml) was stirred for 16 h at room temperature. The reaction mixture was diluted with benzene, and washed with brine. Removal of solvent left a crude product, which without further purification was added to a solution of *p*-TsOH(30 mg) in CH_2Cl_2 (5 ml). After being stirred for 5 h at room temperature, the reaction mixture was diluted with AcOEt, and washed with 5% aq. $NaHCO_3$. Concentration of solvent *in vacuo* left a crude product, which was subjected to column

chromatography on silica gel. Elution with AcOEt/hexane (1:1) afforded **19** (82 mg, 41%) as a colorless oil. $[\alpha]_D^{25}$ -53.8 (*c*=0.53, $CHCl_3$); ^1H NMR 4.95-4.70 (m, 1H), 4.60 (t, *J*=8.4 Hz, 1H), 4.25 (dd, *J*=12.5, 8.6 Hz, 1H), 4.21 (dd, *J*=12.5, 5.5 Hz, 1H), 2.51-2.30 (m, 2H), 2.10 (s, 3H); MS, *m/z* 174 (M^+). Compound **19** was further converted to **20** ($[\alpha]_D^{25}$ -47.5 (*c*=0.72, EtOH)) according to ref. 20.

References

1. Morrison, J. D. *Asymmetric Synthesis*, Vol. 5; Academic Press; New York, 1987.
2. Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamade, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.
3. Jones, J. B. *Tetrahedron* **1986**, *42*, 3351.
4. Kashihara, H.; Suemune, H.; Kawahara, T.; Sakai, K. *Tetrahedron Lett.* **1987**, *28*, 6489; Taura, Y.; Tanaka, M.; Funakoshi, K.; Sakai, K. *ibid.*; **1989**, *30*, 6349; Yamamoto, T.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1992**, 1482.
5. Suemune, H.; Hayashi, N.; Funakoshi, K.; Akita, H.; Oishi, T.; Sakai, K. *Chem. Pharm. Bull.* **1985**, *33*, 2168; Xie, Z.-F.; Funakoshi, K.; Suemune, H.; Oishi, T.; Akita, H.; Sakai, K. *ibid.* **1986**, *34*, 3058; Suemune, H.; Mizuhara, Y.; Akita, H.; Sakai, K. *ibid.* **1986**, *34*, 3440.
6. Xie, Z.-F.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1987**, 838; Xie, Z.-F.; Nakamura, I.; Suemune, H.; Sakai, K. *ibid.* **1988**, 966; Xie, Z.-F.; Suemune, H.; Sakai, K. *Tetrahedron : Asymmetry* **1990**, *1*, 395.
7. For our prelimary communication, Xie, Z.-F.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1638.
8. Dale, J. A.; Dulh, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
9. Both enantiomers of **3** and (*S*)-(-)-**18** are commercially available (Aldrich).
10. Fuganti, C.; Grasselli, P.; Servi, S.; Hogberg, H.-E. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3061.
11. Xie, Z.-F.; Sakai, K. *J. Org. Chem.* **1990**, *55*, 820; Xie, Z.-F.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1988**, 612.
12. Collum, D. B.; McDonald III, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1987**, *109*, 2205.
13. Masamune, C. S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47.
14. Oomura, Y.; Nishimura, H. *Kagaku*, **1987**, *42*, 440.
15. Mohr, P.; Sarcevic, N. W.; Tamm, C.; Gawronski, K. *Helv. Chim. Acta* **1983**, *66*, 2501; Schneider, M.; Engel, N.; Honicke, P.; Heinemann, G.; Gorisch, H. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 67; Sabbioni, G.; Shea, M. L.; Jones, J. B. *J. Chem. Soc., Chem. Commun.* **1984**, 236.
16. Bianchi, D.; Cesti, P.; Battistel, E. *J. Org. Chem.* **1988**, *53*, 5531; Delinck, D.L.; Margolin, A. L. *Tetrahedron Lett.* **1990**, 6797.
17. Francalanci, F.; Cesti, P.; Cabri, W.; Bianchi, D.; Martinengo, T.; Foa, M. *J. Org. Chem.* **1987**, *52*, 5079.
18. Terao, Y.; Tsuji, K.; Murata, M.; Achiwa, K.; Nishio, T.; Watanabe, N.; Seto, K. *Chem. Pharm. Bull.* **1989**, *37*, 1653.
19. Terao, Y.; Murata, M.; Achiwa, K. *Tetrahedron Lett.* **1988**, *29*, 5137.
20. Uchikawa, O.; Okudado, N.; Sakata, T.; Arase, K.; Terada, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2025.