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Highly Asymmetric Enzymatic Hydrolysis and Transesterification of *meso*-Bis(acetoxymethyl)- and Bis(hydroxymethyl)cyclopentane Derivatives: An Insight into the Active Site Model of *Rhizopus Delemar* Lipase

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Key words: *Rhizopus delemar lipase; Pseudomonas fluorescens lipase; carbocyclic nucleoside; (-)-aristeromycin; meso-diacetate*

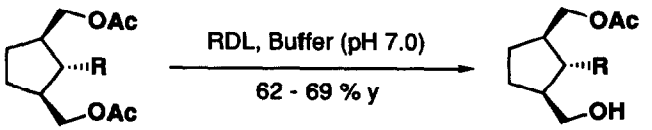
Abstract: *Rhizopus delemar* lipase (RDL)-catalysed hydrolysis of *meso*-1,3-bis(acetoxymethyl)cyclopentane derivatives (**7**, **12**) and *Pseudomonas fluorescens* lipase (PFL)-catalysed hydrolysis of **7** afforded the chiral monoacetates (**15**, **16**) of >99 % ee. In explanation of these high enantioselectivities of RDL, the simple box-type active site model of enzyme was tentatively proposed. On the other hand, PFL-catalysed transesterification of *meso*-bis(hydroxymethyl)cyclopentane (**6**) afforded (+)-**16** of >99 % ee. The obtained (+) and (-)-**16** were converted into the natural carbocyclic nucleoside (-)-aristeromycin (**25**), respectively.

Introduction

The application of enzymes[1] to organic syntheses is one of the most useful and practical methods for the preparation of optically active compounds in high optical purities. Various hydrolytic enzymes, such as pig liver esterase (PLE)[2a], porcine pancreatic lipase (PPL)[2b], and *Pseudomonas fluorescens* lipase (PFL)[2c] have been reported by several groups, and the active site models of these enzymes were tentatively proposed in an attempt to explain their role in the discrimination of the enantiotopic ester groups of symmetric compounds and the resolution of racemic compounds. However, there is a limit to the application of the previously known enzymes to new substrates, and there is a limit to the active site models, too, in the estimation of enantioselectivities and prediction of absolute configurations. Therefore, organic chemists need more widely applicable enzymes with their active site models for the preparation of different types of chiral compounds. In this paper, we describe the novel, widely applicable enzyme-*Rhizopus delemar* lipase (RDL), its active site

model, and the results of other enzymatic hydrolyses and transesterifications for the preparation of sugar moieties of carbocyclic nucleosides[3], together with the total synthesis of (-)-aristeromycin[4].

Previously, we reported the RDL-catalysed hydrolysis of *meso*-1,3-bis(acetoxymethyl)-2-*trans*-alkylcyclopentane (**1**) afforded the chiral monoacetates ((-)-**2**) of >95 % ee in good yields[5] (Scheme 1).



1 aR = *n*Bu
1 bR = octenyl

Scheme 1

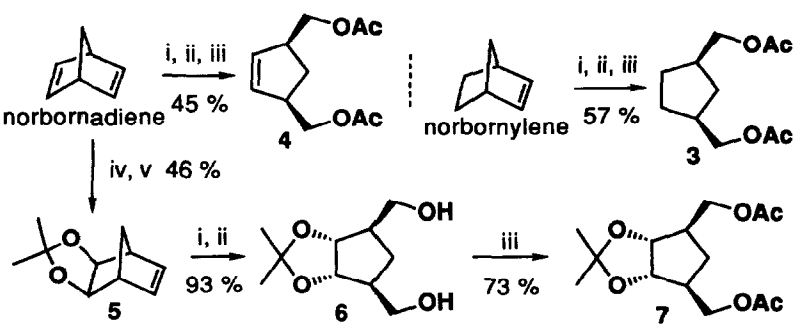
(-)-2a, b
>95 % ee, each

The monoacetate (-)-**2** was applied in the synthesis of the optically active 11-deoxyprostaglandins (PGs)[5]. RDL played an important role in this synthesis, and seemed to be widely applicable to the other *meso*-substrates. This synthetic route using the enzymatic hydrolysis of *meso*-compounds is efficient for the preparation of optically active compounds, and suggested the asymmetric synthesis of sugar moieties of carbocyclic nucleosides[6,7].

Results and Discussion

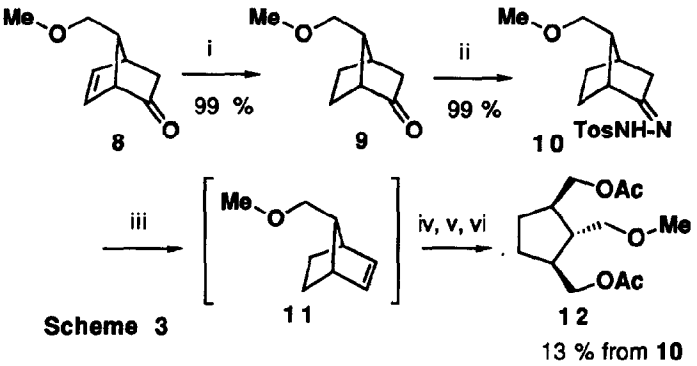
The substrates (**3**, **4**, **6**, **7**, **12**) were prepared as outlined in Scheme 2 and 3[8,9]. The substrates **3** and **4** were prepared from norbornylene and norbornadiene *via* three sequences: i) O_3; ii) $NaBH_4$; iii) Ac_2O / pyridine. Compounds **6** and **7** were prepared as follows: stereoselective osmium oxidation of norbornadiene, and subsequent treatment with acetone-H^+ afforded the *exo*-acetonide (**5**). Ozonolysis of **5**, followed by $NaBH_4$ reduction afforded the diol **6**, and subsequent acetylation gave the diacetate **7**.

Scheme 2



Reagents: (i) O_3; (ii) $NaBH_4$; (iii) Ac_2O/Pyridine; (iv) OsO_4/methyl morpholine *N*-oxide; (v) acetone/H^+.

The 7-substituted bicyclo[2.2.1]heptenone (**8**), Corey's intermediate for the synthesis of PGs, was converted into the tosyl hydrazone (**10**) *via* two sequences: i) H_2, Pd-C; ii) $TsNHNH_2$. Shapiro reaction of **10**, followed by ozonolysis of the olefin, reduction of aldehyde, and acetylation afforded the *meso*-diacetate **12**.



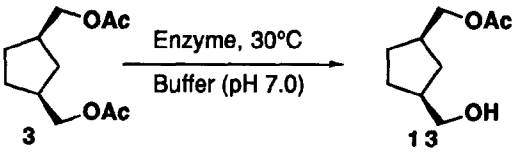
Scheme 3

Reagents: (i) H_2, Pd-C ; (ii) $TsNHNH_2$; (iii) BuLi;
(iv) O_3; (v) $NaBH_4$; (vi) Ac_2O/Pyridine;

It has been thought that these diacetates were useful intermediates for the synthesis of carbovir[10], (1*R*, 4*S*, 5*R*)-9-(4, 5-bishydroxymethyl-cyclopent-2-ene-1-yl)-9*H*-adenine ((-)-BCA)[11], and their analogues, which are high-priority candidates as chemotherapeutic agents for the treatment of AIDS infection[6d].

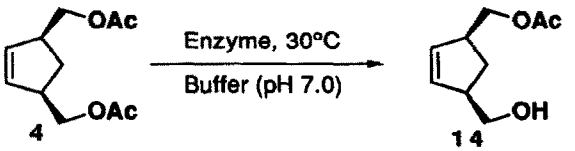
The diacetates **3**, **4**, **7**, **12** were subjected to enzyme-catalysed hydrolysis. The results are summarized in Tables I - IV. In all cases, the ee's of the monoacetates were measured by the Mosher ester procedure[12], and the ^1H NMR spectra of the corresponding racemates were used as reference standards. The enzymatic hydrolysis of substrates **3**, **4** was studied using twelve kinds of lipases and two kinds of esterases[13,14].

Table I. Enzymatic Hydrolysis of meso-Diacetate 3



Enzyme	Reaction time (h)	Monoacetate 13		Diacetate 3
		Yield (%)	% ee	Yield (%)
RDL	48	89	26	38
PFL	18	79	11	---
PPL	18	89	28	---
PLE	0.1	23	13	56

Table II. Enzymatic Hydrolysis of meso-Diacetate 4

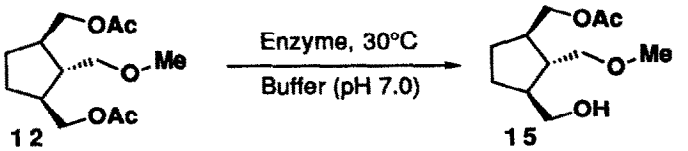


4 14

Enzyme	Reaction time (h)	Monoacetate 14		Diacetate 4
		Yield (%)	% ee	Yield (%)
RDL	22	86	18	4
PFL	16	92	9[a]	---
PPL	68	60	47	31
PLE	5	49	28	42

a: In hydrolysis by PFL, the enantioselectivity was opposite to the other cases.

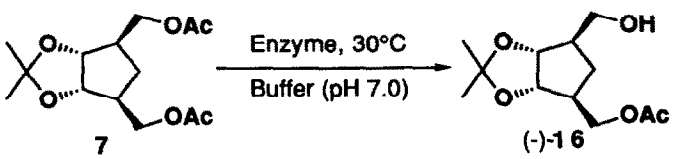
Table III. Enzymatic Hydrolysis of meso-Diacetate 12



12 15

Enzyme	Reaction time (h)	Monoacetate 15		Diacetate 12
		Yield (%)	% ee	Yield (%)
RDL	48	43	>99	57
PFL	24	68	63	27

Table IV. Enzymatic Hydrolysis of meso-Diacetate 7

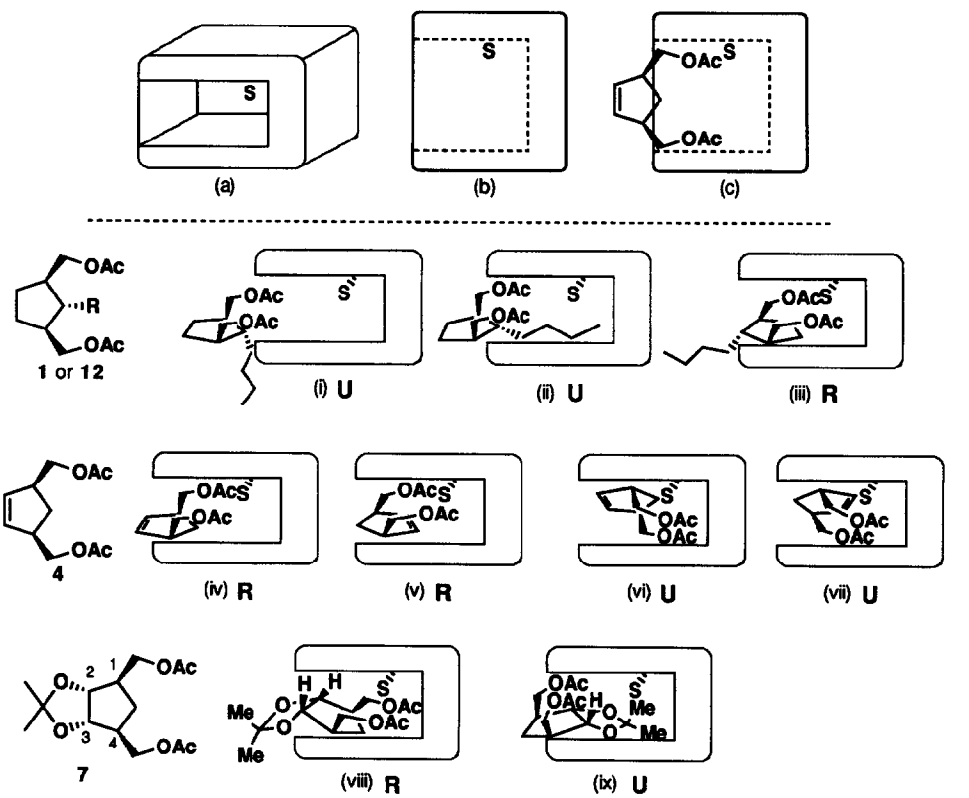


7 (-)-16

Enzyme	Reaction time (h)	Monoacetate 16		Diacetate 7
		Yield (%)	% ee	Yield (%)
RDL	23	47	>99	40
PFL	23	69	>99	---
PPL	19	75	69	18
PLE	1	46	19	43

Unfortunately, the highest enantiomeric excess of monoacetate (**13**) obtained was 28 % ee by PPL, and that of **14** was 47 % ee by PPL, respectively. In the case of RDL-catalysed hydrolysis, the enantiomeric excess of **13** was only 26 % ee, and that of **14** was 18 % ee, respectively, in contrast to >95 % ee of monoacetates **2**. These disappointing results were explained based on the novel box-type active site model of RDL (Figure 1).

Figure 1. Proposed Box-type Active Site Model of *Rhizopus Delemar* Lipase

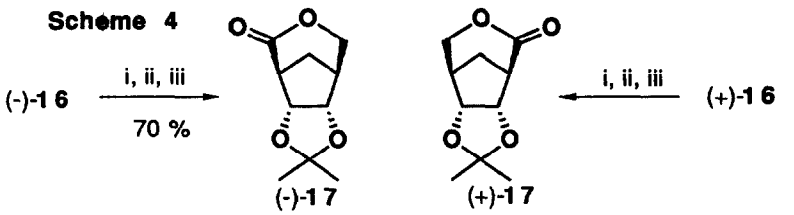


(a) This figure is a side elevation view of RDL; (b) Figure shows top-view of RDL; (c) Figure shows the substrate is uptaken by RDL; (d) S: the serine nucleophile region, R: reactive, U: unreactive; (e) Hydrolysis of compounds could not proceed *via* ES-complex (i, ii, vi, vii, and ix), because the acetyl function could not approach the serine nucleophile region. The acetyl function in ES-complex (iii, iv, v, and viii) could exist in the serine nucleophile region, and hydrolysis could proceed *via* such ES-complex.

Hydrolysis of compound **1** proceeded exclusively *via* enzyme-substrate(ES)-complex (iii) to give the optically pure monoacetate **2**. However, hydrolysis of **3** and **4** proceeded in an indifferent manner *via* both intermediates (iv) and (v) to produce the monoacetate of low enantiomeric excess. In the case of substrate **12**,

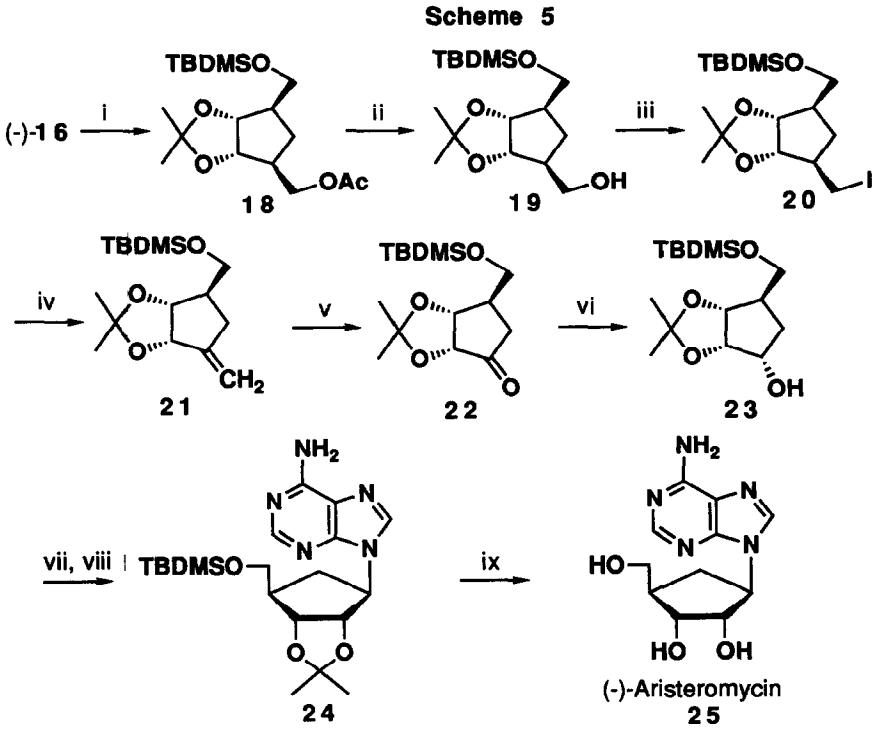
the good result was obtained by RDL, and the obtained monoacetate **15** showed >99 % ee. This high enantiomeric excess provides the proof that the hydrolysis proceeded *via* the corresponding ES-complex (iii), exclusively. On the assumption of this model, *meso*-diacetate **7** could be hydrolysed to monoacetate **16** *via* intermediate (viii), exclusively. Interestingly, the picture (viii) shows that the acetyl function of C_1-position would be hydrolysed by RDL. This hydrolysis of C_1-position-acetate is contrary to that of substrates **1** or **12**. Hydrolysis of the acetyl function of C_4-position would be interrupted by the bulky acetonide, as shown in ES-complex (ix).

Scheme 4



Reagents: (i) RuO_2, $NaIO_4$; (ii) K_2CO_3/MeOH (iii) Ac_2O/pyridine.

Scheme 5



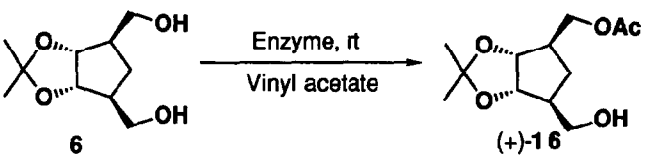
Reagents: (i) TBDMSCl, imidazole; (ii) K_2CO_3/MeOH; (iii) I_2, PPh_3, pyridine; (iv) DBU/benzene; (v) O_3 then Me_2S; (vi) $NaBH_4$/MeOH; (vii) Tf_2O, pyridine; (viii) adenine, NaH, 18-crown-6; (ix) H^+.

Hydrolysis of **7** using RDL in a phosphate buffer (pH 7.0) actually afforded the monoacetate (-)-**16** of >99 % ee in 40 % yield. The absolute configuration of (-)-**16** was unambiguously determined by chemical correlation with Ohno's lactone intermediate (**17**)[6a] for the synthesis of (-)-aristeromycin and (-)-neplanocin A. By mild ruthenium oxidation, followed by solvolysis with K_2CO_3-MeOH, and subsequent lactonization by Ac_2O-pyridine, (-)-**16** was converted into **17** in 70 % yield. The spectroscopic data of **17** were identical with reported values. The specific rotation of **17** derived from (-)-**16** showed $[\alpha]_D^{25}$ -41.0 (Scheme 4). This means that (-)-**16** has the absolute configuration of (1*R*, 2*R*, 3*S*, 4*S*), which is in accordance with the RDL-active site stereomodel (ES-complex(viii and ix)). The obtained (-)-**17** has an undesirable configuration for the synthesis of natural (-)-aristeromycin according to Ohno's route.[6a]

Then, (-)-**16** was converted into (-)-aristeromycin by the following route (Scheme 5). Treatment of (-)-**16** with TBDMSCl-imidazole, followed by solvolysis afforded the silyl alcohol (**19**). The alcohol **19** was dehydrated to the *exo*-olefine (**21**) by two-step sequence: i) I_2, PPh_3, pyridine; ii) DBU. Ozonolysis of alkene gave the ketone (**22**). Reduction of **22** with $NaBH_4$[15], followed by coupling with adenine[16] afforded the nucleoside (**24**), and subsequent deprotection with 5 % HCl afforded (-)-aristeromycin **25** (16 % yield from **22**). The spectroscopic data of product **25** were identical with the reported values[6a]. Total synthesis of (-)-aristeromycin from (-)-**16** has been completed.

Next, we studied transesterification[17] of *meso*-diol **6** using RDL and PFL. The results are summarized in Table V.

Table V. Enzymatic Transesterification of meso-Diol 6



6 (+)-**16**

Enzyme	Reaction time (h)	Monoacetate **16**		Diacetate **7**
		Yield (%)	% ee	Yield (%)
RDL	120	28	66	---
PFL	3	81	>99	14

Contrary to hydrolysis of **7** using RDL, transesterification of **6** by RDL gave (+)-**16** of 66 % ee in 28 % yield. This low yield and low enantiomeric excess might be attributed to the low stability and reactivity of RDL in an organic solvent. Fortunately, PFL-catalysed transesterification of **6** afforded (+)-**16** of >99 % ee in 81 % yield. The obtained (+)-**16** was converted into the lactone (+)-**17** (Scheme 4). The specific rotation of (+)-**17** showed $[\alpha]_D^{24}$ + 40.9. The preparation of (+)-**17** means a formal synthesis of (-)-aristeromycin and (-)-neplanocin A has been attained.[6a]

Conclusion

RDL-catalysed hydrolysis of *meso*-compounds provided enantioselectively the optically pure alcohols for the preparation of sugar moieties of carbocyclic nucleosides. Furthermore, the behavior of RDL to *meso*-compounds was rationally predicted by the box-type active site model.

Our enzymatic procedure provided a new route for the preparation of both enantiomers of (+)- and (-)-monoacetate **16** (each, >99 % ee) on the gram scale, and it is thought that this method is a practical one for the synthesis of both enantiomers of carbocyclic nucleosides. The strategy for the synthesis of (-)-aristeromycin is especially advantageous in that both (+)- and (-)-enantiomers of **16** can be used.

Acknowledgment

We thank the Uehara Memorial Foundation for financial support. We also thank Dr. R. Isobe, Mr. Y. Tanaka, and Mrs. Y. Soeda for the measurement of MS and NMR spectra.

Experimental Section

General Methods. IR spectra were measured with a JASCO A-202 spectrometer, and ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-GX-270 or JEOL JNM-FX-100 spectrometer using $CDCl_3$ as a solvent. EI-MS spectra were taken on a JEOL JMS-D 300 spectrometer and FD-MS spectra were taken on a JEOL JMS-DX 300 spectrometer. FAB(+)-HRMS spectra were taken on a JEOL JMS-SX 102 spectrometer. Optical rotation was measured on a JASCO DIP-360 polarimeter at the sodium line. Melting points were uncorrected. For O_3 oxidation, Ishii ozone generator (7,800 V, O_2 flow rate; 0.5 ml/min) was used. Chemicals were used as received unless otherwise noted. Diethyl ether was distilled from sodium / benzopheonone before use. Benzene and CH_2Cl_2 were distilled from P_2O_5. Vinyl acetate (monomer) was purchased from Tokyo Kasei Corp.. PLE (Esterase Type I) and PPL (Type II) were purchased from Sigma Corp., RDL was purchased from Seikagaku Kogyo Corp.(Japan), and PFL was presented by courtesy of Amano Corp.(Japan), and were used as received.

Preparation of substrates for enzymatic reactions.

***cis*-Cyclopentane-1,3-dimethanol diacetate (3).** Ozone gas was bubbled into a solution of norbornylene (5.0 g, 53.2 mmol) in MeOH (70 ml) and CH_2Cl_2 (40 ml) at -78 °C, and the reaction was monitored by TLC. $NaBH_4$ (2.0 g, 53.0 mol) was portionwise added to the reaction mixture at -78 °C. After 1 h, the reaction mixture was gradually warmed to 0 °C , and neutralised with conc.HCl aq. to pH 7.0. The mixture was evaporated *in vacuo* to leave an oily residue, which was dissolved in pyridine (50 ml) and Ac_2O (20 ml), and the whole was stirred overnight. The reaction mixture was diluted with 5 % HCl aq., and extracted with AcOEt. The AcOEt extract was successively washed with 5 % $NaHCO_3$ aq., brine, then dried. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica

gel. The fraction eluted with 20 % AcOEt in hexane (v/v) afforded **3** (6.5 g, 57 %) as a colorless oil. IR (neat) 2950, 1730, 1240, 1130 cm^{-1}. 100 M Hz - ^1H NMR ($CDCl_3$) δ: 3.99 (4H, d, J = 6.8 Hz), 2.05 (6H, s), 0.80-2.40 (8H, m). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ 171.1, 68.2, 38.7, 33.5, 28.4, 20.9. EI-MS m/z 215 (M^++1), 171, 154, 141. FAB(+)-HRMS m/z: calcd. for $C_{11}H_{19}O_4$ (M^++H): 215.1283; found 215.1279.

***cis*-4-Cyclopentene-1,3-dimethanol diacetate (4).**[14] Ozone gas was bubbled into a solution of norbornadiene (10.0 g, 0.108 mol) in MeOH (120 ml) and CH_2Cl_2 (50 ml) at -78 °C for 1.5 h. Then, $NaBH_4$ (4.0 g, 0.105 mol) was portionwise added to the reaction mixture at -78 °C. After the same procedure described above, **4** (12.5 g, 54 %) was obtained as a colorless oil. IR (neat) 3050, 2950, 2900, 1740, 1385, 1365, 1240, 1030 cm^{-1}. 100 M Hz - ^1H NMR ($CDCl_3$) δ: 5.73 (2H, s), 4.02 (4H, d, J = 6.1 Hz), 3.00 (2H, m), 2.20 (1H, m), 2.06 (6H, s), 1.25 (1H, m). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ 171.1, 133.0, 67.8, 45.0, 30.1, 20.9. EI-MS m/z 213 (M^++1), 184.

***exo*, *cis*-5,6-Isopropylidenedioxy-2-norbornene (5).** Osmium tetraoxide (500 mg, 1.97 mmol) in *t*-BuOH (100 ml) was added to a stirred solution of norbornadiene (160 g, 1.74 mol) and methyl morphorine *N*-oxide (MMNO, 200 ml, 50 % in water) in acetone (1000 ml) and water (150 ml) at room temperature with stirring. The dark red solution was stirred for 2 days at room temperature. A mixture of Florisil (60 g) and $NaHSO_3$ (35 g) was added, and the slurry was stirred for 2 h. After filtration, the filtrate was acidified with 10 % HCl aq., and the solution was evaporated by 70 %. This residue was saturated with NaCl (solid) and extracted with AcOEt. The combined organic layers were dried and evaporated to give an oily residue, which was dissolved in acetone (300 ml), and TsOH (300 mg) was added. The mixture was stirred at room temperature for 5 h. Then $NaHCO_3$ (2 g, solid) was added, and the mixture was filtered. The filtrate was evaporated to afford an oily residue. After silica-gel short column, **5** (64.6 g, 46 % based on MMNO) was obtained as a colorless oil. IR (neat) 3050, 2980, 2920, 1380, 1370, 1260, 1220, 1060 cm^{-1}. 270 M Hz - ^1H NMR ($CDCl_3$) δ 6.06 (2H, t, J = 1.7 Hz), 4.20 (2H, d, J = 1.3 Hz), 2.78 (2H, t, J = 1.7 Hz), 1.98 (1H, d, J = 9.7 Hz), 1.69 (1H, dt, J = 1.7, 9.7 Hz), 1.48 (3H, s), 1.34 (3H, s). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ 136.7, 113.6, 80.4, 45.2, 42.9, 26.2, 24.4. EI-MS m/z 166 (M^+), 151 (M^+-Me).

2,3-Isopropylidenedioxycyclopentane-1,4-dimethanol (6). Ozone gas was bubbled into a solution of **5** (20 g, 0.120 mol) in MeOH (200 ml) and CH_2Cl_2 (100 ml) at -78 °C, and the reaction was monitored by TLC. $NaBH_4$ (1.10 g, 29.1 mmol) was added to the reaction mixture at -78 °C, the solution was gradually warmed to 0 °C, and $NaBH_4$ (4.7 g, 124 mmol) was added again, and stirred for 2 h. Acetone (100 ml) was added, and stirred for 1 h. Then, the mixture was filtered, the filtrate was evaporated *in vacuo* to afford the white crystal, which was washed with AcOEt (100 ml x 3). The crystal was dissolved in MeOH (300 ml), and the solution was neutralized with conc.HCl aq. to pH 7.0. After evaporation, the mixture was dissolved in AcOEt, and the mixture was filtered. Removal of the filtrate afforded the diol **6** (22 g, 93 %) as a colorless oil. IR (neat) 3400, 2920, 1060 cm^{-1}. 100 M Hz - ^1H NMR ($CDCl_3$) δ 4.41 (2H, d, J = 3.9 Hz), 3.65 (4H, d, J = 5.6 Hz), 3.00 (2H, br s), 1.51 (3H, s), 1.31 (3H, s), 1.20-2.40 (4H, m). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ 112.4, 83.4, 64.1, 47.4, 30.6, 27.6, 25.2. FD-MS m/z 203 (M^++1), 187 (M^+-Me). FAB(+)-HRMS m/z: calcd. for $C_{10}H_{19}O_4$ (M^++H): 203.1283; found 203.1281.

2,3-Isopropylidenedioxycyclopentane-1,4-dimethanol diacetate (7). IR (neat) 1740, 1370, 1240, 1070, 1030 cm^{-1}. 270 M Hz - ^1H NMR ($CDCl_3$) δ 4.34 (2H, dd, J = 5.6, 8.9 Hz), 4.12 (2H, dd, J = 6.9, 11.2 Hz), 4.08 (2H, dd, J = 6.3, 11.2 Hz), 2.31-2.44 (2H, m), 2.08 (6H, s), 2.10 (1H, m), 1.50 (3H, s), 1.31 (3H, s), 1.25 (1H, m). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ 170.9, 112.7, 83.0, 65.4, 44.3, 31.3, 27.6, 25.2, 20.8. FD-MS m/z 271 (M^+-Me), 109, 91, 43. FAB(+)-HRMS m/z: calcd. for $C_{14}H_{23}O_6$ (M^++H): 287.1495; found 287.1492.

***anti*-7-Methoxymethylbicylo[2.2.1]heptan-2-one (9).** A solution of **8** (2.36 g, 15.5 mmol) in MeOH (15 ml) was hydrogenated in the presence of 5 % Pd-C (200 mg) under an H_2 atmosphere for 20 min. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 30 % AcOEt in hexane (v/v) afforded **9** (2.37 g, 99 %) as a colorless oil. IR (neat) 2950, 2920, 1740 1110 cm^{-1}. 270 M Hz - ^1H NMR ($CDCl_3$) δ: 3.36 (3H, s), 3.35 (2H, m), 2.54 (2H, m), 1.40-2.30 (7H, m). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ: 216.3, 70.0,, 59.1, 51.4, 48.1, 46.9, 36.7, 25.1, 21.6. EI-MS m/z 154 (M^+), 122, 80.

***anti*-7-Methoxymethylbicylo[2.2.1]heptan-2-one *p*-toluenesulfonylhydrazone (10).** A solution of **9** (600 mg, 3.90 mmol) and $TsNHNH_2$ (870 mg, 4.68 mmol) in EtOH (10 ml) was refluxed for 3 h. Removal of solvent *in vacuo* gave a white solid, which was purified by column chromatography on silica gel to give **10** (1.24 g, 99 %) as a colorless crystal. IR (Nujol) 3200, 1670, 1595 cm^{-1}. 270 M Hz - ^1H NMR ($CDCl_3$) δ: 7.82 (2H, d, J = 8.2 Hz), 7.28 (2H, d, J = 8.2 Hz), 3.30 (3H, s), 3.24 (2H, m), 2.75 (1H, m), 2.43 (3H, s), 1.20-2.45 (9H, m). FD-MS m/z 322 (M^+). mp 106 - 107 °C.

2-Methoxymethylcyclopentane-1,3-dimethanol diacetate (12). *n*-BuLi (1.5 M in hexane, 21 ml) solution was added dropwise to a stirred solution of **10** (3.00 g, 9.32 mmol) in ether (50 ml) and TMEDA (5 ml) at 0 °C under an Ar atomosphere. After being stirred at room temperature for 6 h, H_2O (100 ml) was added at 0 °C, and extracted with ether. The ether extract was washed with 5 % HCl aq., brine, and dried. The solvent was removed *in vacuo* to afford an oily residue **11**. IR (neat) 3060, 2975, 1130, 1100 cm^{-1}. 270 M Hz - ^1H NMR ($CDCl_3$) δ: 6.08 (2H, t, J = 2.0 Hz), 3.31 (3H, s), 3.09 (2H, d, J = 7.3 Hz), 2.66 (2H, m), 1.84 (1H, t, J = 7.3 Hz). Compound **11** was converted to **12** (262 mg, 13 % from **10**) by the same method as mentioned above. colorless oil. IR (neat) 2950, 2880, 1740, 1370, 1250, 1030 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.07 (2H, dd, J = 5.6, 10.7 Hz), 3.98 (2H, dd, J = 7.3, 10.7 Hz), 3.36 (2H, d, J = 6.0 Hz), 3.32 (3H, s), 2.05 (6H,s), 1.40-2.20 (7H, m). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ: 171.2, 75.4, 67.5, 59.0, 45.2, 42.0, 28.5, 21.0. FD-MS m/z 259 (M^++1). FAB(+)-HRMS m/z: calcd. for $C_{13}H_{23}O_5$ (M^++H): 259.1545; found 259.1552.

Enzymatic hydrolysis of *meso*-compounds.

General methods. A suspension of substrate (100 mg) and enzyme (10 mg) in acetone (0.1 ml) and 0.1 M phosphate buffer (10 ml, pH 7.0) was stirred at 30 °C. The reaction was monitored by TLC. When a spot of the diol appeared on TLC, hydrolysis was terminated by extracting the mixture with AcOEt. The AcOEt

extract was dried, then concentrated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel.

***cis*-Cyclopentane-1,3-dimethanol monoacetate (13).** colorless oil. IR (neat) 3400, 2900, 1720, 1355, 1230, 1020 cm^{-1}. 100 M Hz - ^1H NMR ($CDCl_3$) δ: 3.99 (2H, d, J = 6.8 Hz), 3.54 (2H, d, J = 6.4 Hz), 2.05 (3H, s), 0.80-2.40 (9H, m). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ: 171.3, 68.4, 67.1, 42.2, 38.8, 33.2, 28.6, 28.1, 20.9. EI-MS m/z 173 (M^++1), 154, 143. FAB(+)-HRMS m/z: calcd. for $C_9H_{17}O_3$ (M^++H): 173.1178; found 173.1174.

MTPA ester of 13. The enantiomeric excess was calculated by the ratio of the methylene signal [δ: 3.95 (d, J = 6.9 Hz) to 3.94 (d, J = 6.9 Hz)].

***cis*-4-Cyclopentene-1,3-dimethanol monoacetate (14).**[14] colorless oil. IR (neat) 3400, 2870, 1720, 1240, 1030 cm^{-1}. 100 M Hz - ^1H NMR ($CDCl_3$) δ: 5.75 (2H, s), 4.03 (2H, d, J = 6.8 Hz), 3.58 (2H, d, J = 5.6 Hz), 2.95 (2H, m), 2.20 (1H, m), 2.06 (3H, s), 1.75 (1H, br s), 1.30 (1H, m).

MTPA ester of 14. The enantiomeric excess was calculated by the ratio of the methylene signal [δ: 4.34 (dd, J = 6.9, 10.6 Hz) and 5.19 (dd, J = 6.6, 10.6 Hz) to 4.28 (dd, J = 3.3, 7.2 Hz) and 5.19 (dd, J = 3.3, 7.6 Hz)].

2-Methoxymethylcyclopentane-1,3-dimethanol monoacetate (15). colorless oil. IR (neat) 3450, 2950, 1735, 1240, 1030 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.97 (1H, dd, J = 6.9, 10.9 Hz), 4.04 (1H, dd, J = 5.9, 10.9 Hz), 3.65 (1H, brs), 3.58 (1H, d, J = 4.3 Hz), 3.55 (1H, d, J = 4.3 Hz), 3.39 (3H, s), 3.36 (1H, t, J = 9.6 Hz), 3.23 (1H, t, J = 9.6 Hz), 2.06 (3H, s), 1.25-2.05 (7H, m). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ: 171.1, 76.2, 67.4, 66.6, 58.9, 48.6, 47.9, 42.0, 28.3, 28.1, 20.9. EI-MS m/z 216 (M^+), 186. $[\alpha]_D^{25}$ - 60.60 (c = 0.94, $CHCl_3$). FAB(+)-HRMS m/z: calcd. for $C_{11}H_{20}O_4$ (M^++H): 217.1440; found 217.1437.

MTPA ester of 15. 270 M Hz ^1H NMR spectrum of (+)-MTPA ester derived from the monoacetate (±)-**15** showed the methylene signal at δ 4.02 (0.5H, dd, J = 5.9, 10.9 Hz), 4.01 (0.5H, dd, J = 5.6, 10.9 Hz), 3.93 (0.5H, dd, J = 6.9, 10.9 Hz) and 3.92 (0.5H, dd, J = 6.9, 10.9 Hz), while the corresponding signal from (-)-**15** was observed at δ 4.01 (1H, dd, J = 5.6, 10.9 Hz) and 3.92 (1H, dd, J = 6.9, 10.9 Hz), only.

2,3-Isopropylidenedioxycyclopentane-1,4-dimethanol monoacetate (16). PFL (500 mg) was added to a solution of diacetate **7** (7.70 g, 26.9 mmol) in phosphate buffer pH 7.0 (300 ml) and acetone (3 ml). After being stirred for 16 h at 30 °C, the solution was extracted with AcOEt. The combined extracts were dried, and concentrated. Silica-gel column chromatography (50 % AcOEt in hexane) gave (-)-**16** (4.66g, 71 %). colorless crystal. IR (Nujol) 3470, 1730 cm^{-1}. 270 M Hz - ^1H NMR ($CDCl_3$) δ 4.40 (1H, dd, J = 5.1, 7.1 Hz), 4.35 (1H, dd, J = 5.1, 7.1), 4.11 (2H, d, J = 6.3, Hz), 3.70 (1H, dd, J = 6.6, 11.0 Hz), 3.64 (1H, dd, J = 6.9, 11.0), 2.20-2.44 (2H, m), 2.10 (1H, m), 2.07 (3H, s), 1.88 (1H, br s), 1.50 (3H, s), 1.31 (3H, s), 1.25 (1H, m). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ 171.2, 112.7, 83.3, 83.1, 65.6, 64.3, 47.4, 44.5, 30.9, 27.6,

25.2, 20.9. EI-MS m/z 229 (M^+-Me), 109, 79, 43. FAB(+)-HRMS m/z: calcd. for $C_{12}H_{21}O_5$ (M^++H): 245.1389; found 245.1390. $[\alpha]_D^{22}$ - 9.17 (c = 1.15, $CHCl_3$). mp 42 - 43 °C.

MTPA ester of 16. 270 M Hz ^{1}H NMR spectrum of (+)-MTPA ester derived from the monoacetate (±)-**16** showed the methylene signal at δ 4.057 (1H, d, *J* = 5.9 Hz) and 4.065 (1H, d, *J* = 5.9 Hz), while the corresponding signal from (-)-**16** was observed at δ 4.065 (2H, d, *J* = 5.9 Hz), and that from (+)-**16** was observed at δ 4.057 (2H, d, *J* = 5.9 Hz).

Synthesis of aristeromycin.

(1*S*, 5*S*, 6*S*, 7*R*)-6,7-Isopropylidenedioxy-3-oxabicylo[3.2.1]octan-2-one ((-)-17). Alcohol (-)-**16** (500 mg, 2.05 mmol) in a mixture of CCl_4 (8 ml), CH_3CN (8 ml), and H_2O (11 ml) was vigorously stirred with RuO_2 (10 mg) and $NaIO_4$ (2 g) for 5 h. It was then diluted with water, and extracted with CH_2Cl_2. The combined organic layers were dried and swirled with $NaHSO_3$ (200 mg, solid) before being filtered and evaporated. The residue and K_2CO_3 (650 mg) was dissolved in MeOH (15 ml) and stirred overnight. After removal of the solvent, the residue was dissolved in pyridine (6 ml) and Ac_2O (4.5 ml). After being stirred overnight, the reaction mixture was diluted with 5 % $NaHCO_3$, and extracted with AcOEt. The AcOEt extracts were dried, and concentrated. Silica-gel column chromatography (40 % AcOEt in hexane) gave (-)-**17** (285 mg, 70 %) as a colorless crystal. IR (Nujol) 1740 cm^{-1}. 270 M Hz - ^{1}H NMR ($CDCl_3$) δ 4.64 (1H, dd, *J* = 1.0, 5.3 Hz), 4.59 (1H, dd, *J* = 1.0, 5.3 Hz), 4.33 (1H, dd, *J* = 3.6, 11.2 Hz), 4.21 (1H, d, *J* = 11.2 Hz), 3.00 (1H, dd, *J* = 4.0, 1.0 Hz), 2.46 (1H, m), 2.29 (1H, m), 1.88 (1H, d, *J* = 12.2 Hz), 1.47 (3H, s), 1.33 (3H, s). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ 170.3, 111.2, 82.8, 81.5, 72.1, 48.4, 39.5, 25.6, 25.6, 24.0. EI-MS m/z 183 (M^+-Me), 97, 43. FAB(+)-HRMS m/z: calcd. for $C_{10}H_{15}O_4$ (M^++H): 199.0970; found 199.0964. $[\alpha]_D^{25}$ - 41.0 (c = 0.97, $CHCl_3$). mp 139-140 °C.

(1*R*, 5*R*, 6*R*, 7*S*)-6,7-Isopropylidenedioxy-3-oxabicylo[3.2.1]octan-2-one ((+)-17). $[\alpha]_D^{24}$ + 40.9 (c = 1.04, $CHCl_3$). mp 141 - 142 °C. {lit.[2a] $[\alpha]_D^{25}$ + 44.4 (c = 1.0, $CHCl_3$). mp 140 - 141.5 °C.}.

(1*S*, 2*S*, 3*R*, 4*R*)-4-*t*-Butyldimethylsiloxymethyl-2,3-isopropylidenedioxycyclopentane methanol acetate (18). A solution of (-)-**16** (1.50 g, 6.15 mmol), imidazole (480 mg, 7.06 mmol), and TBDMSCl (1.02 g, 6.77 mmol) in DMF (8 ml) was stirred overnight at room temperature. The reaction mixture was diluted with 5 % $NaHCO_3$ aq., and extracted with AcOEt. The AcOEt extract was washed with brine and dried. Silica-gel column chromatography (30 % AcOEt in hexane) afforded **18** (2.21 g, quant) as a colorless oil. IR (neat) 2950, 1740, 1370, 1250, 1100, 1070, 840, 780 cm^{-1}. 100 M Hz - ^{1}H NMR ($CDCl_3$) δ 4.34 (2H, m), 4.10 (2H, d, *J* = 6.1 Hz), 3.65 (2H, d, *J* = 4.6 Hz), 2.06 (3H, s), 1.49 (3H, s), 1.31 (3H, s), 0.89 (9H, s), 0.05 (6H, s), 1.80-2.45 (2H, m). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ 171.0, 112.2, 83.2, 82.5, 65.7, 63.7, 47.0, 44.6, 30.7, 27.7, 25.9, 25.3, 20.9, 18.3, -5.4. FD-MS m/z 343 (M^+-Me), 301. $[\alpha]_D^{22}$ - 2.15 (c = 1.23, $CHCl_3$).

(1*S*, 2*S*, 3*R*, 4*R*)-4-*t*-Butyldimethylsiloxymethyl-2,3-isopropylidenedioxycyclopentane methanol (19). A suspension of **18** (2.21 g, 6.17 mmol) and K_2CO_3 (940 mg, 6.81 mmol) in MeOH (25 ml) was stirred for 1 h at room temperature. After filtration, the filtrate was evaporated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel to give **19** (1.93g, 99 %) as a colorless oil. IR (neat) 3450, 2950, 1380, 1260 cm^{-1}. 100 M Hz - ^1H NMR ($CDCl_3$) δ 4.35 (2H, m), 3.66 (4H, d, *J* = 4.9 Hz), 1.49 (3H, s), 1.30 (3H, s), 1.00 - 2.40 (5H, m), 0.89 (9H, s), 0.05 (6H, s). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ 112.2, 83.8, 82.7, 64.9, 64.1, 47.8, 47.3, 30.6, 27.7, 25.9, 25.3, 18.4, -5.4. EI-MS m/z 301 (M^+-Me), 201, 183, 75. $[\alpha]_D^{23}$ + 8.68 (c = 0.66, $CHCl_3$).

(1*R*, 2*R*, 3*S*, 4*S*)-1-*t*-Butyldimethylsiloxymethyl-4-iodomethyl-2,3-isopropylidenedioxycyclopentane (20). A mixture of Ph_3P (2.56 g, 9.77 mmol) and I_2 (2.32 g, 9.13 mmol) in CH_2Cl_2 was stirred for 1 h at room temperature. After being cooled to 0 °C, a solution of **19** (1.93 g, 6.11 mmol) and pyridine (720 mg, 9.11 mmol) in CH_2Cl_2 (40 ml) was added, and stirred for 4 h at room temperature. The reaction mixture was diluted with dil $Na_2S_2O_3$ aq. (100 ml), and extracted with ether. The ether extract was washed with H_2O, and dried. After removal of the solvent, the residue was subject to column chromatography (10 % AcOEt in hexane) to give **20** (2.41 g, 93 %) as a colorless oil. IR (neat) 2940, 2860, 1380, 1260, 1120, 1070, 840, 780 cm^{-1}. 100 M Hz - ^1H NMR ($CDCl_3$) δ 4.42 (1H, dd, *J* = 3.9, 6.8 Hz), 4.17 (1H, dd, *J* = 4.8, 6.8 Hz), 3.65 (2H, d, *J* = 4.6 Hz), 3.37 (1H, dd, *J* = 5.4, 9.8 Hz), 3.23 (1H, dd, *J* = 6.6, 9.8 Hz), 1.49 (3H, s), 1.30 (3H, s), 0.90 (9H, s), 0.05 (6H, s), 1.40-2.40 (4H, m). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ 112.4, 85.4, 82.9, 63.7, 47.4, 46.7, 35.2, 27.7, 25.9, 25.3, 18.3, 10.1, -5.4. FD-MS m/z 411 (M^+-Me), 369, 262. $[\alpha]_D^{25}$ - 13.9 (c = 1.13, $CHCl_3$).

(1*R*, 2*R*, 3*S*)-1-*t*-Butyldimethylsiloxymethyl-2,3-isopropylidenedioxy-4-methylenecyclopentane (21). A solution of **20** (200 mg, 0.469 mmol) and DBU (142 mg, 0.939 mmol) in benzene (7 ml) was refluxed for 3 h. The solution was diluted with NH_4Cl aq., and extracted with ether. The extract was washed with $Na_2S_2O_3$ aq., H_2O, and dried. The solvent was removed *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 10 % AcOEt in hexane (v/v) afforded **21** (94.1 mg, 67 %) às a colorless oil. IR (neat) 3100, 2950, 2870, 1380, 1370, 1260, 1210, 1165, 1010, 1050, 840, 780 cm^{-1}. 100 M Hz - ^1H NMR ($CDCl_3$) δ 5.17 (1H, m), 5.07 (1H, m), 4.70 (1H, d, *J* = 5.7 Hz), 4.48 (1H, d, *J* = 5.7 Hz), 3.43 (2H, d, *J* = 6.8 Hz), 1.47 (3H, s), 1.33 (3H, s), 0.88 (9H, s), 0.03 (6H, s), 1.90-2.90 (3H, m). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ 149.9, 112.2, 110.3, 82.7, 81.8, 63.8, 45.8, 32.6, 26.9, 25.9, 24.6, 18.3, -5.4. EI-MS m/z 283 (M^+-Me), 241, 183, 83. $[\alpha]_D^{25}$ - 98.2 (c = 0.95, $CHCl_3$).

(2*S*, 3*R*, 4*R*)-4-*t*-Butyldimethylsiloxymethyl-2,3-isopropylidenedioxycyclopentanone (22). Ozone gas was bubbled into a solution of **21** (968 mg, 3.18 mol) in MeOH (45 ml) and CH_2Cl_2 (30 ml) at -78 °C, and the reaction was monitored by TLC. Me_2S (10 ml) was added to the reaction mixture at -78 °C, and the solution was gradually warmed to room temperature, and stirred overnight. After evaporation of the solvent, the residue was purified by silica-gel column chromatography (10 % AcOEt in hexane) to give **22** (969 mg, quant) as a colorless crystal. IR (Nujol) 1760 cm^{-1}. 270 M Hz - ^1H NMR ($CDCl_3$) δ 4.64 (1H, d, *J* = 5.3 Hz), 4.22 (1H, d, *J* = 5.3 Hz), 3.83 (1H, dd, *J* = 2.3, 9.8 Hz), 3.63 (1H, dd, *J* = 2.6, 9.8 Hz), 2.73 (1H,

dd, J = 8.8, 17.8 Hz), 2.51 (1H, d, J = 8.8 Hz), 2.08 (1H, d, J = 17.8 Hz), 1.43 (3H, s), 1.35 (3H, s), 0.85 (9H, s), 0.04 (3H, s), 0.02 (3H, s). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ 212.7, 111.0, 82.0, 79.4, 65.3, 39.1, 37.2, 26.8, 25.8, 24.7, -5.7. EI-MS m/z 300 (M^+), 285 (M^+-Me), 243. FAB(+)-HRMS m/z: calcd. for $C_{15}H_{29}O_4Si$ (M^++H): 301.1835; found 301.1833. $[\alpha]_D^{22}$ - 133.1 (c = 1.00, $CHCl_3$). mp 53 - 54 °C.

(1*S*, 2*S*, 3*R*, 4*S*)-4-*t*-Butyldimethylsiloxymethyl-2,3-isopropylidenedioxycyclopentanol (23). $NaBH_4$ (30 mg, 0.793 mmol) was added to the solution of **22** (200 mg, 0.667 mmol) in MeOH (20 ml) at 0 °C, and the reaction mixture was stirred for 30 min. After addition of acetone (10 ml), the solution was evaporated, diluted with brine, and extracted with AcOEt. The AcOEt extract was washed with brine, and dried. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 20 % AcOEt in hexane (v/v) afforded **23** (189 mg, 94 %) as a colorless oil. IR (neat) 3500, 2930, 2850, 1470, 1380, 1260, 1210, 1090, 1040 cm^{-1}. 270 M Hz - ^{1}H NMR ($CDCl_3$) δ 4.50 (1H, d, J = 5.6 Hz), 4.45 (1H, q, J = 5.6 Hz), 4.21 (1H, ddd, J = 5.6, 8.5, 15.4 Hz), 3.61 (1H, dd, J = 4.6, 10.2 Hz), 3.48 (1H, dd, J = 4.6, 10.2 Hz), 2.48 (1H, d, J = 8.5 Hz), 2.19 (1H, m), 1.50 (3H, s), 1.36 (3H, s), 0.88 (9H, s), 0.04 (6H, s), 1.80-1.90 (2H, m). 25 M Hz - ^{13}C NMR ($CDCl_3$) δ 111.0, 83.1, 79.8, 71.9, 64.7, 44.1, 35.7, 26.3, 25.9, 24.3, 18.3, -5.5. EI-MS m/z 303 (M^++1), 287 (M^+-Me), 169. FAB(+)-HRMS m/z: calcd. for $C_{15}H_{31}O_4Si$ (M^++H): 303.1991; found 303.1985. $[\alpha]_D^{25}$ - 14.0 (c = 1.00, $CHCl_3$).

9-[(1*R*, 2*S*, 3*R*)-4-*t*-Butyldimethylsiloxymethyl-2,3-isopropylidenedioxycyclopentan-1-yl]adenine (24). A solution of **23** (102 mg, 0.338 mmol) and pyridine (30 mg, 0.380 mmol) in CH_2Cl_2 (3 ml) was dropwise added to a solution of Tf_2O (116 mg, 0.369 mmol) in CH_2Cl_2 (1 ml), and the solution was stirred for 30 min. The solution was diluted with CH_2Cl_2 (10 ml), washed with H_2O, and dried. Evaporation of the solvent gave the crude trifrate. NaH (40 mg, 60 %) was washed with hexane (2 ml x 2), and a solution of adenine (140 mg, 1.04 mmol) in DMF (6 ml) was added. After being heated at 80 °C for 20 min, 18-crown-6 (268 mg, 1.04 mmol) and the crude trifrate in DMF (3 ml) was added at 0 °C, and stirred for 6 h. Then the reaction mixture was warmed to room temperature, and stirred overnight. After suction filtration, the filtrate was evaporated *in vacuo*, and diluted with H_2O (5 ml). The solution was extracted with CH_2Cl_2, and dried. Silica-gel column chromatography (10 % EtOH in CH_2Cl_2) gave **24** (24 mg, 17 %) as a colorless crystal. IR ($CHCl_3$) 3400, 1630, 1590, 1470, 1385, 1375 cm^{-1}. 270 M Hz - ^{1}H NMR ($CDCl_3$) δ 8.33 (1H, s), 7.87 (1H, s), 5.99 (2H, s), 5.03 (1H, t, J = 6.9 Hz), 4.80 (1H, m), 4.66 (1H, dd, J = 4.3, 6.9 Hz), 3.77 (2H, d, J = 4.3 Hz), 2.35-2.60 (3H, m), 1.58 (3H, s), 1.32 (3H, s), 0.92 (9H, s), 0.08 (3H, s), 0.07 (3H, s). 68 M Hz - ^{13}C NMR ($CDCl_3$) δ 155.7, 152.8, 150.2, 139.5, 120.4, 113.5, 83.9, 80.8, 63.0, 61.9, 45.8, 33.5, 27.6, 25.9, 25.2, 18.3, -5.4. FD-MS m/z 420 (M^++1), 362. FAB(+)-HRMS m/z: calcd. for $C_{20}H_{34}O_3N_5Si$ (M^++H): 420.2431; found 420.2439. $[\alpha]_D^{24}$ - 27.38 (c = 0.88, $CHCl_3$). mp 138 - 139 °C.

(-)-Aristeromycin (25). A solution of **24** (24 mg, 0.0573 mmol) in 5 % HCl aq. (1.5 ml) and MeOH (1.5 ml) was stirred for 1 day at room temperature. Evaporation of solvent, and column chromatography (CG-120 TYPE1), followed by recrystalisation from EtOH-H_2O afforded aristeromycin **25** (15 mg, 99 %) as a colorless crystal. IR (KBr) 3200 (br), 2950, 2850, 1660, 1610, 1580, 1460, 1340, 1300 cm^{-1}. 270 M Hz - ^{1}H NMR (DMSO-D_6) δ 8.20 (1H, s), 8.12 (1H, s), 7.19 (2H, br s), 4.70 - 4.70 - 5.10 (3H, br), 4.70 (1H, q, J = 8.6 Hz), 4.34 (1H, dd, J = 5.1, 9.2 Hz), 3.84 (1H, dd, J = 2.6, 5.1 Hz), 3.45

(2H, m), 2.25 (1H, dt, J = 8.6, 12.5 Hz), 2.05 (1H, m), 1.75 (1H, ddd, J = 7.9, 10.6, 12.5 Hz). 100 M Hz - ^{1}H NMR (DMSO-D_6) δ 8.19 (1H, s), 8.12 (1H, s), 7.17 (2H, br s), 4.80 - 5.00 (4H, br), 4.30(1H, m), 3.85 (1H, m), 3.45 (2H, m), 1.50 - 2.50 (3H, m);. 68 M Hz - ^{13}C NMR (DMSO-D_6) δ 155.9, 151.9, 149.6, 139.9, 119.2, 74.5, 71.6, 62.9, 59.2, 45.3, 29.2. FD-MS m/z 266 (M^++1). FAB(+)-HRMS m/z: calcd. for $C_{11}H_{16}O_3N_5$ (M^++H): 266.1253; found 266.1251. $[\alpha]_D^{25}$ - 52.1 (c = 0.275, DMF). mp 214 - 216 °C. {lit.[2a] $[\alpha]_D^{20}$ - 53.0 (c = 0.528, DMF). mp 214 - 215 °C.}.

Enzymatic transesterification of *meso*-diol (6). PFL (800 mg) was added to a solution of diol **6** (16.67 g, 82.5 mmol) in vinyl acetate (80 ml). The solution was stirred for 6 h at room temperature, the enzyme was filtered off and then the filtrate was concentrated. After short silica-gel column (100 g), the oily residue was recrystalised from isopropyl ether / hexane to afford (+)-**16** (13.46 g, 67 %). Small scale (diol **6**, 200 mg) reaction gave (+)-**16** in 81 % yield (>99 % ee) by silica gel column chromatography (without recrystalisation). $[\alpha]_D^{24}$ + 8.55 (c = 1.07, $CHCl_3$). mp 42 - 43 °C.

References and Notes:

1. a) Drueckhammer, D. G.; Hennen, W. J.; Pederson, R. L.; Barbas. III., W. J.; Gautheron, C. M.; Krach, T.; Wong, C.-H. *Synthesis* **1991**, 499-525.
   b) Boland, W.; Fröβl, C.; Lorenz, M. *Synthesis* **1991**, 1049-1072.
2. a) Ohno, M; Otsuka, M. *Organic Reactions* **1989**, *37*, 1-55.
   b) Hultin, P. G.; Mueseler, F. J.; Jones, J. B. *J. Org. Chem.* **1991**, *56*, 5375-5380.
   c) Xie, Z.-F.; *Tetrahedron: Asymmetry* **1991**, *2*, 733-750.
3. a) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571-623.
   b) Katagiri, N. *J. Syn. Org. Chem. (Japan)* **1989**, *47*, 707-721.
4. Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T.; Mizuno, K. *J. Antibiot.* **1968**, *21*, 255-263.
5. Suemune, H.; Okano, K.; Akita, H.; Sakai, K. *Chem. Pharm. Bull.* **1987**, *35*, 1741-1747.
6. Synthesis of carbocyclic nucleosides *via* enzymatic procedure:
   a) Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.***1983**, *105*, 4049-4055.
   b) Roberts, S. M.; Shoberu, K. A. *J. Chem. Soc. Perkin Trans. 1* **1991**, 2605-2607.
   c) Cotterill, I. C.; Cox, P. B.; Drake, A. F.; Grand, D. M. L.; Hutchinson, E. J.; Latouche, R.; Pettman, R. B.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Sik, V.; Williams, J. O. *J. Chem. Soc. Perkin Trans. 1* **1991**, 3071-3075;
   d) Evans, C. T.; Roberts, S. M.; Shoberu, K. A.; Sutherland, A. G. *J. Chem. Soc. Perkin Trans.1* **1992**, 589-592.
   e) LeGrand, D. M.; Roberts, S. M. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1751-1752.
   f) Hutchinson, E. J.; Roberts, S. M.; Thorpe, A. J. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2245-2246.
   g) Shoberu, K. A.; Roberts, S. M. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2419-2425.

7. Preliminary communication: Tanaka, M.; Yoshioka, M.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1992**, 1454-1455.
8. Wiberg, K. B.; Saegebarth, K. A. *J. Am. Chem. Soc.* **1957**, *79*, 2822-2824.
9. Compound **8** was prepared according to Corey's method: Corey, E. J.; Koelliker, U.; Neuffer, J. *J. Am. Chem. Soc.* **1971**, 1489-1490.
10. Vince, R.; Brownell, J. *Biochem. Biophys. Res. Commun.* **1990**, *168*, 912-916; and references cited therein.
11. Katagiri, N.; Toyota, A.; Shiraishi, T.; Sato, H.; Kaneko, C. *Tetrahedron Lett.* **1992**, *33*, 3507-3510.
12. a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.
b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.
13. Tested esterases and lipases were described as follows: pig liver esterase (PLE, Sigma), electric eel esterase (Sigma), *Pseudomonas fluorescens* lipase (PFL, Amano), porcine pancreatic lipase (PPL, Sigma), *Rhizopus delemar* lipase (RDL, Seikagaku kogyo), *Candida cylindracea* lipase (CCL, Sigma), *P. fragi* lipase (Seikagaku kogyo), *C. lipolytica* lipase (Fluka), *R. arrhizus* lipase (Fluka), *M. javanicus* lipase (Fluka), wheat germ lipase (Sigma), *A. niger* lipase (Amano), *R. javanicus* lipase (Amano), *P. roqueforti* lipase (Fluka).
14. During our studing on RDL, Mekrami *et al.* reported the lipase-catalysed hydrolysis of *meso*-compound **4** and transesterification of the corresponding *meso*-diol by CCL afforded the monoacetate **14** of 97 % ee.: Mekrami, M.; Sicsic, S. *Tetrahedron: Asymmetry* **1992**, *3*, 431-436.
15. Tadano, K.; Hoshino, M.; Ogawa, S.; Suami, T. *J. Org. Chem.* **1988**, *53*, 1427-1432.
16. Wolfe, M. S.; Borcherding, D. R.; Borchardt, R. T. *Tetrahedron Lett.* **1989**, *30*, 1453-1456.
17. a) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114-120.
b) Faber, K.; Riva, S. *Synthesis* **1992**, 895-910.