Synthesis of Optically Active Nucleoside Analogs Containing 2,3-Dideoxyapiose in the Presence of a Catalytic Amount of Trimethylsilyl Iodide

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Optically pure (*R*)-4,4-diethoxy-2-(hydroxymethyl)butyl acetate (1) was synthesized enantioselectively by lipase-catalyzed transesterification from 4,4-diethoxy-2-(hydroxymethyl)butanol. Coupling of silylated nucleobases and 2-*O*-acetyl-5-*O*-pivaloyl-(3*S*)-2,3-dideoxyapiose (2) prepared from 1 was found to proceed smoothly in the presence of a catalytic amount of trimethylsilyl iodide under mild conditions to afford optically active nucleoside analogs.

Keywords lipase; transesterification; 2,3-dideoxyapiose; trimethylsilyl iodide; nucleoside analog

Enzymes are useful catalysts for the syntheses of optically active compounds.[1] We have obtained many chiral building blocks by the lipase-catalyzed enantioselective reaction of 2-substituted-1,3-propanediol.[2] One of them is (*R*)-4,4-diethoxy-2-(hydroxymethyl)butyl acetate (**1**), which is a useful chiral building block because it has three easily convertible functional groups.[3] In a few reaction steps from **1** we synthesized 1-*O*-acetyl-5-*O*-pivaloyl-(3*S*)-2,3-dideoxyapiose (**2**).[4]

In this paper we present details of the synthesis of **2** and a convenient method for synthesis of nucleoside analogs from **2** and silylated nucleobases with a view to supplying antiviral drugs such as 3′-azido-3′-deoxythymidine (AZT)[5] and 2′,3′-dideoxyinosine (ddI).[6]

Optically active monoacetate (**1**) was prepared enantioselectively from 4,4-diethoxy-2-(hydroxymethyl)butanol with lipase P[7] catalyst. The absolute configuration was determined as *R* by conversion of **1** into (*S*)-2-methyl-1,4-butanediol, reported previously.[8] Esterification with pivaloyl chloride and a few subsequent reaction steps gave **2** in good yield as shown in Chart 1.

Although tin(IV) tetrachloride[9] and trimethylsilyl trifluoromethanesulfonate (TMSOTf)[10] are well known activators for the coupling of a silylated base with a 1-*O*-acetyl sugar, trimethylsilyl iodide (TMSI) was revealed to promote the condensation of **2** and silylated base. When TMSI (0.2 mol eq) was added to a solution of bis(trimethylsilyl)thymine and **2** in acetonitrile at −5—0 °C, the reaction started immediately and **2** disappeared after about 1 h to produce the corresponding dideoxythymidine analogs (**3a, b**) in 93% yield. Table I summarizes the experimental results. The product isolated briefly was a mixture of **3a** and **3b**, the ratio of which was determined by the ^{1}H-NMR analysis. The isomers were separated by flash column chromatography on silica gel and converted to 3′-hydroxymethyl derivatives (**4a, b**) by treatment with sodium methoxide in methanol. The structures of **4a** and **4b** were determined on the basis of elemental analyses, and ^{1}H- and ^{13}C-NMR spectra. The stereochemistry of each isomer was elucidated on the basis of the difference nuclear Overhauser effect (NOE) spectrum. The NOE experimental results are indicated with arrows on the structure in Fig. 1.

In the ^{1}H-NMR spectra, the anomeric proton signal of **4a** (1′,3′-*cis*) appeared as a pseudo-triplet at 6.01 ppm. On the other hand, that of **4b** (1′,3′-*trans*) was observed as a clearly split doublet of doublets at 6.02 ppm. The same splitting patterns are observed in the spectra of the other analogs (**3, 5—8**) we synthesized. Such significant differences seem to be useful for assignment of the isomers in the present series of nucleoside analogs.[11]

Table I shows that the presence of a catalytic amount of TMSI gave a better yield and also increased the ratio of **3a** (1′,3′-*cis*), which seems to be sterically unfavorable. The reaction seems to occur *via* substitution of the acetoxy group on the anomeric carbon with iodide in the first step, and TMSI is regenerated at the condensation step with a silylated base (Chart 2).

According to the hard and soft acids and bases (HSAB)

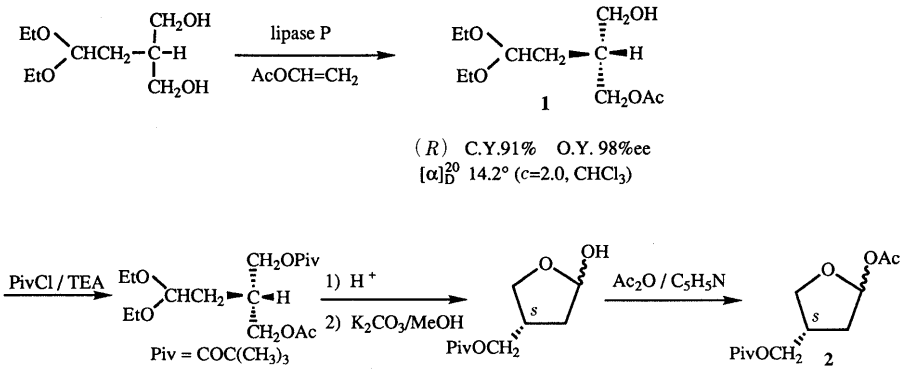
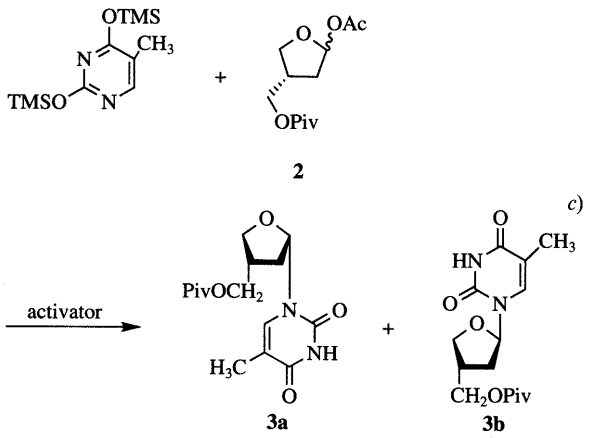


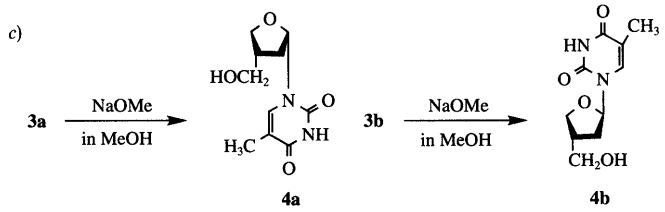
Chart 1. Preparation of 1-*O*-Acetyl-5-*O*-pivaloyl-(3*S*)-2,3-dideoxyapiose (**2**)

TABLE I. Reaction of Bis(trimethylsilyl)thymine with 1-*O*-Acetyl-5-*O*-pivaloyl-(3*S*)-2,3-dideoxyapiose (**2**)[a]



Activator and conditions	Yield (%)	3a/3b[b]
TMSI (0.2 eq) CH_3CN, −5—0 °C, 1 h	93	5/4
TMSOTf (1.1 eq) CH_3CN, −5—0 °C, 2 h	37	1/3
$SnCl_4$ (2 eq) $ClCH_2CH_2Cl$, −5—0 °C, 2 h	40	1/3

a) Piv = $(CH_3)_3CCO$, TMSI = $(CH_3)_3SiI$, TMSOTf = $(CH_3)_3SiOSO_2CF_3$.
b) Ratios were determined from the ^{1}H-NMR spectra.



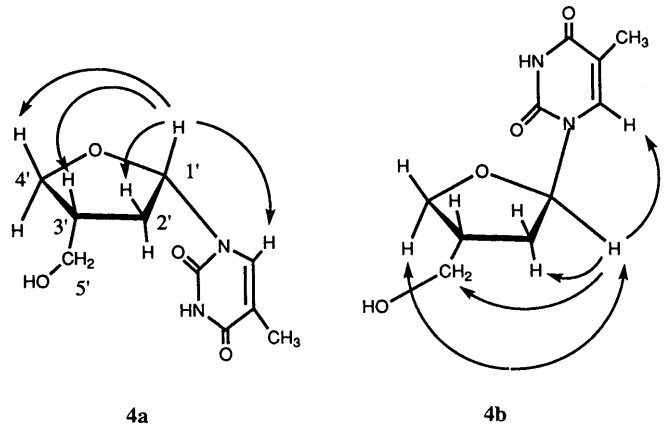


Fig. 1. Results of Difference NOE Experiment

concept,[12] a soft iodide is more effective than a hard trifluoromethanesulfonyloxy or chloride for attack on a soft anomeric carbon. Therefore, only 0.2 mol eq of TMSI activates the anomeric carbon under the conditions used. On the other hand, the 1′,3′-*cis* isomer of the intermediate forms in preference to the *trans* isomer because TMSI attacks from the less-hindered site of **2**, and the subsequent step seems to involve the back attack of thymine nitrogen. Since *S*N 1-like reaction appears to occur in the cases of TMSOTf and $SnCl_4$, the attack of the thymine on the less

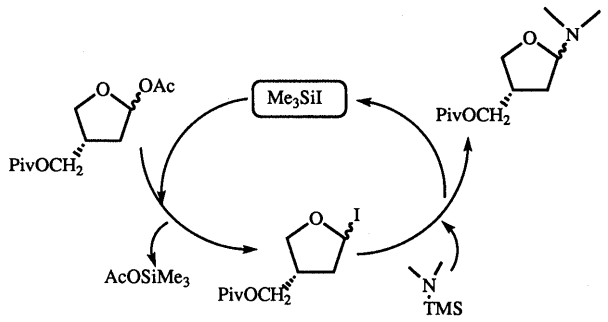
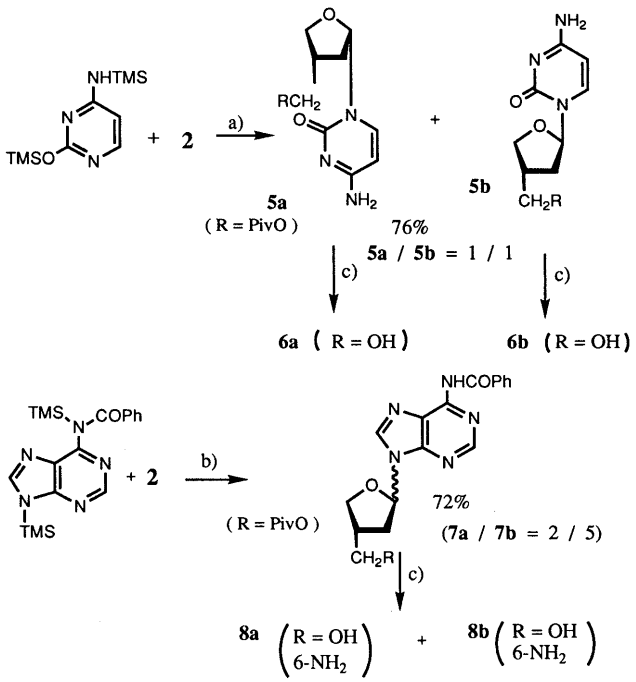


Chart 2



a) TMSI (0.2 eq) / CH_3CN, 0°C, 3 h b) TMSI (0.2 eq) / CH_3CN, −5—0°C, 2 h
c) NaOMe / MeOH, r.t., 10 h

Chart 3

hindered site of the intermediate is favorable. Dideoxycytidine analogs (**6a, b**) were synthesized in the same manner as those of the dideoxythymidines (**4a, b**). The dideoxyadenosine analogs **8a** (1′,3′-*cis*) and **8b** (1′,3′-*trans*) were synthesized by the reaction of fully silylated N^6-benzoyladenine with **2** followed by treatment with sodium methoxide in methanol (Chart 3). In this case, the ratio of 1′,3′-*trans* isomer to 1′,3′-*cis* was increased in comparison with that of the deoxythymidine analog (**3b**) because of the bulkiness of silylated N^6-benzoyladenine. The structures of these products were also determined on the basis of elemental analyses and spectral data.

Application of this method to the coupling reactions of some other sugars is under investigation. The products **5a** and **8a** exhibited weak anti-human immunodeficiency virus (HIV) activity, which will be described elsewhere.

Experimental

All melting points were determined on a Yanagimoto micro hot-stage apparatus and are uncorrected. Spectroscopic measurements were performed with the following instruments: infrared (IR) spectra with JASCO IR-Report-100 spectrometer, positive fast atom bombardment

mass spectra (FAB-MS) with JEOL JMS-SX102 mass spectrometer, and optical rotations with JASCO DIP-140 polarimeter, ^{1}H-NMR and ^{13}C-NMR spectra with a JEOL JNM-GSX270 (270 MHz) Fourier transform (FT)-NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Coupling constants (J values) are given in hertz (Hz) and the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad.

(*R*)-4,4-Diethoxy-2-(hydroxymethyl)butyl Acetate (1) A mixture of 4,4-diethoxy-2-(hydroxymethyl)butanol (19.2 g, 0.1 mol), vinyl acetate (13.0 g, 0.15 mol), and lipase P (300 mg) was stirred at 25 °C for 8 h. The lipase was filtered off and washed with CH_2Cl_2. The combined organic layer was concentrated to give an oily residue which was chromatographed on a column of silica gel with AcOEt–hexane (1 : 5) to afford a colorless oil (21.6 g, 91%), $[\alpha]_D^{21}$ 14.2° (c = 2.0, $CHCl_3$). IR (neat): 1735 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (6H, t, J = 6.8, 2 × CH_3), 1.70 (2H, dd, J = 5.4, 6.7, CH–C$\underline{H_2}$–CH), 1.96—2.09 (1H, m, CH_2–C$\underline{H}$–CH_2), 2.07 (3H, s, $COCH_3$), 2.70 (1H, br, OH), 3.45—3.85 (6H, m, C$\underline{H_2}$OH, 2 × OCH_2), 4.08 (1H, dd, J = 6.7, 11.2, C$\underline{H_A}$HOAc), 4.15 (1H, dd, J = 5.3, 11.2, C$\underline{H_B}$HOAc), 4.62 (1H, t, J = 5.4, O–C$\underline{H}$–O). ^{13}C-NMR ($CDCl_3$) δ: 15.2, 15.2, 20.9, 32.6, 36.9, 61.2, 61.9, 62.7, 64.9, 101.5, 171.4.

After esterification with benzoyl chloride in the presence of triethylamine in the usual manner, the optical yield (98% ee) of **1** was determined by HPLC analysis (Chiralcel OD, isopropanol–hexane).

The absolute configuration of **1** was elucidated in the following way. A solution of methanesulfonyl chloride (0.37 mg, 3.3 mmol) in CH_2Cl_2 (1 ml) was added dropwise to a cooled solution of **1** (730 mg, 3 mmol) and triethylamine (400 mg, 4 mmol) in CH_2Cl_2 (20 ml) with stirring. The solution was stirred at room temperature for 5 h, washed with brine, dried over $MgSO_4$, and concentrated to give an oily residue which was chromatographed on a column of silica gel with AcOEt–hexane (1 : 3) to give an oil, (*S*)-2-(acetoxymethyl)-4,4-diethoxybutyl methanesulfonate, (870 mg, 85%). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (6H, t, J = 7.0, 2 × CH_3), 1.68 (2H, t, J = 6.5, CHC$\underline{H_2}$CH), 2.05 (3H, s, $COCH_3$), 2.2—2.5 (1H, m, CH), 2.95 (3H, s, SO_2CH_3), 3.31—3.90 (4H, m, 2 × CH_2O), 4.07 (2H, d, J = 6.0, CH_2OAc), 4.23 (2H, d, J = 6.5, CH_2OSO_2), 4.53 (1H, t, J = 5.5, O–CH–O). The above compound (680 mg, 2 mmol) was added to a solution of 1 M HCl (1 ml) in tetrahydrofuran (THF) (5 ml). The solution was stirred at 50 °C for 2 h, and neutralized with aqueous $NaHCO_3$. After removal of THF, the residue was extracted with ether. The ethereal layer was dried over $MgSO_4$ and concentrated to afford an oil. In its ^{1}H-NMR (in $CDCl_3$) spectrum, a broad singlet was observed at 9.65 ppm due to CHO. A solution of this oil in THF (1 ml) was added to a mixture of $LiAlH_4$ (220 mg, 6 mmol) in THF (20 ml) with stirring. The reaction mixture was stirred at 60 °C for 3 h and chilled in an ice bath, then 5% HCl (2 ml) was added. The mixture was extracted with ether and the ethereal layer was washed with brine, dried over $MgSO_4$, and concentrated to give a colorless oil (100 mg, 50%). The ^{1}H-NMR spectrum of the product coincided with that of authentic (*RS*)-2-methyl-1,4-butanediol, $[\alpha]_D^{20}$ −13.8° (c = 1.0, MeOH) [lit.,[7] (*S*)-enantiomer, $[\alpha]_D^{20}$ −14.4° (c = 0.6, MeOH)].

(*S*)-2-(Acetoxymethyl)-4,4-diethoxybutyl Pivalate Pivaloyl chloride (7.2 g, 60 mmol) was added to a cooled solution of **1** (9.8 g, 40 mmol) and triethylamine (8.0 g, 80 mmol) in CH_2Cl_2 (80 ml) with stirring. After being stirred overnight, the mixture was poured into ice-water. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The oily residue was chromatographed on silica gel with AcOEt–hexane (1 : 5) to give a colorless oil (11.2 g, 88%), bp 155 °C (bath) (1 mmHg). IR (neat): 1730 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (9H, s, $(CH_3)_3$C–), 1.20 (6H, t, J = 6.8, 2 × C$\underline{H_3}$$CH_2$O–), 1.69 (2H, t, J = 5.8, CH–C$\underline{H_2}$–CH), 2.05 (3H, s, $COCH_3$), 2.20 (1H, m, CH), 3.47—3.55, 3.60—3.69 (4H, m, 2 × OCH_2CH_3), 4.06—4.14 (4H, m, 2 × CH_2OCO), 4.60 (1H, t, 5.8, O–CH–O). ^{13}C-NMR ($CDCl_3$) δ: 15.3, 20.8, 27.0, 27.1 (3 × C), 32.2, 33.9, 38.9, 61.4 (2 × C), 64.0, 64.2, 101.0, 170.9, 178.3. *Anal.* Calcd for $C_{16}H_{30}O_6$: C, 60.36; H, 9.50. Found: C, 60.15; H, 9.38.

1-*O*-Acetyl-5-*O*-pivaloyl-(3*S*)-2,3-dideoxyapiose (2) A solution of **3** (6.4 g, 20 mmol) and 1 M HCl (1 ml) in THF (20 ml) was stirred at 35 °C for 3 h under an argon atmosphere. The mixture was neutralized with aqueous sodium bicarbonate, and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. After removal of the solvent, the oily residue was chromatographed on a short silica gel column (AcOEt : hexane = 1 : 10) to give an oil (3.8 g). In its ^{1}H-NMR (in $CDCl_3$) spectrum, a triplet (J = 1.2 Hz) was observed at 9.79 ppm due to CHO. Subsequently, this product was added to a solution of 10% aqueous K_2CO_3 (5 ml) in methanol (30 ml), and the solution was stirred at room temperature for 2 h. After removal of the methanol, the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated to give an oil, which was treated with acetic anhydride (5 ml) in pyridine (10 ml) at room temperature. Usual work-up of the reaction solution and purification by silica gel column chromatography using AcOEt : hexane = 1 : 5 as an eluent gave an oily product (3.1 g, 64%), bp 150 °C (bath) (1 mmHg). IR (neat): 1730 (CO) cm^{-1}. MS m/z: 201 $(M-COCH_3)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.20, 1.21 (9H, each s, $C(CH_3)_3$). 1.80—1.95, 2.09—2.18, 2.28—2.40 (3H, m, 2-CH_2, 3-CH), 2.04, 2.05 (3H, each s, $COCH_3$), 3.75 (dd, J = 5.8, 8.8), 3.82 (dd, J = 6.6, 8.8), 4.00 (dd, J = 7.3, 10.7), 4.07—4.22 (m) (the total 4H, 4-CH_2, CH_2OCO), 6.29—6.32 (1H, m, 1-CH). ^{13}C-NMR ($CDCl_3$) δ: 21.3, 21.4, 27.1 (3 × C, 1-*R* and *S*), 34.9, 35.3, 36.1, 36.7, 38.8 (2′-*R* and *S*), 65.1, 65.3, 70.8, 71.1, 98.8 (1-*R* and *S*), 170.3 (1-*R* and *S*), 178.2 (1-*R* and *S*). *Anal.* Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.77; H, 8.11.

1-[(3′*S*)-2′,3′-Dideoxyapiosyl]thymines (3a, b, 4a, b) A solution of trimethylsilyl iodide (120 mg, 0.6 mmol) in acetonitrile (1 ml) was added through a syringe to a stirred solution of bis(trimethylsilyl)thymine[13] (810 mg, 3 mmol) and **2** (730 mg, 3 mmol) in acetonitrile (20 ml) under an argon atmosphere in an ice-salt bath. The mixture was stirred at −5—0 °C until **1** had disappeared (1 h) on the basis of TLC analysis, poured into cooled aqueous sodium bicarbonate, and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue chromatographed on silica gel eluting with AcOEt–hexane (1 : 10) to afford a crystalline solid (870 mg, 93%). Its ^{1}H-NMR analysis suggested that the ratio of 1′,3′-*cis* isomer to 1′,3′-*trans* isomer was 5 : 4. Each isomer was separated by flash chromatography with AcOEt–hexane (1 : 15) as an eluent.

3a (1′,3′-*cis*): mp 124—125 °C (from AcOEt), $[\alpha]_D^{20}$ −21.0° (c = 1.0, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (9H, s, $C(CH_3)_3$), 1.68 (1H, ddd, J = 7.3, 9.2, 13.1, 2′-C$\underline{H_A}$H), 1.94 (3H, s, CH_3), 2.63 (1H, ddd, J = 7.3, 9.2, 13.1, 2′-C$\underline{H_B}$H), 2.80 (1H, m, 3′-CH), 3.86 (1H, t, J = 8.3, C$\underline{H_A}$HOCO), 4.06—4.19 (3H, m, 3′-CH_2, C$\underline{H_B}$HOCO), 6.05 (1H, t, J = 7.3, 1′-CH), 7.20 (1H, s, 4′-CH), 9.45 (1H, br, NH). ^{13}C-NMR ($CDCl_3$) δ: 12.6, 27.1 (3 × C), 35.3, 38.1, 38.8, 64.2, 70.9, 86.6, 111.1, 134.6, 150.4, 163.9, 178.2. *Anal.* Calcd for $C_{15}H_{22}N_2O_5$: C, 58.05; H, 7.15; N, 9.03. Found: C, 58.00; H, 7.17; N, 8.96.

3b (1′,3′-*trans*): mp 115—117 °C (from AcOEt), $[\alpha]_D^{20}$ −8.4° (c = 0.6, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.22 (9H, s, $C(CH_3)_3$), 1.94 (3H, s, CH_3), 2.14—2.33 (2H, m, 2′-CH_2), 2.75 (1H, m, 3′-CH), 3.79 (1H, dd, J = 6.8, 8.8, 4′-C$\underline{H_A}$H), 4.05 (1H, dd, J = 6.8, 11.2, C$\underline{H_A}$HOCO), 4.14 (1H, dd, J = 6.3, 11.2, C$\underline{H_B}$HOCO), 4.29 (1H, dd, J = 6.8, 8.8, 4′-C$\underline{H_B}$H), 6.06 (1H, dd, J = 3.9, 6.3, 1′-CH), 7.15 (1H, s, 4-CH), 9.58 (1H, br, NH). ^{13}C-NMR ($CDCl_3$) δ: 12.6, 27.1 (3 × C), 35.6, 37.1, 38.8, 64.4, 71.9, 87.0, 110.6, 135.0, 150.4, 164.1, 178.2.

The product **3a** (155 mg, 0.5 mmol) was added to 1 M MeONa/MeOH (1 ml) in an ice-bath. The solution was stirred at room temperature for 1 h and poured into ice-water. After extraction with CH_2Cl_2, the organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a crystalline solid (**4a**) (105 mg, 98%). Compound **4b** was obtained in the same manner as **4a**.

4a (1′,3′-*cis*): mp 150—151 °C (EtOH), $[\alpha]_D^{20}$ −26.8° (c = 1.2, MeOH). ^{1}H-NMR (CD_3OD) δ: 1.78 (1H, ddd, J = 6.9, 8.7, 13.3, 2′-C$\underline{H_A}$H), 1.89 (3H, s, CH_3), 2.47 (1H, ddd, J = 6.9, 8.3, 13.3, 2′-C$\underline{H_B}$H), 2.62 (1H, m, 3′-CH), 3.58 (1H, dd, J = 6.0, 11.0, C$\underline{H_A}$HOH), 3.63 (1H, dd, J = 7.0, 11.0, C$\underline{H_B}$HOH), 3.94 (1H, t, J = 8.0, 4′-C$\underline{H_A}$H), 4.06 (1H, t, J = 8.0, 4′-C$\underline{H_B}$H), 6.01 (1H, t, J = 6.9, 1′-CH), 7.51 (1H, s, 4-CH). ^{13}C-NMR (CD_3OD) δ: 12.5, 35.6, 42.4, 63.5, 72.4, 88.1, 111.5, 137.7, 152.4, 166.5. *Anal.* Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.00; H, 6.12; N, 12.46.

4b (1′,3′-*trans*): mp 142—143 °C (EtOH), $[\alpha]_D^{20}$ −7.0° (c = 0.8, MeOH). ^{1}H-NMR (CD_3OD) δ: 1.89 (3H, s, CH_3), 2.16 (2H, m, 2′-CH_2), 2.59 (1H, m, 3′-CH), 3.53 (1H, dd, J = 6.9, 11.0, C$\underline{H_A}$HOH), 3.59 (1H, dd, J = 6.0, 11.0, C$\underline{H_B}$HOH), 3.75 (1H, dd, J = 6.9, 8.8, 4′-C$\underline{H_A}$H), 4.31 (1H, dd, J = 7.0, 8.8, 4′-C$\underline{H_B}$H), 6.02 (1H, dd, J = 4.1, 7.0, 1′-CH), 7.42 (1H, s, 4-CH). ^{13}C-NMR (CD_3OD) δ: 12.6, 34.7, 40.1, 63.0, 72.1, 88.2, 111.6, 137.2, 152.2, 166.6. *Anal.* Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.84; H, 6.27; N, 12.20.

The reactions in the presence of trimethylsilyl trifluoromethanesulfonate and tin tetrachloride instead of trimethylsilyl iodide were carried out in essentially the same way as described above.

1-[(3′*S*)-2′,3′-dideoxyapiosyl]cytosines (5a, b, 6a, b) The reaction of bis(trimethylsilyl)cytosine and **1** in the presence of trimethylsilyl iodide was carried out in the same manner as described above. The mixture of both isomers was obtained in 76% yield.

5a (1′,3′-*cis*): mp 201—203 °C. FAB-MS m/z: 296 $(M+H)^+$. ^{1}H-NMR

(CD_3OD) δ: 1.17 (9H, s, $C(CH_3)_3$), 1.74 (1H, ddd, J=6.4, 8.7, 14.2, 2'-CH_AH), 2.66 (1H, ddd, J=6.4, 8.2, 14.2, 2'-CH_BH), 2.79 (1H, m, 3'-CH), 3.89—3.93, 4.05—4.15 (4H, m, 4'-CH_2, CH_2OCO), 5.92 (1H, d, J=7.3, 5-CH), 5.96 (1H, t, J=6.7, 1'-CH), 7.71 (1H, d, J=7.3, 4-CH). ^{13}C-NMR (CD_3OD) δ: 27.5, 36.8, 39.4, 39.8, 65.6, 72.3, 89.3, 95.9, 141.7, 158.1, 167.6, 179.7.

5b (1',3'-*trans*): mp 215—218 °C. FAB-MS *m/z*: 296 $(M+H)^+$. ^{1}H-NMR (CD_3OD) δ: 1.20 (9H, s, $C(CH_3)_3$), 2.16 (1H, ddd, J=3.7, 7.8, 13.7, 2'-CH_AH), 2.27 (1H, ddd, J=6.9, 7.0, 13.7, 2'-CH_BH), 2.70 (1H, m, 3'-CH), 3.79 (1H, dd, J=6.8, 8.7, 4'-CH_AH), 4.06 (1H, dd, J=7.3, 11.0, CH_AHOCO), 4.15 (1H, dd, J=5.5, 11.0, CH_BHOCO), 4.33 (1H, dd, J=7.3, 8.7, 4'-CH_BH), 5.89 (1H, d, J=7.3, 5-CH), 6.02 (1H, dd, J=3.2, 6.4, 1'-CH), 7.65 (1H, d, J=7.3, 4-CH). ^{13}C-NMR (CD_3OD) δ: 27.5, 37.0, 38.2, 39.8, 65.9, 73.0, 89.3, 95.6, 141.9, 158.2, 167.7, 179.8.

6a (1',3'-*cis*): Waxlike masses. FAB-MS *m/z*: 212 $(M+H)^+$. $[\alpha]_D^{20}$ −35.3° (c=0.8, MeOH). ^{1}H-NMR (CD_3OD) δ: 1.69 (1H, ddd, J=6.3, 7.9, 13.6, 2'-CH_AH), 2.60 (2H, m, 2'-CH_BH, 3'-CH), 3.53 (1H, dd, J=4.6, 11.0, CH_AHOH), 3.58 (1H, dd, J=5.0, 11.0, CH_BHOH), 3.94 (1H, dd, J=7.3, 8.7, 4'-CH_AH), 4.10 (1H, dd, J=7.4, 8.7, 4'-CH_BH), 5.91 (1H, d, J=7.6, 5-CH), 5.97 (1H, t, J=6.3, 1'-CH), 7.71 (1H, d, J=7.6, 4-CH). ^{13}C-NMR (CD_3OD) δ: 36.6, 42.2, 63.7, 72.6, 89.2, 95.8, 141.9, 158.3, 167.6.

6b (1',3'-*trans*): mp 178—180 °C (EtOH). FAB-MS *m/z*: 212 $(M+H)^+$. $[\alpha]_D^{20}$ 25.5° (c=1.0, MeOH). ^{1}H-NMR (CD_3OD) δ: 2.10 (1H, ddd, J=3.2, 7.8, 13.3, 2'-CH_AH), 2.22 (1H, ddd, J=6.4, 6.9, 13.3, 2'-CH_BH), 2.50 (1H, m, 3'-CH), 3.54 (1H, dd, J=7.3, 11.0, CH_AHOH), 3.60 (1H, dd, J=6.9, 11.0, CH_BHOH), 3.80 (1H, dd, J=7.3, 8.7, 4'-CH_AH), 4.31 (1H, dd, J=7.4, 8.7, 4'-CH_BH), 5.89 (1H, d, J=7.3, 5-CH), 5.99 (1H, dd, J=3.2, 6.4, 1'-CH), 7.64 (1H, d, J=7.3, 4-CH). ^{13}C-NMR (CD_3OD) δ: 37.1, 41.3, 63.8, 73.5, 89.6, 95.7, 142.1, 158.1, 167.7.

9-[(3'*S*)-2',3'-Dideoxyapiosyl]adenines (7a, b, 8a, b) A suspension of N^6-benzoyladenine (480 mg, 2.0 mmol) and ammonium sulfate (50 mg) in hexamethyldisilazane (10 ml) was refluxed for 3 h.[12] Excess hexamethyldisilazane was removed *in vacuo* from the resulting solution. The residue was dissolved in acetonitrile (10 ml), then **1** (490 mg, 2 mmol) and a solution of trimethylsilyl iodide (80 mg, 0.4 mmol) in acetonitrile (1 ml) were added in an ice-salt bath. The mixture was stirred at −5—0 °C for 2 h, and then poured into cooled saturated sodium bicarbonate. The resultant mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and concentrated to dryness *in vacuo*. The residue was chromatographed on a silica gel column using ethanol–CH_2Cl_2 (1 : 10) as an eluent to give a crystalline solid (610 mg, 72%), the ^{1}H-NMR spectrum of which showed it to be a mixture of 1',3'-*cis* (**7a**) and 1',3'-*trans* isomer (**7b**) (2 : 5). ^{1}H-NMR ($CDCl_3$) δ: 1.20, 1.23 (9H, each s, $C(CH_3)_3$), 2.38 (dt, J=7.3, 13.9), 2.56 (ddd, J=6.2, 8.9, 13.2), 2.70—3.14 (m) (the total 3H, 2'-CH_2, 3'-CH), 3.92 (dd, J=6.2, 8.8), 4.07—4.30 (m), 4.38 (dd, J=7.3, 8.8) (the total 4H, 4'-CH_2, CH_2OCO), 6.30 (t, J=6.6), 6.37 (dd, J=3.0, 7.0) (the total 1H, 1'-CH), 7.40—7.63, 7.79—7.82, 8.01—8.04 (5H, m, C_6H_5), 8.12, 8.16, 8.78 (2H, each s, 2 and 8-CH). *Anal.* Calcd for $C_{22}H_{25}N_5O_4 \cdot 1/2H_2O$: C, 61.16; H, 6.07; N, 16.21. Found: C, 60.87; H, 5.82; N, 15.95.

A solution of **7** (420 mg, 1 mmol) and 1 M MeONa/MeOH (3 ml) was stirred at room temperature for 3 h. Ion-exchange resin (IRC 50, 500 mg) was added to the reaction solution diluted with MeOH (10 ml) and the suspension was stirred for 1 h. After removal of the resin, the methanolic solution was concentrated *in vacuo* to give a crystalline solid. Each isomer was separated by flash chromatography on a silica gel column using EtOH–CH_2Cl_2 (1 : 15) as an eluent.

8a (1',3'-*cis*): mp 195—197 °C (from EtOH), $[\alpha]_D^{20}$ 30.5° (c=0.8, MeOH). FAB-MS *m/z*: 236 $(M+H)^+$. ^{1}H-NMR (CD_3OD) δ: 2.38 (1H, ddd, J=6.5, 7.3, 12.3, 2'-CH), 2.67 (2H, m, 2'- and 3'-CH), 3.68 (1H, dd, J=6.4, 11.0, CH_AHOH), 3.79 (1H, dd, J=5.9, 11.0, CH_BHOH), 4.04 (1H, t, J=8.2, 4'-CH_AH), 4.13 (1H, t, J=8.2, 4'-CH_BH), 6.28 (1H, t, J=6.5, 1'-CH), 8.19 (1H, s, 2-CH), 8.30 (1H, s, 8-CH). ^{13}C-NMR (CD_3OD) δ: 35.7, 42.6, 63.2, 72.2, 80.7, 129.4, 130.7, 140.4, 153.7, 157.3. *Anal.* Calcd for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57; N, 29.77. Found: C, 51.33; H, 5.30; N, 29.69.

8b (1',3'-*trans*): mp 145—146 °C (from EtOH), $[\alpha]_D^{20}$ −52.8° (c=1.0, MeOH). FAB-MS *m/z*: 236 $(M+H)^+$. ^{1}H-NMR (CD_3OD) δ: 2.34 (1H, dt, J=7.2, 13.6, 2'-CH_AH), 2.64 (1H, ddd, J=3.3, 8.3, 13.6, 2'-CH_BH), 2.79 (1H, m, 3'-CH), 3.61 (1H, dd, J=6.8, 11.0, CH_AHOH), 3.65 (1H, dd, J=6.2, 11.0, CH_BHOH), 3.89 (1H, dd, J=5.9, 8.7, 4'-CH_AH), 4.33 (1H, dd, J=6.9, 8.7, 4'-CH_BH), 6.33 (1H, dd, J=3.3, 7.2, 1'-CH), 8.19 (1H, s, 2-CH), 8.21 (1H, s, 8-CH). ^{13}C-NMR (CD_3OD) δ: 35.4, 41.5, 63.8, 72.6, 86.8, 120.4, 140.2, 149.8, 153.5, 156.9. *Anal.* Calcd for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57; N, 29.77. Found: C, 51.21; H, 5.19; N, 29.53.

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