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Synthesis and Optical Properties of 2,3-Dideoxy-D-*erythro*-hex-2-enopyranosyl Nucleosides (Nucleosides and Nucleotides. LXII[1])

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Condensation of 3,4,6-tri-*O*-acetyl-D-glucal and trimethylsilylated nucleobases in the presence of stannic chloride or trimethylsilyl trifluoromethanesulfonate gave anomeric mixtures of 2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl nucleosides. The signs of the circular dichroism (CD) spectra of the anomeric 2-hexenopyranosyl nucleosides are opposite to those of usual nucleosides or glucopyranosyl nucleosides. Other examples illustrating the contribution of an unsaturated bond in the sugar portion of nucleosides to the CD spectra are also presented.

Keywords——3,4,6-tri-*O*-acetyl-D-glucal; 2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl nucleoside; stannic chloride; trimethylsilyl trifluoromethanesulfonate; *N*-glycosylation; NMR; CD

Various nucleosides having an unsaturated bond in the sugar portion are known to have antibiotic activity; these compounds include angustmycin A (**1**),[2] blasticidin S (**2**)[3] and mildiomycin (**3**).[4] Thus, other nucleosides of unsaturated sugars may have interesting biological activities. All the regio-isomers of pentenofuranosyl nucleosides have been prepared.[5] However, these compounds necessarily lack some of the functional groups of usual nucleosides. For example, 1′,2′-dehydro derivatives lack the chirality at the anomeric position as well as the 2′-hydroxyl group, and 2′,3′-unsaturated derivatives lack the hydroxyl groups, and so on. Recently, neplanocin A (**4**),[6] an N^9-cyclopentenyladenine, has been reported as an antitumor antibiotic. This compound is unique in that an sp^2 carbon is present at the 4′-position, yet it has three hydroxyl groups like adenosine. In this respect, 2-hexenopyranosyl nucleosides can be viewed as analogs of 2′-deoxyribosides, since the 4′- and 6′-hydroxyl groups may be regarded as equivalent to the 3′- and 5′-hydroxyl groups in the 2′-deoxynucleoside.

Existing synthetic methods for 2-hexenopyranosyl nucleosides involve condensation of acetylated glycals and nucleobases in the presence of an acid catalyst by fusion,[7] or in a solvent.[8] The use of a Lewis acid, namely, $SbCl_5$, and pertrimethylsilylated uracil was also reported, in connection with the synthesis of nucleoside skeleton of blasticidin S.[9] In addition, catalysts such as stannic chloride[10] and trimethylsilyl trifluoromethanesulfonate[11] are quite effective in the *N*-glycosylation of silylated bases.

This paper describes the condensation of 3,4,6-tri-*O*-acetyl-D-glucal and trimethylsilylated nucleobases, such as 5-fluorouracil, thymine, N^4-acetylcytosine, and adenine, in the presence of stannic chloride or trimethylsilyl trifluoromethanesulfonate to give 2-hexenopyranosyl nucleosides. The sign of the circular dichroism spectra of anomers of the unsaturated nucleosides is also discussed.

Treatment of 3,4,6-tri-*O*-acetyl-D-glucal (**5**) and trimethyl silylated 5-fluorouracil (**6**) with stannic chloride in acetonitrile at room temperature afforded two products (**7a** and **7b**). One anomer (**7a**, 22%) was crystallized from the mixture and the other (**7b**, 36%) was separated by silica gel column chromatography as a foam. Similar results were obtained when thymine and N^4-acetylcytosine were condensed by the use of trimethylsilyl trifluoromethanesulfonate as a catalyst to give the anomers of 2-hexenopyranosyl nucleosides (**8** and **9**). The nuclear

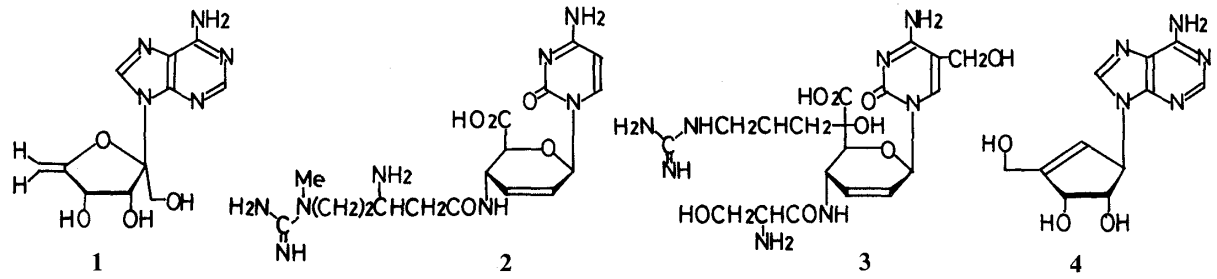

Chart 1

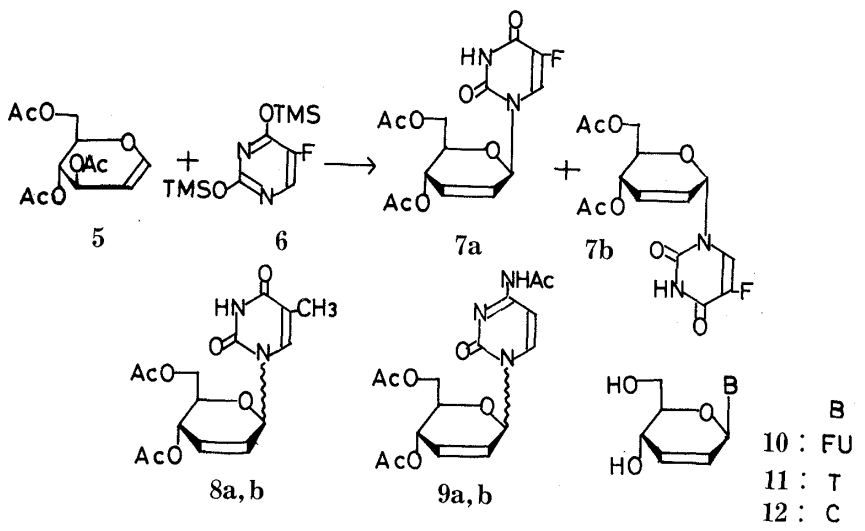

Chart 2

magnetic resonance (NMR) spectra of **7a**, **8a**, and **9a** were very similar to one another, and the chemical shifts and coupling constants of the sugar protons resembled those of the β form of 9-(4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-6-chloropurine[8a] or -6-methylthiopurine.[8b] Therefore, these products can be assigned as the β anomers. Compounds **7b**, **8b**, and **9b** were correspondingly assumed to be the α-anomers. There is also a similarity in the migration of anomers on thin layer chromatography, the β anomers always migrating faster. Although the formation of the regioisomer resulting from substitution at the 3-position of the glucal has been observed previously,[8,9] no trace of such compounds was formed under the present conditions. In general, prolongation of the reaction period favored the formation of the α-anomers. Deacetylation of **7a**, **8a**, and **9a** with sodium methoxide in methanol afforded the corresponding free nucleosides (**10**, **11**, and **12**) in high yields.

The circular dichroism (CD) spectra of the pairs of anomers showed that all β-anomers exhibited negative ellipticities, while all α-anomers showed positive bands at their main absorption regions. This relation is opposite to that of usual pyrimidine ribo- or deoxyribonucleosides. In order to clarify this apparent discrepancy, compound **7a** was converted to 5-fluorouridine 2′,3′-dialdehyde by means of the following reactions. Compound **7a** was treated with *m*-chloroperbenzoic acid (*m*-CPBA) and the product, possibly the 2′,3′-epoxide (**13**), was treated with aqueous acetic acid to give O^2,2′-cyclonucleoside (**14**). This was hydrolyzed under acidic conditions and then the hydrolyzate was treated with sodium periodate to furnish the dialdehyde (**15**). The CD spectra of **15** showed a positive sign, like that of the product derived from periodate oxidation of 5-fluorouridine. Therefore it is clear that the β-anomers of 2-hexenopyranosyl pyrimidines exhibit negative CD bands, unlike usual pyrimidine β-nucleosides.

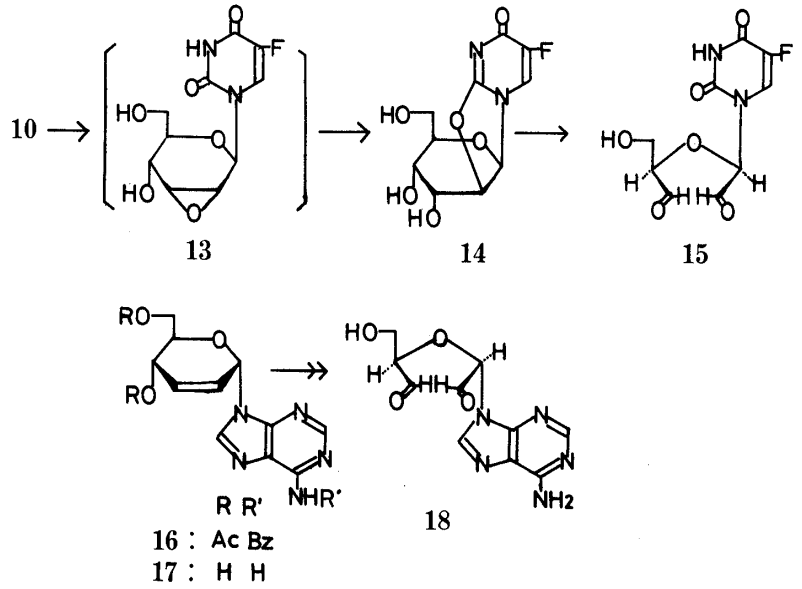

Chart 3

It would be interesting to know whether a similar relation holds with purine nucleosides. Therefore synthesis of hexenopyranosyladenine was undertaken. Treatment of pertrimethylsilylated N^6-benzoyladenine and **5** in the presence of stannic chloride in acetonitrile at room temperature for 2 h gave an anomer (**16**) in crystalline form. It showed a negative CD spectral band at 275 nm. The NMR spectrum is similar to that reported for the α-anomer of 6-chloropurine hexenopyranoside,[8a] suggesting that the product is an α-anomer. Although formation of the other anomer was observed on a thin layer chromatogram, the attempted isolation of the pure form was not successful. Deacetylation of **16** gave the free nucleoside (**17**) which again showed a negative CD band at 259 nm. Oxidation of **17** with osmium tetroxide followed by cleavage of the product with sodium periodate gave the adenosine 2′,3′-dialdehyde (**18**), which showed a weak positive CD spectrum, although the molar ellipticity was too small to measure. Since the adenosine dialdehyde derived from adenosine showed a weak negative CD band, it is clear that compound **18** and hence **17** was the α-anomer. Therefore, in the case of purine hexenopyranosides, the sign of the CD bands of the anomers is again opposite to that of usual purine ribo- or deoxyribonucleosides.

These results suggest that the unsaturated bond in the sugar portion may play some role in determining the sign of the CD spectra of nucleosides in general, and this does appear to be the case. For example, 2′,3′-dehydro-2′,3′-dideoxyadenosine, prepared from 2′-deoxyadenosine,[12] showed a positive band and a 2′,3′-dehydro-2′,3′-dideoxyuridine,[13] -cytidine,[14] and -thymidine[15] showed negative bands. In addition, blasticin S and mildiomycin have been reported to show negative CD bands,[4] whereas a hexopyranosyl nucleoside, 1-(3-amino-3-deoxy-β-D-glucopyranosyluracil,[16] showed a positive CD band.

Therefore it can be generally stated that the 2′,3′-unsaturated bonds of nucleosides contribute strongly to a reversal of the sign of the CD band of the saturated counterparts.

Neplanocin As[17] shows a stronger negative CD band than adenosine. This may be explained in terms of the 4′,5′-double bond contributing in the reverse direction to that of the 2′,3′-double bond; it may make a stronger contribution than the usual lactol ring oxygen (*e.g.* in adenosine).

Preliminary antileukemic activity testing (in L1210-bearing mice)[18] of the hexenopyranosyl 5-fluorouracils and other nucleosides showed less than 10% increase of life span (ILS) at the dose of 100 mg/kg for compound **10a** and no appreciable activities with other hexenopyra-

nosyl nucleosides. These results imply that the 6′-hydroxyl group of the hexenopyranosyl moiety may not be phosphorylated by deoxynucleoside kinase *in vivo*.

Experimental

Melting points were determined on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a JEOL FX-100FT or FX-200FT spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in ppm (δ), and signals are described as s (singlet), d (doublet), t (triplet), m (multiplet), or br (broad). All exchangeable protons were confirmed by addition of D_2O. Ultraviolet absorption spectra (UV) were recorded on a Shimadzu UV-240 spectrophotometer. Mass spectra (MS) were measured on a JEOL D-300 spectrometer. CD spectra were recorded on a JASCO J-40 or J-500 spectropolarimeter at room temperature. Thin layer chromatography (TLC) was carried out on Merck pre-coated plates $60F_{254}$. Silica gel for column chromatography was Wako gel C-200.

1-(4,6-Di-*O*-acetyl-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranosyl)-5-fluorouracil and Its α-Anomer (7a and 7b)——5-Fluorouracil (5.2 g, 40 mmol) was treated with hexamethyldisilazane (40 ml) at 160 °C for 3.5 h. The mixture was evaporated and the residue (bistrimethylsilyl-5-fluorouracil, **6**) was used for the next step. Compound **6** and 3,4,6-tri-*O*-acetyl-D-glucal (**5**, 5.44 g, 20 mmol) were dissolved in 20 ml of acetonitrile and $SnCl_4$ (6.9 ml, 60 mmol) was added dropwise over a period of 15 min, then the mixture was stirred at room temperature for 35 min. Cold water and $NaHCO_3$ were added to the solution and the solvent was removed *in vacuo*. The residue was extracted with $CHCl_3$ and the organic layer was washed with H_2O, then dried over Na_2SO_4. The solvent was evaporated off and the residue was triturated with EtOH to yield crystalline **7a** (1.5 g, 22% based on **5**). The mother liquor was concentrated and the residue was taken up in $CHCl_3$ and applied to a column of silica gel (3.8 × 20 cm). The eluate with $CHCl_3$–MeOH (30 : 1) was concentrated to give 2.47 g (36%, based on **5**) of **7b** as a foam.

Physical constants of **7a**. NMR (200FT, $CDCl_3$): 9.15 (1H, br s, HN^3), 7.24 (1H, d, H-6, $J_{6,F}$ = 5.4 Hz), 6.54 (1H, br s, H-1′), 6.22 (1H, dt, H-3′, $J_{2',3'}$ = 10.2 Hz), 5.81 (1H, dt, H-2′), 5.40 (1H, br d, H-4′, $J_{4',5'}$ = 11.7 Hz), 4.23 (2H, d, H-6′, J = 3.9 Hz), 4.01 (1H, dt, H-5′), 2.13, 2.10 (3H each, s, Ac_2). MS *m/z*: 222 (M − 120), 213 (sugar), 153 (sugar − AcOH), 130 (B + 1). CD (θ) in H_2O: −9570 at 258 nm. *Anal.* Calcd for $C_{14}H_{15}FN_2O_7$: C, 49.13; H, 4.42; N, 8.18. Found: C, 49.15; H, 4.42; N, 8.18.

Physical constants of **7b**. NMR ($CDCl_3$, 200 FT): 8.85 (1H, br, HN^3), 7.55 (1H, d, H-5, $J_{6,F}$ = 5.4 Hz), 6.43 (1H, br s, H-1′), 6.36 (1H, dt, H-3′, $J_{2',3'}$ = 10.2 Hz), 5.89 (1H, dt, H-2′), 5.25 (1H, m, H-4′), 4.30 (1H, m, H-6′a), 4.18 (1H, m, H-6′b), 4.05 (1H, m, H-5′), 2.15, 2.10 (3H each s, Ac_2).

1-(2,3-Dideoxy-*erythro*-β-D-hex-2-enopyranosyl)-5-fluorouracil (10)——A solution of **7a** (1.1 g) in 20 ml of 0.5 N MaOMe–MeOH was stirred at room temperature overnight, then neutralized with Dowex 50 (H^+) resin, and the solvent was evaporated off to leave 0.78 g (94%) of **10**. The product was crystallized from EtOH, mp 167—169 °C. UV $\lambda_{max}^{H_2O}$ nm (ε): 264 (8930), 204 (11280). $\lambda_{min}^{H_2O}$ nm (ε): 232 (2260). $\lambda_{max}^{0.1\,N\,NaOH}$ nm (ε): 265 (6900), $\lambda_{min}^{0.1\,N\,NaOH}$ nm (ε): 247 (5490). CD (θ) in H_2O: 259 nm (−7450), 238 nm (0). NMR (DMSO-d_6, FX200): 11.93 (1H, br, HN^3), 7.66 (1H, d, H-6, $J_{F,6}$ = 6.35 Hz), 6.25 (1H, br s, H-1′), 6.10 (1H, dt, H-3′, $J_{2',3'}$ = 10.3 Hz), 5.65 (1H, dt, H-2′), 5.28 (1H, d, HO-4′, J = 6.4 Hz), 4.71 (1H, m, HO-6′), 4.06 (1H, m, H-4′), 3.66 (1H, m, H-5′), 3.46 (2H, m, H-6′), *Anal.* Calcd for $C_{10}H_{11}FN_2O_5$: C, 46.51; H, 4.29; N, 10.85. Found: C, 46.58; H, 4.35; N, 11.00.

1-(4,6-Di-*O*-acetyl-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranosyl)thymine and Its α-Anomer (8a and 8b)——Bistrimethylsilylthymine (prepared from 2.3 g of thymine) and 3,4,6-tri-*O*-acetyl-D-glucal (5 g) were dissolved in 20 ml of acetonitrile, and trimethylsilyl trifluoromethanesulfonate (4 g) was added through an injector under cooling in an ice-bath. The mixture was stirred at room temperature for 55 min, then H_2O and $NaHCO_3$ were added under cooling. The whole was extracted with $CHCl_3$ and the organic layer was dried over Na_2SO_4. The solvent was removed to leave 6.63 g of syrup (**8a** and **8b**). A part (100 mg) of the syrup was subjected to preparative TLC and developed with $CHCl_3$–MeOH (16 : 1) 4 times to give two bands; the appropriate band was extracted with $CHCl_3$–MeOH (2 : 1). From the eluate of the slow moving band, crystalline **8b** was obtained. The rest of the syrup was taken up in a small volume of EtOH and **8b** (1.28 g, 20.6%) was obtained by seeding with the above crystals, mp 140—141 °C. The remainder was applied to a column of silica gel (5 × 10 cm). The eluate with $CHCl_3$–MeOH (40 : 1) was concentrated to give **8a** (1.5 g) as a foam.

Physical constants of **8a**. UV $\lambda_{max}^{H_2O}$ nm: 265. CD (H_2O): 259 nm θ = −9550 (assuming ε, 10000). NMR ($CDCl_3$): 8.59 (1H, br, HN^3), 6.98 (1H, br s, H-6), 6.52 (1H, br s, H-1′), 6.17 (1H, dt, H-3′, $J_{2',3'}$ = 10.3 Hz), 5.78 (1H, dt, H-2′), 5.40 (1H, m, H-4′), 4.23 (2H, d, H-6′, J = 4.2 Hz), 4.01 (1H, m, H-5′), 2.13, 2.10 (3H each, s, Ac_2), 1.94 (3H, d, Me-5, J = 1.2 Hz).

Physical constants of **8b**. UV $\lambda_{max}^{H_2O}$ nm: 265. CD (H_2O): 261 nm (θ = +16500). NMR ($CDCl_3$): 8.76 (1H, br, HN^3), 7.27 (1H, br s, H-6), 6.42 (1H, dd, H-1′), 6.31 (1H, dt, H-3′), 5.88 (1H, ddd, H-2′, $J_{2',3'}$ = 10.25 Hz), 5.25 (1H, m, H-4′), 4.29 (1H, dd, H-6′a, $J_{a,b}$ = 12.2 Hz, $J_{a,5'}$ = 5.9 Hz), 4.18 (1H, dd, H-6′b, $J_{b,5'}$ = 3.4 Hz), 4.01 (1H, m, H-5′), 2.15, 2.09 (3H each, s, Ac_2), 1.95 (3H, d, Me-5, J = 1.2 Hz). MS *m/z*: 213 (sugar), 153 (sugar − AcOH), 111. *Anal.* Calcd for $C_{15}H_{18}N_2O_7$: C, 53.25; H, 5.36; N, 8.28. Found: C, 53.19; H, 5.31; N, 8.26.

1-(2,3-Dideoxy-β-D-*erythro*-hex-2-enopyranosyl)thymine (11)——Compound **8a** (1.1 g) was dissolved in 10 ml of 0.8 N NaOMe–MeOH and the solution was stirred at room temperature for 5 h. The solution was neutralized with Dowex 50 (H^+) resin and the solvent was removed. The residue was applied to a column of silica gel (3 × 8 cm). The eluate with $CHCl_3$–MeOH (4 : 1) was concentrated and the residue was crystallized from EtOH to give 0.71 g (86%) of **11**, mp 211.5—214 °C. NMR (DMSO-d_6): 11.38 (1H, br, HN^3), 7.18 (1H, q, H-6), 6.26 (1H, dd, H-1′, J=2.44 and 3.91 Hz), 6.11 (1H, dt, H-3′, $J_{2',3'}$=10.3 Hz), 5.66 (1H, dt, H-2′), 5.26 (1H, d, HO-4′, J=6.4 Hz), 4.71 (1H, t, HO-6′, J=5.9 Hz), 4.05 (1H, m, H-4′), 3.66 (1H, m, H-5′), 3.46 (2H, m, H-6′). 1.77 (3H, d, Me-5, J=1.0 Hz). UV $\lambda_{max}^{H_2O}$ nm (ε): 263 (9830), 203 (11410). $\lambda_{min}^{H_2O}$ nm (ε): 233 (2620). $\lambda_{max}^{0.1\,N\,NaOH}$ nm (ε): 263 (7450). $\lambda_{min}^{0.1\,N\,NaOH}$ nm (ε): 244 (5230). CD (H_2O): 260 nm (θ = −7150). MS *m/z*: 254 (M), 205, 206, 129 (sugar), 126 (B+1), 111. *Anal.* Calcd for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5.55; N, 11.02. Found: C, 52.07; H, 5.50; N, 11.08.

1-(4,6-Di-*O*-acetyl-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranosyl)-N^4-acetylcytosine and α-Anomer (9a and 9b)——Bistrimethylsilyl-N^4-acetylcytosine (prepared from 2.82 g of N^4-acetylcytosine) and 3,4,6-tri-*O*-acetyl-D-glucal (5.0 g, 1 eq) were dissolved in 20 ml of acetonitrile. Trimethylsilyl trifluoromethanesulfonate (4 g) was added, and the mixture was stirred at room temperature for 30 min. After neutralization of the mixture by the addition of $NaHCO_3$ and H_2O, $CHCl_3$ was added and the organic layer (containing suspended precipitate) was separated. The $CHCl_3$ suspension was filtered to give crystals of **9b** (3.08 g, 45.9%). The filtrate was concentrated and the residue was set aside at room temperature. The separated crystals of **9a** (1.69 g) were collected and washed with EtOH.

Physical constants of **9a**. mp 171—173 °C (change of crystal form at 165—167 °C). UV $\lambda_{max}^{H_2O}$ nm: 245, 294. CD (H_2O): 290 nm (θ = −8960, assuming ε, 10000). NMR (DMSO-d_6): 10.95 (1H, s, HN^3), 7.90 (1H, d, H-6, $J_{5,6}$ = 7.3 Hz), 7.21 (1H, d, H-5), 6.56 (1H, br s, H-1′), 6.11 (1H, dt, H-3′, $J_{2',3'}$ = 10.2 Hz), 5.93 (1H, dt, H-2′), 5.36 (1H, m, H-4′), 5.11 (3H, m, H-5′,6′), 2.11, 2.07, 2.02 (3H each, s, Ac_3). MS *m/z*: 365 (M), 306 (M − 59), 213 (sugar), 153 (B+1), 111. *Anal.* Calcd for $C_{16}H_{19}N_3O_7$: C, 52.60 H, 5.24; N, 11.50. Found: C, 52.50; H, 5.17; N, 11.39.

Physical constants of **9b**. mp 249—258 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm: 296, 245. CD (H_2O): 290 nm (θ = +21600, assuming ε, 10000), 240 nm (θ = −34500). NMR (DMSO-d_6): 10.94 (1H, s, HN^3), 7.99 (1H, d, H-6, J=7.8 Hz), 7.19 (1H, d, H-5), 6.37 (1H, br s, H-1′), 6.26 (1H, dt, H-3′, $J_{2',3'}$ = 10.25 Hz), 6.06 (1H, dt, H-2′), 5.22 (1H, dd, H-4′, $J_{4',5'}$ = 7.8 Hz, $J_{3',4'}$ = 1.95 Hz), 4.17 (1H, dd, H-6′a, $J_{a,b}$ = 12.2 Hz, $J_{a,5'}$ = 4.9 Hz), 4.08 (1H, dd, H-6′b, $J_{b,5'}$ = 2.9 Hz), 3.91 (1H, m, H-5′), 2.11, 2.09, 1.99 (3H each, s, Ac_3). MS *m/z*: 365 (M), 213 (sugar), 153 (B+1), 111. *Anal.* Calcd for $C_{16}H_{19}N_3O_7$: C, 52.60; H, 5.24; N, 11.50. Found: C, 52.05; H, 5.12; N, 11.42.

1-(2,3-Dideoxy-β-D-*erythro*-hex-2-enopyranosyl)cytosine (12)——A solution of **9a** (1.5 g) in 80 ml of MeOH saturated with NH_3 was kept at room temperature for 2 d in a sealed tube, then the solvent was evaporated off and the residue was taken up in hot EtOH. After cooling, crystals were collected to give 0.94 g (96%) of **12**, mp 245—246.5 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 267 (8930), 235 (shoulder, 8240). $\lambda_{min}^{H_2O}$ nm (ε): 249 (7410). $\lambda_{max}^{0.1\,N\,NaOH}$ nm (ε): 275 (13100). $\lambda_{min}^{0.1\,N\,NaOH}$ nm (ε): 239 (2500). CD (H_2O): 293 nm (θ=0), 261 nm (θ = −12340), 240 nm (θ=0), 225 nm (θ = +9400). NMR (DMSO-d_6): 7.30 (1H, d, H-6, J=7.3 Hz), 7.07 (2H, br s, H_2N-4), 6.34 (1H, br s, H-1′), 6.05 (1H, dt, H-3′, $J_{2',3'}$ = 10.25 Hz), 5.74 (1H, d, H-5), 5.58 (1H, dt, H-2′), 5.08 (1H, d, HO-4′, J=6.34 Hz), 4.52 (1H, t, HO-6′, J= 5.86 Hz), 3.99 (1H, m, H-4′), 3.66 (1H, m, H-5′), 3.47 (2H, m, H-6′). *Anal.* Calcd for $C_{10}H_{13}N_3O_4$: C, 50.20; H, 5.48; N, 17.57. Found: C, 50.13; H, 5.51; N, 17.56.

Conversion of 10 to 5-Fluorouridine 2′,3′-Dialdehyde (15)——Compound **10** (50 mg) in 2 ml of acetonitrile was treated with 50 mg of *m*-CPBA for 4 h. The same treatment was repeated with additional *m*-CPBA (50 mg) for 6 h. The solvent was removed *in vacuo*, and the residue (**13**) was taken up in 50% AcOH and heated at 50 °C for 2 h. The solvent was evaporated off and the residue was crystallized from EtOH to give 28 mg of 2,2′-anhydro-1-(β-D-altropyranosyl)-5-fluorouracil (**14**), mp 255—258 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm: 252, 222. $\lambda_{min}^{H_2O}$ nm: 233. $\lambda_{max}^{0.1\,N\,NaOH}$ nm: 252. $\lambda_{min}^{0.1\,N\,NaOH}$ nm: 238. CD (H_2O): 234 nm (θ = +8100, assuming ε, 10000). MS *m/z*: 274 (M), 256 (M − H_2O), 243, 225, 196, 185, 155, 130 (B+1, base peak). NMR (DMSO-d_6): 8.28 (1H, d, H-6, $J_{6,F}$ = 4.88 Hz), 5.84 (1H, d, H-1′, $J_{1',2'}$ = 5.13 Hz), 5.71 (1H, d, HO-4′(3′), J=5.61 Hz), 5.46 (1H, d, HO-3′(4′), J=4.15 Hz), 4.90 (1H, t, HO-6′, J=5.5 Hz), 4.90 (1H, dd on addition of D_2O, H-2′, $J_{2',3'}$ = 6.0 Hz), 3.93 (1H, dd on addition of D_2O, H-3′, $J_{3',4}$ = 2.2 Hz), 3.81—3.70 (2H, m, H-4′,5′), 3.48 (2H, d on additon of D_2O, H-6′, $J_{5',6'}$ = 4.2 Hz). Compound **14** (26 mg) was dissolved in 1 N H_2SO_4 and the solution was heated at 100 °C for 3 h, then neutralized with $NaHCO_3$. A part of the solution was kept for CD measurement. $NaIO_4$ (41 mg) was added to the rest of the solution and the mixture was kept for 1 h at room temperature. The solvent was removed *in vacuo* and the residue was extracted with EtOH. This was concentrated and the residue was subjected to silica gel TLC ($CHCl_3$–MeOH, 4 : 1). The main band appeared at *Rf* 0.40, which is similar to the *Rf* of 5-fluorouridine 2′,3′-dialdehyde prepared by periodate oxidation of 5-fluorouridine. *Rf* of compound **14** was 0.11. The product was extracted with $CHCl_3$–MeOH (2 : 1) and the solvent was evaporated off to leave **15**. UV $\lambda_{max}^{H_2O}$ nm: 266 nm. CD (H_2O): 266 nm (θ = +1125 assuming ε, 10000), 240 nm (θ = −500). 5-Fluorouridine 2′,3′-dialdehyde prepared from 5-fluorouridine: 270 nm (θ = +2020), 240 nm (θ = −2000). UV and CD data of the acid hydrolyzate of **14** were as follows: UV $\lambda_{max}^{H_2O}$ nm: 268. $\lambda_{min}^{H_2O}$ nm: 233. $\lambda_{max}^{0.1\,N\,NaOH}$ nm: 268. $\lambda_{min}^{0.1\,N\,NaOH}$ nm: 246. CD (H_2O): 260 nm (θ = +14300, assuming ε, 10000). 220 nm (θ = −9900).

9-(4,6-Di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-N^6-benzoyladenine (16)——Bistrimethylsilyl-N^6-benzoyladenine (prepared from 6.6 g of N^6-benzoyladenine) and 3,4,6-tri-*O*-acetyl-D-glucal (5 g, 0.5 eq) were dissolved in 50 ml of acetonitrile, and $SnCl_4$ (6.35 ml) was added dropwise under ice cooling. The mixture was kept at

room temperature for 2 h. The solution was neutralized by the addition of H_2O and $NaHCO_3$. The mixture was concentrated and the residue was extracted with $CHCl_3$. The solvent was evaporated off and the residue was triturated, the insoluble material (N^6-benzoyladenine) was filtered off, and the filtrate was applied to a column of silica gel (3.8 × 15 cm). The eluate with $CHCl_3$–MeOH (20 : 1) was concentrated and the residue was dissolved in hot EtOH. The crystals were collected to give 1.4 g (17.6%) of **16**, mp 108.5—111 °C. UV λ_{max}^{MeOH} nm: 284, 254 (shoulder), 237 (shoulder). λ_{min}^{MeOH} nm: 245. CD(MeOH): 275 nm ($\theta = -13600$, assuming ε_{max}, 15000). NMR ($CDCl_3$): 9.01 (1H, s, HN^6), 8.86 (1H, s, H-2), 8.20 (1H, s, H-8), 8.04 and 7.58 (5H, m, Bz), 6.63 (1H, br s, H-1′), 6.38 (1H, dt, $J_{2',3'}$ = 10.25 Hz), 6.20 (1H, dt, H-2′), 5.47 (1H, dt, H-4′, $J_{4',5'} = 8.8$ Hz), 4.43 (1H, dd, H-6′a, $J_{a,b} = 12.2$ Hz, $J_{a,5'} = 5.37$ Hz), 4.07 (1H, dd, H-6′b, $J_{b,5'} = 2.93$ Hz), 3.95 (1H, m, H-5′), 2.15, 2.01 (3H each, s, Ac_2), 1.73 (H_2O). MS *m/z*: 451 (M), 423, 422, 364, 240 (B+2), 239 (B+1), 213 (sugar), 153 (sugar–AcOH), 111, 105 (Bz). *Anal.* Calcd for $C_{22}H_{21}N_5O_6 \cdot 1/2H_2O$: C, 57.39; H, 4.82; N, 15.21. Found: C, 57.38; H, 4.81; N, 15.14.

There was a faster-migrating spot (probably due to the β-anomer) and other minor spots on the TLC plate of the mother liquor, but these products were not isolated in pure form.

9-(2,3-Dideoxy-α-D-*erythro*-hex-2-enopyranosyl)adenine (17)——Compound **16** (1.5 g) was heated in MeOH saturated with NH_3 (80 ml) in a sealed tube at 50 °C for 2 d. The solvent was evaporated off and the residue was triturated with water, and filtered to give 0.77 g (88%) of **17**, mp 251—252 °C (dec.). This product was recrystallized from H_2O to give an analytically pure sample. UV $\lambda_{max}^{H_2O}$ nm (ε): 260 (13800). CD (H_2O): 256 nm ($\theta = -13750$). NMR (DMSO-d_6): 8.18, 8.16 (1H each, s, H-2,8), 7.30 (2H, s, H_2N), 6.40 (1H, dd, H-1′), 6.24 (1H, dt, H-3′, $J_{2',3'} = 10.0$ Hz), 6.01 (1H, dt, H-2′), 5.20 (1H, d, HO-4′, $J = 8.1$ Hz), 4.63 (1H, d, HO-6′, $J = 5.6$ Hz), 4.01 (1H, m, H-4′), 3.51 (2H, m, H-6′), 3.38 (1H, m, H-5′). MS *m/z*: 263 (M), 245 (M−H_2O), 190 (B+56), 135 (B+1), 129 (sugar), 111. *Anal.* Calcd for $C_{11}H_{13}N_5O_3 \cdot 1/2H_2O$: C, 48.56; H, 5.18; N, 25.72. Found: C, 48.75; H, 5.08; N, 25.96.

Conversion of 17 to α-Adenosine 2′,3′-Dialdehyde (18)——Compound **17** (20 mg) was treated with OsO_4 (20 mg) in 5 ml of pyridine overnight at room temperature. H_2S gas was bubbled through the solution and the insoluble material was filtered off. The filtrate was concentrated and the residue was subjected to preparative TLC, developed with $CHCl_3$–MeOH (2 : 1). The appropriate band (*Rf* 0.1, *Rf* of **17** was 0.5) was extracted with the same solvent and concentrated to leave 5 mg of the product. This was taken up in 50% EtOH, then $NaIO_4$ (6 mg) was added and the mixture was kept at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was subjected to preparative TLC developed with $CHCl_3$–MeOH (4 : 1). The band at *Rf* 0.33 (*Rf* of the substrate was 0.05) was extracted with $CHCl_3$–MeOH (2 : 1) and the solvent was evaporated off to give the dialdehyde (**18**). UV $\lambda_{max}^{H_2O}$ nm: 259 $\lambda_{min}^{H_2O}$ nm: 216 CD (H_2O): very weak positive band at 255 nm. The dialdehyde prepared from adenosine showed the same *Rf* value (0.33) as that of the product **18**, but showed a very weak negative CD band at around 260 nm.

CD Spectra of Unsaturated Nucleosides——CD spectra were determined in H_2O at room temperature. The θ values (nm) were as follows: 2′,3′-didehydro-2′,3′-dideoxyadenosine, +1580 (252 nm); 2′,3′-didehydro-2′,3′-dideoxycytidine, −19850 (266 nm); 2′,3′-didehydro-2′,3′-dideoxythymidine, −13600 (264 nm); 5′-*O*-benzoyl-2′,3′-didehydro-2′,3′-dideoxyuridine, −38000 (252 nm); 3′-amino-3′-deoxy-β-D-glucopyranosyluracil, +4400 (262 nm).

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