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Studies Directed toward the Total Synthesis of Sinefungin. I. Synthesis of 4-(5′-Deoxyuridin-5′-yl)-4-nitrobutyronitrile, 4-(5′-Deoxyadenosin-5′-yl)-4-nitrobutyramide and Closely Related Nucleosides[1)]

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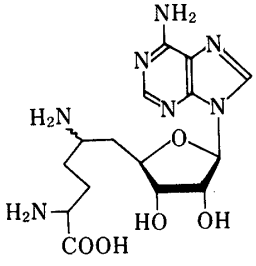
S-Adenosylhomocysteine analogues, 1-(5,6-dideoxy-6-nitro-β-D-*ribo*-hexofuranosyl)uracil (**7a**), 9-(5,6-dideoxy-6-nitro-β-D-*ribo*-hexofuranosyl)adenine (**7b**), 4-(5′-deoxyuridin-5′-yl)-4-nitrobutyronitrile (**15**) and 4-(5′-deoxyadenosin-5′-yl)-4-nitrobutyramide (**20**) were synthesized as potential inhibitors of *S*-adenosylmethionine(SAM)-dependent methyltransferases and *S*-adenosylhomocysteine hydrolases. The chemistry developed for the preparation of these compounds should be useful in the total synthesis of the nucleoside antibiotics sinefungin and A9145C, which are potent inhibitors of certain SAM-dependent methyltransferases.

Keywords——sinefungin; methyltransferase; *S*-adenosylmethionine; *S*-adenosylhomocysteine; potassium fluoride-catalyzed aldol condensation; Michael reaction; transglycosylation

The inhibition of *S*-adenosyl-L-methionine (SAM)-dependent methyltransferase by *S*-adenosylhomocysteine (SAH) has been well documented.[2)] Recently, the inhibitory activity of SAH and its analogues on viral messenger ribonucleic acid (mRNA) methyltransferases has been the subject of intensive studies, since such inhibitors might have potential as antiviral agents.[3)] It was reported[3,4)] that 5′-deoxy-5′-(*S*-isobutylthio)adenosine (SIBA), an SAH analogue, inhibits multiplication of herpes simplex type 1 as a result of inhibition of mRNA methylation and α-protein synthesis. Sinefungin (**1**) and A9145C (**2**)[5)] were found to be more potent than SAH as competitive inhibitors of SAM-dependent methyltransferases. Both antibiotics inhibit plaque formation of vaccinia viruses.[6,7)]

As a part of a search for more effective inhibitors of methyltransferases, and in order to test the working hypothesis[2)] that inhibitors of viral mRNA methyltransferases might function as antiherpetic agents, we have prepared a number of analogues of SAH.[8)] Toward this end, we have focused our attention on the potent activity of the antibiotics sinefungin and



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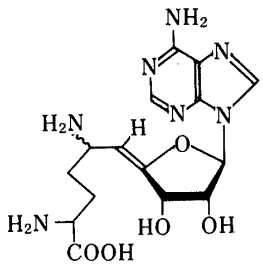

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Fig. 1

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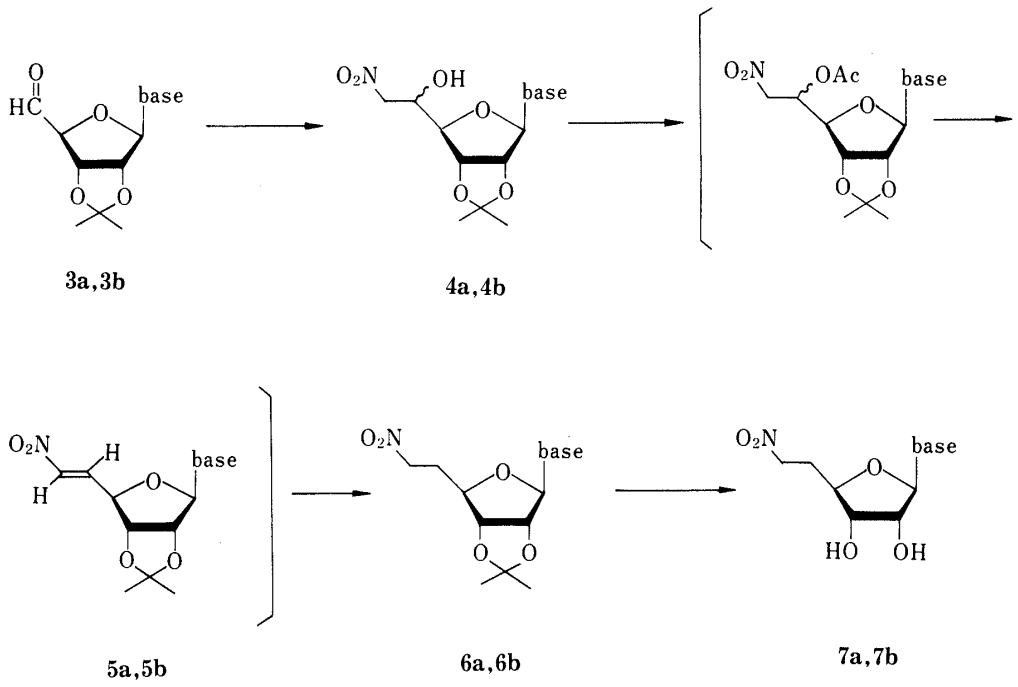
A9145C[5] against various methyltransferases. We have prepared a series of sinefungin analogues which may be potent inhibitors and could also serve as useful intermediates for the total synthesis of these antibiotics.

The syntheses of 1-(5,6-dideoxy-6-nitro-β-D-*ribo*-hexofuranosyl)uracil (**7a**), its adenine analogue (**7b**), 4-(5′-deoxyuridin-5′-yl)-4-nitrobutyronitrile (**15**) and 4-(5′-deoxyadenosin-5′-yl)-4-nitrobutyramide (**20**) from 2′,3′-*O*-isopropylideneuridine 5′-aldehyde (**3a**)[10] were achieved in the following manner: (a) aldol condensation with nitroalkanes, such as nitromethane and methyl 4-nitrobutanoate, (b) Michael reaction of **3a** with acrylonitrile or methyl acrylate, and (c) conversion of the uracil nucleoside into the adenine nucleoside by transglycosylation.

Condensation of **3a** (Chart 1) with nitromethane in the presence of potassium fluoride catalyst[11] afforded a 4:1 mixture of 5′-epimers **4a**.[12] For structural identification, these epimers were separated by preparative thin-layer chromatography (TLC). The major epimer was obtained from the more polar fraction and was tentatively assigned the β-D-allo configuration, while the minor product from the less polar fraction was assigned the α-L-talo configuration by comparison of the proton nuclear magnetic resonance (^{1}H-NMR) spectra of these isomers. In the ^{1}H-NMR spectrum of the major epimer, the anomeric proton signal



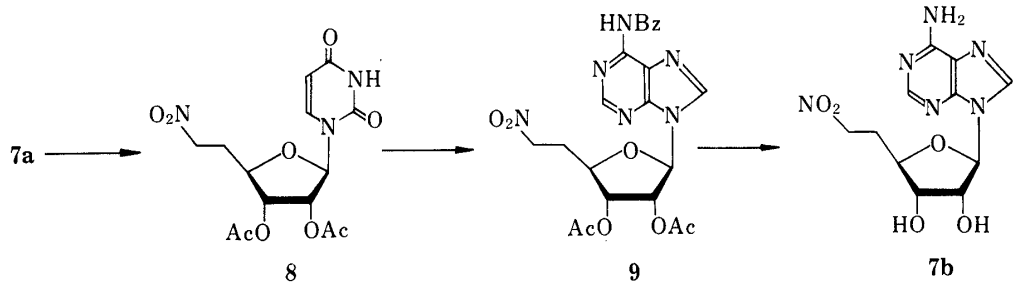


Chart 1

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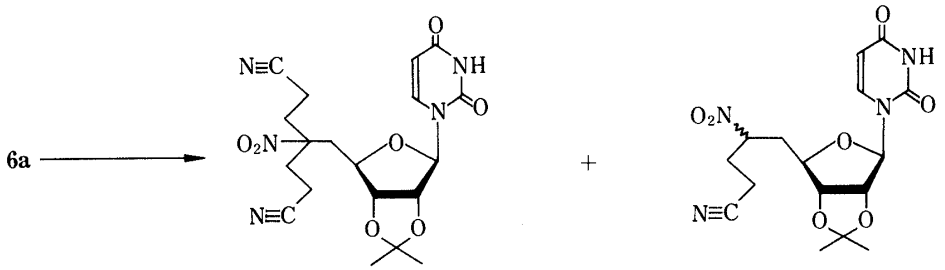
appeared upfield from that of the minor epimer, and the signals due to H-2′, H-3′, and H-4′ were well resolved from each other, while these protons in the minor epimer yielded a three-proton multiplet.

Since both epimers of **4a** are converted into the same 5′-deoxy nucleoside **6a**, the epimeric mixture was treated directly with acetic anhydride and 4-dimethylaminopyridine (DMAP) in dioxane. The 5′,6′-olefinic product **5a**[13] was, without purification, reduced with sodium borohydride to give 1-(5,6-dideoxy-2,3-*O*-isopropylidene-6-nitro-β-D-*ribo*-hexofuranosyl)-uracil (**6a**) in 60% overall yield from **4a**. After treatment of **6a** with 90% formic acid, the unprotected **7a** was obtained in crystalline form in 86% yield.

Transglycosylation reaction of **7a** to yield the adenine nucleoside **7b** was performed according to the reported procedure.[14] Compound **7a** was converted into the di-*O*-acetate **8**. A 1:2 molar mixture of **8** and N^6-benzoyladenine was trimethylsilylated with *N,O*-bis(trimethylsilyl)acetamide (BSA) and the products, without isolation, were treated with trimethylsilyl triflate. The protected adenine nucleoside **9** was obtained from the reaction mixture in 36% yield after chromatographic purification. Saponification of **9** afforded 9-(5,6-dideoxy-6-nitro-β-D-*ribo*-hexofuranosyl)adenine (**7b**) in 62% yield in crystalline form.

In order to establish the β-configuration of **7b**, 2′,3′-*O*-isopropylideneadenosine 5′-aldehyde (**3b**) was converted into 9-(5,6-dideoxy-2,3-*O*-isopropylidene-6-nitro-β-D-*ribo*-hexofuranosyl)adenine (**6b**) in 33% overall yield by condensation with nitromethane followed by acetylation and reduction. Deacetonization of **6a** gave rise to the corresponding unprotected nucleoside, which was identical with **7b** in terms of electron impact-mass spectrum (EI-MS) and ^{1}H-NMR characteristics. These data firmly established the β-configuration of **7b** derived from **8** by transglycosylation.

It is known that aliphatic nitriles may be homologated to α-amino acids.[15] Thus, 4-(5′-deoxy-2′,3′-*O*-isopropylideneuridin-5′-yl)-4-nitrobutyronitrile (**11**) and the corresponding deacetonized nucleoside **15** were prepared, by two different routes (Charts 2 and 3), as intermediates for sinefungin (**1**) which contains the α-amino acid side chain. Treatment of the 6′-nitronucleoside **6a** with acrylonitrile in the presence of potassium fluoride afforded the bis-



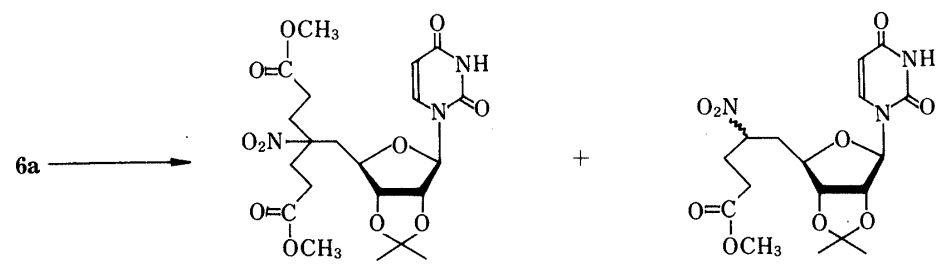


Chart 2

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and mono-adduct (**10** and **11**) which were separated in 34 and 51% yields, respectively. Condensation of **6a** with methyl acrylate, instead of acrylonitrile, again gave rise to two products **12** and **13**.

In order to circumvent the bis-adduct formation, 2′,3′-*O*-isopropylideneuridine 5′-aldehyde (**3a**) was condensed with methyl 4-nitrobutanoate[16] in the presence of potassium fluoride. The diastereomixture of the nitrohydrin **16** was obtained in 74% yield as a homogeneous foam. The ^{1}H-NMR spectrum of this product was consistent with the structure **16**. Treatment of **16** with acetic anhydride and DMAP in dioxane afforded the olefinic product **17** in crystalline form in 65% yield. The structural assignment rested upon ^{1}H-NMR analysis as well as combustion values, leaving, however, the configuration of the 5′-ene system undetermined. Sodium borohydride reduction of **17** occurred smoothly in dioxane and 4-(5′-deoxy-2′,3′-*O*-isopropylideneuridin-5′-yl)-4-nitrobutanoate (**13**) was obtained as an epimeric mixture in 93% yield. Compound **13** (as an epimeric mixture) was converted into the corresponding amide **14** with methanolic ammonia. Treatment of **14** with thionyl chloride in acetonitrile afforded in 87% yield the nitrile, which was identical with **11** obtained by condensation of **6a** with acrylonitrile. After deacetonization of **11**, 4-(5′-deoxyuridin-5′-yl)-4-nitrobutyronitrile **15** was obtained in 75% yield as a C-4 epimeric mixture, from which one isomer was isolated in crystalline form in 33% yeild. This epimer was shown to have the (*S*)-configuration at C-6′ by X-ray crystallography.[17]

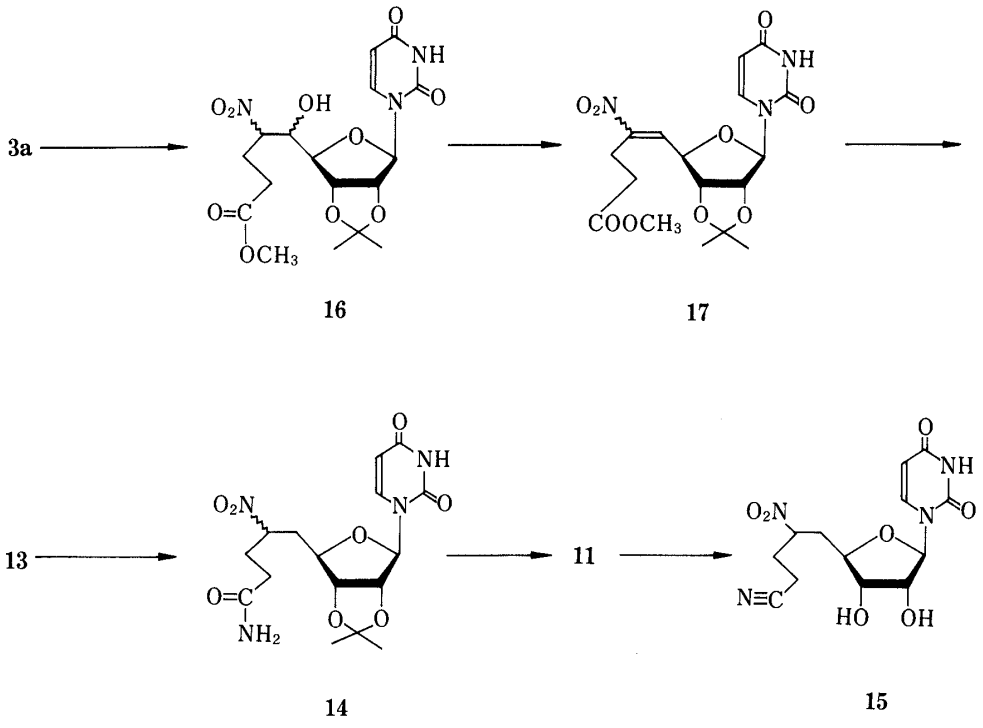

Chart 3

In order to obtain the adenine nucleoside, compound **13** was converted in two steps (Chart 4) into the diacetate **18** which was co-trimethylsilylated with N^6-benzoyladenine by treatment with BSA. The silylated mixture was then subjected to transglycosylation reaction in the presence of trimethylsilyl triflate. Methyl 4-(N^6-benzoyl-2′,3′-di-*O*-acetyladenosin-5′-yl)-4-nitrobutanoate (**19**) was obtained in 41% yield as an apparently homogeneous epimeric mixture after chromatographic purification. The ester **19** was converted into the amide **20** by treatment with ammonium hydroxide in the presence of ammonium chloride. Crystallization

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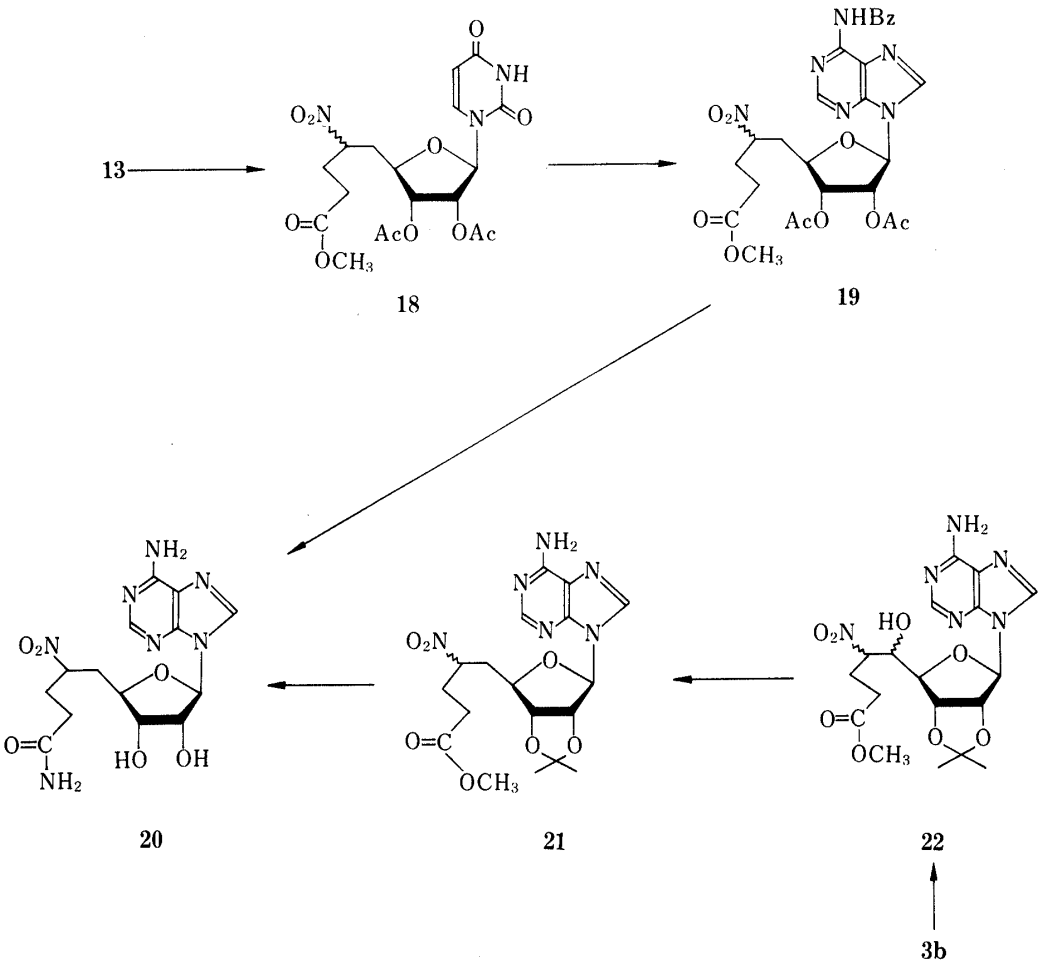

Chart 4

of the product from water afforded **20** in 39% yield. This sample was found to be virtually identical with the product prepared from 2′,3′-*O*-isopropylideneadenosine 5′-aldehyde **3b** (Chart 4) by condensation with methyl 4-nitrobutanoate to **22**, followed by a two-step deoxygenation to **21** and subsequent amidation and deacetonization. The β-configuration of the adenine nucleoside **20** prepared *via* transglycosylation of the uracil nucleoside **18** was established by the ^{1}H-NMR spectral identity with the product derived from **3b**.

The C-5′ extended nucleosides, 4-(5′-deoxyadenosin-5′-yl)-4-nitrobutyronitrile (**15**) and 4-(5′-deoxyadenosin-5′-yl)-4-nitrobutyramide (**20**), (especially their epimerically pure form (*S*)) should be useful intermediates for the synthesis of the antibiotic sinefungin (**1**). Work along this line is in progress in our laboratories.

Experimental

The melting points were taken on a Yamato melting point apparatus and are uncorrected. ^{1}H-NMR spectra were taken on a JEOL FX-100 machine and chemical shifts are reported as δ-values with Me_4Si as the internal standard. The circular dichroism (CD) spectra were taken on a JASCO J-40 spectropolarimeter. The following abbreviations are used: s, singlet, d, doublet, t, triplet, dd, double doublet, br s, broad singlet, m, multiplet, DCC, dicyclohexylcarbodiimide, TMS-Tf, trimethylsilyl triflate, and isopMe, methyl of isopropylidene group. Field desorption mass spectra (FD-MS) were recorded on a JEOL/OISG-2MS spectrometer. Ultraviolet (UV) spectra were taken on a Hitachi 3T spectrometer. TLC and column chromatography were performed with silica gel Kieselgel 60F and Kieselgel 60 (size, 0.063—0.200 mm), respectively.

1-(6-Deoxy-6-nitro-2,3-*O*-isopropylidene-β-D-allofuranosyl)-(allo 4a) and 1-(6-Deoxy-6-nitro-2,3-*O*-isopropylidene-α-L-talofuranosyl)uracil (talo 4a)——DCC (6.2 g, 30 mmol) and dichloroacetic acid (0.4 ml, 5 mmol) were

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added to a stirred solution of 2′,3′-*O*-isopropylideneuridine (2.84 g, 10 mmol) in anhydrous dimethylsulfoxide (DMSO, 20 ml) at 0 °C. The mixture was further stirred at 20 °C for 90 min. The deposited dicyclohexylurea was removed by filtration. Nitromethane (7.26 ml, 135 mmol) and KF (10 mg) were added to the filtrate, and the mixture was stirred at room temperature for 72 h. A solution of oxalic acid dihydrate (2.5 g, 20 mmol) in MeOH (10 ml) was slowly added to the mixture with stirring, and stirring was continued for a further 30 min. The mixture was filtered. The filtrate was diluted with AcOEt (100 ml) and washed with H_2O (50 ml × 3). The organic layer was separated, dried ($MgSO_4$) and evaporated to a yellow foam, which was purified by chromatography (column size, 21 × 1.8 cm; silica gel, 66 g; $CHCl_3$–EtOH (50 : 1)). The yield of an epimeric mixture of allo **4a** and talo **4b** was 2.02 g (50%). An analytical sample of the epimeric mixture was obtained by crystallization from EtOH, mp 164—178 °C; UV λ_{max} (H_2O) 259 nm, λ_{max}^{pH11} 247 nm. *Anal.* Calcd for $C_{13}H_{17}N_3O_8$: C, 45.48; H, 4.99; N, 12.24; Found: C, 45.64; H, 5.12; N, 12.09. Each isomer was separated by preparative TLC ($CHCl_3$–EtOH (20 : 1)). allo **4a**: ^{1}H-NMR (DMSO-d_6) δ: 11.40 (1H, br s, H-3), 7.73 (1H, d, H-6, $J_{5,6}$ = 8 Hz), 6.03 (1H, d, 5′-OH, $J_{5',5'\text{-OH}}$ = 5.6 Hz), 5.74 (1H, d, H-1′, $J_{1',2'}$ = 2 Hz), 5.61 (1H, d, H-5), 5.08 (1H, dd, H-2′, $J_{2',3'}$ = 6.6 Hz), 4.92 (1H, dd, H-3′, $J_{3',4'}$ = 3.4 Hz), 4.46 (1H, m, H-5′), 4.38 (2H, m, H-6′), 3.87 (1H, m, H-4′), 1.47, 1.29 (each 3H, each s, isopMe). talo **4a**: ^{1}H-NMR (DMSO-d_6) δ: 11.38 (1H, br s, H-3), 7.78 (1H, d, H-6, $J_{5,6}$ = 8 Hz), 6.10 (1H, d, 5′-OH, $J_{5',5'\text{-OH}}$ = 5.4 Hz), 5.88 (1H, d, H-1′, $J_{1',2'}$ = 2 Hz), 5.67 (1H, d, H-5), 4.90—4.83 (3H, m, H-2′,3′,5′), 4.40 (2H, m, H-6′), 4.06 (1H, m, H-4′), 1.49, 1.29 (each 3H, each s, isopMe).

1-[2,3-*O*-Isopropylidene-(*E*)-6-nitro-β-D-*ribo*-hex-5-enofuranosyl]uracil (5a)——Acetic anhydride (3.83 g, 37.5 mmol) and DMAP (15 mg) were added to a stirred solution of **4a** (3.95 g, 12.1 mmol) in dioxane (86 ml). The stirring was continued for 1 h at room temperature. The solution was concentrated *in vacuo* and a trace of AcOH was removed by several co-evaporations with EtOH to leave a crystalline residue of **5a**, which was recrystallized from EtOH to give an analytical sample. The *E*-configuration was assigned on the basis of the observed large coupling constant, $J_{5',6'}$ (17 Hz). mp 181—183 °C. EI-MS *m/z* 325 (M^+), 310 ($M^+ - CH_3$). *Anal.* Calcd for $C_{13}H_{15}N_3O_7$: C, 48.00; H, 4.65; N, 12.92. Found: C, 48.03; H, 4.67; N, 12.61. ^{1}H-NMR (DMSO-d_6) δ: 11.48 (1H, br s, H-3), 7.78 (1H, d, H-6, $J_{5,6}$ = 8 Hz), 7.51 (1H, dd, H-5′, $J_{4',5'}$ = 4.4 Hz, $J_{5',6'}$ = 17 Hz), 7.32 (1H, d, H-6′), 5.85 (1H, d, H-1′, $J_{1',2'}$ = 1.5 Hz), 5.64 (1H, dd, H-5, $J_{3,5}$ = 2 Hz), 5.21 (1H, dd, H-2′, $J_{2',3'}$ = 6.3 Hz), 4.98 (1H, dd, H-3′, $J_{3',4'}$ = 3.9 Hz), 4.82 (1H, dd, H-4′), 1.52, 1.31 (each 3H, each s, isopMe).

1-(5,6-Dideoxy-6-nitro-2,3-*O*-isopropylidene-β-D-*ribo*-hexofuranosyl)uracil (6a)——Acetic anhydride (1.55 g, 15.2 mmol) and *ca.* 2 mg of DMAP were added to a solution of **4a** (1.6 g, 4.66 mmol) in dioxane (35 ml). The mixture was stirred at 20 °C for 20 min and then evaporated under reduced pressure below 40 °C. The residue was dissolved in $CHCl_3$ (200 ml). The solution was washed with 5% $NaHCO_3$ (100 ml) and H_2O (100 ml), dried ($MgSO_4$) and evaporated to dryness. The residue was dissolved in dioxane–H_2O (30 ml : 5 ml) and the solution was treated with a suspension of $NaBH_4$ (640 mg, 17.0 mmol) in EtOH (30 ml) at 0 °C. The mixture was stirred for an additional 20 min, neutralized with 10% H_2SO_4 and then evaporated. The residue was partitioned between $CHCl_3$ (100 ml) and H_2O (50 ml). The organic layer was dried ($MgSO_4$), and the residue was crystallized from EtOH to afford 921 mg (60%) of **6a**, mp 134—135 °C. *Anal.* Calcd for $C_{13}H_{17}N_3O_7$: C, 47.71; H, 5.24; N, 12.84. Found: C, 47.58; H, 5.21; N, 12.56. ^{1}H-NMR ($CDCl_3$) δ: 9.47 (1H, br s, H-3), 7.16 (1H, d, H-6, $J_{5,6}$ = 8 Hz), 5.73 (1H, dd, $J_{3,5}$ = 2 Hz), 5.42 (1H, d, H-1′, $J_{1',2'}$ = 2 Hz), 5.10 (1H, dd, H-2′, $J_{2',3'}$ = 6.8 Hz), 4.76 (1H, dd, H-3′, $J_{3',4'}$ = 4.4 Hz), 4.48 (2H, t, H-6′, $J_{5',6'}$ = 7.1 Hz), 4.12 (1H, m, H-4′), 2.46 (2H, m, H-5′), 1.53, 1.33 (each 3H, each s, isopMe).

1-(6-Deoxy-6-nitro-β-D-*ribo*-hexofuranosyl)uracil (7a)——A crystalline sample of **6a** (200 mg, 0.62 mmol) was treated with 90% formic acid (5 ml) at room temperature for 18 h and the solution was then evaporated to dryness. The residue was purified by preparative TLC ($CHCl_3$–EtOH (10 : 1)) to afford a foamy residue (150 mg, 86%). Crystallization from EtOH–hexane gave an analytical sample, mp 145—149 °C. EI-MS *m/z* 287 (M^+), 176 (M^+ − uracil + H). ^{1}H-NMR (DMSO-d_6) δ: 11.35 (1H, br s, H-3), 7.62 (1H, d, H-6, $J_{5,6}$ = 7.8 Hz), 5.68 (1H, d, H-1′, $J_{1',2'}$ = 5 Hz), 5.63 (1H, d, H-5), 5.42, 5.22 (each 1H, each d, OH-2′ and/or OH-3′), 4.63 (2H, t, H-6, $J_{5',6'}$ = 6.8 Hz), 4.10 (1H, m, H-2′), 3.89—3.74 (2H, m, H-3′,4′), 2.30 (2H, m, H-5′). *Anal.* Calcd for $C_{10}H_{13}N_3O_7$: C, 41.81; H, 4.56; N, 14.63. Found: C, 41.77; H, 4.60; N, 14.55.

Reaction of 6a with Acrylonitrile——KF (5 mg) and acryronitrile (6 μl, 138 μmol) were added to a solution of **6a** (15 mg, 44 μmol) in DMF (1 ml). The mixture was stirred at room temperature for 24 h. TLC showed that **6a** still remained. Additional acrylonitrile (3 μl, 69 μmol) was added and the mixture was stirred for a further 19 h. The starting material was almost completely consumed and two UV-absorbing products were detected on the TLC plate ($CHCl_3$–EtOH (50 : 1)). The solvent was evaporated off and each product was separated by preparative TLC (the same solvent system). After work-up, the upper and lower UV-absorbing bands gave, respectively, 7.6 mg (51%) of mono-adduct, 4-(5′-deoxy-2′,3′-*O*-isopropylideneuridin-5′-yl)-4-nitrobutyronitrile (**11**) as a foam which was an equimolar epimeric mixture at C-6′ and 6.8 mg (34%) of bis-adduct, 3-(5′-deoxy-2′,3′-*O*-isopropylideneuridin-5′-yl)-3-nitropentan-1,5-dinitrile (**10**). Compound **11**: UV λ_{max} (H_2O) 258 nm, UV λ_{max}^{pH11} 245 nm (showing a hyperchromic shift in basic media). EI-MS *m/z* 380 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 9.77, 9.70 (total 1H, each br s, H-3), 7.20, 7.14 (total 1H, each d, H-6, $J_{5,6}$ = 8 Hz), 5.77, 5.75 (total 1H, each d, H-5), 5.39 (1H, d, H-1′, $J_{1',2'}$ = 1.5 Hz), 5.15 (1H, dd, H-2′, $J_{2',3'}$ = 6.3 Hz), 4.85—4.71 (2H, m, H-3′, 6′), 4.10 (1H, m, H-4′), 2.94—2.10 (6H, m, H-5′, 7′, 8′), 1.53, 1.34 (each 3H, each s, isopMe). Compound **10**: mp 73—75 °C (crystallized from EtOH). UV λ_{max} (H_2O) 258 nm,

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$\lambda_{max}^{pH\,11}$ 250 nm (shoulder without a hyperchromic shift in base). EI-MS *m/z* 433 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 9.27 (1H, br s, H-3), 7.15 (1H, d, H-6, $J_{5,6}=8$ Hz), 5.74 (1H, d, H-5), 5.37 (1H, d, H-1′, $J_{1',2'}=1.5$ Hz), 5.18 (1H, dd, H-2′, $J_{2',3'}=6.3$ Hz), 4.75 (1H, dd, H-3′, $J_{3',4'}=4.6$ Hz), 4.04 (1H, m, H-4′), 2.66—2.38 (10H, m, $-CH_2-$), 1.53, 1.34 (each 3H, each s, isopMe).

9-(6-Deoxy-6-nitro-2,3-*O*-isopropylidene-β-D-allofuranosyl)adenine (allo 4b) and 9-(6-Deoxy-6-nitro-2,3-*O*-isopropylidene-α-L-talofuranosyl)adenine (talo 4b)——A stirred and cooled solution of 2′,3′-*O*-isopropylideneadenosine (8 g, 26 mmol) in anhydrous DMSO (57 ml) was treated first with DCC (16.7 g, 81 mmol) and then with dichloroacetic acid (1.0 ml, 12 mmol) at 0 °C. The mixture was further stirred at 20 °C for 90 min. The deposited crystalline dicyclohexylurea was filtered off and washed with a small amount of DMSO. The combined filtrate and washing were treated with nitromethane (18.9 ml, 350 mmol) in the presence of KF (6 mg) at room temperature for 36 h. A solution of oxalic acid dihydrate (6.5 g, 52 mmol) in MeOH (62 ml) was added to the reaction mixture and the whole was stirred for 30 min. The deposited urea was filtered off and the filtrate was diluted with AcOEt (400 ml). The solution was washed twice with H_2O (200 ml × 2), dried ($MgSO_4$), and concentrated to dryness. The residue was applied to a column (2.7 × 33 cm) and eluted with EtOAc. The nucleoside-containing fraction was collected and concentrated to give 1.85 g (19%) of an epimeric mixture of allo **4b** and talo **4b**. Crystallization from EtOH gave an analytical sample: mp 193—195 °C. UV λ_{max} (H_2O) 260 nm, $\lambda_{max}^{pH\,2}$ 257 nm, $\lambda_{max}^{pH\,11}$ 254 nm (showing a hyperchromic change in base). *Anal.* Calcd for $C_{14}H_{18}N_6O_6$: C, 45.90; H, 4.95; N, 22.94. Found: C, 45.93; H, 5.05; N, 22.95.

9-(5,6-Dideoxy-6-nitro-2,3-*O*-isopropylidene-β-D-*ribo*-hexofuranosyl)adenine (6b)——Acetic anhydride (170 mg, 1.95 mmol) and a catalytic amount of DMAP were added to a dioxane (4 ml) solution of the above epimeric mixture **4b** (188 mg, 0.51 mmol) with stirring, and the stirring was continued for 15 more minutes at room temperature. The mixture was then concentrated *in vacuo*. The remaining acetic anhydride was removed completely by codistillation with MeOH *in vacuo* below 40 °C and the residue was dissolved in 80% dioxane (4 ml). The solution was treated with a suspension of $NaBH_4$ (70 mg, 1.85 mmol) in EtOH (4 ml) at 0 °C for 20 min. After completion of the reaction, the mixture was neutralized with 10% H_2SO_4, and concentrated to dryness, and the residue was dissolved in H_2O (7 ml). The solution was extracted with $CHCl_3$ (7 ml). The organic layer was separated, dried ($MgSO_4$) and then concentrated. The residue was repeatedly distilled with MeOH to dryness and the residue was purified by preparative TLC ($CHCl_3$–EtOH (19 : 1)). Recrystallization of the product obtained from the major band from the EtOH gave an analytical sample, mp 176—177 °C, yield 60 mg (33%). *Anal.* Calcd for $C_{14}H_{18}N_6O_5$: C, 48.00; H, 5.18; N, 23.99. Found: C, 47.82; H, 5.29; N, 24.13. EI-MS *m/z* 350 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.26, 7.80 (each 1H, each s, H-8 and/or H-2), 6.15 (2H, br s, NH_2), 5.95 (1H, d, H-1′, $J_{1',2'}=2$ Hz), 5.44 (1H, dd, H-2′, $J_{2',3'}=6.4$ Hz), 4.95 (1H, dd, H-3′, $J_{3',4'}=6.4$ Hz), 4.33 (2H, t, H-6′, $J_{5',6'}=6.8$ Hz), 4.40—4.10 (1H, m, H-4′), 2.43 (2H, pseudo q, H-5′, $J_{4',5'}=6.8$ Hz), 1.53, 1.23 (each 3H, each s, isopMe).

9-(5,6-Dideoxy-6-nitro-β-D-*ribo*-hexofuranosyl)adenine (7b)——A solution of **6b** (329 mg, 0.94 mmol) in 50% acetic acid (7 ml) was heated at 100 °C for 6 h. The solvent was evaporated off and the residue was purified by chromatography (silica gel 14 g, $CHCl_3$–EtOH (4 : 1)) to afford **7b** as a powder. Recrystallization of the powder from EtOH gave an analytical sample of **7b** (189 mg, 62%). mp 130—132 °C. EI-MS *m/z* 310 (M^+). *Anal.* Calcd for $C_{11}H_{14}N_6O_5$–1/4EtOH: C, 42.92; H, 4.85; N, 26.11. Found: C, 42.93; H, 4.96; N, 26.12. ^{1}H-NMR (DMSO-d_6) δ: 8.32, 8.14 (each 1H, each s, H-8 and/or H-2), 7.29 (2H, br s, NH_2), 5.87 (1H, d, H-1′, $J_{1',2'}=4.9$ Hz), 5.51, 5.30 (each 1H, each d, 2′-OH and/or 3′-OH), 4.68—4.58 (3H, m, H-2′, 6′), 4.17 (1H, m, H-3′), 3.93 (1H, m, H-4′), 2.37 (2H, pseudo q, H-5′, $J=6.8$ Hz). A small amount of EtOH was detected by ^{1}H-NMR.

Acetylation of 7a——A solution of **7a** (314 mg, 1.09 mmol) in pyridine (5 ml) was treated with acetic anhydride (5 ml, 52.9 mmol) at room temperature for 20 min. The solvent was removed and the residue was partitioned between $CHCl_3$ (30 ml) and H_2O (20 ml). The organic layer was dried ($MgSO_4$). The salt was filtered off and the filtrate was evaporated to dryness. The residue was purified by preparative TLC ($CHCl_3$–EtOH (10 : 1)) to afford 1-(5,6-dideoxy-2,3-di-*O*-acetyl-β-D-*ribo*-hexofuranosyl)uracil **8** (320 mg, 79%). An analytical sample was obtained by crystallization from benzene–EtOH and subsequent recrystallization from EtOH, mp 130—131 °C. EI-MS *m/z* 311 ($M^+ - AcOH$), 260 ($M^+ -$ uracil + H). *Anal.* Calcd for $C_{14}H_{17}N_3O_9$: C, 45.29; H, 4.61; N, 11.32. Found: C, 45.39; H, 4.58; N, 11.27. ^{1}H-NMR ($CDCl_3$) δ: 8.90 (1H, br s, H-3), 7.14 (1H, d, H-6, $J_{5,6}=8$ Hz), 5.79 (1H, dd, H-5, $J_{3,5}=2$ Hz), 5.58 (1H, d, H-1′, $J_{1',2'}=4$ Hz), 5.50 (1H, dd, H-2′, $J_{2',3'}=6.4$ Hz), 5.26 (1H, pseudo t, H-3′, $J=6.4$ Hz), 4.55 (2H, t, H-6′, $J_{5',6'}=6.4$ Hz), 4.17 (1H, m, H-4′), 2.45 (2H, m, H-5′), 2.12 (6H, s, Ac × 2).

9-(5,6-Dideoxy-6-nitro-2,3-di-*O*-acetyl-β-D-*ribo*-hexofuranosyl)-N^6-benzoyladenine (9)——BSA (1.43 ml, 5.73 mmol) was added to a suspension of **8a** (490 mg, 1.32 mmol) and N^6-benzoyladenine (632 mg, 2.64 mmol) in CH_3CN (4.4 ml). The mixture was refluxed for 15 min during which time a clear solution was obtained. After cooling, TMS-Tf (0.31 ml, 2.20 mmol) was added to the mixture, which was then refluxed for 2 h. The solvent was evaporated off. The residue was dissolved in EtOH (20 ml) and the solvent was again evaporated off. The residue was dissolved in $CHCl_3$ (50 ml) and the solution was washed with 5% $NaHCO_3$ (20 ml) then H_2O (20 ml), dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography (silica gel, 70 g; $CHCl_3$–EtOH (19 : 1)) gave **9** (a TLC-homogeneous foam, 237 mg, 36%). UV λ_{max} (MeOH–H_2O) 280.5 nm, $\lambda_{max}^{pH\,1}$ 288.5 nm, $\lambda_{max}^{pH\,11}$ 320 nm. EI-MS *m/z* 498 (M^+), 260 ($M^+ - N^6$-benzoyladenine + H). ^{1}H-NMR ($CDCl_3$) δ: 8.91, 8.81 (each 1H, each s, H-2 and/or H-8),

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8.07—7.55 (5H, m, benzoyl), 6.24—5.92 (2H, m, H-1′, 2′), 5.66 (1H, m, H-3′), 4.53 (2H, t, H-6′), 4.34 (1H, m, H-4′), 2.63 (2H, m, H-5′), 2.17, 2.10 (each 3H, each s, Ac × 2).

9-(5,6-Dideoxy-6-nitro-β-D-*ribo*-hexofuranosyl)adenine (7b)——The nucleoside **9** (520 mg, 1.08 mmol) was treated with 10 ml of EtOH–c.NH_4OH (4 : 1) at room temperature for 48 h. The solvent was removed, and the residue was crystallized from EtOH to give in 66% yield (220 mg) a product which was identical with **7b** obtained from adenosine.

Methyl 4-(2′,3′-*O*-Isopropylideneuridin-5′-yl)-4-nitrobutanoate (16)——Methyl 4-nitrobutanoate (2.20 g, 15 mmol) and KF (290 mg, 5 mmol) were added to a reaction mixture containing **3a** [prepared from 2′,3′-*O*-isopropylideneuridine (2.84 g, 10 mmol) as above]. The reaction mixture was stirred for 48 h and then mixed with a solution of oxalic acid dihydrate (3.3 g, 7.5 mmol) in MeOH (5 ml). The whole was stirred for 30 min, the urea which had deposited was filtered off and the filtrate was diluted with AcOEt (200 ml). The solution was washed with H_2O (150 ml × 2), the organic layer was dried ($MgSO_4$) and concentrated to dryness. Column chromatography (silica gel, 30 g, $CHCl_3$–EtOH (50 : 1)) of the residue afforded, after work-up, a homogeneous foam **16** (3.17 g, 74%). ^{1}H-NMR ($CDCl_3$) δ: 9.99, 9.64 (total 1H, each br s, H-3), 7.27 (1H, d, H-6, $J_{5,6}$ = 8 Hz), 5.79 (1H, d, H-5), 5.43 (1H, d, 1H, $J_{1',2'}$ = < 1 Hz), 5.16—5.23 (2H, m, H-2′, 3′), 4.60 (1H, m, H-6′), 3.82—4.28 (2H, m, H-4′, 5′), 3.67 (3H, s, $-OCH_3$), 2.2—2.6 (4H, m, $-CH_2-$), 1.56, 1.37 (each 3H, each s, isopMe). UV λ_{max} (H_2O) 259.5 nm, λ_{max}^{pH1} 261 nm, λ_{max}^{pH11} 227 nm, showing that UV max undergo hyperchromic and hypsochromic changes in basic media.

Methyl 4-(5′-Deoxy-2′,3′-*O*-isopropylideneuridin-5′-enyl)-4-nitrobutanoate (17)——Acetic anhydride (5.29 g, 51.8 mmol) was added to a solution of **16** (7.41 g, 17.3 mmol) in dry dioxane (170 ml) in the presence of DMAP (10 mg). The mixture was stirred at room temperature for 20 min. The solvent was removed *in vacuo*, and acetic acid was removed by several codistillations with MeOH. Crystallization of the residue from EtOH afforded **17** (4.62 g, 65%, mp 135—137 °C). *Anal.* Calcd for $C_{17}H_{21}N_3O_9$: C, 49.64; H, 5.15; N, 10.21. Found: C, 49.40; H, 5.26; N, 10.02. EI-MS *m/z* 411 (M^+). ^{1}H-NMR ($CDCl_3$ containing two drops of DMSO-d_6) δ: 11.31 (1H, br s, H-3), 7.32 (1H, d, H-6, $J_{5,6}$ = 8 Hz), 7.28 (1H, d, H-5′, $J_{4',5'}$ = 7 Hz), 5.66 (1H, dd, H-5, $J_{3,5}$ = 2 Hz), 5.56 (1H, d, H-1′, $J_{1',2'}$ = 1.2 Hz), 5.18 (1H, dd, H-2′, $J_{2',3'}$ = 5.9 Hz), 4.8—5.1 (2H, m, H-3′, 4′), 3.68 (3H, s, $-OCH_3$), 3.1—2.9 (2H, m, H-7′), 2.59 (2H, t, H-8′), 1.58, 1.35 (each 3H, each s, isopMe).

Methyl 4-(5′-Deoxy-2′,3′-*O*-isopropylideneuridin-5′-yl)-4-nitrobutanoate (13)——A suspension of $NaBH_4$ (1.6 g, 42.3 mmol) in EtOH (100 ml) was added to a solution of **17** (4.62 g, 11.2 mmol) in 80% dioxane (100 ml) at 0 °C. The mixture was stirred at 0 °C for 20 min, then neutralized with 10% H_2SO_4 and the resulting solution was concentrated to a small volume. The solution was partitioned between $CHCl_3$ (100 ml) and H_2O (50 ml). The $CHCl_3$ layer was washed with H_2O (50 ml), dried (Na_2SO_4), and concentrated to a homogeneous foam. Crystallization from EtOH afforded one of the epimers (mp 121—125 °C) in 42% yield. *Anal.* Calcd for $C_{17}H_{23}N_3O_9$: C, 49.39; H, 5.61; N, 10.16. Found: C, 49.39; H, 5.65; N, 10.21. EI-MS *m/z* 413 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.94 (1H, br s, H-3), 7.21 (1H, d, H-6, $J_{5,6}$ = 8 Hz), 5.75 (1H, dd, H-5, $J_{3,5}$ = 2 Hz), 5.41 (1H, d, H-1′, $J_{1',2'}$ = 1.5 Hz), 5.10 (1H, dd, H-2′, $J_{2',3'}$ = 6.3 Hz), 4.5—4.9 (2H, m, H-3′, 6′), 4.10 (1H, m, H-4′), 3.67 (3H, s, $-OCH_3$), 2.0—2.8 (6H, m, $-CH_2-$), 1.52, 1.34 (each 3H, each s, isopMe). Concentration of the mother liquor gave the other apparently homogeneous 6′-epimer as a foam (2.36 g, 51%). ^{1}H-NMR ($CDCl_3$) δ: 8.81 (1H, br s, H-3), 7.16 (1H, d, H-6, $J_{5,6}$ = 8 Hz), 5.74 (1H, dd, H-5, $J_{3,5}$ = 2 Hz), 5.44 (1H, d, H-1′, $J_{1',2'}$ = 1.5 Hz), 5.10 (1H, dd, H-2′, $J_{2',3'}$ = 6.3 Hz), 4.59—4.90 (2H, m, H-3′, 6′), 4.10 (1H, m, H-4′), 3.69 (3H, s, $-OCH_3$), 2.0—2.8 (6H, m, $-CH_2-$), 1.55, 1.34 (each 3H, each s, isopMe).

Methyl 4-(5′-Deoxy-2′,3′-di-*O*-acetyluridin-5′-yl)-4-nitrobutanoate (18)——A solution of **13** (1.4 g, 3.39 mmol) in 50% acetic acid (40 ml) was heated in boiling water for 1.5 h. After removal of the solvent, a trace of acetic acid was removed by several coevaporations with EtOH. The residue was dissolved in dioxane (50 ml) and the solution was treated with acetic anhydride (1.38 g, 13.6 mmol) and DMAP (10 mg) at room temperature for 20 min. The mixture was concentrated to dryness and the residue was purified by column chromatography to give **18** as a homogeneous foam (1.70 g, 69%). EI-MS *m/z* 426 ($M^+ - OCH_3$), 397 ($M^+ - AcOH$). ^{1}H-NMR ($CDCl_3$) δ: 8.81 (1H, br s, H-3), 7.16 (1H, d, H-6, $J_{5,6}$ = 8 Hz), 5.78 (1H, dd, H-5, $J_{3,5}$ = 2 Hz), 5.70, 5.52 (total 1H, each d, H-1′, $J_{1',2'}$ = 4.2 Hz), 5.38 (1H, dd, H-2′, $J_{2',3'}$ = 6.2 Hz), 5.20 (1H, pseudo t, H-3′, J = 6.1 Hz), 4.74 (1H, m, H-6′), 4.10 (1H, m, H-4′), 3.70, 3.69 (total 3H, each s, $-OCH_3$), 2.0—2.8 (6H, m, $-CH_2-$), 2.12, 2.11 (each 3H, each s, Ac × 2).

Dimethyl 4-(5′-Deoxy-2′,3′-*O*-isopropylideneuridin-5′-yl)-4-nitroheptandioate (12) and Methyl 4-(5′-Deoxy-2′,3′-*O*-isopropylideneuridin-5′-yl)-4-nitrobutanoate (13)——KF (30 mg) and methyl acrylate (390 mg, 4.53 mmol) were added to a solution of **13** (218 mg, 0.55 mmol) in DMF (4 ml). The mixture was stirred at room temperature for 7 d and then concentrated to dryness. Two products were detected on TLC ($CHCl_3$–EtOH (30 : 1)) and were separated by preparative TLC (the same solvent system). The upper band provided 17 mg of a product which is putatively a nucleoside bearing an additional methoxycarbonylethyl group at position 3 (EI-MS *m/z* M^+ = 585 and the absence of a signal due to H-3 in the ^{1}H-NMR) and the lower band gave 172 mg (65%) of **12**. EI-MS *m/z* 499 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.81 (1H, br s, H-3), 7.14 (1H, d, H-6, $J_{5,6}$ = 8 Hz), 5.73 (1H, dd, H-5, $J_{3,5}$ = 2.2 Hz), 5.37 (1H, d, H-1′, $J_{1',2'}$ = 1.5 Hz), 5.09 (1H, dd, H-2′, $J_{2',3'}$ = 6.3 Hz), 4.75 (1H, dd, H-3′, $J_{3',4'}$ = 6.6 Hz), 4.10 (1H, m, H-4′), 3.65, 3.64 (each 3H, each s, $-OCH_3$), 2.96—2.11 (10H, m, $-CH_2-$), 1.54, 1.34 (each 3H, each s, isopMe). Determination of the product distribution in the reaction of **6a** and methyl acrylate was performed as follows. Methyl acrylate (192 mg, 0.15 mmol) and KF (5 mg) were added to a solution of **6a** (50 mg, 0.15 mmol) in DMF (10 ml) with stirring. Stirring was continued for 6 h at room temperature. After removal of the solvent, the residue weighed 60 mg. ^{1}H-NMR

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($CDCl_3$) analysis indicated the presence of **6a**, **12**, and **13** in a ratio of 22:12:66, showing that even when one equivalent of methyl acrylate was used, the bisadduct **12** as well as the starting material was present in the reaction mixture.

Methyl 4-(N^6-Benzoyl-2′,3′-di-*O*-acetyladenosin-5′-yl)-4-nitrobutanoate (19)——BSA (2.15 ml, 8.6 mmol) was added to a suspension of **18** (974 mg, 2.13 mmol) and N^6-benzoyladenine (1.02 g, 4.26 mmol) in CH_3CN (13 ml). The mixture was refluxed for 15 min, then cooled. TMS-Tf (0.12 ml, 0.65 mmol) was added, and the whole was refluxed for 6 h then concentrated. The residue was suspended in EtOH (50 ml). The solution was filtered and concentrated, and the residue was chromatographed (silica gel, 10 g, $CHCl_3$–EtOH (50:1)). The title compound **19** (505 mg, 41%) was obtained as a homogeneous foam. EI-MS *m/z* 584 (M^+). UV λ_{max} (H_2O–MeOH) 280 nm, λ_{max}^{pH2} 288 nm, λ_{max}^{pH11} 235, 310 nm. ^{1}H-NMR ($CDCl_3$) δ: 8.82, 8.80 (total 1H, each s, H-2 or H-8), 8.13—8.01 (3H, m, H-2 or H-8 and aromatic protons), 7.47—7.66 (3H, m, aromatic protons), 5.94—6.12 (2H, m, H-1′, 2′), 5.62 (1H, pseudo t, H-3′, J=5.2 Hz), 4.67 (1H, m, H-6′), 4.22 (1H, m, H-4′), 3.67, 3.64 (total 3H, each s, $-OCH_3$), 2.91—2.10 (6H, m, $-CH_2-$), 2.16, 2.15, 2.10, 2.08 (total 6H, each s, Ac×2).

4-(5′-Deoxyadenosin-5′-yl)-4-nitrobutyramide (20)——A suspension of **19** (260 mg, 0.44 mmol) and NH_4Cl (118 mg, 2.2 mmol) in c.NH_4OH (5 ml) was stirred for 3 h at room temperature. The solvent was removed and codistillation with H_2O was repeated twice. The residue was crystallized from EtOH. Yield, 70 mg (39%), mp 112—113 °C. FD-MS *m/z* 382 ($M^+ + 1$). ^{1}H-NMR (DMSO-d_6) δ: 8.29, 8.19 (each 1H, each s, H-2 and/or H-8), 5.87 (1H, d, H-1′, $J_{1',2'}$=5 Hz), 4.60—4.75 (2H, m, H-2′, 6′), 3.9—4.2 (2H, m, H-3′, 4′), 2.0—2.7 (6H, m, $-CH_2-$). *Anal.* Calcd for $C_{14}H_{19}N_7O_6$ (0.1 EtOH + 1.4 H_2O): C, 41.48; H, 5.49; N, 23.85. Found: C, 51.54; H, 5.21; N, 23.90. Small amounts of EtOH and H_2O were detected by ^{1}H-NMR.

Methyl 4-(2′,3′-*O*-Isopropylideneadenosin-5′-yl)-4-nitrobutanoate (22)——Dichloroacetic acid (0.4 ml, 4.85 mmol) was added to a solution of 2′,3′-*O*-isopropylideneadenosine (**3b**, 3.07 g, 10.0 mmol) and DCC (6.20 g, 30.1 mmol) in DMSO (20 ml) at 0 °C. The mixture was stirred at room temperature for 1.5 h. After removal of dicyclohexylurea by filtration, the filtrate was treated with methyl 4-nitrobutanoate (3.0 g, 20.4 mmol) and KF (200 mg, 5.0 mmol), then the mixture was stirred for 3 d at room temperature. A solution of oxalic acid dihydrate (2.5 g, 14.9 mmol) in MeOH (10 ml) was then added dropwise, and stirring was continued for 30 min. The urea which had deposited was filtered off and the filtrate was diluted with AcOEt (150 ml). The solution was washed with H_2O (50 ml×1, 30 ml×2), dried ($MgSO_4$) and concentrated to dryness. The residue was purified by chromatography to yield 1.96 g (48%) of **22** as a homogeneous foam. EI-MS *m/z* 452 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.29, 8.28 (total 1H, each s, H-8 or H-2), 7.84 (1H, s, H-8 or H-2), 7.57 (1H, br s, 5′-OH), 5.93 (2H, br s, NH_2), 5.86 (1H, d, H-1′, $J_{1',2'}$= 4.2 Hz), 5.06—5.21 (2H, m, H-2′, 3′), 4.64 (1H, m, H-6′), 4.30—4.53 (2H, m, H-4′, 5′), 3.67, 3.71 (total 3H, each s, $-OCH_3$), 2.2—2.6 (4H, m, $-CH_2-$), 1.64, 1.32 (each 3H, each s, isopMe).

Methyl 4-(5′-Deoxy-2′,3′-*O*-isopropylideneadenosin-5′-yl)-4-nitrobutanoate (21)——Acetic anhydride (586 mg, 5.74 mmol) and DMAP (5 mg) were added to a solution of **22** (866 mg, 1.91 mmol) in dioxane (20 ml). After standing at room temperature for 20 min, the mixture was concentrated, and AcOH was removed by several codistillations with MeOH. The residue was dissolved in 80% dioxane (17 ml) and a suspension of $NaBH_4$ (273 mg, 7.22 mmol) in EtOH (17 ml) was added in one portion to the solution at 0 °C. After being stirred for 40 min at 0 °C, the mixture was neutralized with 10% H_2SO_4 to pH 7. The solution was concentrated to a small volume then partitioned between $CHCl_3$ (100 ml) and H_2O (50 ml). The organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated. Column chromatography (silica gel, 10 g, $CHCl_3$–EtOH (25:1)) gave a homogeneous foam **21** (436 mg, 51%). EI-MS *m/z* 436 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.33, 7.90 (each 1H, each s, H-2 and/or H-8), 6.18 (2H, br s, NH_2), 6.03 (1H, d, H-1′, $J_{1',2'}$=1.5 Hz), 5.50 (1H, dd, H-2′, $J_{2',3'}$=6.4 Hz), 5.17 (1H, dd, H-3′), 4.64 (1H, m, H-6′), 4.23 (1H, m, H-4′), 3.67, 3.63 (total 3H, each s, $-OCH_3$), 2.8—2.2 (6H, m, $-CH_2-$), 1.59, 1.38 (each 3H, each s, isopMe).

4-(5′-Deoxyadenosin-5′-yl)-4-nitrobutyramide (20). Preparation of an Authentic Sample of 20——Compound **21** (540 mg, 1.24 mmol) and NH_4Cl (317 mg, 5.93 mmol) were added to c.NH_4OH (37 ml) with stirring. The stirring was continued for 18 h at room temperature. The solvent was evaporated off and coevaporation of the residue with EtOH was carried out six times. EtOH was added to the residue and insoluble salt was filtered off. The filtrate was concentrated to dryness. The residue was chromatographed (column size, 140×20 mm, $CHCl_3$–EtOH (20:1)), and the fraction containing 4-(5′-deoxy-2′,3′-*O*-isopropylideneadenosin-5′-yl)-4-nitrobutyramide was collected. The product (178 mg) was dissolved in 90% formic acid (5 ml) and the mixture was allowed to stand for 15 h. The solvent was removed and the residue was chromatographed [Dowex 1×8 (OH^-); 1% AcOH]. Crystallization of the product from EtOH gave an analytical sample of **20** (95 mg, 19%) which was found to be indistinguishable from the sample (*vide supra*) synthesized from uridine based on the criterion of CD spectra, in particular, showing that the sample from uridine was also the β-D-nucleoside. *Anal.* Calcd for $C_{14}H_{19}N_7O_6$ (0.2 EtOH + 0.6 H_2O): C, 43.09; H, 5.37; N, 24.43. Found: C, 42.93; H, 5.17; N, 24.24.

4-(5′-Deoxy-2′,3′-*O*-isopropylideneuridin-5′-yl)-4-nitrobutyramide (14)——A solution of **13** (400 mg, 0.97 mmol) in MeOH (1 ml) was treated with c.NH_4OH (7 ml). The solution was kept at room temperature for 5 d. Removal of the solvent left a carboxamide **14**, which was coevaporated with EtOH six times. The residue was chromatographed (column, 80×16 mm, $CHCl_3$/EtOH 94:6) to give 370 mg (96%) of **14** as a TLC-homogeneous foam. EI-MS *m/z* 399 ($M^+ + 1$), 383 ($M^+ - CH_3$). ^{1}H-NMR ($CDCl_3$) δ: 10.16, 9.76 (total 1H, each br s, H-3), 7.19, 7.18 (total 1H, each

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d, H-6, $J_{5,6}=8$ Hz), 6.34, 5.95 (total 2H, each br s, NH_2), 5.73 (1H, dd, H-5, $J_{3,5}=2$ Hz), 5.41, 5.38 (total 1H, each d, H-1′, $J_{1',2'}=1.5$ Hz), 5.19—5.08 (1H, m, H-2′), 4.81—4.69 (2H, m, H-3′, 6′), 4.16 (1H, m, H-4′), 2.8—2.0 (6H, m, $-CH_2-$), 1.52, 1.33 (each 3H, each s, isopMe).

Alternative Synthesis of 11——A solution of **14** (360 mg, 0.90 mmol) in CH_3CN (2 ml) was treated with thionyl chloride (0.2 ml, 2.75 mmol) at 0 °C, and the mixture was refluxed for 1 h. After removal of the solvent, the residue was partitioned between $CHCl_3$ (50 ml) and H_2O (20 ml). The organic layer was dried ($MgSO_4$), and concentrated to dryness. Column chromatography (column 200 × 16 mm, $CHCl_3$–EtOH (98 : 2)) of the residue gave **11** (278 mg, 87%) as a homogeneous foam, which was identical with a sample prepared as described above, based on the criteria of ^{1}H-NMR and EI-MS.

4-(5′-Deoxyuridin-5′-yl)-4-nitrobutyronitrile (15)——Compound **11** (278 mg, 0.73 mmol) was dissolved in 50% AcOH (10 ml). The solution was heated on a boiling water bath for 1 h and then the solvent was evaporated off. The residue was crystallized from MeOH to give 186 mg (75%) of a C-6′ epimeric mixture. Recrystallization of the mixture from MeOH gave one of the epimers (82 mg, 33%). The absolute configuration at C-6′ was found to be *S* by X-ray structural analysis.[17] mp 173—175 °C. EI-MS *m/z* 340 (M^+). *Anal.* Calcd for $C_{13}H_{16}N_4O_7$: C, 45.89; H, 4.74; N, 16.46. Found: C, 45.88; H, 4.66; N, 16.42. ^{1}H-NMR (DMSO-d_6) δ: 11.37 (1H, br s, H-3), 7.63 (1H, d, H-6, $J_{5,6}=8.1$ Hz), 5.70 (1H, d, H-1′, $J_{1',2'}=4.4$ Hz), 5.63 (1H, dd, H-5, $J_{3,5}=2$ Hz), 5.5—5.0 (2H, br s, 2′-OH and 3′-OH), 4.77 (1H, m, H-6′), 4.11 (1H, m, H-4′), 3.9—3.5 (2H, m, H-2′, 3′), 2.7—2.1 (6H, m, $-CH_2-$). The mother liquor was allowed to stand at room temperature for 4 d. An epimeric mixture was deposited and collected by filtration. Yield, 86 mg (35%), mp 141—149 °C (epimeric ratio, 1 : 1). In the ^{1}H-NMR, no marked difference between the spectra of the (*S*)-epimer and the epimeric mixture was obtained with the exception of the signal due to H-6 (*S*), which appeared at δ 7.63 as a doublet, whereas the that to H-6 (*R*) appeared at δ 7.56 as a doublet with the same coupling constant ($J_{5,6}=8.1$ Hz).

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References and Notes

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