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Nucleosides and Nucleotides. 124. Chemical Reactivity of the Sugar Moiety of 2'-Deoxy-2'-methylidene Pyrimidine Nucleosides: Synthesis of 3'-Amino-2',3'-dideoxy-2'-methylidene Pyrimidine Nucleosides via [2,3]-Sigmatropic Rearrangement of Allylic Selenides as Potential Antitumor Agents[1]

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Key Words: nucleoside; allyl selenide; 2',3'-didehydro-2',3'-dideoxy nucleoside; [2,3]-sigmatropic rearrangement; antitumor activity

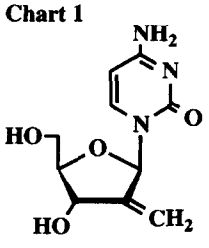
Abstract: Nucleophilic substitution reactions of an allyl alcohol system in the 2'-deoxy-2'-methylidene pyrimidine nucleosides with various nucleophiles were investigated. The allyl alcohol system reacted with softer nucleophiles such as azide, thiophenoxide, and iodo anion through an SN2' manner to afford 2'-substituted-methyl-2',3'-didehydro-2',3'-dideoxy nucleosides, but with hard oxygen-nucleophiles such as benzoyloxy and phenoxide through an SN2 manner to afford 2'-deoxy-2'-methylidene-3'-substituted nucleosides with inversion at the 3'-position. Based on this characteristic reactivity, 2',3'-didehydro-2',3'-dideoxy-2'-phenylselenomethyl pyrimidine nucleosides **16b** and **16c** were synthesized. These nucleosides were converted into 3'-amino-2',3'-dideoxy-2'-methylidene pyrimidine nucleosides **3b** and **3c** via oxidative [2,3]-sigmatropic rearrangement of the allylic selenides as a key step. The cytosine derivative **3a** was also prepared from the corresponding uracil derivative.

Introduction

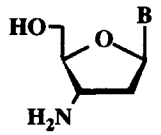
2-Deoxy-2-methylidenecytidine (DMDC; **1**)[2] is one of a new class of 2'-deoxycytidine analogues with a broad spectrum of antitumor activity. DMDC showed, unlike 1-β-D-arabinofuranosylcytidine (*ara*-C), highly potent cytotoxicity against not only mouse leukemia cell lines but also human leukemia, lymphoma, and carcinoma cells *in vitro*.[3,4] DMDC also had a therapeutic activity against some human tumor xenografts[4] and is now in phase I clinical trial in Japan. Unlike *ara*-C, DMDC is not a substrate of cytidine deaminase from mouse kidney, which deaminates *ara*-C to a therapeutically inactive 1-β-D-arabinofuranosyluracil.[3,4] The mechanism of its action has been extensively studied: 5'-Triphosphate of DMDC strongly inhibits DNA polymerases from calf thymus[5] and 5'-diphosphate of DMDC (DMDCDP) time-dependently inhibits ribonucleoside diphosphate reductase from *E. coli*.[6] We have also studied the structural requirements of base and sugar moieties of DMDC for their antitumor properties.[5,7] It was found that the exo-methylene group at the 2'-position of deoxycytidine was essential for the activity. It was reported on the mechanism of inhibition of ribonucleoside diphosphate reductase that stabilization of the 3'-

carbon radical in DMDCDP by the 2'-exo-methylene group was of importance for the activity.[6] We also expected other types of chemical reactions arising from the allylic alcohol or the allylic phosphate ester, which would be formed if DMDC is incorporated in a DNA molecule, during its metabolism.[5] Thus, it is important to have further knowledge on the chemical reactivity of the allylic alcohol system in DMDC.

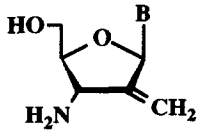
Chart 1



1 ; DMDC



2a, c



3a, b, c

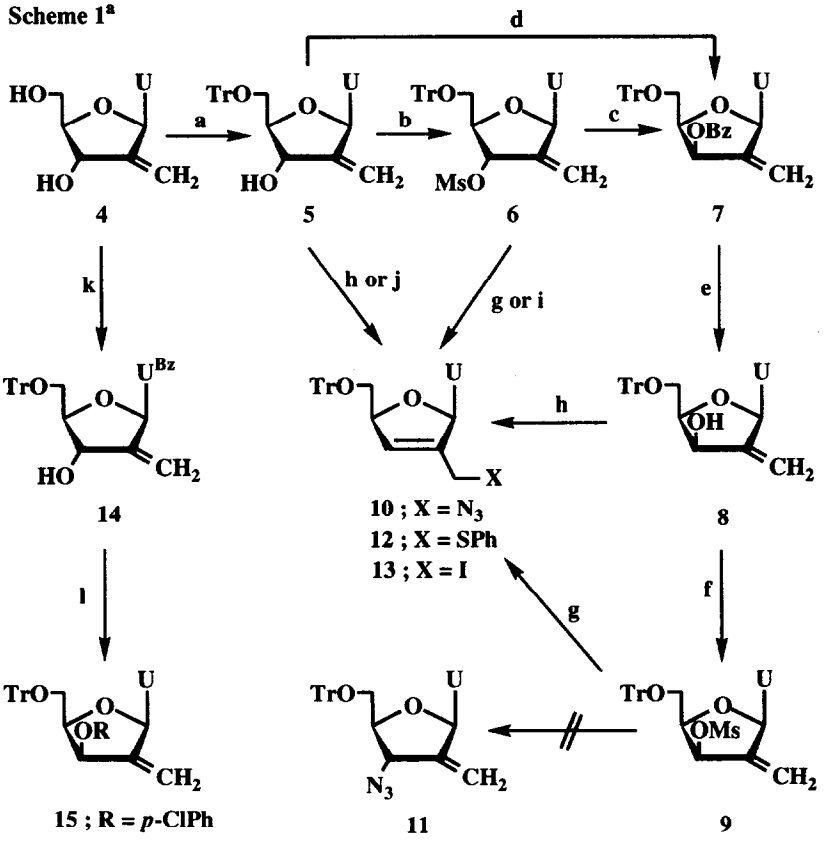
a ; B = cytosin-1-yl
b ; B = uracil-1-yl
c ; B = thymin-1-yl

On the other hand, 3'-amino-2',3'-dideoxycytidine (**2a**) is known to inhibit L1210 leukemia both *in vitro* and *in vivo*.[8] The mechanism of its action is most likely to be a chain terminator of DNA synthesis.[9] 3'-Amino-2',3'-dideoxythymidine (**2c**) is also a potent inhibitor of the proliferation of both murine sarcoma 180 and leukemia L1210 cells *in vitro*.[8] Therefore, whether a combination of both structural features of DMDC and 3'-amino-2',3'-dideoxynucleosides into one molecule would have additive antineoplastic activity or not is of interest. In this paper, we describe the detailed chemical reactivity of the allylic alcohol system and the syntheses of a series of (3'*S*)-3'-amino-2',3'-dideoxy-2'-methylidene pyrimidine nucleosides **3a, b, c** (Chart 1). A preliminary account of this study has appeared.[10]

Results and Discussion

Chemical reactivity of the allyl alcohol system in the sugar moiety of 2'-deoxy-2'-methylidene nucleosides toward nucleophiles. Selective protection of the 5'-hydroxyl group of 2'-deoxy-2'-methylidene-uridine (**4**)[3a,11] by a trityl group gave **5** in good yield. Compound **5** was converted to the 3'-*O*-methanesulfonate **6** by the usual method, which was used for the next reaction with nucleophiles without further purification, because of its instability. Treatment of **6** with sodium benzoate in DMF at 90 °C gave the inversion product **7** in 55% yield from **5**. The benzoate **7** was provided more readily under Mitsunobu reaction conditions; treatment of **5** with benzoic acid in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine in THF at 0 °C gave **7** quantitatively. Alkaline hydrolysis of **7** gave the hydroxyl derivative **8** and the configuration at the 3'-position was confirmed at this stage. In its ^{1}H NMR spectrum, the 3'-proton signal of **8** was observed at 4.67 ppm coupled with the 4'-proton ($J_{3',4'}$ = 4.0 Hz) while that of

Scheme 1[a]



U = uracil-1-yl, U^{Bz} = N^3-benzoyluracil-1-yl

[a]a) TrCl, pyridine, 100 °C; b) MsCl, Et_3N, CH_2Cl_2, 0 °C; c) NaOBz, DMF, 90 °C; d) BzOH, DEAD, Ph_3P, THF, room temperature; e) NaOH, aqueous EtOH, room temperature; f) MsCl, pyridine, 0 °C; g) NaN_3, DMF, 0 °C; h) DPPA, DEAD, Ph_3P, THF, room temperature; i) PhSH, Et_3N, DMF, room temperature; j) Ph_3P, I_2, DMF, room temperature; k) ref. 12; l) i) *p*-chlorophenol, DEAD, Ph_3P, THF, room temperature, ii) NH_3/MeOH, 0 °C

the 3'-stereoisomer **5** was at 4.81 ppm ($J_{3',4'}$ =6.6 Hz). Therefore, both reactions proceeded in an SN2 manner. In contrast with these results, when **6b** was treated with sodium azide in DMF at 0 °C, the reaction proceeded through an SN2' manner to give 2'-azidomethyl-2',3'-didehydro-2',3'-dideoxy nucleoside **10** in 94% yield as a sole product. The ^{1}H-NMR spectrum of **10** showed the presence of one vinylic proton signal due to the 3'-proton at 6.22 ppm as a double doublet and disappearance of two vinylic proton signals corresponding to the 2'-exomethylene group. An evident stretching band due to the azide group was observed at 2100 cm^{-1} in the IR spectrum. Direct treatment of the allylic alcohol **5** under Mitsunobu

reaction conditions with diphenylphosphoryl azide (DPPA)[12] afforded again the same 2',3'-unsaturated nucleoside **10** exclusively.

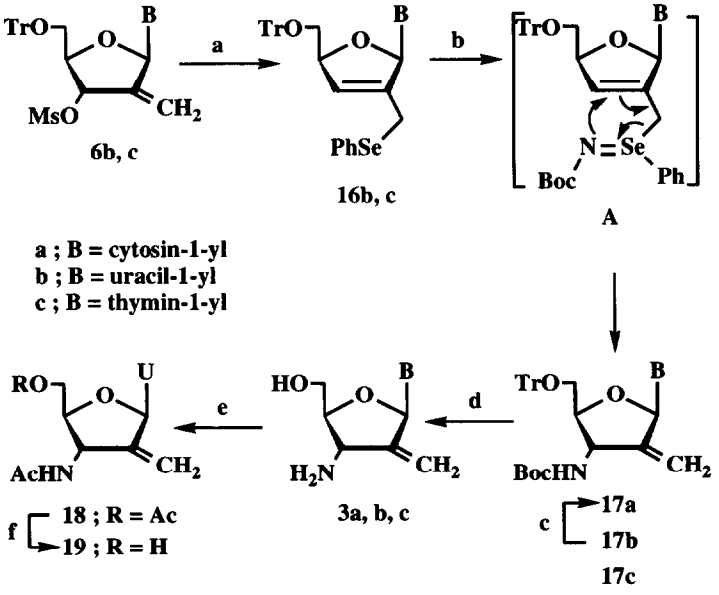
Next, nucleophilic substitution reactions of the allyl alcohol **8**, which have a 3'-hydroxyl group at the β-configuration, in which the α-face would be considerably less hindered than the β-face of **5**, was investigated. After methanesulfonylation of the 3'-hydroxyl group of **8**, a nucleophilic substitution reaction of the resulting methanesulfonate **9** with sodium azide was done in DMF at 0 °C giving again the SN2' product **10** in 86% yield. The SN2 product **11** was not detected in this reaction. The Mitsunobu reaction of **8** with DPPA also afforded the SN2' product **10** in excellent yield, but not the SN2 product **11**.

The different behavior of the exocyclic allylic alcohol system in the 2'-deoxy-2'-methylidene nucleoside toward the two nucleophiles (N_3^- and BzO^-) led us to investigate further its mode of reactions with other nucleophiles. When **6b** was treated with thiophenol in the presence of triethylamine in DMF at room temperature, the reaction proceeded through the SN2' manner affording the 2'-phenylthiomethyl-2',3'-didehydro-2',3'-dideoxy nucleoside **12** in high yield. A similar SN2' reaction was also observed on treatment of the 3'-allyl alcohol **5** with I_2/Ph_3P in DMF at room temperature to give 2'-iodomethyl-2',3'-didehydro-2',3'-dideoxy derivative **13**.[13] On the other hand, treatment of N^3-benzoyl-2'-deoxy-2'-methylidene-5'-*O*-trityluridine (**14**), in which the benzoyl protection was needed for prevention of the reaction at the O^4-position, with *p*-chlorophenol under the Mitsunobu reaction conditions, followed by deblocking of the N^3-benzoyl group with saturated methanolic ammonia, furnished the SN2 product **15** in 69% yield.

These results showed that the allylic alcohol system in the 2'-deoxy-2'-methylidene nucleoside reacts with relatively soft nucleophiles such as azide, thiophenoxide, and iodo anions through the SN2' manner giving the 2'-substituted-methyl-2',3'-unsaturated nucleosides, while it reacts with hard oxygen-nucleophiles such as benzoyloxy and phenoxide anions through the SN2 manner giving 2'-deoxy-2'-methylidene-3'-substituted nucleosides in an inversion mode.

Synthesis of 3'-Amino-2',3'-dideoxy-2'-methylidene Pyrimidine Nucleosides. These results suggested that introduction of a nitrogen functional group at the 3'-position of 2'-deoxy-2'-methylidene nucleosides through the SN2 reaction would not happen.[14] On the other hand, it has been demonstrated that allylic amines could be prepared via an oxidative [2,3]-sigmatropic rearrangement of allylic selenides.[15] Therefore, we planed to synthesize the target compounds, 3'-amino-2',3'-dideoxy-2'-methylidene nucleosides **3a**, **b**, and **c**, from the allylic selenides **16**. From the chemical reactivity of the allylic alcohol system described as above, the allylic selenide **16** was thought to be synthesized readily from the 3'-*O*-methanesulfonate **6** by the SN2' substitution reaction with a soft phenylselenoxide anion as a nucleophile. As shown in scheme 2, if an intermediate **A** is generated *via* oxidation of **16** with *N*-chlorosuccinimide (NCS) followed by reaction with *tert*-butylcarbamate, it can rearrange intramolecularly to form the desired 3'-amido derivative **17**. As expected, treatment of **6b** with phenylselenoxide, generated from diphenyl diselenide and sodium borohydride in EtOH,[16] afforded the desired allylic selenide **16b** exclusively in good yield. In the same way, the thymidine congener **16c** was prepared from 2'-deoxy-2'-methylidene-5'-*O*-trityl-5-methyluridine.[7]

Scheme 2[a]



[a]a) PhSeSePh, $NaBH_4$, EtOH, room temperature; b) NCS, *tert*-BuOC(O)NH_2, Et_3N, THF-MeOH (5 : 1), -78 °C to room temperature; c) TPSCl, DMAP, Et_3N, CH_3CN, then concentrated NH_4OH, room temperature; d) aqueous TFA, CH_2Cl_2; e) Ac_2O, pyridine, room temperature; f) NH_3/MeOH, room temperature

When **16b** was treated with NCS in the presence of *tert*-butylcarbamate and triethylamine in THF/MeOH, the desired 3'-*tert*-butoxycarbonylamino-2',3'-dideoxy-2'-methylidene derivative **17b** was isolated in 71% yield along with traces of **5**.[17] ^1H NMR spectrum of **17b** showed the presence of two vinylic protons at 5.44 and 5.51 ppm each as a broad singlet and a 3'-amide proton at 8.16 ppm as a broad singlet. The configuration at the 3'-position could not be identified at this stage due to low resolution of the protons at 3' and 4' positions in its spectrum. The protecting groups of **17b** were then removed with 98% aqueous trifluoroacetic acid (TFA), followed by treatment with Ac_2O in pyridine to afford the diacetate **18** in 55% yield from **17b**. ^1H NMR spectrum of **18** showed a proton signal at 5.04 ppm due to the 3'-proton coupled with the 4'-proton having a coupling constant of 8.3 Hz. This value is consistent with the *S*-configuration at the 3'-position. This would indicate that the [2,3]-sigmatropic rearrangement proceeded in a stereospecific mode from the intermediate **A** due to the sterically hindered effect of the uracil moiety. In a similar manner, the corresponding thymidine derivative **17c** was prepared from the allylic selenide **16c** by the [2,3]-sigmatropic rearrangement with 46% yield. Deprotection of both the trityl and *tert*-butoxycarbonyl groups in **17b** and **17c** by treating with 98% aqueous TFA afforded the target nucleosides **3b** and **3c** in good yields. The cytosine derivative **3a** was derived from the uracil congener **17b**: Successive treatments of **17b** with 2,4,6-triisopropylbenzenesulfonyl chloride (TSPCl) in the presence of DMAP in CH_3CN and concentrated NH_4OH afforded the cytosine derivative **17a** in 87% yield. Finally, deblocking of the

protecting groups of **17a** by aqueous TFA afforded (3'*S*)-3'-amino-2',3'-dideoxy-2'-methylidenecytidine (**3a**). For biological interest, the 3'-acetamide derivative **19** was also prepared in good yield by selective removal of the *O*-acetyl group of **18** with saturated methanolic ammonia.

The nucleosides newly synthesized, **3a**, **3b**, **3c**, and **19**, were evaluated *in vitro* for cytotoxic effects on proliferation of mouse leukemia L1210 cells and human oral epidermoid carcinoma KB cells. In contrast with the notable cytotoxic effects of DMDC, none of them, including **3a**, which have an amino group at the 3'-α–position in place of a hydroxyl group in DMDC, showed any significant antiproliferative activity against these tumor cells up to 100 μg/ml.[18] This may suggest that the presence of the allylic alcohol system, in which the 3'-hydroxyl group is substituted at the α-configuration, is essential for the cytotoxic effects of the 2'-methylidene nucleoside analogues.

Experimental Section

General methods. Melting points were measured on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Jeol JNM-FX 100 (100 MHz), Jeol JNM-GX 270 (270 MHz), and Jeol JNM EX-400 (400 MHz) with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were detected by addition of D_2O. UV spectra were recorded with a Simadzu UV-240 spectrophotometer. Low and high-resolution mass spectra were taken on a Jeol JMS HX-110 spectrometer. TLC was done on Merk Kieselgel F254 precoated plates. Silica gel for column chromatography was YMC gel 60 A (70-230 mesh). Unless otherwise indicated, all reactions were done under argon. THF was freshly distilled under argon from sodium/benzophenone before use. Dichloromethane, pyridine, and *N*, *N*-dimethylformamide were distilled from calcium hydride. Acetonitrile was distilled from phosphorous pentoxide.

2'-Deoxy-2'-methylidene-5'-*O*-trityluridine (5). A mixture of **4**[3a] (1.4 g, 6 mmol) and trityl chloride (2.0 g, 7.2 mmol) in dry pyridine (25 ml) was heated for 1 h at 100 °C. The mixture was cooled to room temperature and quenched with ice-water. The solvent was evaporated and coevaporated several times with toluene. The residue was partitioned between EtOAc and H_2O. The organic phase was dried (Na_2SO_4) and evaporated, and the residue was applied to a column of silica gel. The eluates with 1% EtOH in $CHCl_3$ were concentrated to leave **5** (2.4 g, 84% as a white solid which was crystallized from EtOH): mp 229.5 °C; MS *m/z* 482 (M^+); ^{1}H-NMR ($CDCl_3$) 8.57 (1 H, br s, H-N^3), 7.61 (1 H, d, H-6, $J_{5,6}$ = 8.1 Hz), 7.42-7.24 (15 H, m, trityl), 6.67 (1 H, d, H-1', J = 1.5 Hz), 5.56 (1 H, t, H-2"a, J = 2.2 Hz), 5.48 (1 H, t, H-2"b, J = 2.2 Hz), 5.41 (1 H, dd, H-5, $J_{5,6}$ = 8.1, J = 2.2 Hz), 4.81 (1 H, m, H-3'), 3.85 (1 H, ddd, H-4', $J_{3',4'}$ = 6.6, $J_{4',5'a}$ = 3.3, $J_{4',5'b}$ = 2.9 Hz), 3.60 (1 H, dd, H-5'a, $J_{4',5'a}$ = 3.3, J_{gem} = 11.0 Hz), 3.53 (1 H, dd, H-5'b, $J_{4',5'b}$ = 2.9, J_{gem} = 11.0 Hz), 2.00 (1 H, d, 3'-OH, J = 6.6 Hz). *Anal.* Calcd for $C_{29}H_{26}N_2O_5$: C, 72.19; H, 5.43; N, 5.81. Found: C, 72.04; H, 5.38; N, 6.02.

(3'*R*)-3'-*O*-Benzoyl-2'-deoxy-2'-methylidene-5'-*O*-trityluridine (7). a) Triethylamine (0.1 ml, 0.8 mmol) was added to a mixture of **5** (290 mg, 0.6 mmol) and MsCl (60 μl, 0.8 mmol) in CH_2Cl_2 (10 ml) at 0 °C. The mixture was stirred for 15 min at 0 °C and then ice-H_2O was added. The separated organic phase was washed with H_2O, dried (Na_2SO_4), and concentrated to dryness. The dried residue in DMF (10 ml) was

heated with NaOBz (340 mg, 2.36 mmol) for 24 h at 90 °C. The solvent was concentrated and the residue was partitioned between EtOAc and H_2O. The organic phase was concentrated and purified on a silica gel column to give **7** (190 mg, 54% as a white solid, crystallized from EtOH/hexane): FAB-MS *m/z* 587 (M^++1), 509 (M^+-Ph), 244 (M^+-trityl); ^{1}H-NMR ($CDCl_3$) 8.37 (1 H, br s, H-N^3), 7.78 (1 H, d, H-6, $J_{5,6}$ = 7.2 Hz), 7.43-7.15 (22 H, m, trityl, benzoyl), 6.67 (1 H, s, H-1'), 6.10 (1 H, d, H-3',$J_{3',4'}$ = 3.8 Hz), 5.61 (1 H, br d, H-2"a), 5.53 (1 H, br d, H-2"b), 5.41 (1 H, dd, H-5, $J_{5,6}$ = 7.2, J = 2.2 Hz), 4.39 (1 H, m, H-4'), 3.52 (1 H, dd, H-5'a, $J_{4',5'a}$ = 5.5, J_{gem} = 9.4 Hz), 3.51 (1 H, dd, H-5'b, $J_{4',5'b}$ = 4.9, J_{gem} = 9.4 Hz); FAB-HR-MS *m/z* calcd for $C_{36}H_{30}N_2O_6$ (M^++1): 587.2182. Found: 587.2151. b) A solution of diethyl azodicarboxylate (1.56 ml, 10.1 mmol) in THF (5 ml) was added to a mixture of **5** (2.44 g, 5.06 mmol), triphenylphosphine (2.64 g, 10.1 mmol), and benzoic acid (1.33 g, 10.1 mmol) in dry THF (40 ml). The mixture was stirred for 30 min at 0 °C and EtOH was added. The solvent was evaporated *in vacuo* and the residue was partitioned between EtOAc and H_2O. The separated organic layer was dried (Na_2SO_4), and purified on a silica gel column. The eluates with 40% EtOAc in hexane were concentrated to leave **7** (2.86 g, 96% as a solid).

(3'*R*)-2'-Deoxy-2'-methylidene-5'-*O*-trityluridine (8). To a solution of **7** (700 mg, 1.2 mmol) in EtOH (10 ml) was added 1% aqueous NaOH (6.6 ml, 1.7 mmol). The mixture was stirred for 1 h at room temperature and then neutralized with AcOH. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and H_2O. The separated organic phase was dried (Na_2SO_4) and purified on a silica gel column. The eluates with 1% EtOH in $CHCl_3$ were evaporated to afford **8** (430 mg, 74% as a white foam): FAB-MS *m/z* 483 (M^++1); ^{1}H-NMR ($CDCl_3$) 8.49 (1 H, br s, H-N^3), 7.67 (1 H, d, H-6, $J_{5,6}$ = 8.1 Hz), 7.52-7.23 (15 H, m, trityl), 6.52 (1 H, d, H-1', J = 3.4 Hz), 5.68 (1 H, br s, H-2"a), 5.61 (1 H, dd, H-5, $J_{5,6}$ = 8.1 Hz, J = 2.2 Hz), 5.42 (1 H, br s, H-2"b), 4.67 (1 H, dd, H-3', $J_{3',4'}$ = 4.0, $J_{3',OH}$ = 4.4 Hz), 4.10 (1 H, m, H-4'), 3.61 (1 H, dd, H-5'a, $J_{4',5'a}$ = 4.8, J_{gem} = 10.3 Hz), 3.51 (1 H, dd, H-5'b, $J_{4',5'b}$ = 5.5, J_{gem} = 10.3 Hz), 3.06 (1 H, d, 3'-OH, J = 4.4 Hz).

2'-Azidomethyl-2',3'-didehydro-2',3'-dideoxy-5'-*O*-trityluridine (10). a) Triethylamine (88 µl, 0.66 mmol) was added to a mixture of **5** (230 mg, 0.48 mmol), and MsCl (50 µl, 0.66 mmol) in CH_2Cl_2 (1 ml) at 0 °C. The mixture was stirred for 15 min at 0 °C and then ice-water was added. The separated organic phase was washed with H_2O, dried (Na_2SO_4), and concentrated to dryness. The dried residue in DMF (10 ml) was treated with NaN_3 (110 mg, 0.95 mmol) for 15 min at 0 °C. The solvent was concentrated and the residue was partitioned between EtOAc and H_2O. The organic phase was dried (Na_2SO_4), evaporated, and purified on a silica gel column to give **10** (228 mg, 94% as a colorless foam): IR ($CHCl_3$) υ_{N3} 2100 cm^{-1}; FAB-MS *m/z* 508 (M^++1); ^{1}H-NMR ($CDCl_3$) 8.43 (1 H, br s, H-N^3), 7.88 (1 H, d, H-6, $J_{5,6}$ = 8.1 Hz), 7.38-7.26 (15 H, m, trityl), 6.95 (1 H, br d, H-1'), 6.22 (1 H, dd, H-3', J = 1.1, J = 1.5 Hz), 5.02 (1 H, dd, H-5, $J_{5,6}$ = 8.1, J = 2.2 Hz), 4.96 (1 H, m, H-4'), 3.97 (1 H, d, H-2"a, J = 15.4 Hz), 3.83 (1 H, d, H-2"b, J = 15.4 Hz), 3.54 (1 H, dd, H-5'a, $J_{4',5'a}$ = 2.9, J_{gem} = 11.0 Hz), 3.51 (1 H, dd, H-5'b, $J_{4',5'b}$ = 2.6, J_{gem} = 11.0 Hz). b) A mixture of DEAD (0.3 ml, 2.2 mmol) and DPPA (0.5 ml, 2.2 mmol) in THF (3 ml) was added dropwise to a mixture of **5** (270 mg, 0.56 mmol) and triphenylphosphine (600 mg, 2.2 mmol) in THF (10 ml) at 0 °C. The mixture was stirred for 30 min at 0 °C and EtOH was added. The solvent was evaporated and the residue was purified on a silica gel column to give **10** (254 mg, 90% as a colorless foam). c) MsCl (65 µl, 0.4 mmol) was added to a solution of **8** (140 mg, 0.29 mmol) in dry pyridine (5 ml). After being stirred for 16 h at 0 °C, the

solvent was evaporated and coevaporated several times with toluene. The residue was partitioned between EtOAc and H_2O. The separated organic phase was dried (Na_2SO_4) and evaporated to dryness. The dried residue was dissolved in dry DMF (5 ml) was treated with NaN_3 (66 mg, 0.9 mmol) for 30 min at 0 °C. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and H_2O. The separated organic phase was dried (Na_2SO_4), concentrated, and purified on silica gel column to afford **10** (110 mg, 75% as a colorless foam). d) A mixture of DEAD (0.1 ml, 0.8 mmol) and DPPA (0.16 ml, 0.8 mmol) in THF (1 ml) was added dropwise to a solution of **8** (193 mg, 0.4 mmol) and triphenylphosphine (209 mg, 0.8 mmol) in THF (4 ml) at 0 °C. The mixture was stirred for 30 min and then EtOH was added to the mixture. The solvent was removed *in vacuo* and the resirue was purified on a silica gel column to afford **10** (174 mg, 86% as a colorless foam).

2',3'-Didehyro-2',3'-dideoxy-2'-phenylthiomthyl-5'-*O*-trityluridine (12). Triethylamine (0.2 ml, 1.5 mmol) was added to an ice-cooled solution of **5** (500 mg, 1.1 mmol) and MsCl (0.1 ml, 1.5 mmol) in dry THF (15 ml). The mixture was stirred for 1 h at 0 °C. The reaction was quenched with addition of ice-water and the mixture was partitioned between CH_2Cl_2 and H_2O. The separated organic phase was dried (Na_2SO_4) and evaporated to dryness. The dried residue containing **6b** in dry DMF (10 ml) was treated with thiophenol (0.16 ml, 1.6 mmol) and Et_3N (0.2 ml, 1.6 mmol) for 4 h at room temperature and then EtOH was added. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and H_2O. The organic phase was dried (Na_2SO_4), concentrated, and purified on a silica gel column. The eluates with $CHCl_3$ were concentrated to leave **12** (541 mg, 91% as a foam): FAB-MS *m/z* 575 (M^++1); ^{1}H-NMR ($CDCl_3$) 8.35 (1 H, br s, H-N^3), 7.82 (1 H, d, H-6, $J_{5,6}$ = 7.8 Hz), 7.46-7.18 (20 H, m, trityl, 2'-CH_2SPh), 7.00 (1 H, d, H-1', $J_{allylic}$ = 2.4 Hz), 6.02 (1 H, dd, H-3', $J_{3',4'}$ = 1.5, J = 2.9 Hz), 5.04 (1 H, dd, H-5, $J_{5,6}$ = 7.8, J = 2.4 Hz), 4.23 (1 H, br s, H-4'), 3.55 (1 H, d, 2"-CH_2, J_{gem} = 15.2 Hz), 3.41 (1 H, dd, H-5'a, $J_{4',5'a}$ = 3.4 , J_{gem} = 11.2 Hz), 3.36 (1 H, dd, H-5'b, $J_{4',5'b}$ = 2.9, J_{gem} = 11.2 Hz).

2',3'-Didehydro-2',3'-dideoxy-2'-iodomethyl-5'-*O*-trityluridine (13). A mixture of **5** (310 mg, 0.63 mmol), triphenylphosphine (510 mg, 1.93 mmol), and iodine (480 mg, 1.93 mmol) in DMF (5 ml) was stirred for 6 h at room temperature. The solvent was removed *in vacuo* and the residue in EtOAc was washed with aqueous $Na_2S_2O_3$ and H_2O. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified on a silica gel column to give **13** (350 mg, 95% as a white solid): FAB-MS *m/z* 593 (M^++1); ^{1}H-NMR ($CDCl_3$) 8.31 (1 H, br s, H-N^3), 7.92 (1 H, d, H-6, $J_{5,6}$ = 8.2 Hz), 7.38-7.24 (15 H, m, trityl), 7.03 (1 H, d, H-1', $J_{allylic}$ = 2.2 Hz), 6.26 (1 H, s, H-3'), 5.05 (1 H, dd, H-5, $J_{5,6}$ = 8.2, J = 2.2 Hz), 4.85 (1 H, br s, H-4'), 3.91 (1 H, d, 2"-CH_2I, J_{gem} = 10.4 Hz), 3.85 (1 H, d, 2"-CH_2I, J_{gem} = 10.4 Hz), 3.52 (1 H, dd, H-5'a, $J_{4',5'a}$ = 2.8, J_{gem} = 11.0 Hz), 3.46 (1 H, dd, H-5'b, $J_{4',5'b}$ = 3.3, J_{gem} = 11.0 Hz).

(3'*R*)-3'-*O*-*p*-Chlorophenyl-2'-deoxy-2'-methylidene-5'-*O*-trityluridine (15). A mixture of DEAD (55 µl, 0.34 mmol) and triphenylphosphine (90 mg, 0.34 mmol) in THF (1 ml) was added to a mixture of **14** (100 mg, 0.17 mmol) and *p*-chlorophenol (44 mg, 0.34 mmol) in THF (3 ml). The mixture was stirred for 20 min at room temperature and then EtOH was added. The solvent was evaporated *in vacuo* and the residue was treated in NH_3/MeOH (saturated at 0 °C, 3 ml) for 1 h at room temperature The solvent was evaporated and the residue was partitioned between EtOAc and H_2O. The organic phase was dried (Na_2SO_4), and evaporated. The residue was purified on a silica gel column to give **15** (67 mg, 66% as a colorless foam):

FAB-MS *m/z* 594 (M^++1); ^{1}H-NMR ($CDCl_3$) 8.47 (1 H, br s, H-N^3), 7.56 (1 H, d, H-6, $J_{5,6}$ = 8.2 Hz), 7.40-7.19 (17 H, m, trityl, 3'-*O*-*p*-chlorophenyl), 6.77 (2 H, m, 3'-*O*-*p*-chlorophenyl), 6.64 (1 H, br s, H-1'), 5.62 (1 H, d, H-5, $J_{5,6}$ = 8.2 Hz), 5.54 (2 H, br s, H-2"a, 2"b), 5.12 (1 H, d, H-3', $J_{3',4'}$ = 3.8 Hz), 4.32 (1 H, ddd, H-4', $J_{3',4'}$ = 3.8, $J_{4',5'a}$ = 6.1, $J_{4',5'b}$ = 5.5 Hz), 3.59 (1 H, dd, H-5'a, $J_{4',5'a}$ = 6.1, J_{gem} = 9.9 Hz), 3.49 (1 H, dd, H-5'b, $J_{4',5'b}$ = 5.5, J_{gem} = 9.9 Hz); FAB-HR-MS *m/z* calcd for $C_{35}H_{29}ClN_2O_5$ (M^++1): 593.1843. Found; 593.1880.

2',3'-Didehydro-2',3'-dideoxy-2'-phenylselenomethyl-5'-*O*-trityluridine (16b). Triethylamine (0.6 ml, 4.2 mmol) was added to an ice-cooled solution of **5** (1.3 g, 2.8 mmol) and MsCl (0.3 ml, 4.2 mmol) in dry THF (20 ml). The mixture was stirred for 1 h at 0 °C and then ice-water was added. The whole was partitioned between CH_2Cl_2 and H_2O. The organic phase was dried (Na_2SO_4), and the solvent was evaporated to dryness. The dried residue was dissolved in absolute EtOH (10 ml) and was added dropwise to a solution of NaSePh in absolute EtOH [$NaBH_4$ (110 mg, 3.3 mmol) was added to a solution of PhSeSePh (410 mg, 3.6 mmol) in freshly dist. EtOH (15 ml)]. The mixture was stirred for 4 h at room temperature. The solvent was evaporated *in vacuo* and the residue was purified on a flash silica gel column. The eluates with 1% EtOH in $CHCl_3$ were evaporated to leave **16a** (1.6 g, 96% as a colorless foam): FAB-MS *m/z* 623 (M^++1); ^{1}H-NMR ($CDCl_3$) 8.42 (1 H, br s, H-N^3), 7.81 (1 H, d, H-6, $J_{5,6}$ = 8.1 Hz), 7.50-7.22 (20 H, m, trityl, CH_2SePh), 7.04 (1 H, d, H-1', $J_{allylic}$ = 2.2 Hz), 5.83 (1 H, br s, H-3'), 5.04 (1 H, dd, H-5, $J_{5,6}$ = 8.1 Hz, J = 2.2 Hz), 4.79 (1H, m, H-4'), 3.61 (1 H, d, 2"-CH_2SePh, J_{gem} = 13.2 Hz), 3.42 (3 H, m, 2"-CH_2SePh, H-5'a,b, $J_{4',5'a}$ = 2.9, $J_{4',5'b}$ = 4.8, $J_{5'a,5'b}$ = 11.2 Hz).

2',3'-Didehydro-2',3'-dideoxy-2'-phenylselenomethyl-5'-*O*-trityl-5-methyluridine (16c). Triethylamine (0.9 ml, 6.2 mmol) was added to an ice-cooled solution of 2'-deoxy-2'-methylidene-5'-*O*-trityl-5-methyluridine[7] (2.2 g, 4.5 mmol) and MsCl (0.9 ml, 6.2 mmol) in dry THF (20 ml). The mixture was stirred for 20 min at 0 °C and then ice-water was added. The mixture was partitioned between CH_2Cl_2 and H_2O. The separated organic phase was dried (Na_2SO_4) and concentrated. A solution of the dried residue in EtOH was added to a solution of NaSePh [prepared from a mixture of PhSeSePh (1.67 g, 5.35 mmol) and $NaBH_4$ (0.4 g, 10.7 mmol) in EtOH (30 ml)]. The mixture was stirred for 30 min at room temperature and the solvent was removed *in vacuo*. The residue was purified on a silica gel column to give **16c** (2.37 g, 84% as a pale yellow foam): MS *m/z* 636 (M^++1); ^{1}H-NMR ($CDCl_3$) 8.19 (1 H, br s, H-N^3), 7.48-7.22 (21 H, m, trityl, 2'-CH_2SePh, H-6), 7.04 (1 H, dd, H-1', J = 2.2, J = 3.9 Hz), 5.90 (1 H, br s, H-3'), 4.84 (1 H, m, H-4'), 3.62 (1 H, d, 2'-CH_2SePh, J_{gem} = 13.7 Hz), 3.43 (1 H, d, 2'-CH_2SePh, J_{gem} = 13.7 Hz), 3.34 (1 H, dd, H-5'a, $J_{4',5'a}$ = 2.9, J_{gem} = 10.7 Hz), 3.26 (1 H, dd, H-5'b, $J_{4',5'b}$ = 4.4, J_{gem} = 10.7 Hz), 1.59 (3 H, d, 5-CH_3, J = 1.5 Hz).

(3'*S*)-3'-*tert*-Butoxycarbonylamino-2',3'-dideoxy-2'-methylidene-5'-*O*-trityluridine (17b). A solution of NCS (1.2 g, 3.5 mmol) in dry THF (10 ml) was added to a mixture of **16b** (2.2 g, 3.6 mmol), *tert*-butylcarbamate (1.05 g, 9 mmol), and Et_3N (1.25 ml, 9 mmol) in a mixture of THF and MeOH (5 : 1, 15 ml) at -78 °C under Ar. The mixture was warmed gradually to room temperature and after being stirred for 3 h, the solvent was concentrated *in vacuo*. The residue was purified on a silica gel column. The eluates with 35% EtOAc in hexane were evaporated to leave **17b** (1.5 g, 73% as a foam): FAB-MS *m/z* 582 (M^++1), 524 (M^+-*t*-Bu); ^{1}H-NMR ($CDCl_3$) 8.49 (1 H, br s, H-N^3), 8.16 (1 H, s, 3'-NH), 7.72 (1 H, d, H-6, $J_{5,6}$ = 8.3 Hz),

7.46-7.23 (15 H, m, trityl), 6.62 (1 H, d, H-1', J = 1.5 Hz), 5.51 (1 H, br s, H-2"a), 5.44 (1 H, br s, H-2"b), 5.29 (1 H, d, H-5, $J_{5,6}$ = 8.3 Hz), 5.13 (1 H, m, H-3'), 3.73 (1 H, m, H-4'), 3.54 (1 H, dd, H-5'a, $J_{4',5'a}$ = 2.4, J_{gem} = 10.7 Hz), 3.46 (1 H, d, H-5'b, J_{gem} = 10.7 Hz), 1.45 (9 H, s, *t*-Bu).

(3'*S*)-3'-*tert*-Butoxycarbonylamino-2',3'-dideoxy-2'-methylidene-5'-*O*-trityl-5-methyluridine (17c). A solution of NCS (1.14 g, 8.5 mmol) in dry THF (10 ml) was added to an ice-cooled mixture of **16c** (2.2 g, 3.5 mmol), Et_3N (2.4 ml, 17.1 mmol), and *t*-butylcarbamate (1.0 g, 8.5 mmol) in THF-MeOH (5:1, 15 ml) at -78 °C under Ar. The mixture was stirred for 4 h at room temperature and the solvent was evaporated. The residue was purified on a silica gel column to give **17c** (970 mg, 47%) and **5c** (579 mg, 34%). Physical data for **17c**: FAB-MS *m/z* 596 (M^++1); ^{1}H-NMR ($CDCl_3$) 8.52 (1 H, br s, H-N^3), 8.26 (1 H, br s , 3'-H), 7.47-7.21 (16 H, m, trityl and H-6), 6.65 (1 H, d, H-1', J = 2.0 Hz), 5.46 (1 H, br s, H-2"a), 5.41 (1 H, br s, H-2"b), 4.99 (1 H, m, H-3'), 3.73 (1 H, m, H-4'), 3.74 (1 H, d, H-5'a, J_{gem} = 10.7 Hz), 3.49 (1 H, d, H-5'b, $J_{4',5'b}$ = 3.4, J_{gem} = 10.7 Hz), 1.58 (3 H, s, 5-CH_3), 1.42 (9 H, s, *t*-Bu); FAB-HR-MS *m/z* calcd for $C_{35}H_{38}N_3O_6$ (M^++1): 596.2760. Found: 596.2733.

(3'*S*)-3'-*tert*-Butoxycarbonylamino-2',3'-dideoxy-2'-methylidene-5'-*O*-tritylcytidine (17a). Triethylamine (0.8 ml, 6.0 mmol) was added to an ice-cooled solution of **17b** (1.0 g, 1.7 mmol), TPSCl (1.8g, 6.0 mmol), and DMAP (8.4 mg) in CH_3CN (25 ml) under Ar. The mixture was stirred for 8 h at room temperature and then concentrated NH_4OH (28%, 10 ml) was added. The mixture was stirred for a further 4 h. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and H_2O. The organic phase was washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was purified on a silica gel column. The eluates with 5% EtOH in $CHCl_3$ were evaporated to leave **17a** (0.9 g, 90%, crystallized from EtOAc/hexane): mp > 260 °C (dec.); FAB-MS *m/z* 581 (M^++1), UV λ max (MeOH) 277 nm, (acidic) 284 nm; ^{1}H-NMR ($CDCl_3$) 7.58 (1 H, d, H-6, J = 7.3 Hz), 7.39-7.20 (18 H, m, trityl, 4-NH_2, 3'-NH), 6.52 (1 H, s, H-1'), 5.67 (1 H, d, H-5, $J_{5,6}$ = 7.3 Hz), 5.19 (1 H, br s, H-2"a), 5.15 (1 H, br s, H-2"b), 4.76 (1 H, m, H-3'), 3.86 (1 H, m, H-4'), 3.21 (2 H, m, H-5'a, H-5'b), 1.37 (9 H, s, *t*-Bu). *Anal.* Calcd for $C_{34}H_{36}N_4O_5$·0.5 H_2O C; 69.25, H; 6.32, N;9.50. Found: C; 69.64, H; 6.25, N; 9.52.

(3'*S*)-3'-Amino-2',3'-dideoxy-2'-methylidenecytidine Hydrochloride (3a). Aqueous 98% TFA (3 ml) was added to a solution of **17a** (185 mg, 0.32 mmol) in CH_2Cl_2 (3 ml) at 0 °C. The mixture was stirred for 2 h at 0 °C. The solvent was evaporated and coevaporated several times with EtOH. The residue was dissolved in EtOH and neutralized with 1 N NaOH. The solvent was evaporated and the residue was applied to a Dowex 50 (H^+) column. The eluates with 1 N NH_4OH were evaporated to leave **3a** (70 mg, 92% as a solid). A part of the solid was dissolved in EtOH and treated with 1 N HCl. After evaporation of the solvent, a white solid came out which was crystallized from EtOH/H_2O: mp >120 °C (dec); UV λ max (MeOH) 270 nm, (acidic) 276 nm; ^{1}H-NMR (DMSO-d_6) 8.84 (3 H, br s, 3'-NH_3^+), 8.68 (1 H, br s, 4-NH_2), 8.12 (1 H, br s, 4-NH_2), 7.74 (1 H, d, H-6, J = 7.8 Hz), 6.62 (1 H, s, H-1'), 6.01 (1H, br d, H-5, $J_{5,6}$ = 7.3 Hz), 5.87 (1 H, br s, H-2"a), 5.42 (1 H, br s, H-2"b), 5.19 (1 H, br s, 5'-OH), 4.32 (1 H, m, H-3'), 4.08 (1 H, m, H-4'), 3.72 (2 H, m, H-5'a, 5'b); *Anal.* Calcd. for $C_{10}H_{14}N_4O_3$·1.5 HCl·0.7 H_2O: C; 39.31, H; 5.57, N; 18.33. Found: C; 39.42, H; 5.31, N; 18.26.

(3'*S*)-3'-Amino-2',3'-dideoxy-2'-methylideneuridine (3b). Aqueous 98% TFA (5 ml) was added to a solution of **17b** (200 mg, 0.34 mmol) in CH_2Cl_2 (5 ml) at 0 °C. After the mixture was stirred for 20 min at 0

°C, the solvent was evaporated and coevaporated several times with EtOH. The residue was purified by a silica gel column. The eluates with 8% MeOH in $CHCl_3$ were evaporated to leave **3b** (113 mg, 93% as a trifluroacetate). A part of the salt was neutralized with Et_3N, and re-purified on a silica gel column to give a salt-free **3b**: mp 145 °C; UV λ_{max} (MeOH) 261 nm, (acidic) 266 nm; FAB-MS *m/z* 240 (M^++1), ^{1}H-NMR (DMSO-d_6) 7.53 (1 H, d, H-6, $J_{5,6}$ = 7.8 Hz), 6.40 (1 H, s, H-1'), 5.61 (1 H, d, H-5, $J_{5,6}$ = 7.8 Hz), 5.37 (1 H, br s, H-2"a), 5.22 (1 H, br s, H-2"b), 4.91 (1 H, br s, 5'-OH), 3.72 (1 H, dd, H-5'a, $J_{4',5'a}$ = 3.8, J_{gem} = 12.2 Hz), 3.64 (1 H, m, H-3'), 3.58 (1 H, dd, H-5'b, $J_{4',5'b}$ = 3.9, J_{gem} = 12.2 Hz), 3.47 (1 H, m, H-4'), 3.32 (2 H, br d, 3'-NH_2). *Anal.* Calcd for $C_{10}H_{13}N_3O_4$: C, 50.21, H, 5.48, N, 17.56. Found: C, 50.28, H, 5.57, N, 17.43.

(3'*S*)-3'-Amino-2',3'-dideoxy-2'-methylidene-5-methyluridine (3c). Aqueous 98% TFA (5 ml) was added to a solution of **17c** (0.47 g, 0.8 mmol) in CH_2Cl_2 (5 ml) at 0 °C. The mixture was stirred for 20 min at 0 °C. The solvent was evaporated and coevaporated several times with EtOH. The residue was dissolved in EtOH and neutralized with 0.1 N NaOH. The solvent was evaporated and the residue was purified on a silica gel column to give **3c** (145 mg, as a foam): FAB-MS *m/z* 254 (M^++1); ^{1}H-NMR (DMSO-d_6 + D_2O) 7.40 (1 H, d, H-6, J = 1.1 Hz), 6.56 (1 H, s, H-1'), 5.81 (1 H, br s, H-2"a), 5.40 (1 H, br s, H-2"b), 4.31 (1 H, m, H-3'), 4.04 (1 H, m, H-4'), 3.86 (2 H, m, H-5'a, 5'b, J_{gem} = 12.0 Hz), 1.58 (3 H, s, 5-CH_3); FAB-HR-MS *m/z* calcd for $C_{11}H_{15}N_3O_4$ (M^++1): 254.1141. Found: 254.1137.

(3'*S*)-3'-Acetylamino-5'-*O*-acetyl-2',3'-dideoxy-2'-methylideneuridine (18). Aqueous 98% TFA (5 ml) was added to a solution of **17b** (250 mg, 0.43 mmol) in CH_2Cl_2 (5 ml) at 0°C. The mixture was stirred for 30 min at room temperature. The solvent was evaporated and coevaporated several times with pyridine. Ac_2O (0.16 ml, 1.72 mmol) was added to a solution of the residue in pyridine (10 ml). The mixture was stirred for 2 h at room temperature and then EtOH was added. The solvent was evaporated and coevaporated several times with toluene. The residue was purified on silica gel column and the eluates with 3% EtOH in $CHCl_3$ were evaporated to leave **18** (76 mg, 55% as a white solid): FAB-MS *m/z* 324 (M^++1); ^{1}H-NMR ($CDCl_3$) 9.42 (1 H, br s, H-N^3), 7.28 (1 H, d, H-6, $J_{5,6}$ = 8.3 Hz), 6.65 (1 H, d, H-1', J = 2.0 Hz), 6.14 (1 H, d, 3'-H, J = 8.8 Hz), 5.79 (1 H, dd, H-5, $J_{5,6}$ = 8.3, J = 1.0 Hz), 5.47 (1 H, br s, H-2"a), 5.38 (1 H, br s, H-2"b), 5.04 (1 H, ddd, H-3', $J_{3',NH}$ = 8.8, $J_{3',4'}$ = 8.3, J = 2.9 Hz), 4.47 (1 H, dd, H-5'a, $J_{4',5'a}$ = 2.4, J_{gem} = 12.2 Hz), 4.24 (1 H, dd, H-5'b, $J_{4',5'b}$ = 5.4, J_{gem} = 12.2 Hz), 3.95 (1 H, ddd, H-4', $J_{4',5'a}$ = 2.4, $J_{4',5'b}$ = 5.4, $J_{3',4'}$ = 8.3 Hz), 2.10 (3 H, s, 5'-Ac), 2.08 (3 H, s, 3'-Ac).

(3'*S*)-3'-Acetylamino-2',3'-dideoxy-2'-methylideneuridine (19). Compound **18** (149 mg, 0.46 mmol) was treated with NH_3/MeOH (saturated at 0 °C, 3 ml) for 5 days at room temperature. The solvent was evaporated and the residue was crystallized from EtOH to give **19** (105 mg, 81%): mp 217 °C, MS *m/z* 282 (M^++1), ^{1}H-NMR (DMSO-d_6) 11.37 (1 H, br s, H-N^3), 8.21 (1 H, br d, 3'-NH, J = 8.3 Hz), 7.60 (1 H, d, H-6, $J_{5,6}$ = 7.8 Hz), 6.46 (1 H, br d, H-1'), 5.64 (1 H, dd, H-5, $J_{5,6}$ = 8.3, J = 2 Hz), 5.25 (1 H, br s, H-2"a), 5.22 (1 H, br s, H-2"b), 4.97 (1 H, br s, 5'-OH), 4.83 (1 H, ddd, H-3', $J_{3',NH}$ = 8.3, $J_{3',4'}$ = 7.8, J = 2.0 Hz), 3.73 (1 H, ddd, H-4', $J_{4',5'a}$ = 2.4, $J_{4',5'b}$ = 4.4, $J_{3',4'}$ = 7.8 Hz), 3.62 (1 H, d, H-5'a, J_{gem} = 12.2 Hz), 3.51 (1 H, dd, H-5'b, $J_{4',5'b}$ = 4.4, J_{gem} = 12.2 Hz), 1.88 (3 H, s, 3'-Ac). *Anal.* Calcd. for $C_{12}H_{15}N_3O_5$: C; 51.24, H; 5.38, N; 14.94. Found: C; 50.90; H, 5.38; N, 14.69.

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18. The cytotoxic test against tumor cells was done by Dr. T. Sasaki at Kanazawa University, to whom our thanks are due.

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