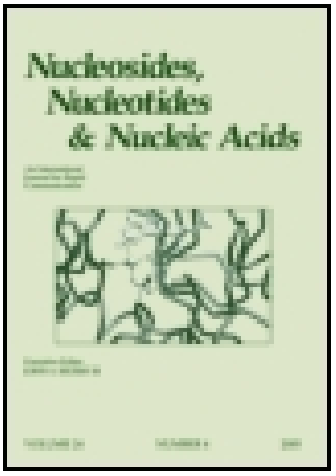

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Nucleosides and Nucleotides. 125. Synthesis and Biological Evaluation of 2′,3′-Dideoxy-3′-fluoro-2′-methylidene Pyrimidine Nucleosides

Abdalla Elsayed A. Hassan [a] , Satoshi Shuto [a] & Akira Matsuda [a]
[a] Faculty of Pharmaceutical Sciences Hokkaido University , Kita-12, Nishi-6, Kita-ku, Sapporo, 060, Japan
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NUCLEOSIDES AND NUCLEOTIDES. 125. SYNTHESIS AND BIOLOGICAL EVALUATION OF 2',3'-DIDEOXY-3'-FLUORO-2'-METHYLIDENE PYRIMIDINE NUCLEOSIDES#,1

Abdalla Elsayed A. HASSAN, Satoshi SHUTO, and Akira MATSUDA*
Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan.

Abstract: Reaction of 2'-deoxy-2'-methylidene-5'-*O*-trityluridine (**1**) with diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 resulted in the formation of a mixture of (3'*R*)-2',3'-dideoxy-3'-fluoro-2'-methylidene derivative **3** and 2',3'-didehydro-2',3'-dideoxy-2'-fluoromethyl derivative **4** (**3**:**4** = 1:1.5) in 65% yield. A similar treatment of 1-(2-deoxy-2-methylidene-5-*O*-trityl-β-D-*threo*-pentofuranosyl)uracil (**19**) with DAST in CH_2Cl_2 afforded (3'*S*)-2',3'-dideoxy-3'-fluoro-2'-methylidene derivatives **20** and **4** in 38% and 17% yields respectively. Transformation of the uracil nucleosides **4**, **12**, and **20** into cytosines followed by deprotection furnished the corresponding cytidine derivatives **29**, **18**, and **25**, respectively. The corresponding thymidine congener **27** was also synthesized in a similar manner. All of the newly synthesized nucleosides were evaluated for their inhibitory activities against HIV and for their antiproliferative activities against L1210 and KB cells.

INTRODUCTION

Various nucleoside analogues have been synthesized and their activities against human immunodeficiency virus (HIV) have been reported.[2] One of the most potent anti-HIV agents has been reported thus far is 3'-deoxy-3'-fluorothymidine[3] (FLT) the 5'-triphosphate of which acts as a selective inhibitor of HIV-reverse transcriptase (HIV-RT), like 3'-azido-3'-deoxythymidine (AZT). Although the 5'-triphosphate of FLT inhibits HIV-RT more effectively than does that of AZT,[4] the chemotherapeutic index of the former is smaller than that of AZT.[5]

On the other hand, we have been engaged in the synthesis of 2'-substituted nucleoside analogues as potential antitumor and/or antiviral agents.[6] During these studies, we found that 2'-deoxy-2'-methylidenecytidine (DMDC) showed potent antineoplastic

#This paper is dedicated to the memory of Professor Roland K. Robins who passed away in the summer of 1992.

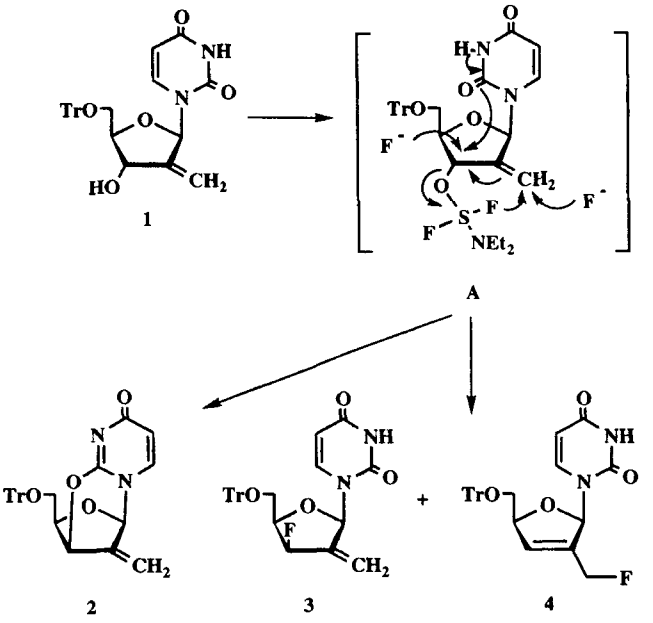
activities against human tumor cells *in vitro* as well as *in vivo*.[7-9] Moreover, we found that certain 5-substituted 2'-deoxy-2'-methylidene pyrimidine nucleosides showed potent antiviral activities against herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), varicella zoster virus (VZV), and human cytomegalovirus (HCMV).[10]

With the aim to attempt to reduce the cytotoxic effects of FLT and DMDC, both features of the 3'-fluoro substituent and the 2'-methylidene substituent are combined together thus affording (3'*R* and *S*)-2',3'-dideoxy-3'-fluoro-2'-methylidene pyrimidine nucleosides, which could be obtained from the corresponding 5'-protected 2'-deoxy-2'-methylidene pyrimidine nucleosides with reactions with diethylaminosulfur trifluoride (DAST).

Results and Discussion

We have observed that the exocyclic allylic alcohol system in the 2'-deoxy-2'-methylidene derivative **1** or **19** reacted with softer nucleophiles such as selenoate, thioate, iodide, and azide anions in an SN2' manner producing 2'-substituted methyl-2',3'-didehydro-2',3'-dideoxy nucleosides predominantly, while they reacted with hard oxygen nucleophiles (benzoate and phenoxide anions) in an SN2 manner affording 3'-substituted 2'-deoxy-2'-methylidene nucleosides.[1,11] These observations suggested that a hard fluoride anion would give the corresponding SN2 product **3**.

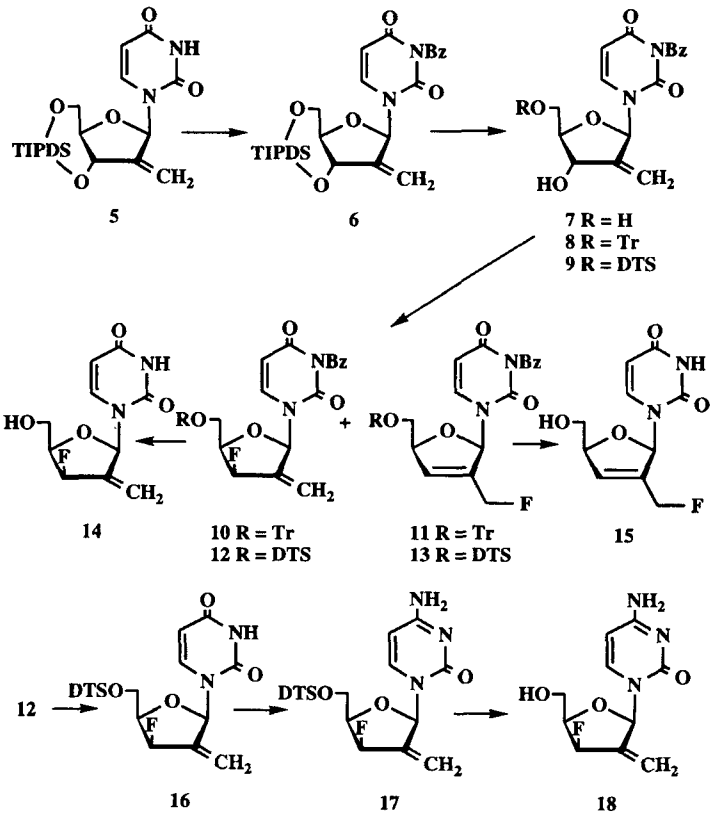
When **1** was treated with DAST in CH_2Cl_2 at -78 °C, a mixture of two products was obtained in 65% yield, in a ratio of 1 : 1.5 (measured by the integration ratio in the ^{1}H-NMR spectrum) (Scheme 1). The less polar product was assigned as (3'*R*)-2',3'-dideoxy-3'-fluoro-2'-methylidene derivative **3** as two vinylic protons corresponding to H-2" at 5.90 ppm and one proton attached to a carbon bearing fluorine due to H-3' at 5.32 ppm ($J_{3',F}$ = 56.1 Hz) appeared in the ^{1}H-NMR spectrum of the mixture. The more polar product, which is the major product, was assigned as 2',3'-didehydro-2',3'-dideoxy-2'-fluoromethyl derivative **4** as the ^{1}H-NMR spectrum of the mixture showed one vinylic proton due to H-3' at 6.25 ppm, and two methylene protons due to 2'-CH_2F at 5.02 and 4.90 ppm with a geminal coupling constant of 12.5 Hz and a characteristic proton-fluorine coupling constant of 46.5 Hz. It was expected that the fluoride anion from DAST would react with the allylic alcohol system of **1** in a similar manner to the reaction with the hard oxygen nucleophile producing predominantly the SN2 product **3**. The formation of 2',3'-unsaturated nucleoside **4** may occur *via* an SNi' mechanism involving an intramolecular fluorine transfer from an intermediate **A** as depicted in Scheme 1. Whether the reaction of **1** with DAST proceeded *via* a mixed SN2 and SNi' or a mixed SN2 and SN2' remains undetermined.



Scheme 1

In attempts to increase the ratio of the desired 3'-fluoro derivative **3** several solvents were examined, but the use of a polar solvent such as diglyme increased the ratio of **4** to **3** (**3** : **4** = 1 : 5.5, 52% yield). Moreover, when the above reaction was carried out in CH_3CN, only the O^2,3'-anhydro derivative **2** was isolated in 83% yield.[12] Therefore, to prevent the intramolecular nucleophilic attack of the 2-carbonyl group on the 3'-position of the sugar moiety, the N^3-sition of the uracil moiety was protected with a benzoyl group.[6f] N^3-Benzoylation of 1-[2-deoxy-2-methylidene-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)]uracil (**5**), followed by de-*O* -silylation with TBAF in THF, then selective protection of the 5'-hydroxyl group with a trityl or a dimethylthexylsilyl group afforded **8** and **9**, respectively (Scheme 2). Treatment of **8** with DAST in CH_2Cl_2 at -78 °C gave a mixture of the desired (3'*R*)-3'-fluoro derivative **10** and the 2',3'-unsaturated derivative **11** in a ratio of 1 : 3.5 in 67% yield. On treatment of **9** with DAST under similar conditions, an easily separable mixture of (3'*R*)-3'-fluoro derivative **12** and 2',3'-unsaturated derivative **13** was obtained in 29% and 27% yields, respectively. In both cases, the chemical yields and the product ratio were not improved.

Deprotection of **12** and **13** with TBAF in THF, followed by saturated methanolic ammonia afforded **14** and **15**, respectively. The *R* configuration of the introduced

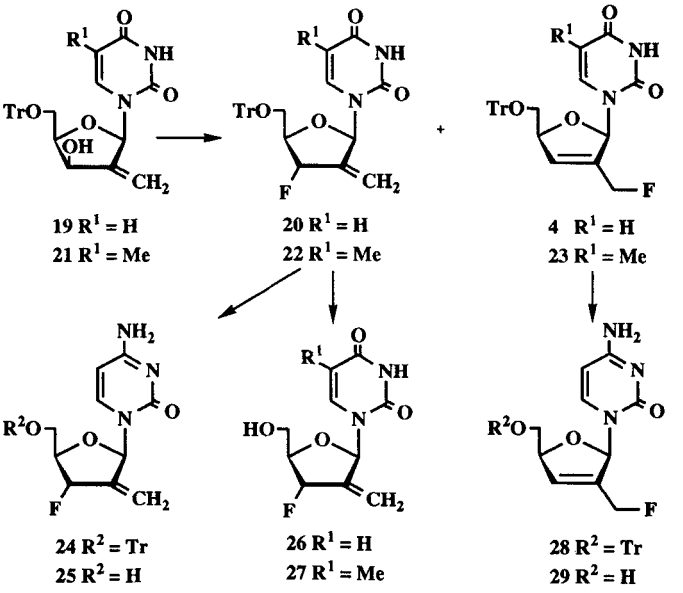


Scheme 2

fluorine atom in **14** was established on the basis of coupling constants between the 3'-H and the 4'-H of 2.7 Hz in the ^{1}H-NMR spectrum.

De-N^3-benzoylation of **12** with methanolic ammonia afforded **16**. Treatment of **16** with 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl) and triethylamine in the presence of 4-methylaminopyridine (DMAP) in CH_3CN, followed by concentrated NH_4OH afforded **17**. Finally the silyl protecting group of **17** was removed using TBAF in THF to afford the cytidine derivative **18**.

Introduction of a fluorine atom with the *S* configuration at the 3'-position of the allyl alcohol derivatives **19** was next examined. Treatment of **19**[1] with DAST in CH_2Cl_2 at room temperature afforded a separable mixture of (3'*S*)-2',3'-dideoxy-3'-fluoro-2'-methylidene derivative **20** and **4** in 38% and 17% yields, respectively (Scheme 3).



Scheme 3

Deprotection of **20** with TFA at 0 °C furnished **26** in 86% yield. In a similar manner, the thymidine derivative **21** was treated with DAST in CH_2Cl_2 to afford a separable mixture of **22** (52%) and **23** (28%). The cytidine derivatives **24** and **28** were also prepared from the uridine derivative **20** and **4** in 72% and 95% yields in an analogy to the method used above. Finally, the fluorinated nucleosides **20**, **22**, **24**, and **28** were deprotected with aqueous trifluoroacetic acid to give the corresponding free nucleoside **26**, **27**, **25**, and **29**, respectively.

The *S* configuration of the introduced fluorine atom in **26** and **27** was confirmed again on the basis of the observed coupling constants in the ^{1}H-NMR [(**26**; $J_{3',4'}$ = 7.7, $J_{F,3'}$ = 54.9 Hz) and (**27**; $J_{3',4'}$ = 7.7, $J_{F,3'}$ = 56.6 Hz)].

Cytotoxicity of **14**, **15**, **18**, **25**, **26**, **27**, and **29** against mouse leukemia L1210 and human oral epidermoid carcinoma KB cells *in vitro* was examined.[13] None of these nucleosides showed any significant cytotoxicity up to 100 μg/ml. None of these nucleosides showed substantial anti-HIV activity.[14]

Experimental Section

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) spectrometer with tetramethylsilane as the 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. The silica gel and the neutralized silica gel for column chromatography was YMC gel 60 A (70-230 mesh) and ICN silica 60A (ICN biochemicals, Germany), respectively. Unless otherwise indicated, all reactions were done under argon. THF was freshly distilled under argon from sodium/benzophenone before use. Dichloromethane was distilled from calcium hydride. Acetonitrile was distilled from phosphorous pentoxide.

(3'*R*)-2',3'-Dideoxy-3'-fluoro-2'-methylidene-5'-*O*-trityluridine (3) and 2',3'-didehydro-2',3'-dideoxy-2'-fluoromethyl-5'-*O*-trityluridine (4). a) DAST (31 µl, 0.24 mmol) in CH_2Cl_2 (1 ml) was added to a solution of **1**[1] (110 mg, 0.2 mmol) in CH_2Cl_2 (4 ml) at -78 °C. The mixture was stirred for 5.5 h at room temperature and then aqueous 5% $NaHCO_3$ was added to the mixture. The organic phase was separated, washed with H_2O, and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was chromatographed on a silica gel column to afford a mixture of **3** and **4** (71 mg, 65% in a ratio of 1 : 1.5). Physical data for the mixture **3** and **4**: MS *m/z* 485 (M^++1); ^{1}H-NMR ($CDCl_3$) compound **3**: 8.50 (1 H, br s, H-N^3), 7.82-7.22 (16 H, m, 5'-*O*-trityl and H-6), 6.67 (1 H, dd, H-1', J = 2, J = 4.4 Hz), 5.90 (1 H, d, H-5, $J_{5,6}$ = 7.7 Hz), 5.68 (2 H, m, H-2"a, b), 5.32 (1 H, dd, H-3', $J_{3',F}$ = 56.1, $J_{3',4'}$ = 2.9 Hz), 4.12 (1 H, m, H-4'), 3.51 (2 H, m, H-5'a, b). Compound **4**: 8.39 (1 H, br s, H-N^3), 7.51 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 7.38-7.24 (15 H, m, 5'-*O*-trityl), 7.01 (1 H, br s, H-1'), 6.25 (1 H, dd, H-3', $J_{3',F}$ = 3.7, $J_{3',4'}$ = 1.5 Hz), 5.04 (1 H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 2.2 Hz), 5.02 (1 H, dd , 2'-CH_2F, J_{gem} = 12.5, $J_{2',F}$ = 46.5 Hz), 4.95 (1 H, m, H-4'), 4.90 (1 H, dd , 2'-CH_2F, J_{gem} = 12.5, $J_{2',F}$ = 46.5 Hz), 3.54 (1 H, dd, H-5'a, $J_{4',5'a}$ = 3.3, J_{gem} = 11.4 Hz), 3.48 (1 H, dd, H-5'b, $J_{4',5'b}$ = 2.9, J_{gem} = 11.4 Hz). b) DAST (16 µl, 0.12 mmol) was added to a solution of **1** (56 mg, 0.12 mmol) in diglyme (2 ml) at -60 °C. The mixture was stirred for 10 min and then warmed to room temperature. Aqueous 5% $NaHCO_3$ was added to the mixture and the whole was concentrated to dryness. The residue was purified on a silica gel column to give a mixture of **3** and **4** (25 mg, 52% in a ratio of 1:5.5).

***O*^{2},3'-Anhydro-2'-deoxy-2'-methylidene-5'-*O*-trityluridine (2).** DAST (16 µl, 0.12 mmol) was added to a suspension of **1** (53 mg, 0.11 mmol) in CH_3CN (2 ml) at -10 °C. The mixture was stirred for 5 min and warmed to room temperature. The

solvent was removed and the residue was purified on a silica gel column to give **2** (43 mg, 83% as a white solid): UV λ_{max} (MeOH) 250 nm shoulder, (Acidic) 257 nm, (Basic), 267 nm; FAB-MS *m/z* 465 (M^++1); ^{1}H-NMR (DMSO-d_6, 270 MHz) 7.70 (1 H, d, H-6, $J_{6,5}$ = 7.7 Hz), 7.38-7.22 (15 H, m, 5'-*O*-trityl), 6.20 (1 H, br s, H-1'), 5.80 (1 H, d, H-5, $J_{5,6}$ = 7.7 Hz), 5.69 (1 H, br s, H-2"a), 5.68 (1 H, br s, H-2"b), 5.60 (1 H, d, H-3', $J_{3',4'}$ = 2.2 Hz), 4.36 (1 H, m, H-4'), 3.12 (2 H, m, H-5'a,b). HR-FAB Calcd for $C_{29}H_{24}N_2O_4$ (M^++1); 465.1736. Found; 465.1784.

***N*^{3}-Benzoyl-2'-deoxy-2'-methylidene-3',5'-*O*-(tetraisopropyldisiloxane-1,3-diyl)uridine (6).** Triethylamine (0.4 ml, 2.8 mmol) was added to a mixture of **5**[6e] (900 mg, 1.9 mmol) and benzoyl chloride (0.3 ml, 2.8 mmol) in CH_2Cl_2 (10 ml) at 0 ° C. The mixture was stirred for 20 h at room temperature and then ice-water was added. The separated organic phase was washed with H_2O and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified on a silica gel column to give **6** (940 mg, 86% as a colorless foam): MS *m/z* 587 (M^++1); ^{1}H-NMR ($CDCl_3$, 270 MHz) 7.95 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 7.65-7.47 (5 H, m, Bz), 6.51 (1 H, d, H-1', $J_{1',2''}$ = 1.5 Hz), 5.82 (1 H, d, H-5, $J_{5,6}$ = 8.1 Hz), 5.57 (1 H, dd, H-2"a, $J_{2"a,1'}$ = 1.5, J = 2.9 Hz), 5.47 (1 H, dd, H-2"b, $J_{2"b,1'}$ = 1.5, J = 2.6 Hz), 4.85 (1 H, dd, H-3', $J_{3',4'}$ = 7.3, J = 1.5 Hz), 4.18 (1 H, dd, H-5'a, $J_{4',5'}$ = 1.8, J_{gem} = 13.6 Hz), 4.06 (1 H, dd, H-5'b, $J_{4',5'}$ = 2.6, J_{gem} = 13.6 Hz), 3.73 (1 H, ddd, H-4', $J_{3',4'}$ = 7.3, $J_{4',5'a}$ = 1.8, $J_{4',5'b}$ = 2.6 Hz), 1.23-1.05 (28 H, m, isoPr).

***N*^{3}-Benzoyl-2'-deoxy-2'-methylideneuridine (7).** A THF solution of TBAF (1 M, 3.2 ml) was added to a solution of **6** (931 mg, 1.6 mmol) in THF (10 ml). The mixture was stirred for 18 h at room temperature and the solvent was removed *in vacuo*. The residue was purified on a silica gel column to give **7** (490 mg, 89% as a colorless foam): MS *m/z* 346 (M^++1); ^{1}H-NMR ($CDCl_3$, 270 MHz) 7.98 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 7.96-7.59 (5 H, m, Bz), 5.93 (1 H, d, H-5, $J_{5,6}$ = 8.1 Hz), 5.71 (1 H, d, 3'-OH, J = 6.2 Hz), 5.46 (1 H, br s, H-2"a), 5.42 (1 H, br s, H-2"b), 5.03 (1 H, t, 5'-OH, J = 5.1 Hz), 4.53 (1 H, m, H-3'), 3.75-3.65 (3 H, m, H-4', 5'a, b).

***N*^{3}-Benzoyl-2'-deoxy-2'-methylidene-5-*O*-trityluridine (8).** Triethylamine (0.13 ml, 0.91 mmol) was added to a mixture of **7** (265 mg, 0.76 mmol), and trityl chloride (255 mg, 0.9 mmol) in CH_2Cl_2 (15 ml) at 0 °C. The mixture was stirred for 10 min at 0 °C and then ice-water was added. The organic phase was washed with H_2O, dried (Na_2SO_4), and concentrated to dryness. The residue was purified on a silica gel column to give **8** (460 mg, 95% as a white solid): MS *m/z* 587 (M^++1); ^{1}H-NMR ($CDCl_3$, 270 MHz) 7.95-7.91 (2 H, m, Bz), 7.75 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 7.68-7.28 (17 H, m, trityl, Bz), 6.64 (1 H, d, H-1', $J_{1',2''}$ = 1.8 Hz), 5.57 (1 H, dd, H-

2"a , $J_{2"a,1'}$ = 1.8, J = 2.2 Hz), 5.54 (1 H, d, H-2"b , $J_{2"b,1'}$ = 1.8 Hz), 5.48 (1 H, d, H-5, $J_{5,6}$ = 8.1 Hz), 4.86 (1 H, m, H-3'), 3.84 (1 H, ddd, H-4', $J_{4',5a'}$ = 2.9, $J_{3',4'}$ = 7.0, $J_{4',5'b}$ = 2.9 Hz), 3.65 (1 H, dd, H-5'a, $J_{4',5'a}$ = 2.9, J_{gem} = 11.0 Hz), 3.55 (1 H, dd, H-5'b, $J_{4',5'b}$ = 2.9, J_{gem} = 11.0 Hz).

N^3-Benzoyl-2'-deoxy-5'-*O*-dimethylthexylsilyl-2'-methylidene-uridine (9). Dimethylthexylsilyl chloride (60 µl, 0.3 mmol) was added to a solution of **7** (95 mg, 0.3 mmol) in pyridine (3 ml). The mixture was stirred for 27 h at room temperature and the solvent was concentrated to dryness. The residue was purified on a silica gel column to give **9** (108 mg, 79% as a colorless foam): MS *m/z* 487 (M^+); ^{1}H-NMR ($CDCl_3$, 270 MHz) 7.93 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 7.92 (1 H, d, Bz), 7.58 (4 H, m, Bz), 6.64 (1 H, d, H-1', $J_{1',2"}$ = 1.5 Hz), 5.80 (1 H, d, H-5, $J_{5,6}$ = 8.1 Hz), 5.56 (1 H, dd, H-2"a, $J_{2"a,1'}$ = 1.5, J = 2.2 Hz), 5.53 (1 H, dd, H-2"b , $J_{2"b,1'}$ = 1.5, J = 1.8 Hz), 4.76 (1 H, m, H-3'), 3.99 (1 H, dd, H-5', $J_{4',5'}$ = 2.9, J_{gem} = 11.7 Hz), 3.91 (1 H, dd, H-5'b, $J_{4',5'b}$ = 2.6, J_{gem} = 11.7 Hz), 3.81 (1 H, ddd, H-4', $J_{3',4'}$ = 7.0, $J_{4',5'a}$ = 2.9, $J_{4',5'b}$ = 2.6 Hz), 2.08 (1 H, br s, 3'-OH), 1.62 (1 H, s, thexyl), 0.91-0.88 (12 H, thexyl), 0.16 (3 H, s, CH_3Si), 0.13 (3 H, s, CH_3Si).

(3'*R*)-N^3-Benzoyl-2',3'-dideoxy-3'-fluoro-2'-methylidene-5'-*O*-trityl-uridine (10) and N^3-Benzoyl-2',3'-didehydro-2',3'-dideoxy-2'-fluoro-methyl-5'-*O*-tritylуridine (11). Compound **8** (422 mg, 0.7 mmol) in CH_2Cl_2 (10 ml) was treated with DAST (0.1 ml, 0.8 mmol) for 1 h at 0 °C . Work-up was done similarly to that described above and purification by a silica gel column gave a mixture of **10** and **11** (283 mg, 67% in a ratio of 1 : 3.5). The physical data for the mixture of **10** and **11**: FAB-MS *m/z* 589 (M^++1); ^{1}H-NMR ($CDCl_3$, 270 MHz) **10**: 7.93 (2 H, m, H-6, Bz), 7.68-7.28 (19 H, m, 5'-*O*-trityl, Bz), 6.65 (1 H, br d, H-1'), 5.92 (1 H, dd, H-2"a , $J_{1',2"a}$ = 2.0, $J_{2"a,F}$ = 7.0 Hz), 5.78 (1 H, d, H-5, $J_{5,6}$ = 8.1 Hz), 5.76 (1 H, d, H-2"b, $J_{2"b,F}$ = 6.0 Hz), 5.34 (1 H, dd, H-3', $J_{3',F}$ = 56.4, $J_{3',4'}$ = 2.6 Hz), 4.14 (1 H, dq, H-4', $J_{4',F}$ = 28.2, $J_{3',4'}$ = 2.6, $J_{4',5'a}$ = 5.5, $J_{4',5'b}$ = 3.7 Hz), 3.45 (2 H, m; H-5'a,b, J_{gem} = 9.9 Hz). **11**: 8.01 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 7.92 (2 H, m, Bz), 7.53 (3 H, m, Bz), 7.31(15 H, m, trityl), 7.00 (1 H, d, H-1', J = 1.8 Hz), 6.27 (1 H, dd, H-3', J = 2.6, J = 1.5 Hz), 5.14 (1 H, d, H-5, $J_{5,6}$ = 8.1 Hz), 4.97 (2 H, dd , 2"-CH_2, $J_{2',F}$ = 46.9, J_{gem} = 11.0 Hz), 4.95 (1 H, m, H-4'), 3.56 (2 H, m, H-5'a, b).

(3'*R*)-N^3-Benzoyl-2',3'-dideoxy-5'-*O*-dimethylthexylsilyl-3'-fluoro-2'-methylideneuridine (12) and **N^3-Benzoyl-2',3'-didehydro-2',3'-dideoxy-5'-*O*-dimethylthexylsilyl-2'-fluoromethyluridine (13).** Compound **9** (1.0 g, 2.1 mmol) in CH_2Cl_2 (20 ml) was treated with DAST (0.3 ml, 2.31 mmol) for 1 h at 0 °C. Work-up was done similarly to that described above and purification by a silica gel column gave **12** (290 mg, 29% as a glassy solid) and **13** (270 mg, 27% as a foam). Physical data

for **12**: FAB-MS *m/z* 489 (M^++1); ^{1}H-NMR ($CDCl_3$) 7.95 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 7.93-7.50 (5 H, m, Bz), 6.66 (1 H, d, H-1', $J_{1',2''}$ = 1.8 Hz), 5.94 (1 H, dd, H-2"a, $J_{1',2''a}$ = 1.8, $J_{2''a,F}$ = 7.0 Hz), 5.86 (1 H, d, H-5, $J_{5,6}$ = 8.1 Hz), 5.74 (1 H, d, H-2"b, $J_{2''b,F}$ = 6.0 Hz), 5.31 (1 H, dd, H-3', $J_{3',F}$ = 59.7, $J_{3',4'}$ = 2.6 Hz), 4.09-4.91 (3 H, m, H-4', H-5'a, b), 1.56 (1 H, s, thexyl), 0.90-0.86 (12 H, thexyl), 0.15 (3 H, s, CH_3Si), 0.13 (3 H, s, CH_3Si). Physical data for **13**: FAB-MS *m/z* 489 (M^++1); ^{1}H-NMR ($CDCl_3$) 8.08 (1 H, d, H-6, $J_{6,5}$ = 8.4 Hz), 7.94-7.49 (5 H, m, Bz), 6.99 (1 H, br s, H-1'), 6.28 (1 H, d, H-3', J = 1.5 Hz), 5.80 (1 H, d, H-5, $J_{5,6}$ = 8.4 Hz), 4.94 (2 H, dd , 2"-CH_2, $J_{2',F}$ = 46.5, J_{gem} = 12.1 Hz), 4.94 (1 H, m, H-4'), 3.91 (1 H, dd, H-5'a, $J_{4',5'a}$ = 2.6, J_{gem} = 11.7 Hz), 3.37 (1 H, dd, H-5'b, $J_{4',5'b}$ = 2.6, J_{gem} = 11.7 Hz), 1.56 (1 H, s, thexyl), 0.89 (12 H, m, thexyl), 0.16 (3 H, s, CH_3Si), 0.13 (3 H, s, CH_3Si).

(3'*R*)-2',3'-Dideoxy-3'-fluoro-2'-methylideneuridine (14). A THF solution of TBAF (1 M, 0.5 ml) was added to a solution of **12** (100 mg, 0.2 mmol) in THF (5 ml). The mixture was stirred for 2 h at room temperature and the solvent was removed *in vacuo*. The residue was treated with NH_3/MeOH (saturated at 0 °C, 5 ml) for 20 h at room temperature. The solvent was removed and the residue was purified on a silica gel column to give **14** (32 mg, 65% as a yellow foam): FAB-MS *m/z* 243 (M^++1); ^{1}H-NMR (DMSO-d_6, 270 MHz) 11.43 (1 H, br s, H-N^3), 7.24 (1 H, d, H-6, $J_{6,5}$ = 8.2 Hz), 6.52 (1 H, d, H-1', $J_{1',2''}$ = 2.2 Hz), 5.94 (1 H, dd, H-2"a , $J_{2''a,1'}$ = 2.2, $J_{2''a,F}$ = 6.6 Hz), 5.73 (1 H, d, H-5, $J_{5,6}$ = 8.2 Hz), 5.66 (1 H, d, H-2"b , $J_{2''b,F}$ = 4.4 Hz), 5.49 (1 H, dd, H-3', $J_{3',F}$ = 56.1, $J_{3',4'}$ = 2.7 Hz), 4.99 (1 H, t, 5'-OH, J = 5.5 Hz), 4.03 (1 H, dq, H-4', $J_{4',F}$ = 28.6, $J_{4',3'}$ = 2.7, $J_{4',5'}$ = 6.1 Hz), 3.73 (1 H, dd, H-5'a, $J_{4',5'a}$ = 6.1, J_{gem} = 11.5 Hz), 3.68 (1 H, m, H-5'b, J_{gem} = 11.5 Hz).

2',3'-Didehydro-2',3'-dideoxy-2'-fluoromethyluridine (15). A THF solution of TBAF (1 M, 0.8 ml) was added to a solution of **13** (160 mg, 0.4 mmol) in THF (5 ml). The mixture was stirred for 2 h at room temperature and the solvent was removed *in vacuo*. The residue was dissolved in methanolic ammonia (saturated at 0 °C, 10 ml) and stirred for 23 h at room temperature. The solvent was evaporated and the residue was purified on a silica gel column to give **15** (85 mg, 83% as a foam): FAB-MS *m/z* 243 (M^++1); ^{1}H-NMR (DMSO-d_6 + D_2O, 270 MHz) 7.81 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 6.86 (1 H, br s, H-1'), 6.50 (1 H, dd, H-3', J = 2.9, $J_{3',4'}$ = 1.5 Hz), 5.61 (1 H, d, H-5, $J_{5,6}$ = 8.1 Hz), 4.99 (2 H, d , 2"-CH_2, $J_{2',F}$ = 46.9 Hz), 4.83 (1 H, m, H-4'), 3.65 (2 H, m, H-5'a, b, J_{gem} = 11.4 Hz). *Anal.* Calcd for $C_{10}H_{11}FN_2O_4$: C; 49.59, H; 4.58. N; 11.54. Found: C; 49.72, H; 4.61, N; 11.47.

(3'*R*)-2',3'-Dideoxy-5'-*O*-dimethylthexylsilyl-3'-fluoro-2-methylideneuridine (16). A solution of **12** (100 mg, 0.21 mmol) in methanolic ammonia (saturated at 0 °C, 5 ml) was stirred for 24 h at room temperature. The solvent was

evaporated and the residue was purified on a silica gel column to give **16** (73 mg, 91% as a colorless foam): EI-MS *m/z* 384 (M^+); ^{1}H-NMR ($CDCl_3$, 270 MHz) 8.86 (1 H, br s, H-N^3), 7.45 (1 H, d, H-6, $J_{6,5}$ = 8.2 Hz), 6.67 (1 H, d, H-1', J = 2.2 Hz), 5.91 (1 H, dd, H-2"a , $J_{2"a,F}$ = 4.9, $J_{2"a,1'}$ = 2.2 Hz), 5.76 (1 H, dd, H-5, $J_{5,6}$ = 8.2, $J_{5,NH}$ = 2.2 Hz), 5.66 (1 H, dd, H-2"b , $J_{2"b,F}$ = 5.5 Hz), 5.30 (1 H, dd, H-3', $J_{3',F}$ = 56.6, $J_{3',4'}$ = 2.2 Hz), 4.09-3.84 (3 H, m; H-4', H-5'a,b), 1.65 (1 H, s, thexyl), 0.89-0.85 (12 H, m, thexyl), 0.12 (3 H, s, CH_3Si), 0.11 (3 H, s, CH_3Si).

(3'*R*)-2',3'-Dideoxy-5'-*O*-dimethylthexylsilyl-3'-fluoro-2'-methylidenecytidine (17). Triethylamine (0.1 ml, 0.7 mmol) was added to a mixture of **16** (90 mg, 0.2 mmol), TPSCl (220 mg, 0.7 mmol), and DMAP (1 mg) in CH_3CN (5 ml) at 0 °C. The mixture was stirred for 24 h at room temperature and concentrated NH_4OH (28%, 10 ml) was added to the mixture. The whole was stirred for 4 h more. The solvent was concentrated and the residue was partitioned between EtOAc and H_2O. The organic phase was dried (Na_2SO_4) and concentrated to dryness. The residue was put on a neutralized silica gel column to give **17** (58 mg, 73% as a foam): EI-MS *m/z* 383 (M^+); ^{1}H-NMR ($CDCl_3$+D_2O, 270 MHz) 7.43 (1 H, d, H-6, $J_{6,5}$ = 7.7 Hz), 6.82 (1 H, br d, H-1'), 5.81 (1 H, dd, H-2"a , $J_{2"a,F}$ = 6.6, $J_{2"a,1'}$ = 1.5 Hz), 5.73 (1 H, d, H-5, $J_{5,6}$ = 7.7 Hz), 5.70 (1 H, d, H-2"b , $J_{2"b,F}$ = 5.5 Hz), 5.27 (1 H, m, H-3', $J_{3',F}$ = 56.4 Hz), 4.00 (1 H, m, H-4'), 3.91 (2 H, m, H-5'a, b), 1.25 (1 H, s, thexyl), 0.89-0.85 (12 H, m, thexyl), 0.12 (3 H, s, CH_3Si), 0.11 (3 H, s, CH_3Si).

(3'*R*)-2',3'-Dideoxy-3'-fluoro-2-methylidenecytidine Hydrochloride (18). A THF solution of TBAF (1 M, 0.3 ml) was added to a solution of **17** (50 mg, 0.13 mmol) in THF (2 ml). The mixture was stirred for 1 h at room temperature and the solvent was removed *in vacuo*. The solvent was evaporated and the residue was purified on a silica gel column to give **18** (28 mg, 89%, crystallized as a hydrochloride salt from EtOH): ^{1}H-NMR (DMSO-d_6, 270 MHz) 9.82 (1 H, br s, 4-NH_2), 8.77 (1 H, br s, 4-NH_2), 7.61 (1 H, dd, H-6, $J_{6,5}$ = 7.7 Hz), 6.51 (1 H, d, H-1', $J_{1',2"}$ = 1.7 Hz), 6.21 (1 H, d, H-5, $J_{5,6}$ = 7.7 Hz), 5.76 (1 H, dd, H-2"a , $J_{2"a,1'}$ = 1.7, $J_{2"a,F}$ = 6.6 Hz), 5.73 (1 H, d, H-2"b, $J_{2"b,F}$ = 4.4 Hz), 5.49 (1 H, m, H-3', $J_{3',F}$ = 55.5 Hz), 4.08 (1 H, dq, H-4', $J_{4',F}$ = 28.6, $J_{4',3'}$ = 2.8, $J_{4',5'a}$ = 6.0, $J_{4',5'b}$ = 5.0 Hz), 3.73 (1H, dd, H-5'a, $J_{4',5'a}$ = 6.0, J_{gem} = 11.5 Hz), 3.63 (2 H, dd, H-5'b, 5'-OH, $J_{4',5'b}$ = 5.0, J_{gem} = 11.5 Hz). *Anal.* Calcd for $C_{10}H_{12}FN_3O_3$·HCl: C; 43.25, H; 4.72, N; 15.13. Found: C; 43.27, H; 4.76, N; 14.95.

(3'*S*)-2',3'-Dideoxy-3'-fluoro-2'-methylidene-5'-*O*-trityluridine (20) and 2',3'-didehydro-2',3'-dideoxy-2'-fluoromethyl-5'-*O*-trityluridine (4). These compounds were prepared from **19** (1.9 g, 3.9 mmol) in CH_2Cl_2 (20 ml) and DAST (1 ml, 7.7 mmol) with stirring for 30 min at 0 °C. Purification by a silica gel

column of the reaction mixture gave **20** (720 mg, 38% as glassy solid) and **4** (322 mg, 17% as a foam). The physical data for **20**: FAB-MS *m/z* 485 (M^++1); ^{1}H-NMR ($CDCl_3$, 270 MHz) 8.66 (1 H, br s, H-N^3), 7.51 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 7.46-7.20 (15 H, m, trityl), 7.01 (1 H, br d, H-1'), 5.85 (1 H, dd, H-2"a , $J_{2"a,F}$ = 5.1, J = 2.6 Hz), 5.57 (1 H, dd, H-3', $J_{3',F}$ = 56.8, J = 1.1 Hz), 5.49 (1 H, m, H-2"b), 5.27 (1 H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 2.2 Hz), 4.29 (1 H, dq, H-4', $J_{4',F}$ = 24.2, $J_{3',4'}$ = 6.6, $J_{4',5'a}$ = 2.9, $J_{4',5'b}$ = 2.9 Hz), 3.53 (1 H, dd, H-5'a, $J_{4',5'a}$ = 2.9, J_{gem} = 11.0 Hz), 3.48 (1 H, dd, H-5'b, $J_{4',5'b}$ = 2.9, J_{gem} = 11.0 Hz). HR-FAB Calcd for $C_{29}H_{26}FN_2O_4$ (M^++1): 485.1876. Found: 485.1900. Compound **4**: FAB-MS *m/z* 485 (M^++1); ^{1}H-NMR ($CDCl_3$, 270 MHz) 8.39 (1 H, br s, H-N^3), 7.51 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 7.38-7.24 (15 H, m, trityl), 7.01 (1 H, br s, H-1'), 6.25 (1 H, dd, H-3', $J_{3',F}$ = 3.7, $J_{3',4'}$ = 1.5 Hz), 5.04 (1 H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 2.2 Hz), 5.02 (1 H, dd , 2"-CH_2, $J_{2',F}$ = 46.9, J_{gem} = 12.5 Hz), 4.95 (1 H, m, H-4'), 4.90 (1 H, dd , 2"-CH_2, $J_{2',F}$ = 46.9, J_{gem} = 12.5 Hz), 3.54 (1 H, dd, H-5'a, $J_{4',5'a}$ = 3.3, J_{gem} = 11.4 Hz), 3.48 (1 H, dd, H-5'b, $J_{4',5'b}$ = 2.4, J_{gem} = 11.4 Hz). HR-FAB Calcd for $C_{29}H_{26}FN_2O_4$ (M^++1); 485.1876. Found: 485.1864.

(3'*S*)-2',3'-Dideoxy-3'-fluoro-2'-methylidene-5'-*O*-trityl-5-methyluridine (22) and **2',3'-didehydro-2',3'-dideoxy-2'-fluoromethyl-5'-*O*-trityl-5-methyluridine (23)**. These compounds were prepared from **21** (470 mg, 1.0 mmol) in CH_2Cl_2 (10 ml) and DAST (0.14 ml, 1.1 mmol) with stirring for 4 h at room temperature. The residue was chromatographed on a silica gel column to give **22** (250 mg, 52% as a glassy solid) and **23** (139 mg, 29% as a foam). The physical data for **22**: FAB-MS *m/z* 499 (M^++1); ^{1}H-NMR ($CDCl_3$, 270 MHz) 7.33 (1 H, br s, H-N^3), 7.64-7.25 (16 H, m, trityl, H-6), 6.84 (1 H, d, H-1', $J_{1',2"}$ = 1.7 Hz), 5.88 (1 H, d, H-2"a, $J_{2"a,F}$ = 5.5 Hz), 5.58 (1 H, m, H-3', $J_{3',F}$ = 56.6 Hz), 5.46 (1 H, br d, H-2"b), 4.29 (1 H, dq, H-4', $J_{4',F}$ = 25.3, $J_{3',4'}$ = 6.6, $J_{4',5'}$ = 2.8, $J_{4',5'b}$ = 3.3 Hz), 3.54 (1 H, dd, H-5'a, $J_{4',5'a}$ = 2.8, J_{gem} = 10.4 Hz), 3.42 (1 H, dd, H-5'b, $J_{4',5'b}$ = 3.3, J_{gem} = 10.4 Hz), 1.34 (3 H, s, 5-CH_3). HR-FAB Calcd for $C_{30}H_{28}FN_2O_4$ (M^++1); 499.2024. Found; 499.2043. The physical data for **23**: FAB-MS *m/z* 499 (M^++1); ^{1}H-NMR ($CDCl_3$, 270 MHz) 8.28 (1 H, br s, H-N^3), 7.45-7.22 (16 H, m, trityl, H-6), 7.06 (1 H, dd, H-1', J = 2.2, $J_{1',3'}$ = 1.8 Hz), 6.37 (1 H, ddd, H-3', $J_{3',4'}$ = 1.5, $J_{3',F}$ = 3.3, $J_{3',1'}$ = 1.8 Hz), 5.07 (1 H, dd , 2"-CH_2, $J_{2",F}$ = 46.2, J_{gem} = 12.8 Hz), 5.01 (1 H, m, H-4'), 4.92 (1 H, dd , 2"-CH_2, $J_{2",F}$ = 46.2, J_{gem} = 12.8 Hz), 3.47 (1 H, dd, H-5'a, $J_{4',5'a}$ = 2.9, J_{gem} = 10.6 Hz), 3.39 (1 H, dd, H-5'b, $J_{4',5'b}$ = 4.0, J_{gem} = 10.6 Hz), 1.21 (3 H, s, 5-CH_3). HR-FAB Calcd for $C_{30}H_{28}FN_2O_4$ (M^++1); 499.2024. Found; 499.2033.

(3'*S*)-2',3'-Dideoxy-3'-fluoro-2'-methylidene-5'-*O*-tritylcytidine (24). Triethylamine (0.3 ml) was added to a stirred mixture of **20** (340 mg, 0.7 mmol), TPSCl

(740 mg, 2.5 mmol), and DMAP (4 mg) in CH_3CN (15 ml) at 0 °C. The mixture was stirred for 22 h at room temperature and then concentrated NH_4OH (28%, 10 ml) was added. The mixture was stirred for further 3 h. The solvent was evaporated and the residue was partitioned between EtOAc and H_2O. The organic phase was concentrated and put on a neutralized silica gel column to give **24** [185 mg, 72% (based on the recovered starting material) as a solid, crystallized from EtOH): mp 210-211 °C; Ms *m/z* 484 (M^++1); ^{1}H-NMR ($CDCl_3$ + D_2O) 7.56 (1 H, d, H-6, $J_{6,5}$ = 7.3 Hz), 7.44-7.25 (15 H, m, trityl), 6.91 (1 H, br d, H-1'), 5.72 (1 H, dd, H-2"a , J = 2.2, J = 2.6 Hz), 5.53 (1 H, m, H-3', $J_{3',F}$ = 56.8 Hz), 5.50 (1 H, dd, H-2"b , J = 2.2, J = 1.8 Hz), 5.38 (1 H, d, H-5, J = 7.3 Hz), 4.24 (1 H, dq, H-4', $J_{4',F}$ = 23.5, $J_{3',4'}$ = 7.0, $J_{4',5'a}$ = 3.3, $J_{4',5'b}$ = 3.3 Hz), 3.51 (1 H, dd, H-5'a, $J_{4',5'a}$ = 3.3, J_{gem} = 10.6 Hz), 3.45 (1 H, dd, H-5'b, $J_{4',5'b}$ = 3.3, J_{gem} = 10.6 Hz). *Anal.* Calcd for $C_{29}H_{26}FN_3O_3 \cdot 0.5$ EtOH: C; 71.84, H; 5.49, N; 8.61. Found: C; 71.64, H; 5.41, N; 8.74.

(3'*S*)-2',3'-Dideoxy-3'-fluoro-2'-methylidenecytidine Hydrochloride (25). A solution of **24** (170 mg, 0.4 mmol) in 50% aqueous TFA (6 ml) was stirred for 3 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 chromatographed on a silica gel column to give **25** (88 mg, 72% as foam). A part of the foam was treated with 1 N HCl in EtOH, followed by evaporation, and coevaporation several times with EtOH. The solid was crystallized from EtOH/hexane: mp 169-170 °C; ^{1}H-NMR (DMSO-d_6, 270 MHz) 8.59 (1 H, br s, 4-NH_2), 8.03 (1 H, br s, 4-NH_2), 7.73 (1 H, d, H-6, $J_{6,5}$ = 7.3 Hz), 6.61 (1 H, d, H-1', $J_{1',2"}$ = 1.5 Hz), 5.96 (1 H, d, H-5, $J_{5,6}$ = 7.3 Hz), 5.76 (1 H, dd, H-2"a , $J_{2"a,1'}$ = 1.5, J = 3.3 Hz), 5.51 (1 H, dd, H-3', $J_{3',F}$ = 56.6, J = 2.0 Hz), 5.45 (1 H, br d, H-2"b), 5.19 (1 H, br s, 5'-OH), 4.14 (1 H, dq, H-4', $J_{4',F}$ = 24.9, $J_{3',4'}$ = 7.8, $J_{4',5'}$ = 3.9 Hz), 3.65 (1 H, dd, H-5'a, $J_{4',5'a}$ = 3.9, J_{gem} = 11.7 Hz), 3.53 (1 H, dd, H-5'b, $J_{4',5'b}$ = 3.9, J_{gem} = 11.7 Hz). *Anal.* Calcd for $C_{10}H_{12}FN_3O_3 \cdot HCl \cdot 0.15$ EtOH: C; 43.46, H; 4.92, N; 14.76. Found: C; 43.58, H; 4.67, N; 14.49.

(3'*S*)-2',3'-Dideoxy-3'-fluoro-2'-methylideneuridine (26). A solution of **20** (210 mg, 0.5 mmol) in $CHCl_3$ (5 ml) was treated with 90% aqueous TFA (5 ml) with stirring for 2 h at 0 °C. The solvent was evaporated and coevaporated several times with EtOH and toluene. The residue was chromatographed on a silica gel column to give **26** (111 mg, 86% as a foam): MS *m/z* 242 (M^+); ^{1}H-NMR (DMSO-d_6, 270 MHz) 11.41 (1 H, br s, H-N^3), 7.58 (1 H, d, H-6, $J_{6,5}$ = 7.7 Hz), 6.58 (1 H, d, H-1', $J_{1',2"}$ = 1.6 Hz), 5.77 (1 H, dd, H-2"a, J = 3.3, $J_{2"a,1'}$ = 1.6 Hz), 5.65 (1 H, dd, H-5, $J_{5,6}$ = 7.7, $J_{5,NH}$ = 2.2 Hz), 5.51 (1 H, m, H-3', $J_{3',F}$ = 54.9 Hz), 5.47 (1 H, m, H-2"b), 5.14 (1 H, t, 5'-OH, J = 5.5 Hz), 4.12 (1 H, dq, H-4', $J_{4',F}$ = 24.2, $J_{3',4'}$ = 7.7, $J_{4',5'a}$ = 3.8, $J_{4',5'a}$ = 4.4

Hz), 3.61 (2 H, m, H-5'a, b, J_{gem} = 12.1, $J_{4',5'b}$ = 4.4 Hz). HR-FAB Calcd for $C_{10}H_{11}FN_2O_4$ (M^+); 242.0702. Found; 242.0703.

(3'*S*)-2',3'-Dideoxy-3'-fluoro-2'-methylidene-5-methyluridine (27). A solution of **22** (200 mg, 0.4 mmol) in $CHCl_3$ (5 ml), was treated with 90% aqueous TFA (5 ml) with stirring for 4 h at 0 °C. The solvent was evaporated and coevaporated several times with EtOH and toluene. The residue was chromatographed on a silica gel column to give **27** (75 mg, 75% as a solid): MS *m/z* 257 (M^++1); ^{1}H-NMR (DMSO-d_6, 270 MHz) 11.53 (1 H, br s, H-N^3), 7.37 (1 H, d, H-6, $J_{6,Me}$ = 1.1 Hz), 6.52 (1 H, d, H-1', $J_{1',2''}$ = 1.5 Hz), 5.70 (1 H, m, H-2"a), 5.46 (1 H, m, H-3', $J_{3',F}$ = 56.6 Hz), 5.39 (1 H, m, H-2"a), 5.10 (1 H, t, 5'-OH, J = 5.0 Hz), 4.05 (1 H, dq, H-4', $J_{4',F}$ = 24.2, $J_{3',4'}$ = 7.7, $J_{4',5'a}$ = 4.4, $J_{4',5'b}$ = 3.9 Hz), 3.57 (2 H, m, H-5'a,b, J_{gem} = 11.5, $J_{4',5'a}$ = 4.4, $J_{4',5'b}$ = 3.9, $J_{5',OH}$ = 5.0 Hz), 1.68 (3 H, 5-Me, $J_{Me,6}$ = 1.1 Hz). *Anal.* Calcd for $C_{11}H_{13}FN_2O_4$: C; 51.56, H; 5.11, N; 10.93. Found: C; 51.40, H; 5.16, N; 10.77.

2',3'-Didehydro-2',3'-dideoxy-2'-fluoromethyl-5'-*O*-tritylcytidine (28). Triethylamine (0.1 ml, 0.72 mmol) was added to a stirred mixture of **4** (350 mg, 0.72 mmol), TPSCl (650 mg, 2.4 mmol), and DMAP (4 mg) in CH_3CN (10 ml) at 0 °C. The mixture was stirred for 30 h at room temperature and then concentrated NH_4OH (28%, 10 ml) was added. The mixture was stirred for 1 h more. The solvent was evaporated and the residue was partitioned between EtOAc and H_2O. The organic phase was concentrated and put on a neutralized silica gel column to give **28** (329 mg, 95% as a foam): FAB-MS *m/z* 484 (M^++1); ^{1}H-NMR ($CDCl_3$+D_2O, 270 MHz) 7.81 (1 H, d, H-6, $J_{6,5}$ = 7.7 Hz), 7.38-7.23 (15 H, m, trityl), 7.12 (1 H, d, H-1', $J_{1',2''}$ = 1.5 Hz), 6.14 (1 H, br d, H-3'), 5.19 (1 H, d, H-5, $J_{5,6}$ = 7.7 Hz), 4.89 (2 H, dd, 2"-CH_2, $J_{2'',F}$ = 46.5, J_{gem} = 13.2 Hz), 4.91 (1 H, br s H-4'), 3.42 (2 H, br d, H-5'a,b). HR-FAB Calcd for $C_{29}H_{27}FN_3O_3$ (M^++1): 484.2036. Found: 484.2037.

2',3'-Didehydro-2',3'-dideoxy-2'-fluoromethylcytidine (29). A solution of **28** (320 mg, 0.63 mmol) in EtOH (5 ml) was treated with 50% aqueous TFA (10 ml) at 0 °C. The mixture was stirred for 40 min 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. After removal of the solvent, the residue was purified on a silica gel column to give **29** (115 mg, 76%), which was further purified on HPLC (YMC D-ODS, 10% MeOH in H_2O) and was crystallized from EtOH: mp 136-137 °C; UV λ_{max} (MeOH) 269 nm , (acidic) 275 nm, (basic) 279 nm; MS *m/z* 242 (M^++1); ^{1}H-NMR (DMSO-d_6, 270 MHz) 7.71 (1 H, d, H-6, $J_{6,5}$ = 7.8 Hz), 7.22 (1 H, br s, 4-NH_2), 7.19 (1 H, br s, 4-NH_2), 7.21 (1 H, br d, H-1'), 6.14 (1 H, dd, H-3', J = 1.5, J = 2.4 Hz), 5.71 (1 H, d, H-5, $J_{5,6}$ = 7.8 Hz), 5.01 (1 H, t, 5'-OH, J = 5.4 Hz), 4.90 (2 H, d , 2"-

CH_2, $J_{2'',F}$ = 46.5 Hz), 4.79 (1 H, m, H-4', $J_{3',4'}$ = 1.5 Hz), 3.59 (2 H, br dd, H-5'a,b). HR-FAB Calcd for $C_{10}H_{13}FN_3O_3$ (M^++1): 242.0941. Found: 242.0941.

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(12) When 2'-deoxy-3'-*O*-mesyl-5'-*O*-trityl-2'-methylideneuridine was treated with anhydrous TBAF, **2** was exclusively obtained in 77% yield.

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