Diethylaminosulfur Trifluoride (DAST) as a Fluorinating Agent of Pyrimidine Nucleosides Having a 2′,3′-Vicinal Diol System

Hiroyuki HAYAKAWA, Fumi TAKAI, Hiromichi TANAKA, Tadashi MIYASAKA,* and Kentaro YAMAGUCHI

School of Pharmaceutical Sciences, Showa University, Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142, Japan. *Received September 11, 1989*

Displacement of a hydroxyl group in pyrimidine nucleosides having a vicinal diol system by a fluorine atom was investigated by using diethylaminosulfur trifluoride (DAST). Though participation of the base moiety often thwarts the desired introduction of a fluorine atom, it was found that appropriate modification of the base and/or sugar moieties allowed the desired fluorodehydroxylation to occur, giving 5′-, 3′-β-, and 2′-α-fluorinated uracilnucleosides in good yields.

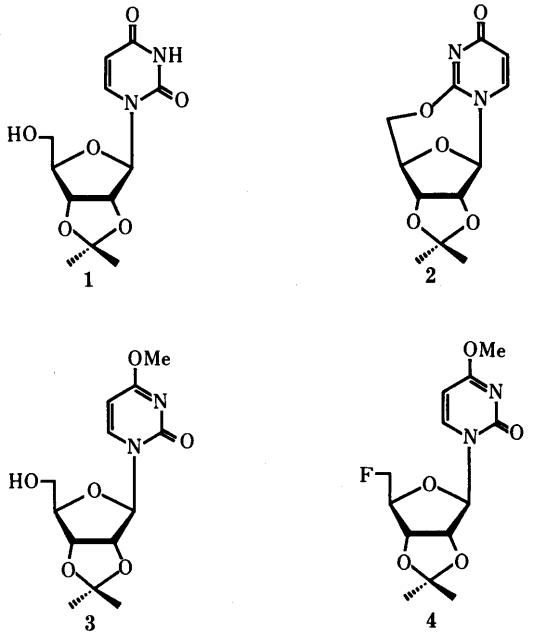
Keywords DAST; fluorodehydroxylation; uracilnucleoside; fluorosugar nucleoside; X-ray crystallography

Substitution of a hydrogen atom or a hydroxyl group in organic molecules by a fluorine atom often brings about dramatic changes in their behavior in biological systems.[1] For the purpose of such modification in the sugar portion of nucleosides, diethylaminosulfur trifluoride (Et_2NSF_3: DAST) seems to be very attractive,[2] since it can provide leaving ability to a hydroxyl function and, at the same time generates a fluoride anion which can act as a nucleophile.

However, despite the widespread use of the reagent for fluorodehydroxylation in carbohydrate chemistry,[3] only a few recent reports[4-6] have dealt with the use of DAST for the preparation of fluorosugar nucleosides.[7] In addition, most of the reactions of DAST have been studied by using 2′- or 3′-deoxynucleosides, simply from the viewpoint of the expected biological activities of their fluorinated products, and no systematic study seems to have been carried out in the cases of nucleosides having a vicinal diol system. In the present article, we report that DAST can be used to a certain extent for the fluorodehydroxylation of pyrimidine nucleosides having a 2′,3′-vicinal diol system.

First, 2′,3′-*O*-isopropylideneuridine (**1**) was treated with 1.2 eq of DAST in CH_2Cl_2 at 0 °C under an argon atmosphere. On adding the reagent, the initial suspension changed into a solution to give a highly polar product. As anticipated from both the well-known *C3′-endo* conformation of 2′,3′-*O*-isopropylidene derivatives, wherein the base is in proximity to the 5′-hydroxyl group,[8] and the dehydrating properties of DAST,[9] the product isolated in quantitative yield was O^2,5′-anhydro-2′,3′-*O*-isopropylideneuridine (**2**). When a similar reaction was attempted with the 4-methoxy-2-pyrimidinone derivative **3**, no reaction took place at 0 °C, but upon conducting the reaction at room temperature, the desired product **4** was obtained in 48% yield. Though the yield of **4** increased to 65% at the refluxing temperature of CH_2Cl_2 (15 h), the use of a higher boiling solvent, 1,2-dichloroethane, gave a rather lower yield of **4** (55%) at 50 °C.

The fluorodehydroxylation at the 3′-position of uridine was next examined by using 2′,5′-di-*O*-trityluridine (**5**)[10] as a substrate. Reaction of **5** with 1 eq of DAST in CH_2Cl_2 resulted in the sole formation of the cyclized product **6**.[10] Addition of 2 eq of the reagent, on the other hand, appeared to give a fluorinated product (**7**) with concomitant formation of **6** (isolated yields: at 0 °C, a trace amount of **6** *vs.* 21% of **7**; at refluxing temperature, 33% of **6** *vs.* 40% of **7**). The ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spec-



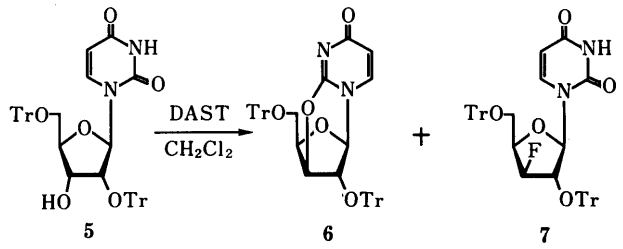


Chart 1

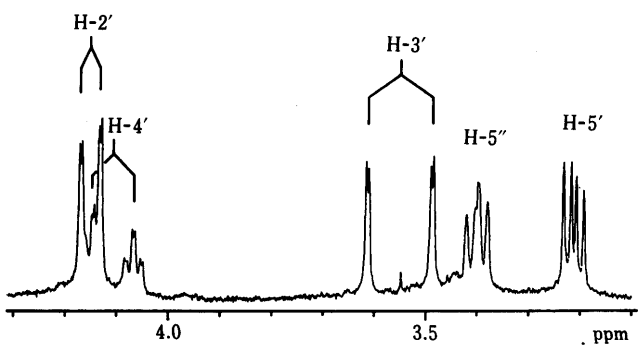
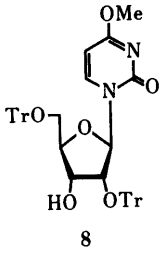
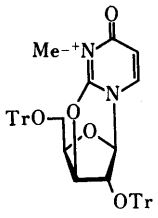


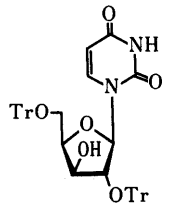
Fig. 1. Partial ^{1}H-NMR Spectrum of **7**



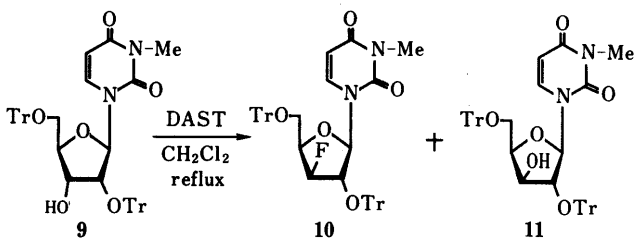
8



12

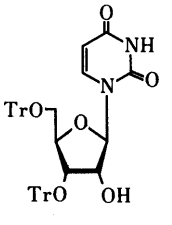


13

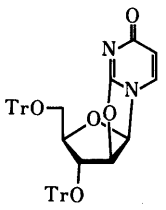


9 10 11

Chart 2



14

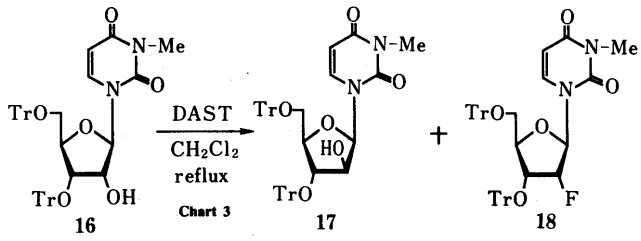


15

trum of **7** in the region of δ 3.10—4.30 ppm (400 MHz, in $CDCl_3$) is shown in Fig. 1 with all assignments confirmed by HOMO-SD (homonuclear-spin-decoupling) experiments. The stereochemistry of the introduced fluorine atom was assumed to be beta by analysis of $J_{H,F}$ values. That is, the coupling constant between F and H-4′ (31.1 Hz) was significantly larger than that between F and H-2′ (14.7 Hz), which suggests the *trans*-orientation of F and H-4′. When **6** was further treated with DAST under similar conditions to the above, no reaction could be observed. This suggests that **7** was derived directly from **5** with inversion of configuration, competing with the intramolecular cyclization.

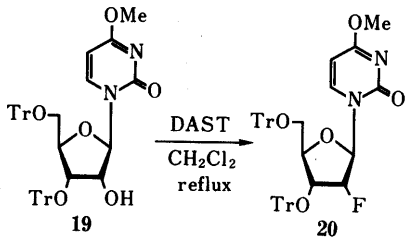
In an attempt to eliminate the cyclization process during the 3′-fluorodehydroxylation, both compounds **8** and **9** were subjected to the reaction with DAST (2 eq) in CH_2Cl_2 at refluxing temperature. Quite unexpectedly, the starting material was quantitatively recovered in the reaction of **8**, while two products were formed in the case of **9**. The ^{1}H-NMR spectrum of the less polar product from the latter reaction was almost identical, except for the presence of a methyl signal at δ 3.38 ppm, with that of **7** and hence its structure was elucidated to be **10** (48%).[11] The structure of the more polar product, a xylofuranosyluracil (**11**: 29%), was determined based on an alternative synthesis from **6** *via* alkaline hydrolysis followed by methylation with CH_2N_2. This result suggested the intervention of a cyclic intermediate **12** which underwent hydrolysis during aqueous work-up. The observed difference in reactivity between **8** and **9** towards DAST might be related to a discrepancy in their $J_{1',2'}$ values (**8**: 2.0 Hz *vs.* **9**: 7.8 Hz) which reflects their conformational difference in the sugar portion. Examination of a space-filling molecular model suggested that, in the case of **8**, the 2′-*O*-trityl group could thwart the approach of DAST to the 3′-hydroxyl group from the α-side. The attempted preparation of a 3′-α-fluorinated derivative by using **13** gave an inseparable mixture of at least four products–the absence of **7** in this mixture was confirmed by ^{1}H-NMR spectroscopy.

As one would anticipate from the facile formation of the O^2,2′-anhydro bond in pyrimidine ribonucleosides,[12] the reaction of 3′,5′-di-*O*-trityluridine (**14**) with 1 eq of DAST in CH_2Cl_2 gave the corresponding O^2,2′-cyclo derivative



16 17 18

Chart 3



19 20

Chart 4

(**15**)[13] in quantitative yield even at 0 °C. On the other hand, when N^3-methyl-3′,5′-di-*O*-trityluridine (**16**) was treated with DAST (1.5 eq) in refluxing CH_2Cl_2 for 3 h, arabinofuranosyl (**17**) and 2′-deoxy-2′-fluoro (**18**) derivatives were formed in equal amounts (49% each). In contrast to the reaction at the 3′-position, the 3′,5′-di-*O*-trityl-β-D-ribofuranosyl derivative of 4-methoxy-2-pyrimidinone (**19**) was an excellent substrate. Thus, upon reaction with 2 eq of DAST at refluxing temperature of CH_2Cl_2 for 3 h, a 2′-fluorinated product (**20**) was obtained in 60% yield–an even higher yield of 94% could be attained by the use of 4 eq after 4.5 h. α-Stereochemistry of the introduced fluorine atom in **20** was established, again on the basis of the observed coupling constants ($J_{1',F}$ = 15.4 Hz *vs.* $J_{3',F}$ = 20.5 Hz). The unexpected retention of configuration during the formation of **18** and **20** would be explicable in terms of neighboring group participation by the respective O^2-atom, which compels the fluoride anion to attack from the α-side. The introduction of fluoride anion from the α-side could also be accomplished in the case of an arabinofuranosyluracil derivative **21** in 80% yield (in refluxing CH_2Cl_2, for 3 h).

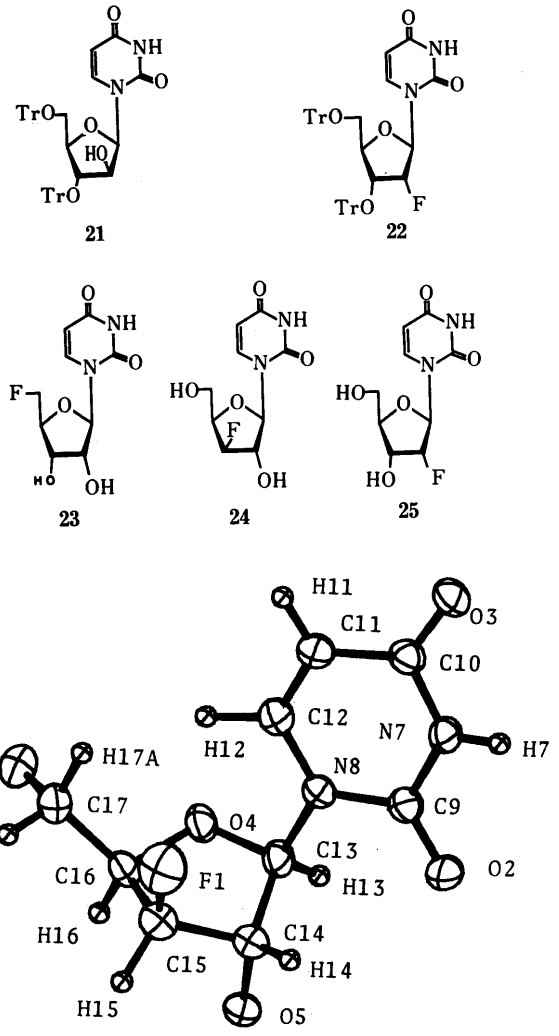


Fig. 2. ORTEP Drawing of 1-(3-Deoxy-3-fluoro-β-D-xylofuranosyl)-uracil (**24**)

Finally, the fluorinated nucleosides **4**, **7**, **22** were deprotected to the corresponding free nucleosides (**23**—**25**).[14] Among the three, **24** was subjected to X-ray crystallographic analysis, the result of which is depicted in Fig. 2 by an ORTEP drawing. Configuration at the C-3′ position of **24** was unequivocally determined at this stage. Atomic coordinates used for the analysis are given in Table I. As can be seen from Fig. 2, the sugar ring conformation of this compound was found to be *C3′-endo*, which may be a reflection of the previously reported relationship of sugar puckering to the electronegativity of substituents.[15]

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured with tetramethylsilane (TMS) as an internal standard with either a JEOL JNM-FX 100 or a JEOL-GX 400 spectrometer. Mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer. Ultraviolet (UV) spectra were recorded on a Shimadzu UV-240 spectrophotometer. Column chromatography was carried out on silica gel (Wakogel® C-200). Thin layer chromatography (TLC) was performed on silica gel (precoated silica gel plate F_{254}, Merck).

1-(2′,3′-*O*-Isopropylidene-β-D-ribofuranosyl)-4-methoxy-2-pyrimidinone (3) This compound was prepared from 1-(β-D-ribofuranosyl)-4-methoxy-2-pyrimidinone (539 mg, 2.09 mmol)[15] in a conventional way (acetone/2,2-dimethoxypropane/*p*-toluenesulfonic acid, at room temperature) in 89% yield as a powder. ^{1}H-NMR ($CDCl_3$) δ: 1.36 and 1.57 (6H, each as s, $CH\underline{Me}_2$), 3.63 and 3.88 (2H, each as m, CH_2-5′), 3.97 (3H, s, OMe), 4.33 (1H, m, H-4′), 5.11 (1H, dd, $J_{2',3'}$=6.3 Hz, $J_{3',4'}$=3.4 Hz, H-3′), 5.27 (1H, dd, $J_{1',2'}$=2.9 Hz, $J_{2',3'}$=6.3 Hz, H-2′), 5.42 (1H, d, $J_{1',2'}$=2.9 Hz, H-1′), 5.93 (1H, d, $J_{5,6}$=7.3 Hz, H-5), 7.50 (1H, d, $J_{5,6}$=7.3 Hz, H-6). MS *m/z*: 298 (M^+), 283 (M^+-Me). UV absorption in MeOH: max 280 nm, min 243 nm.

General Procedure for Fluorodehydroxylation Using DAST A CH_2Cl_2 solution of a nucleoside was treated dropwise with DAST under positive pressure of dry Ar. After being stirred at refluxing temperature, the reaction mixture was carefully quenched with chilled saturated aqueous $NaHCO_3$. Extraction with $CHCl_3$ followed by silica gel column chromatography gave the corresponding product.

1-(5-Deoxy-5-fluoro-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-4-methoxy-2-pyrimidinone (4) This compound was prepared from **3** (157 mg, 0.53 mmol) in CH_2Cl_2 (4 ml) and DAST (83 μl, 0.63 mmol). The reaction was continued for 15 h. Column chromatography ($CHCl_3$) of the reaction mixture gave **4** (102 mg, 65%), which was crystallized from EtOH to give an analytical sample (mp 125—126 °C). *Anal.* Calcd for $C_{13}H_{17}FN_2O_5$; C, 52.00; H, 5.71; F, 6.33; N, 9.33. Found: C, 52.08; H, 5.67; F, 6.19 N, 9.35. ^{1}H-NMR ($CDCl_3$) δ: 1.36 and 1.59 (6H, each as s, $CH\underline{Me}_2$), 3.96 (3H, s, OMe), 4.43 (1H, m, $J_{3',4'}$=4.4 Hz, $J_{4',5'}$=8.2 Hz, $J_{4',F}$=23.1 Hz, H-4′), 4.70 (2H, m, $J_{5',F}$=46.9 Hz, CH_2-5′), 4.91 (1H, dd, $J_{2',3'}$=6.2 Hz, $J_{3',4'}$=4.0 Hz, H-3′), 5.01 (1H, d, $J_{2',3'}$=6.2 Hz, H-2′), 5.77 (1H, s, H-1′), 5.90 (1H, d, $J_{5,6}$=7.3 Hz, H-5), 7.54 (1H, d, $J_{5,6}$=7.3 Hz, H-6). MS *m/z*: 300 (M^+), 285 (M^+-Me), 175 (M^+-B), 126 (B+1). UV absorption in MeOH: max 275 nm (ε 6200), min 237 nm (ε 1600).

1-(3-Deoxy-3-fluoro-2,5-di-*O*-trityl-β-D-xylofuranosyl)uracil (7) This compound was prepared from **5** (1.05 g, 1.45 mmol) in CH_2Cl_2 (15 ml) and DAST (382 μl, 2.89 mmol). The reaction was continued for 4 h. Column chromatography ($CHCl_3$) of the reaction mixture gave **6** (342 mg, 33%) as a powder and **7** (421 mg, 40%) as a foam. Physical data of **7** are as follows. ^{1}H-NMR ($CDCl_3$) δ: 3.21 (1H, dd, $J_{4',5'}$=5.9 Hz, J_{gem}=9.9 Hz, H-5′), 3.39 (1H, dd, $J_{4',5'}$=7.7 Hz, J_{gem}=9.9 Hz, H-5′), 3.54 (1H, dd, $J_{3',F}$=50.6 Hz, $J_{3',4'}$=1.8 Hz, H-3′), 4.12 (1H, m, $J_{4',F}$=31.1 Hz, H-4′), 4.16 (1H, dd, $J_{1',2'}$=1.8 Hz, $J_{2',F}$=14.7 Hz, H-2′), 5.59 (1H, dd, $J_{5,6}$=8.1 Hz, $J_{5,NH}$=2.2 Hz, H-5), 6.47 (1H, d, $J_{1',2'}$=1.8 Hz, H-1′), 7.07 (1H, dd, $J_{5,6}$=8.1 Hz, $J_{6,F}$=1.8 Hz, H-6), 7.16—7.52 (30H, m, Tr), 8.22 (1H, br, NH). UV absorption in MeOH: max 258 nm, min 245 nm.

1-(2,5-Di-*O*-trityl-β-D-ribofuranosyl)-4-methoxy-2-pyrimidinone (8) This compound was prepared as a foam from **5** in 49% yield according to the published procedure.[16] ^{1}H-NMR ($CDCl_3$) δ: 2.95 (1H, d, $J_{3',4'}$=2.9 Hz, H-3′), 3.14 (1H, dd, $J_{4',5'}$=6.4 Hz, J_{gem}=9.8 Hz, H-5′), 3.49 (1H, dd,

TABLE I. Atomic Coordinates of Non-hydrogen Atoms Used for Crystallographic Analysis of Compound **24**

	x	*y*	*z*	B_{eq}
F 1	0.4272 (2)	0.2828 (0)	0.4944 (5)	4.22 (9)
O 2	0.1701 (3)	0.7550 (8)	0.5180 (6)	3.33 (11)
O 2	−0.0306 (3)	0.4027 (8)	0.9850 (5)	3.04 (10)
O 4	0.2294 (2)	0.3026 (8)	0.1604 (5)	2.52 (9)
O 5	0.3953 (4)	0.6077 (8)	0.0807 (7)	4.10 (12)
O 6	0.2918 (3)	−0.0685 (8)	0.0244 (7)	3.89 (11)
N 7	0.0742 (4)	0.5744 (9)	0.7562 (7)	2.59 (12)
N 8	0.1769 (4)	0.4463 (9)	0.4761 (6)	2.36 (11)
C 9	0.1435 (4)	0.6032 (10)	0.5796 (8)	2.45 (13)
C 10	0.0380 (4)	0.4097 (10)	0.8326 (8)	2.43 (13)
C 11	0.0856 (5)	0.2545 (10)	0.7272 (8)	2.73 (14)
C 12	0.1500 (4)	0.2783 (10)	0.5548 (8)	2.64 (13)
C 13	0.2324 (4)	0.4716 (9)	0.2662 (8)	2.36 (13)
C 14	0.3648 (5)	0.5297 (10)	0.2770 (10)	2.93 (14)
C 15	0.4305 (5)	0.3496 (11)	0.2856 (9)	3.25 (15)
C 16	0.3529 (5)	0.2329 (10)	0.1405 (9)	2.77 (14)
C 17	0.3545 (5)	0.0332 (10)	0.1881 (10)	3.33 (15)
H 7	0.054 (6)	0.672 (11)	0.823 (12)	2.0 (16)
H 11	0.069 (6)	0.129 (11)	0.789 (11)	1.9 (16)
H 12	0.191 (6)	0.164 (11)	0.473 (11)	2.2 (16)
H 13	0.186 (5)	0.564 (11)	0.176 (10)	1.9 (14)
H 14	0.389 (5)	0.612 (11)	0.399 (11)	1.8 (14)
H 15	0.525 (5)	0.367 (10)	0.236 (9)	2.0 (15)
H 16	0.381 (5)	0.252 (11)	−0.018 (10)	2.0 (15)
H 17A	0.316 (5)	0.009 (10)	0.347 (10)	1.9 (14)
H 17B	0.435 (6)	−0.006 (10)	0.181 (10)	1.9 (15)

$J_{4',5'}=6.0$ Hz, $J_{gem}=9.8$ Hz, H-5'), 3.96 (3H, s, OMe), 4.18 (1H, d, $J_{1',2'}=2.0$ Hz, H-2'), 4.26 (1H, m, H-4'), 5.74 (1H, d, $J_{5,6}=7.3$ Hz, H-5), 6.63 (1H, d, $J_{1',2'}=2.0$ Hz, H-1'), 7.21—7.60 (30H, m, Tr), 7.64 (1H, d, $J_{5,6}=7.3$ Hz, H-6). UV absorption in MeOH: max 270 nm, min 248 nm.

N^3-Methyl-2',5'-di-*O*-trityluridine (9) This compound was prepared as a foam in 89% yield by treating a $CHCl_3$ solution of **5** with CH_2N_2 in ether. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (1H, br, 3'-OH), 2.83 (1H, d, $J_{2',3'}=4.4$ Hz, H-3'), 3.11 (2H, m, CH_2-5'), 3.43 (3H, s, N-Me), 3.98 (1H, m, H-4'), 4.50 (1H, dd, $J_{2',3'}=4.4$ Hz, $J_{1',2'}=7.8$ Hz, H-2'), 5.19 (1H, d, $J_{5,6}=8.3$ Hz, H-5), 6.59 (1H, d, $J_{1',2'}=7.8$ Hz, H-1'), 7.18—7.68 (31H, m, H-6 and Tr). UV absorption in MeOH: max 260 nm, min 245 nm.

1-(3-Deoxy-3-fluoro-2,5-di-*O*-trityl-β-D-xylofuranosyl)-N^3-methyluracil (10) This compound was prepared from **9** (230 mg, 0.31 mmol) in CH_2Cl_2 (5 ml) and DAST (82 μl, 0.62 mmol). The reaction was continued for 4 h. Column chromatography ($CHCl_3$) of the reaction mixture gave **10** (110 mg, 48%) as a foam and **11** (66 mg, 29%) as a powder. Physical data of **10** are as follows. ^{1}H-NMR ($CDCl_3$) δ: 3.20 (1H, dd, $J_{4',5'}=5.9$ Hz, $J_{gem}=9.9$ Hz, H-5'), 3.34—3.43 (1H, m, H-5'), 3.38 (3H, s, N-Me), 3.60 (1H, dd, $J_{3',F}=50.6$ Hz, $J_{3',4'}=1.8$ Hz, H-3'), 4.06—4.17 (2H, m, $J_{4',F}=31.3$ Hz, $J_{2',F}=15.2$ Hz, $J_{1',2'}=1.8$ Hz, H-2' and H-4'), 5.64 (1H, d, $J_{5,6}=8.1$ Hz, H-5), 6.51 (1H, d, $J_{1',2'}=1.8$ Hz, H-1'), 7.02 (1H, d, $J_{5,6}=8.1$ Hz, $J_{6,F}=1.8$ Hz, H-6), 7.16—7.46 (30H, m, Tr). UV absorption in MeOH: max 258 nm, min 243 nm.

N^3-Methyl-3',5'-di-*O*-trityluridine (16) This compound was prepared as a foam in 88% yield by treating a $CHCl_3$ solution of **14** with CH_2N_2 in ether. For physical data of this compound, see ref. 17.

N^3-Methyl-1-(3,5-di-*O*-trityl-β-D-arabinofuranosyl)uracil (17) and 1-(2-Deoxy-2-fluoro-3,5-di-*O*-trityl-β-D-ribofuranosyl)-N^3-methyluracil (18) These compounds were prepared from **16** (193 mg, 1.41 mmol) in CH_2Cl_2 (5 ml) and DAST (52 μl, 0.39 mmol). The reaction was continued for 3 h. Column chromatography ($CHCl_3$) of the reaction mixture gave **17** (94 mg, 49%, as a foam) and **18** (94 mg, 49%, as a foam). Physical data of **17** are as follows. ^{1}H-NMR ($CDCl_3$) δ: 2.92 (1H, dd, $J_{4',5'}=3.9$ Hz, $J_{gem}=10.7$ Hz, H-5'), 3.23 (1H, d, $J=9.3$ Hz, 2'-OH), 3.31 (3H, s, N-Me), 3.44 (1H, dd, $J_{4',5'}=2.4$ Hz, $J_{gem}=10.7$ Hz, H-5'), 3.70—3.79 (2H, m, H-2' and H-4'), 4.00 (1H, s, H-3'), 6.67 (1H, d, $J_{5,6}=8.3$ Hz, H-5), 6.14 (1H, d, $J_{1',2'}=2.9$ Hz, H-1'), 7.25 (30H, m, Tr), 7.59 (1H, d, $J_{5,6}=8.3$ Hz, H-6). UV absorption in MeOH: max 261 nm, min 243 nm. Physical data of **18** are as follows. ^{1}H-NMR ($CDCl_3$) δ: 3.21 (dd, $J_{4',5'}=3.3$ Hz, $J_{gem}=11.4$ Hz, H-5'), 3.27 (3H, s, N-Me), 3.52 (1H, dd, $J_{4',5'}=1.8$ Hz, $J_{gem}=11.4$ Hz, H-5'), 3.98 (1H, m, H-4'), 4.04 (1H, m, $J_{2',F}=49.9$ Hz, H-2'), 4.16 (1H, m, $J_{2',3'}=4.0$ Hz, $J_{3',4'}=6.3$ Hz, $J_{3',F}=15.1$ Hz, H-3'), 5.24 (1H, d, $J_{5,6}=8.1$ Hz, H-5), 6.08 (1H, dd, $J_{1',2'}=2.6$ Hz, $J_{1',F}=14.7$ Hz, H-1'), 7.17—7.41 (30H, m, Tr), 7.51 (1H, d, $J_{5,6}=8.1$ Hz, H-6). UV absorption in MeOH: max 258 nm, min 244 nm.

1-(3,5-Di-*O*-trityl-β-D-ribofuranosyl)-4-methoxy-2-pyrimidinone (19) This compound was prepared as a foam from **14**[10] in 49% yield according to the published procedure.[16] ^{1}H-NMR ($CDCl_3$) δ: (1H, d, $J=8.3$ Hz, 2'-OH), 3.18 (2H, m, CH_2-5'), 3.80 (1H, dd, $J_{1',2'}=2.9$ Hz, $J_{2',3'}=8.8$ Hz, H-2'), 3.92 (3H, s, OMe), 4.00 (2H, m, H-3' and H-4'), 5.75 (1H, d, $J_{5,6}=7.3$ Hz, H-5), 6.27 (1H, d, $J_{1',2'}=2.9$ Hz, H-1'), 7.18—7.38 (30H, m, Tr), 7.77 (1H, d, $J_{5,6}=7.3$ Hz, H-6). UV absorption in MeOH: max 270 nm, min 247 nm.

1-(2-Deoxy-2-fluoro-3,5-di-*O*-trityl-β-D-ribofuranosyl-4-methoxy-2-pyrimidinone (20) This compound was prepared from **19** (152 mg, 0.20 mmol) in CH_2Cl_2 (5 ml). DAST (54 μl, 0.41 mmol) was added to the above solution and the mixture was refluxed for 5 h, after which another 54 μl of the reagent was added and the reaction was continued for a further 1.5 h. Column chromatography ($CHCl_3$) of the reaction mixture gave **20** (140 mg, 94%) as a foam. ^{1}H-NMR ($CDCl_3$) δ: 3.41 (1H, dd, $J_{4',5'}=3.3$ Hz, $J_{gem}=11.4$ Hz, H-5'), 3.61 (1H, dd, $J_{4',5'}=2.0$ Hz, $J_{gem}=11.4$ Hz, H-5'), 3.87—4.02 (1H, m, H-2'), 3.91 (3H, s, OMe), 4.13 (1H, m, $J_{2',3'}=3.7$ Hz, $J_{3,4'}=8.2$ Hz, $J_{3',F}=20.5$ Hz, H-3'), 4.28—4.30 (1H, m, H-4'), 5.23 (1H, d, $J_{5,6}=7.3$ Hz, H-5), 5.99 (1H, $J_{1',F}=15.4$ Hz, H-1'), 7.15—7.50 (30H, m, Tr), 7.84 (1H, d, $J_{5,6}=7.3$ Hz, H-6). UV absorption in MeOH: max 269 nm, min 246 nm.

2'-Deoxy-2'-fluoro-3',5'-di-*O*-trityluridine (22) This compound was prepared from **21** (155 mg, 0.21 mmol) in CH_2Cl_2 (5 ml) and DAST (56 μl, 0.43 mmol). The reaction was continued for 3 h. Column chromatography ($CHCl_3$) of the reaction mixture gave **22** (124 mg, 80%) as a foam. ^{1}H-NMR ($CDCl_3$) δ: 3.25 (1H, dd, $J_{4',5'}=2.9$ Hz, $J_{gem}=11.4$ Hz, H-5'), 3.54 (1H, d, $J_{gem}=11.4$ Hz, H-5'), 3.98 (1H, m, H-4'), 4.00 (1H, m, $J_{2',F}=51.7$ Hz, H-2'), 4.20 (1H, m, $J_{3',F}=15.2$ Hz, H-3'), 5.10 (1H, d, $J_{5,6}=8.4$ Hz, H-5), 6.05 (1H, dd, $J_{1',2'}=2.4$ Hz, $J_{1',F}=14.5$ Hz, H-1'), 7.12—7.41 (30H, m, Tr), 7.57 (1H, d, $J_{5,6}=8.4$ Hz, H-6), 8.08 (1H, br, NH). UV absorption in MeOH; max 259 nm, min 243 nm.

5'-Deoxy-5'-fluorouridine (23) This compound was prepared from **4** in 89% yield by treatment with 50% aqueous CF_3CO_2H (at room temperature, overnight). For physical data of **23**, see ref. 14.

1-(3-Deoxy-3-fluoro-β-D-xylofuranosyl)uracil (24) This compound was prepared from **7** in 62% yield by treatment with 80% aqueous CH_3CO_2H (at 100 °C for 6 h). Crystallization from H_2O gave an analytical sample (mp 158—159 °C). *Anal.* Calcd for $C_9H_{11}FN_2O_5$: C, 43.91; H, 4.50; F, 7.72; N, 11.38. Found: C, 43.89; H, 4.45; F, 7.69; N, 11.40. ^{1}H-NMR (DMSO-d_6) δ: 3.69—3.78 (2H, m, CH_2-5'), 4.16—4.27 (2H, m, H-2' and H-4'), 4.98 (1H, m, $J_{3',F}=64.8$ Hz, H-3'), 5.04 (1H, m, 5'-OH), 5.65 (1H, d, $J_{5,6}=8.1$ Hz, H-5), 5.73 (1H, d, $J_{1',2'}=1.8$ Hz, H-1'), 6.17 (1H, d, $J=4.4$ Hz, 2'-OH), 7.47 (1H, d, $J_{5,6}=8.1$ Hz, H-6), 11.38 (1H, br NH). MS m/z: 246 (M^+), 228 (M^+-H_2O). UV absorption in H_2O: max 262 nm (ε 10000), min 230 nm (ε 2400).

2'-Deoxy-2'-fluorouridine (25) This compound was prepared from **22** in 91% yield by treatment with 80% aqueous CH_3CO_2H (100 °C for 6 h). For physical data of **25**, see ref. 14.

X-Ray Crystallographic Analysis of 24 Crystal data: monoclinic $P2_1$, $a=10.983$ (2), $b=7.352$ (1), $c=6.326$ (1) Å, $\beta=91.87$ (1)°, $V=510.6$ (1) Å^3, $Z=2$, $D_x=1.601$ Mgm^{-3}. The reflection data were collected on a Rigaku AFC-5 diffractometer using graphite-monochromated Cu$K\alpha_1$ ($\lambda=1.5405$ Å) radiation by the θ–2θ scan method. A total of 899 reflections were collected within the 2θ range of 120°. Intensity data were corrected for Lorentz and polarization factors, but no absorption correction was applied. The crystal structure was determined by the direct method and refined by the full-matrix least-squares method. The final R value was 0.043 for 803 reflections with $F>\sigma(F)$ including anisotropic thermal parameters for non-hydrogen atoms and isotopic parameters for hydrogen atoms.

References and Notes

1) R. Filler and Y. Kobayashi, "Biomedical Aspects of Fluorine Chemistry," Kodansha Ltd., Tokyo and Elsevier Biomedical Press, Amsterdam, 1982.
2) 2-Chloro-1,1,2-trifluorotriethylamine has also been used for the same purpose: R. A. Earl and L. B. Townsend, *J. Carbohydr. Nucleosides and Nucleotides*, **7**, 35 (1980).
3) P. J. Card, *J. Carbohydr. Chem.*, **1986**, 451.
4) P. Herdewijn, J. Balzarini, E. De Clercq, R. Pauwels, M. Baba, S. Broder, and H. Vanderhaeghe, *J. Med. Chem.*, **30**, 1270 (1987).
5) P. Herdewijn, R. Pauwels, M. Baba, J. Balzarini, and E. De Clercq, *J. Med. Chem.*, **30**, 2131 (1987).
6) P. Herdewijn, J. Balzarini, M. Baba, R. Pauwels, A. Van Aerschot, G. Janssen, and E. De Clercq, *J. Med. Chem.*, **31**, 2040 (1988).
7) For a recent review: P. Herdewijn, A. Van Aerschot, and L. Kerremans, *Nucleosides and Nucleotides*, **8**, 65 (1989).
8) For an example: D. V. Santi and C. F. Brewer, *J. Am. Chem. Soc.*, **90**, 6236 (1968).
9) Dehydrative cyclization has been observed by using DAST: G. Kowollik, K. Gaertner, and P. Langen, *Tetrahedron Lett.*, **1969**, 3863; K. Agyei-Aye, S. Yan, A. K. Hebbler, and D. C. Baker, *Nucleosides and Nucleotides*, **8**, 327 (1989).
10) N. C. Yung and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 3060 (1961).
11) Through-space coupling between H-6 and 3'-F ($J=1.8$ Hz) was observed in the ^{1}H-NMR spectra of both **7** and **10**.
12) J. F. Codington, R. Fecher, and J. J. Fox, *J. Am. Chem. Soc.*, **82**, 2794 (1960).
13) Preparation of **15** from **14** has been reported: H. Loibner and E. Zbiral, *Justus Liebigs Ann. Chem.*, **1978**, 78.
14) Preparations of **23** and **25** have been reported: J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 558 (1964); S. Ajmera and P. V. Danenberg, *J. Med. Chem.*, **25**, 999 (1982).
15) S. Uesugi, H. Miki, M. Ikehara, H. Iwahashi, and Y. Kyogoku, *Tetrahedron Lett.*, **42**, 4073 (1979).
16) A Matsuda, K. Obi, and T. Miyasaka, *Chem. Pharm. Bull.*, **33**, 2575 (1985).
17) A. F. Cook and J. G. Moffatt, *J. Am. Chem. Soc.*, **89**, 2697 (1967).