Nucleosides and Nucleotides. XLIII. On the Stereoselectivity of Alkyl Addition Reaction of Pyrimidine 2′-Ketonucleosides[1)]

Kenji TAKENUKI, Hiroko ITOH, Akira MATSUDA,* and Tohru UEDA

Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan. *Received April 11, 1990*

The β-face of a 2′-ketonucleoside is sterically more hindered than the α-face because of the bulky nucleobase on the β-side at the 1′-position. However, on the reaction of 4-ethoxy-1-[3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-β-D-*erythro*-2-pentofuranos-2-ulos-1-yl]-2(1*H*)-pyrimidinone (6d) with methylmagnesium bromide, the β-methyl addition product (8d) was obtained in a considerable amount. It was found that Lewis basicity of the 2-carbonyl oxygen in the pyrimidine moiety, which is influenced inductively by the substituent at the 5-position, governs the stereoselectivity of the methyl addition reaction.

Keywords Grignard reagent; stereoselectivity; methyl addition reaction; 2′-ketonucleoside; branched chain sugar nucleoside

Recently, we have reported the alkyl addition reaction of various organometallic reagents to 4-ethoxy-1-[3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-β-D-*erythro*-2-pentofuranos-2-ulos-1-yl]-2(1*H*)-pyrimidinone (**6d**), yielding the 2′-branched-chain sugar pyrimidine nucleosides.[2-4)] This method provides a useful alternative for the synthesis of 2′-branched-chain pyrimidine nucleosides, which have previously been synthesized by condensation of an appropriate branched-chain sugar and a nucleobase.[5)] We have also reported the radical deoxygenation of the 2′-*tert*-alcohols in such 2′-branched-chain pyrimidine nucleosides to furnish various 2′-alkyl-2′-deoxy pyrimidine nucleosides.[2)] Among the 2′-alkyl-2′-deoxy nucleosides, (2′*S*)-2′-deoxy-2′-methylcytidine is a potent inhibitor of murine leukemic cell (L1210) growth *in vitro*, being as active as 1-β-D-arabinofuranosylcytosine.

In the reaction of the 2′-ketonucleoside **6d** with methyllithium or trimethylaluminum in Et_2O or $CHCl_3$, the 2′-methyl arabinoside **7d** was obtained exclusively, due to α-attack.[2)] This stereochemical course of the nucleophilic addition at C-2′ position is consistent with the previous accumulated data from the reduction of 2′-ketonucleosides by sodium borohydride[6)] and lithium triethylborohydride[7)] and also from the nucleophilic addition reactions of carbon-nucleophiles[8-11)] to the 2′-ketonucleosides. However, in the reaction with methylmagnesium bromide (MeMgBr) in Et_2O, β-attack was observed to afford the 2′-methyl ribofuranoside **8d**, the ratio of α-attack to β-attack being 1 : 0.75.[3)] In the 2′-ulosyl nucleoside **6**, this latter result is somewhat surprising, since the attack at the β-face of the sugar moiety is considerably more sterically hindered than

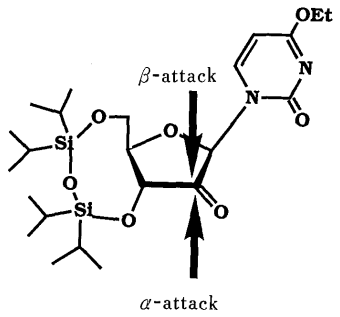

Fig. 1. Direction of the Nucleophilic Addition to **6d**

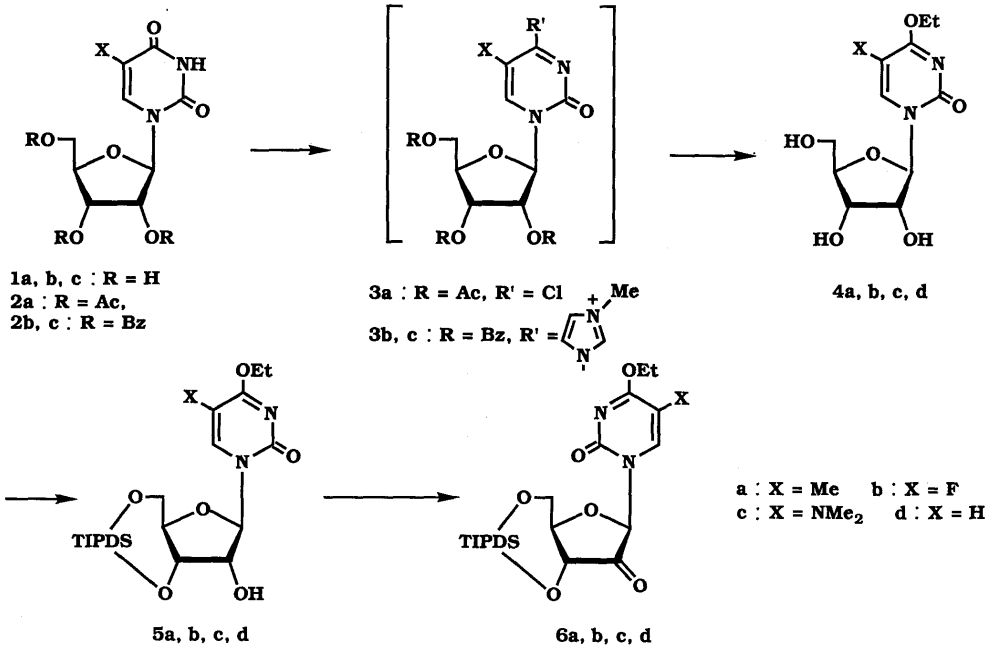

Chart 1

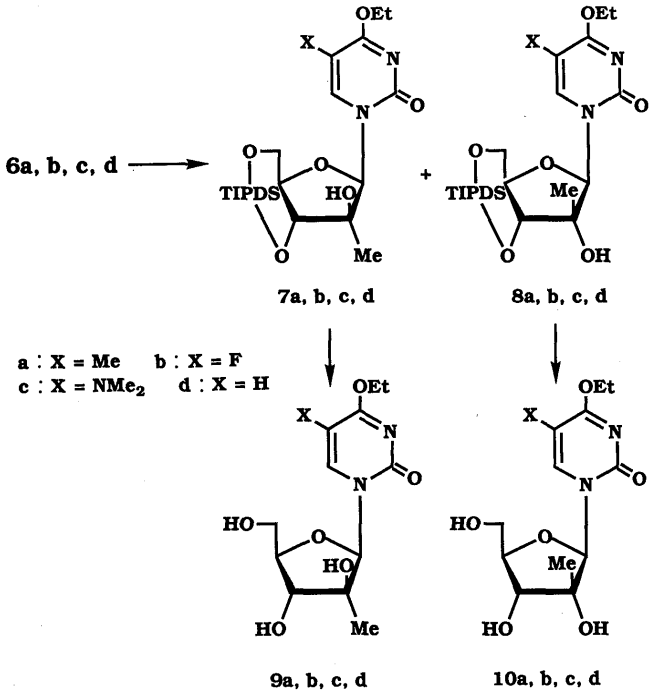

Chart 2

Table I. Influence of the 5-Substituents on the Stereoselectivity of the Methyl Addition Reaction

5-Substituents	α-Me : β-Me	Combined yield (%)
F	1 : 0.27	86.6
NMe_2	1 : 0.51	71.4
H	1 : 0.75	93.3
Me	1 : 1.09	69.2

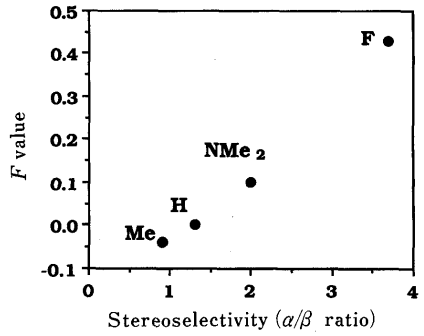

Fig. 2. Relationship between Hansch's *F* Value and the Stereoselectivity

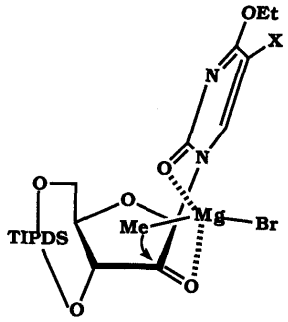

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Chart 3

that at the α-face because of the bulky nucleobase on the β-side (Fig. 1). Therefore, we have carried out some mechanistic studies of the alkyl addition reaction to the pyrimidine 2′-ketonucleosides by the Grignard reagent.

When the 2′-keto-5-methyl derivative **6a**, which was synthesized by the reaction sequence shown in Chart 1, was allowed to react with MeMgBr in Et_2O at −50 °C, the 2′-α-methyl and 2′β-methyl derivatives **7a** and **8a** were obtained in 33% and 36% yields (α : β = 1 : 1.09), respectively. The increase of the β-methylated product, compared with the reaction with **6d**, was rather small but was reproducible. From the above results, we postulated a role of the 5-substituents in the stereoselectivity. The distance between the 5-substituent in the pyrimidine moiety and the reactive center, the 2′-carbonyl carbon, is too far for the 5-substituent to affect the stereoselectivity of the reaction electrostatically or stereochemically. It seems that the inductive effect of the 5-substituent influences the 2-carbonyl group in the pyrimidine moiety, thus modulating the Lewis basicity of the 2-carbonyl group. It is well known that the dissociation of the uracil base at N-3 is affected by the 5-substituents. In order to test this possibility, we next examined the reaction of other 2′-keto-5-substituted pyrimidine nucleosides such as the 5-fluoro and 5-dimethylamino derivatives, with MeMgBr.

The corresponding 2′-keto nucleosides **6b, c** were synthesized as illustrated in Chart 1. At first, the sugar hydroxyls of 5-fluorouridine (**1b**) or 5-dimethylaminouridine (**1c**)[12] were benzoylated. Then, these nucleosides were converted into the corresponding 4-(1-methylimidazolium) salts **3b, c**[13] followed by treatment with EtOH and Et_3N to afford the 4-ethoxy derivatives, from which the free 4-ethoxy-2(1*H*)-pyrimidinone nucleosides **4b, c** were obtained. Compounds **4b, c** were selectively protected at the 3′,5′-hydroxyls with the tetraisopropyldisiloxanyl (TIPDS) group to give **5b, c**. Compounds **5b, c** were subjected to the Swern oxidation[14] to furnish the key compounds, 4-ethoxy-5-fluoro-1-[3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-β-D-*erythro*-2-pentofuranos-2-ulos-1-yl]-2(1*H*)-pyrimidinone (**6b**) and 5-(dimethylamino)-4-ethoxy-1-[3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-β-D-*erythro*-2-pentofuranos-2-ulos-1-yl]-2(1*H*)-pyrimidinone (**6c**).

The results of the methyl addition reactions to these compounds with 3 eq of MeMgBr in Et_2O at −78 °C are summarized in Table I. In the case of the 5-fluoro derivative **6b**, the ratio of the β-methylated product was greatly reduced. With the 5-dimethylamino derivative **6c**, about a 2 : 1 ratio in favor of α-attack was obtained. The order of the α/β ratio in this series is consistent with the order of Hansch's electronic parameters (*F*)[15] at the 5-substituents (Fig. 2). This result is suggestive that β-attack of the methylcarbanionoid may be correlated with the Lewis basicity of the 2-carbonyl oxygen of the pyrimidine moiety, which is influenced inductively by the 5-substituent.

The conformation of naturally occurring pyrimidine nucleosides around the glycosyl bonds has been recognized as *anti*, where the 2-carbonyl group of pyrimidine base is located outside of the sugar ring. Repulsion between the 2-carbonyl group and the 2′-"up"-proton in the sugar moiety may be the principal determinant for the

anti-conformation. However, the 2′-ketonucleoside **6d** adopts the *syn*-conformation in the solid state based on an X-ray diffraction analysis.[16] The glycosyl torsion angle [χ(O4′–C1′–N1–C6)] of crystalline **6d** was determined as 104° for molecule A and −93° for molecule B. Thus, the 2-carbonyl oxygen is located just above the 2′-carbonyl of the sugar moiety. Furthermore, it has been reported that the presence or absence of long-range spin–spin coupling between the anomeric proton and the fluorine substituent in the proton nuclear magnetic resonance (^{1}H-NMR) spectra of 5-fluoropyrimidine nucleosides is a good indicator of the glycosyl torsion angle. While 5-fluorouridines existing predominantly in the *anti*-conformer showed a long-range H–F coupling,[17] the analogues having *syn* or high-*anti*-conformations, such as 2,2′-anhydro-5-fluorouridine[17] and 6-substituted 5-fluoropyrimidine nucleosides,[18] do not show any long-range coupling. The anomeric proton in **6b** appeared as a singlet at δ 4.91. This indicates that the 5-fluoro-2′-keto derivative **6b** also takes *syn*-form in solution. From molecular model studies, we consider that the magnesium of the Grignard reagent might coordinate between the 2-carbonyl oxygen and the 2′-carbonyl oxygen. It seems likely that, through such complexes as I, the methyl carbanion can attack from the β-face. On the other hand, the α-attack occurs by a non-chelation process from the less-hindered face or by a chelation process between the 2′-carbonyl oxygen and the 3′-oxygen atom. Therefore the preference of the β-attack should be controlled by the ease of complexation, which may be facilitated by the Lewis basicity of the 2-carbonyl oxygen.

Experimental

Melting points were measured on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a JEOL JNM-FX 100 (100 MHz) or JEOL JNM-GX 270 (270 MHz) spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), dd (doublet-of-doublets), dt (doublet-of-triplets), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were confirmed by addition of D_2O. Ultraviolet (UV) absorption spectra were recorded with a Shimadzu UV-240 spectrophotometer. Mass spectra (MS) were measured on a JEOL JMS-DX-303 spectrometer. Thin layer chromatography (TLC) was done on Merck Kieselgel F254 precoated plates. Silica gel used for column chromatography was YMC gel 60A (70—230 mesh). The configuration at the 2′-position of **9** and **10** was determined by the methods described before.[3]

2′,3′,5′-Tri-*O*-acetyl-5-methyluridine (2a) Triethylamine (22.1 ml, 160 mmol) was added to a mixture of 5-methyluridine[19] (**1a**, 10.3 g, 40 mmol), 4-dimethylaminopyridine (50 mg), and acetic anhydride (5.3 ml, 160 mmol) in acetonitrile (150 ml).[20] An exothermic reaction occurred and the mixture was stirred for 1 h at ambient temperature. The mixture was quenched by addition of MeOH (5 ml) with stirring for a further 10 min, then concentrated *in vacuo*. The resulting oil was partitioned between H_2O and $CHCl_3$. The organic phase was dried (Na_2SO_4) and evaporated to dryness to leave an oily residue, which was chromatographed over a silica gel column (5 × 23 cm) with 4% EtOH in $CHCl_3$ as the eluent. The main UV-absorbing fractions were combined and concentrated to dryness to give **2a** (14.8 g, 97%) as a syrup. MS *m/z*: 384 (M^+). NMR ($CDCl_3$): 1.94 (3H, d, 5-Me, $J_{5Me,6}$ = 1.3 Hz), 2.12 (9H, t, Ac), 4.36 (3H, br s, 4′, 5′, 5″-H), 5.34 (2H, d, 2′,3′-H), 6.09 (1H, d, 1′-H, $J_{1',2'}$ = 3.2 Hz), 7.19 (1H, d, H-6), 9.47 (1H, br s, NH). This compound was used for the next step without further purification.

4-Ethoxy-5-methyl-1-β-D-ribofuranosyl-2(1*H*)-pyrimidinone (4a) A mixture of **2a** (3.84 g, 10 mmol), thionyl chloride (8.0 ml, 112 mmol) and *N*,*N*-dimethylformamide (0.5 ml) in anhydrous $CHCl_3$ (50 ml) was heated under reflux for 8 h. The solution was concentrated to dryness *in vacuo* and the residue was coevaporated with toluene (30 ml × 2). The residue was dissolved in absolute EtOH (20 ml) and 1 N NaOEt in EtOH (50 ml) was added to the solution at 0 °C. The mixture was stirred for 17 h at room temperature and then neutralized with 1 N aqueous HCl. The precipitate was removed by filtration and the filtrate was concentrated under reduced pressure to a small volume, to which silica gel (*ca.* 30 g) was added. The mixture was evaporated to dryness. The residue was placed on top of a silica gel column (3 × 25 cm), which was washed with 8% EtOH in $CHCl_3$ and then eluted with 16% EtOH in $CHCl_3$. The main UV-absorbing fractions were combined and concentrated to dryness. The residue was crystallized from EtOH to give **4a** (1.86 g, 65%), mp 143—144 °C. MS *m/z*: 286 (M^+), 155 ($B^+ + 1$). NMR (DMSO-d_6): 1.30 (3H, t, $OCH_2C\underline{H}_3$, J = 7.1 Hz), 1.87 (3H, d, 5-Me, $J_{5Me,6}$ = 0.7 Hz), 3.50—3.89 (5H, m, 2′, 3′, 4′, 5′, 5″-H), 4.31 (2H, q, $OC\underline{H}_2CH_3$), 4.99 (1H, d, 2′- or 3′-OH), 5.15 (1H, t, 5′-OH), 5.40 (1H, d, 2′- or 3′-OH), 5.78 (1H, d, 1′-H, $J_{1',2'}$ = 3.2 Hz), 8.11 (1H, d, 6-H). *Anal.* Calcd for $C_{12}H_{18}N_2O_6$: C, 50.34; H, 6.34; N, 9.78. Found: C, 50.22; H, 6.33; N, 9.76.

4-Ethoxy-5-methyl-1-[3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-β-D-ribofuranosyl]-2(1*H*)-pyrimidinone (5a) 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (7.18 ml, 1.1 eq) was added to a solution of compound **4a** (6.0 g, 21 mmol) in dry pyridine (60 ml) at 0 °C. The mixture was stirred for 2 h at 0 °C, then for 1 h at room temperature. H_2O (5 ml) was added to the reaction mixture and the solution was concentrated to dryness *in vacuo*. The residue was partitioned between H_2O (20 ml) and EtOAc (80 ml) and the separated organic phase was washed with H_2O (20 ml × 2), and dried (Na_2SO_4). The residue obtained on evaporation of the solvent *in vacuo* was purified by silica gel column (4 × 17.5 cm) chromatography with 40% EtOAc in hexane. The main UV-absorbing fractions were combined and concentrated to dryness to leave **5a** as an oil (7.79 g, 70%), which was subjected to further reaction without purification. MS *m/z*: 528 (M^+), 485 (M^+ − isoPr), 155 ($B^+ + 1$). NMR ($CDCl_3$): 1.00—1.10 (28H, m, isoPr), 1.37 (3H, t, $OCH_2C\underline{H}_3$, J = 7.1 Hz), 1.93 (3H, d, 5-Me, $J_{5\text{-}Me,6}$ = 1.0 Hz), 3.04 (1H, d, 2′-OH), 3.94—4.26 (5H, m, 2′, 3′, 4′, 5′, 5″-H), 4.45 (2H, q, $OC\underline{H}_2CH_3$), 5.73 (1H, s, 1′-H), 7.65 (1H, d, 6-H).

4-Ethoxy-5-methyl-1-[3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-β-D-*erythro*-2-pentofuranos-2-ulos-1-yl]-2(1*H*)-pyrimidinone (6a) A solution of dimethyl sulfoxide (DMSO) (3.8 ml, 53.5 mmol) in CH_2Cl_2 (20 ml) was added dropwise over 20 min to a solution of oxalyl chloride (2.1 ml, 24.8 mmol) in CH_2Cl_2 (40 ml) at −70 °C under argon. To this mixture, a solution of **5a** (10.1 g, 19.1 mmol) in CH_2Cl_2 (50 ml) was added dropwise over 20 min. The whole was stirred for a further 2.5 h, then Et_3N (16 ml, 6 eq) was added in a single portion. The reaction mixture was stirred for a further 1 h, then the cooling bath was removed. After warming to room temperature, the mixture was washed with H_2O (25 ml × 2). The separated organic was dried (Na_2SO_4) and concentrated to dryness. The residue was purified over a silica gel column (5 × 24 cm) with 20% EtOAc in hexane to yield **6a** as a colorless oil (8.51 g, 84.6%). MS *m/z*: 526 (M^+), 483 (M^+ − isoPr), 155 ($B^+ + 1$). NMR ($CDCl_3$): 1.03—1.13 (28H, m, isoPr), 1.35 (3H, t, $OCH_2C\underline{H}_3$, J = 7.1 Hz), 1.93 (3H, d, 5-Me, J = 1.1 Hz), 3.99—4.17 (3H, m, 4′, 5′, 5″-H), 4.44 (2H, q, $OC\underline{H}_2CH_3$), 4.94 (1H, s, 1′-H), 5.16 (1H, d, 3′-H, $J_{3',4'}$ = 7.6 Hz), 7.15 (1H, d, 6-H). *Anal.* Calcd for $C_{24}H_{42}N_2O_7Si_2$: C, 54.74; H, 8.04; N, 5.34. Found: C, 54.54; H, 8.03; N, 5.29.

4-Ethoxy-5-fluoro-1β-D-ribofuranosyl-2(1*H*)-pyrimidinone (4b) Phosphoryl oxychloride (2.0 ml, 21 mmol) was added to a solution of 1-methylimidazole (5.6 ml, 70 mmol) in dry acetonitrile (50 ml) with stirring at 0 °C. 2′,3′,5′-Tri-*O*-benzoyl-5-fluorouridine (**2b**, 4.02 g, 7 mmol) was added to this mixture at room temperature. The whole was stirred for 5 h, then EtOH (7 ml) and Et_3N (9.8 ml) were added, and the reaction mixture was stirred for a further 11 h at room temperature, then partitioned between EtOAc (200 ml) and H_2O (200 ml). The separated organic phase was washed with H_2O (20 ml × 2), and dried (Na_2SO_4). The residue obtained on evaporation of the solvent was purified over a silica gel column (3 × 24 cm) with 1% EtOH in $CHCl_3$. The main UV-absorbing fractions were combined and concentrated to dryness to leave 3.4 g (81%) of 4-ethoxy-5-fluoro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2(1*H*)-pyrimidinone as a foam, which was subjected to further reaction without purification. NMR ($CDCl_3$): 1.41 (3H, t, $OCH_2C\underline{H}_3$, J = 7.1 Hz), 4.52 (2H, q, $OC\underline{H}_2CH_3$), 5.65—5.92 (2H, m, 2′, 3′-H), 6.47 (1H, dd, 1′-H, $J_{1',2'}$ = 4.9, $J_{1',F}$ = 1.5 Hz), 7.30—7.72 (10H, m, Ph, 6-H), 7.91—8.15 (6H, m, Ph). A solution of 1 N NaOEt (0.2 ml) in EtOH was added to a suspension of the crude compound (3 g, 4.98 mmol) in EtOH (20 ml). The reaction mixture was stirred for 5 h at room temperature and then neutralized with 1 N aqueous HCl. The mixture was concentrated to about a half the initial volume, silica gel was added, and the whole was evaporated to dryness. The residue was placed on top of a silica gel column (2.4 × 27 cm), which was washed with 1% EtOH in $CHCl_3$ and eluted with 10% EtOH in $CHCl_3$.

The main UV-absorbing fractions were combined and concentrated to dryness, and the residue was crystallized from EtOH– hexane to yield **4b** (1.15 g, 80% from **2b**), mp 164—166 °C. MS *m/z*: 290 (M^+). NMR (DMSO-d_6): 1.33 (3H, t, OCH_2CH_3, J=7.1 Hz), 3.68 (2H, m, 5′, 5″-H), 3.81—3.94 (3H, m, 2′, 3′, 4′-H), 4.39 (2H, q, OCH_2CH_3, J=7.1 Hz), 5.02 (1H, d, 2′- or 3′-OH, J=5.4 Hz), 5.32 (1H, t, 5′-OH, J=4.6 Hz), 5.50 (1H, d, 2′- or 3′-OH, J=4.6 Hz), 5.70 (1H, dd, 1′-H, $J_{1',2'}=J_{1',F}$= 2.0 Hz), 8.63 (1H, d, 6-H, $J_{6,F}$=6.8 Hz). *Anal.* Calcd for $C_{11}H_{15}FN_2O_6$: C, 45.52; H, 5.21; N, 9.65. Found: C, 45.39; H, 5.24; N, 9.42.

4-Ethoxy-5-fluoro-1-[3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-β-D-ribofuranosyl]-2(1*H*)-pyrimidinone (5b) 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (1.25 ml, 1.05 eq) was added to a solution of **4b** (1.1 g, 3.79 mmol) in pyridine (10 ml). The reaction mixture was stirred for 1 h at 0 °C, then for 5 h at room temperature. H_2O (5 ml) was added, then the mixture was concentrated to dryness. The residue was partitioned between EtOAc (100 ml) and H_2O (20 ml × 2) and the separated organic phase was dried (Na_2SO_4). The residue obtained on evaporation of solvent *in vacuo* was chromatographed on a silica gel column (2.4 × 26 cm) with 20% EtOAc in hexane to yield **5b** as a colorless oil (1.31 g, 65%). High-resolution MS *m/z*: M^+ Calcd for $C_{23}H_{41}FN_2O_7Si_2$: 532.2436. Found: 532.2408. NMR ($CDCl_3$): 0.99—1.10 (28H, m, isoPr), 1.42 (3H, t, OCH_2CH_3, J=7.1 Hz), 2.83 (1H, s, 2′-OH), 3.93—4.39 (5H, m, 2′, 3′, 4′, 5′, 5″-H), 4.53 (2H, q, OCH_2CH_3, J=7.1 Hz), 5.75 (1H, d, 1′-H, $J_{1',F}$=1.2 Hz), 8.02 (1H, d, 6-H, $J_{6,F}$=5.9 Hz).

4-Ethoxy-5-fluoro-1-[3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-β-D-*erythro*-2-pentofuranos-2-ulos-1-yl]-2(1*H*)-pyrimidinone (6b) A solution of DMSO (111 μl, 6 eq) in dry CH_2Cl_2 (2 ml) was added dropwise over 5 min to a mixture of oxalyl chloride (62 μl, 1.5 eq) in CH_2Cl_2 (5 ml) at −80 °C under argon. To this mixture, a solution of **5b** (300 mg, 0.56 mmol) in CH_2Cl_2 (5 ml) was added dropwise over 10 min. The whole was stirred for a further 3 h, then Et_3N (0.5 ml) was added. The reaction mixture was stirred for a further 1 h, then warmed to room temperature and diluted with CH_2Cl_2 (30 ml). This mixture was washed with H_2O (20 ml × 2) and the separated organic phase was dried (Na_2SO_4). The product obtained on evaporation of the solvent was then purified by chromatography on a silica gel column (2 × 13 cm) with 25% EtOAc in hexane to yield **6b** as a colorless oil, which could be crystallized from EtOAc–hexane to give **6b** (202 mg, 68%), mp 126—127 °C. MS *m/z*: 487 (M^+ −isoPr). NMR ($CDCl_3$): 1.03—1.12 (28H, m, isoPr), 1.47 (3H, t, OCH_2CH_3, J=7.1 Hz), 3.92—4.17 (3H, m, 4′, 5′, 5″-H), 4.48 (2H, q, OCH_2CH_3, J=7.1 Hz), 4.91 (1H, s, 1′-H), 5.14 (1H, d, 3′-H, $J_{3',4'}$=8.1 Hz), 7.36 (1H, d, 6-H, $J_{6,F}$=4.9 Hz). *Anal.* Calcd for $C_{23}H_{39}FN_2O_7Si_2$: C, 52.05; H, 7.41; N, 5.28. Found: C, 51.85; H, 7.41; N, 5.16.

5-(Dimethylamino)-4-ethoxy-1-β-D-ribofuranosyl-2(1*H*)-pyrimidinone (4c) Benzoyl chloride (12.94 ml, 3.3 eq) was added dropwise over 10 min to a solution of 5-dimethylamino)uridine[12] (2.2 g, 7.68 mmol) in dry pyridine (20 ml) at 0 °C. The reaction mixture was stirred for 1 h at room temperature, then EtOH (5 ml) was added and the whole was evaporated *in vacuo*. The residue was partitioned between EtOAc (100 ml) and H_2O (30 ml × 2) and the separated organic phase was dried (Na_2SO_4). The residue obtained on evaporation of the solvent was chromatographed over a silica gel column (2.4 × 22 cm) with 2% EtOH in $CHCl_3$ to give 2′,3′,5′-tri-*O*-benzoyl-5-(dimethylamino)uridine (**2c**, 2.9 g, 63%) as a foam, which was subjected to further reaction without purification. MS *m/z*: 494 (M^+ −Bz). NMR ($CDCl_3$): 2.46 (6H, s, NMe_2), 4.56—4.93 (3H, m, 4′, 5′, 5″-H), 5.78 (1H, dd, 2′-H, $J_{1',2'}$=6.6, $J_{2',3'}$=6.1 Hz), 5.93 (1H, dd, 3′-H, $J_{3',4'}$=2.4 Hz), 6.47 (1H, d, 1′-H), 6.62 (1H, s, 6-H), 7.39—8.20 (15H, m, Ph), 8.29 (1H, br s, 3-NH). Phosphoryl oxychloride (0.75 ml, 6.5 mmol) was added to a solution of 1-methylimidazole (2.13 ml, 21.7 mmol) in dry acetonitrile (20 ml) at 0 °C. The mixture was stirred for 10 min at room temperature, then a solution of compound **2c** (1.3 g, 2.17 mmol) in acetonitrile (5 ml) was added to it. The reaction mixture was stirred for a further 10 h, then EtOH (5 ml) and Et_3N (5 ml) were added. After being stirred for a further 5 h, the mixture was evaporated to a small volume and partitioned between $CHCl_3$ (100 ml) and H_2O (80 ml × 2). The separated organic phase was dried (Na_2SO_4). The residue obtained on evaporation of solvent was purified over a silica gel column (3 × 16 cm) with 40% EtOAc in hexane to give 5-(dimethylamino)-4-ethoxy-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2(1*H*)-pyrimidinone as a foam (1.02 g, 74.9%). MS *m/z*: 502 (M^+ −Bz). NMR ($CDCl_3$): 1.40 (3H, t, OCH_2CH_3, J=7.1 Hz), 2.40 (6H, s, NMe_2), 4.50 (2H, q, OCH_2CH_3), 4.62—4.95 (3H, m, 4′, 5′, 5″-H), 5.74 (1H, dd, 2′-H, $J_{1',2'}$=6.4, $J_{2',3'}$=6.1 Hz), 5.96 (1H, dd, 3′-H, $J_{3',4'}$=3.2 Hz), 6.66 (1H, d, 1′-H), 7.04 (1H, s, 6-H), 7.42—8.19 (15H, m, Ph). A solution of 1 N NaOEt (0.3 ml) in EtOH was added to a solution of this compound (1.0 g, 1.6 mmol) in EtOH (30 ml). The mixture was stirred for 2 h at room temperature, then neutralized with 1 N aqueous HCl, and silica gel was added. The mixture was concentrated to dryness *in vacuo*. The residue was placed on top of a silica gel column (2.4 × 22 cm), which was washed with 2% EtOH in $CHCl_3$ and eluted with 10% EtOH in $CHCl_3$. The main UV-absorbing fractions were combined and concentrated to dryness to leave a solid, which was crystallized from EtOH–Et_2O to give **4c** (403 mg, 80%), mp 126—127 °C. MS *m/z*: 315 (M^+). NMR (DMSO-d_6): 1.32 (3H, t, OCH_2CH_3, J=7.1 Hz), 2.53 (6H, s, NMe_2), 3.61—4.02 (5H, m, 2′, 3′, 4′, 5′, 5″-H), 4.34 (2H, q, OCH_2CH_3), 4.99 (1H, d, 2′- or 3′-OH), 5.24 (1H, t, 5′-OH), 5.41 (1H, d, 2′- or 3′-OH), 5.79 (1H, d, 1′-H, $J_{1',2'}$=2.7 Hz), 7.92 (1H, s, 6-H). *Anal.* Calcd for $C_{13}H_{21}N_3O_6$: C, 49.52; H, 6.71; N, 13.33. Found: C, 49.49; H, 6.86; N, 13.52.

5-(Dimethylamino)-4-ethoxy-1-[3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-β-D-ribofuranosyl]-2(1*H*)-pyrimidinone (5c) 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (710 μl, 1.1 eq) was added to a solution of compound **4c** (650 mg, 2.06 mmol) in dry pyridine (8 ml) at 0 °C. The mixture was stirred for 3 h at room temperature and the reaction was quenched by addition of EtOH (1 ml). The mixture was concentrated to dryness *in vacuo*, and the residue was partitioned between EtOAc (80 ml) and H_2O (20 ml × 2). The separated organic phase was dried (Na_2SO_4) and concentrated to dryness, and the residue was chromatographed over a silica gel column (2.4 × 18 cm) with 20% EtOAc in hexane to yield an oily product (**5c**, 610 mg, 53%). MS *m/z*: 557 (M^+), 514 (M^+ −isoPr). NMR ($CDCl_3$): 1.03—1.08 (28H, m, isoPr), 1.42 (3H, t, OCH_2CH_3, J=7.1 Hz), 2.65 (6H, s, NMe_2), 3.12 (1H, d, 2′-OH), 3.96—4.63 (7H, m, 2′, 3′, 4′, 5′, 5″-H, OCH_2CH_3), 5.61 (1H, s, 1′-H), 7.29 (1H, s, 6-H). *Anal.* Calcd for $C_{25}H_{47}N_3O_7Si_2$: C, 53.83; H, 8.49; N, 7.53. Found: C, 53.55; H, 8.46; N, 7.41.

5-(Dimethylamino)-4-ethoxy-1-[3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-β-D-*erythro*-2-pentofuranos-2-ulos-1-yl]-2(1*H*)-pyrimidinone (6c) A solution of DMSO (490 μl, 6.83 mmol) in dry CH_2Cl_2 (4 ml) was added dropwise over 5 min to a mixture of oxalyl chloride (300 μl, 3.4 mmol) in CH_2Cl_2 (5 ml) at −78 °C under argon. A solution of compound **5c** (950 mg, 1.7 mmol) in CH_2Cl_2 (5 ml) was added dropwise over 15 min to this mixture. The whole was stirred for a further 3 h, then Et_3N (1.7 ml, 12.2 mmol) was added in a single portion. The mixture was stirred for a further 1 h, then the cooling bath was removed. After warming to room temperature, the mixture was diluted with CH_2Cl_2 (50 ml), washed with H_2O (30 ml × 2), and dried (Na_2SO_4). The residue obtained on evaporation of the solvent was chromatographed over a silica gel column (2.4 × 18 cm) with 20% EtOAc in hexane. The main UV-absorbing fractions were combined and concentrated to dryness to give **6c** as an oil (800 mg, 85%). MS *m/z*: 512 (M^+ −isoPr). NMR ($CDCl_3$): 1.06—1.33 (28H, m, isoPr), 1.40 (3H, t, OCH_2CH_3, J=7.1 Hz), 2.65 (6H, s, NMe_2), 3.94—4.18 (3H, m, 4′, 5′, 5″-H), 4.50 (2H, q, OCH_2CH_3, J=7.1 Hz), 4.93 (1H, s, 1′-H), 5.19 (1H, d, 3′-H, $J_{3',4'}$=7.8 Hz), 6.83 (1H, s, 6-H). *Anal.* Calcd for $C_{25}H_{45}N_3O_7Si_2$: C, 54.02; H, 8.16; N, 7.56. Found: C, 53.85; H, 8.24; N, 7.62.

Reaction of 6a with MeMgBr A solution of MeMgBr in Et_2O (3 M, 7 ml, 3 eq) was added dropwise over 5 min to a solution of **6a** (3.7 g, 7.03 mmol) in Et_2O (100 ml) at −80 °C under argon. The mixture was stirred for 1.5 h, then aqueous 1 N NH_4Cl solution (25 ml) was added. After warming to room temperature, the reaction mixture was partitioned between EtOAc (150 ml) and H_2O (30 ml × 2) and the organic phase was dried (Na_2SO_4) then concentrated to dryness. The residue was purified on a silica gel column (3 × 45 cm) with 20% EtOAc in hexane. From this fraction, compound **7a** (1.26 g, 33%) was obtained as an oil. Elution was continued with 40% EtOAc in hexane to afford **8a** (1.38 g, 36%), which could be crystallized from hexane.

Physical Data for 4-Ethoxy-5-methyl-1-[2α-methyl-3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-β-D-arabinofuranosyl]-2(1*H*)-pyrimidinone (**7a**): MS *m/z*: 542 (M^+), 499 (M^+ −isoPr), 155 (B^+ + 1). NMR ($CDCl_3$): 1.03—1.10 (28H, m, isoPr), 1.37 (3H, t, OCH_2CH_3, J=7.1 Hz), 1.56 (3H, s, 2′-Me), 1.96 (3H, d, 5-Me, $J_{5\text{-Me},6}$=1.0 Hz), 2.88 (1H, s, 2′-OH), 3.79—4.22 (4H, m, 3′, 4′, 5′, 5″-H), 4.44 (2H, q, OCH_2CH_3, J=7.1 Hz), 5.75 (1H, s, 1′-H), 7.80 (1H, d, 6-H). *Anal.* Calcd for $C_{25}H_{46}N_2O_7Si_2$: C, 55.32; H, 8.54; N, 5.16. Found: C, 55.30; H, 8.52; N, 5.37.

Physical Data for 4-Ethoxy-5-methyl-1-[2β-methyl-3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-β-D-ribofuranosyl]-2(1*H*)-pyrimidinone (**8a**): mp 182—183 °C, MS *m/z*: 542 (M^+), 499 (M^+ −isoPr), 155 (B^+ + 1). NMR ($CDCl_3$): 1.05—1.11 (28H, m, isoPr), 1.19 (3H, s, 2′-Me), 1.37 (3H, t, OCH_2CH_3, J=7.1 Hz), 1.93 (3H, d, 5-Me, J=1.0 Hz), 2.72 (1H, s, 2′-OH), 3.96—4.35 (4H, m, 3′, 4′, 5′, 5″-H), 4.45 (2H, q, OCH_2CH_3, J=7.1 Hz), 6.10 (1H, s, 1′-H), 7.62 (1H, d, 6-H). *Anal.* Calcd for

$C_{25}H_{46}N_2O_7Si_2$: C, 55.32; H, 8.54; N, 5.16. Found: C, 55.19; H, 8.54; N, 5.40.

Reaction of 6b with MeMgBr A solution of MeMgBr in Et_2O (3 M, 0.5 ml, 3 eq) was added dropwise for 1 min to a solution of **6b** (240 mg, 0.45 mmol) in dry Et_2O (20 ml) at −80 °C under argon. The mixture was stirred for 1 h, then aqueous 1 N NH_4Cl solution (5 ml) was added. After warming to room temperature, the reaction mixture was partitioned between EtOAc (30 ml) and H_2O (10 ml × 2) and the separated organic phase was dried (Na_2SO_4) and concentrated to dryness to leave an oily residue. The residue was chromatographed over a silica gel column (1.8 × 13 cm) with 20% EtOAc in hexane. From the first fractions, **7b** was obtained as a crystalline foam (168 mg, 68%). From the next fractions, **8b** was obtained as a crystalline foam (45 mg, 18%).

Physical Data for 4-Ethoxy-5-fluoro-1-[2α-methyl-3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-β-D-arabinofuranosyl]-2(1*H*)-pyrimidinone (**7b**): mp 190—192 °C (EtOAc–hexane). MS *m/z*: 546 (M^+), 503 (M^+ − isoPr). NMR ($CDCl_3$): 1.01—1.11 (28H, m, isoPr), 1.42 (3H, t, $OCH_2C\underline{H}_3$, J=7.1 Hz), 1.57 (3H, s, 2′-Me), 2.77 (1H, s, 2′-OH), 3.82—4.22 (4H, m, 3′, 4′, 5′, 5″-H), 4.53 (2H, q, $OC\underline{H}_2CH_3$, J=7.1 Hz), 5.73 (1H, d, 1′-H, $J_{1',F}$=1.5 Hz), 8.13 (1H, d, 6-H, $J_{6,F}$=5.9 Hz). High-resolution MS *m/z*: M^+ Calcd for $C_{24}H_{43}FN_2O_7Si_2$: 546.2593. Found: 546.2639.

Physical Data for 4-Ethoxy-5-fluoro-1-[2β-methyl-3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-β-D-ribofuranosyl]-2(1*H*)-pyrimidinone (**8b**): mp 201—203 °C (EtOAc–hexane). MS *m/z*: 546 (M^+), 503 (M^+ − isoPr). NMR ($CDCl_3$): 1.05—1.11 (28H, m, isoPr), 1.23 (3H, s, 2′-Me), 1.42 (3H, t, $OCH_2C\underline{H}_3$, J=7.1 Hz), 2.70 (1H, s, 2′-OH), 3.94—4.33 (4H, m, 3′, 4′, 5′, 5″-H), 4.53 (2H, q, $OC\underline{H}_2CH_3$), 6.08 (1H, d, 1′-H, $J_{1',F}$= 1.7 Hz), 8.00 (1H, d, 6-H, $J_{6,F}$=5.9 Hz). High-resolution MS *m/z*: M^+ Calcd for $C_{24}H_{43}FN_2O_7Si_2$: 546.2593. Found: 546.2603.

Reaction of 6c with MeMgBr A solution of MeMgBr in Et_2O (3 M, 1.4 ml, 3 eq) was added dropwise over 3 min to a solution of **6c** (740 mg, 1.33 mmol) in dry Et_2O (20 ml) at −80 °C under argon. The mixture was stirred for 2 h, then aqueous 1 N NH_4Cl solution (5 ml) was added. After warming to room temperature, the reaction mixture was partitioned between EtOAc (30 ml) and H_2O (10 ml × 2) and the separated organic phase was dried (Na_2SO_4) and concentrated to dryness to leave an oily residue. The residue was chromatographed over a silica gel column (2.4 × 23 cm) with 20% EtOAc in hexane. From the first fraction, **8c** was obtained as a foam (183 mg, 24%). From the next fractions, **7c** was obtained as a foam (360 mg, 47%).

Physical Data for 5-(Dimethylamino)-4-ethoxy-1-[2β-methyl-3,5-*O*-(1,1,-3,3-tetraisopropyl-1,3-disiloxanediyl)-β-D-ribofuranosyl]-2(1*H*)-pyrimidinone (**8c**): NMR ($CDCl_3$): 1.05—1.11 (28H, m, isoPr), 1.20 (3H, s, 2′-Me), 1.42 (3H, t, $OCH_2C\underline{H}_3$, J=7.1 Hz), 2.66 (6H, s, NMe_2), 2.93 (1H, s, 2′-OH), 3.97—4.17 (4H, m, 3′, 4′, 5′, 5″-H), 4.52 (2H, q, $OC\underline{H}_2CH_3$, J=7.1 Hz), 6.00 (1H, s, 1′-H), 7.30 (1H, s, 6-H). High-resolution MS *m/z*: M^+ Calcd for $C_{26}H_{49}N_3O_7Si_2$: 571.3108. Found: 571.3127.

Physical Data for 5-(Dimethylamino)-4-ethoxy-1-[2α-methyl-3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-β-D-arabinofuranosyl]-2(1*H*)-pyrimidinone (**7c**): NMR ($CDCl_3$): 1.01—1.35 (28H, m, isoPr), 1.42 (3H, t, $OCH_2C\underline{H}_3$, J=7.1 Hz), 1.57 (3H, s, 2′-Me), 2.68 (6H, s, NMe_2), 3.06 (1H, s, 2′-OH), 3.75 (1H, dt, 4′-H, $J_{4',5'}$=2.4, $J_{3',4'}$=9.5 Hz), 4.05—4.27 (3H, m, 3′, 5′, 5″-H), 4.52 (2H, q, $OC\underline{H}_2CH_3$, J=7.1 Hz), 5.70 (1H, s, 1′-H), 7.55 (1H, s, 6-H). High-resolution MS *m/z*: M^+ Calcd for $C_{26}H_{49}N_3O_7Si_2$: 571.3108. Found: 571.3130.

Deprotection of TIPDS Group General Procedure: A solution of tetra-*n*-butylammonium fluoride (1 M in tetrahydrofuran (THF), 2.2 eq) was added to a solution of **7** or **8** in THF. The reaction was almost completed within 20 min. The reaction mixture was neutralized with AcOH and mixed with silica gel. This mixture was concentrated to dryness *in vacuo* and the residue was placed on top of a silica gel column, which was eluted with 10—16% EtOH in $CHCl_3$ to afford the free nucleoside.

4-Ethoxy-5-methyl-1-(2α-methyl-β-D-arabinofuranosyl)-2(1*H*)-pyrimidinone (9a) From 1.99 g (3.66 mmol) of **7a**, 865 mg (78%, EtOH) of **9a** was obtained, mp 199—200 °C, MS *m/z*: 301 (M^+), 283 ($M^+ - H_2O$), 155 ($B^+ + 1$). NMR (DMSO-d_6): 1.16 (3H, s, 2′-Me), 1.31 (3H t, $OCH_2C\underline{H}_3$, J=7.1 Hz), 1.88 (3H, d, 5-Me, $J_{6,Me}$=1.0 Hz), 3.68—3.70 (4H, m, 3′, 4′, 5′, 5″-H), 4.32 (2H, q, $OC\underline{H}_2CH_3$, J=7.1 Hz), 5.11 (1H, s, 2′-OH), 5.22 (1H, t, 5′-OH), 5.47 (1H, d, 3′-OH), 5.91 (1H, s, 1′-H), 5.78 (1H, d, 6-H, $J_{6,Me}$=1.0 Hz). *Anal.* Calcd for $C_{13}H_{21}N_2O_6$: C, 51.82; H, 7.03; N, 9.30. Found: C, 51.93; H, 7.11; N, 9.13.

4-Ethoxy-5-methyl-1-(2β-methyl-β-D-ribofuranosyl)-2(1*H*)-pyrimidinone (10a) From 1.66 g (3.07 mmol) of **8a**, compound **10a** was obtained (870 mg, 94% EtOH), mp 162—164 °C. MS *m/z*: 301 (M^+), 155 ($B^+ + 1$). NMR (DMSO-d_6): 0.94 (3H, s, 2′-Me), 1.30 (3H, t, $OCH_2C\underline{H}_3$, J=7.1 Hz), 3.71—3.77 (4H, m, 3′, 4′, 5′, 5″-H), 4.31 (2H, q, $OC\underline{H}_2CH_3$, J=7.1 Hz), 5.06 (1H, d, 3′-OH), 5.10 (1H, s, 2′-OH), 5.28 (1H, t, 5′-OH), 5.88 (1H, s, 1′-H), 8.28 (1H, d, 6-H). *Anal.* Calcd for $C_{13}H_{21}N_2O_6$: C, 51.82; H, 7.03; N, 9.30. Found: C, 51.67; H, 6.93; N, 9.28.

4-Ethoxy-5-fluoro-1-(2α-methyl-β-D-arabinofuranosyl)-2(1*H*)-pyrimidinone (9b) From 169 mg of **7b**, compound **10b** was obtained (72 mg, 77%, EtOH–Et_2O), mp 158—161 °C. MS *m/z*: 304 (M^+), 159 ($B^+ + 1$). NMR (DMSO-d_6): 1.19 (3H, s, 2′-Me), 1.34 (3H, t, $OCH_2C\underline{H}_3$, J=7.0 Hz), 3.63—3.76 (4H, m, 3′, 4′, 5′, 5″-H), 4.40 (2H, q, $OC\underline{H}_2CH_3$, J=7.0 Hz), 5.19 (1H, s, 2′-OH), 5.25 (1H, t, 5′-OH, J=5.3 Hz), 5.47 (1H, d, 3′-OH, J=4.8 Hz), 5.86 (1H, d, 1′-H, $J_{1',F}$=2.2 Hz), 8.16 (1H, d, 6-H, $J_{6,F}$=7.0 Hz). *Anal.* Calcd for $C_{12}H_{17}FN_2O_6$: C, 47.37; H, 5.63; N, 9.21. Found: C, 47.32; H, 5.84; N, 9.08.

4-Ethoxy-5-fluoro-1-(2β-methyl-β-D-ribofuranosyl)-2(1*H*)-pyrimidinone (10b) From 51 mg of **8b**, compound **10b** was obtained (26 mg, 92%, EtOH–Et_2O), mp 162—163 °C. MS *m/z* 304 (M^+), 159 ($B^+ + 1$). NMR (DMSO-d_6): 0.99 (3H, s, 2′-Me), 1.33 (3H, t, $OCH_2C\underline{H}_3$, J=7.1 Hz), 3.62—3.87 (4H, m, 3′, 4′, 5′, 5″-H), 4.38 (2H, q, $OC\underline{H}_2CH_3$, J=7.1 Hz), 5.11 (1H, d, 3′-OH, J=6.7 Hz), 5.19 (1H, s, 2′-OH), 5.44 (1H, t, 5′-OH, J=4.4 Hz), 5.81 (1H, d, 1′-H, $J_{1',F}$=1.7 Hz), 8.79 (1H, d, 6-H, $J_{6,F}$=7.1 Hz). *Anal.* Calcd for $C_{12}H_{17}FN_2O_6$: C, 47.37; H, 5.63; N, 9.21. Found: C, 47.29; H, 5.70; H, 9.16.

5-(Dimethylamino)-4-ethoxy-1-(2α-methyl-β-D-arabinofuranosyl)-2(1*H*)-pyrimidinone (9c) From 206 mg of **7c**, compound **9c** was obtained (81 mg, 68%, EtOH–Et_2O), mp 124—126 °C. MS *m/z*: 329 (M^+), 183 (B^+). NMR (DMSO-d_6): 1.19 (3H, s, 2′-Me), 1.33 (3H, t, $OCH_2C\underline{H}_3$, J=7.0 Hz), 2.54 (6H, s, NMe_2), 3.60—3.80 (4H, m, 3′, 4′, 5′, 5″-H), 4.33 (2H, q, $OC\underline{H}_2CH_3$, J=7.0 Hz), 5.11 (1H, s, 2′-OH), 5.24 (1H, br s, 5′-OH), 5.41 (1H, d, 3′-OH, J=5.1 Hz), 5.91 (1H, s, 1′-H), 7.60 (1H, s, 6-H). *Anal.* Calcd for $C_{14}H_{27}N_3O_6$: C, 51.06; H, 7.04; N, 12.76. Found: C, 50.87; H, 7.27; N, 12.56.

5-(Dimethylamino)-4-ethoxy-1-(2β-methyl-β-D-ribofuranosyl)-2(1*H*)-pyrimidinone (10c) From 77 mg of **8c**, compound **10c** was obtained (33 mg, 75%, EtOH–Et_2O), mp 83—86 °C. MS *m/z* 329 (M^+), 183 (B^+). NMR (DMSO-d_6): 0.92 (3H, s, 2′-Me), 1.32 (3H, t, $OCH_2C\underline{H}_3$, J=7.0 Hz), 2.52 (6H, s, NMe_2), 3.59—3.87 (4H, m, 3′, 4′, 5′, 5″-H), 4.33 (2H, q, $OC\underline{H}_2CH_3$, J=7.0 Hz), 5.05 (1H, d, 3′-OH, J=6.6 Hz), 5.10 (1H, s, 2′-OH), 5.32 (1H, t, 5′-OH, J=4.4 Hz), 5.92 (1H, s, 1′-H), 7.98 (1H, s, 6-H). *Anal.* Calcd for $C_{14}H_{27}N_3O_6$: C, 51.06; H, 7.04; N, 12.76. Found: C, 51.21; H, 7.18; N, 12.52.

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References and Notes

1) Part XLII: A. Matsuda, M. Satoh, T. Ueda, M. Machida, and T. Sasaki, *Nucleosides & Nucleotides*, **9**, 587 (1990).
2) A. Matsuda, K. Takenuki, H. Itoh, T. Sasaki, and T. Ueda, *Chem. Pharm. Bull.*, **35**, 3967 (1987).
3) A. Matsuda, H. Itoh, K. Takenuki, T. Sasaki, and T. Ueda, *Chem. Pharm. Bull.*, **36**, 945 (1988).
4) T. Ueda, A. Matsuda, Y. Yoshimura, and K. Takenuki, *Nucleosides & Nucleotides*, **8**, 743 (1989).
5) J. Yoshimura, *Adv. Carbohydr. Chem. Biochem.*, **42**, 69 (1984) and references cited therein.
6) F. Hansske, D. Madej, and M. J. Robins, *Tetrahedron*, **40**, 125 (1984).
7) F. Hansske and M. J. Robins, *J. Am. Chem. Soc.*, **105**, 6736 (1983).
8) T. Ueda, S. Shuto, and H. Inoue, *Nucleosides & Nucleotides*, **3**, 173 (1984).
9) T. Ueda, S. Shuto, M. Satoh, and H. Inoue, *Nucleosides & Nucleotides*, **4**, 401 (1985).
10) T. Sano, S. Shuto, H. Inoue, and T. Ueda, *Chem. Pharm. Bull.*, **33**, 3617 (1985).
11) H. Usui and T. Ueda, *Chem. Pharm. Bull.*, **34**, 1518 (1986).
12) T. Ueda, *Chem. Pharm. Bull.*, **10**, 788 (1962).
13) A. Matsuda, K. Obi, and T. Miyasaka, *Chem. Pharm. Bull.*, **33**, 2575 (1985).
14) A. J. Mancuso, S.-L. Huang, and D. Swern, *J. Org. Chem.*, **43**, 2480 (1978).
15) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, **16**, 1207 (1973).

16) Y. Yamagata, K. Tomita, A. Matsuda, K. Takenuki, and T. Ueda, Abstracts of Papers, 108th Annual Meeting of the Pharmaceutical Society of Japan, Hiroshima, April 1988, p. 731.
17) R. J. Cushley, I. Wempen, and J. J. Fox, *J. Am. Chem. Soc.*, **90**, 709 (1968).
18) H. Tanaka, A. Matsuda, S. Iijima, H. Hayakawa, and T. Miyasaka, *Chem. Pharm. Bull.*, **31**, 2164 (1983).
19) Purchased from Yamasa Shoyu Co., Ltd. (Chosi, Chiba, Japan).
20) A. Matsuda, M. Shinozaki, M. Suzuki, K. Watanabe, and T. Miyasaka, *Synthesis*, **1986**, 385.