Nucleosides. 130. Synthesis of 2′-Deoxy-2′-substituted- and 5′-Deoxy-5′-substituted-ψ-uridine Derivatives. Crystalline and Molecular Structure of 2′-Chloro-2′-deoxy-1,3-dimethyl-ψ-uridine. Studies Directed Toward the Synthesis of 2′-Deoxy-2′-substituted-*arabino*-Nucleosides. 1 [1]

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A method was developed to prepare 5′-deoxy-5′-substituted-ψ-uridine derivatives **4** from 3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-1,3-dimethyl-ψ-uridine **1** *via* a silyl rearrangement reaction. Nucleophilic displacement of the mesyloxy function of 2′-*O*-mesyl-1,3-dimethyl-ψ-uridine **7** afforded products with the 2′-substituent in the "down" *ribo* configuration **8**. X-Ray crystallographic analysis of the 2′-chloro derivative **8a** firmly established the molecular structure of **8** and provided evidence for neighboring group participation of the 4-carbonyl function of **7** during the nucleophilic reactions.

Treatment of 1,3-dimethyl-ψ-uridine **11** with α-acetoxyisobutyryl chloride afforded a mixture from which two 2′-chloro-2′-deoxy-*C*-nucleosides were obtained. The major product (33% yield) was identical with **8**. The minor product (7% yield) was consequently assigned the *arabino* nucleoside **14**. This is the first direct introduction of a 2′-substituent in the "up" configuration in a preformed pyrimidine nucleoside.

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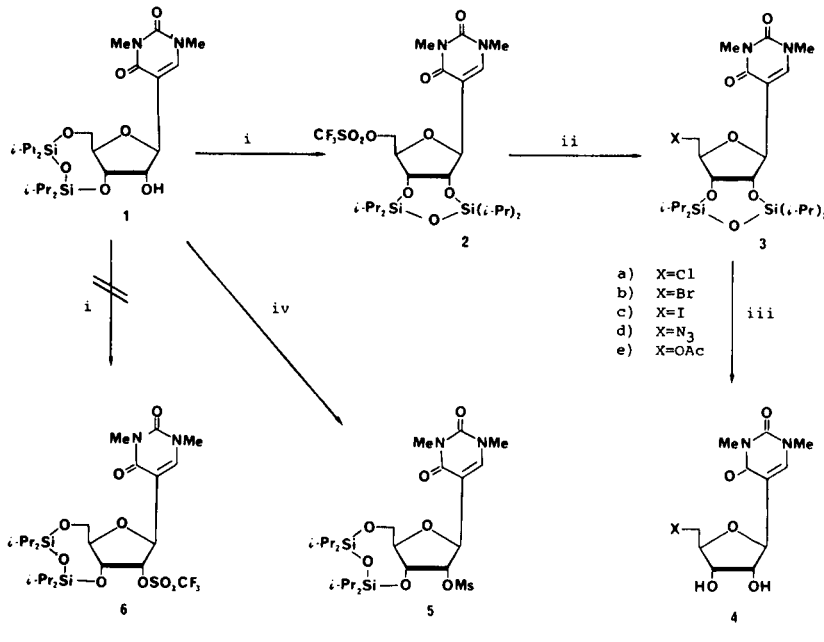
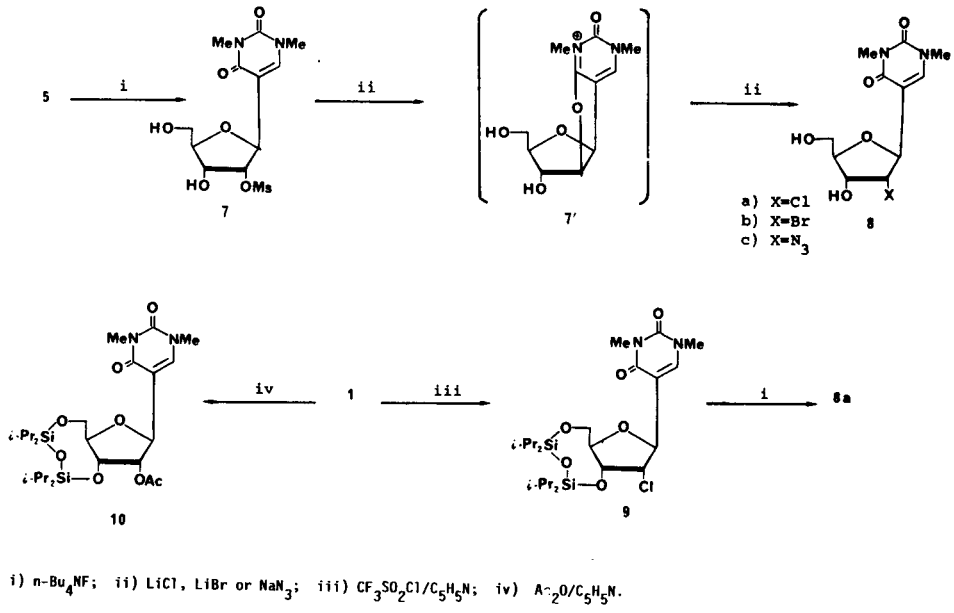
The recent discovery in our laboratory that certain pyrimidine nucleosides containing the 2′-deoxy-2′-fluoro-β-D-*arabino*-furanosyl moiety exhibit extremely potent and selective antiherpetic activity [2-4] prompted us to synthesize some of their *C*-nucleoside analogs. The synthesis of 2′-"up" substituted *N*-nucleosides is usually performed by condensation of an appropriate sugar with a base. This approach is not applicable in the *C*-nucleoside area but,

Chart 1



i) $CF_3SO_2)O/C_5H_5N$; ii) LiCl, LiBr, KI, NaN_3 or NaOAc; iii) n-Bu_4NF; iv) $MsCl/C_5H_5N$.

Chart 2



rather, requires the chemical construction of the aglycone. Therefore, a method of direct introduction of a substituent in the C2′-"up" position is of great interest. Although several purine nucleosides have been modified at the C2′ position by nucleophilic displacement of the C2′-"down" leaving group, this goal in pyrimidine nucleosides has not yet been achieved. In order to prepare such *C*-nucleosides, we planned to synthesize 1,3-dimethyl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-2′-*O*-trifluoromethylsulfonyl-ψ-uridine **6** (Chart 1) and displace the 2′-trifluoromethylsulfonyloxy function with a fluoride nucleophile. Application of the novel heterocyclic ring transformation reactions developed in our laboratory [5-7] to the fluorinated product would then provide various *C*-nucleosides containing the 2′-deoxy-2′-fluoro-*arabino*-furanosyl moiety.

Though introduction of a substituent to the C2′-"up" position of a preformed *pyrimidine-N-nucleoside* by nucleophilic reactions has not been achieved due to close proximity of the 2-carbonyl group to the C2′ position [8], the distance between the base and sugar in **6** is further apart than in uridine due to the longer bond length of the C-C glycosyl linkage in **6** [9]. In addition, the C-C glycosyl linkage in *C*-nucleosides should render a leaving group on C2′ more susceptible to nucleophilic displacement than would the more electronegative C-N linkage in *N*-nucleosides or the C-O glycosyl linkage in a methyl 2-*O*-trifluoromethylsulfonyl-D-ribofuranoside [10]. We hoped, therefore, that direct introduction of a fluorine atom into the C2′-"up" position of the ψ-uridine might be possible by this approach.

Treatment of 1,3-dimethyl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-ψ-uridine **1** [11] with trifluoromethylsulfonic (triflic) anhydride in the presence of base afforded an almost quantitative yield of a crystalline product which, however, was not the desired 2′-triflate **6** but the isomeric 5′-triflate **2** [12]. Nucleophilic displacement of the 5′-triflate group occurred smoothly when **2** was treated with li-

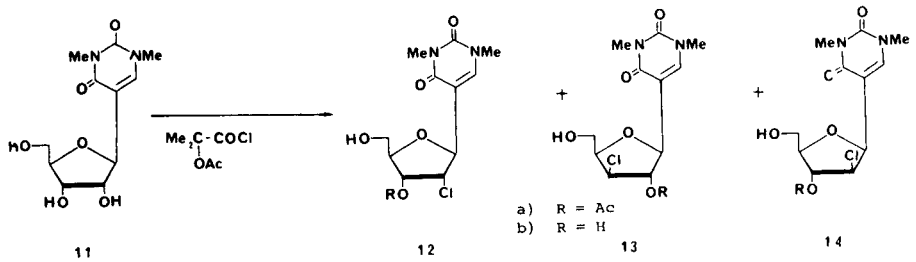
Table I

Bond Lengths (Å) in Molecules **A** and **B** [a]

	Molecule A	Molecule B
N1—C1	1.46	1.47
N1—C2	1.37	1.36
C2—O2	1.23	1.23
C2—N3	1.35	1.34
N3—C3	1.47	1.49
C4—O4	1.23	1.22
C4—C5	1.44	1.42
C5—C6	1.34	1.32
C6—N1	1.38	1.42
C5—C1′	1.51	1.55
C1′—O4′	1.44	1.41
C1′—C2′	1.56	1.56
C2′—C12′	1.81	1.81
C2′—C3′	1.51	1.51
C3′—O3′	1.43	1.45
C3′—C4′	1.53	1.51
C4′—O4′	1.45	1.47
C4′—C5′	1.49	1.48
C5′—O5′	1.47	1.43

[a] Standard deviations are 0.01 Å.

Chart 3



thium chloride, potassium iodide, sodium azide or sodium acetate in hexamethylphosphoric triamide and the corresponding 5′-substituted *C*-nucleosides (**3a-e**) were obtained in high yields. Treatment of **3e** with tetra-*n*-butylammonium fluoride followed by saponification afforded 1,3-dimethyl-ψ-uridine [5], indicating that **3e** was not the *arabino*-*C*-nucleoside. However, **3e** was not identical with 2′-*O*-acetyl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-1,3-dimethyl-ψ-uridine **10** prepared by acetylation of **1** (Chart 2). The only explanation of the above results was to assume that the acetyl group was at the C5′ position in **3e**. Reduction of **3a** with tri-*n*-butyltin hydride in the presence of 2,2′-azobis(2-methylpropionitrile) afforded the 5′-deoxy derivative (**3**, X = H) which was further converted into 5′-deoxy-1,3-dimethyl-ψ-uridine [12] (**4**, X = H). Compounds **3b-d** were also converted into the corresponding deprotected *C*-nucleosides **4b-d** by treatment with tetra-*n*-butylammonium fluoride. These experiments confirmed the structures of **2** and **3**, and established the fact that rearrangement of the 3′,5′-cyclic disiloxanyl structure into the 2′,3′-cyclic isomer had occurred during triflation of **1**. Such a rearrangement with similarly silylated *N*-nucleosides has been reported [13] to occur *only* in *N,N*-dimethylformamide under acid catalysis in low yields (up to 50%). The rearrangement we report herein is unique in that it occurred *quantitatively* and in methylene chloride.

In order to gain insight into the mechanism of this isomerization, we treated compound **1** with triflic anhydride with varying amounts of base (pyridine or 1,8-diazabicyclo[5,4,0]undec-7-ene) in methylene chloride, and found that even a small molar excess of the triflating agent over the base brought about quantitative isomerization and **2** was obtained as the sole product. On the other hand, even a slight molar excess of the base over the triflating agent prevented triflation and **1** was recovered unchanged. Treatment of **1** with the equivalent of pyridinium triflate in methylene chloride did not cause 5′ → 2′ migration of the silyl group. However, a slight excess of triflic acid did catalyze the migration (isomerization) of the silyl group of **1**. The major product observed on the thin layer chromatography plate was the 2′,3′-*O*-disiloxanyl-1,3-dimethyl-ψ-

Table II

Bond Angles (Deg) in Molecules **A** and **B** [a]

	Molecule A	Molecule B
C1—N1—C2	118.7(8)	119.3(8)
C1—N1—C6	120.1(8)	119.5(8)
C2—N1—C6	121.1(7)	121.2(8)
N1—C2—N3	117.6(8)	117.5(8)
N1—C2—O2	120.7(8)	120.6(9)
O2—C2—N3	121.7(9)	121.8(9)
C2—N3—C3	117.5(7)	116.9(8)
C2—N3—C4	124.0(8)	125.1(7)
C3—N3—C4	118.5(7)	117.9(8)
N3—C4—O4	120.7(8)	118.9(8)
N3—C4—C5	116.1(7)	114.0(7)
O4—C4—C5	123.2(8)	127.0(9)
C4—C5—C6	119.0(8)	122.3(8)
C5—C6—N1	122.0(8)	119.7(8)
C4—C5—C1′	118.0(7)	116.8(7)
C6—C5—C1′	122.8(8)	120.3(8)
O4′—C1′—C5	110.0(7)	109.1(7)
O4′—C1′—C2′	104.4(7)	106.0(7)
C2′—C1′—C5	111.5(7)	111.2(7)
C1′—C2′—C3′	101.7(7)	101.4(7)
C1′—C2′—C12′	106.5(6)	107.0(6)
C3′—C2′—C12′	111.5(7)	111.5(6)
C2′—C3′—C4′	102.6(7)	103.7(7)
C2′—C3′—O3′	115.2(8)	112.0(8)
C4′—C3′—O3′	107.3(7)	111.6(7)
C3′—C4′—O4′	104.2(7)	104.1(7)
C3′—C4′—C5′	112.3(8)	116.1(9)
O4′—C4′—C5′	110.4(7)	110.1(7)
C4′—C5′—O5′	108.0(7)	107.9(8)

[a] Standard deviations are in parenthesis.

Table III

Selected Dihedral Angles (Deg)

	Molecule A	Molecule B
C4—C5—C1′—C2′	80	71
C4—C5—C1′—O4′	−165	−172
C6—C5—C1′—C2′	−104	−116
C6—C5—C1′—O4′	11	0.3
C3′—C4′—C5′—O5′	−174	53
O4′—C4′—C5′—O5′	70	−65

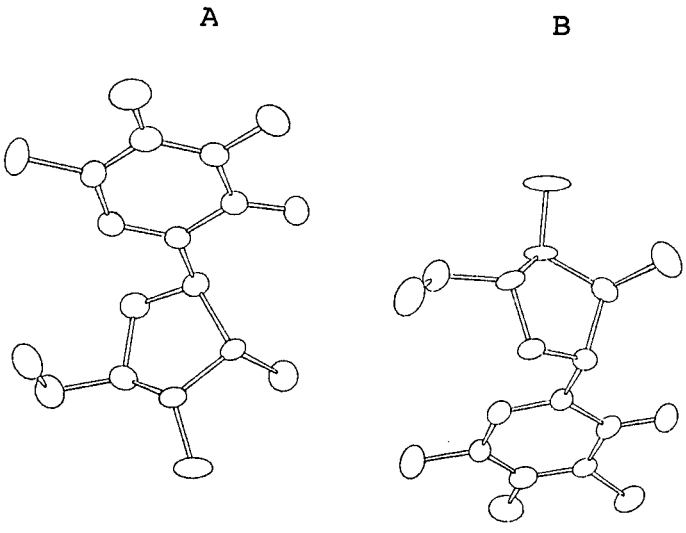


Figure 1. ORTEP stereoview of 2'-chloro-2'-deoxy-1,3-dimethyl-ψ-uridine.

uridine, along with a host of unidentified degradation products.

Mesylation of **1** in the presence of excess pyridine did not cause silyl rearrangement and the 2'-mesylate (**5**, Chart 1) was obtained in high yield. After desilylation of **5** with tetra-*n*-butylammonium fluoride, the crystalline product **7** (Chart 2) was treated with lithium chloride, lithium bromide or sodium azide in *N,N*-dimethylformamide. The corresponding 2'-substituted-1,3-dimethyl-ψ-uridines (**8**) were obtained in high yields in crystalline form. The 2'-chloro derivative (**8a**) was also obtained by treatment of **1** with triflic chloride in pyridine followed by desilylation of the product **9**. Reduction of **8a** with tri-*n*-butyltin hydride afforded the known 2'-deoxy-1,3-dimethyl-ψ-uridine [11, 14]. *The position of the chloro substituent at C2' is therefore firmly established.* In order to establish the configuration of the chloro substituent at C2', we attempted to prepare 2'-chloro-2'-deoxy-1,3-dimethyl-ψ-uridine by an alternative route, as follows.

1,3-Dimethyl-ψ-uridine (**11**) was treated with α-acetoxyisobutyryl chloride in the hope that the reaction would result in the formation of 2'-chloro-2'-deoxy-1,3-dimethyl-ψ-uridine and its 3'-chloro-*xylo* isomer. After all the starting material was consumed, the products were briefly treated with ethanolic hydrogen chloride in chloroform to remove the unstable 2,5,5-trimethyldioxolan-2-yl group from the 5'-position. The resultant mixture was subjected to silica gel column chromatography, which gave two nucleoside fractions. A 3'-*O*-acetyl-2'-chloro-nucleoside was obtained as a foam from the less polar fraction in 33% yield overall from **11**. After deacylation, this compound gave a crystalline nucleoside identical to **8a**. The more polar fraction contained two nucleosides (pmr), one of which was directly crystallized from the mixture in 9% yield. This crystalline product afforded 3'-deoxy-1,3-dimethyl-ψ-uridine [14] after deacetylation and tri-*n*-butyltin hydride reduction, and is therefore assigned the 3'-chloro-*xylo* structure **13a**. From the mother liquor of crystalline **13a**, the third product was isolated in 7% yield overall from **11** as a foam after deacetylation followed by chromatographic separation. This nucleoside was *not* identical with **8a** but was

Table IV

Some Physical Constants of 5'-Substituted (**2-4**) and 2'-Substituted (**7-14**) 1,3-Dimethylpseudouridines

Compound	Mp (°C) (Yield %)	Formula	Analyses % Calcd./Found C	H	N	X	^{1}H NMR Parameters [a] Chemical Shifts (δ) H-1'	H-2'	H-3'	H-4'	H-5'5''	H-6	NMe	Other	J1',2' [b] (Hz)
2	117-120	$C_{24}H_{42}F_3N_2O_9SSi_2$	44.56	6.39	4.33		4.01	—	—	—	4.62 m	7.75 s	3.18 s	1.02 m	
	(100)		44.49	6.34	4.24								3.34 s	(*i*-Pr, 28H)	
3a	115-116	$C_{23}H_{41}ClN_2O_6Si_2$	52.87	7.58	5.14	6.50	4.68 d	4.52 m	4.25 m	3.82-	4.01 m	7.70 s	3.16 s	1.02 m	2.7
	(88)		52.72	7.77	5.13	6.59							3.32 s	(*i*-Pr, 28H)	
3b	114-115	$C_{23}H_{41}BrN_2O_6Si_2$	48.88	7.01	4.75	13.55	4.67 d	4.55 m	4.22 m	3.95 m	3.75 m	7.72 s	3.16 s	1.02 m	3.0
	(68)		48.71	7.25	4.70	13.59							3.32 s	(*i*-Pr, 28H)	
3c	105	$C_{23}H_{41}IN_2O_6Si_2$	45.27	6.49	4.50	19.93	4.67 d	4.53 m	4.13 m	3.70 m	3.48 m	7.76 s	3.16 s	1.02 m	3.0
	(73)		45.02	6.56	4.50	19.95							3.32 s	(*i*-Pr, 28H)	
3d	74-75	$C_{23}H_{41}N_5O_6Si_2$	52.24	7.49	12.69		4.66 d	4.51 m	4.26 m	3.86 m	3.58 m	7.76 s	3.16 s	1.02 m	1.8
	(98)		51.97	7.51	12.76								3.32 s	(*i*-Pr, 28H)	
3e	73	$C_{25}H_{44}N_2O_6Si_2$	53.93	7.96	5.03		4.66 d	4.51 m	4.26 m	3.86 m	3.58 m	7.76 s	3.16 s	1.02 m	2.1
	(74)		54.04	8.06	4.91								3.33 s	(*i*-Pr, 28H)	
3	132-135	$C_{23}H_{42}N_2O_6Si_2$	53.66	8.22	5.44		4.63 d	4.35 m	4.25 m	3.39-	3.75 m	7.83 s	3.16 s	1.02 m	2.0
(X = OH)	(98)		53.50	8.04	5.49								3.30 s	(*i*-Pr, 28H)	
3	foam	$C_{23}H_{42}N_2O_6Si_2$	53.38	8.49	5.62		4.57 d	4.43 m	3.80-	—	3.99 m	7.60 s	3.15 s	1.02 m	2.0
(X = H)	(70)		55.46	8.51	5.50								3.33 s	(*i*-Pr, 28H)	
														1.27 d	
														(4'-Me, 3H)	

Table IV continued

Some Physical Constants of 5′-Substituted (**2-4**) and 2′-Substituted (**7-14**) 1,3-Dimethylpseudouridines

Compound	Mp (°C) (Yield %)	Formula	Analyses % Calcd./Found C	H	N	X	^{1}H NMR Parameters [a] Chemical Shifts (δ) H-1′	H-2′	H-3′	H-4′	H-5′5″	H-6	NMe	Other	J1′,2′ [b] (Hz)
4a	168	$C_{11}H_{15}ClN_2O_5$	45.45	5.20	9.63	12.19	4.56 d	3.80-	—	—	4.04 m	7.67 s	3.17 s		4.0
	(62)		45.70	5.16	9.44	12.24							3.32 s		
4b	134-136	$C_{11}H_{15}BrN_2O_5$	39.42	4.51	8.36	23.84	4.55 d	3.68-	—	—	4.05 m	7.69 s	3.16 s		4.0
	(65)		39.56	4.67	8.29	23.93							3.32 s		
4c	159-160	$C_{11}H_{15}IN_2O_5$	34.57	3.95	7.33	33.20	4.54 d	4.06 m	368-	381 m	3.46 m	7.70 s	3.17 s		4.0
	(71)		34.64	4.04	7.18	33.09							3.32 s		
4d	118-120	$C_{11}H_{15}N_5O_5$	44.44	5.08	23.56		4.54 d	4.00 m	3.85 m	3.85 m	3.50 m	7.66 s	3.16 s		4.0
	(67)		44.38	5.11	23.58								3.32 s		
4e	143	$C_{13}H_{18}N_2O_7$	49.68	5.77	8.99		4.54 d	3.83-			4.20 m	7.61 s	3.16 s	2.05 s	3.0
	(65)		49.68	5.73	8.86								3.32 s	(5′-Ac, 3H)	
4	173	$C_{11}H_{16}N_2O_5$	51.55	6.29	10.93		4.45 d	3.93 m	3.45-		3.78 m	7.57 s	3.16 s	1.22 d	4.0
(X = H)	(88)		51.43	6.22	10.81								3.32 s	(4′-Me)	
7	150	$C_{12}H_{18}N_2O_8S$	41.14	5.18	7.99		4.84-	4.94 m	4.15dd	3.43-	3.75 m	7.92 s	3.19 s	3.31 s	
	(72)		40.96	5.19	7.85								3.31 s	(Ms, 3H)	
8a	165	$C_{11}H_{15}ClN_2O_5$	45.45	5.20	9.63	12.19	4.80 d	4.44 t	4.15 q	3.80 m	3.60 m	7.93 s	3.18 s		5.2 [d]
	(91)		45.20	5.24	9.50	12.40			[c]				3.32 s		
8b	175	$C_{11}H_{15}BrN_2O_5$	39.42	4.51	8.36	23.84	4.95 d	4.53 t	4.03 q	3.78 m	3.56 m	7.93 s	3.15 s		6.1 [e]
	(72)		39.41	4.64	8.40	24.00							3.32 s		
8c	171-172	$C_{11}H_{15}N_5O_5$	44.44	5.08	23.56		4.64 d	3.80 t	4.80 q	3.48-	3.85 m	7.83 s	3.18 s		4.9 [f]
	(90)		44.28	5.14	23.48				[c]				3.32 s		
9	104-105	$C_{23}H_{41}ClN_2O_6Si_2$	52.87	7.58	5.14	6.50	4.89 s	4.37-	4.51 m	3.84-	4.01 m	7.56 s	3.17 s	1.02 m	0
	(66)		52.65	7.66	5.20	6.56							3.29 s	(*i*-Pr, 28H)	
10	128	$C_{25}H_{44}N_2O_8Si_2$	53.93	7.96	5.03		4.64 s	5.32 d	4.42dd	3.67-	3.96 m	7.60 s	3.15 s	1.02 m	0
														(*i*-Pr, 28H)	
	(90)		53.80	7.89	4.93								3.29 s	2.06 s	
														(2′-Ac, 3H)	
12a	foam	$C_{13}H_{17}N_2O_6Cl$	46.92	5.15	8.42	10.65	4.63-	4.85 m	5.23 t	4.03 m	3.60 m	7.96 s	3.18 s	2.11 s	
	(32)		46.97	5.07	8.43	10.54							3.33 s	(3′-Ac, 3H)	
12b	See **8a**														
13a	181	$C_{13}H_{17}N_2O_6Cl$	46.92	5.15	8.42	10.65	4.71dd	5.18dd	4.53dd	4.19 m	3.72 t	7.62 d	3.16 s	2.08 s	3.1 [g]
	(11)		46.80	5.25	8.31	10.60							3.31 s	(2′-Ac, 3H)	
13b	foam	$C_{11}H_{15}N_2O_6Cl$	45.45	5.20	9.63	12.19	4.55 d	4.21-	—	4.26 m	3.70 d	7.56 s	3.18 s		3.0
			45.23	5.20	9.50	12.35							3.34 s		
14b	foam	$C_{11}H_{15}N_2O_5Cl$	45.45	5.20	9.63	12.19	5.02 d	4.45 d	4.19 d	3.53-	3.83 m	7.60 s	3.18 s		3.6 [h]
	(7)		45.20	5.24	9.50	12.40							3.34 s		

[a] Solvent is DMSO-d_6, s = singlet, d = doublet, dd = doublet doublet, t = triplet, q = quartet. [b] J values are first order. [c] Collapses to an apparent triplet upon addition of deuterium oxide. [d] $J_{2',3'} = 5.2$, $J_{3',4'} = 4.9$. [e] $J_{2',3'} = 4.9$, $J_{3',4'} = 4.9$. [f] $J_{2',3'} = 5.0$, $J_{3',4'} = 5.5$. [g] $J_{2',3'} = 1.2$, $J_{3',4'} = 3.7$, $J_{4',5'} = J_{4',5''} = J_{5',5''} = 5.5$, $J_{1'-6} = 1.0$. [h] $J_{3',4'} = 2.5$.

converted into the same 2′-deoxy-1,3-dimethyl-ψ-uridine derived from **8a** upon reduction. Thus, the reaction of **11** with α-acetoxyisobutyryl chloride produced both the 2′-chloro-*arabino* **14** and the 2′-chloro-*ribo* **12** nucleosides, of which the major product was identical to **8a**, but unambiguous assignment of the configuration of these products was not chemically possible. Therefore, **8a** was subjected to X-ray analysis (see Experimental).

It was found that the 2′-Cl in **8a** is in the "down" *ribo* configuration. Apparently, the neighboring group participation of the 4-carbonyl group was involved during the nucleophilic displacement of the 2′-mesyl function even in the *C*-nucleoside **7** with extended bond length of the glycosyl linkage, and the reaction proceeded *via* the 4,2′-anhydro intermediate (**7′**, Chart 2). The X-ray analysis also revealed (as with the case of the crystalline structure of the potent antiviral nucleoside 1-(2-deoxy-2-fluoro-β-D-*arabino*-furanosyl)-5-iodocytosine or FIAC [15]) that there are two equally populated molecular structures A and B (Figure 1) due to the two independent conformations of the 5′-OH group. The bond lengths and bond angles of the independent molecules A and B are given in Table I and II. Some selected dihedral angles are listed in Table III. The conformation of the sugar ring is the C3′-*endo*-C2′-*exo*-($^3T_2$), and of the base to sugar is *anti*. It is also interesting to note that the ribosyl ring conformation of the *C*-nucleosides **8** in solution appears to be controlled in large measure by the nature of the 2′-substituent as evidenced by pmr spectroscopy. The $J_{1',2'}$ value of **8** is smallest for the 2′-N_3 substituent (**8c**, Table IV) and largest for the

2'-Br (**8b**), indicating the dihedral angle defined by C1'-H1' and C2'-H2' is largest in **8c** and smallest in **8b**.

These data are consistent with the earlier reports that the more electronegative [16,17] the C-2' substituent, the more the C-2' is pulled toward the side of the substituent. It should be noted, however, that the 2'-fluoro-*arabino*-nucleosides exist as an approximately 50:50 mixture of the C3'-*endo* and C2'-*endo* conformers *in solution* [17].

The X-ray data also established the *arabino* structure of the minor product **14**. This is the first example of direct introduction of a substituent in the C2'-"up" position. Though the yield of **14** is very low, this result indicates that nucleophilic displacement of 2'-"down" function is possible in pyrimidine *C*-nucleosides. It is also clear that decreasing the nucleophilicity of the 4-carbonyl group might increase the amount of *arabino* derivatives. Further studies are underway in our laboratory.

EXPERIMENTAL

General Methods.

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. The pmr spectra (Table IV) were recorded on a JEOL-PFT-100 spectrometer, tetramethylsilane was the internal standard for organic solvents and sodium 2,2-dimethyl-2-silapentane-5-sulfonate for deuterium oxide, chemical shifts are reported in parts per million (δ). Values given for coupling constants are first order. Thin layer chromatography was performed on Uniplates (Analtech Co., Newark, DE) and column chromatography on Woelm silica gel (70-230 mesh). Microanalyses were performed by Galbraith Laboratories, Inc., or by M.H.W. Laboratories.

Trifluoromethylsulfonylation (Triflation) of 1,3-Dimethyl-3',5'-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-ψ-uridine (**1**).

Compound **1** [11] (5.14 g, 10 mmoles) was dissolved in dry methylene chloride (100 ml) containing pyridine (0.79 g, 10 mmoles). The mixture was cooled to $-60°$, and a solution of triflic anhydride (3.38 g, 12 mmoles) in methylene chloride (20 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature and then was washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was coevaporated with petroleum ether to give **2** as a white solid (6.2 g, 96%). Some physical constants for **2** are given in Table IV.

5'-Deoxy-5'-substituted-2',3'-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-1,3-dimethyl-ψ-uridine (**3**).

A mixture of **2** (646 mg, 1 mmole) and lithium chloride, lithium bromide, potassium iodide, sodium azide or sodium acetate (2 to 5 mmoles) in hexamethylphosphoramide (5 ml) was stirred for 30 minutes at room temperature and was then partitioned between ethyl acetate (100 ml) and water (50 ml). The organic layer was separated, washed with water, dried (sodium sulfate) and concentrated *in vacuo*. The residue was purified by column chromatography using methylene chloride-acetone (50:1 v/v) as the eluent to give **3a-e** crystals. Some physical constants of these products are listed in Table IV.

2',3'-*O*-(1,1,3,3-Tetraisopropyldisiloxanyl)-1,3-dimethyl-ψ-uridine (**3**, X = OH).

Compound **3e** (278 mg, 0.5 mmole) was dissolved in methanolic ammonia (5 ml, saturated at 0°). After 4 hours at room temperature, the mixture was concentated *in vacuo* to a small volume and the precipitated crystals were filtered and washed with methanol to give 250 mg (98%) of **3** (X = OH). (Table IV lists some physical properties of this compound.)

5'-Deoxy-2',3'-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-1,3-dimethyl-ψ-uridine (**3**, X = H).

A mixture of tri-*n*-butyltin hydride (1.1 g, 6.4 mmoles) and 2,2'-azobis-(2-methylpropionitrile) (150 mg) in dry toluene (10 ml) was added dropwise to a refluxing solution of **3a** (850 mg, 1.6 mmoles) in toluene (10 ml). The reaction was monitored by tlc (chloroform-ethyl acetate 7:1 v/v). When the starting material disappeared, the mixture was concentrated *in vacuo* and the residue subjected to chromatographic purification on a silica gel column using chloroform-ethanol (15:1 v/v) as the eluent. From the uv-absorbing fraction, 800 mg (100%) of **3** (X = H) was obtained as a foam. (For pmr data, see Table IV.)

5'-Deoxy-5'-substituted-1,3-dimethyl-ψ-uridine (**4**).

A mixture of **3** (0.5 mmole) and tetra-*n*-butylammonium fluoride (1 mmole) in tetrahydrofuran (6 ml) was stirred for 5 minutes at room temperature and then concentrated *in vacuo*. The residue was chromatogaphed on a silica gel column using chloroform-acetone (1:1 v/v) as the eluent to give **4a-e** and **4** (X = OH), as crystalline products. Compound **4** (X = OH) was identical with an authentic sample of 1,3-dimethyl-ψ-uridine [5]. Some physical constants of **4a-e** are given in Table IV.

5'-Deoxy-1,3-dimethyl-ψ-uridine (**4**, X = H).

Compound **3** (X = H) (320 mg, 0.64 mmole) was dissolved in tetrahydrofuran (5 ml) and treated with 1 mole solution of tri-*n*-butylamine hydrofluoride [18] in tetrahydrofuran (1 ml). Crystalline **4** (X = H) precipitated was collected by filtration and washed with tetrahydrofuran (145 mg, 88%). (See Table IV for some physical properties of this compound.)

2'-*O*-Mesyl-3',5'-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-1,3-dimethyl-ψ-uridine (**5**).

A mixture of 1,3-dimethyl-ψ-uridine [5] (5.4 g, 20 mmoles) and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane [19] (7.0 g, 22 mmoles) in pyridine (60 ml) was stirred at room temperature for 5 hours. Mesyl chloride (6 ml) was then added and the mixture was stirred for 5 hours. The solvent was removed *in vacuo* and the residue divided between methylene chloride (100 ml) and water (100 ml). The organic layer was separated, washed several times with water, dried (sodium sulfate) and concentrated to a syrup which was purified on a silica gel column (chloroform-acetone 1:1) to give **5**: pmr (dimethylsulfoxide-d_6): δ 1.02 (28H, m, *i*-Pr), 3.19 (3H, s, NMe), 3.30 (3H, s, NMe), 3.34 (3H, s, Ms), 3.86-4.17 (3H, m, H4', 5', 5''), 4.35 (1H, dd, H3', $J_{2',3'}$ = 4.6, $J_{3',4'}$ = 9.8 Hz), 4.86 (1H, s, H1'), 5.00 (1H, d, H2'), 7.53 (1H, s, H6). This compound was not further purified but used directly in the next step.

Compound **5** is slowly hydrolysed during a prolonged storage in open atmosphere to give 2'-*O*-mesyl-3'-*O*-(1,1,3,3-tetraisopropyldisiloxan-3-ol)-1,3-dimethyl-ψ-uridine (mp 150°) which was separated by column chromatography and characterized by pmr (dimethyl sulfoxide-d_6): δ 0.86-0.99 (28H, m, *i*-Pr), 3.18 (3H, s, NMe), 3.31 (3H, s, NMe), 3.37 (3H, s, Ms), 3.60-3.88 (3H, m, H4', 5', 5''), 4.50 (1H, dd, H3', $J_{2',3'}$ = 3.7, $J_{3',4'}$ = 7.0 Hz), 4.89-4.94 (2H, m, H1', H2'), 5.20 (1H, t, OH), 6.06 (1H, s, OH), 7.98 (1H, s, H6).

2'-*O*-Mesyl-1,3-dimethyl-ψ-uridine (**7**).

To a solution of **5** (10.9 g, 18.5 mmoles) in tetrahydrofuran (25 ml) was added to 1 mole solution of triethylamine hydrofluoride in tetrahydrofuran (55 ml) and the mixture stirred for 3 hours, then concentrated *in vacuo*. The residue was chromatographed on a silica gel column using chloroform-ethanol (9:1 v/v) as the eluent to give **7** as colorless crystals (4.64 g, 72%). (Some physical constants of **7** are listed in Table IV.)

2'-Deoxy-2'-substituted-1,3-dimethyl-ψ-uridine (**8**).

Compound **7** (700 mg, 2 mmoles) was dissolved in *N,N*-dimethylformamide (5 ml), and lithium chloride, lithium bromide or sodium azide (2 to 5 mmoles) was added. The mixture was stirred at 100-110° for 4 to 10 hours. After cooling to room temperature, the mixture was filtered and the filtrate concentrated to dryness *in vacuo*. The residue was purified by chromatography on a silica gel column using chloroform-ethanol (95:5 v/v) as the eluent to give **8a, 8b** or **8c** in crystalline form. Table IV lists

some physical properties of **8**.

2'-Chloro-2'-deoxy-3',5'-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-1,3-dimethyl-ψ-uridine (**9**).

To a solution of **1** (2.5 g, 5 mmoles) in pyridine (30 ml) was added triflic chloride (4.2 g, 25 mmoles) dropwise. The mixture was stirred for 2 days at room temperature and then concentrated *in vacuo*. The residue was dissolved in methylene chloride and the solution placed on a column of silica gel. The column was washed with methylene chloride followed by methylene chloride-ethyl acetate (95:5 v/v). Compound **9** was then eluted with methylene chloride-ethyl acetate (9:1 v/v) in 66% yield as colorless crystals after crystallization from *n*-hexane. Some physical parameters are given in Table IV.

Upon treatment of **9** with triethylamine hydrofluoride in tetrahydrofuran [18], the corresponding desilylated product was obtained in 94% yield which was identical with **8a** prepared from **7**.

2'-Deoxy and 3'-deoxy-1,3-dimethyl-ψ-uridine.

a) Compound **9** (533 mg, 1 mmole) was dissolved in toluene (15 ml) and heated under reflux. To this solution, a mixture of 2,2'-azobis(2-methylpropionitrile) (100 mg) and tri-*n*-butyltin hydride (708 mg, 4 mmoles) in toluene (10 ml) was added dropwise. The mixture was concentrated *in vacuo*, and the residue chromatographed on a silica gel column (chloroform-ethyl acetate 9:1 v/v) to give the 2'-deoxy derivative (200 mg, 79%), mp 136° (lit mp 137-138°). The pmr spectrum of this sample was identical with that previously reported [11].

b) Compound **12b** (100 mg, 0.3 mmole) and **14b** (100 mg, 0.3 mmole) were treated as described above and products were purified on a silica gel column(chloroform-methanol 12:1) to give 2'-deoxy-1,3-dimethyl-ψ-uridine (55 mg, 62%). The pmr spectrum of this sample was identical with that previously reported [14].

Compound **13b** (100 mg, 0.3 mmole) was reduced in the same manner as above to give 3'-deoxy-1,3-dimethyl-ψ-uridine (60 mg, 68%). Analytical data of this compound were identical with that previously reported [14].

2'-*O*-Acetyl-3',5'-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-1,3-dimethyl-ψ-uridine (**10**).

A mixture of **1** (514 mg, 1 mmole) in acetic anhydride (500 mg, 4.9 mmoles) in pyridine (2.5 ml) was stirred overnight at room temperature and then concentrated *in vacuo*. The residue was chromatographed on a silica gel column (chloroform-ethyl acetate 9:1 v/v), and the product **10** crystallized from *n*-hexane. For some physical constants of **10**, see Table IV.

Reaction of 1,3-Dimethyl-ψ-uridine with 2-Acetoxyisobutyryl Chloride.

1,3-Dimethyl-ψ-uridine [5] (**11**, 1.5 g, 5.5 mmoles) and 2-acetoxyisobutyryl chloride (2.5 g) in dry acetonitrile (75 ml) was heated under reflux until the solution became clear (1/2-1 hour). The mixture was evaporated *in vacuo*, the residue was dissolved in chloroform (100 ml) and this solution was treated with ethanol saturated with hydrogen chloride (2 ml). The mixture was kept at room temperature until hydrolysis of the 5'-protected, 2,5,5-trimethyldioxolan-4-on-2-yl ortho ester group was completed (tlc) and the mixture was evaporated *in vacuo*. The residue was chromatographed on a silica gel column with chloroform-acetone 21:1 followed by 10:1 as eluents. Compound **12a** (600 mg, 33%) was eluted first followed by a mixture of **13a** and **14a**. This mixture was crystallized from ethanol to give crystalline **13a** (150 mg, mp 181°). The mother liquor was treated with methanolic ammonia for 15 minutes and evaporated. The residue was separated on a silica gel column with chloroform-ethanol 19:1 to give **13b** (50 mg) and **14b** (125 mg, 7%). Compound **12a** (400 mg) and **13a** (100 mg) were treated with methanolic ammonia for 30 minutes at room temperature, then evaporated and purified on a column of silica gel with chloroform-ethanol 19:1 as the eluent to give **12b** (320 mg) and **13b** (60 mg), respectively. (Table IV lists some physical properties of these compounds.)

Crystallographic Measurement.

The crystal of **8a** used for the measurement had the dimensions (mm^3) of 0.4 × 0.3 × 0.2. The density was determined by the flotation method in carbon tetrachloride-light petroleum. Cell dimensions were determined by a least squares fit of the 20 values of the 24 strong reflections in the range of $15° < 20° < 35°$. The intensities were measured by a means of a Rigaku four-circle diffractometer using CuKα (λ = 1.5418Å). The following data were obtained for the crystal: Space group P21, monoclinic, a = 14.677(4), b = 16.655(4), c = 5,420(1)Å, β = 95.41(2) (standard deviation in parentheses); Dm = 1.5 g cm^{-3}, Dx = 1.54 g cm^{-3}, and Z = 4. Three standard reflections, measured at intervals of every 50 reflections, showed no significant decrease in intensity during the course of data collection. The intensities were corrected for Lorentz and polarization factors but not for absorption. The atomic scattering factors for C, I, N and Cl were given by Cromer and Mann [20], and those for H by Stewart *et al.* [21]. The total numbers of independently observed reflections of the compound above the $3\sigma >$ level were 2334.

Determination of Structure.

The structure was determined by the heavy atom method. From the Patterson map, the position of one Cl atom was easily deduced. From the Fourier synthesis with the chlorine phases, the second Cl atom was deduced. From the Fourier synthesis with the two Cl atoms, all the non-hydrogen atoms in asymmetric unit were obtained. The O and N atoms were identified by structural considerations. Refinement of atomic parameters was carried out by the full-matrix least-squares method, the quantity minimized being $\Sigma\omega(|Fo|-|Fc|)$, with $\omega = 1.0$ for all the reflections used. With anisotropic thermal parameters for atoms, the final R value was 7.00%. The final atomic parameters are given in Tables I-III.

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