that some of the polar solvent is cocrystallized with the valinomycin in the orthorhombic cell and that the conformation of the molecule is different than that reported in this paper.

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Supplementary Material Available. Tables of observed and calculated structure factors will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JACS-75-4379.

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4′-Substituted Nucleosides. I. Synthesis of 4′-Methoxyuridine and Related Compounds

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Abstract: The reactions of iodine and methanol with a number of differently substituted derivatives of 1-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)uracil have been examined. The 2′,3′-di-*O*-acetyl or di-*O*-benzoyl derivatives lead to 5′-deoxy-5′-iodo-4′-methoxy nucleosides with both the β-D-ribo and the α-L-lyxo configurations as well as to diastereomeric 4′,5′-ortho esters. On the other hand, the olefins containing 2′,3′-diol or 2′,3′-cyclic carbonate functions lead stereoselectively to 5′-iodo-4′-methoxy adducts with only the β-D-ribo configuration. Both β-D-ribo and α-L-lyxo adducts arise from the corresponding 2′,3′-*O*-isopropylidene derivative. The various products have been correlated by chemical interconversions and free 4′-methoxyuridine has been obtained via displacement of the 5′-iodo group in a suitable derivative by benzoate anion followed by hydrolysis to the free alcohol function. Acid-catalyzed equilibration of the 4′-methoxy nucleosides has been demonstrated and considerable data on the proton and ^{13}C NMR spectra of the various products are presented.

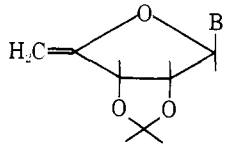
Recent years have witnessed the synthesis of a vast number of nucleoside analogs in the search for therapeutically useful agents.[1] These have included an impressive variety of base analogs of the normal purine and pyrimidine nucleosides as well as a myriad of variations of the sugar moiety. With respect to the latter, extensive modification of the stereochemistry and functionalization of most of the carbon atoms in the normal ribose or 2-deoxyribose unit has been achieved. Due largely to a paucity of convenient synthetic methods for introducing functionality at C_4 of a furanose sugar, only very few modifications at $C_{4'}$ of nucleosides have been reported. These have included the introduction of either 3′,4′[2] or 4′,5′[3] unsaturation, replacement of the furanose ring oxygen by sulfur,[4] and inversion of configuration leading to α-L-lyxofuranosyl nucleosides.[2b,5]

Impetus for the development of synthetic methodology leading to the preparation of $C_{4'}$-substituted nucleosides came from the elucidation of the structure of the nucleoside antibiotic nucleocidin as 4′-fluoro-5′-*O*-sulfamoyladenosine.[6] This structure was unique in that it is the only naturally occurring fluoro sugar derivative and also the first reported 4-substituted glycofuranoside. We have initiated a broad program concerning the synthesis of variously 4′-substituted nucleosides and have previously described a synthesis of nucleocidin.[7] A part of our work has recently been surveyed.[8] During the course of our work the synthesis of a novel methyl 4-methoxyhexofuranoside was described by Dmytraczenko et al.[9] via an interesting concerted addition-elimination reaction on a 5-keto-6-tosylhexofuranoside. Also, the preparation of a 4-alkoxy-5-deoxy-β-D-ribofura-

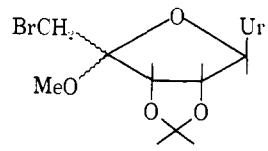
noside by photolysis of a 4,5-unsaturated furanoside in lactonitrile has very recently been reported by Matsuura et al.[10]

As in our work on 4′-fluoro nucleosides[7,8] we have approached the synthesis of 4′-methoxy nucleosides via addition reactions to the exocyclic vinyl ether moiety of 4′,5′-unsaturated nucleosides. Most other studies with carbohydrate vinyl ethers have centered upon the endocyclic double bond of glycals. Early work by Fisher[11] has reported the sequential bromination and methanolysis of tri-*O*-acetyl-D-glucal as a route for preparation of methyl 2-bromo-2-deoxypyranosides. Subsequently, this work has been reinvestigated by Lemieux and Fraser-Reid,[12] who have shown that direct halomethoxylation of glycals can be achieved by reaction with the free halogen in methanol in the presence of silver acetate. This latter method is the one we have chosen to explore in the nucleoside series.

Since the desired 4′-methoxy nucleosides (e.g., **16b**) contain a quite unusual furan related bis(acetal) structure, we anticipated that such compounds would be rather acid labile. Accordingly, since we wished to isolate the free 4′-methoxy nucleoside for biological study, it was necessary to avoid protecting groups that require acidic treatment for their removal. This would appear to exclude the use of the readily available 1-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)uracil (**1a**)[3b,13] as a starting



1a, B = uracil
b, B = N^6-benzoyladenine



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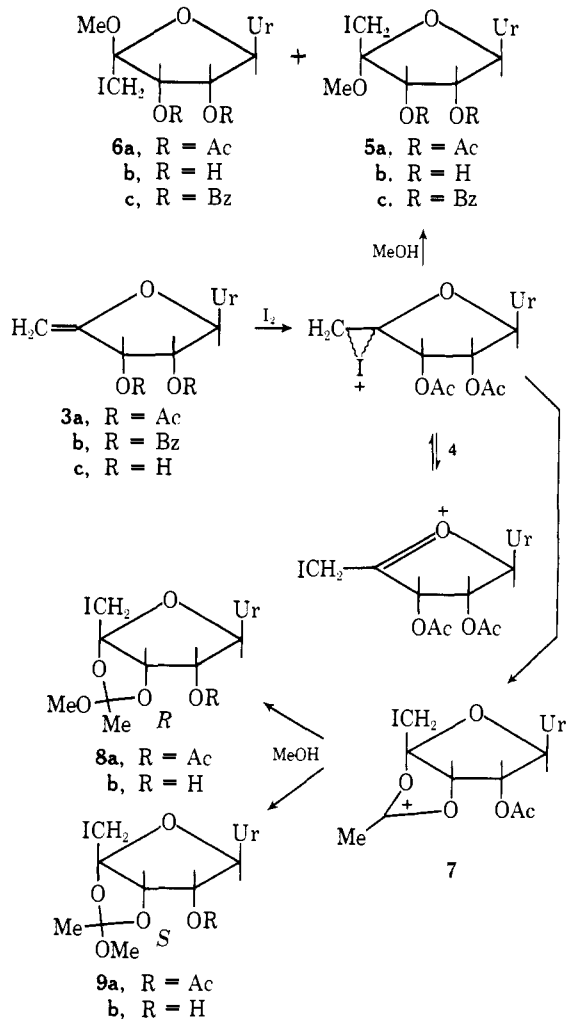
material. During the course of our work two preliminary communications by Sasaki et al.[14] appeared describing the reaction of the isopropylidene vinyl ethers **1a,b** with *N*-bromosuccinimide in methanol. As applied to **1a**, this reaction gave a 4′-methoxy-5′-bromo nucleoside **2** of unassigned configuration in 14% yield. Further comment will be made on this point later in this paper.

Since only base-labile protecting groups were suited to our purpose, we initially studied 1-(2,3-di-*O*-acetyl-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)uracil (**3a**), the synthesis of which we have previously described.[3b,15] The addition of a small excess of iodine to a solution of **3a** in methanol in the presence of solid silver acetate led to the rapid disappearance of the starting material and formation of three close-moving product bands as judged by TLC. By a combination of direct crystallization and preparative TLC a total of four isomeric products arising by addition of the elements of iodine and methanol to **3a** were isolated. By a combination of spectroscopic and degradative means these products have been shown to have the structures **5a, 6a, 8a,** and **9a**. The desired 5′-deoxy-5′-iodo-4′-methoxy nucleosides with the β-D-ribo (**5a**) and α-L-lyxo (**6a**) configurations were obtained in crystalline form in yields of 16 and 34%, respectively. The two diastereomers (**8a, 9a**) of an unusual 3′,4′-ortho ester were obtained, each in about 19% yield, but neither was completely pure and the less polar isomer could not be separated from residual **6a**. Their structures could, however, be clearly defined after deacetylation. Thus each of the four products was separately treated with methanolic ammonium hydroxide at room temperature. This treatment cleanly deacetylated **5a** and **6a** giving the corresponding vicinal diols **5b** and **6b** in satisfactory yields. Similar treatment of crude **8a** and **9a,** however, led to the



loss of only single acetyl groups and gave the crystalline compounds **8b** and **9b** which retained the orthoacetate structure (methyl and methoxyl singlets at 1.72 and 3.60 ppm and at 1.59 and 3.76 ppm, respectively, in their NMR spectra) and were accordingly not oxidized by periodate.[16] By analogy with previous work on the NMR spectra of acetals derived from both cyclic[17] and acyclic[18] diols it is possible to assign definitive stereochemistry to both **8** and **9**. Thus **8b,** in which the orthoacetate function has the *R* configuration with the methyl group endo to the bicyclic system, shows its methyl singlet (1.72 ppm) downfield of that in **9b** (1.59 ppm). Conversely, **9b,** in which the methoxyl group is endo disposed, has its methoxyl singlet (3.76 ppm) downfield of that in **8b** (3.60 ppm).

Clearly, the formation of all four products can be explained in terms of the initial addition of iodine to the exocyclic vinyl ether to give either the iodonium or iodooxonium ions **4**. Direct addition of methanol to these species can then give the 4′-methoxy nucleosides **5a** or **6a** while participation by the 3′-*O*-acetyl function can lead to the 4′,5′-acyloxonium ion **7** and thence to the diastereomeric ortho esters **8a** and **9a** by addition of methanol to **7**.

The assignment of configuration at C_4 in compounds **5a,b** and **6a,b** was made on the basis of ^{13}C NMR spectroscopy (see Table I). It is well known from the work of Roberts and coworkers[19] that the ^{13}C chemical shift of a carbon atom is exquisitely sensitive to steric crowding, especially by vicinal oxygen substituents. Thus, the chemical shift of the methyl group, as well as those of C_1 and C_2, is known to occur at higher field in *cis*-2-methylcyclopentanol than it does in the trans isomer.[19] This same shielding effect has

Table I. 22.62-MHz ^{13}C Chemical Shifts (ppm) of Selected Compounds

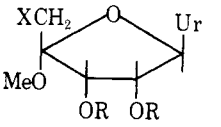
Compd	Solvent[a]	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	C_2	C_4	C_5	C_6	OMe	$COCH_3$	$COCH_3$	CMe_2	CMe_2
5a	C	88.59	71.96 or	71.77	102.90	3.30	149.6	162.3	103.3	139.7	49.12	169.1, 168.7	20.38, 29.57		
6a	C	86.20	72.41 or	74.23	107.6	−1.61	149.9	162.1	104.2	137.9	48.79	168.6, 169.6	20.38, 20.38		
5b	A–D_2O	92.13	74.19	73.53	104.42	4.68	151.40	163.72	103.41	142.42	49.28				
6b	A–D_2O	90.08	75.58 or	74.93	109.72	1.17	152.04	162.45	104.19	141.03	48.93				
12a	A–D_2O	90.80	74.28	74.08	83.74	6.92	151.72	164.53	103.15	142.36					
16b	A–D_2O	90.85	72.89	70.36	106.23	59.64	151.18	165.68	102.38	142.11	49.50				
17	A–D_2O	89.11	74.44	74.44	111.12	56.92	152.30	165.57	104.16	142.10	49.67				
18	A	92.39	84.85	85.24	106.27	5.95	151.30	163.78	103.22	143.79	49.51			116.32	26.17, 26.43
19a	A	92.33	85.82	84.07	111.64	0.52	151.88	163.46	102.92	142.26	48.28			114.20	25.03. 26.66
5'-Iodo-2',3'-IpUr	A	95.45	85.40	85.08	88.13	6.11	151.36	163.84	103.05	144.21				114.79	25.45, 27.37

[a] Solvents are $CDCl_3$ (C), acetone-d_6 (A).

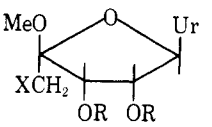
also been observed in furanose sugars, compounds having, for example, a cis relationship between C_5 and C_3OH showing resonances for C_5 at higher field than those in the corresponding compounds with a trans configuration.[20] The chemical shift of the anomeric carbon has recently been used to distinguish between α- and β-furanose forms of both O-glycosides[21] and nucleosides.[22] We have recently had occasion to make extensive use of such ^{13}C NMR correlations for establishing the configurations of a variety of C-glycosides.[23] Details of the ^{13}C NMR spectra of the various compounds prepared in the present work are to be found in Table I, and the assignments presented there are based upon the results of both off-resonance and single-frequency proton decoupling techniques.[24,25] In the present case the presence of both the iodomethyl and methoxyl substituents at $C_{4'}$ makes assignments of configuration based upon a consideration of the chemical shifts of $C_{3'}$ or $C_{4'}$ equivocal. The chemical shift of $C_{5'}$, however, should provide clear evidence as to the configurations at $C_{4'}$ since in the β-D-ribo series (**5a,b**) $C_{5'}$ and $O_{3'}$ are trans disposed, while in the α-L-lyxo series (**6a,b**) these atoms are cis. Fortunately, the assignments of chemical shifts for $C_{5'}$ are quite unequivocal since it is well known that the resonance of carbon bearing iodine occurs at very high field.[24] An examination of the ^{13}C NMR spectra of **5a,b** and **6a,b** (Table I) shows that the $C_{5'}$ signals for **6a** and **6b** occur respectively 4.91 and 3.51 ppm upfield relative to $C_{5'}$ in **5a** and **5b.** This clearly shows that **6a** and **6b** have a cis relationship between $C_{5'}$ and $O_{3'}$ and accordingly have the α-L-lyxo configuration, while **5a** and **5b** are in the β-D-ribo series. It might be noted from Table I that the chemical shift of $C_{5'}$ in **5b** (4.68 ppm) is very much closer to that in the model compound **12a** (6.92 ppm) than is the α-L-lyxo compound **6b** (1.17 ppm).

While both mechanistic considerations and the apparent chemical stability of the adducts **5** and **6** strongly suggest that the iodine atom is located at $C_{5'}$, chemical confirmation was desired. Accordingly, both **5a** and **6a** were hydrogenolyzed in the presence of a palladium catalyst giving the corresponding crystalline 5'-deoxy-4'-methoxy nucleosides **10a** and **11a.** The proton NMR spectra of these compounds clearly show the presence of two 3-proton singlets corresponding to the 4'-methoxyl and $C_{5'}$-methyl groups (Table II), thus confirming the regioselectivity of the addition reaction.

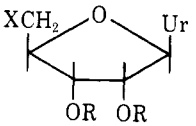
Our earlier work on the synthesis of 4'-fluoro nucleosides[7,8] had shown that nucleophilic displacement of the 5'-iodo function in 5'-deoxy-4'-fluoro-5'-iodo nucleosides was extremely difficult and could only be achieved using azide ion. The resulting 5'-azido compounds, however, were valuable intermediates for introduction of the desired 5'-hydroxyl moiety. In the adenosine series[7,8] this was achieved via photolysis and hydrolysis to the 5'-aldehyde while in the uridine series the azido to hydroxyl conversion was accomplished through reaction with nitrosonium fluoroborate[27] by way of a readily hydrolyzed intermediate O^2,5'-anhydro nucleoside.[8,26] In order to test the suitability of the latter method in the 4'-methoxy derivatives we have reacted **5b** and **6b** with lithium azide in dimethylformamide at 110° for 20 hr. In the case of **6b** crystalline 1-(5-azido-5-deoxy-4-methoxy-α-L-lyxofuranosyl)uracil (**11b**) was obtained in 67% yield and then acetylated giving **11c.** A small-scale azide displacement with **5a** led to the isolation of slightly impure **10b** and its acetate **10c** as judged by NMR studies. A preliminary investigation of the reactions of **10c** and **11c** with nitrosonium fluoroborate and Na_2HPO_4 in acetonitrile was not encouraging and led to the formation of a number of products. Significantly, one of the products from the ribo isomer **10c** had the uv spectrum (λ_{max} 238) expected for the desired O^2,5'-anhydro nucleoside.[8,28] In view of the observations made later in this paper this route was not further explored.



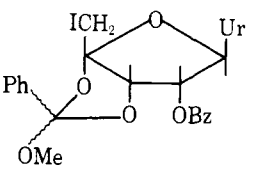
10a, X = H; R = Ac
b, X = N_3; R = H
c, X = N_3; R = Ac



11a, X = H; R = Ac
b, X = N_3; R = H
c, X = N_3; R = Ac



12a, X = I; R = H
b, X = I; R = Bz
c, X = Cl; R = Bz



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Since the 2',3'-di-O-acetyl olefin **3a** gave the desired 5'-iodo-4'-methoxy adduct **5a** with the β-D-ribo configuration in only modest yield, we have also prepared and studied the corresponding dibenzoate **3b.** This compound was readily obtained by benzoylation of 5'-deoxy-5'-iodouridine (**12a**)[29] with benzoic anhydride in pyridine followed by treatment of the resulting **12b** with silver fluoride in pyridine in a similar way to that used to prepare **3a.**[3b,15] It should be noted that attempted benzoylation of **12a** using benzoyl chloride led to the formation of a considerable amount of the corresponding 5'-chloro nucleoside **12c** by a halide exchange reaction. The treatment of **3b** with iodine and methanol gave a mixture that was separated into three bands by preparative

Table II. 100-MHz Proton NMR Chemical Shifts (ppm)

Compd	Solvent[a]	$C_1'H$	$C_2'H$	$C_3'H$	$C_4'H$	$C_5'_aH$	$C_5'_bH$	C_5H	C_6H	OMe	Other
3b	C	6.40 (d)	5.74 (dd)	6.25 (br d)		4.62 (dd)	4.80 (dd)	5.85 (d)	*b*		7.2–8.2 (m, 11, Ar and C_5H)
5a	P	6.44 (d)	6.07 (dd)	6.22 (d)		3.85 (s)		5.86 (d)	7.88 (d)	3.43 (s)	2.02 and 2.10 (s, 3, OAc)
5b	P	6.63 (d)	4.85 (dd)	4.93 (d)		3.72 (d)	3.90 (d)	5.88 (d)	7.84 (d)	3.42 (s)	
5c	C	6.14 (d)	5.62 (dd)	5.89 (d)		3.59 (d)	3.75 (d)	5.83 (d)	7.49 (d)	3.46 (s)	7.85–8.05 (m, 10, Ar)
6a	P	6.93 (d)	6.05 (dd)	5.81 (d)		3.51 (d)	3.69 (d)	5.87 (d)	7.64 (d)	3.32 (s)	1.88 and 2.18 (s, 3, OAc)
6b	P	7.09 (d)	5.04 (dd)	5.59 (d)		3.68 (d)	4.04 (d)	5.88 (d)	7.70 (d)	3.39 (s)	
6c	P	6.5–6.7 (m)[b]	6.5–6.7 (m)[b]	6.5–6.7 (m)[b]		4.01 (s)		5.92 (d)	8.05 (d)	3.58 (s)	7.2–8.3 (m, 10, Ar)
8b	P	7.10 (d)	4.97 (dd)	5.05 (d)		3.85 (d)	3.99 (d)	5.84 (d)	7.97 (d)	3.60 (s)	1.72 (s, 3, $MeCO_3$)
9a	P	7.14 (d)	5.71 (dd)	5.33 (d)		3.87 (d)	3.99 (d)	5.87 (d)	7.98 (d)	3.51 (s)	1.69 (s, 3, $MeCO_3$), 2.04 (s, 3, OAc)
9b	P	6.82 (d)	4.89 (dd)	4.98 (d)		3.82 (d)	3.97 (d)	5.85 (d)	7.98 (d)	3.76 (s)	1.59 (s, 3, $MeCO_3$)
10a	P	6.33 (d)	6.06 (dd)	5.85 (d)		1.62 (s)		5.85 (d)	7.87 (d)	3.34 (s)	1.98 and 2.09 (s, 3, OAc)
10c	P	6.42 (d)	6.07 (dd)	6.21 (d)		3.73 (d)	3.87 (d)	5.83 (d)	7.86 (d)	3.44 (s)	2.00 and 2.07 (s, 3, OAc)
11a	P	6.94 (d)	5.94 (dd)	5.66 (d)		1.41 (s)		5.94 (d)	7.51 (d)	3.26 (s)	1.93 and 2.11 (s, 3, OAc)
11b	P	7.06 (d)	5.05 (dd)	4.55 (d)		3.73 (d)	4.10 (d)	5.90 (d)	7.51 (d)	3.40 (s)	
11c	P	6.92 (d)	6.12 (dd)	5.85 (d)		3.60 (d)	3.97 (d)	5.95 (d)	7.75 (d)	3.40 (s)	1.92 and 2.14 (s, 3, OAc)
12b	C	6.28 (d)	5.65 (dd)	5.53 (dd)	4.29 (m)	3.58 (dd)	3.75 (dd)	5.82 (d)	7.63 (d)		7.1–8.0 (m, 10, Ar)
12c	C	6.33 (d)	5.56 (dd)	5.71 (dd)	4.61 (ddd)	3.92 (dd)	4.08 (dd)	5.83 (d)	7.61 (d)		7.1–8.0 (m, 10, Ar)
13	P	6.79 (d)	5.99 (dd)	5.67 (d)		4.07 (d)	4.20 (d)	5.91 (d)	8.05 (d)	3.24 (s)	7.2–8.1 (m, 10, Ar)
14	P	6.44 (s)	6.21 (s)	6.21 (s)		4.58 (d)	4.80 (d)	5.85 (d)	8.87 (d)		
15	P	6.83 (d)	5.98 (dd)	5.74 (d)		3.70 (d)	3.90 (d)	5.84 (d)	7.83 (d)	3.29 (s)	
16a	C	6.13 (d)	5.76 (dd)	6.03 (d)		4.61 (d)	4.79 (d)	5.59 (d)	7.37 (d)	3.56 (s)	
16b	P	6.77 (d)	4.77 (dd)	5.05 (d)		4.08 (d)	4.25 (d)	5.75 (d)	8.21 (d)	3.55 (s)	
17	P	7.10 (d)	5.10 (dd)	4.74 (d)		4.18 (d)	4.58 (d)	5.93 (d)	7.82 (d)	3.56 (s)	
18	D	5.86 (d)	4.97 (dd)	4.78 (d)		3.41 (d)	3.62 (d)	5.62 (d)	7.72 (d)	3.24 (s)	1.26 and 1.46 (s, 3, CMe_2)
19a	D	6.08 (br s)	5.25 (dd)	4.75 (d)		3.28 (d)	3.60 (d)	5.62 (dd)	7.54 (d)	2.99 (s)	1.31 and 1.46 (s, 3, CMe_2)
19b	D	6.07 (br s)	5.26 (dd)	4.73 (d)		3.50 (d)	3.83 (d)	5.62 (d)	7.52 (d)	3.00 (s)	1.30 and 1.45 (s, 3, CMe_2)
19b[c]	D	6.13 (d)	5.29 (dd)	4.75 (d)		3.53 (d)	3.84 (d)	5.65 (dd)	7.58 (d)	3.07 (s)	1.34 and 1.50 (s, 3, CMe_2)

[a] Solvents are $CDCl_3$ (C), pyridine-d_5 (P), DMSO-d_6 (D). [b] Unresolved. [c] See ref 14a.

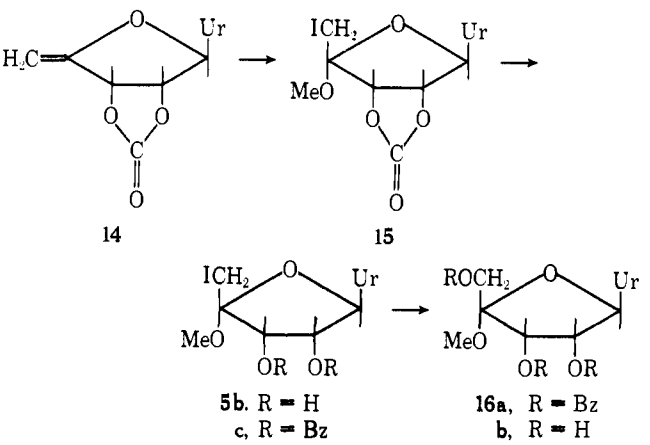
TLC. In this case two of the bands proved to contain the pure 4′-methoxy-5′-iodo-α-L-lyxofuranosyl nucleoside **6c** in 16% yield and one diastereomer of the 4′,5′-orthobenzoate **13** in 24% yield, respectively. The third band contained 30% of an inseparable mixture of the desired 4′-methoxyuridine derivative **5c** and the second diastereomer of **13**. Hydrolysis of this mixture with ammonia then allowed the isolation of a 15% yield of the crystalline diol **5b** identical with that from **3a**. Similar hydrolysis of **6c** gave only the α-L-lyxo diol **6b**, thus confirming its configuration. Clearly the use of the benzoate **3b** offered no advantage over **3a**.

It was thus evident that the substituent at $C_{3'}$ must be base labile but incapable of participation with the intermediate **4** (leading to ortho esters such as **8, 9,** or **13**). The cyclic carbonate ester **14** appeared attractive for this purpose. This compound could be obtained in crystalline form in 51% yield via reaction of the previously reported 1-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)uracil (**3c**)[3b,15] with phosgene in pyridine–benzene at low temperature. More conveniently, the readily available 5′-deoxy-5′-iodouridine (**12a**)[29] was dehydrohalogenated by reaction with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in pyridine and the resulting **3c** was directly reacted with phosgene as above giving crystalline **14** in an overall yield of 60%.

The reaction of the olefin carbonate **14** with iodine and methanol was carried out essentially as above except that lead carbonate (see later) was used rather than silver acetate to trap hydrogen iodide. Under these conditions a single crystalline product was isolated in 85% yield and shown to have the ribo configuration (**15**) by hydrolysis of the carbonate ester giving pure **5b** identical by TLC and NMR with that obtained from **3a**. The hydrolysis step has been investigated under a number of conditions and the best results (88% yield) are obtained using aqueous barium hydroxide at room temperature followed by neutralization with carbon dioxide.

Our work on the preparation of the azides **10b** and **11b** had suggested that while the iodo functions in **5b** and **5c** are still extremely inert toward nucleophilic displacement, they are considerably more reactive than in the 4′-fluoro-5′-iodo nucleosides previously studied.[7,8] This encouraged us to attempt direct displacement of the iodo group by benzoate anion, a reaction that had totally failed with the 4′-fluoro counterparts. Preliminary experiments with the diols (**5b** or **6b**) showed that benzoate displacement did indeed occur under forcing conditions but was accompanied by some degradation and release of uracil. Since it is known that uridine 2′,3′-carbonate quite readily collapses to O^2,2′-cyclouridine,[30] the carbonate **14** also appears unsuitable. Accordingly, the diol **5b** was benzoylated using benzoyl chloride in pyridine giving a mixture of the 2′,3′-dibenzoate **5c** and a tribenzoate, presumably the 2′,3′-N^3-tribenzoyl derivative. The *N*-benzoyl group could be cleanly and selectively cleaved by heating at 100° in pyridine containing 2% water[31] giving crystalline 2′,3′-di-*O*-benzoyl-5′-deoxy-5′-iodo-4′-methoxyuridine (**5c**) in 83% yield.

Displacement of iodide from **5c** was achieved by treatment with lithium benzoate in dimethylformamide at 120° for 60 hr which gave 51% of crystalline 2′,3′,5′-tri-*O*-benzoyl-4′-methoxyuridine (**16a**). The inertness of the iodine function in **5c** is, as in the case of the 4′-fluoronucleosides, closely related to the known resistance of 1-tosyl ketose derivatives toward nucleophilic displacement.[32] This effect has been explained by Richardson in terms of adverse dipole interactions in the transition state.[33] Completion of the synthesis of 4′-methoxyuridine (**16b**) then only required hydrolysis of the benzoyl groups, which is conveniently accomplished using methanolic ammonium hydroxide at 100° giving **16b** as an analytically and spectroscopically pure foam in 71% yield. For preparative purposes it is convenient to conduct the benzoylation and benzoate displacements sequentially without purification of the intermediate **16c**. Some advantage was also found in the use of hexamethylphosphoramide as the solvent for the displacement reaction and in this way **5a** was converted into **16a** and **16b** in overall yields of 61 and 41%, respectively.

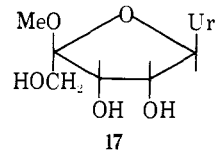


We have also investigated the addition of iodine and methanol to the 2′,3′-unsubstituted olefin **3c**[3b,15] in the presence of lead carbonate. Somewhat to our surprise, the product of this reaction, isolated in 77% yield as a clear syrup, proved to be the ribo adduct **5b** to an extent of greater than 95%. Only a trace of the lyxo adduct **6b** could be detected by TLC and NMR. Clearly this reaction obviates both the introduction of the carbonate group into **14** and its removal from **15**. The direct preparation and purification of **3c** from **12a** without passing through acylated intermediates is difficult to achieve in good yield. Since, however, both **14** and **15** are readily crystalline compounds there is some advantage in their use in terms of the ease of their purification. If, however, the addition of iodine and methanol to **3c** was conducted in the presence of silver acetate instead of lead carbonate, the reaction gave a mixture of the ribo adduct **5b** and its α-L-lyxo isomer **6b** in a ratio of 2:1. We consider that this is a reflection of a facile, acid-catalyzed equilibration of the 4′-methoxyfuranose system. The use of silver acetate as a trap for hydrogen iodide leads to the release of an equivalent amount of acetic acid while lead carbonate gives volatile and less acidic carbon dioxide. To test this point we have treated samples of the pure 4′-methoxy-5′-iodo nucleosides **5b** and **5c** in anhydrous methanol with carefully dried Dowex 50 (H^+) resin. The α-L-lyxo isomer **6b** proved to be quite stable under these conditions, only traces of uracil and no **5b** being present after 48 hr. The β-D-ribo isomer **5b**, however, underwent quite rapid change leading to formation of the 4′-epimer **6b** and to significant amounts of uracil. After 4 hr the ratio of **5b** to **6b** was 2:1 as judged by TLC and after 48 hr only the α-L-lyxo isomer **6b** and uracil were present in equal amounts. In a preparative experiment the equilibration of **5b** appeared to be somewhat slower and the reaction was kept for 7 days to remove all of the starting material. From this experiment pure **6b** was isolated by preparative TLC in 25% yield and shown to be identical with an authentic sample by NMR.

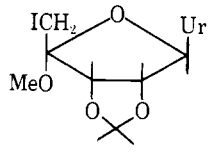
In a very similar way we have shown that 4′-methoxyuridine itself can be equilibrated to its α-L-lyxo isomer **17** by treatment with dried Dowex 50 (H^+) resin in methanol. In this way a 40% yield of pure **17** could be isolated by preparative TLC. The availability of **17** made possible an independent check of the assigned configurations by use of borate electrophoresis at pH 6. It is known that under these condi-

tions the order of increasing mobility of 1-pentofuranosylpyrimidines is arabino, xylo, ribo, and lyxo, the rapid migration of the lyxo isomer being consistent with the formation of a highly stable 2′,3′,5′-tridentate complex.[34] In the present work the lyxo isomer **17** has a substantially greater electrophoretic mobility than does its ribo counterpart **16b.** It is interesting to note that the mobility of **17** is roughly three times that of **16b** while the ratio of mobilities of 1-(β-D-lyxofuranosyl)uracil and uridine is 1.3–1.7 under various conditions. This can be explained on steric grounds since the mobility of **16b** is only 0.5–0.6 that of uridine, presumably due to some hindrance to borate bonding by the *cis*-4′-methoxyl group. On the other hand, the α-L-lyxo isomer **17** is completely unhindered toward tridentate complex formation while the reported 1-(β-D-lyxofuranosyl)uracil should experience some modest hindrance due to the cis-disposed uracil ring. Regardless of these quantitative differences in relative mobilities the electrophoretic behavior of **16b** and **17** strongly supports the assigned configurations. From Table I it can also be seen that, as expected, the ^{13}C chemical shift of $C_{5'}$ in the α-L-lyxo isomer **17** is 2.72 ppm upfield of that in **16b** as a consequence of the cis relationship to $C_{3'}OH$.

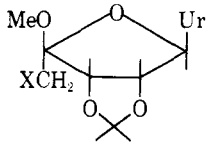
Finally, in view of the influence of the substituents at $O^{2'}$ and $O^{3'}$ on the nature of the products, we have investigated the addition reaction on the 2′,3′-*O*-isopropylidene olefin **1a.** The reaction of **1a** with iodine and methanol in the presence of lead carbonate led to the rapid formation of a chromatographically inseparable mixture of the β-D-ribo (**18**) and α-L-lyxo (**19a**) adducts in a yield of 74% and in a ratio of 3:2. The assignment of configuration to **18** and **19a** was made by an independent preparation of both compounds through treatment of pure **5b** and **6b** with acetone in the presence of a catalytic amount of perchloric acid. The use



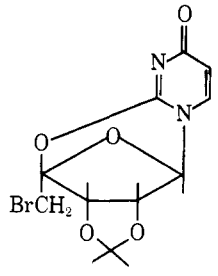
17



18



19a, X = I
b, X = Br



20

of perchloric acid as the catalyst[35] led to very fast acetal formation and the avoidance of epimerization. In this way **19a** was obtained in crystalline form while **18** was isolated as an analytically pure syrup that was distinguishable from **19a** by NMR. (See Table II.) As in the other cases, $C_{5'}$ of **18** is deshielded by 5.43 ppm relative to that in **19a** and has a very similar chemical shift to that in the model compound 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneuridine (Table I).

We have consistently found that the NMR spectra of variously substituted 5′-chloro, 5′-bromo, and 5′-iodo nucleosides are very similar to one another except for characteristic chemical shifts of the $C_{5'}$ protons.[29,36] Sasaki et al.[14a] have reported the NMR spectrum of the crystalline 5′-bromo-4′-methoxy nucleoside which they obtained from **1a** and *N*-bromosuccinimide in methanol but for which no assignment of configuration was made. By a direct comparison of the Japanese workers' data (which, for convenience, are included in Table II) with those for the pure 4′-methoxy-5′-iodo isomers **18** and **19a** one can, with reasonable assurance, conclude that the compound isolated by Sasaki et al. has the α-L-lyxo configuration (**19b**). With the exception of the expected differences for $C_{5'}H_2$, the chemical shifts reported by Sasaki et al. are extremely close to those for **19a** and differ from those for **18** especially in the cases of C_6H, $C_{1'}H$, $C_{2'}H$, and the methoxyl group. It also might be noted that C_5H in **19a** (and in the Sasaki spectrum) shows coupling to N_3H ($J_{5,NH}$ = 2 Hz) while that in **18** does not. Finally, the difference in chemical shift for the isopropylidene methyl groups is 20 Hz for **18,** 15 Hz for **19a,** and 16 Hz for the 5′-bromo compound. The latter observation may be related to recent work by Imbach et al.[37] who have shown that α-nucleosides derived from 2′,3′-*O*-isopropylidene-D-ribose have values of Δδ less than 15 Hz while the β anomers are greater than 15 Hz. We have also recently shown that a qualitatively similar situation exists with 2,3-*O*-isopropylidene-D-ribofuranosyl *C*-glycosides.[23] In the present case it would appear that the 4′-halomethyl group has a more significant effect upon the value of Δδ than does the 4′-methoxyl.

In order to attempt a direct correlation with the work of Sasaki, we have treated the 5′-iodo-α-L-lyxo compound **19a** with lithium bromide in DMSO-d_6 at 100° for 36 hr, following the course of the reaction by NMR. Preparative TLC of the resulting product led to the isolation of crystalline **19b** with an NMR spectrum almost identical with that of **19a** with the expected exception of the $C_{5'}$ protons. The spectrum was also very similar to that reported by Sasaki et al.,[14a] minor variations being perhaps explainable in terms of instrumental differences. It might be noted that the spectrum of **19b** reported in Table II was run using a very dilute solution of highly purified product in DMSO-d_6 from a freshly opened bottle. Under these conditions the coupling of C_5H to N_3H was not observed, although this was seen in the more concentrated spectra obtained during the displacement reaction. While the melting point of our material is 10° lower than was reported, the NMR data leave no doubt in our minds as to the configuration of the product. The formation of the α-L-lyxofuranosyl isomer in the Japanese work is interesting since the same compound could be prepared in 20–29% yields by treatment of the O^2,4′-anhydro nucleoside **20** with methanol under various conditions. This would appear to be another example of a relatively facile equilibration of the presumably initially formed β-D-ribo isomer. Isolation of the isomerized material would be facilitated by the general crystallinity observed in the α-L-lyxo series while the β-D-ribo isomers frequently tend to be syrups.

An examination of Tables II and III shows that the configuration of 4′-methoxy nucleosides having either free or esterified 2′- and 3′-hydroxyl groups has a marked effect upon the conformation of the furanose ring. Thus $C_{1'}H$ in the β-D-ribo isomers (**5, 10, 16**) is consistently at considerably higher field than that in the α-L-lyxo series (**6, 11, 17**). In addition, $J_{1',2'}$ and $J_{2',3'}$ in the β-D-ribo compounds are 3–4 and 6.5–8 Hz, respectively, while in the α-L-lyxo series these values are 7–8 and 4–5 Hz, respectively. The presence of a 2′,3′-*O*-isopropylidene function, however, appears to largely overcome these differences since the values of $J_{1',2'}$ and $J_{2',3'}$ are essentially the same in the isomers **18** and **19.** The cyclic carbonate function appears to have a similar effect as an isopropylidene group since the coupling constants of **15** are very similar to those of **18** and **19** and are typical of other ribo compounds. We have not as yet examined a carbonate derivative in the α-L-lyxo series.

Table III. Coupling Constants (Hz)

Compd	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	$J_{5,6}$	Other
3b	5	5				3	7.5	$J_{3',5'a}$ ~0.5, $J_{3',5'b}$ ~1.5
5a	3.5	7.5				0[b]	8	
5b	3.5	6.5				11	7.5	
5c	4	8				11	7.5	
6a	8	5				11.5	8	
6b	7.5	4				10.5	8	
6c	*a*	*a*				0[b]	8	
8b	6.5	5.5				11	8	
9a	7.5	6				12	8	
9b	7.5	5				11	8	
10a	3	7.5					7.5	
10c	3	7.5				12.5	7.5	
11a	7	4.5					8	
11b	7.5	4				13	8	
11c	7	4.5				13.5	8	
12b	6	6	4	2	3	12	8	
12c	6	6	3	3	3	12	8	
13	8	5				10.5	8	
14	0	0				2.5	8	$J_{3',5'} = 0$
15	2	7.5				11	8	
16a	3.5	7				12	7.5	
16b	3.5	8				11	8	
17	7	4				12	8	
18	2	6.5				11	8	
19a	~1	6				11	8	$J_{5,NH} = 2$
19b	~1	6				11	8	
19b[c]	1.5	6				11	8	$J_{5,NH} = 2$

[a] Unresolved. [b] By first-order analysis. [c] See ref 14a.

Future papers in this series will describe the synthesis of a number of other 4'-methoxy nucleosides as well as of nucleosides bearing other 4' substituents.

Experimental Section

General Methods. The general methods used are basically the same as those previously described.[29] ^{13}C nuclear magnetic resonance (^{13}C NMR) spectra were obtained using a Bruker WH-90 spectrometer operating at 22.62 MHz and chemical shifts are reported in parts per million downfield from an internal standard of tetramethylsilane. We are particularly grateful to Dr. M. L. Maddox and Mrs. J. Nelson for their invaluable help with NMR spectroscopy. Silica column chromatography was done using Merck silica gel G (type 60) and a column height of roughly 20 cm. Melting points are corrected.

Reaction of 3a with Iodine and Methanol. A solution of iodine (3.5 g, 14 mmol) in methanol (50 ml) was added dropwise over 10 min to a vigorously stirred solution of **3a** (3.1 g, 10 mmol) in methanol (50 ml) in the presence of silver acetate (2.2 g, 14 mmol). The mixture was stirred for a further 20 min and then filtered. The filtrate was evaporated and the residue was dissolved in chloroform, washed with 10% sodium thiosulfate, and dried ($MgSO_4$). Evaporation of the solvent and crystallization of the residue (5.3 g) twice from benzene gave 1.57 g (34%) of pure 1-(2,3-di-*O*-acetyl-5-deoxy-5-iodo-4-methoxy-α-L-lyxofuranosyl)uracil (**6a**): mp 241–242°; λ_{max} (MeOH) 258 nm (ε 11,200).

Anal. Calcd for $C_{14}H_{17}N_2O_8I$ (468.21): C, 35.91; H, 3.66; N, 5.98. Found: C, 35.69; H, 3.70; N, 5.86.

The mother liquors from **6a** were chromatographed on a column of silicic acid (500 g) using benzene–ether (1:1) in order to separate three major components. The least polar component (900 mg, 19%) had the same R_f as **6a** on TLC but could not be further purified and was identified as the orthoacetate **9a** by hydrolysis to **9b** (see below). The second product (900 mg, 19%) was a slightly impure syrup characterized as **8a** by NMR and hydrolysis to **8b** (see below).

Elution of the most polar compound gave 740 mg (16%) of crystalline 2',3'-di-*O*-acetyl-5'-deoxy-5'-iodo-4'-methoxyuridine (**5a**) which could be recrystallized from acetone: mp 203–204°; λ_{max} (MeOH) 257 nm (ε 10,700).

Anal. Calcd for $C_{14}H_{17}N_2O_8I$ (468.21): C, 35.91; H, 3.66; N, 5.98. Found: C, 35.71; H, 3.61; N, 5.70.

5'-Deoxy-5'-iodo-4'-methoxyuridine (5b). A solution of **5a** (117 mg, 0.25 mmol) in methanol (5 ml) and concentrated ammonium hydroxide (5 ml) was kept overnight at room temperature and then evaporated. The residue was purified by preparative TLC (chloroform–methanol, 9:1) giving essentially a single band that was eluted and then dried in vacuo at 110° to remove a trace of acetamide (NMR) giving **5b** as a homogeneous foam: λ_{max} (MeOH) 260 nm (ε 10,400).

Anal. Calcd for $C_{10}H_{13}N_2O_6I$ (384.13): C, 31.27; H, 3.41; N, 7.29. Found: C, 31.51; H, 3.49; N, 7.20.

1-(5-Deoxy-5-iodo-4-methoxy-α-L-lyxofuranosyl)uracil (6b). A solution of **6a** (1.17 g, 2.5 mmol) in methanol (50 ml) and concentrated ammonium hydroxide (50 ml) was kept overnight at room temperature and then evaporated to dryness. Two recrystallizations of the residue from acetone–hexane gave 600 mg (63%) of **6b**: mp 181–182°; λ_{max} (MeOH) 261 nm (ε 10,700).

Anal. Calcd for $C_{10}H_{13}N_2O_6I$ (384.13): C, 31.27; H, 3.41; N, 7.29. Found: C, 31.48; H, 3.43; N, 7.12.

5'-Deoxy-4'-hydroxy-5'-iodo-3',4'-*O*-[(*R*)-1-methoxyethylidene]uridine (8b). A solution of the more polar orthoacetate **8a** (117 mg, 0.25 mmol) in methanol (5 ml) and concentrated ammonium hydroxide (5 ml) was stored at room temperature for 15 hr and then evaporated to dryness. Preparative TLC of the residue using chloroform–methanol (19:1) gave a major product that was crystallized from acetone giving 60 mg (56%) of pure **8b**: mp 170–BNT.5°; λ_{max} (MeOH) 259 nm (ε 10,700).

Anal. Calcd for $C_{12}H_{15}N_2O_7I$ (426.17): C, 33.82; H, 3.55; N, 6.57. Found: C, 34.08; H, 3.47; N, 6.42.

5'-Deoxy-4'-hydroxy-5'-iodo-3',4'-*O*-[(*S*)-1-methoxyethylidene]uridine (9b). The crude, less polar orthoacetate **9a** (262, mg, contaminated with some **6a**) was treated with methanolic ammonium hydroxide as above. Partial evaporation of the mixture gave 107 mg of crystalline **9b** with mp 179–180° from methanol. Preparative TLC of the mother liquors separated 40 mg (19%) of **6b** that was identical with the material described above and a further 50 mg (total yield 157 mg, 66%) of **9b**: λ_{max} (MeOH) 258 nm (ε 10,500).

Anal. Calcd for $C_{12}H_{15}N_2O_7I$ (426.17): C, 33.82; H, 3.55; N, 6.57. Found: C, 33.97; H, 3.57; N, 6.48.

1-(2,3-Di-*O*-acetyl-5-deoxy-4-methoxy-α-L-lyxofuranosyl)uracil (11a). A solution of **6a** (117 mg, 0.25 mmol) in methanol (10 ml) was vigorously stirred in the presence of 10% palladium-on-carbon catalyst (25 mg) and sodium acetate (1 ml of 0.5 *M*) for 90 min. The mixture was then filtered and the evaporated filtrate was dissolved in chloroform, washed with aqueous bicarbonate, aqueous sodium thiosulfate, and water, dried ($MgSO_4$), and evaporated. Several crystallizations of the residue from chloroform–hexane gave 42 mg (50%) of **11a**: mp 220° dec; λ_{max} (MeOH) 259 nm (ε 10,000).

Anal. Calcd for $C_{14}H_{18}N_2O_8$ (342.30): C, 49.12; H, 5.30; N, 8.19. Found: C, 49.01; H, 5.28; N, 8.11.

2',3'-Di-*O*-acetyl-5'-deoxy-4'-methoxyuridine (10a). Reduction of **5a** (117 mg, 0.25 mmol) was carried out as above for **6a** giving, after crystallization from ethyl acetate and then acetone, 27 mg (32%) of **10a**: mp 175.5–176.5°; λ_{max} (MeOH) 258 nm (ε 9700).

Anal. Calcd for $C_{14}H_{18}N_2O_8$ (342.30): C, 49.12; H, 5.30; N, 8.19. Found: C, 49.20; H, 5.47; N, 7.80.

1-(5-Azido-5-deoxy-4-methoxy-α-L-lyxofuranosyl)uracil (11b). A solution of **6b** (384 mg, 1 mmol) and lithium azide (384 mg, 7.8 mmol) in dimethylformamide (8 ml) was heated at 110° for 20 hr and then evaporated to dryness. The residue was purified by preparative TLC using two developments with chloroform–methanol (9:1) giving 200 mg (67%) of **11b**: mp 215–216° from acetone; λ_{max} (MeOH) 261 nm (ε 10,200).

Anal. Calcd for $C_{10}H_{13}N_5O_6$ (299.20): C, 40.13; H, 4.38; N, 23.41. Found: C, 40.30; H, 4.35; N, 23.54.

1-(2,3-Di-*O*-acetyl-5-azido-5-deoxy-4-methoxy-α-L-lyxofuranosyl)uracil (11c). A solution of **11b** (82 mg) and acetic anhydride (0.8 ml) in pyridine (1 ml) was kept at room temperature overnight and then evaporated to dryness after addition of methanol.

Decolorization with charcoal followed by three crystallizations from chloroform–hexane gave 42 mg (40%) of **11c**: mp 194–195°; λ_{max} (MeOH) 258 nm (ϵ 10,500).

Anal. Calcd for $C_{14}H_{17}N_5O_8$ (383.32): C, 43.86; H, 4.47; N, 18.27. Found: C, 43.55; H, 4.50; N, 18.10.

2′,3′-Di-*O*-benzoyl-5′-deoxy-5′-iodouridine (12b). A solution of **12a** (14.16 g, 40 mmol)[29] and benzoic anhydride (90 g, 400 mmol) in pyridine (100 ml) was stored at room temperature for 15 hr and then water (50 ml) was added. After 30 min the mixture was diluted with chloroform and washed with a large volume (3 l.) of aqueous sodium bicarbonate. The dried ($MgSO_4$) organic phase was evaporated and the residue triturated with ether giving 16.5 g (73%) of crystalline **12b.** An analytical sample from benzene–hexane had mp 108.5–111.5° unchanged upon further recrystallization: λ_{max} (MeOH) 231 nm (ϵ 28,300), 256 (13,600).

Anal. Calcd for $C_{23}H_{19}N_2O_7I$ (562.31): C, 49.12; H, 3.41; N, 4.98. Found: C, 49.55; H, 3.63; N, 4.69.

1-(2,3-Di-*O*-benzoyl-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)uracil (3b). A solution of **12b** (11.24 g, 20 mmol) in pyridine (200 ml) was stirred in the dark with powdered silver fluoride[38] (6.0 g, 47 mmol) for 4 days. After evaporation of the solvent in vacuo the residue was partitioned between ethyl acetate and water. After removal of an insoluble material the organic phase was decolorized with charcoal, dried ($MgSO_4$), and evaporated. The residue was dissolved in benzene, filtered, and evaporated leaving 6.76 g (76%) of **3b** as a TLC homogeneous foam after careful drying under high vacuum. An analytical sample was prepared by preparative TLC (hexane–acetone, 3:1): λ_{max} (MeOH) 230 nm (ϵ 27,600), 255 (12,400).

Anal. Calcd for $C_{23}H_{18}N_2O_7$ (434.39): C, 63.59; H, 4.18; N, 6.45. Found: C, 63.55; H, 4.28; N, 6.01.

2′,3′-Di-*O*-benzoyl-5′-chloro-5′-deoxyuridine (12c). A solution of **12a** (17.7 g, 50 mmol) and benzoyl chloride (16.8 g, 120 mmol) in pyridine (100 ml) was kept at room temperature for 18 hr and then evaporated to dryness after addition of methanol. The residue was partitioned between chloroform and water and the evaporated organic phase was treated with pyridine–water (49:1) at 100° for 2 hr to cleave the *N*-benzoyl group (TLC, CCl_4–acetone, 4:1). After evaporation of the solvent the residue was partitioned between chloroform and water giving an insoluble precipitate that was collected and crystallized from acetone. The resulting material (7.7 g, mp 182–186°) was shown by NMR to be a 4:1 mixture of **12c** and **12b,** and pure **12c** was obtained by four recrystallizations from ethyl acetate: mp 189–191°: λ_{max} (MeOH) 231 nm (ϵ 27,600), 256 (13,000).

Anal. Calcd for $C_{23}H_{19}N_2ClO_7$ (470.86): C, 58.66; H, 4.06; N, 5.95; Cl, 7.53. Found: C, 58.56; H, 4.16; N, 5.86; Cl, 7.62.

Reaction of 3b with Iodine and Methanol. A solution of iodine (700 mg, 2.8 mmol) in methanol (20 ml) was added over 10 min to a stirred solution of **3b** (868 mg, 2 mmol) in methanol (10 ml) in the presence of silver acetate (440 mg, 2.8 mmol). After a work-up identical with that used above with **3a** the crude product was purified by preparative TLC using two developments with chloroform–ethyl acetate (3:1) giving three uv-absorbing bands. Elution of the fastest band followed by decolorization with charcoal gave 280 mg (24%) of a single diastereomer of **13:** λ_{max} (MeOH) 233 nm (ϵ 17,500), 256 (12,100).

Anal. Calcd for $C_{24}H_{21}N_2O_8I$ (592.34): C, 48.66; H, 3.57; N, 4.73. Found: C, 48.76; H, 3.50; N, 4.72.

Elution of the middle band gave 350 mg (30%) of a mixture of the other diastereomer of **13** and the 4′-methoxyuridine derivative **5c** that could not be resolved. Hydrolysis of this material with methanolic ammonium hydroxide (1:1) for 18 hr at room temperature followed by preparative TLC using chloroform–methanol (93:7) gave 110 mg of the diol **5b** that was crystallized from acetone–hexane and shown to be identical with that from hydrolysis of **5a.** The other product of the above hydrolysis was 80 mg of impure debenzoylated **13** that appeared to be unstable and was not further examined.

Elution of the slowest band followed by repurification by preparative TLC (chloroform–ethyl acetate, 4:1) and treatment with charcoal in benzene gave 190 mg (16%) of pure 4′-methoxy-α-L-lyxo nucleoside **6c** as a clear syrup still containing some benzene: λ_{max} (MeOH) 230 nm (ϵ 30,800), 255 (14,200).

Anal. Calcd for $C_{24}H_{21}N_2O_8I$ (0.5C_6H_6) (631.39): C, 51.36; H, 3.83; N, 4.44. Found: C, 51.06; H, 3.71; N, 4.65.

Hydrolysis of a small sample of **6c** with methanolic ammonium hydroxide as above gave only **6b** and no **5b** as shown by TLC.

1-(2,3-*O*-Carbonyl-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)uracil (14). (a) A solution of **12a** (10.62 g, 30 mmol) and DBN (12.4 g, 100 mmol) in pyridine (250 ml) was stirred at 40° for 24 hr and then cooled to −80°. A 12.5% solution of phosgene in benzene (48 ml, 60 mmol) was added through a septum and the mixture was allowed to warm to room temperature. After evaporation of the solvent the residue was dissolved in ethyl acetate, washed with aqueous sodium thiosulfate and then water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on a column of silicic acid (500 g) using hexane–acetone (2:1, 1:1, and 1:2). Evaporation of the major uv-absorbing product gave 4.55 g (60%) of crystalline **14:** mp 143–146° from acetone–hexane; λ_{max} (MeOH) 256 nm (ϵ 9000).

Anal. Calcd for $C_{10}H_8N_2O_6$ (252.18): C, 47.62; H, 3.20; N, 11.11. Found: C, 47.34; H, 3.34; N, 10.93.

(b) A 12.5% solution of phosgene in benzene (1.6 ml, 2 mmol) was added to a solution of **3c** (226 mg, 1 mmol) in pyridine (6 ml) at −80°. After warming to room temperature the mixture was evaporated and the residue partitioned between ethyl acetate and water. The dried organic phase was decolorized with charcoal, evaporated, and crystallized from ethyl acetate–chloroform giving 130 mg (51%) of pure **14** identical with that above.

5′-Deoxy-5′-iodo-4′-methoxyuridine 2′,3′-*O*-Carbonate (15). A solution of iodine (19.8 g, 78 mmol) in methanol (1200 ml) was added over 2 hr to a vigorously stirred solution of **14** (15.12 g, 60 mmol) in methanol (600 ml) in the presence of lead carbonate (16.0 g, 60 mmol). After a further hour the mixture was filtered through Celite and the yellow solid was washed well with methanol and hot acetone. The filtrates were evaporated and the residue was partitioned between ethyl acetate (1.5 l.) and 10% sodium thiosulfate (600 ml). The aqueous phase was back extracted twice with ethyl acetate and the combined organic phases were dried and evaporated giving 20.8 g (85%) of pure (TLC, NMR), crystalline **15:** mp 223–249° dec from acetone–hexane (unchanged upon recrystallization); λ_{max} (MeOH) 255 nm (ϵ 10,800).

Anal. Calcd for $C_{11}H_{11}N_2O_7I$ (410.13): C, 32.11; H, 2.70; N, 6.83. Found: C, 31.80; H, 2.80; N, 6.47.

5′-Deoxy-5′-iodo-4′-methoxyuridine (5b). A suspension of **15** (22.55 g, 55 mmol) in 0.2 *M* barium hydroxide (550 ml) was shaken vigorously at room temperature for 1.5 hr. Carbon dioxide was then bubbled into the mixture for 45 min and the precipitated barium carbonate was removed by filtration. The precipitate was thoroughly washed with hot methanol and the filtrates were evaporated to dryness leaving a 21-g residue. The latter was chromatographed on a column of silicic acid (1500 g) using a gradient (30–50%) of ethyl acetate in benzene giving 18.6 g (88%) of pure **5b** that was identical (TLC, NMR) with that obtained above by hydrolysis of **5a.**

2′,3′-Di-*O*-benzoyl-5′-deoxy-5′-iodo-4′-methoxyuridine (5c). A solution of **5b** (1.54 g, 4 mmol) and benzoyl chloride (2.0 ml, 17 mmol) in pyridine (16 ml) was stored at room temperature for 6 hr and the reaction was then quenched with methanol (5 ml). After evaporation of the solvent the residue was coevaporated with ethanol–water (1:1) to remove methyl benzoate and dried in vacuo. The product, a 9:1 mixture of N^3,2′,3′- and 2′,3′-benzoates, was dissolved in pyridine (9.8 ml) and water (0.2 ml) and heated at 100° for 2 hr. Following evaporation of the solvent the residue was dissolved in ethyl acetate, filtered, and evaporated leaving a syrup (3.5 g) that was chromatographed on a column of silicic acid (200 g) using benzene–ethyl acetate (9:1 and 4:1). This gave 2.0 g (83%) of **5c:** mp 191–192° from ethyl acetate–hexane; λ_{max} (MeOH) 230 nm (ϵ 27,800), 255 (13,900).

Anal. Calcd for $C_{24}H_{21}N_2O_8I$ (592.34): C, 48.67; H, 3.57; N, 4.73. Found: C, 48.36; H, 3.65; N, 4.47.

2′,3′,5′-Tri-*O*-benzoyl-4′-methoxyuridine (16a). A solution of **5c** (1.52 g, 2.56 mmol) and lithium benzoate (1.3 g, 10 mmol) in dimethylformamide (30 ml) was heated at 120° for 60 hr. After evaporation of the solvent in vacuo the residue was dissolved in dichloromethane, washed with water, dried, and evaporated to dryness. The residue was purified by preparative TLC on two 1-m plates using benzene–ethyl acetate (7:3), elution of the major band giving 750 mg (51%) of **16a:** mp 180–182° from ethanol; λ_{max} (MeOH) 230 nm (ϵ 39,000), 255 (14,200).

Anal. Calcd for $C_{31}H_{26}N_2O_{10}$ (586.54): C, 63.48; H, 4.47; N,

4.78. Found: C, 63.62; H, 4.45; N, 5.08.

4'-Methoxyuridine (16b). (a) From 16a. A solution of **16a** (570 mg, 1 mmol) in methanol (10 ml) and concentrated ammonium hydroxide (10 ml) was heated in a stainless steel bomb at 100° for 2 hr. The solvent was evaporated in vacuo and the residue coevaporated with aqueous ethanol. The residue was purified by preparative TLC using chloroform–methanol (85:15), elution of the major band giving 195 mg (71%) of **16b** as an analytically and spectroscopically pure foam: λ_{max} (MeOH) 261 nm (ϵ 9700); $[\alpha]^{23}D$ −67.2° (*c* 1, H_2O); ORD (H_2O) $[\Phi]_{284}^{pk}$ 1900°, $[\Phi]_{275}$ 0°, $[\Phi]_{252}^{tr}$ −9300°; mass spectrum (70 eV) *m/e* 275 ($M^+ + H$), 243 ($M^+ - OMe$), 225 ($M^+ - OCH_3 - H_2O$), 163 (sugar), 155 (sugar − H_2O).

Anal. Calcd for $C_{10}H_{14}N_2O_7$ (274.23): C, 43.79; H, 5.15; N, 10.22. Found: C, 43.78; H, 5.01; N, 10.31.

(b) From 5b. A solution of **5b** (768 mg, 2 mmol) and benzoyl chloride (0.8 ml, 6.8 mmol) was kept at 20° for 7 hr, quenched with methanol, and evaporated to dryness. After coevaporation with aqueous ethanol (1:1) the residue was partitioned between ethyl acetate and water and the organic phase was evaporated. The resulting syrup (1.3 g) and lithium benzoate (1.28 g, 10 mmol) were dissolved in hexamethylphosphoramide and heated at 125° for 15 hr. The solvent was evaporated in a short-path apparatus (90°, 0.1 mm) and the residue was dissolved in ethyl acetate (50 ml) and filtered through Celite. The filtrate was evaporated and the residual syrup was chromatographed on a column of silicic acid (250 g) using benzene–ethyl acetate (7:2) giving 720 mg (61% overall) of crystalline **16a.** The latter was treated with methanolic ammonium hydroxide (20 ml, 1:1) at 100° for 3 hr and then purified as above by preparative TLC using chloroform–methanol (4:1) to give 225 mg (41% from **5b**) of **16b** identical with that from (a) above.

Reaction of 1-(5-Deoxy-β-D-*erythro*-pent-4-enofuranosyl)uracil (3c) with Iodine and Methanol. (a) A solution of iodine (250 mg, 1 mmol) in methanol (10 ml) was added dropwise over 2 hr to a vigorously stirred solution of **3c** (226 mg, 1 mmol) in methanol (10 ml) containing lead carbonate (375 mg, 1.4 mmol). Fresh lead carbonate (190 mg) was added after 40, 80, and 120 min and the final mixture was stirred for an additional 30 min. Solid sodium thiosulfate was added until the iodine color was discharged and the mixture was filtered through Celite. The filtrate and methanol washings were evaporated and the residue was purified by preparative TLC (chloroform–methanol, 9:1). Elution of the single uv-absorbing band gave 295 mg (77%) of a colorless syrup that was more than 95% pure **5b** by NMR. Only traces of **6b** were present by TLC using benzene–acetone (1:1).

(b) A similar experiment using iodine (1.4 equiv) in the presence of silver acetate (1.4 equiv) instead of lead carbonate gave a mixture of **5b** and **6b** in a ratio of 2:1.

Equilibration of 5b and 6b. (a) Samples of **5b** and **6b** (3 mg) were separately stirred in methanol (0.5 ml) in the presence of dried Dowex 50 (H^+) resin, aliquots being examined by TLC (acetone–benzene, 1:1) after 1, 2, 4, 48, and 72 hr. The lyxo isomer **6b** proved to be quite stable, only traces of uracil and no **5b** being present after 48 hr. The ribo isomer **5b**, however, quickly equilibrated and after 4 hr contained a mixture of **6b** and **5b** (2:1) and a considerable amount of uracil. After 72 hr only **6b** and uracil were present in a ratio of ~1:1.

(b) A solution of **5b** (120 mg) in methanol (12 ml) containing dried Dowex 50 (H^+) resin (1.2 g) was kept at room temperature for 7 days at which point only **6b** and uracil were present. The suspension was filtered and the filtrate was immediately made basic with ammonium hydroxide and evaporated to dryness. The residue was purified by preparative TLC (acetone–benzene, 1:1), elution of the faster band giving 30 mg (25%) of pure **6b** that was identical with an authentic sample by NMR.

Equilibration of 4'-Methoxyuridine to 17. A solution of **16b** (100 mg), in dry methanol (10 ml), was stirred at room temperature for 18 hr in the presence of carefully dried Dowex 50 (H^+) resin (1 g). The mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by preparative TLC using chloroform–methanol (4:1). Elution of the major band moving between **16b** and uracil gave 40 mg (40%) of pure **17** as a syrup: λ_{max} (MeOH) 260 nm (ϵ 9000).

Anal. Calcd for $C_{10}H_{14}N_2O_7$ (274.23): C, 43.79; H, 5.15; N, 10.22. Found: C, 44.06; H, 5.31; N, 10.25.

1-(5-Deoxy-5-iodo-2,3-*O*-isopropylidene-4-methoxy-α-L-lyxofuranosyl)uracil (19a). A solution of **6b** (140 mg, 0.36 mmol) in acetone (10 ml) containing 70% perchloric acid (10 μl) was kept at room temperature for 15 min. Concentrated ammonium hydroxide (10 μl) was then added and after evaporation of the solvent the residue was purified by preparative TLC using benzene–acetone (3:1). Elution of the major band gave 105 mg (65%) of crystalline **19a.** After recrystallization from acetone–hexane **19a** melted at 201.5–203°, resolidified, and melted at 217.5–219°: λ_{max} (MeOH) 258 nm (ϵ 10,600).

Anal. Calcd for $C_{13}H_{17}N_2O_6I$ (424.20): C, 36.81; H, 4.04; N, 6.61. Found: C, 36.79; H, 4.15; N, 6.72.

5'-Deoxy-5'-iodo-2',3'-*O*-isopropylidene-4'-methoxyuridine (18). The diol **5b** (96 mg, 0.25 mmol) was treated with acetone and perchloric acid as described for **19a** above. Preparative TLC using benzene–acetone (3:1) gave 90 mg (85%) of pure **18** as a clear syrup: λ_{max} (MeOH) 258 nm (ϵ 11,000).

Anal. Calcd for $C_{13}H_{17}N_2O_6I$ (424.20): C, 36.81; H, 4.04; N, 6.61. Found: C, 36.73; H, 4.19; N, 6.40.

Reaction of 1-(5-Deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)uracil (1a) with Iodine and Methanol. A solution of iodine (140 mg, 1.1 mmol) in methanol (7 ml) was added over 1 hr to a stirred solution of **1a** (106 mg, 0.4 mmol) in methanol (5 ml) in the presence of lead carbonate (150 mg, 0.56 mmol) with fresh lead carbonate (75 mg) being added after addition of 1, 2, and 3 ml of the iodine solution. After a further 30 min at room temperature solid sodium thiosulfate was added until the iodine color disappeared and the mixture was filtered. The filtrate was evaporated and the residue purified by preparative TLC (chloroform–methanol, 19:1) giving a major band containing 125 mg (74%) of a 3:2 mixture of **18** and **19a** as judged by NMR. No resolution of **18** and **19a** was achieved using a large number of solvent systems.

1-(5-Bromo-5-deoxy-2,3-*O*-isopropylidene-4-methoxy-α-L-lyxofuranosyl)uracil (19b). A solution of **19a** (25 mg) and dried lithium bromide (26 mg) in hexadeuteriodimethyl sulfoxide (0.5 ml) was kept at 100°. After 36 hr NMR showed the absence of **19a** and the solvent was evaporated. The residue was purified by preparative TLC using benzene–acetone (7:3) giving essentially a single band. Elution with acetone gave 10 mg (45%) of crystalline **19b.** Two recrystallizations from acetone–hexane gave 6 mg of **19b** with mp 225–225.5° (cf. mp 235–237° for compound described by Sasaki et al.[14a]) and an NMR spectrum very similar to that described by Sasaki.[14a]

Anal. Calcd for $C_{13}H_{17}N_2O_6Br$ (377.21): C, 41.39; H, 4.54; N, 7.42. Found: C, 41.29; H, 4.89; N, 7.23.

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