nm) provided a separation of compounds 4 and 26 (see Figure 1).

Two fractions were collected, centered at times t_A = 45.5 min and t_B = 51.8 min, corresponding to isomers A and B, respectively. These fractions were lyophilized to obtain diastereomer A (100 mg) as an amorphous glass and diasteromer B (33 mg) as a white powder. Isomer A has been tentatively assigned the *S* configuration (26) at C-8 and isomer B and the *R* configuration (4). These assignments have been made on the relative inhibitory activities[22] against adenosine deaminase of A and B. Isomer A (amorphous glass): k' (HPLC)^{23} = 3.14; $[\alpha]^{23}_D$ −29.4° (*c* 2.18, H_2O); UV λ_{max} [methanol] 277 nm ($\log_{10} \epsilon$ 3.90), [pH 1] 260 (3.78), [pH 11] 276 (3.96). Isomer B: mp 210 °C, dec; k' (HPLC)^{23} = 3.71; $[\alpha]^{23}_D$ −79.70 (*c* 1.33, H_2O); UV λ_{max} [methanol] 278 nm ($\log_{10} \epsilon$ 3.88), [pH 1] 260 (3.88), [pH 11] 277 (4.05). For ^{1}H NMR data, see Table III. For ^{13}C NMR data see Table II.

Acknowledgment. This investigation was supported by Grant CA-28381, by the National Cancer Institute, DHEW, and in part by the Filariasis Working Group of the World Bak/UNDP/WHO Special Program for Research and Training in Tropical Diseases (I.D. 800134 and 840398).

Registry No. 3, 88970-13-2; 4, 98720-84-4; 5, 123-06-8; 6, 55781-00-5; 7, 55726-09-5; 8, 99249-11-3; 9, 99249-12-4; 10, 99249-13-5; 11, 99249-14-6; 12 (isomer 1), 99249-15-7; 12 (isomer 2), 99249-16-8; 14 (isomer 1), 99249-18-0; 14 (isomer 2), 99249-17-9; 15, 88970-12-1; 17, 7408-41-5; 18, 38874-49-6; 19, 99249-19-1; 20, 99249-20-4; 21, 99249-22-6; 22, 99249-21-5; 23 (isomer 1), 99267-48-8; 23 (isomer 2), 99267-49-9; 24 (isomer 1), 99249-23-7; 24 (isomer 2), 99249-24-8; 25 (isomer 1), 99249-25-9; 25 (isomer 2), 99249-26-0; 26, 99249-27-1; 2,3-*O*-isopropylidene-D-ribose, 13199-25-2; *N*,*N*-dimethylformamide, 4637-24-5; trimethylsilyl cyanide, 7677-24-9; cyanoacetamide, 107-91-5.

A Novel Three-Step Synthesis of a Pyrrolo[3,2-*d*]pyrimidine C-Nucleoside[1]

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The phosphorus ylide, [(2,4-dimethoxy-5-nitropyrimidin-6-yl)methyl]triphenylphosphorane (10) was synthesized in two steps from 6-(bromomethyl)-2,4-dimethoxy-5-nitropyrimidine (8). Compound 10 was condensed with 2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-D-ribofuranose (1) to form the anomeric pair of protected homo-C-nucleosides, 2,4-dimethoxy-5-nitro-6-*C*-[(2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-β-D-ribofuranosyl)-methyl]pyrimidine (11) and 2,4-dimethoxy-5-nitro-6-*C*-[(2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-α-D-ribofuranosyl)methyl]pyrimidine (12). Compound 10 also reacted with 2,3-*O*-isopropylidene-D-ribofuranose (6) to form the nontritylated compounds 2,4-dimethoxy-6-*C*-[(2,3-*O*-isopropylidene-β- and -α-D-ribofuranosyl)-methyl]-5-nitropyrimidines (14 and 15). Acid treatment of 11 or 12 afforded the deblocked homo-C-nucleoside 6-*C*-[(β-D-ribofuranosyl)methyl]-5-nitropyrimidine-2,4-dione (16), while reduction of 11 produced the 5-amino-pyrimidine homo-C-nucleoside 17 in quantitative yield. 6-(Cyanomethyl)-2,4-dimethoxy-5-nitropyrimidine (18) reacted with 2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-D-ribofuranosyl chloride (19) to form the *R* and *S* diastereomers of 2-(2,4-dimethoxy-5-nitropyrimidin-6-yl)-2-(2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-α-D-ribofuranosyl)acetonitrile (20a and 20b). The major component (20a) was reduced catalytically to the pyrrolo[3,2-*d*]pyrimidine 21. Under mild acid treatment 21 was deblocked to form 2,4-dimethoxy-7-*C*-(α-D-ribofuranosyl)pyrrolo[3,2-*d*]pyrimidine (22). Strong, aqueous acid treatment of 21 afforded a 1/1 mixture of 22 and the β anomer 23.

Homo-C-nucleosides are a growing class of nucleosides[2-6] which are composed structurally of a sugar portion and an aglycon linked via a methylene bridge between the anomeric carbon atom in the sugar and a carbon atom in the aglycon. Viewed as synthons, it was thought that these homo-C-nucleosides should provide an attractive alternative synthetic route to the preparation of bicyclic C-nucleosides with potential biological activity. The present study explores the applicability of this synthetic strategy, and we now report two new procedures for the formation of 6-*C*-[(1-D-ribofuranosyl)methyl]pyrimidine homo-C-nucleosides, one of which leads to the three-step synthesis of a novel pyrrolo[3,2-*d*]pyrimidine C-nucleoside which is an analogue of the 9-deazapurine C-nucleoside, 9-deazaxanthosine.[7]

Results and Discussion

The condensation of stabilized ylides such as (carboethoxymethylene)triphenylphosphorane (2) or (cyanomethylene)triphenylphosphorane (3) with the sugar 1 has afforded[8] the versatile C-nucleoside precursors ethyl 2-[2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-β-D-ribofuranosyl]acetate (4) and 2-[2,3-*O*-isopropylidene-5-*O*-

(1) This study was supported in part by funds from the National Institutes of Health (Training Grant 5-T32-GM 07767) and the American Cancer Society (Grant CH-133).

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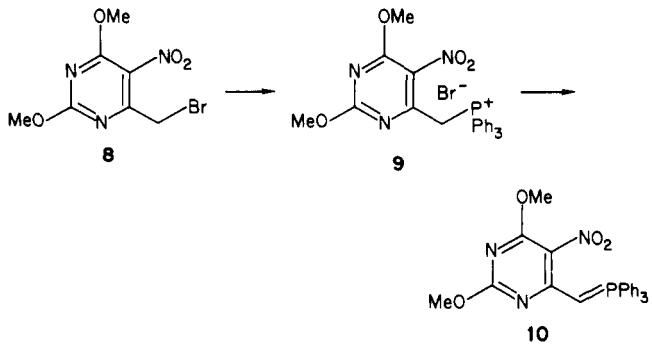
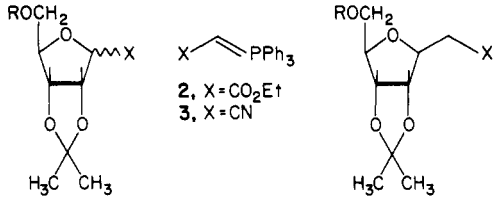
0022-3263/86/1951-1058$01.50/0

Scheme I



(triphenylmethyl)-β-D-ribofuranosyl]acetonitrile (**5**), respectively. The condensations involving **2** or **3** and 2,3-



1, X=OH; R=Tr
6, X=OH; R=H
19, X=Cl; R=Tr

4, R=Tr; X=CO_2Et
5, R=Tr; X=CN
7a, R=H; X=CO_2Et
7b, R=H; X=CN

O-isopropylidene-D-ribofuranose (**6**) have in addition yielded[8,9] ethyl 2-(2,3-*O*-isopropylidene-1-β-D-ribofuranosyl)acetate (**7a**) or 2-(2,3-*O*-isopropylidene-1-β-D-ribofuranosyl)acetonitrile (**7b**), respectively. In spite of the fact that compounds **4** and **5** have played key roles in the synthesis[10] of a variety of biologically active C-nucleosides, it was somewhat surprising to see on reviewing the literature that no studies have been reported to extend the scope and versatility of this sugar–ylide condensation reaction. An obvious extension of this procedure would be to carry out the condensation of either of the sugars **1** or **6** with a different stabilized ylide, and it occurred to us that one such alternate phosphorus ylide might be one in which the electron-withdrawing group is a suitably substituted pyrimidine.

A number of pyrimidine phosphorus ylides have been synthesized[11,12] and successfully reacted with a variety of aldehydes to give unsaturated alkylpyrimidines. However, in each case the phosphorane species was generated in situ by addition of a base to a mixture of the phosphonium salt and the aldehyde. Presumably, these reactions were carried out in this manner because of the demonstrated[13] difficulty in the isolation of many reactive alkyl- and arylphosphoranes. It was felt that in order to obtain a stable, isolable pyrimidine ylide necessary for our proposed condensation, it would have to be a very electron-deficient pyrimidine system such as would be the case in a 5-nitropyrimidine. Therefore, we chose to prepare as a target the 6-*C*-[(D-ribofuranosyl)methyl]pyrimidine homo-C-nucleoside, [(2,4-dimethoxy-5-nitropyrimidin-6-yl)-methylene]triphenylphosphorane (**10**).

The synthesis of compound **10** proved to be straightforward and proceeded in two steps from 6-(bromomethyl)-2,4-dimethoxy-5-nitropyrimidine[14] (**8**) (Scheme I). Compound **8** reacted with triphenylphosphine to produce [(2,4-dimethoxy-5-nitropyrimidin-6-yl)methylene]triphenylphosphonium bromide (**9**) as a white solid, which yellowed on standing. Without further purification, **9** was treated with sodium hydroxide and converted to compound **10** in 79% yield from **8**. Compound **10** was very stable as evidence by its high melting point (mp 205–206 °C) and its long shelf life (>6 months).

In order to investigate the feasibility of a condensation of **10** with the protected ribofuranose **1**, a solution of the two reactants in a variety of solvents was heated at reflux. In acetonitrile, only a minimal reaction was observed even after 72 h. In benzene, a less polar solvent, only a slight improvement in the amount of detectable products was observed. However, in toluene a complete disappearance of starting material **1** was observed after 72 h. The use of *p*-xylene led to considerable darkening of the reaction mixture and decomposition of **1**. When the progress of the condensation reaction in toluene was monitored on thin-layer chromatography (TLC), the gradual disappearance of **10** and **1** was accompanied by the appearance of three distinct products, 2,4-dimethoxy-6-*C*-[(2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-β-D-ribofuranosyl)-methyl]-5-nitropyrimidine (**11**), 2,4-dimethoxy-6-*C*-[(2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-α-D-ribofuranosyl)]methyl-5-nitropyrimidine (**12**) and a small amount of olefinic material **13** (Scheme II). The olefinic product was assumed to be trans/cis mixture of a condensation product in which the sugar moiety was ring-opened. The formation of a similar species was reported[10] for the condensation of **2** with **1**. This assignment was supported by its 360-MHz ^{1}H NMR spectrum, which contained chemical shifts for the olefinic protons at 6.74 and 7.47 ppm for the trans isomer (J = 15.1 Hz) and at 6.49 and 6.12 ppm for the cis isomer (J = 12.1 Hz) (see Table I for 360-MHz ^{1}H NMR chemical shift data and Table II for coupling constants). The addition of a small amount of sodium methoxide to a solution of the product mixture in methanol, caused **13** to be rapidly converted into **11** and/or **12**. Interestingly, compound **11** was only sparingly soluble in methanol, whereas **12** was quite soluble. This fact facilitated the isolation of pure **11** without the use of chromatography. Since both anomers[15] were obtained in the reaction, a comparison of ^{1}H NMR data allowed an unequivocal structure assignment. As expected[16] the chemical shift of the anomeric proton in **11** (4.37 ppm) occurred upfield relative to that of **12** (4.84 ppm).

The condensation of **10** with the nontritylated sugar **6** was also carried out in toluene. However, to effect complete solubility of **6**, dry acetonitrile was added to the reaction mixture. The reaction proceeded rapidly (13 h) under these conditions, and the formation of the olefinic ring-opened product corresponding to **13** was not observed when the reaction was monitored by TLC. The major product obtained from the reaction was 2,4-dimethoxy-6-*C*-[(2,3-*O*-isopropylidene-β-D-ribofuranosyl)methyl]-5-nitropyrimidine (**14**), while the α anomer, 2,4-dimethoxy-6-*C*-[(2,3-*O*-isopropylidene-α-D-ribofuranosyl)methyl]-5-

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(15) The term anomeric is not strictly applicable to *C*-glycosides but is used for convenience.
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Table I. 360-MHz Proton Magnetic Resonance Spectra[a] of Certain C-Nucleosides

compd	C1′-H	C2′-H	C3′-H	C4′-H	C5′-H_a	C5′-H_b	others
11	4.37 (ddd)[b]	4.50 (dd)	4.46 (dd)	4.04 (m)	3.15 (dd)	3.10 (dd)	1.44, 1.22 (2 s, $C(CH_3)_2$, $\Delta\delta$ = 0.22), 7.26 (m, trityl), 3.05 (dd, pyr-CH_a), 2.96 (dd, pyr-CH_b), 3.97 (s, OCH_3), 3.99 (s, OCH_3)
12	4.84 (ddd)	4.78 (dd)	4.64 (dd)	4.10 (pt)	3.23 (dd)	3.00 (dd)	1.44, 1.23 (2 s, $C(CH_3)_2$, $\Delta\delta$ = 0.18), 7.23 (m, trityl), 3.19 (dd, pyr-CH_a), 3.07 (dd, pyr-CH_b), 3.79 (s, OCH_3), 4.01 (s, OCH_3)
cis-**13**	6.12 (dd)	5.63 (dd)	4.40 (dd)	3.75 (m)	*c*	*c*	6.49 (dd, pyr-CH), 1.37 (s, $C(CH_3)_2$), 1.36 (s, $C(CH_3)_2$), 7.3 (m, trityl), 4.04 (s, OCH_3), 4.09 (s, OCH_3)
trans-**13**	6.74 (dd)	4.91 (ddd)	4.25 (dd)	3.60 (m)	3.32 (d)	3.32 (d)	7.47 (dd, pyr-CH), 1.39 (s, $C(CH_3)_2$), 1.36 (s, $C(CH_3)_2$), 7.3 (m, trityl), 4.06 (s, OCH_3), 4.03 (s, OCH_3)
14	4.40 (ddd)	4.49 (dd)	4.70 (dd)	4.00 (m)	3.77 (dd)	3.59 (dd)	1.50, 1.32 (2 s, $C(CH_3)_2$, $\Delta\delta$ = 0.18), 3.08 (d, pyr-CH_a), 3.07 (d, pyr-CH_b), 4.06 (s, OCH_3), 4.03 (s, OCH_3), 1.9 (br s, C5′-OH)
15	4.55 (m)	4.63 (dd)	4.73 (dd)	4.09 (m)	3.57 (d)	3.56 (d)	1.45, 1.28 (2 s, $C(CH_3)_2$, $\Delta\delta$ = 0.17), 3.20 (dd, pyr-CH_a), 3.10 (dd, pyr-CH_b), 4.05 (s, OCH_3), 4.00 (s, OCH_3), 2.1 (br s, C5′-OH)
16[d]	3.87 (dt)	3.67 (m)	3.82 (t)	3.67 (m)	3.40 (dd)	3.34 (dd)	2.89 (dd, pyr-CH_a), 2.64 (dd, pyr-CH_b), 3.3 (C2′-OH), 4.84 (C3′-OH), 3.3 (C5′-OH), 11.81 (NH)
17	4.24 (ddd)	4.55 (dd)	4.41 (dd)	4.01 (pq)	3.23 (dd)	3.08 (dd)	2.97 (dd, pyr-CH_a), 2.87 (dd, pyr-CH_b), 1.53, 1.32 (2 s, $C(CH_3)_2$, $\Delta\delta$ = 0.21), 7.2 (m, trityl), 3.88 (s, OCH_3), 3.84 (s, OCH_3)
20a	5.21 (dd)	4.57 (dd)	4.61 (d)	4.28 (pt)	3.48 (dd)	3.13 (dd)	4.67 or 4.61 (d, pyr-CH), 1.41, 1.18 (2 s, $C(CH_3)_2$, $\Delta\delta$ = 0.23), 7.3 (m, trityl), 4.12 (s, OCH_3), 3.87 (s, OCH_3)
20b	4.95 (dd)	5.06 (dd)	4.75 (dd)	4.08 (m)	3.26 (dd)	2.94 (dd)	4.83 (d, pyr-CH), 1.52, 1.35 (2 s, $C(CH_3)_2$, $\Delta\delta$ = 0.17), 7.3 (m, trityl), 4.13 (s, OCH_3), 3.86 (s, OCH_3)
21	5.83 (d)	4.95 (dd)	4.87 (d)	4.28 (t)	3.38 (dd)	3.27 (dd)	1.55, 134 (2 s, $(C(CH_3)_2$, $\Delta\delta$ = 0.21), 7.3 (m, trityl, C6-H), 4.05 (s, OCH_3), 3.79 (s, OCH_3), 11.7 (br s, N5-H)
22[d]	5.19 (d)	3.99 (*c*)	4.10 (dd)	3.79 (m)	3.57 (dd)	3.49 (1c)	7.48 (br s, C6-H), 4.00 (s, OCH_3), 3.85 (s, OCH_3), 11.70 (br s, N5-H), 4.66 (t, C5′-OH), 4.92 (d, C2′-OH), 4.86 (d, C3′-OH)
23[d]	4.76 (d)	4.32 (dd)	4.03 (dd)	3.81 (m)	3.59 (dd)	3.47 (dd)	7.53 (br s, C6-H), 4.03 (s, OCH_3), 3.87(s, OCH_3), 11.71 (br s, N5-H), 4.93 (dd, C5′-OH), 4.8 (m, C2′-OH, C3′-OH)

[a] Spectra were obtained in deuterated chloroform ($CDCl_3$), and chemical shifts are relative to chloroform ($CHCl_3$). [b] Multiplicity abbreviations are defined in the general methods portion of the Experimental Section. [c] Undetermined. [d] Spectrum recorded in Me_2SO-d_6 to obtain the OH and NH peaks and then in Me_2SO-d_6/D_2O to record all other peaks after deuterium exchange.

Table II. ^1H Coupling Constants (*J*, Hz) of Certain C-Nucleosides

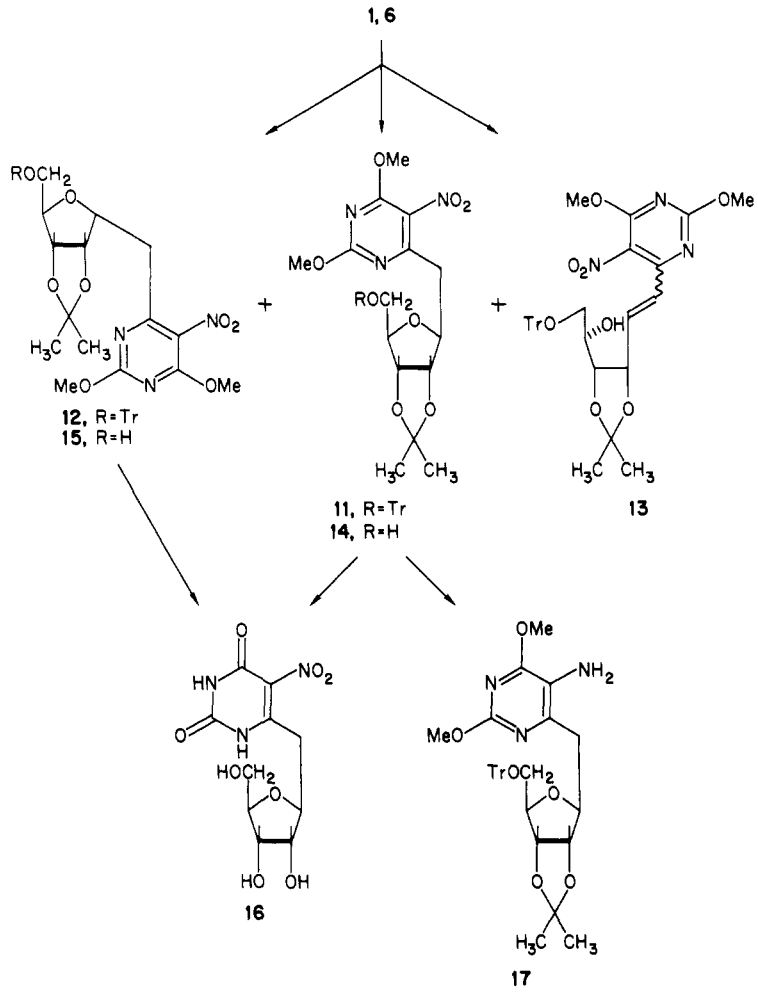
compd	H_a,H_b	H_a,1′	H_b,1′	H_a,2′	1′,2′	2′,3′	3′,4′	4′,5a′	4′,5b′	5a′,5b′
11	14.3	7.1	6.2		4.6	6.6	3.4	4.6	4.6	10.0
12	15.4	7.1	6.1		4.2	6.1	1.0	3.8	3.8	10.3
cis-**13**		12.1		1.2	8.8	*a*	*a*	*a*	*a*	*a*
trans-**13**		15.1		1.7	4.7	6.6	9.0	3.7	5.1	
14	0	5.1	8.5		3.9	6.6	3.9	2.7	3.4	12.5
15	15.6	7.6	6.1		1.4	6.2	4.5	4.5	6.3	*a*
16	13.3	8.7	4.7		*a*	*a*	*a*	4.0	4.4	12.0
17	13.7	4.3	7.3		5.0	6.8	4.3	3.5	5.2	10.1
20a		9.5			4.2	6.1	0	3.1	3.0	10.4
20b		9.8			4.0	6.0	0.9	3.4	2.8	10.3
21					3.5	6.0	0	4.4	4.6	10.0
22					3.4	4.8	7.5	2.8	*a*	11.9
23					6.9	5.4	*a*	3.8	3.8	12.7

[a] Undetermined.

nitropyrimidine (**15**) was the minor product. Although **15** was not isolated as an analytically pure sample due to residual triphenylphosphine oxide, the ratio of **14**/**15** was estimated by TLC to be approximately 3/2. Initial structure assignment of **14** was made by comparing its ^1H NMR spectrum with that of **15**. This assignment was confirmed chemically, however, by the conversion of **14** to **11** upon treatment with triphenylmethyl chloride in pyridine.

The protected homo-C-nucleoside **11** was readily deblocked by using hydrochloric acid in dioxane to furnish what was assumed to be 6-*C*-[(β-D-ribofuranosyl)-methyl]-5-nitropyrimidin-2,4-dione (**16**) in 50% yield. The configurational assignment for **16** was firmly established as β on the basis of ^{13}C NMR chemical shift data. It has been observed that isopropylidene methyl group ^{13}C NMR signals of isopropylidene-derivatized nucleosides occur at chemical shift values of 25.5 ± 0.2 and 27.5 ± 0.2 ppm for β anomers and at 24.9 ± 0.3 and 26.3 ± 0.2 ppm for α anomers.[8] The 2,3-*O*-isopropylidene derivative of **16**, which was prepared by treatment of **16** with 2,2-dimethoxypropane and acetone in the presence of a catalytic amount of 70% perchloric acid, exhibits chemical shifts at 25.53 and 27.38 ppm consistent with a β assignment. In addition, it has been established that the ^{13}C $\Delta\delta$ for these two methyl groups is 1.90 ± 0.2 and 1.25 ± 0.2 ppm for β and α anomers, respectively.[8] The ^{13}C $\Delta\delta$ observed for the methyl groups of the isopropylidene derivative of **16** was 1.85 ppm, again consistent with a β configuration. In order to further confirm the β configuration of **16** by a comparison with the α anomer, the α anomer **12** was also deblocked by using similar reaction conditions. However, the product isolated was not the expected α anomer but rather the β anomer, **16**, in 87% yield. Finally the ease with which the 5-nitro group in **11** is reduced was demonstrated by the virtually quantitative, catalytic reduction of **11** to afford 5-amino-2,4-dimethoxy-6-*C*-[(2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-β-D-ribofuranosyl)methyl]pyrimidine (**17**).

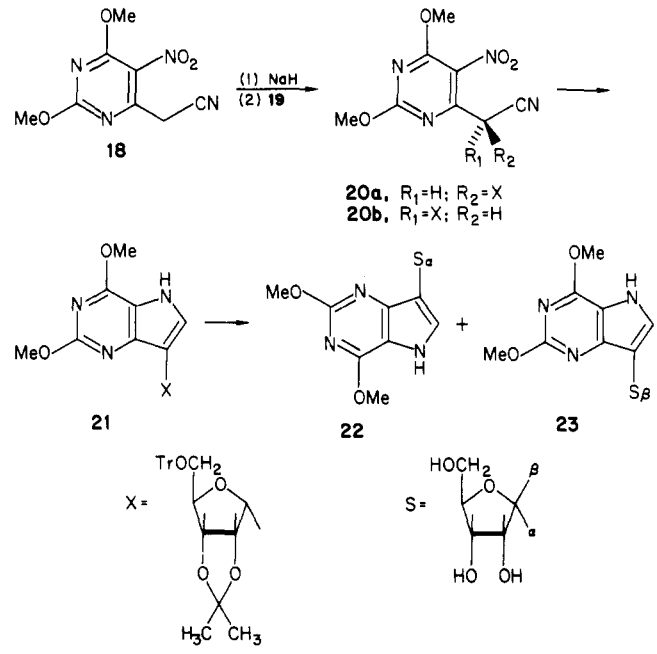
Scheme II



The second method which we developed for the synthesis of pyrimidine homo-C-nucleoside was based on one of the traditional methods[10] for glycosidic bond formation. This method involved the direct nucleophilic displacement of a halide on the sugar's anomeric center by a stabilized carbanion. As an example,[8a] the sodium salt of diethyl malonate has been condensed with 2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-D-ribofuranosyl chloride (**19**), and although an anomeric mixture of C-nucleoside products was obtained from this reaction, evidence was presented which indicated that close control of the reaction conditions (i.e., reaction time and the use of specific amounts of potassium iodide as a catalyst) could result in the formation of predominently the β anomer. This anomeric preference, plus the generally excellent product yields, prompted us to carry out a similar reaction involving **19** and 6-(cyanomethyl)-2,4-dimethoxy-5-nitropyrimidine[14] (**18**).

Thus, compound **18**, as a sodium salt, was reacted with **19** in refluxing 1,2-dimethoxyethane in the presence of potassium iodide. When the reaction was interrupted after 90 min and worked up, a single, crystalline product, 2-(2,4-dimethoxy-5-nitropyrimidin-6-yl)-2-(2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-α-D-ribofuranosyl)-acetonitrile (**20a**) was obtained (Scheme III). On the other hand, workup of a similar reaction after a 4-h reaction time resulted in the isolation of an inseparable mixture of the diastereomers **20a** and **20b**. Although Scheme III depicts **20a** and **20b** as each possessing an absolute configuration about the methine carbon (pyr–C) which connects the pyrimidine and sugar moieties, this is merely illustrative since the actual stereochemical assignment (*R* or *S*) was not readily obtainable from available spectra data.

Scheme III



The assignment of the configuration of the anomeric carbon for **20a** and **20b** was based on ^{1}H NMR spectral data which agreed with literature reports. In these reports,[8a,17] convincing evidence was presented that in a series

(17) De Bernardo, S.; Weigele, M. *J. Org. Chem.* **1977**, *42*, 109.

of C-glycosides derived from **1**, including **4** and **5**, plus the epimers of **4** and **5**, those C-glycosides with the α configuration at the anomeric carbon have values for $J_{3',4'}$ of 1–0 Hz, while for those with the β configuration the magnitude of $J_{3',4'}$ is 4–5 Hz. Presumably this observation is attributable to the fact that the heavily substituted tetrahydrofuran ring assumes a preferred conformation which results in a dihedral angle between C3′–H and C4′–H of about 60° in the α anomer and about 160° in the β anomer.[8a] In agreement with the trend, the ^{1}H NMR signals observed for C4′–H in **20a** and **20b** appeared, respectively, as a triplet at 4.28 ppm ($J_{3',4'}$ = 0 Hz) and as a multiplet at 4.08 ppm ($J_{3',4'}$ = 0.9 Hz). It should be noted that the same rule also held for the epimers **11** (β, $J_{3',4'}$ = 3.4 Hz) and **12** (α, $J_{3',4'}$ = 1.0 Hz).

Compound **20a** was catalytically reduced to 2,4-dimethoxy-7-*C*-[2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-α-D-ribofuranosyl)pyrrolo[3,2-*d*]pyrimidine (**21**) by a procedure using 10% palladium on carbon recently communicated[14] from our laboratory. Its identity was readily confirmed by mass spectrometry and by elemental analysis, and its anomeric configuration was assigned on the basis of its ^{1}H NMR spectrum. The value of the coupling constant $J_{3',4'}$ for **21** was essentially 0 resulting in a triplet for the C4′ signal at 4.28 ppm (coupled only to C5′-H_a and -H_b). This is in agreement with the trend[8a,17] just cited for compounds **11**, **12**, **20a**, and **20b**. The downfield chemical shift of the C1′-H (5.83 ppm) also appears to be consistent with the δ values for the anomeric protons of the recently reported[18,19] 2′,3′-*O*-isopropylidene-5′-*O*-(triphenylmethyl)-blocked α anomers of 9-deazaadenosine (5.49 ppm) and 9-deazainosine (5.53 ppm). The anomeric protons of the β anomers of 9-deazaadenosine and 9-deazainosine both occurred at 5.22 ppm.

The removal of the sugar protecting groups in compound **21** was readily accomplished in methanolic hydrogen chloride and afforded 2,4-dimethoxy-7-*C*-(α-D-ribofuranosyl)pyrrolo[3,2-*d*]pyrimidine (**22**) in 55% yield. Interestingly, when the deprotection was carried out in refluxing dioxane containing aqueous hydrochloric acid, a 1/1 mixture of **22** and the β anomer **23** was obtained. This apparent anomerization was accompanied by considerable decomposition resulting in a combined yield of only 12% for **22** and **23**. The assignment of anomeric configuration was again made as a result of ^{1}H NMR considerations, particularly the chemical shift differences between the anomeric protons.[17] Although the acid-catalyzed anomerization of 3-*C*-(α-D-ribofuranosyl)indole C-nucleosides has been reported,[20] this is the first report of such a conversion involving a 7-C-ribosylated pyrrolo-[3,2-*d*]pyrimidine. It should also be noted that the synthesis of **22** and **23** is the first reported conversion of a pyrimidine homo-C-nucleoside into a 9-deazapurine C-nucleoside.

In summary, two facile new approaches for the synthesis of pyrimidine homo-C-nucleosides have been worked out. The first involved a Wittig condensation between the novel (pyrimidylmethylene)phosphorane **10** and either of the protected ribofuranoses **1** or **6** affording compounds **11** and **12**. The second procedure involved the ribosylation of the active methylene carbon in compound **18** with the sugar **19** to produce the diastereomeric homo-C-nucleoside products **20a** and **20b**. Although both methods led to the formation of either anomeric mixtures of products or predominantly the α anomer, subsequent chemical manipulations, which included a deblocking with aqueous acid, led to the formation of the β anomers **16** and **23**. We are currently investigating the possible uses of these procedures for the synthesis of additional C-nucleosides as well as new and novel homo-C-nucleosides.

Experimental Section

General Methods. Low-pressure column chromatography was performed by using Merck Lobar (silica gel 60) prepacked columns (size C) with typical flow rates of 5–10 mL/min delivered by Fluid Metering Instruments metering pump. Fractions (15 mL) were collected with an ISCO Retriever III automatic fraction collector. For compounds which were UV-absorbing, the fractions containing the compound were detected with an Altex Model 152 dual wavelength UV detector (254 nm) with a preparative flow cell. Gravity column chromatography was accomplished by using 70–230 mesh Merck silica gel. Thin-layer chromatography (TLC) was accomplished using SilicAR 7GF (250-μm layer) on prescored glass plates (2.5 × 8 cm) purchased from Analtech, Inc., Newark, DE. Solvent systems used were as follows: (a) hexanes[21]/ethyl acetate (2:1, v/v), (b) hexanes/ethyl acetate (3:1, v/v), (c) hexanes/ethyl acetate (4:1, v/v), (d) toluene/diethyl ether (1:1, v/v), (e) ethyl acetate/1-propanol/water (4:1:2, v/v/v, organic layer), (f) benzene/ethyl acetate (85:15, v/v), (g) methanol/methylene chloride (3:97, v/v), (h) methanol/water (35:65, v/v), and (i) toluene/diethyl ether (20:1 v/v). High-performance liquid chromatography (HPLC) was carried out with a Varian Vista 54 chromatograph using a Varian UV-50 variable wavelength detector set at 254 nm and the following columns: (a) Varian Micropak Si-5 silica gel column (4.5 × 300 mm); (b) Varian MCH-10, C-18 reverse-phase column (4.5 × 300 mm); (c) Whatman, Inc. Magnum 9, ODS-3 reverse-phase column (9.5 × 500 mm). The following linear reverse phase elution gradients were used: (a) methanol/water (v/v), 10% methanol to 30% methanol over 20 min, 30% methanol to 35% methanol over the next 5 min, and then 35% methanol to 40% methanol over the last 5 min; (b) methanol/water (v/v), 30% methanol to 35 methanol over 15 min. Retention times (t_R, min) were measured from time of injection and flow rates of 1.3 (analytical) and 3.0 mL/min (preparative) were maintained. In vacuo evaporations were carried out with a Buchler flash evaporator using a water aspirator and room-temperature water bath unless otherwise noted. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained with a Varian EM-360 (60 MHz) or Brucker Wm 360 spectrometer (360 MHz). The following abbreviations were used to designate the multiplicity of individual signals: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, pq = pseudoquartet, and pt = pseudotriplet. Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus. Optical rotations were measured with a Perkin-Elmer Model 141 automatic polarimeter. UV spectra were recorded on a Hewlet-Packard UV 8450 spectrometer. IR spectra were recorded on a Perkin-Elmer 281 spectrophotometer. Lyophilizations were carried out by using a FD-4 Flexi-dry freeze dryer at −60 °C and 50 mtorr for 12 h. Mass spectral data were obtained on a Finnigan Model 4023 GC/MS using electron ionization (EI). Exact mass values were recorded with a Varian MAT 731 mass spectrometer and determined by peak matching at resolution 12 000, using per fluoroalkanes as internal standard under the following conditions: ionizing energy, 70 eV: ion source temperature, 250 °C. Samples were introduced by direct probe. Elemental analyses were obtained from M-H-W Laboratories, Phoenix, AZ 85018.

[(2,4-Dimethoxy-5-nitropyrimidin-6-yl)methyl]triphenylphosphonium Bromide (9) and [(2,4-Dimethoxy-5-nitropyrimidin-6-yl)methylene]triphenylphosphorane (10). A solution of **8** (5.90 g, 2.1 × 10^{-2} mol) in dry benzene (50 mL)

(18) Lim, M.-I.; Klein, R. S. *Tetrahedron Lett.* **1981**, *22*, 25.
(19) Lim, M.-I.; Klein, R. S.; Fox, J. J. *Tetrahedron Lett.* **1980**, *21*, 1013.
(20) Sokolova, T. N.; Yartseva, I. V.; Preobrashenskaya, M. N. *Carbohydr. Res.* **1981**, *93*, 19.

(21) Hexanes were purchased as such from Mallinckrodt, Inc., St. Louis, MO.

was treated dropwise with a solution of triphenylphosphine (7.80 g, 3.0×10^{-2} mol) in dry benzene (30 mL) at room temperature and under a nitrogen atmosphere. The solution was stirred vigorously for 4 h. The white precipitate which had formed was collected by filtration, washed with benzene (2 × 25 mL), and air-dried for 1 h. Its structure was shown to be that of **9** by its ^{1}H NMR spectrum: ^{1}H NMR (60 MHz, Me_2SO-d_6) δ 3.43 and 4.08 (6, 2 s, 2-OCH_3 and 4-OCH_3), 5.82 (1, s, 6-CH_a), 6.05 (1, s, 6-CH_b), 7.83 (15, m, Ar). Without further purification, compound **9** was dissolved in a biphasic mixture of water (50 mL) containing crushed ice (100 mL) and chloroform (200 mL). To this mixture was added in one portion a 1 N sodium hydroxide solution (22 mL) and stirring was continued for 60 min. The aqueous layer was separated and washed with chloroform (3 × 25 mL). The organic layers were combined, dried over magnesium sulfate, then filtered, and evaporated to a yellow solid, which was crystallized from ethanol to yield orange prisms of **10** (7.00 g), mp 205–206 °C. The mother liquor was evaporated to an orange solid, which was crystallized from ethanol to yield additional **10** (0.69 g, total yield = 79% from **8**): R_f 0.10 (solvent system b); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.68 and 4.00 (6, 2 s, 2-OCH_3, 4-OCH_3), 7.53 (16, m, Ar and 6-CH=PPH_3). Anal. Calcd for $C_{25}H_{22}N_3O_4P$: C, 65.36; H, 4.83; N, 9.15. Found: C, 65.50; H, 5.05; N, 9.03.

2,4-Dimethoxy-5-nitro-6-*C*-[(2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-β-D-ribofuranosyl)methyl]pyrimidine (11) and 2,4-Dimethoxy-5-nitro-6-*C*-[(2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-α-D-ribofuranosyl)methyl]pyrimidine (12). A solution of **10** (3.2 g, 7.0×10^{-3} mol) and (3.0 g, 6.9×10^{-3} mol) in dry toluene (25 mL) was stirred under reflux in a nitrogen atmosphere for 72 h. After this time, three new compounds were detected (TLC) in the reaction which had R_f values of 0.27, 0.24, and 0.15 (solvent system b), respectively. The solution was allowed to cool to 20 °C and evaporated to an orange residue, which was suspended in refluxing methanol (75 mL). After the suspension had cooled to 25 °C, it was treated with sodium methoxide (10 mg). TLC (solvent system b) showed the disappearance of the slowest of the three spots and a relative increase of the top-running spot. From a similar reaction, the compound corresponding to the slowest TLC spot was isolated as an oil by a chromatographic (Lobar, size A; solvent system c) workup of the product mixture prior to addition of sodium methoxide. Its structure was shown to be that of **13** upon analysis of its ^{1}H NMR spectrum (Table I). The suspension from the initial reaction was filtered, and the precipitate was washed with methanol (2 × 20 mL) and air-dried to yield compound **11** (2.25 g, 53%, mp 202–202.5 °C). The filtrate was evaporated to an orange residue, which was chromatographed on a silica column (75 × 4 cm i.d.) eluting with methylene chloride. Fractions were collected and those that contained compound (TLC, solvent system b) were pooled and evaporated to a soft foam, **12** (1.79 g, 42%).

Compound **11**: R_f 0.24 (solvent system b), t_R 11.2 (solvent system c); $[\alpha]^{21}_D$ −0.87° (*c* 0.6, $CHCl_3$). Anal. Calcd for $C_{34}H_{35}N_3O_8$: C, 66.55; H, 5.75; H, 6.85. Found: C, 66.63; H, 5.80; N, 6.76.

Compound **12**: R_f 0.27 (solvent system b), t_R 8.4 (solvent system c), $[\alpha]^{21}_D$ +42.61° (*c* 1.6, $CHCl_3$). Anal. Calcd for $C_{34}H_{35}N_3O_8$: C, 66.55; H, 5.75; H, 6.85. Found: C, 66.39; H, 5.88; N, 6.95.

Compound **13**: R_f 0.15 (solvent system b), t_R 19.6 (solvent system c).

2,4-Dimethoxy-6-*C*-[(2,3-*O*-isopropylidene-α-D-ribofuranosyl)methyl]-5-nitropyrimidine (14) and 2,4-Dimethoxy-6-*C*-[(2,3-*O*-isopropylidene-α-D-ribofuranosyl)methyl]-5-nitropyrimidine (15). A solution of **6** (1.16 g, 6.1×10^{-3} mol) in a mixture of dry toluene (50 mL) and acetonitrile (10 mL) in a dry nitrogen atmosphere was heated at reflux for 1 h under a water separator to azeotropically remove water. The solution was allowed to cool to 20 °C, compound **10** (3.06 g, 6.7 × 10^{-3} mol) was then added, and the resulting solution was heated at reflux for 13 h. The orange solution was allowed to cool to 20 °C and then evaporated (40 °C bath) to a reddish oil. This oil was treated with diethyl ether (50 mL), causing the precipitation of unreacted **10** and triphenylphosphine oxide, which were collected by filtration. The filtrate was evaporated to a residue, which, upon treatment with diethyl ether (25 mL), yielded a second crop of **10** and triphenylphosphine oxide. The mixture was again filtered, and the filtrate evaporated to an oil, which was chromatographed on silica gel (Lobar size C) by eluting with solvent system d. Fractions (20 mL) were collected and those containing compound (TLC, solvent system d) were pooled into three parts: the first containing some residual **10** and compound **14**; the second containing **15** and triphenylphosphine oxide; the third containing triphenylphosphine oxide. The third part was discarded. The first part was evaporated to a syrup, which was rechromatographed on silica gel (50 g, 4-cm i.d. column) by eluting first with toluene/diethyl ether (3:1, v/v) to remove **10** and then with diethyl ether. Fractions were collected, and those that contained compound (solvent system d) were pooled and evaporated to yield a golden syrup, **14** (0.67 g, 30% based on **6**), R_f 0.36 (solvent system d) and 0.16 (solvent system f). Anal. Calcd for $C_{15}H_{20}N_3O_8 \cdot {}^1/_2H_2O$: C, 47.49; H, 5.58; N, 11.08. Found: C, 47.80; H, 5.60; N, 10.86.

The second part was evaporated to a residue, which was triturated with isopropyl ether, and the precipitated triphenylphosphine oxide was collected by filtration. The filtrate was evaporated to a residue, which was chromatographed on silica gel (50 g, 4-cm i.d. column) by eluting with diethyl ether. Fractions were collected and those containing compound (TLC, solvent system d) were pooled and evaporated to yield crude compound **15** (0.4 g, still contaminated with triphenylphosphine oxide), R_f 0.16 (solvent system d) and 0.07 (solvent system f).

6-*C*-[(β-D-Ribofuranosyl)methyl]-5-nitropyrimidine-2,4-dione (16). A solution of **11** (0.61 g, 1.0×10^{-3} mol) in *p*-dioxane (10 mL) was treated with 6 N hydrochloric acid (1 mL), stirred at 20 °C for 1 h, and subsequently heated at reflux for 2 h. The reaction mixture was allowed to cool to 20 °C, and the pH of the solution was adjusted to about pH 7 by the dropwise addition of concentrated ammonium hydroxide. The solution was evaporated to dryness to yield a residue, which was treated with water (10 mL). The insoluble portion was collected by filtration and washed with hot water (15 mL). The aqueous layers were combined and evaporated to yield a residue, which was suspended in boiling ethanol (100 mL). When the suspension had cooled to 20 °C, the precipitated salts were collected by filtration and washed with hot ethanol (10 mL). The combined filtrate and washes were evaporated to a residue, which was chromatographed on silica gel (20 × 2 cm i.d. column) by eluting with solvent system e. Fractions were collected, and those that contained compound (TLC, solvent system e) were pooled and evaporated to a solid, which was crystallized from ethanol to yield compound **16** (0.15 g, 50%); mp 208–209 °C dec; R_f 0.53 (solvent system e); UV λ_{max}^{MeOH} 274 nm (ε 6200), 335 (2400), $\lambda_{max}^{pH\,1}$ 254 (sh, 5700), 276 (6100), 335 (1800), $\lambda_{max}^{pH\,11}$ 268 (4800), 273 (sh, 4700), 352 (6000). Anal. Calcd for $C_{10}H_{13}N_3O_8$: C, 39.61; H, 4.32; N, 13.86. Found: C, 39.79; H, 4.60; N, 13.53.

Deprotection of 12. A solution of **12** (0.63 g, 1.03×10^{-3} mol) in *p*-dioxane (10 mL) was treated with 6 N hydrochloric acid (5 mL) and heated at reflux for 1 h. The solution was allowed to cool to 20 °C and then neutralized by addition of AG 2 × 8 anion-exchange resin ($^-$OH form) to the stirred solution. The resin was collected by filtration and washed with hot water (2 × 10 mL). The combined filtrates were evaporated (40 °C bath), resulting in a residue, which was suspended in hot water (50 mL) and allowed to stand overnight. The precipitate was collected by filtration and washed with hot water (10 mL). The combined filtrates were evaporated to a residue, which was chromatographed on silica gel (20 × 2 cm i.d. column) by eluting with solvent system e. Fractions were collected, and those that contained compound (TLC, solvent system e) were pooled and evaporated to a golden syrup. This syrup was dissolved in a minimum of ethanol and treated to turbidity with ethyl acetate and allowed to crystallize. The solid was collected by filtration, washed with acetone, and dried (70 °C, 0.1 mmHg) to yield **16** (0.27 g, 87%): mp 215 °C dec; R_f 0.53 (solvent system e); UV λ_{max}^{MeOH} 274 nm (ε 6300), 337 (2100), $\lambda_{max}^{pH\,1}$ 254 (sh, 6000), 276 (6700), $\lambda_{max}^{pH\,11}$ 269 (5000), 287 (sh, 4500), 352 (6200). Anal. Calcd for $C_{10}H_{13}N_3O_8$: C, 39.61; H, 4.32; N, 13.86. Found: C, 39.70; H, 4.43; N, 13.88.

5-Amino-2,4-dimethoxy-6-*C*-[(2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-β-D-ribofuranosyl)methyl]pyrimidine (17). A solution of compound **11** (0.25 g, 4.1×10^{-4} mol) in ethyl acetate (30 mL) and ethanol (10 mL) was treated with Raney nickel (0.15 g, wet weight in methanol) and then hydrogenated at ambient pressure and temperature. The reaction was inter-

rupted after 3 h and additional Raney nickel (0.10 g, wet weight in methanol) was added. After 24 h the mixture was purged with a stream of nitrogen for 30 min and then filtered through a Celite pad. The nickel was washed well with ethyl acetate (2 × 10 mL) then ethanol (1 × 10 mL). The filtrates were combined and evaporated to a stiff foam, **17** (0.25 g, 100%). A small amount of the product was purified for microanalysis by low-pressure chromatography (Lobar size A, eluting with solvent system a): R_f 0.19 (solvent system b); mass spectrum (EI), m/z 583 (M^+), 568, 324, 310, 266, 243 (parent); IR (film) 3440, 3340, 3060, 2980, 2930, 1575, 1462, 1400, 1372, 1210, 1080 cm^{-1}. Anal. Calcd for $C_{34}H_{37}N_3O_6$: C, 6.97; H, 6.39; N, 7.20. Found: C, 69.69; H, 6.58; N, 6.95.

(*R*)- and (*S*)-2-(2,4-Dimethoxy-5-nitropyrimidin-6-yl)-2-(2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-α-D-ribofuranosyl)acetonitrile (20a and 20b). A slurry of sodium hydride (50% oil dispersion, 0.22 g, 4.6 × 10^{-3} mol) in 1,2-dimethoxyethane (DME) was treated dropwise with a solution of **18** (1.00 g, 4.46 × 10^{-3} mol) in DME (30 mL) over 5 min, at 0 °C, and under an atmosphere of nitrogen. The red solution was then allowed to warm to 20 °C and stirred for 60 min. It was then treated with **19** (3.02 g, 6.69 × 10^{-3} mol) and potassium iodide (0.26 g, 1.54 × 10^{-3} mol), resulting in a suspension, which was stirred at reflux for 90 min. After cooling to 25 °C, the red mixture was diluted with diethyl ether (100 mL), washed with saturated ammonium chloride solution (3 × 25 mL) and with saturated sodium chloride solution (2 × 15 mL), and then dried over magnesium sulfate. Filtration and evaporation of the solution yielded a brownish syrup, which was chromatographed on a silica gel column (100 g, 3 cm i.d.) by eluting with solvent system i. Product-containing fractions (determined by TLC, solvent system b) were collected and evaporated to a syrup, which was rechromatographed on silica gel (EM silica gel 60, 230–400 mesh, 40–63 μm, 30-cm Michel-Miller column) by eluting with solvent system b. Fractions (10 mL) were collected and pooled, and then evaporated to a syrup, 0.74 g. This syrup was dissolved in hot methanol and allowed to crystallize yielding compound **20a** (0.38 g, 13%). The mother liquor contained a small amount of **20b** as seen by TLC (R_f 0.38, solvent system b) which was not isolated. The 360-MHz ^1H NMR spectrum of **20b** (see Tables I and II) was recorded from an unseparated mixture of **20a** and **20b** obtained from a similar reaction.

Compound **20a**: mp 207–209 °C; R_f 0.34 (solvent system b); mass spectrum (EI), m/z 395 (M^+ – triphenylmethyl), 379 (M^+ – *O*-triphenylmethyl), 365 (M^+ – CH_2O – triphenylmethyl), 243 (triphenylmethyl, parent); IR ($CDCl_3$) 2250 cm^{-1} (CN). Anal. Calcd for $C_{35}H_{34}N_4O_8 \cdot H_2O$: C, 64.02; H, 5.53; N, 8.53. Found: C, 64.25; H, 5.55; H, 8.60.

2,4-Dimethoxy-7-*C*-[2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-α-D-ribofuranosyl]pyrrolo[3,2-*d*]pyrimidine (21). A solution of **20a** (0.35 g, 5.48 × 10^{-4} mol) in ethyl acetate (20 mL) was treated with palladium on carbon (10%, 0.37 g), and the resulting suspension was hydrogenated in a steel bomb (250 psig, 90 °C) for 24 h while stirring. The mixture was allowed to cool to 20 °C and then filtered through a Celite pad. The collected catalyst was washed with hot ethyl acetate (2 × 20 mL) and then with hot methanol (2 × 20 mL). The combined filtrate and washes were evaporated to a foam (0.25 g), which was chromatographed on a Lobar column (size B) by eluting with solvent system g. Fractions were collected and those containing compound (UV flow detector) were combined and evaporated to an off-white foam, **21** (0.10 g, 31%): R_f 0.15 (solvent system a), 0.30 (solvent system g); mass spectrum (EI), m/z 350 (M^+ – triphenylmethyl), 334 (M^+ – *O*-triphenylmethyl), 320 (M^+ – triphenylmethyl – OCH_2), 262, 242 (triphenylmethyl, parent), 208, 165. Anal. Calcd for $C_{35}H_{35}N_3O_6 \cdot {}^1/_2H_2O$: C, 69.75; H, 6.02; N, 6.97. Found C, 69.64; H, 6.15; H, 6.89.

2,4-Dimethoxy-7-*C*-(α-D-ribofuranosyl)pyrrolo[3,2-*d*]pyrimidine (22). Method 1. A solution of compound **21** (0.09 g, 1.52 × 10^{-4} mol) in methanol (3 mL) was treated with methanolic hydrogen chloride (6 N, 1.0 mL) and stirred at 0 °C for 24 h. The solution was then evaporated to a tan solid, which was dissolved in methanol/water (4:1, v/v, 5 mL) and treated portionwise with solid sodium bicarbonate until no further evolution of carbon dioxide was noted. The solution was evaporated to about 1 mL, then filtered, and purified by preparative reverse-phase HPLC (column c) eluting with solvent system h. The eluent was monitored by UV detection 254 nm), and compound-containing fractions (3 mL) were combined and evaporated to a glass. The residue was dissolved in water (2 mL) and lyophilized, resulting in a white material, which was dried at 75 °C and 0.01 mmHg for 24 h to yield compound **22** (0.026 g, 55%): mp 157–159 °C; R_f 0.51 (solvent system e), t_R 9.9 (column b, gradient b); UV λ_{max}^{MeOH} 266 nm (ε 7500), 283 (sh, 5100), $\lambda_{max}^{pH\ 1}$ 278 (13 000), $\lambda_{max}^{pH\ 11}$ 265 (8000), 283 (sh, 5300); mass spectrum (EI), m/z 311 (M^+), 236, 222, 208 (parent, base, M^+ 30), 193, 178 (base). Anal. Calcd for $C_{13}H_{17}N_3O_6 \cdot H_2O$: C, 47.42, H, 5.82; N, 12.76. Found: C, 47.27, H, 5.72; N, 12.71.

Compound 29 and 2,4-Dimethoxy-7-*C*-(β-D-ribofuranosyl)pyrrolo[3,2-*d*]pyrimidine (23). Method 2. A solution of **21** (0.12 g, 2.02 × 10^{-4} mol) in *p*-dioxane (3 mL) was treated with concentrated hydrochloric acid (0.5 mL), heated at reflux for 60 min, and then allowed to cool to 20 °C. The stirring was maintained for 16 h, after which time solid sodium bicarbonate was added portionwise until carbon dioxide evolution had ceased. The resulting suspension was then filtered through a Celite pad, and the pad was washed with water (5 × 10 mL). The combined filtrate and washes were evaporated to a tan solid, which was suspended in boiling methanol and filtered while still hot. The collected salts were washed with hot methanol (2 × 20 mL), and the combined methanol washes were evaporated to a volume of about 3 mL and chromatographed by using preparative HPLC (column c, elution gradient a). The eluent was monitored by UV detection (254 nm), and the two compound-containing fractions were evaporated to two separate residues. These residues were dissolved in water (1 mL) and lyophilized, resulting in compounds **22** (0.004 g, 6.5%) and **23** (0.004 g, 6.5%).

Compound **23**: mp 130 °C (softened at 98 °C); R_f 0.69 (solvent system e), t_R 12.2 (column b, elution gradient b); λ_{max}^{MeOH} 265 nm (ε 7900), 283 (sh, 5500); $\lambda_{max}^{pH\ 1}$ 277 (14 000), $\lambda_{max}^{pH\ 11}$ 266 (8500), 283 (sh, 5700; mass spectrum (EI), m/z 311.1109 (M^+), calcd for $C_{13}H_{17}N_3O_6$ m/z 311.1117, 312 (M^+H^+), 236 m, 222 m, 208 (parent, base + 30), 193, 178 (base).

Registry No. 1, 55726-19-7; **6**, 13199-25-2; **8**, 84538-41-0; **9**, 99232-78-7; **10**, 99232-79-8; **11**, 99232-80-1; **12**, 99295-20-2; *cis*-**13**, 99232-81-2; *trans*-**13**, 99232-82-3; **14**, 99232-83-4; **15**, 99295-21-3; **16**, 99232-84-5; **17**, 99232-85-6; **18**, 84538-44-3; **19**, 58166-67-9; **20a**, 99232-86-7; **20b**, 99232-87-8; **21**, 99232-88-9; **22**, 99248-98-3; **23**, 99232-89-0; AG 2 × 8, 69279-93-2.