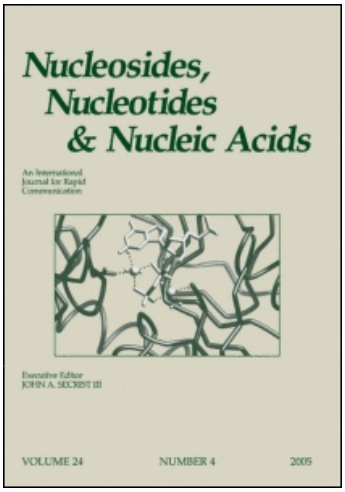

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S. H. Gray[a]; C. F. Ainsworth[b]; C. L. Bell[a]; S. S. Danyluk[b]; M. Maccoss[b]
[a] Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, Health Sciences Center, University of Illinois at Chicago, Chicago, Illinois [b] Division of Biological and Medical Research, Argonne National Laboratory, Argonne, Illinois

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SYNTHESIS OF DEOXYRIBONUCLEOTIDYL(3'-5')ARABINONUCLEOSIDES

S. H. Gray,[a] C. F. Ainsworth,[b] C. L. Bell,[a]
S. S. Danyluk,[b] and M. MacCoss*[b,1]

[a]Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, Health Sciences Center, University of Illinois at Chicago, Chicago, Illinois 60680, and [b]Division of Biological and Medical Research, Argonne National Laboratory, Argonne, Illinois 60439

Abstract: Two different synthetic routes using phosphotriester methodology have been utilized to prepare deoxyribonucleotidyl(3'-5')arabinonucleosides containing 9-β-D-arabinofuranosyladenine (ara-A, vidarabine) and 1-β-D-arabinofuranosylcytosine (ara-C, cytarabine) at the 3'-terminus in amounts and purity (greater than 95%) suitable for NMR analysis.

It has long been established that the D-arabinosyl nucleosides, ara-A and ara-C, are effective antineoplastic agents.[2,3] The molecular mode of action is believed to involve metabolism to the respective triphosphates, which inhibit DNA polymerase.[4,5] The detailed mechanism by which these arabinonucleoside 5'-triphosphates inhibit the polymerase has been the subject of much investigation[6] and two possibilities have been considered,[6] namely (i) by direct competition with the corresponding deoxynucleoside triphosphate or (ii) by inhibition after incorporation of the arabinonucleotides into the terminus of the growing DNA chain. This latter inhibitory effect is presumed to occur by the arabinonucleotide on the 3'-terminus providing a poor primer for the incoming nucleoside 5'-triphosphate and so slowing chain growth.[7,8]

The choice between these two possible models for the inhibitory process has been the subject of some debate[9] and it was felt that the synthesis of all

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Abbreviations used: ara-A, 9-β-D-arabinofuranosyladenine; ara-C, 1-β-D-arabinofuranosylcytosine; TSNI, p-toluenesulfonyl-4(5)-nitroimidazole; TBDMS, t-butyldimethylsilyl; TMG, tetramethylguanidinium; PAO, 2-pyridinealdoximate; TBAF, tetra-butylammonium fluoride. Abbreviations for dinucleoside monophosphates follow IUPAC-IUB guidelines.

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eight possible deoxyribonucleotidyl(3'-5')arabinofuranosyladenine(cytosine) derivatives and the careful comparison of their conformational properties, with the corresponding deoxyribonucleotidyl(3'-5')deoxyadenosine(deoxycytidine) derivatives, would provide some clues as to whether the conformation of the growing DNA chain was perturbed by incorporation of an arabinoside rather than a deoxyriboside at the 3'-terminus. The work described herein details the synthesis of all eight deoxyribonucleotidyl(3'-5')arabinofuranosyladenine(cytosine) derivatives using phosphotriester methodology. A ^{1}H-NMR study describing the conformational analyses will be reported elsewhere.

It should be noted that some of these arabino-containing dimers have been synthesized previously using phosphodiester approaches.[10a,b] These methods gave only poor yields and the products could not be analyzed completely by NMR spectroscopic methods.

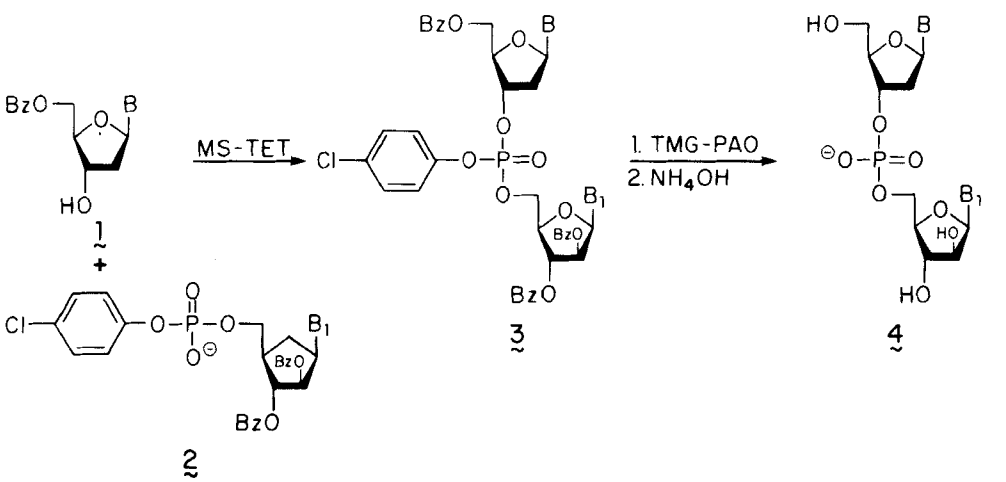
Although several synthetic approaches were attempted, the final product purity (greater than 95%) necessary for NMR analysis was achieved only after considerable study. For instance, long exposure to aqueous acid or alkaline conditions usually resulted in a considerable amount of chain cleavage and/or isomerization. The extent of this side-product formation during deblocking was as much as 40%, and it became necessary to select blocking groups which could be removed in short reaction times and under mild conditions. Extended aqueous acid or alkaline treatments resulted in loss of both yield and final product purity.

For all the dimers (**4**), except those containing guanine in the deoxyribose portion (i.e., **4**, B = guanine), the synthetic scheme utilized only a single blocking group (the benzoyl; see Figure 1). The condensation reaction was carried out between a 5'-O-benzoylated deoxynucleoside (**1**) and a suitably protected arabinonucleoside 5'-phosphate chlorophenyl ester (**2**). The 5'-O-benzoyldeoxynucleosides (**1**) were prepared by the method of Gerzon and Kau[11] and the 2',3',N-tribenzoylarabinonucleosides (the precursors to compounds **2**) by the method of Baker et al.[12] Phosphorylation of the protected arabinonucleosides to give **2**, and subsequent condensation to give the intermediate phosphotriesters **3** utilized modifications of the method of Sadana and Loewen.[13] The triesters **3** were isolated by silica gel chromatography and several deblocking conditions were examined in order to obtain the highest yield of pure unprotected dimer. These conditions included (a) conc. NH_4OH-pyridine (1:1 by vol.), 25°C for 4 days; (b) conc. NH_4OH-EtOH (1:1), 60°C, 4 hr; (c) 2N NaOH in EtOH, 60°C, 20 min; (d) Et_3N-EtOH-H_2O (4:1:2), 60°C, 2 hr; (e) 1N tetramethylguanidinium-2-pyridinealdoximate at 25°C for 2 days, followed by conc. NH_4OH-pyridine (9:1) at 25°C for 2 days. In all cases where the p-chlorophenyl group was not

selectively removed prior to the benzoyl group [i.e., (a)-(d)], a considerable amount of chain cleavage and/or isomerization [i.e., formation of dX (3'-2')ara-A (or ara-C)] occurred.[14] Only method (e) gave readily purified products and was used in all the preparations that did not contain deoxyguanosine.

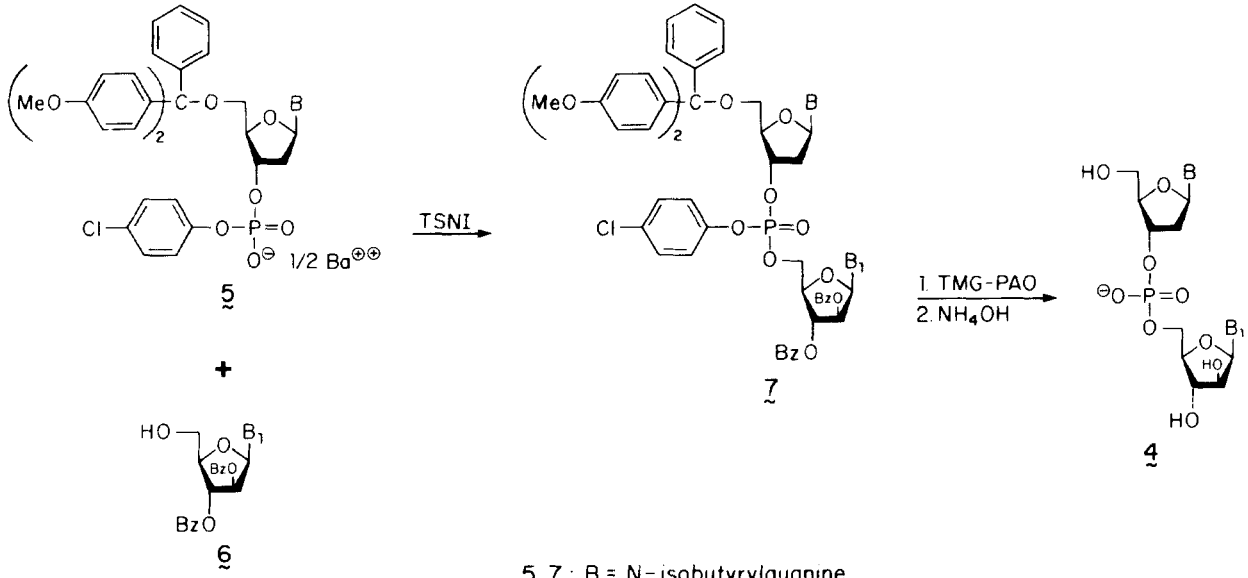
The use of the synthetic route depicted in Figure 1 to prepare nucleoside monophosphates containing guanine bases resulted in poor yields (ca. 1%). This problem was partially the result of the condensing agent, mesitylenesulfonyl-1H-tetrazole reacting directly with the guanine moiety. Recent work has suggested that such condensing agents may interact directly with the O^6-position of the base.[15,16] Therefore, in an attempt to limit this competing reaction, p-toluene-sulfonyl-4(5)-nitroimidazole (TSNI) was used as the condensing agent.[17] For the synthesis of deoxyguanylyl(3'-5')arabinofuranosyladenine (dGparaA), the use of the above synthetic scheme and TSNI resulted in a reasonable yield (ca. 20%). For the synthesis of deoxyguanylyl(3'-5')arabinofuranosylcytosine (dGparaC), the method of Gough et al. was used.[17] In this instance, the condensation was carried out between a suitably protected 3'-deoxynucleotide and a 2',3',N-protected arabinonucleoside. The scheme is shown in Figure 2.

The use of TSNI in conjunction with the readily prepared and high purity nucleotide barium salt (**5**) ensured excellent yield of the intermediate phosphotriester, **7**, and of the final product. Our only modification of the published



1, 3; B = adenine, N-benzoylcytosine, thymine, N-isobutyrlguanine
2, 3; B_1 = N-benzoyladenine, N-benzoylcytosine
4; B = adenine, cytosine, thymine, guanine
B_1 = adenine, cytosine

FIGURE 1



5, 7 ; B = N-isobutyrylguanine

6, 7 ; B_1 = N-benzoylcytosine

4 ; B = guanine, B_1 = cytosine

FIGURE 2

methodology[16,17] was in the preparation of 2-N-isobutyryldeoxyguanosine. The use of t-butyldimethylsilyl chloride (TBDMS-Cl) to specifically block the 3'- and 5'-hydroxyl functions resulted in high yields during the nucleoside transformations and the preparation is depicted in Figure 3. A "one-pot" procedure reflecting this approach, but using trimethylsilyl to protect the hydroxyl functions, has recently been published.[16]

All final dimers were obtained in high purity (greater than 95%) as judged by ^{1}H-NMR analysis and the chemical shifts of the products are shown in Table 1. The complete NMR analysis and conformational evaluation will be published elsewhere. Furthermore, all the dimers were degraded with spleen phosphodiesterase and snake venom phosphodiesterase and all gave the appropriate nucleoside and nucleotide in a 1:1 molar ratio.

Finally, a synthetic scheme similar to that shown in Figure 2 was evaluated in which the arabinonucleoside was protected at the 2'- and 3'-positions by the TBDMS group.[18] The preparation of the blocked arabinosides is shown in Figure 4. Synthesis of **12** and **13** by reaction of the nucleoside with TBDMS-Cl, followed by 5'-deprotection with acid was carried out essentially as described by others[19]

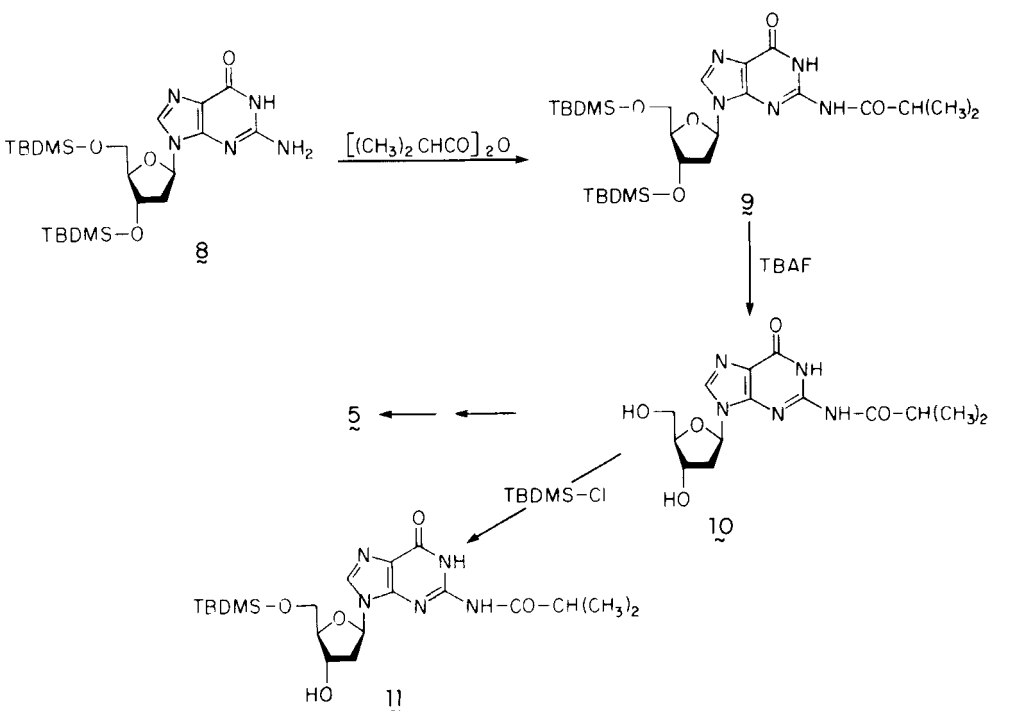


FIGURE 3

TABLE 1

CHEMICAL SHIFTS[a] OF DEOXYRIBONUCLEOTIDYL(3'-5')ARABINONUCLEOSIDES IN D_2O[b]

Nucleotide		8(6)	2(5, Me)	1'	2'	2"	3'	4'	5'	5"
TparaC[c]	Tp-	7.658	1.874	6.226	2.416	2.582	4.776	4.190	3.844	3.794
	-paraC	7.854	6.062	6.235	4.466	-	4.200	4.070	4.217	4.132
TparaA	Tp-	7.369	1.814	6.013	1.854	2.360	4.662	4.098	3.716	3.685
	-paraA	8.373	8.173	6.380	4.685	-	4.568	4.128	4.225	4.169
dAparaC	dAp-	8.280	8.128	6.385	2.868	2.868	4.891	4.345	3.895	3.857
	-paraC	7.550	5.654	6.092	4.404	-	4.163	4.054	4.289	4.144
dAparaA	dAp-	8.050	7.897	6.164	2.493	2.709	4.855	4.280	3.793	3.793
	-paraA	8.184	7.922	6.183	4.619	-	4.500	4.135	4.326	4.203
dCparaC	dCp-	7.831	6.016	6.171	2.429	2.610	4.712	4.205	3.874	3.801
	-paraC	7.814	5.971	6.214	4.459	-	4.197	4.065	4.214	4.134
dCparaA	dCp-	7.561	5.816	5.997	1.958	2.430	4.600	4.096	3.766	3.706
	-paraA	8.393	8.190	6.370	4.673	-	4.522	4.122	4.222	4.157
dGparaC	dGp-	7.980	-	6.222	2.784	2.788	4.891	4.288	3.847	3.817
	-paraC	7.640	5.740	6.189	4.438	-	4.189	4.082	4.280	4.151
dGparaA[d]	dGp-	8.03	-	5.98	2.42	2.58	4.82	e	3.73	3.73
	-araA	8.47	8.26	6.32	4.66	-	4.53	e	e	e

[a]Computer simulated shifts.
[b]pD = 6.5-7.5; concentration = .01-.015M; t = 20 2°C.
[c]Spectrum analyzed at 360 MHz.
[d]Spectrum not simulated; shifts estimated directly from spectrum.
[e]Shifts not shown due to inaccuracy in measurement.

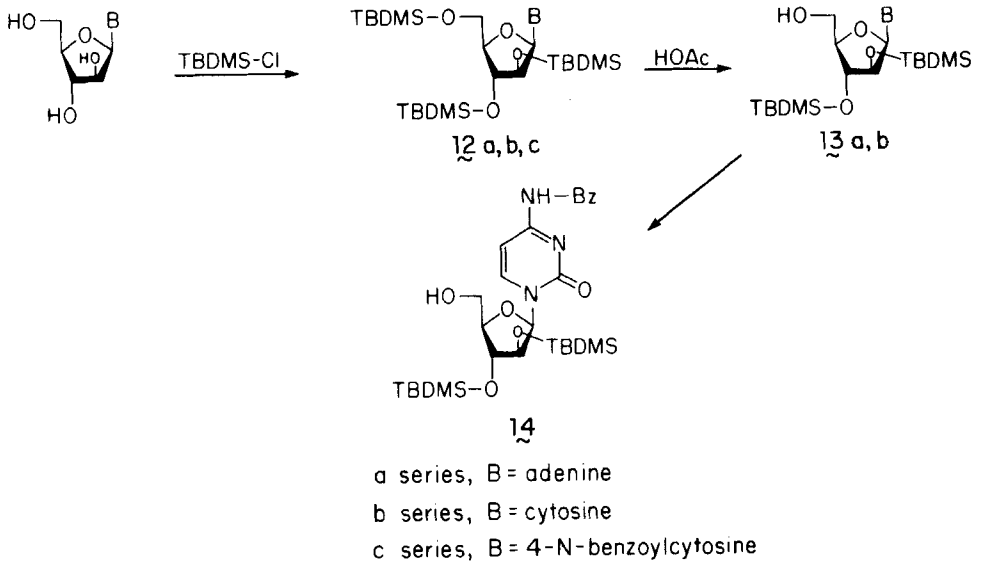


FIGURE 4

in the deoxy and ribo series. Selective N-benzoylation of the cytosine heterocycle in **13b** to give **14** was carried out using the method of Watanabe and Fox.[20] Benzoylation of **12b** gave 2',3',5'-tri-TBDMS-N^4-benzoyl-ara-C (**12c**) but this proved to be somewhat unstable (it readily lost the benzoyl group in methanolic solution) in parallel to similar observations in the ribose series.[19b] An analogous instability was noted for **14**. In addition, it was observed that fully protected triesters such as **3** (B = thymine, B_1 = adenine), when treated with 1M tetrabutylammonium fluoride in THF at 25°C for 2 days, followed by conc. NH_4OH at 25°C for 2 days gave much degradation of the dimer and so this use of TBDMS as a blocking group for the preparation of the dimers described herein was not pursued further.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Ultraviolet spectra were recorded on a Beckman Model 25 spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian HR-220 spectrometer, operating in the CW or FT mode, with either Me_4Si ($CDCl_3$, CD_3OD, DMSO-d_6) or 2,2,3,3,-d_4 sodium trimethylsilylpropanesulfonate (D_2O) as internal standard unless otherwise stated. Elemental analyses were determined by Galbraith Laboratories, Knoxville, TN. Evaporations of solvents were effected

using a Buchi rotary evaporator under aspirator or mechanical pump at 40°C or lower (15-0.1 mm Hg). Thin-layer chromatography (TLC) was performed on Merck silica gel 60, F-254, or Merck cellulose F-254 plates unless otherwise stated. UV-absorbing material was detected by visualization under UV lamp (254 nm). Silica gel column chromatography was carried out on Merck silica gel 60 (70-230 mesh) or SilicAr CC-7 Special (Mallinckrodt); anion exchange chromatography was performed using DEAE-Sephadex (HCO^-_3 form) obtained from Whatman, Inc. Medium pressure HPLC chromatography utilized an AS Pellionex SAX (Whatman) column. Paper chromatography (descending technique) was performed on Whatman 3MM cellulose sheets eluted with solvent A (2-propanol:ammonia:water, 4:1:5) or solvent B (1-butanol:ethanol:H_2O, 7:1:2). The following materials were obtained from commercial sources: thymidine, 2'-deoxyguanosine, arabinofuranosyladenine, arabinofuranosylcytosine (Sigma Chemical Co.), 1,2,4-triazole, imidazole, 4(5)-nitroimidazole, mesitylenesulfonyl chloride, 2,4,6-triisopropylbenzenesulfonyl chloride, p-toluenesulfonyl chloride, p-anisyldiphenylmethyl chloride, bis(p-anisyl)phenylmethyl chloride, t-butyldimethylsilyl chloride, 2-pyridinealdoxime, tetra-n-butylammonium fluoride (Aldrich Chemical Co.), and tetramethylguanidine (Eastman Co.). Mesitylenesulfonyl-1-H-tetrazole,[21] p-toluenesulfonyl-4(5)-nitroimidazole,[22] and p-chlorophenylphosphodichloridate[23] were prepared by published methods. 2,6-Lutidine, dioxane and triethylamine were distilled from CaH_2 and stored over molecular sieves (4A). Pyridine was distilled from p-toluenesulfonyl chloride onto KOH then redistilled onto CaH_2 and finally distilled onto molecular sieves (4A).

The assignments of the various resonances in the eight deoxyribonucleotidyl(3'-5')arabinonucleosides were made by ^{31}P-decouplings, comparison with the data for the corresponding ribo- and deoxyribofuranosyl series,[23-25] and computer line simulations using the ITRCAL routine. Chemical shift data for the title compounds is presented in Table 1.

1-(5-O-Benzoyl-2-deoxy-β-D-ribofuranosyl)thymine (1, B = thymine). This was prepared by the method of Gerzon and Kau[11] in 70% yield.

9-(5-O-Benzoyl-2-deoxy-β-D-ribofuranosyl)adenine (1, B = adenine). This was prepared by the method of Gerzon and Kau[11] in 63% yield.

1-(5-O-Benzoyl-2-deoxy-β-D-ribofuranosyl)-4-N-benzoylcytosine (1, B = N-benzoylcytosine). N^4-Benzoyldeoxycytidine (0.300 g, 0.91 mmol) was dissolved in anhydrous pyridine (6 mL). To this was added 0.14 mL (1.2 mmol) benzoyl chloride in 2 mL anhydrous benzene. The solution was stirred with the exclusion of moisture overnight. Water (2 mL) was added and the solution stirred for 2 hr. Ethyl acetate (75 mL) and cold saturated $NaHCO_3$ (50 mL) were added

and the mixture separated. The organic layer was then washed with water (2 x 20 mL), dried over $MgSO_4$, filtered, and evaporated to a clear gum. This was dissolved in boiling water to which sufficient ethanol was added to dissolve the gum. After cooling to 5°C overnight, the solid was filtered and dried in vacuo over P_2O_5 at 80°C to give 0.350 g of product (85% yield): mp 230°C (dec.); ^{1}H-NMR ($CDCl_3$ and 10 λ D_2O), δ 2.32 and 3.10 (m, H-2',2"), 4.78 (m, H-4' and H-5',5"), 5.65 (m, H-3'), 6.42 (t, H-1'), 7.54 (m, H-5, meta and para protons), 7.92 (d, ortho protons), 8.07 (m, H-6 + ortho protons); UV (MeOH), λ_{max} 302 nm (15,820), 259 nm (38,290), λ_{min} 288 nm (13,830), 247 nm (31,500). Anal. Calcd. for $C_{23}H_{21}N_3O_6 \cdot 1/2H_2O$: C, 62.44; H, 4.86, N, 9.65. Found: C, 62.42; H, 4.91; N, 9.38.

9-(3,5-Di-O-t-butyldimethylsilyl-2-deoxy-β-D-ribofuranosyl)guanine (8). This nucleoside was prepared according to the method of Ogilvie[19a] in 80% yield.

2-N-Isobutyryl-9-(3,5-di-O-t-butyldimethylsilyl-2-deoxy-β-D-ribofuranosyl)-guanine (9). To anhydrous pyridine (40 mL) was added **8** (1.9 g,3.84 mmol) and 4-dimethylaminopyridine (0.02 g, 0.204 mmol). To this stirred suspension was added 6 mL of isobutyric anhydride and the suspension was stirred in a desiccator for four days, finally heating to 50°C for 2 hr. The reaction mixture was treated with 10 mL water for 2 hr and evaporated to a thick oil. This oil was dissolved in $CHCl_3$ (100 mL) and extracted with cold saturated $NaHCO_3$ (2 x 50 mL) and water (3 x 50 mL), dried over $MgSO_4$, filtered, and evaporated to a yellow foam. The foam was suspended in hot methanol and upon dissolution, water was added until the solution became opalescent. After cooling to 5°C for 24 hr, the precipitate was filtered and dried over P_2O_5 in vacuo to give 2.06 g (90% yield): mp 156-157°C (dec.); ^{1}H-NMR ($CDCl_3$ and 10 λ D_2O), δ 0.08 [two singlets, $(CH_3)_2$-Si], 0.91 [s, $(CH_3)_3$C-Si], 1.24 (m, methyl protons on isobutyl), 2.40 and 2.66 (m, H-2',2" and proton on alpha carbon of isobutyl), 3.76 (m, H-5',5"), 3.97 (m, H-4'), 4.58 (m, H-3'), 6.20 (t, H-1'), 7.80 (s, H-8). The product contained a trace contaminant (by TLC) but could be used in this slightly contaminated form.

2-N-Isobutyryl-9-(2-deoxy-β-D-ribofuranosyl)guanine (10). Compound **9** (1.80 g, 3.4 mmol) was dissolved in 1M tetrabutylammonium fluoride in tetrahydrofuran (7.8 mL) and shaken for one hour. The reaction mixture was evaporated to a thick gum and reevaporated from ethanol (2 x50 mL). The oil was absorbed on silica gel (1 g, Merck silica gel 60, 70-230 mesh) and the suspension evaporated. The adsorbed reaction mixture was placed on a dry-packed column of Merck silica gel (150 g) and this was developed with $CHCl_3$ (650 mL), 4% MeOH in $CHCl_3$ (750 mL) and 15% MeOH in $CHCl_3$ (1500 mL). The product peak was

pooled, evaporated to dryness, and the residue was recrystallized from water-MeOH. The product was filtered off after cooling to 5°C for 2 days, washed with 10 mL $CHCl_3$, and dried at 100° over P_2O_5 in vacuo to give 1.19 g of product (78% yield): mp greater than 280°C (dec.); ^{1}H-NMR (DMSO-d_6 and 10 λ D_2O), δ1.11 (d, methyl protons on isobutyryl), 2.27 (m, methylene proton on isobutyryl), 2.53, 2.75 (m, H-2',2"), 3.52 (m, H-5',5"), 3.82 (m, H-4'), 4.38 (m, H-3'), 6.20 (t, H-1'), 8.23 (s, H-8): UV (MeOH), λ_{max} 257 nm (12,580); λ_{min} 226 nm (2,330). Anal. Calcd. for $C_{14}H_{19}N_5O_5$; 0.5 H_2O. C, 48.55; H,5.82; N, 20.22. Found: C, 48.71; H, 5.71; N, 20.20.

2-N-Isobutyryl-9-(5-O-t-butyldimethylsilyl-2-deoxy-β-D-ribofuranosyl)guanine (11). To 1.3 mL of warm, dry dimethylformamide was added **10** (0.500 g, 1.36 mmol) and imidazole (0.205 g, 2.99 mmol). After cooling to room temperature, TBDMS-Cl (0.255 g, 1.50 mmol) was added. The flask was shaken overnight with protection from moisture. The solution was evaporated, dissolved in $CHCl_3$ (10 mL) and extracted wtih cold saturated $NaHCO_3$ (10 mL) and water (3 x 10 mL). The organic layer was dried over $MgSO_4$ and then evaporated to dryness. The residue was applied to four silica gel preparative plates (Merck silica gel HF-254, 11 x 11 cm, ca. 250 microns thick) and these were developed with ether and then 10% MeOH in $CHCl_3$, the eluant evaporated, and the gum recrystallized from 10% water in ethanol to give 0.537 g (88%) of **11a**: mp 154-157°C; ^{1}H-NMR ($CDCl_3$ and 10 λ D_2O), δ 0.02 [s, $(CH_3)_2$-Si), 0.83 [s, $(CH_3)_3$C-Si), 1.25 (m, methyl proton on isobutyl), 2.41 and 2.93 (m, H-2,2" and proton on alpha carbon of isobutyl), 3.77 (m, H-5',5"), 4.10 (m, H-4'), 4.57 (m, H-3'), 6.10 (t, H-1'), 8.02 (s, H-8); UV (MeOH) λ_{max} 255 nm (13,980), λ_{min} 225 nm (4,090). Anal. Calcd. for $C_{20}H_{33}N_5O_5Si$: C, 53.19; H, 7.37; N, 15.51. Found: C, 52.95; H, 7.40; N, 15.31.

6-N-Benzoyl-9-(2,3-di-O-benzoyl-β-D-arabinofuranosyl)adenine. This nucleoside was prepared by the method of Baker et al.[12] in a yield of 52%.

9-(2,3,5-Tri-O-t-butyldimethylsilyl-β-D-arabinofuranosyl)adenine (12a). Ara-A (0.267 g, 1.0 mmol) and imidazole (0.588 g, 8.64 mmol) were added to anhydrous dimethylformamide (10 mL) and evaporated to dryness in vacuo. The evaporation was repeated twice. Dimethylformamide (10 mL) and t-butyldimethylsilyl chloride (.605 g, 3.432 mmol) were added to the white foam and the suspension was evaporated to ca. 1 mL. The reaction was stirred overnight with protection from moisture. After this time, the solution was heated to 60°C for 2 hr, MeOH (10 mL) was then added and heating resumed for 30 min. The solution was evaporated to dryness in vacuo, the residue was dissolved in ether (50 mL) and the solution extracted with cold saturated $NaHCO_3$ (2 x 50 mL) and water

(3 x 50 mL). The ether layer was evaporated to dryness, and the foam reevaporated from EtOH and then $CHCl_3$. The stiff foam was dissolved in a small amount of $CHCl_3$ and placed atop a Merck silica gel 60 column (50 g, 3 x 100 cm). After elution with 500 mL of $CHCl_3$, the column was developed with a stepwise gradient of 200 mL 2% MeOH in $CHCl_3$, 400 mL 5% MeOH in $CHCl_3$, 200 mL 6% MeOH in $CHCl_3$, and then 200 mL 10% MeOH in $CHCl_3$. The yield of **12a** was 0.420 g (69%): mp 96-98°C; ^{1}H-NMR ($CDCl_3$ and 10 λ D_2O) δ 3.83 and 3.85 (m, H-5',5"), 3.97 (m, H-4'), 4.31 (m, H-3'), 4.15 (m, H-2'), 6.44 (d, H-1'), 7.88 (s, H-8), 8.29 (s, H-2); UV (MeOH) λ_{max} 258 nm (11,000); λ_{min} 226 nm (1,960). Anal. Calcd. for $C_{28}H_{55}N_5O_4Si_3$: C, 55.13; H, 9.09; N, 11.48. Found: C, 55.20; H, 9.15; N, 11.31.

9-(2,3-Di-O-t-butyldimethylsilyl-β-D-arabinofuranosyl)adenine (13a). **12a** (0.800 g, 1.31 mmol) was dissolved in 80% acetic acid (500 mL) and heated to 100-110°C for 3-4 hr. 1-Butanol (100 mL) was added and the solution evaporated in vacuo. Further evaporations from 1:1 1-butanol:toluene (3 x 100 mL) gave a stiff white foam. The residue was dissolved in a little chloroform and applied to a Merck silica gel 60 column (100 g, 4.5 x 17 cm). A stepwise gradient utilized $CHCl_3$ (700 mL), 4% MeOH in $CHCl_3$ (500 mL), 5% MeOH in $CHCl_3$ (500 mL), and 6% MeOH in $CHCl_3$ (600 mL). After evaporation of the required fractions, the solid residue was triturated with 1:1 ether:heptane to give a yield of 0.371 g (44%): mp 148-150°C; ^{1}H-NMR (CD_3OD and 10 λ D_2O), δ 3.77 and 3.83 (m, H-5',5"), 4.00 (m, H-4'), 4.30 (m, H-3'), 4.25 (m, H-2'), 6.37 (d, H-1'), 8.15 (s, H-8), 8.18 (s, H-2); UV (MeOH) λ_{max} 258 nm (11,590), λ_{min} 226 nm (1,965). Anal. Calcd. for $C_{22}H_{41}N_5O_4Si_2$: C, 53.50; H, 8.34; N, 14.13. Found: C, 53.28; H, 8.51; N, 14.30.

1-(2,3,5-Tri-O-t-butyldimethylsilyl-β-D-arabinofuranosyl)-4-N-benzoylcytosine (12c). N^4-Benzoylara-C[20] (0.300 g, 0.864 mmol) and imidazole (0.820 g, 12.04 mmol) were dissolved in warm anhydrous dimethylformamide (4.2 mL). After cooling, TBDMS-Cl (0.908 g, 6.03 mmol) was added and the solution protected from moisture while shaking the flask overnight. After evaporation, ether (20 mL) and cold saturated $NaHCO_3$ (20 mL) were added to the gum and separated. The ether layer was extracted with water (2 x 20 mL). After evaporation of the ether layer, the residue was dissolved in a small amount of $CHCl_3$ and placed on a Merck silica gel 60 column (60 g). This was developed with $CHCl_3$ (1000 mL), 2% MeOH in $CHCl_3$ (250 mL), 4% MeOH in $CHCl_3$ (250 mL), and 6% MeOH in $CHCl_3$ (250 mL) to give 0.578 g of **12c** (97%): mp 151-152°C; ^{1}H-NMR ($CDCl_3$ and 10 λ D_2O), δ 0.14 [m, $(CH_3)_2$-Si], 0.91 and 0.97 [two singlets, $(CH_3)_3$C-Si], 3.82 (m, H-4'), 4.00 (m, H-5',5"), 4.34 (m, H-2',H-3'),

6.26 (d, H-1'), 7.56 (m, H-5 and meta and para protons), 7.92 (d, ortho protons), 8.22 (d, H-6); UV (MeOH) λ_{max} 304 nm (12,500), 258 nm (24,900); λ_{min} 282 nm (8,900), 228 nm (12,200). Methanolysis of the N^4-benzoyl group occurred readily with a $t_{1/2}$ ca. 1 hour.

1-(2,3,5-Tri-O-t-butyldimethylsilyl-β-D-arabinofuranosyl)cytosine (12b). Ara-C (2.304 g, 9.49 mmol) and imidazole (9.01 g, 132.29 mmol) were dissolved in hot dry DMF (46 mL) to which was added TBDMS-Cl (9.96 g, 66.12 mmol) and the solution was shaken with exclusion of moisture overnight at room temperature. After evaporation of the solvent, ether (100 mL) and cold saturated $NaHCO_3$ (100 mL) were added and separated. The organic layer was washed with water (3 x 50 mL). The ether layer was evaporated, the residue dissolved in chloroform and placed on a Merck silica gel 60 column (340 g). The column was eluted with $CHCl_3$ (500 mL), 4% MeOH in $CHCl_3$ (1000 mL) and 5% MeOH in $CHCl_3$ (100 mL). The yield of the product after evaporation of the eluant was 2.996 g (53%): mp 98-99°C ^{1}H-NMR ($CDCl_3$ and 10 λ D_2O) δ 0.034, 0.081, 0.102 [s, $(CH_3)_2$-Si], 0.79, 0.89 and 0.91 [s, $(CH_3)_3$C-Si], 3.72 (m, H-5',5"), 3.93 (m, H-4'), 4.10 (m, H-3'), 5.59 (c, H-5'), 6.19 (d, H-1'), 7.51 (d, H-6); UV (MeOH) λ_{max} 273 nm (8,970); λ_{min} 252 nm (6,300). Anal. Calcd. for $C_{27}H_{55}N_3O_5Si_3$: C, 55.34; H, 9.46; N, 7.17. Found: C, 55.34; H, 9.52; N, 7.14.

1-(2,3-Di-O-t-butyldimethylsilyl-β-D-arabinofuranosyl)cytosine (13b). Compound **12b** (2.40 g, 4.09 mmol) was dissolved in 80% acetic acid (50 mL) and heated to 110°C for 3-1/2 hr. 1-Butanol (100 mL) was added and the solution evaporated under a high vacuum. The solvent addition and evaporation was repeated several times. The residue was dissolved in chloroform and placed atop a Merck silica gel 60 column (200 g). The column was developed with a stepwise gradient of 0-10% MeOH in $CHCl_3$ in 2% increments (500 mL each). The product peak was pooled and evaporated to give 1.079 g of **13b** (56%): mp 106-111°C; ^{1}H-NMR ($CDCl_3$ and 10 λ D_2O), δ 0.07, 0.124 and 0.126 [s, $(CH_3)_2$-Si], 0.82 and 0.91 [s, $(CH_3)_3$C-Si)] 3.81 (d, H-5',5"), 4.06 (m, H-3' and H-4'), 4.20 (d, H-2'), 5.66 (d, H-5), 6.20 (d, H-1'), 7.67 (d, H-6); UV (MeOH) λ_{max} 272 nm (8.700); λ_{min} 254 nm (6,100). Anal. Calcd. for $C_{21}H_{41}N_3O_5Si_2$: C, 53.47; H, 8.76; N, 8.91. Found: C, 53.22; H, 8.59; N, 8.72.

1-(2,3-Di-O-benzoyl-5-O-t-butyldimethylsilyl-β-D-arabinofuranosyl)-4-N-benzoylcytosine (14). Compound **13b** (0.450 g, 0.912 mmol) was suspended in anhydrous ethanol (25 mL) and heated to reflux. Benzoic anhydride (0.450 g, 3.74 mmol) was added once every hour for 5 hr with refluxing continued one extra hour. The solution was evaporated, dissolved in $CHCl_3$, placed atop a

Merck silica gel 60 column (150 g) and eluted with $CHCl_3$ (1500 mL) followed by 2% MeOH in $CHCl_3$ (1000 mL). The product was recrystallized quickly from aqueous methanol and dried at 25°C in vacuo over P_2O_5 to give 0.293 g of **14** (56%): mp 153-154°C; ^{1}H-NMR ($CDCl_3$ and 10 λ D_2O) and δ 0.148 [s, $(CH_3)_2$-Si], 0.84 and 0.95 [s, $(CH_3)_3$C-Si], 3.94 (d, H-5',5"),4.18 (m, H-3' and H-4'), 4.43 (m, H-2'), 5.86 (d, H-1'), 7.59 (m, meta and para protons, H-5), 7.93 (d, ortho protons), 8.15 (d, H-6); UV (MeOH) λ_{max} 304 nm (10,400), λ_{max} 259 nm (21,360); λ_{min} 283 nm (7,260), λ_{min} 229 nm (9,810). Anal. Calcd. for $C_{28}H_{46}N_3O_6Si_2$: C, 58.29; H, 8.04; N, 7.28. Found: C, 57.98; H, 8.08; N, 6.86. The product underwent methanolysis with a $t_{1/2}$ ca. 1 hr.

1-(5-O-t-Butyldimethylsilyl-β-D-arabinofuranosyl)cytosine. This nucleoside was prepared by the method of Ogilvie[19a] in a yield of 74%.

1-(2,3-Di-O-benzoyl-5-O-t-butyldimethylsilyl-β-D-arabinofuranosyl)-4-N-benzoylcytosine. This was prepared in a fashion similar to that described by Baker et al.[12] for the ara-A derivative. The foregoing 5'-O-TBDMSara-C (1.0 g, 2.8 mmol) and 4-dimethylaminopyridine (0.40 g, 0.326 mmol) were dissolved in anhydrous pyridine to which benzoic anhydride (2.64 g, 11.8 mmol) was added. The solution was heated to 50°C with protection from moisture and was stirred for 4 hr. Methanol (30 mL) was added and the solution refluxed for 30 min, cooled, and evaporated. The gum was extracted between $CHCl_3$ (100 mL) and cold saturated $NaHCO_3$ (2 x 50 mL). The $CHCl_3$ layer was backwashed with water (3 x 50 mL) and evaporated to dryness. The reflux for 30 min over methanol/pyridine and the extraction steps described above were repeated. The gum obtained by evaporation of the organic layer was placed on a Merck silica gel 60 column (300 g) which was developed with $CHCl_3$ (000 mL), 1% MeOH in $CHCl_3$ (2500 mL). The product was recrystallized from ethyl acetate:hexane to provide 1.445 g (77%): mp 152-153°C; ^{1}H-NMR ($CDCl_3$ and 10 λ D_2O), δ 0.136 [s, $(CH_3)_2$-Si], 0.91 [s, $(CH_3)_3$C-Si], 4.08 (m, H-5',5"), 4.32 (m, H-4'), 5.23 (m, H-3'), 6.24 (m, H-2'), 6.59 (d, H-1'), 7.40 (d, H-5), 7.53 (m, meta and para protons), 7.85 (m, ortho protons), 8.10 (d, H-6); UV (MeOH) λ_{max} 302 nm (9,700), 260 nm (23,700), λ_{min} 289 nm (8,900), 249 nm (19,800). Anal. Calcd. for $C_{35}H_{39}N_3O_8Si$: C, 63.90; H, 5.97; N, 6.39. Found: C, 63.87; H, 5.91; N, 6.25.

1-(2,3-Di-O-benzoyl-β-D-arabinofuranosyl)-4-N-benzoylcytosine (6). This was prepared in a similar fashion to that described by Baker et al.[12] for the ara-A derivative. The foregoing 5-O-TBDMS-N^4, 2',3'-tribenzoylara-C (0.700 g, 1.05 mmol) was dissolved in a mixture of glacial acetic acid (0.19 mL) and 1M TBAF in THF solution (4.8 mL). The final volume was diluted to 7 mL with

dry THF. After shaking the solution for 1.5 hr, it was evaporated several times from 1:1 1-butanol:toluene until a stiff foam resulted. This foam was dissolved in $CHCl_3$ and placed atop a Merck silica gel 60 column (50 g) which was developed with $CHCl_3$ (1000 mL), 0.5% MeOH in $CHCl_3$ (1000 mL), and 1% MeOH in $CHCl_3$ (1000 mL). The product was recrystallized from ethyl acetate:hexane to provide 0.497 g (86%): mp 176-178°C: ^{1}H-NMR ($CDCl_3$ and 10 λ D_2O), δ 4.14 (m, H-5',5"), 4.36 (m, H-4'), 5.65 (m, H-3'), 6.06 (m, H-2'), 6.55 (d, H-1'), 7.34 (d, H-5), 7.56 (m, meta and para protons), 7.85 (t, ortho protons), 8.07 (d, H-6); UV (MeOH) λ_{max} 301 nm (10,300), 260 nm (25,300); λ min 288 nm (9,400), 248 nm (21,500). Anal. Calcd. for $C_{30}H_{25}N_3O_8 \cdot 0.5\ H_2O$: C, 63.82; H, 4.64; N, 7.44. Found: C, 63.73; H, 4.89; N, 7.32.

2-N-Isobutyryl-9-[3-p-chlorophenylphosphatidyl-5-O-bis-(p-anisyl)phenylmethyl-2-deoxy-β-D-ribofuranosyl] guanine (5). This nucleotide was prepared by the method of Gough et al.[17] from N^2-isobutyryl-5'-DMTrdG in 72% yield; ^{1}H-NMR (DMSO-d_6 and 10 λ D_2O), δ 0.845 [m, $(CH_3)_2C$], 2.72 (m, H-2',2" and iBu-CH-), 3.05 (H-5',5" and H-4'), 3.65 (m, H-3'), 5.87 (t, H-1'), 6.65, 6.93 and 7.11 (m, aromatic), 8.22 (s, H-8); UV (MeOH) showed λ_{max} 280 nm, 267 nm; λ_{min} 245 nm.

6-N-Benzoyl-9-(2,3-di-O-benzoyl-5-p-chlorophenylphosphatidyl-β-D-arabinofuranosyl) adenine (2, B_1 = N-benzoyladenine). This nucleotide was prepared by the method of Sadana and Loewen[13] except that the product was extracted into ethylene dichloride. Evaporation and exhaustive drying in vacuo produced a clear foam which was chromatographically pure. This material was used directly without further purification.

1-(2,3-Di-O-benzoyl-5-p-chlorophenylphosphatidyl-β-D-arabinofuranosyl)-4-N-benzoylcytosine (2, B_1 = N-benzoylcytosine). This nucleoside was prepared by the method of Sadana and Loewen[13] with the exceptions mentioned for the synthesis of the corresponding ara-A analog (see above) in 94% yield by weight. TLC showed some slower moving impurities, but the product was suitable for use in the condensation steps. An aliquot of this nucleotide in pyridine solution was treated with 2N NaOH in ethanol for 20 min and gave ara-CMP p-chlorophenyl ester in 94% yield after paper chromatographic purification.

Condensation Reactions. The procedures outlined in this section start with the protected nucleotides and nucleosides whose preparation is described above. The exact synthetic steps reported are those developed from adjusting experimental conditions to optimize yields. No attempt has been made to outline all the changes made from those described in the literature.

Except where specifically isolated as a solid, blocked nucleotides (2) were added to each reaction as an aliquot of the phosphorylated product in anhydrous

pyridine solution. Overall yields of dimers, estimated by UV analysis, are reported based on the limiting nucleoside or nucleotide used for each condensation. Table 1 contains chemical shift data for the title compounds.

Thymidylyl(3'-5')arabinofuranosylcytosine (4, B = thymine, B_1 = cytosine). Compound **2** (B_1 = N-benzoylcytosine) was prepared as described previously. The gum so obtained was dried by azeotropic distillation of anhydrous pyridine (at least 4 x 5 mL). Anhydrous pyridine was then added to make a stock solution from which an aliquot (0.133 mmol) was removed for subsequent condensations. To this aliquot was added 5'-O-benzoylthymidine (0.900 g, 0.28 mmol) and anhydrous pyridine (5 mL). The solid was dried by addition and evaporation of three 5-mL portions of anhydrous pyridine, finally concentrating to ca. 1 mL. 1-H-Mesitylenesulfonyl tetrazole (0.130 g, 0.56 mmol) was added and the suspension was shaken with exclusion of moisture for 2 hr. Ice (2.0 g) was added and shaking resumed for 30 min. The suspension was extracted with ethyl acetate and the organic layer was extracted with cold 5% triethylammonium bicarbonate (2 x 3 mL) and 10% sodium chloride (2 x 3 mL). The organic layer was placed over solid Na_2SO_4 for 2 hr, filtered, and evaporated to a clear gum. The gum was applied to a Merck silica gel 60 HF-254 with 10% MeOH in $CHCl_3$, and evaporated to yield the fully blocked TparaC triester (**3**) in 96% yield. A small amount (25 mg) of this product was further purified on a Whatman KC_{18} analytical plate developed with 25% H_2O in acetone and evaporated to give a final yield of the triester of 85%: mp 120-125°C; TLC (6:94, MeOH:$CHCl_3$) R_f 0.41.

The fully blocked triester was deblocked using the method of Gough et al.[19] After deblocking, the solution was evaporated several times from 20% EtOH in H_2O, was streaked on Merck cellulose analytical plates (6 plates) and eluted with solvent A. The product band was eluted with water to give a yield of 75% for the deblocking step, 62% overall yield based on the amount of nucleotide used initially; TLC (solvent A) R_f 0.42; ^{1}H-NMR (see Table 1); UV (H_2O) λ_{max} 259 nm, λ_{min} 239 nm.

Thymidylyl(3'-5')arabinofuranosyladenine (4, B = thymine, B_1 = adenine). This dinucleotide was prepared in a similar fashion to that described above for TparaC. Compound **2** (B_1 = N-benzoyladenine; 1 equiv.) and compound **1** (B = thymine; 2 equiv.) were reacted with MS-TET (3 equiv.) to provide the fully blocked triester in a yield of 78%; TLC (4:96; MeOH:$CHCl_3$) R_f 0.47; mp 120-125°C. The overall yield of product after deblocking was 58%; TLC cellulose (solvent A) R_f 0.49; ^{1}H-NMR (D_2O) (see Table 1); UV (H_2O) λ_{max} 259 nm, λ_{min} 239 nm.

Deoxyadenylyl(3'-5')arabinofuranosylcytosine (4, B = adenine, B_1 = cytosine). This dinucleotide was prepared as described above for TparaC to provide the fully blocked triester in 72% yield; mp 120-125°C; TLC (6:94, MeOH:$CHCl_3$) R_f 0.34 and 0.41 (diastereomeric pair). After deblocking, the dinucleotide was prepared in an overall yield of 40%; TLC cellulose (solvent A) R_f 0.38; ^{1}H-NMR (D_2O) (see Table 1); UV (H_2O) λ_{max} 260 nm, λ_{min} 231 nm.

Deoxyadenylyl(3'-5')arabinofuranosyladenine (4, B = B_1 = adenine). This dinucleotide was prepared as described above for TparaC to provide the triester in 68% yield; mp 120-125°C; TLC (6:94, MeOH:$CHCl_3$) R_f 0.29 and 0.33 (diastereomeric pair). After deblocking, the final product was obtained in 48% overall yield; TLC (solvent A) R_f 0.40; ^{1}H-NMR (D_2O) (see Table 1); UV (H_2O) λ_{max} 257 nm, λ_{min} 229 nm.

Deoxycytidylyl(3'-5')arabinofuranosylcytosine (4, B = B_1 = cytosine). This dinucleotide was prepared as described above to give the fully blocked triester in 65% yield; mp 120-125°C; TLC (6:94, MeOH:$CHCl_3$)R_f 0.26. After deblocking, the final product was obtained in 35% overall yield; TLC cellulose (solvent A) R_f 0.35; ^{1}H-NMR (D_2O) (see Table 1); UV (H_2O) λ_{max} 277 nm, λ_{min} 247 nm.

Deoxycytidylyl(3'-5')arabinofuranosyladenine (4, B = cytosine, B_1 = adenine). The fully blocked triester was prepared as described above in 70% yield; mp 120-125°C; TLC (6:94, MeOH:$CHCl_3$) R_f 0.24. After deblocking, the product was obtained in 35% overall yield; TLC (solvent A) R_f 0.42; ^{1}H-NMR (D_2O) (see Table 1); UV (H_2O) λ_{max} 259 nm, λ_{min} 229 nm.

Deoxyguanylyl(3'-5')arabinofuranosyladenine (4, B = guanine, B_1 = adenine). 5'-O-MMTr-N^2-iBu-dG and compound **2** (B_1 = adenine) were condensed in a similar manner to that described above except mesitylenesulfonyl-4(5)-nitroimidazole (3 equiv.) was used as the condensing agent and 16-24 hr was the reaction time. The fully blocked triester was obtained in 58% yield; mp 120-125°C, TLC (6:94, MeOH:$CHCl_3$) R_f 0.82. The dinucleotide was deblocked as described above for the synthesis of TparaC with the addition of an 80% acetic acid deblocking of the trityl group for 6 hr at room temperature. The acetic acid was removed by repeated evaporation of the solution from water-saturated n-butanol and the usual chromatography on cellulose provided the product in 30% overall yield; TLC (solvent A) R_f 0.20; ^{1}H-NMR (D_2O) (see Table 1); UV (H_2O), λ_{max} 257 nm, λ_{min} 231 nm.

Deoxyguanylyl(3'-5')arabinofuranosylcytosine (4, B = guanine, B_1 = cytosine). Compounds **5**[17] (0.063 g, 0.65 mmol) and **6** (0.079 g, 0.084 mmol) were dissolved in warm pyridine (5 mL) and evaporated to a gum. After addition and evaporation of 4 more 5-mL portions of pyridine, the solution was concentrated to 0.5 mL.

To this solution was added p-toluenesulfonyl-4(5)-nitroimidazole (0.050 g, 0.20 mmol) and the solution was stirred under anhydrous conditions with the exclusion of moisture for 16 hr. Water (1 mL) was added and stirring resumed for 40 min. The suspension was evaporated to ca. 0.5 mL and placed atop a Mallinckrodt SilicAr CC-7 (special) silica gel column (10 g). The column was developed with $CHCl_3$ (200 mL) and then with 2% MeOH in $CHCl_3$ (100 mL). The fractions containing the required product were pooled, evaporated and rigorously dried under high vacuum to give a 51% yield of fully blocked triester: mp 110-115°C, TLC MeOH-$CHCl_3$ (2:98), R_f 0.73. The product was deblocked with TMG-PAO and base[17] to give, after chromatography on cellulose, a 42% overall yield of dGparaC. TLC (solvent A) R_f 0.12; ^{1}H-NMR (D_2O) (see Table 1); UV (H_2O) λ_{max} 262 nm, λ_{min} 245 nm.

Enzyme Analyses. The deoxyribonucleotidyl(3'-5')arabinonucleosides were also checked by the method of Wechter[10a] using spleen phosphodiesterase and snake venom diesterase to degrade the dimers to monomers. All the dimers (**4**) showed complete degradation of the dinucleotide to give at least 96% recovery of optical density and the molar ratio of nucleoside to nucleotide was 1:1 in all cases.

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