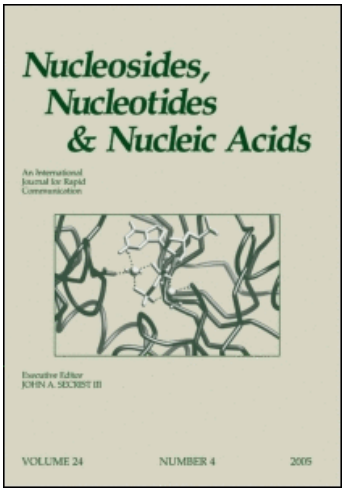

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and Biological Activity of 5-halo-2-Pyrimidinone 3'-Azido-2',3'-Dideoxyribosides

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To cite this Article Efange, S. M. N. and Dutta, A. K.(1991) 'Synthesis and Biological Activity of 5-halo-2-Pyrimidinone 3'-Azido-2',3'-Dideoxyribosides', Nucleosides, Nucleotides and Nucleic Acids, 10: 7, 1451 — 1463
To link to this Article: DOI: 10.1080/07328319108046674
URL: http://dx.doi.org/10.1080/07328319108046674

NUCLEOSIDES & NUCLEOTIDES, 10(7), 1451-1463 (1991)

SYNTHESIS AND BIOLOGICAL ACTIVITY OF 5-HALO-2-PYRIMIDINONE 3'-AZIDO-2',3'-DIDEOXYRIBOSIDES

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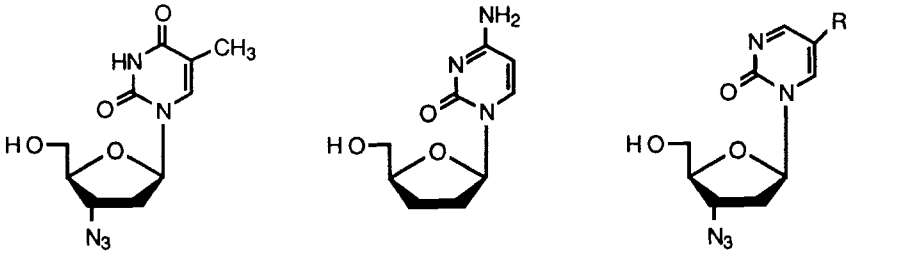
Abstract

The synthesis of two nucleosides, 1-(3-azido-2,3-dideoxy-β-D-ribofuranosyl)-5-iodo- and -5-bromo-2(1H)-pyrimidinone, 1a and 1b, is described. Neither 1a nor 1b exhibited significant inhibition of T_4 lymphocyte growth. However, both compounds were unable to protect T_4 lymphocytes from the cytopathic effects of HIV.

Introduction

Among the synthetic pyrimidine nucleosides, 3'-azidothymidine (AZT) and 2',3'-dideoxycytidine (ddC) have emerged as two of the most potent anti-HIV compounds. The anti-HIV activity of these and other 2',3'-dideoxyribosides is attributed to their ability, following bioactivation by the corresponding cellular kinases, to bind viral reverse transcriptase and thereby inhibit DNA replication (1-3). In addition, these synthetic nucleosides can be incorporated into a growing DNA chain, and thus act as chain terminators. Although AZT has been demonstrated to prolong the life expectancy of AIDS patients by improving their immunological status, the use of this compound is also associated with undesirable dose-limiting side effects such as bone marrow toxicity (4). Preliminary clinical studies with ddC, while encouraging, have produced undesirable side effects such as peripheral neuropathy (5). These limitations have, in part, provided the impetus for the development of more efficacious antiretroviral drugs. This manuscript describes one attempt at the

Figure 1:



AZT DDC 1 a: R = I b: R = Br

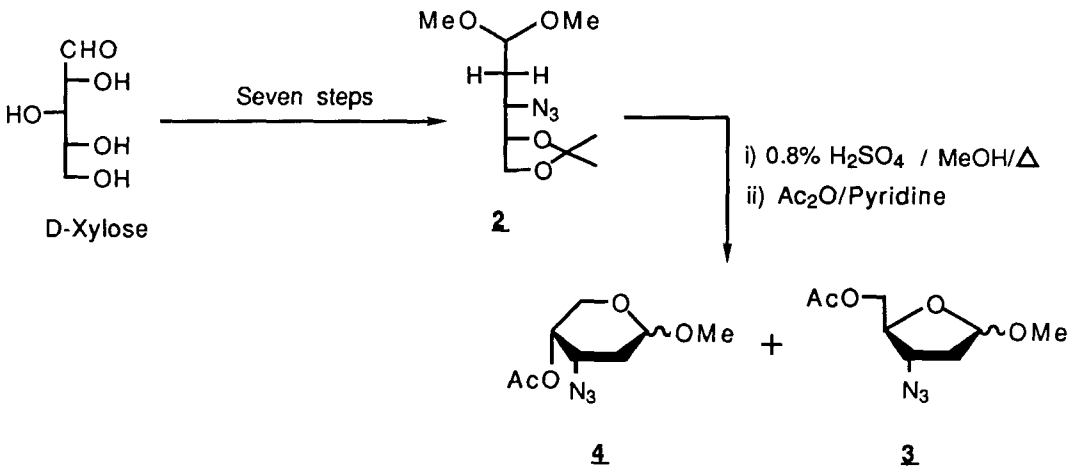
development of a potential antiretroviral agent by incorporating some of the structural attributes of AZT and ddC.

The target compounds 1a and 1b (Fig. 1) were based on earlier studies of 2-pyrimidinone nucleosides. 2(1H)-pyrimidinone is an intermediate in the exhaustive reduction of either uracil or cytosine (6,7). Given the possibility of the lactam-lactim tautomerization of uracil and cytosine, 2(1H)-pyrimidinone may be viewed as either 4-desaminocytosine or 4-deoxyuracil. In accordance with this view, 2-pyrimidinones and related nucleosides exhibit a wide range of antimetabolic activity. A number of 2-pyrimidinone ribonucleosides have been reported to inhibit the growth of E•coli (8). In addition, 5-halo-2-pyrimidinone ribonucleosides inhibit cytidine deaminase and exhibit modest cytotoxicity (9). Furthermore, 5-methyl- and 5-fluoro-2-pyrimidinone 2'-deoxyribosides inhibit thymidylate synthetase, a key enzyme in the de novo synthesis of thymidylate (10). In other studies, 5-methylmercapto, 5-iodo-, 5-bromo- and 5-ethynyl-2-pyrimidinone 2-deoxyribosides have demonstrated significant antiherpes activity both *in vitro* and *in vivo* (11-14). Finally, the presence of the 2-pyrimidinone nucleus renders the nucleoside stable to degradation by thymidine phosphorylase (8,11). Given these earlier encouraging results, it was of interest to investigate 2-pyrimidinone nucleosides as potential anti-HIV agents.

Results and Discussion

Compound 3 was prepared from D-xylose following literature methods. The protected azidoacetal 2 was synthesized from D-xylose, in seven steps,

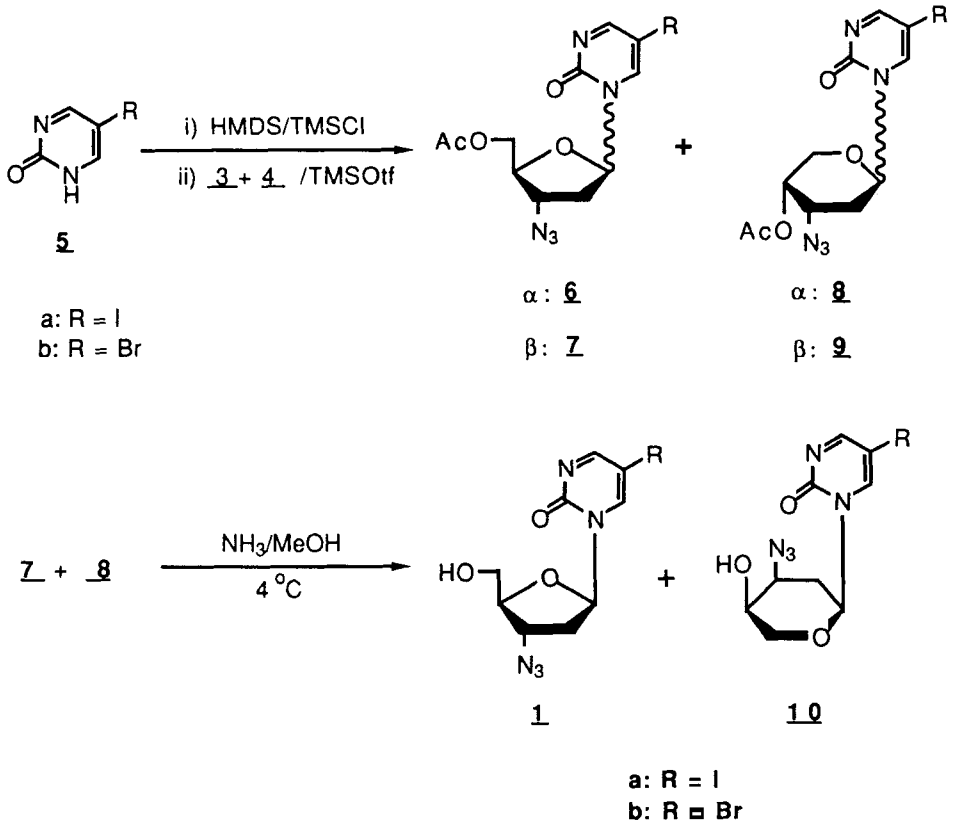
Scheme 1.



following procedures elaborated earlier (15-17). However, the deprotection and subsequent cyclization of 2 yielded both the desired ribofuranoside 3 and the by-product 4 in a combined yield of 31% (Scheme 1). The combined overall yield of 3 and 4 from D-xylose was 8%.

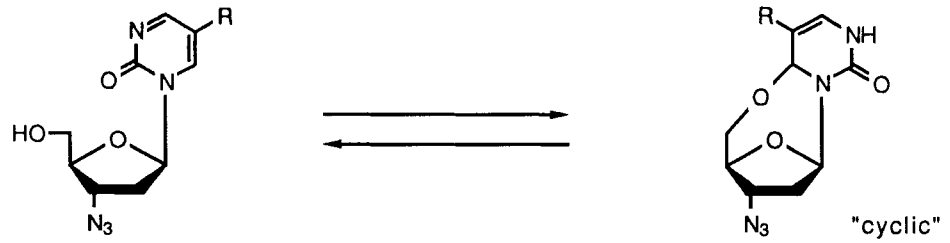
The reaction of this mixture of 3 and 4 with the silylated derivative of the previously reported 5a (14) yielded a complex mixture of the protected nucleosides (Scheme 2). The mixture was separated to yield pure 6a, pure 9a, and a mixture containing the β-ribofuranoside 7a and the pyranoside 8a. On tlc (silica gel; 40% EtOAc-CH_2Cl_2), 9a exhibited the highest mobility while 6a was least mobile; the mixture of 7a and 8a had an intermediate Rf. The assignment of stereochemistry at the anomeric carbon was based on NMR data. Discussions of the NMR splitting patterns of anomeric protons of ribofuranosides and ribopyranosides have been provided in earlier literature (18-22). In the ^1H NMR spectrum, the anomeric proton of the α-furanoside 6a appears as the characteristic doublet of doublets at 6.06 δ, with a primary coupling constant of 6.8 Hz (18). However, the primary coupling constant for the anomeric proton of the α-pyranoside 8a was 10.0 Hz. The larger coupling constant is characteristic of the pyranosides (19). While the furanosides and pyranosides could be distinguished by the magnitude of the coupling constant, the assignment of pyranoside C1'-stereochemistry was based on

Scheme 2



chemical shifts. The anomeric proton of the α-pyranoside 8a was visualized as a doublet of doublets at 5.67 δ while the corresponding signal for the β-anomer 9a appeared at 5.86 δ. The downfield shift has been attributed, as shown earlier for 3'-acetoxy pyranosides, to diamagnetic anisotropy of the C-3'-substituent of the six-membered ring (21,22). Similar observations were made for the brominated analogs. The mixture of 7a and 8a was treated with methanolic ammonia to yield the desired 1a in 15% overall yield from 5a. The pyranoside 10a was similarly obtained in 15% yield. A similar condensation-purification-deprotection sequence yielded the corresponding 5-bromo analogs 1b and 10b in yields of 12% and 17%, respectively, from 5b. Although 1a and 1b were found to be homogeneous by HPLC (SiO_2, i-PrOH:hexane:E_3tN, 15:84:1; data not shown), they could not be obtained in analytically pure form. In solution, both

Figure 2 :



1 11

1a and 1b were found to exist in the "cyclic" and "open" forms (Fig. 2). The 5',O^6-cyclonucleoside 11, was detected in the NMR spectrum (DMSO-d_6) by the signals at δ 5.45 (s,1H,H-6), 5.86 (dd,1H,H-1') and 6.61 (d,1H,H-4). The latter doublet collapses to a singlet, attributed to loss of coupling to the N_3-H, on addition of D_2O. From the ratio of the anomeric protons, the ratio of 1a:11a was estimated to be 6:4. A similar ratio for 1b and 11b was 1:4. Similar observations had been earlier reported by us and by others for other 5'-substituted 2-pyrimidinone nucleosides (14,20).

Biological:

The target compounds 1a and 1b were tested for their ability to protect T_4 lymphocytes (CEM-V) from the cytopathic effects of HIV. Both 1a and 1b failed to show significant growth-inhibitory properties at concentrations of up to 28 uM and 94 uM, respectively. However, neither compound was effective in protecting T_4 lymphocytes from the cytopathic effects of HIV.

The failure of 1a and 1b to protect T_4 lymphocytes from the cytopathic effects of HIV may be due to a number of factors, including a) lack of bioactivation by the cellular thymidine and/or deoxycytidine kinase; and b) inability to bind reverse transcriptase. Given that the 2-pyrimidinone nucleus has been successfully utilized in the development of a number of antimetabolites (e.g., inhibitors of thymidylate synthetase, cytidine deaminase and anti-HSV compounds), there is little doubt as to the ability of this nucleus to substitute for either thymine or cytosine in a number of metabolic processes. The apparent inactivity of 1a and 1b against HIV

may, therefore, be attributed to the inability of the cellular kinases to phosphorylate and thereby activate these compounds for subsequent metabolic processes. This view is consistent with the higher substrate specificity of cellular thymidine kinase relative to the viral enzymes (23,24). Further support for the stringent substrate requirements of cellular thymidine and deoxycytidine kinase is evident in the decreased phosphorylation rates of 2',3'-dideoxypyrimidine nucleosides relative to endogenous pyrimidine nucleosides (25,26). Although the formation of the cyclonucleosides 11a and 11b results in the sequestration of the 5'-hydroxyl group, 11a and 11b are in equilibrium with the "open" forms 1a and 1b, respectively. These cyclonucleosides could conceivably serve as depot forms of the corresponding "open" nucleosides. However, the presence of the cyclonucleosides should not interfere with the recognition of 1a and 1b by the relevant kinases. Thus, we conclude that the simultaneous modification, such as we have effected, of both the aglycone and sugar portions of the pyrimidine nucleosides results in a total loss of recognition by eukaryotic thymidine and/or deoxycytidine kinase. Our results, therefore, underscore the importance of a C-4-bonded heteroatom as a requirement for optimum substrate binding to eukaryotic thymidine kinase. These observations may be useful in the design of potentially useful antiretroviral agents.

Experimental

General: Synthetic intermediates were purchased from Aldrich, Inc. (Milwaukee, WI) and were used as received. Solvents were distilled immediately prior to use. Commercially available reagents were used without subsequent purification.

All air-sensitive reactions were carried out under nitrogen. Standard handling techniques for air-sensitive materials were employed throughout this study. Yields are not optimized.

Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. ^1H spectra were recorded on an IBM-Brucker spectrometer at 200 MHz. NMR spectra are referenced to the deuterium lock frequency of the spectrometer. With this condition, the chemical shifts (in ppm) of residual solvent in the ^1H NMR were found to be respectively: $CHCl_3$, 7.26; DMSO, 2.56; HOD, 4.81. The following abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d

= doublet, t = triplet, q = quartet, m = multiplet. Both low- and high-resolution MS were performed on an AEI MS-30 instrument. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

Column chromatography was performed using "Baker Analyzed" silica gel (60-200 mesh). Preparative chromatography was performed on a Harrison Research Chromatotron using Merck 60 PF_{254} silica gel. Analytical TLC was performed on Analtech glass TLC plates coated with silica gel GHLF and were visualized with UV light and/or methanolic iodine.

Methyl 5-O-acetyl-3-azido-2,3-dideoxy-α/β-D-ribofuranoside (3) and methyl 4-O-acetyl-3-azido-2,3-dideoxy-α/β-D-ribopyranoside (4)

The protected sugar 3 was synthesized from the previously described azide 2 following literature methods (15-17). A solution of compound 2 (7.6 g, 31mmol) in 56 ml of 0.8% aq. H_2SO_4 and 60 ml of methanol was refluxed for 21 hours, cooled to room temperature and neutralized with barium carbonate (3 g). The resulting mixture was filtered through a bed of Celite and the filtrate was concentrated in vacuo to a residue. Traces of water were removed by co-evaporation with benzene (4x50 ml). The residue was subsequently dissolved in pyridine (30 ml) and acetic anhydride (18 ml), and stirred at room temperature for 5 hours. At this time, the reaction mixture was diluted with ice-cold water and extracted with methylene chloride (400 ml). The organic extract was washed consecutively with cold 10% HCl (150 ml), 10% aq. $NaHCO_3$ (150 ml) and water (200 ml). After drying over anhydrous Na_2SO_4, the organic extract was concentrated to a residue which was purified by chromatography on a silica gel column (hexane : ethyl acetate, 6:1) to yield 2.85 g (31%) of a colorless oil. IR (neat)ν 2950, 2150, 1750, 1450, 1360, 1225, 1080, 1040 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.06 (s,3H), 2.30-2.44 (m, 2H), 3.34 (s,3H), 3.77-4.17 (m,4H), 5.03 (dd,1H), m/e (CI/NH_3), 233 ($M+NH_4^+$).

Anomeric 1-[5-O-acetyl-3-azido-2,3-dideoxy-D-ribofuranosyl)-5-iodo-2(1H)-pyrimidinone (6a, 7a) and anomeric 1-[4-O-acetyl-3-azido-2,3-dideoxy-D-ribopyranosyl)-5-iodo-2(1H)-pyrimidinone (8a, 9a)

A suspension containing 0.97 g (4.4 mmol) of 5-iodo-2(1H)-pyrimidinone, 9a, in 6 ml of hexamethyldisilazane was refluxed, with

exclusion of moisture, for one hour. Complete dissolution occurred during this time. The resulting solution was concentrated, under anhydrous conditions, to a residue which was redissolved in 6 ml of dry acetonitrile. To this solution was added a solution containing 0.73 g (3.3 mmol) of the mixture of sugars 3 and 4 in 10 ml of acetonitrile. The solution was cooled in an icebath and treated with 1 ml (5.2 mmol) of trimethysilyl triflate. Following the addition, the reaction mixture was stirred at room temperature for 1 hour, treated with a saturated solution of $NaHCO_3$ and stirred for an additional 30 minutes. The mixture was filtered and extracted with ethyl acetate (2 x 100 ml). The organic extract was washed with a 20% solution of brine (100 ml), dried over anhydrous Na_2SO_4 and concentrated in vacuo to a residue. The latter was subjected to radial flow chromatography (80-g silica gel plate, solvent: 40% EtoAc-CH_2Cl_2) to yield three major fractions. a) The fraction showing the shortest chromatographic retention (fraction 1) was concentrated to yield 0.19 g (15%) of a foam which was identified as the β-pyranoside 9a. ^1H NMR ($CDCl_3$) δ 1.62-1.72 (m, 1, 2'-H), 2.13 (s, 3, CH_3CO), 2.53 (m, 1, 2'-H), 3.94-4.12 (m, 2, 5'-H), 4.29 (m, 1, 4'-H), 5.02-5.08 (m, 1, 3'-H), 5.86 (d, 1, 1'-H, $J_{1',2'}$=10.4 Hz), 8.04 (d, 1, 6-H, $J_{4,6}$=3.1 Hz), 8.62 (d, 1, 4-H). HRMS (CI/CH_4): calcd. for $C_{11}H_{12}IN_5O_4$, 404.9932 (M^+); Found, 406.00123 $(M+H)^+$.

b) Fraction 2 (intermediate Rf) yielded 0.32 g (25%) of a mixture identified as containing the β-furanoside 7a and the α-pyranoside 8a. ^1H NMR ($CDCl_3$) δ 2.19 (s, 3, CH_3CO), 1.67-2.83 (m, 2, 2'-H), 3.67-4.45 (m, 4, 5'-H, 4'-H & furanosyl 3'-H); for the α-pyranoside 8a : 5.12 (br s, 1, 3'-H), 5.67 (dd, 1, 1'-H, $J_{1',2'}$=10.0 Hz, $J_{1',2''}$=2.2 Hz), 8.07 (d, 1, 6-H, $J_{6,4}$=3.1 Hz), 8.64 (d, 1, 4-H); for the β-furanoside 7a : 6.03 (pseudotriplet, 1, 1'-H, $J_{1',2'}$=6.7 Hz), 8.26 (d, 1, 6-H, $J_{6,4}$=3.1 Hz), 8.65 (d, 1, 4-H).

c) Fraction 3, the least mobile, was concentrated to yield 0.45 g (35%) of a foam identified as the α-furanoside 6a. ^1H NMR ($CDCl_3$) δ 2.10 (s, 3, CH_3CO), 2.52-3.00 (m, 2, 2'-H), 4.10-4.32 (m, 3, 4'-H, 5'-H), 4.56 (m, 1, 3'-H), 6.06 (dd, 1, 1'-H, $J_{1',2'}$=6.8 Hz, $J_{1',2''}$=2.3 Hz), 8.06 (d, 1, 6-H, $J_{6,4}$=3.1 Hz), 8.62 (d, 1, 4-H). HRMS (CI/CH_4): calcd. for $C_{11}H_{12}IN_5O_4$, 404.9932 (M^+); Found, 406.00123 $(M+H)^+$.

1-(3-azido-2,3-dideoxy-β-D-ribofuranosyl)-5-iodo-2(1H)-pyrimidinone, 1a, and 1-(3-azido-2,3-dideoxy-α-D-ribopyranosyl)-5-iodo-2(1H)-pyrimidinone, 10a.

A 6:4 mixture (ratio determined by NMR) of the protected β-furanoside 7a and the protected α-pyranoside 8a (0.38 g, 0.94 mmol) was dissolved in 25 ml of cold MeOH saturated with ammonia. The resulting solution was stirred at 4°C overnight. After 20 hours, excess solvent was removed in vacuo to yield a residue which was chromatographed on 20 x 20 silica gel plates (30% EtOAc-CH_2Cl_2) to yield 2 major bands. The more mobile band was extracted from the stationary phase with EtOAc and concentrated to yield a white solid. The latter was triturated with ether, collected by filtration and dried to provide 120 mg (58%) of the β-furanoside 1a; mp 133.3°C. In DMSO, the latter exists in equilibrium with the "cyclic" form 11a. ^{1}H NMR (DMSO-d_6) δ 2.31-2.47 (m, 2, 2'-H), 3.58-4.50 (m, 4, 3'-H, 4'-H, 5'-H); for the open form 1a : 5.93 (t, 1, 1'-H, $J_{1',2'}$=5.5 Hz), 8.63 (d, 1, 6-H, $J_{6,4}$=3.1 Hz), 8.76 (d, 1, 4-H); for the cycloadduct 11a : 5.40 (s, 1, 6-H), 5.83 (d, 1, 1'-H, $J_{1',2'}$=4.0 Hz), 6.61 (d, 1, 4-H, $J_{4,3}$=5.0 Hz). Following the addition of D_2O, the latter signal collapses to a singlet. FAB-MS:calcd., 362.9787 (M^+), Found; 363.9899 $(M+H)^+$. Anal. calcd. for $C_9H_{10}IN_5O_3$:C,29.75; H,2.77;N,19.28. Found: C, 29.94; H,2.87; N,18.20.

The less mobile band was similarly extracted and concentrated to yield a white solid 80 mg (62%) of a white solid identified as the α-pyranoside 10a; mp 85.9°C. ^{1}H NMR ($CDCl_3$ + D_2O) δ 1.94 (m, 1, 2'-H), 2.42 (m, 1, 2'-H), 3.68-3.78 (m, 2, 5'-H), 3.95 (s, 1, 4'-H), 4.28 (m, 1, 3'-H), 5.66 (dd, 1, 1'-H, $J_{1',2'}$=10.4 Hz, $J_{1',2''}$=2.2 Hz), 8.28 (d, 1, 6-H, $J_{6,4}$=3.0 Hz), 8.63 (d, 1, 4-H). FAB-MS: calcd. for $C_9H_{10}IN_5O_3$, 362.9787 (M^+); found, 363.9897 $(M+H)^+$.

Anomeric 1-[5-O-acetyl-3-azido-2,3-dideoxy-D-ribofuranosyl)-5-bromo-2(1H)-pyrimidinone (6b, 7b) and anomeric 1-[4-O-acetyl-3-azido-2,3-dideoxy-D-ribopyranosyl)-5-bromo-2(1H)-pyrimidinone (8b, 9b).

A sample of 0.63 g (3.6 mmol) of 5-bromo-2(1H)-pyrimidinone, 5b, was silylated in a manner similar to that outlined above. The silylated pyrimidine was subsequently reacted with 0.62 g (2.8 mmol) of a mixture

of the protected sugars 3 and 4, under the conditions outlined above for the iodinated analog. Three major fractions, similar to those identified above, were obtained following chromatography (30% EtOAc-ether; silica gel).

a) Fraction 1, identified as the β-pyranoside 9b, showed the greatest mobility and was obtained as a foam (150 mg, 16%) ^{1}H NMR ($CDCl_3$) δ 1.62-1.70 (m, 1,2'-H), 2.14 (s, 3, CH_3CO), 2.54 (m, 1, 2'-H), 3.95-4.08 (m, 2, 5'-H), 4.31 (br s, 1, 4'-H), 5.06 (m, 1, 3'-H), 5.87 (d, 1, 1'-H, $J_{1',2'}$=8.7 Hz), 7.98 (d, 1, 6-H, $J_{6,4}$=3.0 Hz), 8.57 (d, 1, 4-H). HRMS (CI/CH_4): calcd., 357.0073 (M^+); found, 358.01509 $(M+H)^+$.

b) Fraction 2 (intermediate Rf) was concentrated to yield 200 mg (20%) of a foam which was found to contain the β-furanoside 7b and the α-pyranoside 8b in a 1:1 ratio. ^{1}H NMR ($CDCl_3$) δ 1.69-2.67 (m, 5, CH_3CO and 2'-H), 3.68-4.43 (m, 4, 5'-H, 4'-H and furanosyl 3'-H); for the α-pyranoside 8b : 5.14 (br s, 1, 3'-H), 5.69 (dd, 1, 1'-H, $J_{1',2'}$=10.4 Hz, $J_{1',2''}$=2.3 Hz), 8.03 (d, 1, 6-H, $J_{4,6}$= 3 Hz), 8.60 (d, 1, 4-H); for the β-furanoside 7b : 6.04 (dd, 1, 1'-H, $J_{1',2'}$=7.0 Hz, $J_{1',2''}$=4.0 Hz), 8.26 (d, 1, 6-H, $J_{6,4}$=3.1 Hz), 8.60 (d, 1, 4-H).

c) Fraction 3, the least mobile, was concentrated to yield 0.45 g (35%) of a foam identified as the α-furanoside 6a. ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3, CH_3CO), 2.52-3.00 (m, 2, 2'-H), 4.10-4.32 (m, 3, 4'-H, 5'-H), 4.56 (m, 1, 3'-H), 6.06 (dd, 1, 1'-H, $J_{1',2'}$=6.8 Hz, $J_{1',2''}$=2.3 Hz), 8.06 (d, 1, 6-H, $J_{6,4}$=3.1 Hz), 8.62 (d, 1, 4-H). HRMS (CI/CH_4): calcd. for $C_{11}H_{12}IN_5O_4$, 404.9932 (M^+); Found, 406.00123 $(M+H)^+$.

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Acknowledgements: We thank Ms. Helen Durgin for her help in the preparation of this manuscript. We also thank the NCI for providing the biological data for the target compounds. Financial support was provided by the American Foundation for AIDS Research (Grant #000404-3-RGT).

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Received 9/17/90

Accepted 3/27/91