# 4-Azido-2-pyrimidinone Nucleosides and Related Chemistry

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As a part of azide prodrug approach, we synthesized a 4-azido analog of ara-C (**4**) as a prodrug for ara-C. The compound **4** was obtained from 1-(β-D-arabinofuranosyl)uracil (**1**) in three steps. At pH 7.0 and 11.0, a loss of UV absorption of the compound **4** was observed resulting from a transformation that was proved by identifying the transformed product **5** by 1-D, and 2-D NMR as well as tandem mass spectral studies. In NMR studies, changes in the chemical shifts were observed at positions 5, 6, 1′, and 2′ between the compounds **4** and **5**. A molecular peak at *m*/*z* 270.1 ($MH^+$) was observed in the mass spectra of compounds **4** and the transformed product **5**. A fragment at 180.2 was identified to be the compound **6**, containing the 6,2′-anhydro linkage of compound **5**. The X-ray analysis indicated that compound **4** exists as 1-(β-D-arabinofuranosyl)tetrazolo[4,5-*c*]pyrimidin-2-one, with the azide moiety cyclized. To understand if the chemical instability of the nucleoside **4** was due to the arabino configuration of 2′-OH or due to the azido moiety, we also studied 1-(2,3-dideoxy-2-fluoro-β-D-arabinofuranosyl)tetrazolo[4,5-*c*]pyrimidin-2-one (**11**) and 4-azido-1-methyl-2-pyrimidinone (**15**). At pH 2.0 and 7.0, similar UV profiles were observed for compounds **11** and **15**. However, at pH 11.0, $\lambda_{max}$ shifted slowly to lower wavelength for both compounds **11** and **15**. In a separate kinetic study, they were stable at pH 7.4 for up to 2.45 h. From the NMR and high-resolution mass spectral studies, it was concluded that in the presence of ammonium hydroxide, an addition of amine occurred at 6-position of compound **11**. Thus, the stability profiles of compounds **4**, **11**, and **15** were different. The instability and the formation of 2′,6-anhydro bond in compound **4** in nonacidic media was due to the presence of 2′-OH in the arabino configuration and probably not due to the azide group.

Recently, as a part of azide prodrug approach we reported the synthesis and biotransformation of 6-azido-9-(2,3-dideoxy-2-fluoro-β-D-arabinofuranosyl)purine (FAAddP) as a prodrug for 9-(2,3-dideoxy-2-fluoro-β-D-arabinofuranosyl)hypoxanthine (2′-F-ara-ddI).[1] We also investigated 6-azido-(1-β-D-arabinofuranosyl)purine (6-AAP) as a prodrug for 1-(β-D-arabinofuranosyl)adenine (ara-A) and demonstrated that unlike ara-A, 6-AAP was stable to adenosine deaminase, which generates ara-A both *in vitro* and *in vivo* in mice.[2] These azide prodrugs are reduced to their amine analogs by the cytochrome P450-NADPH reductase system after entering the biological system to deliver the amine-containing drugs.

In continuation of our efforts to develop prodrugs for various antitumor and antiviral agents to enhance the pharmacokinetic properties, utilizing the azide prodrug approach, we synthesized the 4-azido analog of ara-C (**4**, Scheme 1) as a prodrug for 1-(β-D-arabinofuranosyl)cytosine (ara-C). It was anticipated that the azide moiety would be stable to cytidine deaminase but upon reduction by the cytochrome P450-NADPH reductase system *in vivo*, it would generate ara-C.

The compound **4** was obtained from 1-(β-D-arabinofuranosyl)uracil (**1**) in three steps (Scheme 1). Compound **1** was synthesized from uridine, according to the published procedure,[3] which was protected by the treatment with acetic anhydride, treated with 4-chlorophenyl dichlorophosphate and 1,2,4-triazole to give compound **2**. The triazolide **2** was treated with $LiN_3$ in DMF at 50 °C to obtain compound **3** in 27% yield from compound **1**. Deprotection of the acetyl groups of compound **3** using basic conditions such as $NH_3$/MeOH, NaOMe, or neutral conditions (NaCN in ethanol) did not result in the desired product but compounds of destruction. However, the deprotection of acetyl groups was achieved by treatment of compound **3** with 1 N HCl/MeOH at rt to afford compound **4** in 72% yield. The compound **4** was characterized by $^1$H NMR, $^{13}$C NMR, UV spectroscopy, and elemental analysis. Interestingly, single crystal X-ray crystallography of compound **4**[4] (Figure 1, Table 1) showed that the azido group at 4-position had cyclized to form a tetrazole ring in conjugation with N3 of the pyrimidine ring, forming 1-(β-D-arabinofuranosyl)tetrazolo[4,5-*c*]pyrimidin-2-one and such phenomenon was also observed by other groups for similar systems.[5] During *in vitro* biotransformation studies of compound **4** in the biological media, we failed to detect the prodrug or its product by a HPLC assay. This prompted us to study the chemical stability of the compound **4** at various pHs, and the UV spectral pattern is shown in Table 2.

The UV profiles of compound **4** in methanol and at pH 2.0 had similar patterns and did not show any changes

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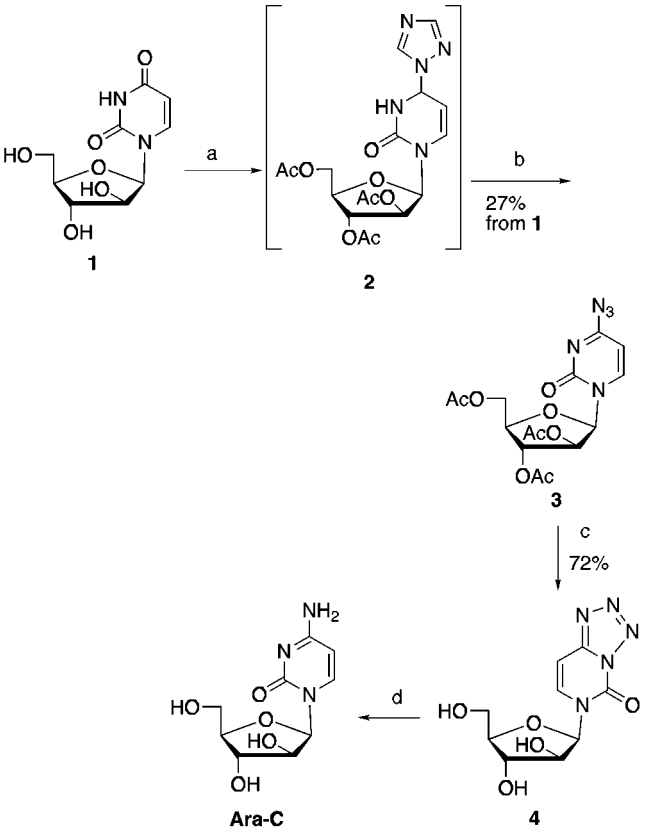
(1) Koudriakova, T.; Manouilov, K. K.; Shanmuganathan, K.; Kotra, L. P.; Boudinot, F. D.; Cretton-Scott, E.; Sommadossi, J.-P.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **1996**, *39*, 4676−4681.
(2) Kotra, L. P.; Manouilov, K. K.; Cretton-Scott, E.; Sommadossi, J. -P.; Boudinot, F. D.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **1996**, *39*, 5202−5207.
(3) Schinazi, R. F.; Chen, M. S.; Prusoff, W. H. *J. Med. Chem.* **1979**, *22*, 1273−1277.
(4) Primitive orthorhombic crystals with space group $P2_12_12_1$ with lattice parameters $a = 6.565(2)$ Å, $b = 13.108(3)$ Å, $c = 14.265(3)$ Å, $V = 1227.7(6)$ Å$^3$.
(5) Napoli, L. D.; Mayol, L. *J. Heterocycl. Chem.* **1986**, *23*, 1401−1403.

S0022-3263(97)00761-5 CCC: $14.00 

**Scheme 1.[a] Synthesis of Compound 4**




[a] Reagents: (a) (i) $Ac_2O$, pyridine, 0−4 °C, 16 h; (ii) chlorophenyl dichlorophosphate, 1,2,4-triazole, pyridine, rt; (b) $LiN_3$, anhyd DMF, 50 °C, 3 h; (c) 1 N HCl/MeOH, rt, 26 h; (d) $H_2/PdCl_2$, MeOH, 50 psi, rt, 30 h.

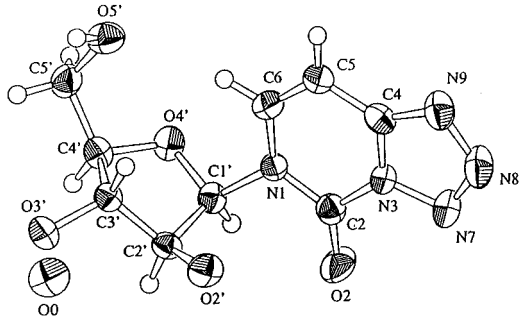



**Figure 1.** ORTEP drawing of the X-ray structure of compound **4**.

**Table 1. Conformational Parameters for Compounds 4 and 11**

| compd | pseudo-rotation angle, *P* | torsion angles C3′−C4′−C5′−O5′ ($\gamma$) | torsion angles C2′−C1′−N1−C2 ($\chi$) | conformation |
|---|---|---|---|---|
| **4** | 21.9° | 56.6° | −155.6° | C3′-endo |
| **11** | 159.4° | 175.0° | −132.2° | C2′-endo |

in the $\lambda_{max}$ for up to 2.45 h. However, at higher pHs (7.0 and 11.0), $\lambda_{max}$ shifted to lower wavelengths, indicating a change in the base moiety of the compound **4**. In order to elucidate the structural changes in the compound **4** at higher pHs, it was treated with ammonium hydroxide and the solvent was evaporated to dryness. It provided a single product (later assigned to be compound **5**) as determined by NMR and mass spectra, and its UV profile was similar to that observed in nonacidic media for compound **4**. Ammonium hydroxide was used merely to provide basic environment and for the easy isolation of the product.

**Table 2. UV Profiles of Compounds 4, 11, and 15**

| compd | solvent | UV ($\lambda_{max}$) |
|---|---|---|
| **4** | MeOH | 268.5 nm (shoulder), 257.0 nm |
| | $H_2O$, pH 2.0 | 267.5 nm (shoulder), 255.5 nm |
| | $H_2O$, pH 7.0 | 245.5 nm |
| | $H_2O$, pH 11.0 | 239.0 nm |
| **11** | $H_2O$, pH 2.0 | 266.5 nm (shoulder), 252.0 nm |
| | $H_2O$, pH 7.0 | 266.5 nm, 253.0 nm |
| | $H_2O$, pH 11.0 | 256.0 nm |
| **15** | MeOH | 257.0 |
| | $H_2O$, pH 2.0 | 256.5 |
| | $H_2O$, pH 7.0 | 256.0 |
| | $H_2O$, pH 11.0 | 248.0 |

**Table 3. $^1$H and $^{13}$C Chemical Shifts ($\delta$ ppm) for the Compounds 4, 5, 11, and 12**

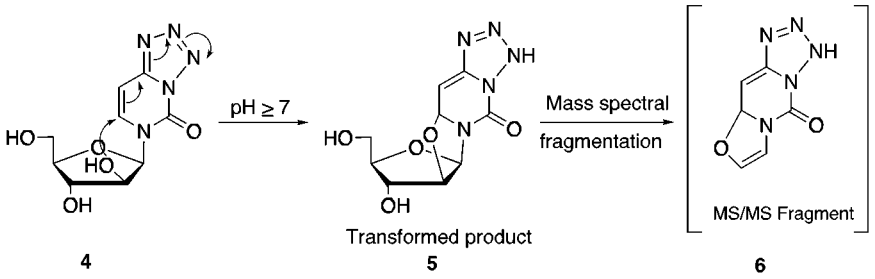
| | compd **4** | compd **5** | Δδ |
|---|---|---|---|
| | $^1$H Signal | | |
| H-5 | 7.1 | 4.9 | 2.2 |
| H-6 | 8.0 | 7.2 | 0.8 |
| H-1′ | 6.2 | 6.3 | −0.1 |
| H-2′ | 4.2 | 6.1 | −1.9 |
| H-3′ | 4.0 | 4.3 | −0.3 |
| H-4′ | 3.9 | 3.8 | 0.1 |
| H-5′ | 3.6 | 3.2 | 0.4 |
| | $^{13}$C Signal | | |
| C-2 | 151.5 | 156.5 | −5.0 |
| C-4 | 143.0 | 155.0 | −12.0 |
| C-5 | 75.4 | 83.6 | −8.2 |
| C-6 | 137.2 | 86.5 | 50.7 |
| C-1′ | 87.8 | 119.4 | −31.6 |
| C-2′ | 75.4 | 105.2 | −29.8 |
| C-3′ | 75.3 | 74.5 | 0.8 |
| C-4′ | 86.3 | 86.6 | −0.3 |
| C-5′ | 60.8 | 60.7 | 0.1 |

| | compd **11** | compd **12** | Δδ |
|---|---|---|---|
| | $^1$H Signal | | |
| H-5 | 7.18 | 6.23 | 0.95 |
| H-6 | 8.11 | 6.31 | 1.80 |
| H-1′ | 6.29 | 5.94 | 0.35 |
| H-2′ | 5.48 ($J_{H,F}$ = 54.6) | 5.20 ($J_{H,F}$ = 55.1) | 0.28 |
| H-3′ | 2.17, 2.57 | 1.94, 2.37 | 0.23, 0.20 |
| H-4′ | 4.26 | 3.84 | 0.42 |
| H-5′ | 3.62 | 3.49 | 0.13 |
| $NH_2$ | | 6.09 (2 H) | |
| | $^{13}$C Signal | | |
| C-2 | 151.6 | 157.6 | −6.0 |
| C-4 | 143.1 | 135.4 | 7.7 |
| C-5 | 93.0 | 113.2 | −20.2 |
| C-6 | 136.8 | 126.6 | 10.2 |
| C-1′ | 86.8 | 87.1 | −0.3 |
| C-2′ | 91.7 | 92.6 | −0.9 |
| C-3′ | 32.5 | 33.8 | −1.3 |
| C-4′ | 79.4 | 75.6 | 3.8 |
| C-5′ | 62.8 | 63.3 | −0.5 |

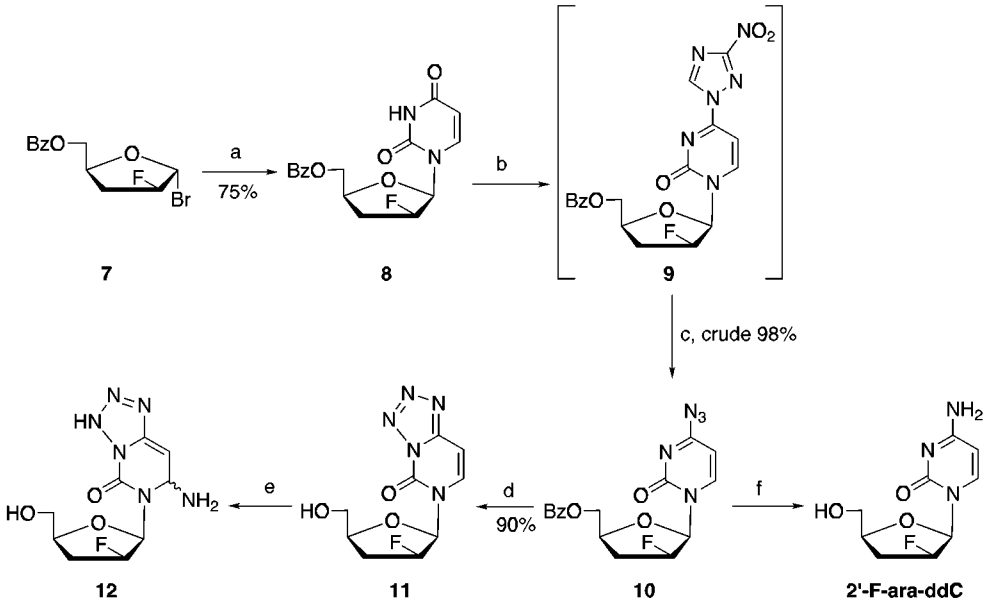
On the basis of the structure of compound **4** and previously known literature,[6,7] the structure of compound **5** was predicted to be as shown in Scheme 2. The proof for the structure **5** was obtained from 1-D and 2-D NMR and tandem mass spectral studies. Table 3 lists the chemical shifts of various protons in compounds **4** and **5**. Chemical shifts of the protons were assigned using the 1-D proton and 2-D COSY spectra. Comparison of the chemical shifts of protons in the compounds **4** and **5** showed that the major changes occurred for H-5 (2.2 ppm upfield), H-6 (0.8 ppm upfield), and H-2′ (1.9 ppm downfield). The other proton signals shifted less than 0.5 ppm either upfield or downfield.

(6) Fox, J. J.; Miller, N. C.; Cushley, R. J. *Tetrahedron Lett.* **1966**, 4627−4634.
(7) Major, P. P.; Egan, E. M.; Herrick, D.; Kufe, D. W. *Biochem. Pharamcol.* **1982**, *31*, 861−866.

**Scheme 2. Transformation of Compound 4 Forming the 2′,6-Anhydro Linkage**




**Scheme 3.[a] Synthesis of Compound 11**




[a] Reagents: (a) Silylated uracil, DCE, reflux; (b) 4-chlorophenyl dichlorophosphate, 3-nitro-1,2,4-triazole, py, rt; (c) $LiN_3$, DMF, rt; (d) saturated $NH_3$/MeOH, rt; (e) $NH_4OH$; (f) $H_2$, Pd/C, MeOH, 50 psi, rt, 15 h.

The chemical shifts of various carbon signals for the compounds **4** and **5** are also shown in Table 3, and the signals were assigned on the basis of $^1H$ decoupled $^{13}C$, DEPT-45, DEPT-90, DEPT-135, and heteronuclear COSY (HETCOR) experiments. Major changes in the chemical shifts of carbon signals were observed for C-4 (12.0 ppm downfield), C-5 (8.2 ppm downfield), C-6 (50.7 ppm upfield), C-1′ (31.6 ppm downfield), and C-2′ (29.8 ppm downfield). Thus, the chemical shift changes of $^1H$ and $^{13}C$ signals between compounds **4** and **5** indicated that the transformation of **4** involves the positions 4, 5, 6, 1′, and 2′. This supports the structure of the predicted compound **5**. Further support for the structure of compound **5** was obtained by high-resolution and tandem mass spectral studies.

Mass spectra (liquid secondary ion mass spectroscopy, LSIMS) of compounds **4** and **5** revealed a molecular peak ($MH^+$) at *m*/*z* 270.1 for both compounds. The experimentally determined empirical formulas for both compounds were identical suggesting that compound **5** was formed by a simple transformation from compound **4** at higher pH. In the mass spectrum of compound **5**, a major fragment with *m*/*z* 180.2 was observed along with the molecular peak at *m*/*z* 270.1 ($MH^+$). However, in the mass spectrum of compound **4**, major fragments were at *m*/*z* 270.1 ($MH^+$) and 138.2 ($MH^+$ − arabinose), but no significant fragment was observed at 180.2. From the tandem and high-resolution mass spectral analysis, the fragment at 180.2 was identified to be the MS fragment **6** (Scheme 2). The fragment **6** (containing the 2′,6-anhydro linkage of compound **5**) could only be obtained by the fragmentation of the C1′−O4′ bond and C2′−C3′ bond. In retrospect, the structure of the MS fragment **6** suggests the 2′,6-linkage in compound **5** and the proposed transformation could occur as shown in Scheme 2.

Previously, it was known that ara-C forms a 2′,6-anhydro linkage under alkaline conditions.[6,7] When ara-C was treated with 0.1 N NaOH at 60−70 °C, a loss of UV absorption maxima was observed within 30 min.[6] When 1-(β-D-arabinofuranosyl)-5-fluorocytosine was treated under the same conditions, a loss of its UV absorption maxima was observed and the structure of the transformed compound contained the 2′,6-linkage. However, compounds containing 2′-OH in the ribo configuration did not show loss of UV absorption under similar conditions. This suggested that compounds containing 2′-OH in arabino configuration could undergo intramolecular rearrangement, resulting in the formation of the 2′,6-anhydro linkage. In the case of compound **4**, this rearrangement even occurs at neutral pH (7.0) and under physiological conditions (pH 7.4).

To understand if the chemical instability of the pyrimidine nucleoside **4** in the base moiety was due to the arabino configuration of 2′-OH or due to the azido moiety, we also studied the chemical stability of 1-(2,3-dideoxy-2-fluoro-β-D-arabinofuranosyl)tetrazolo[4,5-*c*]pyrimidin-2-one (**11**). Compound **11** was designed as a prodrug of 1-(2,3-dideoxy-2-fluoro-1-β-D-arabinofuranosyl)cytosine (2′-F-ara-ddC) by utilizing the azide prodrug approach.[8,9] The compound **11** differs from compound **4** in that it has a

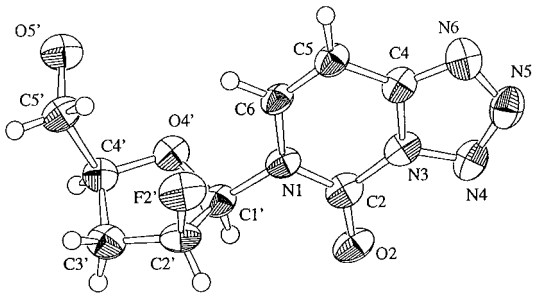



**Figure 2.** ORTEP drawing of the X-ray structure of compund **11**.

fluorine atom in the place of 2′-OH in the ara configuration and lacks the 3′-OH moiety.

Compound **11** was synthesized from the bromo sugar **7**[10] *via* the triazolide **9**. The compound **7** was condensed with silylated uracil under refluxing conditions to give compound **8** in 75% yield. The compound **8** was treated with 4-chlorophenyl dichlorophosphate and 3-nitro-1,2,4-triazole in pyridine at rt to obtain the crude triazolide **9**. Treatment of the crude compound **9** with lithium azide in DMF at rt to obtain compound **10** followed by the deprotection of benzoyl group with saturated ammonia in methanol afforded the desired compound **11**. Single crystal X-ray studies showed that the azide group at 4-position of compound **11** also forms a tetrazole ring with N3 of the pyrimidine ring (Figure 2, Table 1), similar to that in compound **4**.[11] The UV profiles of compound **11** at various pH are shown in Table 2.

At pH 2.0 and 7.0, UV profiles were similar for compound **11** and there was no change in the $\lambda_{max}$ value. However, at pH 11.0, $\lambda_{max}$ shifted to 256.0 nm. In a separate kinetic study, compound **11** was stable at pH 7.4 and there was no change observed in the $\lambda_{max}$ and the extinction coefficient, for up to 4 h. This indicated that compound **11** was stable at physiological pH. To investigate if the compound **11** can undergo any transformations similar to compound **4**, it was treated in a similar fashion as compound **4** to obtain the transformed product, which was later assigned to be compound **12**. In NMR studies, no major change was observed in the chemical shifts of the sugar moiety. However, there were major differences observed in the carbon and proton chemical shifts of the base moiety, indicating that the sugar moiety was not involved in the rearrangement. In the proton spectrum (Table 3), H-5 and H-6 signals showed a change of 0.95 and 1.80 ppm upfield, respectively. In the $^{13}C$ NMR spectrum (Table 3), major changes in the chemical shifts between compound **11** and **12** were observed at C-2 (6.0 ppm downfield), C-4 (7.7 ppm upfield), C-5 (20.2 ppm downfield), and C-6 (10.2 ppm upfield), confirming that the base moiety was involved in the transformation of compound **11** to **12**. Additionally, a broad singlet peak was observed at 6.09 in the proton spectrum of compound **12**. High-resolution mass spectral analysis suggested an amine addition, which could possibly be at the 6-position (from the changes in the NMR signals), from which the structure was confirmed to be **12**. The addition of the amine was also confirmed by deuterium exchange studies and subsequent MS/MS analysis.

The high-resolution mass spectrum (LSIMS) of compound **11** showed only the molecular peak at *m/z* 256.0857 ($MH^+$, calcd 256.0846 corresponding to $C_9H_{11}N_5O_3F$) and the MS/MS analysis of the molecular peak showed the fragment peaks at *m/z* 138.1 ([M − sugar moiety]$^+$), 118.8 ([M − base]$^+$) and 110.1 ([138 − $N_2$]$^+$). The high-resolution mass spectrum of compound **12** showed the molecular peak at 273.1123 ($MH^+$, calcd 273.1111 corresponding to $C_9H_{14}N_6O_3F$), confirming the addition of an amine moiety. The complete details of the mass spectral and fragmentation analysis of compounds **4**, **5**, **11**, and **12** will be published elsewhere.

To further confirm the structures and to investigate if they could be reduced chemically, we performed hydrogenation of the compounds **4** and **11** in the presence of Pd/C or $PdCl_2$, obtaining their corresponding amine analogues, ara-C and 2′-F-ara-ddC, respectively.

We have also synthesized 4-azido-1-methyl-2-pyrimidinone (**15**) as a model system to further support the results obtained from compounds **4** and **11**. The compound **15** contains an azide moiety but no glycosidic bond. The compound **15** was synthesized from 1-methyluracil (**13**) *via* the triazolide intermediate **14**. The UV profile of the compound **15** is shown in Table 2. Compound **15** did not show any significant changes in the UV profile at pH 2.0 and 7.0, indicating no change in the base moiety under these experimental conditions. However at pH 11.0, the $\lambda_{max}$ shifted to 248.0 nm, similar to that of compound **11**. The above results, i.e., the UV profiles of compounds **11** and **15** when compared to that of **4**, suggested that the instability/transformation of compound **4** at pH 7.0 was not due to the azido group on the pyrimidine ring (*vide infra*). While we did not perform X-ray structure analysis on compound **15** to see if the azide is cyclized; it is not critical at this point for our analysis.

In conclusion, the instability and 2′,6-anhydro bond formation in compound **4** was due to the presence of 2′-OH in the arabino configuration. The intramolecular attack of the 2′-OH is faster and facilitated the transformation to form the 2′,6-anhydro linkage. Due to the lack of the 2′-OH, compounds **11** and **15** were relatively more stable than the compound **4**, especially at physiological pH. However, compound **11** was not stable to alkaline conditions like ara-C and exhibits susceptibility to nucleophilic attack at C-6 position.

## Experimental Section

Melting points were determined on a MelTemp-II melting point apparatus and are uncorrected. UV spectra were recorded on a Beckman DU-7 or DU-650 spectrophotometer either in methanol, buffer solution (pH 2.0, 7.0 or 11.0), or phosphate-buffered saline (pH 7.4). Buffer powders were purchased from Aldrich Chemical Co. NMR data were recorded on a Bruker-200 AC, Bruker-300 AM or Bruker-400 AMX spectrometer using DMSO-$d_6$ as solvent unless otherwise specified, and the chemical shifts are reported in ppm ($\delta$). Coupling constants (*J*) are reported in hertz (Hz). The abbreviations used are s (singlet), d (doublet), t (triplet), m (multiplet), pd (pseudo doublet), pt (pseudo triplet), brs (broad singlet), and dm (doublet of multiplet). Mass spectra were recorded either on a Micromass AutoSpec high-resolution mass spectrometer (LSIMS) or a Micromass Quatro II triple quadrupole mass spectrometer (ESI, MS/MS). Elemental analyses

(8) Martin, J. A.; Bushnell, D. J.; Duncan, I. B.; Dunsdon, S. J.; Hall, M. J.; Machin, P. J.; Merrett, J. H.; Parkes, K. E. B.; Roberts, N. A.; Thomas, G. J.; Galpin, S. A.; Kinchington, D. *J. Med. Chem.* **1990**, *33*, 2137−2145.

(9) Sterzycki, R. Z.; Ghazzouli, I.; Brankovan, V.; Martin, J. C.; Mansuri, M. M. *J. Med. Chem.* **1990**, *33*, 2150−2157.

(10) Shanmuganathan, K.; Koudriakova, T.; Nampalli, S.; Du, J.; Gallo, J. M.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **1994**, *37*, 821−827.

(11) Monoclinic crystals with space group *C*2 with lattice parameters $a = 20.186(4)$ Å, $b = 5.252(8)$ Å, $c = 10.354(2)$ Å, $\beta = 105.5(2)°$, $V = 1058(1)$ Å$^3$.

were performed either by Atlantic Microlabs, Inc., Norcross, GA, or by Galbraith Laboratories, Knoxville, TN. The standard workup procedure followed in the reactions, where specified, was to wash the reaction mixture with an equal volume of saturated $NaHCO_3$ solution and brine and to dry the organic layer ($Na_2SO_4$ or $MgSO_4$).

**1-(2,3,5-Tri-*O*-acetyl-*β*-D-arabinofuranos-1-yl)-4-triazolyl-2-pyrimidinone (2).** A solution of compound **1**[3] (950 mg, 3.9 mmol) in pyridine (20 mL) was treated with acetic anhydride (1.2 mL, 11.7 mmol) at 0 °C and stirred for 12 h. The solvent was evaporated and the resulting yellow syrup was dissolved in EtOAc (50 mL). The organic layer was subjected to the standard workup procedure and concentrated, and the residue was dissolved in anhydrous pyridine (20 mL). The solution was treated with 4-chlorophenyl dichlorophosphate (0.9 mL, 5.2 mmol) at 0 °C under argon and 3-nitro-1,2,4-triazole (1.4 g, 11.9 mmol) was added. The reaction mixture was stirred at rt for 24 h and the solvent was evaporated. The residue was dissolved in $CH_2Cl_2$ and followed the standard workup procedure. The solvent was evaporated and the crude yellow compound **2** was used as such for the next reaction.

**1-(2,3,5-Tri-*O*-acetyl-*β*-D-arabinofuranos-1-yl)-4-azido-2-pyrimidinone (3).** Crude compound **2** was dissolved in dimethyl formamide (30 mL), and $LiN_3$ (953 mg, 19.5 mmol) was added. The reaction mixture was stirred at 50 °C for 3 h and dissolved in ethyl acetate (70 mL). The organic layer was subjected to standard workup procedure and concentrated, and the crude was purified by silica gel column chromatography (15−50% EtOAc:Hx) to yield compound **3** (560 mg, 27% from **3**) as white crystals: mp 160−161 °C; UV (MeOH) $\lambda_{max}$ 266.0 nm (sh), 255.0 nm, 203.0 nm; IR (KBr) 3125.80, 2984.26, 1743.87. Anal. Calcd for $C_{15}H_{17}N_5O_8$: C, 45.57; H, 4.33; N, 17.71. Found: C, 45.50; H, 4.34; N, 17.50.

**1-(*β*-D-Arabinofuranosyl)tetrazolo[4,5-*c*]pyrimidin-2-one (4).** Compound **3** (495 mg, 1.3 mmol) was treated with 1 N HCl in methanol (25 mL) and stirred for 26 h at rt. The solvent was evaporated, the resulting white crystals were washed with 2-propanol and dried under high vacuum to yield compound **4** (261 mg, 72%): mp 123−126 °C; UV (MeOH) $\lambda_{max}$ 267.5 nm (shoulder), 257.5 nm, 206.0 nm; 267.5 nm (sh, 6141), 255.5 nm (6572) (pH 2.0); 245.5 nm (9537) (pH 7.0); 239.5 nm (12 876) (pH 11.0); $^1$H NMR (DMSO-$d_6$/$D_2O$) $\delta$ 7.99 (d, $J$ = 7.7, 1H, H-6), 7.12 (d, $J$ = 7.96, 1H, H-5), 6.23 (d, $J$ = 4.12, 1H, H-1′), 4.20 (t, $J$ = 3.6, 1H, H-2′), 3.98 (pt, $J_1$ = 1.57, $J_2$ = 3.16, 1H, H-3′), 3.90 (dd, $J_1$ = 8.69, $J_2$ = 5.20, 1H, H-4′), 3.67 (d, $J$ = 5.17, 2H, H-5′). Anal. Calcd for $C_9H_{11}N_5O_5 \cdot H_2O$: C, 37.63; H, 4.56; N, 24.38. Found: C, 37.74; H, 4.56; N, 24.35.

**1-(5-*O*-Benzoyl-2,3-dideoxy-2-fluoro-*β*-D-arabinofuranos-1-yl)uracil (8).** Uracil (3.2 g, 28.5 mmol) was treated with 1,1,1,3,3,3-hexamethyldisilazane (50 mL) under argon and refluxed for 6 h. Excess solvent was removed under reduced pressure and was treated with freshly prepared bromo sugar **7**[10] in 1,2-dichloroethane (150 mL). The reaction mixture was refluxed at 80 °C for 4 h and cooled to rt. The reaction mixture was quenched with MeOH (10 mL) and concentrated. The residue was dissolved in EtOAc and the workup followed the standard procedure. The organic layer was concentrated and purified on a silica column (2% MeOH:$CHCl_3$) to obtain compound **8** (2.4 g, 74%) as a major product: mp 171−172 °C; UV (MeOH) $\lambda_{max}$ 260 nm. Anal. Calcd for $C_{16}H_{15}N_2O_5F$: C, 57.48; H, 4.52; N, 8.38; F, 5.68. Found: C, 56.96; H, 4.56; N, 8.15; F, 5.21.

**1-(2,3-Dideoxy-2-fluoro-*β*-D-arabinofuranosyl)tetrazolo[4,5-*c*]pyrimidin-2-one (11).** A solution of compound **8** (2.6 g, 7.6 mmol) in pyridine (50 mL) was cooled in an ice bath and 4-chlorophenyl dichlorophosphate (1.9 mL, 11.5 mmol) was slowly added followed by 3-nitro-1,2,4-triazole (2.6 g, 22.9 mmol). The reaction mixture was stirred for 3 h and the solvent was evaporated to dryness. The residue was dissolved in chloroform and subjected to the standard workup procedure. Upon concentration of the organic layer, a golden yellow foam was obtained (**9**). The crude compound **9** was dissolved in DMF (30 mL), and $LiN_3$ (1.5 g, 30.6 mmol) was added. The reaction mixture was stirred at rt for 1 h and the solvent was evaporated to dryness under high vacuum. The residue was dissolved in ethyl acetate and the workup followed the standard procedure. Then the organic layer was concentrated to give compound **10** as a yellow solid (2.7 g, crude 98%), which was treated with saturated ammonia in methanol (300 mL) and stirred for 4 h at rt. Then the solvent was evaporated and the residue was neutralized with AcOH (0.5 mL) in MeOH (200 mL). The crude product was purified by silica gel column chromatography (5% MeOH:$CHCl_3$) to yield compound **11** (1.7 g, 90%) as a white solid: mp 133 °C; UV ($H_2O$) $\lambda_{max}$ 252.0 (9322); 266.5 (sh, 8704) (pH 2.0); 253.0 (7981), 266.5 (shoulder, 7302) (pH 7.0); 256.0 (12 490); $^1$H NMR $\delta$ 8.11 (d, $J$ = 7.83, 1H, H-6), 7.18 (d, $J$ = 8.86, 1H, H-5), 6.29 (dd, $J_1$ = 3.71, $J_2$ = 15.62, 1H, H-1′), 5.48 (dm, $J$ = 54.46, 1H, H-2′), 5.20 (brs, 1H, 5′-OH, $D_2O$ exchangeable), 4.26 (m, 1H, H-4′), 3.62 (m, 2H, H-5′), 2.17, 2.57 (2m, 2H, H-3′); HRMS (LSMSI, $m/z$) 256.0857 (calcd 256.0846). Anal. Calcd for $C_9H_{10}N_5O_3F$: C, 42.37; H, 3.95; N, 27.44; F, 7.45. Found: C, 42.59; H, 3.98; N, 27.30; F, 7.05.

**1-Methyl-4-(3-nitro-1,2,4-triazol-1-yl)-2-pyrimidinone (14).** A solution of 1-methyluracil (**13**) (150 mg, 1.2 mmol) in anhyd pyridine (10 mL) was cooled in an ice bath and treated with 4-chlorophenyl dichlorophosphate (0.34 mL, 1.4 mmol) followed by 3-nitro-1,2,4-triazole (410 mg, 3.6 mmol). The reaction mixture was stirred at rt for 2 h and quenched with methanol (1 mL). The solvent was evaporated and the residue was dissolved in saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with $CHCl_3$ (5 × 30 mL), and the combined organic layers were dried ($Na_2SO_4$). The organic layer was concentrated to obtain the crude compound **14**.

**4-Azido-1-methyl-2-pyrimidinone (15).** A solution of the crude compound **14** in DMF (10 mL) was treated with $LiN_3$ (233 mg, 4.2 mmol) and stirred at 50 °C for 3 h. The reaction mixture was then poured into water (30 mL) and extracted with $CHCl_3$ (5 × 40 mL). The combined organic layers were concentrated and recrystallized from ethanol (5 mL) to give the compound **15** as a white solid (93 mg, 52%): UV ($H_2O$) $\lambda_{max}$ 256.5 (10 481) (pH 2.0); 256.0 (10 958) (pH 7.0); 248.0 (13 253) (pH 11.0); $^1$H NMR $\delta$ 7.95(d, 1H, $J$ = 7.59, H-6), 7.09 (d, 1H, $J$ = 7.61, H-5), 3.59 (s, 3H, $CH_3$). Anal. Calcd for $C_5H_5N_5O$: C, 39.74; H, 3.33; N, 46.34. Found: C, 39.66; H, 3.38; N, 46.23.

**Preparation of Compounds 5 and 12.** Either compound **4** or **11** (100 mg) was dissolved in ammonium hydroxide (compound **11** was warmed to dissolve completely) and the solvent was evaporated to dryness. The transformation of compound **4** took place in less than 5 min. The transformation of compound **11** was slower and took 30 min to 1 h. The residue was dissolved in water and freeze-dried to yield the product **5** or **12**.

**Reduction of Compounds 4 and 11.** Either compound **4** or **11** (100 mg) was dissolved in MeOH (10 mL) and hydrogenated in the presence of Pd/C or $PdCl_2$ (20 mg) at 55 psi at rt for 15 h. The reaction mixture was filtered through a pad of Celite and the solvent was evaporated. The crude mixture was purified by prep TLC (20% MeOH:$CHCl_3$) to give ara-C (21%) or 2′-F-ara-ddC (28%), and the spectral data corresponds to previously published reports.[9,12]

**Preparation of Crystals.** Either compound **4** or **11** was dissolved in 1 mL of MeOH until the solution was saturated and the solution was left at rt while the crystals grew. When crystals of required size were seen, the solution was filtered, the crystals were washed with cold MeOH and dried.

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